MOTOR PERFORMANCE FOLLOWING CHEMOTHERAPY FOR CHILDHOOD CANCER

Annelies Hartman

ACKNOWLEDGEMENTS

The work presented in this thesis was conducted at the department of Pediatric Oncology/Hematology and the department of Physiotherapy at the Erasmus MC Sophia Children's Hospital, Rotterdam, the Netherlands.
Financial support by ???????????? is gratefully acknowledged.

- Jurriaanse stichting
- Afdeling fyiotherapie
- KOCR
- Transfergroep Rotterdam
- Afdeling fysiotherapie

ISBN 978-90-8559-473-4

Layout and printing by Optima Grafische Communicatie, Rotterdam, The Netherlands

MOTOR PERFORMANCE FOLLOWING CHEMOTHERAPY FOR CHILDHOOD CANCER

Motorisch prestatieniveau na chemotherapie voor kanker op de kinderleeftijd

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificius
Prof. Dr. S.W.J. Lamberts
en volgens het besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
woensdag 21 januari 2009 om 11.45 uur

door

Johanna Elisabeth Maria Hartman

geboren te Leidschendam

PROMOTIECOMMISSIE

Promotor: Prof. Dr. R. Pieters

Overige leden: Prof. Dr. A.J. van der Heijden
Dr. M.M. van den Heuvel - Eibrink
Prof. Dr. H.J. Stam
Prof. Dr. W.F.M. Arts
Prof. Dr. W.A. Kamps
Prof. Dr. P.J.M. Helders
Prof. Dr. H.C.G. Kemper

Contents

CHAPTER 1

GENERAL INTRODUCTION

INTRODUCTION

Malignancies are the second most frequent cause of death in children in the Netherlands. Every year approximately 500-600 children aged 0-18 years are diagnosed with cancer [1]. Survival rates of children with malignancies have increased tremendously, particularly in the last decennium. The survival rate of children with acute lymphatic leukemia (ALL) for example, has risen to almost 85% [2]. One of the reasons for the increase in survival has been stepwise improvement in combination chemotherapy. With the increased survival, more attention is now being paid to the unwanted side effects of the treatment. A number of chemotherapeutic agents used in the treatment of childhood malignancies have side effects that may lead to decreased motor performance. Especially the use of vincristine is mentioned as a cause of problems during, and also after completion of chemotherapy.

Vincristine

Vincristine (VCR) has been used widely in anticancer therapy for almost forty years [3]. It is used more frequently in pediatric patients than in adults. This may be due to the higher efficacy in childhood malignancies and to a better tolerance of children to relatively high doses [3]. Cytotoxic drugs interfere with the synthesis or function of DNA, resulting in necrosis of cells or in apoptosis (cell death). As with most anticancer drugs VCR is active in a specific phase of the cell cycle, the metaphase of the mitotic process [3]. During mitosis the microtubular network disappears and the spindle apparatus necessary for partitioning chromosomes is formed [4]. Vincristine damages the microtubuli of the mitotic spindle in the cell nucleus, causing failure of the chromosomes to segregate, thus arresting cell proliferation which results in apoptosis [3]. However, the toxic effect of VCR also occurs in axonal microtubuli. Axonal microtubuli enable materials necessary for the maintenance of structural and functional integrity of the axon and the axonal terminal, to be transported along the axon [5]. When damage to the microtubuli occurs axonal transport is reduced and sometimes even obstructed, causing a degeneration which clinically results in peripheral neuropathy, with the most distal parts of the axon first affected ('dying-back neuropathy') [6]. Axonal demyelinisation has been considered a secondary effect [7,8] although others have since suggested that it may in fact be primary [9]. The neurotoxic effect of VCR is cumulative and thought to increase with higher doses per administration, shorter intervals between administrations and higher cumulative dose, but inter-patient variability in response to treatment is large [10,11]. Vincristine is one of the key drugs in the treatment of ALL, B non-Hodgkin lymphoma (NHL), Wilms' tumor (WT) and malignant mesenchymal tumors (MMT). The number of VCR administrations, dose, maximum dose and cumulative dose vary markedly in these treatment protocols. In view of the fact that ALL, WT, B-NHL and MMT represent approximately 45% of all childhood

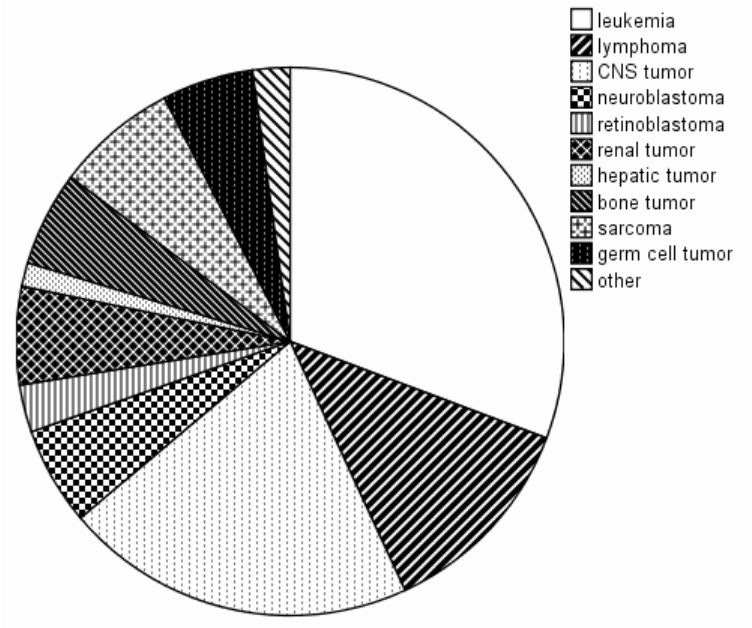

Figure 1 Prevalence of malignancies of children aged 0-18 years in the Netherlands.

malignancies, a substantial number of children can be considered at risk for developing peripheral neuropathy (Figure 1)[1].

Peripheral neuropathy

Peripheral neuropathy is the most frequent dose-limiting toxicity of VCR [12,13]. VCR treatment causes a symmetrical sensorimotor neuropathy which first presents with depressed ankle jerks and paraesthesias, followed by muscle weakness [6]. Peripheral neuropathy can manifest itself in various ways. The symptoms reported first, as early as week 1 of treatment, are diminished or absent tendon reflexes of ankle and knee. Many children also experience reduced muscle power, most noticeably in the foot dorsiflexors and sometimes in the hands. Gait disturbance can be seen from the third week of treatment onwards. Sensory changes such as paresthesias, reduced joint position sense and reduced light touch sensation have also been reported [14].

Several studies have reported the prevalence of peripheral neuropathy in patients treated with VCR. Figures vary, depending on dosage and on the outcome parameters used. Decreased ankle tendon reflexes occur in 57%-100% of patients, paraesthesias in 46%-57% and weakness in 23%-36% [7,15-18].

Clinical signs of neuropathy do not necessarily lead to alterations in chemotherapy. However, treatment with VCR may be discontinued if neurotoxicity starts affecting ambulation. When children develop peripheral neuropathy as a side effect of VCR treatment,

the reduction in muscle strength puts them at risk for losing motor ability. Children with reduced strength of the foot dorsiflexors also have an increased risk for developing a plantigrade contracture of the ankle joint [19].

Many of the clinical signs of vincristine neuropathies are reversible once treatment is completed, with paresthesias being the most readily reversible followed by motor and other sensory deficits [14]. Complete recovery of neuropathy following cessation of VCR treatment has been reported in a study of adult patients [20]. However, some contradictory data were supplied by a study of adult patients showing neurological signs and symptoms > 6 years after cessation of chemotherapy [20]. In the short term, interference with axonal transport leads to distal axonal degeneration. In the long term it may result in neuronal death as the cell is separated from its growth factors [21]. Vincristine neuropathy is considered reversible unless the degenerative process has reached the nerve cell [3]. This raises the question whether some children treated with VCR may not fully recover but will experience impairment of motor performance as a late effect of treatment.

Treatment with vincristine and motor performance

Several authors have reported impaired motor performance in 30-100% of children treated for ALL as long as 2-7 years after completion of treatment [22-25]. However, these studies had limitations. Some treatment protocols also included cranial radiation in addition to chemotherapy [22-24]. Another study used the Gross Motor Function Measure to measure motor performance, which is a test developed specifically for children with cerebral palsy and not suitable for children with ALL [26].

Patients who receive VCR often experience cramps and difficulty in writing [14,27,28]. Follow-up studies have been published in children treated for ALL [25,29]. Vincristine neuropathy causes weakness in the dorsiflexors of the foot, which puts children at risk for developing contractures of the ankle joint. Reduced passive ankle dorsiflexion was shown in long-term survivors of ALL compared to healthy controls matched for age and gender. Whether this resulted in impaired motor performance was not reported [19].

So far, only studies investigating children treated for ALL have been published. As mentioned before, VCR is also used in the treatment of children with B-NHL, WT and MMT, but no data are available on children in these patient groups.

Treatment with other drugs and motor performance

Although VCR is the most frequently mentioned drug causing motor impairment, there are other chemotherapeutic agents that may also affect motor performance.

Besides VCR, treatment protocols for ALL, B-NHL and WT contain a considerable amount of corticosteroids (prednisone and/or dexamethasone) which may cause myopathy leading to weakness of proximal musculature of upper and lower limbs [12]. In addition corticosteroids are known to cause avascular necrosis predominantly of weight bearing

joints, causing pain and loss of function [30]. Five year cumulative incidence of avascular necrosis in children treated for ALL is 5%-7% [31,32]. The highest frequency is observed in adolescents. Osteoporosis is another side effect which, although unlikely to affect motor performance directly, is associated with an increased risk of fractures [33].
Cytosine arabinoside (Ara-C), which is used in the treatment of ALL and B-NHL may cause cerebral or cerebellar dysfunction but this is rare in children [13]. Intrathecal methotrexate (MTX) administered in the ALL and B-NHL protocols can cause transient paraplegia [13].

Other factors related to motor performance

Impairment of motor performance is not dependent on muscle strength and coordination only. The International Classification of Functioning, Disability and Health (ICF) shows the relationships between various aspects of disorder/disease and level of functioning [34]. The ICF describes the effects of a disorder/disease in terms of impairment in body function and structure, impairment in activity and impairment in participation (Figure 2). Environmental and personal factors (e.g. age, motivation, self-image) are also of importance as they can contribute to the level of functioning in positive or negative way. The ICF model and its' application to polyneuropathy was used as a framework for the research presented in this thesis.

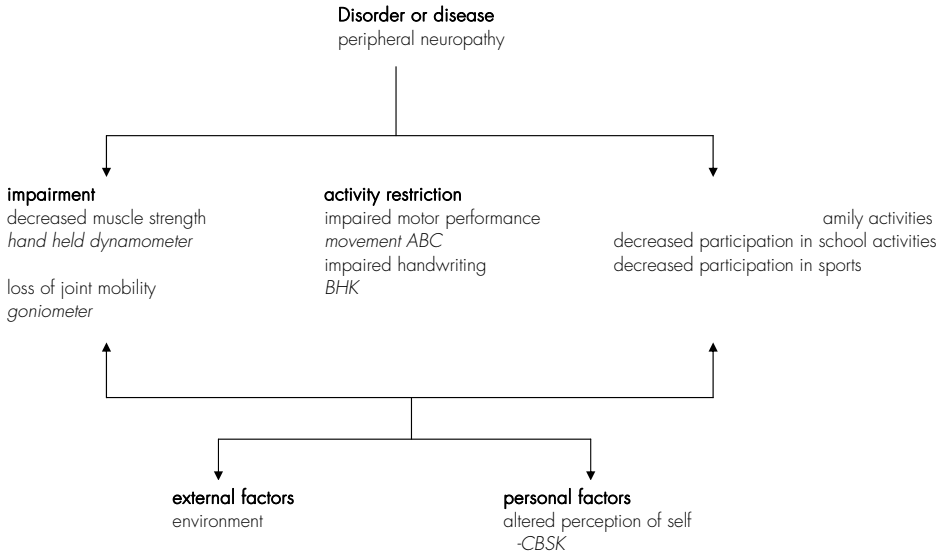

Figure 2 The International Classification of Functioning, Disability and Health (ICF) model showing the relationships between various aspects of disorder/disease and level of functioning. **Bold text** = ICF terminology; regular text = impairments associated with peripheral neuropathy; ***italics*** = instruments used to measure impairments

Measuring motor performance in children

Motor performance in children varies with age. Therefore any standardized test for motor performance has to contain age related motor tasks. Motor ability in children is affected by experience and standardized motor tasks should resemble activities of every day life. Thirdly, age-related reference values should be available in order to compare a child's ability to the ability of healthy peers. Two tests of motor performance meet these criteria: the Bayley Scales of Infant Development Second Edition (BSID-II) and the Movement Assessment Battery for Children (m-ABC) [35-37]. The BISD-II is used to measure motor performance of children aged 1-42 months. The number of items the child manages to perform is calculated. The movement-ABC consists of a series of eight standardized tasks covering hand function, ball skills and balance skills. Age-related norms exist for children aged 4-12 years.

Writing is a also a motor skill. Research has shown that difficulty writing is not necessarily associated with an impairment in motor performance in general [38]. Measuring hand writing ability therefore requires a specialised test. The 'Beknopte Beoordelingsmethode voor Kinderhandschriften' (Concise Assessment Scale for Children's Handwriting) was developed for Dutch children attending grade 4 (aged 7-9 years) and 5 (aged 8-10 years) of regular primary education [39].

The ICF model shows how 'personal factors' contribute to level of functioning. It is therefore also important to know the child's own opinion on whether he considers his motor performance to be impaired. An instrument which measures self-perceived motor performance is the motor supplement of the 'Competentie BelevingsSchaal voor Kinderen' (m-CBSK) which was developed for Dutch children aged 8-12 years [40].

In order to understand why motor performance becomes impaired, impairment of 'function and structures' such as muscle strength and joint mobility need to be investigated. Muscle strength is measured using a hand held dynamometer. Joint mobility can be recorded using a goniometer. Figure 2 shows the instruments used to investigate impairments placed in the context of the ICF model.

Effect of intervention

Neuronal damage due to the toxic effect of vincristine will only be affected by withdrawal of the drug. However, it may be possible to reduce the impact of polyneuropathy on motor performance. Some types of intervention have already been investigated. A positive effect of preventative education and stretching and strengthening exercises during treatment for ALL on passive ankle dorsiflexion compared to historical controls has been demonstrated [41]. Whether this also improved functional ability is unclear. In another study in children receiving treatment for ALL the effect of a four month period of physical therapy improved ankle mobility and knee extension strength but had no effect on functional outcome i.e. there was no significant improvement in ability to run or to walk the stairs [42].

Genetic variation

Response to vincristine treatment can vary considerably. Polymorphisms in genes involved in the metabolisation of vincristine are a likely cause. Vincristine belongs to the group of vinca-alkaloid drugs metabolised by the cytochrome P450 system in the liver [43]. Isoforms of this system expressed in humans are *CYP3A4* and *CYP3A5*. Polymorphisms of *CYP3A4* exist but are rare, whereas polymorphisms of *CYP3A5* are relatively common [44-46]. The multi drug resistance (*MDR-1* or *ABCB1*) gene is also involved in the pharmacokinetics of VCR. Upregulation of the *MDR-1* gene encoding for P-glycoprotein (P-gp), an efflux pump, results in a decrease in intracellular concentration of VCR and an increase in biliary clearance [47,48]. Genetic variation in the microtubule-associated protein tau (*MAPT*) gene may influence VCR effects at the tissue level. *MAPT* promotes the assembly and stabilisation of microtubules, which form a target for VCR as described above. *MAPT* abnormalities have been linked to a number of neurodegenerative disorders e.g. Parkinson's disease, progressive supranuclear palsy, and Alzheimer's disease [49-51].
As vincristine neuropathy can give rise to motor problems, a link may exist between the presence of polymorphisms in these genes and the level of motor performance of children treated with VCR as part of their chemotherapy.

Outline of the thesis

The occurrence of motor problems in children during treatment for ALL has often been reported and has been attributed to polyneuropathy, a side effect of VCR. It has been assumed that VCR neuropathy is reversible and when the drug is withdrawn previous function recovers. However, no studies were available on the long-term motor outcome in children treated for ALL, or in children treated with VCR for other childhood malignancies. Therefore the aim of the work described in this thesis was to study the long-term effects of VCR containing chemotherapy on motor performance and handwriting in children and to investigate which other factors were of influence.
In Chapter 2 we investigate motor performance in children who were treated for ALL, WT, B-NHL or MMT and had completed treatment for at least one year. The effect of cumulative dose of VCR and use of corticosteroids on motor performance is analysed.
Handwriting often deteriorates in children who receive VCR, which is frequently noted by parents and teachers. Vincristine causes a polyneuropathy that can affect peripheral hand muscles and therefore hand function. We hypothesised that handwriting of children treated with VCR would still differ from healthy peers in the long-term. Chapter 3 describes a study investigating this hypothesis by means of a standardised writing test. Polyneuropathy results in weakness of the peripheral muscles of hands and feet. We were interested to know whether any muscle weakness would still be present in the long term and whether this would affect motor performance. Also, dorsiflexors of the foot are often affected in children with VCR neuropathy leading to inadequately lifting the

foot whilst walking. This can result in reduced passive dorsiflexion of the ankle that may persist even when muscle strength improves. In Chapter 4 we report on a study investigating peripheral strength of hands and feet and passive ankle dorsiflexion. Results of children who completed VCR containing chemotherapy are compared to healthy peers. The relationship of strength and passive ankle mobility with motor performance is also investigated. Earlier in this introduction it was suggested that motor performance might be affected by a number of factors. Children who have been treated with chemotherapy may perceive their motor performance differently for various reasons. If they do not rate their performance very highly this may have an adverse effect on undertaking physical activity or participating in sports. If they rate their motor performance as adequate it could raise the question whether impaired motor performance requires intervention or not. In Chapter 5 we investigate the hypothesis that self perceived motor competence of children treated with VCR containing chemotherapy differs from their healthy peers. We also examined the relationship between the rated motor performance and the actual motor performance level to establish whether they rate themselves appropriately.

Large interindividual differences in the adverse effect of VCR treatment in children exist. We hypothesised that his may be due to genetic variation in drug metabolising (*CYP3A5*) or VCR-toxicity related (*MDR-1, MAPT*) genes. In the study described in Chapter 6 the presence of polymorphisms of these genes is in children with ALL is studied in relation to motor performance.

Although impaired motor performance and passive ankle dorsiflexion are known side effects of VCR there is little information on whether these side effects can be prevented. One study shows an effect of stretching exercises on passive ankle dorsiflexion mobility and another on strengthening exercises on muscle power of the knee extensors, but functional outcome is not measured. In Chapter 7 we report on a randomised trial in children with ALL comparing the effect of an intervention programme with standard care on motor performance and bone density. Chapter 8 contains a summary of the research presented in this thesis. In Chapter 9 the results are discussed and future prospects outlined. Chapter 10 provides a summary in Dutch.

REFERENCES

1 SKION. Registration Childhood Malignancies. The Hague: Stichting Kinderkanker Nederland, 2006
2 Pieters R, Carroll WL. Biology and treatment of acute lymphoblastic leukemia. Pediatr Clin North Am 2008; 55:1-20
3 Gidding CE, Kellie SJ, Kamps WA, et al. Vincristine revisited. Crit Rev Oncol Hematol 1999; 29:267-287
4 Darnell J, Lodish H, Baltimore D. The cytoskeleton and cellular movements: microtubules. In: Darnell J, Lodish H, Baltimore D, eds. Molecular cell biology. New York: Scientific American Books, 1986; 771-811
5 Lundborg G. Nerve injury and repair. Edinburgh: Churchill Livingstone, 1988
6 Ouvrier RA, McLeod JG, Pollard JD. Peripheral neuropathy in childhood. 2nd ed. London: Mac Keith Press, 1999
7 Bradley WG, Lassman LP, Pearce GW, et al. The neuromyopathy of vincristine in man. Clinical, electrophysiological and pathological studies. J Neurol Sci 1970; 10:107-131
8 Thant M, Hawley RJ, Smith MT, et al. Possible enhancement of vincristine neuropathy by VP-16. Cancer 1982; 49:859-864
9 Djaldetti R, Hart J, Alexandrova S, et al. Vincristine-induced alterations in Schwann cells of mouse peripheral nerve. Am J Hematol 1996; 52:254-257
10 Gidding CE, Meeuwsen-de Boer GJ, Koopmans P, et al. Vincristine pharmacokinetics after repetitive dosing in children. Cancer Chemother Pharmacol 1999; 44: 203-209
11 Reinders-Messelink HA, Van Weerden TW, Fock JM, et al. Mild axonal neuropathy of children during treatment for acute lymphoblastic leukaemia. Eur J Paediatr Neurol 2000; 4:225-233
12 Macdonald DR. Neurologic complications of chemotherapy. Neurol Clin 1991; 9: 955-967
13 Riccardi R, Lasorella A, Mastrangelo R. Principles of cancer therapy in children. In: Voute P, Kalifa C, Barrett A, eds. Cancer in children: clinical management. 1998: Oxford University Press, 1998; 44-59
14 Hussain M, Wozniak AJ, Edelstein MB. Neurotoxicity of antineoplastic agents. Crit Rev Oncol Hematol 1993; 14:61-75
15 Sandler SG, Tobin W, Henderson ES. Vincristine-induced neuropathy. Neurology 1969; 19:367-374
16 Holland JF, Scharlau C, Gailani S, et al. Vincristine treatment of advanced cancer: a cooperative study of 392 cases. Cancer Res 1973; 33:1258-1264

17 Tuxen MK, Hansen SW. Neurotoxicity secondary to antineoplastic drugs. Cancer Treat Rev 1994; 20:191-214
18 Reddy AT, Witek K. Neurologic complications of chemotherapy for children with cancer. Curr Neurol Neurosci Rep 2003; 3:137-142
19 Wright MJ, Halton JM, Barr RD. Limitation of ankle range of motion in survivors of acute lymphoblastic leukemia: a cross-sectional study. Med Pediatr Oncol 1999; 32:279-282
20 Postma TJ, Benard BA, Huijgens PC, et al. Long-term effects of vincristine on the peripheral nervous system. J Neurooncol 1993; 15:23-27
21 McDonald ES, Windebank AJ. Mechanisms of neurotoxic injury and cell death. Neurol Clin 2000; 18:525-540
22 Eiser C, Lansdown R. Retrospective study of intellectual development in children treated for acute lymphoblastic leukaemia. Arch Dis Child 1977; 52:525-529.
23 Harten G, Stephani U, Langermann H-J, et al. Slight impairment of psychomotor skills in children after treatment of acute lymphoblastic leukemia. Eur J Pediatr 1984; 142: 189-197
24 Vainionpaa L. Clinical neurological findings of children with acute lymphoblastic leukaemia at diagnosis and during treatment. Eur J Pediatr 1993; 152:115-119.
25 Reinders-Messelink HA, Schoemaker MM, Hofte M, et al. Fine motor and handwriting problems after treatment for childhood acute lymphoblastic leukemia. Med Pediatr Oncol 1996; 27:551-555.
26 Wright MJ, Halton JM, Martin RF, et al. Long-term gross motor performance following treatment for acute lymphoblastic leukemia. Med Pediatr Oncol 1998; 31:86-90.
27 Cousens P. Specific learning problems among children treated for acute lymphoblastic leukemia. Int J Ped Hematol/Oncol 1997; 4:353-362
28 Haim N, Barron SA, Robinson E. Muscle cramps associated with vincristine therapy. Acta Oncol 1991; 30:707-711
29 Reinders-Messelink H, Schoemaker M, Goeken L, et al. Handwriting and fine motor problems after treatment for acute lymphoblastic leukemia. In: Simner ML, Leedham CG, Thomassen AJWM, eds. Handwriting and drawing research: basic and applied issues. Amsterdam: IOS Press, 1996; 215-225
30 Patel B, Richards SM, Rowe JM, et al. High incidence of avascular necrosis in adolescents with acute lymphoblastic leukaemia: a UKALL XII analysis. Leukemia 2008; 22:308-312
31 Strauss AJ, Su JT, Dalton VM, et al. Bony morbidity in children treated for acute lymphoblastic leukemia. J Clin Oncol 2001; 19:3066-3072
32 Mattano LA, Jr., Sather HN, Trigg ME, et al. Osteonecrosis as a complication of treating acute lymphoblastic leukemia in children: a report from the Children's Cancer Group. J Clin Oncol 2000; 18:3262-3272

33 van der Sluis IM, van den Heuvel-Eibrink MM, Hahlen K, et al. Altered bone mineral density and body composition, and increased fracture risk in childhood acute lymphoblastic leukemia. J Pediatr 2002; 141:204-210
34 WHO. International Classification of Functioning, Disability and Health, ICF full version. Geneve: WHO, 2001
35 Van der Meulen BF, Ruiter SAJ, Lutje Spelberg HC, et al. Manual BSID-II NL. Lisse: Swets Test Publishers, 2002
36 Henderson S, Sugden D. Movement Assessment Battery for Children. Sidcup, England: The Psychological Corporation, 1992
37 Smits-Engelsman BC. Movement Assessment Battery for Children; Nederlandse bewerking. Lisse, Nederland: Swets & Zeitlinger, 1998
38 Smits-Engelsman BC, Schoemaker MM. Effects of physical therapy on psychomotor aspects of poor handwriting. International Conference Improving the Quality of Physical Therapy. Den Bosch, the Netherlands, 1994
39 Hamstra-Bletz L, De Bie J, Den Brinker BPLM. Beknopte beoordelingsmethode voor kinderhandschriften (A brief evaluation method for for children's handwriting). Lisse: Swets & Zeitlinger, 1987
40 Van Rossum JHA, Vermeer A. Manual ' Competentie Belevingsschaal voor Kinderen'. Lisse: Swets & Zeitlinger, 2000
41 Wright MJ, Hanna SE, Halton JM, et al. Maintenance of ankle range of motion in children treated for acute lymphoblastic leukeamia. Ped Physiother 2003; 15:146-152
42 Marchese VG, Chiarello LA, Lange BJ. Effects of physical therapy intervention for children with acute lymphoblastic leukemia. Pediatr Blood Cancer 2004; 42:127-133.
43 Zhou-Pan XR, Seree E, Zhou XJ, et al. Involvement of human liver cytochrome P450 3A in vinblastine metabolism: drug interactions. Cancer Res 1993; 53:5121-5126.
44 Van Schaik RH, de Wildt SN, Brosens R, et al. The CYP3A4*3 allele: is it really rare? Clin Chem 2001; 47:1104-1106
45 Kuehl P, Zhang J, Lin Y, et al. Sequence diversity in CYP3A promoters and characterization of the genetic basis of polymorphic CYP3A5 expression. Nat Genet 2001; 27:383-391
46 Hustert E, Haberl M, Burk O, et al. The genetic determinants of the CYP3A5 polymorphism. Pharmacogenetics 2001; 11:773-779
47 Song S, Suzuki H, Kawai R, et al. Effect of PSC 833, a P-glycoprotein modulator, on the disposition of vincristine and digoxin in rats. Drug Metab Dispos 1999; 27: 689-694

48 Watanabe T, Miyauchi S, Sawada Y, et al. Kinetic analysis of hepatobiliary transport of vincristine in perfused rat liver. Possible roles of P-glycoprotein in biliary excretion of vincristine. J Hepatol 1992; 16:77-88
49 Scott WK, Nance MA, Watts RL, et al. Complete genomic screen in Parkinson disease: evidence for multiple genes. Jama 2001; 286:2239-2244
50 Pastor P, Ezquerra M, Perez JC, et al. Novel haplotypes in 17q21 are associated with progressive supranuclear palsy. Ann Neurol 2004; 56:249-258
51 Veerman AJ, Hahlen K, Kamps WA, et al. High cure rate with a moderately intensive treatment regimen in non-high-risk childhood acute lymphoblastic leukemia. Results of protocol ALL VI from the Dutch Childhood Leukemia Study Group. J Clin Oncol 1996; 14:911-918

CHAPTER 2

DECREASE IN MOTOR PERFORMANCE IN CHILDREN WITH CANCER IS INDEPENDENT OF THE CUMULATIVE DOSE OF VINCRISTINE

A. Hartman [1,2], C. van den Bos [3], Th. Stijnen [4], R. Pieters [1]

[1]Department of Pediatric Oncology / Hematology, Erasmus MC Sophia Children's Hospital, Rotterdam, The Netherlands;
[2]Department of Pediatric Physiotherapy, Erasmus MC Sophia Children's Hospital, Rotterdam, The Netherlands;
[3]Department of Pediatric Oncology, Emma Children's Hospital Academic Medical Center, Amsterdam, The Netherlands;
Department of Epidemiology and Biostatistics [4], Erasmus MC, Rotterdam, The Netherlands.

Cancer 2006; 106 (6) 1395 - 1401

ABSTRACT

Background

Impaired performance on motor tasks in children treated for acute lymphoblastic leukemia (ALL) after completion of treatment is often attributed to vincristine. Whether motor problems persist in other children who receive different cumulative doses of vincristine is not known. The aim of the present study was to determine the extent of motor problems in children with ALL, Wilms' tumor (WT), B non-Hodgkin lymphoma (B-NHL) and malignant mesenchymal tumors (MMT) and whether these were related to vincristine dose.

Methods

In 127 children who completed treatment at least one year and were aged 4-12 years, motor performance was measured by the Movement Assessment Battery for Children (m-ABC).

Results

The m-ABC scores of the total study group were significantly lower than those of the normal population ($p<0.001$). There were no differences in scores between children with ALL, WT, B-NHL and MMT. There were also no differences between children with ALL who had or had not received pulses of VCR and steroids during maintenance therapy. All groups showed large variability in scores. Scores were not significantly different between children who had received low (0-20 mg/m^2) intermediate (20-40 mg/m^2) or high (> 40 mg/m^2) cumulative doses of vincristine. Cumulative doses of corticosteroids and methotrexate did not affect scores, nor did age at diagnosis and time since completion of therapy.

Conclusions

Although motor performance was impaired in all patient groups, no relationship was found between motor performance and cumulative dose of vincristine or other drugs, age and follow-up time. Future studies have to address whether for instance polymorphisms in drug metabolizing genes or drug target genes explain the large variability in long-term motor outcome of children with cancer.

INTRODUCTION

A number of chemotherapeutic agents used in the treatment of childhood malignancies have side effects that might lead to decreased motor performance. The occurrence of motor problems is often attributed to vincristine, which is successfully used in the treatment of acute lymphoblastic leukemia (ALL). Vincristine causes the development of polyneuropathy which may lead to pain [1], sensory loss and a decrease in muscle power in upper and lower extremities [2]. Several authors found motor problems in 30% to 100% of children with ALL, 2 to 7 years after treatment had been completed [3-8]. However, all these studies had limitations because children had received cranial radiotherapy in addition to chemotherapy [3-5], numbers were small [6], ankle mobility was used as the only outcome measure [7], or a motor test for children with cerebral palsy was used to assess motor performance [8].

Some ALL protocols contain vincristine /steroid pulses during maintenance therapy whereas other protocols do not, leading to large differences in cumulative vincristine and steroid doses (see Table I). Whether motor problems differ depending on the use of pulses is unknown. Vincristine is also used to treat Wilms' tumor (WT), B non-Hodgkin lymphoma (B-NHL) and malignant mesenchymal tumors (MMT). Limited data have been reported on motor problems in these patient groups. Two studies in adult lymphoma patients have been published. One study describes motor problems during chemotherapy treatment in all 27 patients studied [9]. Furthermore, overall motor weakness was described in 20% of patients with a median follow-up time of 11 months after completion of therapy [10]. So far, no data have been published on motor problems in children treated with chemotherapy for malignancies other than ALL.

The aim of the present study was to determine 1) the extent of motor problems in children with ALL, Wilms' tumor (WT), B non-Hodgkin lymphoma (B-NHL) and malignant mesenchymal tumors (MMT), 2) whether these motor problems differed between patient groups and 3) and whether this was dependent on administered cumulative vincristine dose and the use of vincristine / steroid pulses during maintenance therapy.

Table I Vincristine schedules

	ALL-8	ALL-9	WT	NHL	MMT
number of doses vincristine	8-10	31-34	8-24	3-7	10-13
dose in mg/m^2	1.5	2.0	1.5	2.0	1.5
cumulative dose in mg/m^2	12-15	62-68	12-36	6-14	15-19.5
duration of vincristine treatment in weeks	22-23	103	10-33	4-24	15-24

ALL-8 = acute lymphoblastic leukemia treated with DCOG protocol 8, ALL-9 = acute lymphoblastic leukemia treated with DCOG protocol 9, WT = Wilms' tumor, NHL = non Hodgkin lymphoma, MMT = malignant mesenchymal tumor, mg/m^2 = milligrams per square meter body surface.

MATERIAL AND METHODS

Patients

The study was conducted at the pediatric oncology departments of the Erasmus MC Sophia Children's Hospital and the Emma Children's Hospital AMC in the Netherlands. Approval of the Medical Ethical Committees in both hospitals was obtained. Informed consent was obtained from the parents of all participating children.

Inclusion criteria:

- age 4-12 years at time of testing (because the motor test which was used, is validated for this age category only)
- diagnosed with ALL, WT, B-NHL or MMT
- at least one year after completion of therapy

Exclusion criteria:

- a solid tumor whereby the location of the tumor itself could contribute to motor problems, such as a bone tumor of the femur or tibia for example.
- attending special education, as cognitive impairment is known to influence results of the m-ABC motor test.

Treatment

Children with ALL were treated according to the treatment protocols of the Dutch Childhood Oncology Group: the BFM based ALL-8[11] that does not contain VCR/steroid pulses during maintenance and protocol ALL-9, which is almost identical to the previously used protocol ALL-6 and does contain VCR/steroid pulses during maintenance therapy [12]. Protocols of the Societé Internationale d'Oncologie Pédiatrique were used to treat children with WT and MMT [13,14]. Children with B-NHL were treated with DCOG-NHL-94 or LMB-96 protocol; these two protocols are very similar. Cumulative vincristine doses were obtained for each child by medical record extraction.

Assessment of motor problems

Motor performance was measured using the Dutch version of the Movement Assessment Battery for Children (m-ABC) [15,16]. The m-ABC consists of a series of eight standardized tasks divided in three subsections: hand function, ball skills and balance skills. The tasks vary with age and are designed to resemble every day activities of children. The total score of the m-ABC summarizes performance on all eight tasks and is transformed by age-related norms into a percentile score. A score below the 5th percentile is indicative of a motor problem, between 5th and 15th percentile is borderline and higher than the 15th percentile is normal. In addition to the total score the child's performance on each of the subsections can also be expressed as either below or above the 15th percentile.

Validity of the m-ABC to test motor ability in children aged 4-12 years has been shown before [17].

Physical assessment

Height and weight of the children at time of assessing motor performance were measured. Measurements of height and weight at the onset of chemotherapy were obtained from the medical records.
Sensory loss in hands and feet was assessed by clinically examining perception of pain, light touch sensation, vibration and joint position sense. A structured interview was conducted with parents and children to establish the extent of symptoms such as pain in upper and/or lower extremities, activity level and participation in sports.
The same senior pediatric physiotherapist performed assessments of all children.

Statistics

The SPPS statistical package (version 10.1) was used to analyze the data. Mean group differences in m-ABC percentile scores were analyzed with t-tests and one-way ANOVA. Paired t-tests were used to analyze differences in height and weight SD scores at the onset of chemotherapy and at follow-up. Pearson's correlation coefficient was calculated to evaluate the relationship between weight for height SD scores and percentile scores. Analysis of covariance was performed to determine the effect of age at diagnosis and time since completion of treatment on percentile scores, adjusted for patient groups.

RESULTS

Patients

A total number of 142 children were invited to participate in the study. The parents of 13 children did not respond. One child was excluded because he was diagnosed with Gilles de la Tourette syndrome. The results of the remaining 128 children, 61% boys and 39% girls, were used for analysis. Of these, 16 children had been treated with ALL-8 protocol, 41 children with ALL-9, 43 children had been treated for WT, 12 children for B-NHL and 16 children for MMT. Mean age at time of follow-up was 8.1 years (range 4.1-12.8) and mean time since completion of treatment was 3.2 years (range 1.0-7.1). Characteristics of the patient groups are shown in Table II.

Motor performance

Percentile scores on the m-ABC of the total study group were significantly lower than scores of the normal population, whereby 65% of the children in the study group scored

Table II Characteristics of patient groups

	ALL-8 (n=16)	ALL-9 (n=41)	WT (n=43)	NHL (n=12)	MMT (n=16)	total group (n=128)
boys- girls (%)	9 (56%) 7 (44%)	23 (56%) 18 (44%)	24 (56%) 19 (44%)	11 (92%) 1 (8%)	11 (69%) 5 (31%)	78 (61%) 50 (39%)
mean age at testing in years ± sd	9.7 ± 1.4	8.0 ± 2.2	7.7 ± 2.4	8.7 ± 1.7	7.7 ± 2.2	8.1 ± 2.2
mean age at diagnosis in years ± sd	3.1 ± 1.1	3.8 ± 2.2	3.3 ± 2.1	5.6 ± 1.6	3.8 ± 2.1	3.7 ± 2.1
mean time since stop chemotherapy in years ± sd	4.7 ± 1.3	2.0 ± 0.6	3.8 ± 1.5	2.8 ± 1.1	3.3 ± 1.3	3.2 ± 1.5

ALL-8 = acute lymphoblastic leukemia treated with DCOG protocol 8, ALL-9 = acute lymphoblastic leukemia treated with DCOG protocol 9, WT = Wilms' tumor, NHL = non Hodgkin lymphoma, MMT = malignant mesenchymal tumor, sd = standard deviation.

below the 50th percentile ($p<0.001$), 25% of the children scored below the 15th percentile ($p<0.001$), and 11% scored below the 5th percentile ($p<0.001$).

There were no significant differences in percentile scores between children treated with ALL-8, ALL-9, WT, MMT and B-NHL protocols (see figure 1). All groups showed large variability in m-ABC scores, with median percentile scores of 26.5 (ALL-8), 35.0 (ALL-9), 40.0 (WT), 25.0 (B-NHL) and 44.0 (MMT).

In order to investigate specifically the effect of vincristine treatment, children were grouped according to cumulative dose of vincristine received. The first group had received < 20

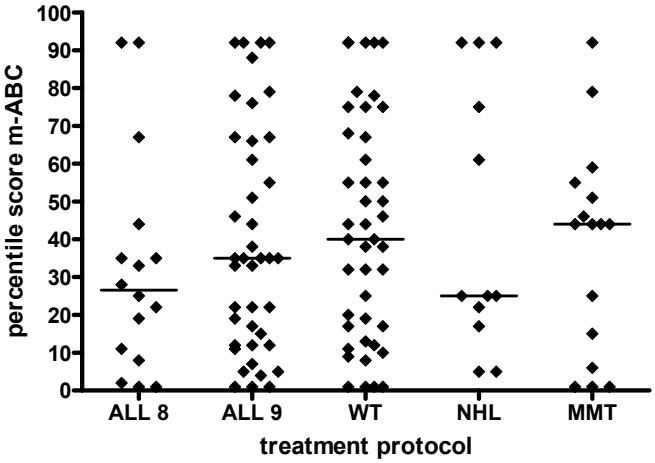

Figure 1 Relationship between percentile scores on m-ABC motor performance test after treatment for: ALL = acute lymphoblastic leukemia, WT = Wilms' tumor, NHL = non-Hodgkin lymphoma, MMT = malignant mesenchymal tumor. The horizontal bars represent the median values.

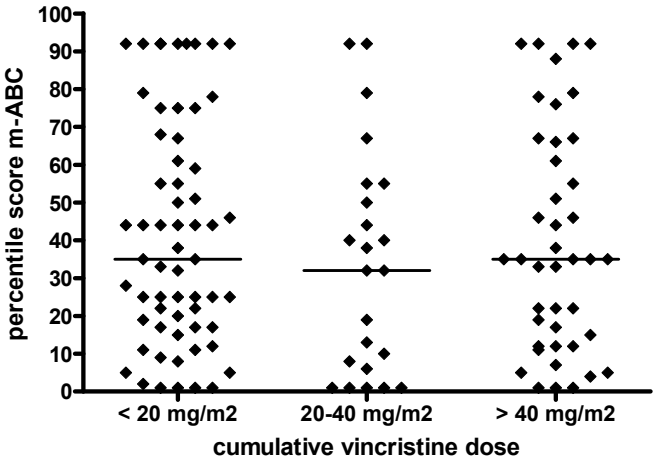

Figure 2 Relationship between percentile scores on m-ABC motor performance test after treatment with low (20 mg/m^2) intermediate (20-40 mg/m^2) and high (> 40 mg/m^2) cumulative doses of vincristine. The horizontal bars represent the median values.

mg/m^2 (low), the second group 20-40 mg/ m^2 (intermediate) and the third group > 40 mg/ m^2 (high). No significant differences in m-ABC percentile scores between the low, intermediate and high vincristine groups were found (one way ANOVA, see figure 2).
There was also no significant difference in percentile scores of children treated with ALL-8 (without VCR/steroid pulses during maintenance) and ALL-9 regimen (with pulses).
As an effect of cumulative vincristine dose could not be demonstrated, the effect of other drugs was analyzed. Two groups were formed: a group treated with corticosteroids, consisting of children who had been treated with ALL-8, ALL-9 or B-NHL protocols, and a non-corticosteroid group with children treated with WT or MMT protocols. A two-sample t-test showed no difference in percentile scores between these two groups.
All but one of the children treated with corticosteroids received MTX and it was confirmed that there was also no significant difference in scores between MTX and non-MTX groups.
Analysis of covariance showed that age at diagnosis and time since completion of treatment had no significant effect on percentile scores, corrected for patient groups. The effect of male or female sex on percentile scores was not significant.

Physical assessment

We analyzed whether weight for height at time of follow up affected percentile scores: there was a weak but significant correlation of r_p = -0.25 (p=0.005). The correlation between weight gain during treatment and percentile scores was not significant (r_p = -0.12).

Sensory loss was found in small numbers of children only: diminished light touch sensation in 10%, loss of joint position sense in 2% and one child had diminished vibration sense. It should be noted that 10% of the children could not be tested because they were too young to fully understand the procedure.
A structured interview was completed for all children whereby 5% reported paraesthesia and 23% still regularly experienced pain. Neither paraesthesia nor sensory loss had an effect on m-ABC scores, but regularly experiencing pain was significantly related to lower percentile scores (p=0.034). Physical education at school was attended by 91% of the children and 70% participated in sports after school, which is average in the Netherlands [18].

DISCUSSION

This study shows that motor performance is impaired in children who were treated for ALL, WT, B-NHL and MMT tested 3.2 (range 1.0-7.1) years after completion of treatment. These results are in accordance with those of Reinders-Messelink [6] who also used the m-ABC to measure motor performance and found that 33% of children treated for ALL scored below the 15th percentile. The current study demonstrates that motor problems do not only occur in children with ALL. Performance was also impaired in patients treated for WT, B-NHL or MMT, but no differences between groups were found. This implies that a negative effect on motor outcome as a result of that childhood cancer and/or its treatment is a more frequently occurring phenomenon.
All these children had received vincristine as part of their chemotherapy, which is known to cause neuropathy. The relationship between vincristine dose and motor performance has not been reported before, but it was expected that scores on the motor test of these patient groups would be dependent on the cumulative vincristine dose. For example children with high cumulative doses of vincristine, such as those treated for ALL with VCR/steroid pulses during maintenance were expected to show poorer scores than ALL children treated with maintenance without VCR/steroid pulses. Surprisingly the data did not support this. There was large interindividual variability in scores in all patient groups, irrespective of cumulative vincristine dose. Cumulative vincristine dose was therefore not the determining factor in motor performance and these findings suggest that even a low dose can cause impairment. Although we did not study children who received no vincristine at all, children who received a minimal amount were included in the study. The lack of correlation between cumulative vincristine dose and motor performance supports the policy of not reducing the dose in case of for instance a decrease of ankle dorsiflexion.
Use of other drugs was also considered. Corticosteroids can cause myopathy [19], osteoporosis [11] and avascular necrosis [20-22] and therefore may have a negative effect on motor

outcome. Corticosteroids are used in the treatment of both ALL and B-NHL, but not in WT and MMT. Treatment for ALL and B-NHL also includes the use of methotrexate (MTX), which can cause encephalopathy [19,23-25] and could adversely affect motor performance. However, performance was impaired to the same extent in all patient groups and not only in those children who had ALL or B-NHL. We therefore concluded that differences in scores could not be explained by use of steroids nor MTX. To the best of our knowledge there are no reports on other drugs used in the treatment of ALL, WT, B-NHL and MMT that could offer an explanation.

Motor outcome may also be influenced by age at diagnosis. It has been suggested that degree of neuropathy in children treated with vincristine is influenced by age, with infants most heavily affected [2]. In the present study age at diagnosis did not affect percentile scores. It should be noted however that our study group did not include any infants.

As the m-ABC motor test is only suitable for children aged 4 to 12 years, older children were excluded from the study. Whether our results hold true for older children is therefore uncertain. It is known that older children more often show severe side effects of steroids [26,27] and they might also respond differently to vincristine.

We also hypothesized that time since completion of treatment could influence motor outcome. It has been shown that neurotoxic signs and symptoms tend to disappear over time [28] and therefore motor performance could be expected to improve over time. However, time since completion of chemotherapy did not influence motor outcome, which suggests that some children may have irreversible damage. This is known to occur when the degeneration process caused by vincristine reaches the perikaryon of the peripheral nerves [29-32].

As in many other studies, the children in our study did significantly gain weight during chemotherapy treatment (data not shown). The effect of weight itself on percentile scores was significant but small; weight gain did not influence percentile scores.

There may be a relationship between pain, which was experienced by 23% of the children, and poorer scores on the m-ABC. As the data on pain were collected by structured interview and not by a validated pain measure, the nature of the relationship between pain and motor performance could not be explored any further.

An explanation for variability in motor performance in all patient groups may be that the m-ABC percentiles scores are a reflection of motor performance prior to the onset of illness. Being ill and having chemotherapy causes motor performance in all children to decrease, resulting in lower scores but with the same variability as before.

Another reason for the large variability in percentile scores in all patient groups could be that sensitivity to vincristine in children differs. Vincristine could have a greater impact in children sensitive to vincristine. Polymorphisms in vincristine metabolizing genes or vincristine target genes could be the underlying cause of this differential sensitivity.

The results of our study seem to be at odds with a recently published study on 114 adults with lymphoma where more damage was noted after a cumulative vincristine dose of 12 mg/m^2[33]. However, patients in this study were adults, the last measurements were taken only 4 weeks after completion of treatment and the authors did not use a standardized test for motor performance. Results of both studies can therefore not be compared.

In conclusion, we found impaired motor performance in all patient groups (ALL, WT, B-NHL, MMT) but no relationship with cumulative doses of vincristine or other drugs, age and follow up time. At present it is not possible to predict which children are likely to become affected and what their motor outcome will be.

Future studies will have to address whether for instance polymorphisms in vincristine metabolizing genes or vincristine target genes or gene mutations leading to an increased tendency to (hereditary) neuropathies such as Charcot-Marie-Tooth disease [34,35], may identify children at increased risk of developing motor problems.

REFERENCES

1 Riccardi R, Lasorella A, Mastrangelo R. Principles of cancer therapy in children. In: Voute P, Kalifa C, Barrett A, eds. Cancer in children: clinical management. 1998: Oxford University Press, 1998; 44-59

2 Gidding CE, Kellie SJ, Kamps WA, et al. Vincristine revisited. Crit Rev Oncol Hematol 1999; 29:267-287

3 Eiser C, Lansdown R. Retrospective study of intellectual development in children treated for acute lymphoblastic leukaemia. Arch Dis Child 1977; 52:525-529.

4 Harten G, Stephani U, Langermann H-J, et al. Slight impairment of psychomotor skills in children after treatment of acute lymphoblastic leukemia. Eur J Pediatr 1984; 142: 189-197

5 Vainionpaa L. Clinical neurological findings of children with acute lymphoblastic leukaemia at diagnosis and during treatment. Eur J Pediatr 1993; 152:115-119.

6 Reinders-Messelink HA, Schoemaker MM, Hofte M, et al. Fine motor and handwriting problems after treatment for childhood acute lymphoblastic leukemia. Med Pediatr Oncol 1996; 27:551-555.

7 Wright MJ, Halton JM, Barr RD. Limitation of ankle range of motion in survivors of acute lymphoblastic leukemia: a cross-sectional study. Med Pediatr Oncol 1999; 32:279-282.

8 Wright MJ, Halton JM, Martin RF, et al. Long-term gross motor performance following treatment for acute lymphoblastic leukemia. Med Pediatr Oncol 1998; 31:86-90.

9 DeAngelis LM, Gnecco C, Taylor L, et al. Evolution of neuropathy and myopathy during intensive vincristine/corticosteroid chemotherapy for non-Hodgkin's lymphoma. Cancer 1991; 67:2241-2246

10 Haim N, Epelbaum R, Ben-Shahar M, et al. Full dose vincristine (without 2-mg dose limit) in the treatment of lymphomas. Cancer 1994; 73:2515-2519

11 Kamps WA, Bokkerink JPM, Hakvoort-Cammel FGAJ, et al. Results of the DCLSG-study ALL8 (1991-1997): BFM oriented treatment without cranial irradiation (CI) and comparing conventional oral and high-doses intravenous 6-mercaptopurine. Med Pediatr Oncol 1999; 33:O-109 (abstract)

12 Veerman AJ, Hahlen K, Kamps WA, et al. High cure rate with a moderately intensive treatment regimen in non-high-risk childhood acute lymphoblastic leukemia. Results of protocol ALL VI from the Dutch Childhood Leukemia Study Group. J Clin Oncol 1996; 14:911-918

13 D'Angio GJ. SIOP (International Society of Paediatric Oncology) and the management of Wilms' tumor. J Clin Oncol 1983; 1:595-596

14 Graf N, Tournade MF, de Kraker J. The role of preoperative chemotherapy in the management of Wilms' tumor. The SIOP studies. International Society of Pediatric Oncology. Urol Clin North Am 2000; 27:443-454
15 Henderson S, Sugden D. Movement Assessment Battery for Children. Sidcup, England: The Psychological Corporation, 1992
16 Smits-Engelsman BC. Movement Assessment Battery for Children; Nederlandse bewerking. Lisse, Nederland: Swets & Zeitlinger, 1998
17 Croce RV, Horvat M, McCarthy E. Reliability and concurrent validity of the movement assessment battery for children. Percept Mot Skills 2001; 93:275-280
18 CBS. Participatie vrije tijd: Centraal Bureau Statistiek, 2004
19 Vainionpaa L, Kovala T, Tolonen EU, et al. Vincristine therapy for children with acute lymphoblastic leukemia impairs conduction in the entire peripheral nerve. Ped Neurol 1995; 13:314-318
20 Gaynon PS, Lustig RH. The use of glucocorticoids in acute lymphoblastic leukemia of childhood. Molecular, cellular, and clinical considerations. J Pediatr Hematol Oncol 1995; 17:1-12
21 Thornton MJ, O'Sullivan G, Williams MP, et al. Avascular necrosis of bone following an intensified chemotherapy regimen including high dose steroids. Clin Radiol 1997; 52:607-612
22 Wei SY, Esmail AN, Bunin N, et al. Avascular necrosis in children with acute lymphoblastic leukemia. J Pediatr Orthop 2000; 20:331-335
23 Shuper A, Stark B, Kornreich L, et al. Methotrexate-related neurotoxicity in the treatment of childhood acute lymphoblastic leukemia. Isr Med Assoc J 2002; 4:1050-1053
24 Sanchez-Carpintero R, Narbona J, Lopez de Mesa R, et al. Transient posterior encephalopathy induced by chemotherapy in children. Pediatr Neurol 2001; 24: 145-148
25 Ruggiero A, Conter V, Milani M, et al. Intrathecal chemotherapy with antineoplastic agents in children. Paediatr Drugs 2001; 3:237-246
26 Mattano LA, Jr., Sather HN, Trigg ME, et al. Osteonecrosis as a complication of treating acute lymphoblastic leukemia in children: a report from the Children's Cancer Group. J Clin Oncol 2000; 18:3262-3272
27 Strauss AJ, Su JT, Dalton VM, et al. Bony morbidity in children treated for acute lymphoblastic leukemia. J Clin Oncol 2001; 19:3066-3072
28 Tuxen MK, Hansen SW. Neurotoxicity secondary to antineoplastic drugs. Cancer Treat Rev 1994; 20:191-214
29 Shiraishi S, Le Quesne PM, Gajree T, et al. Morphometric effects of vincristine on nerve regeneration in the rat. J Neurol Sci 1985; 71:165-181

30 Tanaka EM, Kirschner MW. Microtubule behavior in the growth cones of living neurons during axon elongation. J Cell Biol 1991; 115:345-363
31 Tanaka E, Ho T, Kirschner MW. The role of microtubule dynamics in growth cone motility and axonal growth. J Cell Biol 1995; 128:139-155
32 Lehtinen SS, Huuskonen UE, Harila-Saari AH, et al. Motor nervous system impairment persists in long-term survivors of childhood acute lymphoblastic leukemia. Cancer 2002; 94:2466-2473
33 Verstappen CC, Koeppen S, Heimans JJ, et al. Dose-related vincristine-induced peripheral neuropathy with unexpected off-therapy worsening. Neurology 2005; 64: 1076-1077
34 Mercuri E, Poulton J, Buck J, et al. Vincristine treatment revealing asymptomatic hereditary motor sensory neuropathy type 1A. Arch Dis Child 1999; 81:442-443
35 Schiavetti A, Frascarelli M, Uccini S, et al. Vincristine neuropathy: neurophysiological and genetic studies in a case of Wilms tumor. Pediatr Blood Cancer 2004; 43: 606-609

CHAPTER 3

NO ADVERSE EFFECT OF VINCRISTINE ON HANDWRITING IN CHILDREN AFTER COMPLETION OF THERAPY

A. Hartman [1,2], C. van den Bos [3], N. van Dartel [4], Th. Stijnen [5], R. Pieters [1]

[1]Department of Pediatric Oncology / Hematology, Erasmus MC Sophia Children's Hospital, Rotterdam, the Netherlands.
[2]Department of Pediatric Physiotherapy, Erasmus MC Sophia Children's Hospital, Rotterdam, the Netherlands.
[3]Emma Children's Hospital Academic Medical Center, Amsterdam, the Netherlands.
[4]Physiotherapy Practice, Bennekom, the Netherlands.
[5]Department of Epidemiology and Biostatistics, Erasmus MC, Rotterdam, the Netherlands.

Pediatr Blood Cancer 2007; 49 (6) 841- 845

ABSTRACT

Background

Long-term writing difficulties in children after treatment with vincristine for acute lymphoblastic leukemia, Wilms' tumor, B non-Hodgkin lymphoma and malignant mesenchymal tumors, were investigated.

Procedure

Handwriting of 33 survivors and 33 controls matched for age, sex and grade, was assessed with the BHK-scale. The examiner was blinded for whether a child was a case or a control.

Results

No significant difference in writing speed was found. Mean difference in number of letters produced during five minutes was 6.4 (± 67.1, range –103 to +169). No significant difference was found in quality of writing scores; mean difference in points was 1.5 (± 7.7, range -19 to +22). Cumulative vincristine dose, age at diagnosis or time since completion of treatment did not affect writing speed or quality.

Conclusion

Chemotherapy, including vincristine, does not lead to long-term problems in speed or quality of writing in children treated for cancer.

INTRODUCTION

Vincristine is a chemotherapeutic agent, which is used in the treatment of a number of childhood malignancies. A well-known side effect of vincristine is polyneuropathy, which can lead to a decrease of muscle power and coordination problems in the distal part of upper and lower extremities. Sensory loss has also been reported [1-6].

Patients who receive vincristine often experience difficulty in writing, as is frequently reported by parents and teachers [7]. Some patients mention cramps during writing, others state that the quality of their handwriting has decreased. Only one follow-up study on the effect of vincristine on handwriting has been published, studying children with acute lymphoblastic leukemia (ALL). This suggested a significant difference in quality of writing between 17 children who were at least two years since completion of treatment for ALL (range 2.3-7.9 years) and controls, using the BHK handwriting test [8]. However, the results of the study are questionable because children were older than the guidelines for the BHK test stipulate.

Vincristine is also used to treat Wilms' tumor (WT), B non-Hodgkin lymphoma (B-NHL) and malignant mesenchymal tumors (MMT). No data have been reported on writing problems in these patients groups. The aim of the present study was to determine the extent of long term writing problems in children treated for ALL, WT, B-NHL and MMT.

MATERIALS AND METHODS

Patients and controls

The study was conducted in the pediatric oncology departments of the Erasmus MC Sophia Children's Hospital and the Emma Children's Hospital in the Netherlands. Approval of the Medical Ethical Committees in both hospitals was obtained.

Inclusion criteria: 1) diagnosed with ALL, WT, B-NHL or MMT; 2) at least one year after completion of therapy; 3) attending primary school grade 4 (7-9-years) or grade 5 (8-10 years) at time of testing. Children performed a handwriting test individually as part of a larger study [9], in which hand function was also measured with the Dutch version of the Movement Assessment Battery for Children (m-ABC) [10,11]. A large cohort of healthy controls performed the handwriting test, group wise in their classrooms. Out of this cohort 33 controls were selected, who matched the survivors for primary school grade, age and sex. Informed consent was obtained from the parents of all participating children.

Treatment

Children with ALL were treated according to the protocols of the Dutch Childhood Oncology Group: the BFM based ALL-8 [12] that does not contain vincristine (VCR)/steroid

Table I Vincristine schedules

	ALL-8	ALL-9	WT	B-NHL	MMT
number of doses vincristine	8-10	31-34	8-24	3-7	10-13
dose in mg/m^2	1.5	2.0	1.5	2.0	1.5
cumulative dose in mg/m^2	12-15	62-68	12-36	6-14	15-19.5
duration of vincristine treatment in weeks	22-23	103	10-33	4-24	15-24

ALL-8 = acute lymphoblastic leukemia treated with DCOG protocol 8, ALL-9 = acute lymphoblastic leukemia treated with DCOG protocol 9, WT = Wilms' tumor, NHL = non Hodgkin lymphoma, MMT = malignant mesenchymal tumor, mg/m^2 = milligrams per square meter body surface.

pulses during maintenance and protocol ALL-9, which is almost identical to the previously used protocol ALL-6 and does contain VCR/steroid pulses during maintenance [13]. Both protocols consist of chemotherapy only and do not include cranial irradiation. Protocols of the Societé Internationale d'Oncologie Pédiatrique were used to treat children with WT and MMT [14,15]. Children with B-NHL were treated with DCOG-NHL-94 or LMB-96 protocol; these two protocols are very similar [16]. Cumulative vincristine doses in the above mentioned treatment protocols vary, as does duration of treatment (see Table I). For each child in the patient group cumulative vincristine doses were obtained by medical record extraction.

Assessment of handwriting problems

Handwriting was assessed using the Concise Assessment Scale for Children's Handwriting, known as the BHK-scale, which was developed for Dutch children attending grade 4 (aged 7-9 years) and 5 (aged 8-10 years) of regular primary education [17]. Children are asked to copy a standard text for five minutes at their normal speed, with their commonly used writing utensil. The writing paper is unlined. The standard text gradually increases in difficulty. The first five sentences are at grade 3 reading level.

Writing speed is calculated by counting the number of letters produced during the five minute period. These can be converted into age referenced decile scores. Scores in deciles 1- 2 are considered too slow, scores in deciles 3-10 are within the norm. The quality of handwriting is rated by examining the first five sentences written. The quality items used in the BHK-scale are listed in Table II. The first two items are measured on an ordinal scale (0-6 penalty points) weighted differently for children in grade 4 and 5. The other eleven items are yes/no items indicating for each of the five sentences whether an abnormality is present or not, resulting in 0-5 penalty points for each item. Total BHK scores range from 0 – 67 points, with a higher number of points indicating poorer quality of handwriting. Scores can be converted into three handwriting categories: normal (0 - 21 points), ambiguous (22 - 28 points), or abnormal (> 28 points). Validity and reliability of the BHK-scale have been reported elsewhere [18].

Table II Items of the BHK scale for rating quality of writing

1.	Large letter size
2.	Widening of left hand margin
3.	Poor line alignment
4.	Insufficient word spacing
5.	Angular connections between letters
6.	Irregular connections between letters
7.	Colliding letters
8.	Inconsistent letter size
9.	Inconsistent letter height
10.	Distorted letters
11.	Ambiguous letter shapes
12.	Corrected letters
13.	Unsteady writing trace

Items of the BHK scale (= standardized instrument for measurement of handwriting) for rating quality of handwriting. The first two items are measured on an ordinal scale (0-6) weighted differently for children in grade 4 and 5. The other 11 items are yes/no items indicating whether an abnormality is present or not and are applied to each of the first five sentences written.

In addition to performing the handwriting test, children who had been treated with vincristine were asked whether they had any complaints regarding their handwriting at the time of testing. Parents were asked whether there were any changes in their child's handwriting as far as speed or legibility were concerned.

There was one examiner who rated the handwriting samples and she was kept blind to whether a child had a history of childhood cancer or was a healthy control. The handwriting samples of the whole group were presented to the examiner in random order. Prior to the study intra-rater reliability was determined by presenting the examiner with ten samples of handwriting of children in grade 4 or 5. The same samples were returned to the examiner again one week later, in random order and without the examiner being informed that they were the same handwriting samples as in the previous batch.

Statistics

The SPSS statistical package (version 10.1) was used to analyse the data. The intraclass correlation coefficient was calculated to measure agreement between first and second ratings of the ten handwriting samples. Paired t-tests were used to analyse differences between survivors and controls in number of letters written and in total BHK scores.

In the patient group, Pearson's correlation coefficients were calculated to investigate relationships between age at time of testing, age at diagnosis, time since completion of treatment, cumulative vincristine dose and hand function scores measured by the m-ABC versus speed and quality of writing. The Mann Whitney test was used to analyse differences between children with and without hand writing complaints.

Comparison of ordinal categorical scores between survivors and controls was carried out with the linear-by-linear association test.

RESULTS

Patients

A total number of 33 survivors participated in the study, 20 boys (61%) and 13 girls (39%). Fifteen children (45%) attended grade 4 and 18 children (55%) attended grade 5. Left-handedness was seen in five children (15%).

Of the 33 children, seven children had been treated with ALL-8 protocol, eight children with ALL-9, eleven had been treated for WT, three for MMT and four for B-NHL. All protocols use a maximum vincristine dose, but none of the survivors reached the maximum. Mean age at time of follow-up was 8.6 years (range 7.3-10.2) and mean time since completion of treatment was 3.6 years (range 1.4-6.5). There was no significant difference in age between the survivors and controls; the mean age difference was 0.1 years. Characteristics of all participating survivors are shown in Table III.

Table III Characteristics of the patient groups

	ALL-8 (n=7)	ALL-9 (n=8)	WT (n=11)	B-NHL (n=4)	MMT (n=3)
boys:girls	2 : 5	5 : 3	7 : 4	3 : 1	3 : 0
mean age at testing in years ± sd	9.0 ± 0.7	8.5 ± 0.8	8.3 ± 0.6	8.4 ± 0.9	8.7 ± 0.3
mean age at diagnosis in years ± sd	2.6 ± 0.4	4.3 ± 0.8	3.4 ± 1.8	5.4 ± 1.1	5.0 ± 1.1
mean time since stop chemotherapy in years ± sd	4.4 ± 0.7	2.3 ± 0.5	4.3 ± 1.6	2.8 ± 0.6	3.2 ± 0.8

ALL-8 = acute lymphoblastic leukemia treated with DCOG protocol 8, ALL-9 = acute lymphoblastic leukemia treated with DCOG protocol 9, WT = Wilms' tumor, NHL = non Hodgkin lymphoma, MMT = malignant mesenchymal tumor, sd = standard deviation.

Intra-rater agreement

The intra-class correlation coefficient of ratings of ten handwriting samples on the first and second occasion was good (0.81).

Writing speed and quality of handwriting

No significant difference was found between survivors and their paired controls in writing speed. Mean number of letters produced during five minutes by the survivors and controls was 135.45 and 129.03 respectively. The mean difference between survivors and controls was 6.4 (± 67.1, range -103 to +169) (Figure 1). Mean age referenced decile scores for writing speed was 5.03 in the survivor group and 5.00 in the control group. Mean difference in age referenced decile scores for writing speed between survivors and controls was 0.03 (± 4.6, range −8 to +9).

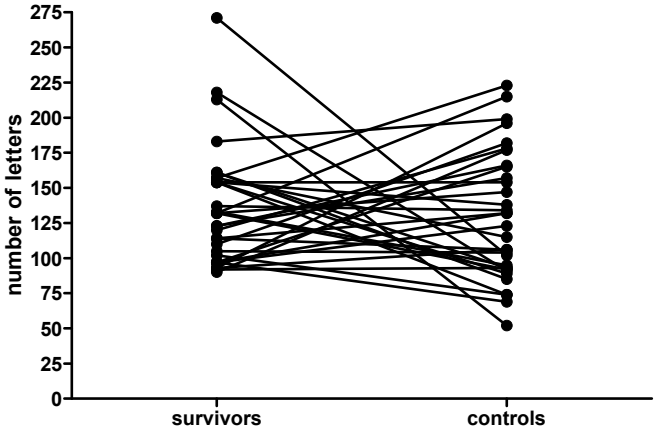

Figure 1 Writing speed of patients who had completed treatment with vincristine for at least one year and paired healthy controls, matched for age, sex and school grade. Scores are obtained by counting the number of letters written during five minutes of copying a standard text. The patient group consisted of children treated for acute lymphoblastic leukemia, Wilms' tumor, B non-Hodgkin lymphoma, or malignant mesenchymal tumor.

There was also no significant difference in quality of handwriting. Mean number of penalty points scored by survivors and controls was 20.36 and 18.88 respectively. The mean difference in number of penalty points between survivors and paired controls was 1.48 (± 7.7, range -19 to +22), see Figure 2.

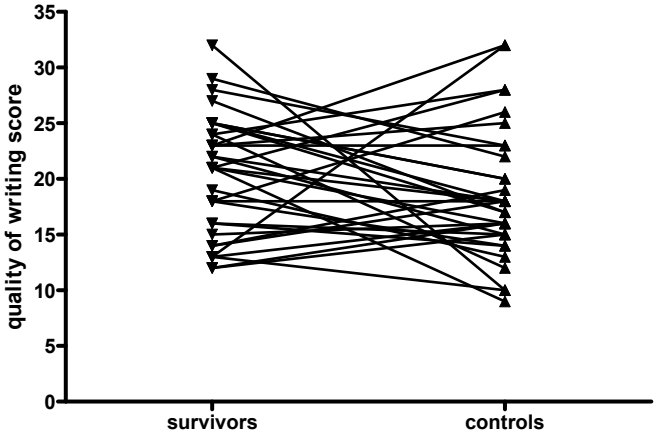

Figure 2 Quality of writing scores on BHK scale (= standardized instrument for measurement of handwriting) of patients who had completed treatment with vincristine for at least one year and matched paired healthy controls. Scores are obtained by rating the first five sentences written when copying a standard text. Scores of 0-21 points are considered 'normal', 22-28 points 'ambiguous' and > 28 points 'abnormal'. The patient group consisted of children treated for acute lymphoblastic leukemia, Wilms' tumor, B non-Hodgkin lymphoma, or malignant mesenchymal tumor.

Table IV Quality of writing category scores on the BHK scale

	normal (0-21 points)	ambiguous (22-28 points)	abnormal (> 28 points)
patients	18 (55%)	13 (39%)	2 (6%)
controls	23 (70%)	9 (27%)	1 (3%)

Quality of writing scores on the BHK scale (= standardized instrument for measurement of handwriting) when converted into the categories 'normal', 'ambiguous' and 'abnormal' for patients and paired healthy controls, matched for age, sex and school grade. The patient group consisted of children treated for acute lymphoblastic leukemia, Wilms' tumor, B non-Hodgkin lymphoma, or malignant mesenchymal tumor. Treatment had been completed for at least one year. Differences in distribution of categories between patients and controls were not significant (linear-by-linear association test, p=0.16).

Table V The effect of several variables on age referenced scores of writing speed and quality of handwriting in survivors

	writing speed	writing quality
age at testing	rp = -0.42 (p=0.02*)	r_p = -0.12 (p=0.52)
age at diagnosis	r_p = 0.17 (p=0.34)	r_p = -0.16 (p=0.93)
time since completion of therapy	rp = -0.42 (p=0.02*)	r_p = 0.01 (p=0.98)
cumulative vincristine dose	rp = 0.36 (p=0.04*)	r_p = 0.21 (p=0.24)

The effect of age at time of testing, age at diagnosis, time since completion of therapy and cumulative vincristine dose on age referenced scores for writing speed and quality of handwriting in the survivor group (n=33). The survivor group consisted of children treated for acute lymphoblastic leukemia, Wilms' tumor, B non-Hodgkin lymphoma, or malignant mesenchymal tumor. r_p = Pearson's correlation. * denotes statistical significance.

The results of total BHK scores when converted into the categories 'normal', 'ambiguous' and 'abnormal' are shown in Table IV. There were no significant differences in distribution in these categories between survivors and controls.

In the patient group the effect of age at time of testing, age at diagnosis, time since completion of therapy and cumulative vincristine dose on age referenced scores of writing speed and quality of handwriting was analyzed (Table V). A moderate inverse correlation between age at time of testing and age referenced scores for writing speed was found (r_p = -0.42, p=0.02). This correlation was also inversed in the control group (r_p = -0.15) but did not reach significance.

There was a moderate inverse correlation between time since completion of therapy and age referenced decile scores for writing speed (r_p = -0.42, p=0.02); this was no longer significant after correcting for cumulative vincristine dose (r_p = -0.31, p=0.09). There was also a moderate positive correlation between writing speed and cumulative vincristine dose (r_p =0.36, p = 0.04), this was no longer significant after correcting for time since completion of therapy (r_p = 0.22, p = 0.24). A significant inverse correlation

was found between time since completion of therapy and cumulative vincristine dose (r_p = -0.45, p=0.01).
As no adverse effect of vincristine was demonstrated, the role of other drugs was also examined. There were no significant differences in age-referenced scores for writing speed or in scores of writing quality between children who received methotrexate and those who did not, or between children who were treated with corticosteroids and those who were not.
In the survivor group there was no relationship between age-referenced scores for writing speed and total BHK score. There was also no relationship between m-ABC hand function score (data not shown) and writing speed or total BHK score.
In the survivor group nine (29%) of 31 children, or their parents, had complaints regarding their handwriting. Children with and without complaints did not differ in writing speed, but there was a significant difference in quality of handwriting (p=0.04); children with complaints produced poorer scores. There was no significant difference in time since completion of chemotherapy between children with and without complaints.

DISCUSSION

Two main outcome parameters are important in handwriting: speed and legibility, i.e., quality of writing. The present study shows that there is no difference in writing speed or in quality of writing between children attending grade 4 and 5 who have been treated with vincristine and healthy matched controls.
Our results are in contrast to a study by Reinders-Messelink et al. in which a significant difference in quality of writing between 17 children who had been treated for ALL and their controls was found [8]. These discordant results may be explained by the fact that the children in the Reinders-Messelink et al. study were asked to write as fast as possible, whereas the BHK guidelines stipulate to write at normal speed. It is known that children who have difficulty writing manage to increase their speed by 'trading-off' against accuracy. It could be that in the Reinders-Messelink et al. study children who had been treated with vincristine increased their writing speed but at the expense of quality, whereas the controls managed to increase their speed and maintain quality. Another explanation for the difference between survivors and controls could be that the examiner in the Reinders-Messelink et al. study was not blinded to the diagnosis and some bias favoring the control group may therefore have taken place. In addition, the quality score of the BHK scale is validated for children attending grade 4 and 5 only and some of the children who took part in their study were older than the BHK guidelines specify, which may have been of influence.

Testing of the survivors in our study was carried out individually; controls were tested group wise in their classroom. This could introduce a bias in the results; however, there is no evidence to suggest that either group would have been favored or disadvantaged by the mode of administration of the test.

There was a weak but significant inverse relationship in the patient group between age at time of testing and age referenced scores for writing speed in our study. The speed-accuracy trade-off effect may also explain these findings. The demand on speed and accuracy both increase with age. In order to maintain accuracy, writing speed of the survivors relatively remains behind. However, survivors did not significantly differ from their controls.

We hypothesized that writing speed should improve the greater the time since completion of therapy and the smaller the cumulative vincristine dose. In our study we found the opposite: a negative correlation between time since completion of therapy and writing speed and a positive correlation between cumulative vincristine dose and writing speed. There was an inverse correlation between time since completion of therapy and cumulative vincristine dose. Further analysis revealed however, that neither variable was independently associated with writing speed.

About 30% of the children treated with vincristine, or their parents, complained of changes in the handwriting since completion of treatment. It appears that their complaints refer to quality of writing as we found that children with complaints had poorer quality of writing than children without complaints, but there was no difference in writing speed.

In conclusion, the long-term quality of handwriting and writing speed had not deteriorated in children treated with chemotherapy including vincristine. Cumulative dose and age at time of treatment did not adversely affect writing quality or speed in the long term.

REFERENCES

1 Macdonald DR. Neurologic complications of chemotherapy. Neurol Clin 1991; 9: 955-967

2 DeAngelis LM, Gnecco C, Taylor L, et al. Evolution of neuropathy and myopathy during intensive vincristine/corticosteroid chemotherapy for non-Hodgkin's lymphoma. Cancer 1991; 67:2241-2246

3 Postma TJ, Benard BA, Huijgens PC, et al. Long-term effects of vincristine on the peripheral nervous system. J Neurooncol 1993; 15:23-27

4 Vainionpaa L. Clinical neurological findings of children with acute lymphoblastic leukaemia at diagnosis and during treatment. Eur J Pediatr 1993; 152:115-119.

5 Posner JB. Neurologic complications of cancer. Philadelphia: FA Davis, 1995

6 Ouvrier RA, McLeod JG, Pollard JD. Peripheral neuropathy in childhood. 2nd ed. London: Mac Keith Press, 1999

7 Cousens P. Specific learning problems among children treated for acute lymphoblastic leukemia. Int J Ped Hematol/Oncol 1997; 4:353-362

8 Reinders-Messelink H, Schoemaker M, Goeken L, et al. Handwriting and fine motor problems after treatment for acute lymphoblastic leukemia. In: Simner ML, Leedham CG, Thomassen AJWM, eds. Handwriting and drawing research: basi and applied issues. Amsterdam: IOS Press, 1996; 215-225

9 Hartman A, Van den Bos C, Stijnen T, et al. Decrease in motor performance in children with cancer is independent of cumulative vincristine dose. Cancer (in press) 2005

10 Henderson S, Sugden D. Movement Assessment Battery for Children. Sidcup, England: The Psychological Corporation, 1992

11 Smits-Engelsman BC. Movement Assessment Battery for Children; Nederlandse bewerking. Lisse, Nederland: Swets & Zeitlinger, 1998

12 Kamps WA, Bokkerink JPM, Hakvoort-Cammel FGAJ, et al. Results of the DCLSG-study ALL8 (1991-1997): BFM oriented treatment without cranial irradiation (CI) and comparing conventional oral and high-doses intravenous 6-mercaptopurine. Med Pediatr Oncol 1999; 33:O-109 (abstract)

13 Veerman AJ, Hahlen K, Kamps WA, et al. High cure rate with a moderately intensive treatment regimen in non-high-risk childhood acute lymphoblastic leukemia. Results of protocol ALL VI from the Dutch Childhood Leukemia Study Group. J Clin Oncol 1996; 14:911-918

14 D'Angio GJ. SIOP (International Society of Paediatric Oncology) and the management of Wilms' tumor. J Clin Oncol 1983; 1:595-596

15 Graf N, Tournade MF, de Kraker J. The role of preoperative chemotherapy in the management of Wilms' tumor. The SIOP studies. International Society of Pediatric Oncology. Urol Clin North Am 2000; 27:443-454
16 Patte C, Gerrard M, Auperin A, et al. Final results and prognostic factors of the randomised international trial FAB LMB 96 for the 'inetermediate risk' in cihldhood and adolescent b-cell lymphoma (abstract). Pediatric Blood Cancer 2004; 43:348
17 Hamstra-Bletz L, De Bie J, Den Brinker BPLM. Beknopte beoordelingsmethode voor kinderhandschriften (A brief evaluation method for for children's handwriting). Lisse: Swets & Zeitlinger, 1987
18 Hamstra-Bletz L, Blote AW. A longitudinal study on dysgraphic handwriting in primary school. J Learn Disabil 1993; 26:689-699.

CHAPTER 4

DECREASE IN PERIPHERAL MUSCLE STRENGTH AND ANKLE DORSIFLEXION AS LONG TERM SIDE EFFECTS OF TREATMENT FOR CHILDHOOD CANCER

A. Hartman [1,2], C. van den Bos [3], Th. Stijnen [4], R. Pieters [1]

[1]Department of Pediatric Oncology / Hematology, Erasmus MC Sophia Children's Hospital, Rotterdam, The Netherlands;
[2]Department of Pediatric Physiotherapy, Erasmus MC Sophia Children's Hospital, Rotterdam, The Netherlands;
[3]Department of Pediatric Oncology, Emma Children's Hospital Academic Medical Center, Amsterdam, The Netherlands;
[4]Department of Epidemiology and Biostatistics, Erasmus MC, Rotterdam, The Netherlands.

Pediatr Blood Cancer 2008; 50 (4) 833-837

ABSTRACT

Background

This study investigated muscle strength, passive ankle dorsiflexion and their association with motor performance in children after treatment for acute lymphoblastic leukemia, Wilms' tumor, B-non-Hodgkin lymphoma and malignant mesenchymal tumors.

Procedure

Muscle strength was assessed with a hand-held dynamometer and ankle dorsiflexion with a goniometer in 92 and 64 survivors respectively. Motor performance was measured with the Movement Assessment Battery for Children (movement-ABC). Age at testing: 6.1-12.9 years. Mean time since completing treatment: 3.3 years. Results were compared to 155 healthy controls.

Results

Muscle strength of the survivors was reduced in ankle dorsiflexors on both sides ($p< 0.001$), wrist dorsiflexors on the non-dominant side ($p< 0.001$) and pinch grip on the non-dominant ($p=0.001$) and dominant side ($p=0.01$). Passive ankle dorsiflexion of the survivors was significantly less on both sides ($p<0.01$). Movement-ABC percentile score was affected by pinch grip strength on the non-dominant ($p<0.004$), and dominant side ($p=0.024$) but not by strength of other muscle groups or by passive ankle dorsiflexion.

Conclusion

Peripheral muscle strength and ankle dorsiflexion are reduced in the long term in children treated for cancer with chemotherapy. However, neither decreased muscle strength nor reduced ankle dorsiflexion could completely explain reduced scores on the movement-ABC.

INTRODUCTION

During the last decades the survival of children diagnosed with cancer has increased substantially. One of the antineoplastic drugs contributing to the increased survival rate is vincristine, which is used among others in the treatment of acute lymphoblastic leukemia (ALL), Wilms' tumor (WT), B-non-Hodgkin lymphoma (B-NHL) and malignant mesenchymal tumors (MMT).

It is known from previous studies that children treated with vincristine for ALL show a decrease in motor performance, which may last a number of years following completion of chemotherapy [1-4]. We recently showed that not only children with ALL but also with other malignancies, demonstrated impaired motor performance after chemotherapy containing vincristine [5]. The underlying mechanism leading to this impaired motor performance is as yet unknown.

Reduced muscle strength may contribute to impaired motor performance and was reported in three studies of patients treated for ALL [4,6,7]. However these studies had limitations, because muscle strength was not measured with myometry but assessed with a motor performance test [4], patients had received radiotherapy in addition to chemotherapy [4,6], or strength measurements were carried out whilst patients were still receiving chemotherapy treatment [7]. Also, no data have been published on muscle strength in children who have completed chemotherapy treatment for childhood malignancies other than ALL.

Corticosteroids can cause myopathy [8] and may therefore have a negative effect on muscle strength. Corticosteroids are used in the treatment of both ALL and B-NHL.

Some ALL protocols contain vincristine /steroid pulses during maintenance therapy whereas other protocols do not, leading to large differences in cumulative vincristine and steroid doses. Whether muscle strength is affected by the use of these pulses during maintenance is unknown.

Reduced passive ankle dorsiflexion, which may also impair motor performance, was shown in 54 long-term survivors of ALL [9]. Whether there was a relationship between loss of ankle dorsiflexion and impaired motor performance was not investigated.

The aims of the present study were to 1) investigate muscle strength and ankle dorsiflexion in children who had completed treatment for ALL, WT, B-NHL, and MMT, which included vincristine for all four types of malignancies and steroids for ALL and B-NHL, and 2) to determine whether muscle strength or ankle dorsiflexion were related to an impaired motor performance score.

METHODS

Patients

The study was conducted at the paediatric oncology departments of the Erasmus MC Sophia Children's Hospital and the Emma Children's Hospital AMC in the Netherlands. Approval of the Medical Ethical Committees in both hospitals was obtained. Children were included if they were aged 6-12 years at time of testing, had been diagnosed with ALL, WT, B-NHL or MMT and therapy had been completed at least one year prior to the study. They were excluded if they had a solid tumor whereby the location of the tumor itself could have contributed to motor problems, such as a tumor of the upper or lower limb. Cognitive impairment was also an exclusion criterion, as this may limit the child's ability to understand and participate in muscle strength testing. The children took part in a larger study investigating motor problems in children treated for childhood cancer published by us earlier [5] and were selected on the basis of having received vincristine. Children attending a local school for primary education were invited to participate as controls. Informed consent was obtained from their parents.

Treatment

Children with ALL were treated according to the protocols of the Dutch Childhood Oncology Group (DCOG): the Berlin-Frankfurt-Munster (BFM) based ALL-8 [10] that does not contain VCR/steroid pulses during maintenance and protocol ALL-9, which is almost identical to the previously used protocol ALL-6 and does contain VCR/steroid pulses during maintenance therapy [11]. Protocols of the Societé Internationale d'Oncologie Pédiatrique (SIOP) were used to treat children with WT and MMT [12,13]. Children with B-NHL were treated with DCOG-NHL-94 or LMB-96 protocol; these two protocols are very similar [14]. Vincristine and steroid schedules are shown in Table I. Cumulative vincristine and steroid doses were obtained for each child by medical record extraction.

Table I Vincristine schedules

	ALL-8	ALL-9	WT	NHL	MMT
cumulative vincristine dose in mg/m^2	12-15	62-68	12-36	6-14	15-19.5
vincristine dose per administration in mg/m^2	1.5	2.0	1.5	2.0	1.5
maximum vincristine dose per administration in mg	2.0-2.5	2.5	2.0	2.0	2.0
cumulative prednisone dose in mg/m^2	1933-1957	-	-	1417-1605	-
cumulative dexamethasone dose in mg/m^2	236	1244-1370	-	-	-

ALL-8 = acute lymphoblastic leukemia treated with DCOG protocol 8, ALL-9 = acute lymphoblastic leukemia treated with DCOG protocol 9, WT = Wilms' tumor, NHL = non Hodgkin lymphoma, MMT = malignant mesenchymal tumor, mg/m^2 = milligrams per square meter body surface.

Assessments

Height (in centimetres) and weight (in kilograms) of the children were measured. Muscle strength of dorsiflexors of feet and hands was assessed with a Citec 3001 hand held dynamometer (CIT Technics, Groningen, the Netherlands). The 'break' technique, defined as 'the examiner applying force to a child's limb until the child's capacity to hold is exceeded and the limb gives way' was used to measure dorsiflexors of ankle and wrist (Figure 1)[15]. To measure grip strength children were asked to grip the hand held dynamometer, with a flexed elbow. Strength was measured in the positions described by Van der Ploeg [16]. Measurements were carried out bilaterally and repeated three times each, as recommended by Horvat [17].

Figure 1 Measuring strength of the wrist dorsiflexors, as an example of measuring muscle strength with a hand held dynamometer.

To assess joint mobility of the ankle, passive dorsiflexion was measured in supine position with the knee extended (Figure 2). A range of motion past the neutral position had a positive notation and less than neutral was negative.

The same physiotherapist - not blinded to whether a child was a survivor or a control - carried out all measurements.

Assessment of motor performance

Motor performance of the survivors was assessed with the Dutch version of the Movement Assessment Battery for Children (movement-ABC) [18,19] and was published earlier [5,18,19]. The movement-ABC consists of a series of eight standardized tasks, which vary with age,

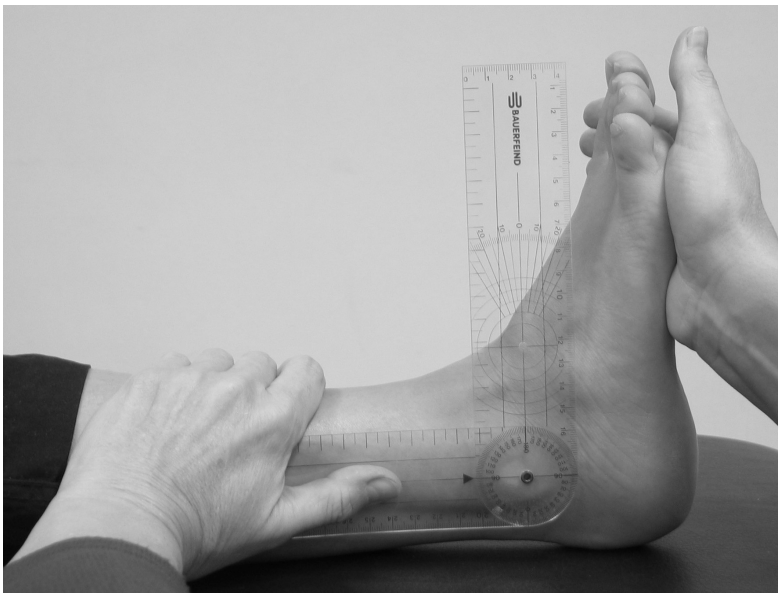

Figure 2 Measurement of passive ankle dorsiflexion in supine position, with the knee extended.
A goniometer is placed in line with the fibula and the lateral border of the foot. The axis of rotation is on the lateral malleolus.

divided in three subsections: hand function, ball skills and balance skills. The total score of the movement-ABC is transformed by age-related norms into a percentile score. In addition the child's performance on each of the subsections can be expressed as either below or above the 15th percentile. Validity of the movement-ABC to test motor ability in children has been shown before [20].

Statistical analysis

The SPSS statistical package (version 10.1) was used to analyse the data. Linear regression analysis was used to determine whether muscle strength and passive ankle dorsiflexion differed between survivors and controls, taking into account age, gender, height and weight. In the survivors group the effect of cumulative vincristine, prednisone and dexamethasone dose on muscle strength was examined, controlling for the same variables as before and also for elapsed time since diagnosis.
Student's t-test was used to determine differences in percentile score on the movement-ABC of survivors with and without impaired ankle dorsiflexion.

RESULTS

Patients

One hundred and sixteen children were eligible to participate in the study. The parents of 13 children did not respond to the request to participate. One child was excluded because he was diagnosed with Gilles de la Tourette syndrome. A total number of 102 survivors entered the study. The results of ten children could not be used because they did not cooperate sufficiently. The remaining 92 children, 60 boys and 32 girls, had a mean age at follow-up time of 8.9 years (range 6.1-12.9) and mean time since completion of treatment was 3.3 years (range 1.0-7.5). Three children treated for MMT received radiotherapy, two to the facial area and one retroperitoneally. Five children who had been treated for WT received radiotherapy to the abdominal area and one child to the lungs. The control group consisted of 155 children, 77 boys and 78 girls, mean age 9.5 years (range 6.5 to 12.9). Characteristics of the survivor and control groups are shown in Table II.

Table II Characteristics of survivors and controls

	ALL-8 (n=14)	ALL-9 (n=30)	WT (n=28)	B-NHL (n=10)	MMT (n=10)	survivors (n=92)	controls (n=155)
boys:girls	8 : 6	17:13	16:12	10 : 0	9 : 1	60 : 32	77 : 78
mean age at testing in years ± sd	9.6 ± 1.5	8.6 ± 2.1	8.9 ± 1.8	8.9 ± 1.6	8.9 ± 1.7	8.9 ± 1.8	9.5 ± 1.9
mean age at diagnosis in years ± sd	3.1 ± 1.0	4.3 ± 2.2	3.9 ± 2.2	5.7 ± 1.6	5.1 ± 1.7	4.3 ± 2.0	-
mean time since stop chemotherapy in years ± sd	4.6 ± 1.5	2.0 ± 0.6	4.2 ± 1.7	2.9 ± 1.2	3.3 ± 0.9	3.3 ± 1.6	-

ALL-8 = acute lymphoblastic leukemia treated with DCOG protocol 8, ALL-9 = acute lymphoblastic leukemia treated with DCOG protocol 9, WT = Wilms' tumor, NHL = non Hodgkin lymphoma, MMT = malignant mesenchymal tumor, sd = standard deviation.

Muscle strength

Muscle strength was evaluated in 92 survivors; the mean value of three repeated measurements was used. Linear regression (controlling for gender, age, weight and height) showed that muscle strength of the survivors was reduced in the dorsiflexors of the ankle on both sides ($p < 0.001$), dorsiflexors of the wrist on the non-dominant side ($p < 0.001$), and pinch grip on both sides (non dominant $p=0.001$, dominant $p=0.013$) compared to the controls. Surprisingly, hand grip on the dominant side was significantly stronger in the survivor group ($p = 0.025$).

Table III Differences in mean strength and peak strength values between survivors and controls

	Mean strength		Peak strength	
ankle dorsiflexors				
non-dominant side	-13.0 (2.2)	p<0.001*	- 14.4 (2.5)	p<0.001*
dominant side	-12.2 (2.1)	p<0.001*	- 13.4 (2.4)	p<0.001*
wrist dorsiflexors				
non-dominant side	- 4.2 (0.9)	p<0.001*	- 3.5 (1.1)	p=0.002*
dominant side	- 0.5 (1.2)	p=0.675	- 0.04 (1.4)	p=0.979
pinch grip				
non-dominant side	- 4.2 (1.3)	p=0.001*	- 4.5 (1.4)	p=0.001*
dominant side	- 3.4 (1.3)	p=0.013*	- 3.7 (1.4)	p=0.011*
hand grip				
non-dominant side	2.1 (1.4)	p=0.121	1.9 (1.4)	p=0.199
dominant side	3.1 (1.4)	p=0.025*	2.6 (1.5)	p=0.08

Mean strength (standard error) and peak strength (standard error) in Newtons; negative values indicate that survivors are weaker than controls; * denotes statistical significance.

Analysing the data using peak instead of mean strength values caused the difference in hand grip strength to lose its significance (Table III). Mean and peak strength values for survivors and controls, grouped by age, are presented in Table IV.

Passive ankle dorsiflexion

Passive dorsiflexion of the ankle was measured in 64 survivors. We first examined whether dorsiflexion was affected by age, gender, height or weight by analysing the data of the controls and found that only weight had a significant effect (p=0.007). When controlling for weight, passive ankle dorsiflexion of the survivors was significantly less on the non-dominant side (mean difference 1.6 °, s.e. 0.9, p = 0.009) and on the dominant side (mean difference 1.8 °, s.e. 0.6, p=0.004) compared to the controls. Ankle dorsiflexion values for survivors and controls, grouped by age, are presented in Table V.

During a normal gait cycle active ankle dorsiflexion reaches 5° or more [21]. Passive dorsiflexion mobility needs to be at least 5° in order for the ankle to move normally. We therefore defined ≤ 5° of passive dorsiflexion as 'impaired'. With this criterion applied, 32% of the survivors would be impaired compared to 14% of the controls. There were no significant differences in percentile score on the movement-ABC between survivors with normal or impaired ankle dorsiflexion (p=0.52).

Cumulative vincristine and steroid dose

In the survivor group regression analysis, controlling for age, gender, weight, height and elapsed time since diagnosis, showed that neither cumulative vincristine, prednisone or dexamethasone dose decreased muscle strength. We found a positive effect of predni-

Table IV Muscle strength values of survivors (s) and controls (c)

Muscle group	Gender	Age						
		6	7	8	9	10	11	12
ankle dorsiflexors non-dominant side	boys (s)	40.6 (6.7)	50.0 (13.0)	45.5 (7.5)	50.1 (11.8)	52.9 (8.1)	67.9 (21.5)	63.2 (11.7)
	boys (c)	68.6 (11.8)	54.8 (12.0)	56.8 (10.1)	61.5 (9.2)	85.8 (30.7)	73.6 (24.1)	76.8 (12.0)
	girls (s)	41.6 (2.8)	40.7 (5.8)	53.7 (5.5)	50.7 (12.0)	47.9 (8.5)	60.4 (16.2)	47.7 (1.0)
	girls (c)	51.8 (16.4)	58.9 (17.0)	59.5 (11.4)	67.7 (22.9)	65.5 (16.6)	77.5 (20.1)	74.3 (16.0)
ankle dorsiflexors dominant side	boys (s)	41.8 (7.3)	51.6 (12.2)	46.0 (7.0)	52.2 (14.3)	53.1 (5.4)	67.6 (17.5)	60.2 (20.0)
	boys (c)	69.9 (11.7	57.5 (8.8)	60.4 (10.8)	61.6 (10.8)	80.9 (26.2)	66.0 (12.1)	79.3 (15.0)
	girls (s)	38.8 (7.2)	44.3 (8.1)	51.8 (11.2)	45.9 (10.3)	48.8 (13.5)	50.7 (11.9)	56.3 (10.4)
	girls (c)	48.0 (12.3)	55.3 (16.1)	57.1 (13.0)	72.4 (22.9)	63.6 (14.9)	78.0 (21.9)	78.7 (23.7)
wrist dorsiflexors non-dominant side	boys (s)	32.8 (6.7)	37.2 (7.6)	32.2 (6.2)	41.0 (9.8)	38.4 (7.9)	49.1 (8.1)	46.2 (14.1)
	boys (c)	38.1 (4.2)	38.6 (7.3)	38.0 (5.9)	40.7 (5.2)	46.1 (4.5)	47.3 (4.1)	50.5 (8.9)
	girls (s)	27.7 (3.8)	30.2 (7.1)	35.7 (11.4)	28.7 (1.7)	36.4 (13.5)	42.2 (5.0)	39.0 (9.0)
	girls (c)	34.6 (5.9)	34.7 (3.1)	37.0 (4.7)	39.9 (3.8)	44.0 (5.3)	47.6 (3.7)	53.1 (9.4)
wrist dorsiflexors dominant side	boys (s)	33.7 (7.6)	36.4 (9.4)	37.8 (9.9)	44.0 (9.8)	47.5 (10.1)	56.5 (18.3)	54.2 (22.0)
	boys (c)	38.5 (4.9)	36.3 (4.6)	41.9 (10.4)	41.7 (4.7)	49.7 (3.8)	48.4 (8.9)	49.8 (8.6)
	girls (s)	28.1 (3.0)	34.4 (6.4)	37.5 (13.4)	34.9 (12.1)	38.1 (11.4)	45.6 (11.0)	43.2 (7.9)
	girls (c)	33.0 (4.6)	35.1 (6.1)	36.4 (9.0)	43.4 (5.8)	48.6 (6.6)	45.5 (6.3)	50.9 10.0)
3-point grip non-dominant side	boys (s)	28.0 (5.7)	40.0 (10.5)	39.0 (6.9)	50.8 (4.7)	51.8 (7.7)	55.5 (10.8)	56.0 (14.7)
	boys (c)	36.0 (6.82)	46.6 (11.4)	45.3 (8.1)	48.5 (6.3)	55.8 (9.7)	61.0 (8.7)	72.0 (12.0)
	girls (s)	28.9 (6.2)	35.6 (9.9)	37.8 (11.7)	38.6 (7.7)	48.1 (11.5)	54.8 (10.9)	58.2 (7.8)
	girls (c)	33.3 (5.8)	36.0 (8.8)	41.8 (11.2)	46.2 (8.4)	50.5 (18.1)	64.4 (6.5)	62.5 10.1)
3-point grip dominant side	boys (s)	29.8 (6.4)	42.2 (9.6)	44.9 (8.0)	53.5 (8.6)	57.5 (12.5)	63.3 (11.2)	61.5 (7.7)
	boys (c)	32.4 (7.0)	48.7 (11.5)	49.5 (8.3)	54.3 (9.7)	61.5 (9.3)	67.2 (9.7)	78.5 (10.9)
	girls (s)	27.1 (6.8)	38.0 (8.2)	43.7 (10.8)	43.4 (12.9)	51.9 (5.7)	59.0 (10.6)	59.2 (3.1)
	girls (c)	32.6 (5.4)	36.2 (9.4)	46.5 (10.5)	51.8 (11.3)	55.3 (14.4)	70.6 (9.9)	66.0 (14.0)
hand grip non-dominant side	boys (s)	29.1 (3.7)	42.4 (9.9)	42.6 (12.7)	56.4 (8.8)	57.3 (11.2)	59.5 (15.0)	66.2 (11.9)
	boys (c)	32.3 (6.5)	39.4 (7.8)	43.0 (11.0)	50.6 (8.9)	56.2 (5.6)	57.1 (7.8)	73.7 (11.6)
	girls (s)	25.7 (5.2)	39.0 (6.7)	43.7 (7.0)	42.0 (8.4)	42.0 (8.0)	64.3 (15.0)	53.0 (1.9)
	girls (c)	28.1 (4.0)	34.3 (7.4)	37.1 (9.4)	43.5 (10.8)	47.2 (14.2)	68.2 (14.0)	60.0 (9.1)
hand grip dominant side	boys (s)	32.9 (8.2)	44.8 (11.5)	48.5 (13.0)	57.7 (12.8)	64.4 (10.7)	68.9 (11.6)	74.6 (15.9)
	boys (c)	33.0 (4.8)	43.2 (7.5)	46.8 (14.3)	56.0 (11.8)	63.6 (9.1)	63.7 (10.1)	82.5 (9.0)
	girls (s)	24.0 (3.2)	39.6 (3.5)	41.5 (9.3)	44.1 (11.5)	47.1 (4.6)	68.3 (17.0)	64.3 (1.0)
	girls (c)	29.9 (4.9)	34.3 (8.0)	40.1 (10.9)	44.6 (11.6)	49.4 (13.9)	70.8 (12.8)	65.8 (12.1)

Mean values (sd) in Newtons.

Table V Ankle dorsiflexion mobility of survivors (s) and controls (c)

	Gender	Age						
		6	7	8	9	10	11	12
ankle dorsiflexion non-dominant side	boys (s)	8.3 (5.8)	9.5 (5.1)	7.4 (6.2)	5.0 (2.5)	8.0 (2.6)	4.5 (3.7)	5.3 (5.5)
	boys (c)	10.2 (5.7)	9.5 (5.5)	10.9 (5.1)	9.1 (3.6)	9.7 (4.0)	9.5 (2.5)	12.0 (5.8)
	girls (s)	6.4 (4.2)	7.6 (3.4)	9.3 (1.9)	6.7 (2.9)	7.2 (7.2)	6.8 (3.9)	5.5 (4.2)
	girls (c)	10.0 (1.6)	9.1 (1.8)	11.8 (5.1)	10.0 (3.5)	8.8 (3.3)	11.9 (4.3)	12.8 (4.7)
ankle dorsiflexion dominant side	boys (s)	8.3 (5.8)	9.5 (5.1)	6.9 (4.7)	5.7 (3.1)	8.7 (2.7)	5.8 (3.4)	7.5 (3.5)
	boys (c)	9.3 (5.1)	8.9 (4.9)	10.8 (3.0)	11.6 (4.2)	10.5 (3.8)	9.1 (2.6)	11.3 (2.2)
	girls (s)	6.8 (3.4)	8.0 (2.7)	9.3 (1.9)	6.7 (2.9)	6.2 (5.0)	6.3 (4.3)	7.5 (3.5)
	girls (c)	9.6 (1.6)	9.4 (1.8)	10.6 (2.7)	9.8 (4.3)	9.3 (4.6)	11.5 (4.7)	10.5 (0.8)

Mean values (sd) in degrees.

sone on strength of dorsiflexors of the ankle on both the non-dominant and the dominant side (factor 0.003, p=0.03).
Analysing the data, using peak instead of mean strength values did not change the results. Analysing the results omitting four cases where the VCR dose was topped also made no difference.

Motor performance

In the survivors group the relationships between muscle strength and movement-ABC scores were also examined. Regression analysis, controlling for age, gender, weight, height and elapsed time since diagnosis, showed that decrease in strength of wrist dorsiflexors on the dominant side had a significant adverse effect on hand function score (factor 0.06, p=0.02) and on total score (factor -0.147, p=0.03) but not on percentile score (p=0.61). Decrease in pinch grip strength on both sides adversely affected ball skill score (non-dominant side factor -0.06, p=0.03; dominant side factor -0.07, p=0.01), total score (non-dominant side factor -0.17, p=0.04; dominant side factor -1.9, p=0.03) and percentile score (non-dominant side factor 1.1, p=0.004; dominant side factor 0.8, p=0.02). Analysing the data using peak strength values did not alter the results.

DISCUSSION

This study shows decreased strength of dorsiflexors of ankles and wrists and of pinch grip in children treated with chemotherapy including vincristine for ALL, WT, B-NHL and MMT,

tested at least one year after completion of treatment. Vincristine is known to decrease peripheral muscle strength during treatment [22,23]. In the present study, several years after completion of treatment, we did not find that the decrease depended on cumulative vincristine dose.

Another cause for the reduction in muscle strength could have been treatment with corticosteroids. Steroid-induced myopathy, resulting in muscle weakness predominantly in the proximal muscles of upper and lower limbs has been described [22].

However, we did not study proximal muscle groups, such as flexors and extensors of hip and knee, because values of more than 350 N were found in those muscle groups in healthy children [24] and values over 350 N are less reliable than values below 350 N when measured with a hand held dynamometer [25]. Also, reliability is reduced if the measured muscles are strong relative to the strength of the tester [26]. From our data we can conclude that steroids had no adverse effect on the peripheral muscle groups we tested. The only significant effect was a positive effect of prednisone on ankle dorsiflexor strength, which we consider a spurious finding. Measuring strength of the ankle plantar flexors, which have an important function in every day activities such as walking, running and jumping would be of interest to us. Normal strength of the ankle plantar flexors is considerable, as is demonstrated by the fact that healthy children are able to stand on tiptoe of only one foot. In addition leverage on the foot is very short. This makes it difficult to obtain reliable data.

Muscle strength values for healthy Dutch children have been published before [24]. However, no inter-observer or intra-observer reliability data were reported. Also the numbers in the various age groups were small. We therefore decided we could not use them as normative values and measured our own controls.

Nine children were treated with radiation, but this was applied to areas which would have no effect on muscle strength or ankle dorsiflexion mobility.

Reduction of passive ankle dorsiflexion following treatment for ALL has been shown [4,9,27]. Our study also demonstrates reduced ankle dorsiflexion mobility in children who have been treated for other types of childhood cancers. The loss of mobility is likely to be caused by weakness of the ankle dorsiflexors, which occurs during treatment [7] and continues after treatment (present study), resulting in shortening of the gastrocnemius muscle.

In the present study impaired ankle dorsiflexion mobility did not affect percentile score on the movement-ABC test. Whether the loss of passive ankle dorsiflexion has an adverse affect on activities of daily life cannot be deducted from these results, as the movement-ABC does not measure activities such as walking or running, [21].

Apart from pinch grip strength on both sides, we could not show a relationship between impaired muscle strength in any of the other muscle groups and the reduced movement-ABC scores we reported earlier [5]. The considerable decrease in strength of

the ankle dorsiflexors was not associated with a reduction in motor performance score. The movement-ABC is designed to assess the every day motor competence of children [18], but gives no information about the actual cause of a potential impairment in performance [28], which may explain the lack of relationship.

Our results suggest that the impaired scores on the movement-ABC cannot be completely explained by the reduction in muscle strength we demonstrated in the ankle and wrist dorsiflexors and in pinch grip strength. They also show that muscle strength in the survivors group is not impaired to such an extent that it affects every day activities as measured by the movement-ABC. The clinical relevance of the reduction in strength is difficult to determine and the impact may differ depending on the children's motor competence prior to the onset of their illness. Those children who used to be 'good performers' may still perform relatively well, even with reduced muscle strength, whereas children who were previously less skilled no longer manage to score within the norm on the movement-ABC. Because movement-ABC scores were not measured prior to starting chemotherapy, a possible reduction in motor competence in individual children could not be determined.

In conclusion, this study shows reduced strength of ankle and wrist dorsiflexors and pinch grip and reduced ankle dorsiflexion mobility in the long-term in children treated for cancer with chemotherapy. However, neither decreased muscle strength nor reduced ankle dorsiflexion could completely explain he reduction in score on the movement-ABC.

REFERENCES

1 Harten G, Stephani U, Langermann H-J, et al. Slight impairment of psychomotor skills in children after treatment of acute lymphoblastic leukemia. Eur J Pediatr 1984; 142: 189-197

2 Vainionpaa L. Clinical neurological findings of children with acute lymphoblastic leukaemia at diagnosis and during treatment. Eur J Pediatr 1993; 152:115-119.

3 Reinders-Messelink HA, Schoemaker MM, Hofte M, et al. Fine motor and handwriting problems after treatment for childhood acute lymphoblastic leukemia. Med Pediatr Oncol 1996; 27:551-555.

4 Wright MJ, Halton JM, Martin RF, et al. Long-term gross motor performance following treatment for acute lymphoblastic leukemia. Med Pediatr Oncol 1998; 31:86-90.

5 Hartman A, van den Bos C, Stijnen T, et al. Decrease in motor performance in children with cancer is independent of cumulative vincristine dose. Cancer 2006; 106:1395-1401

6 Hovi L, Era P, Rautonen J, et al. Impaired muscle strength in female adolescents and young adults surviving leukemia in childhood. Cancer 1993; 72:276-281

7 Marchese V, Chiarello L, Lange B. Strength and functional mobility in children with acute lymphoblastic leukemia. Med Pediatr Oncol 2003; 40:230-232

8 Vainionpaa L, Kovala T, Tolonen EU, et al. Vincristine therapy for children with acute lymphoblastic leukemia impairs conduction in the entire peripheral nerve. Ped Neurol 1995; 13:314-318

9 Wright MJ, Halton JM, Barr RD. Limitation of ankle range of motion in survivors of acute lymphoblastic leukemia: a cross-sectional study. Med Pediatr Oncol 1999; 32:279-282.

10 Kamps WA, Bokkerink JPM, Hakvoort-Cammel FGAJ, et al. Results of the DCLSG-study ALL8 (1991-1997): BFM oriented treatment without cranial irradiation (CI) and comparing conventional oral and high-doses intravenous 6-mercaptopurine. Med Pediatr Oncol 1999; 33:O-109 (abstract)

11 Veerman AJ, Hahlen K, Kamps WA, et al. High cure rate with a moderately intensive treatment regimen in non-high-risk childhood acute lymphoblastic leukemia. Results of protocol ALL VI from the Dutch Childhood Leukemia Study Group. J Clin Oncol 1996; 14:911-918

12 D'Angio GJ. SIOP (International Society of Paediatric Oncology) and the management of Wilms' tumor. J Clin Oncol 1983; 1:595-596

13 Graf N, Tournade MF, de Kraker J. The role of preoperative chemotherapy in the management of Wilms' tumor. The SIOP studies. International Society of Pediatric Oncology. Urol Clin North Am 2000; 27:443-454

14 Patte C, Gerrard M, Auperin A, et al. Final results and prognostic factors of the randomised international trial FAB LMB 96 for the 'intermediate risk' in childhood and adolescent b-cell lymphoma (abstract). Pediatric Blood Cancer 2004; 43:348
15 Bohannon RW. The clinical measurement of strength. Clin Rehab 1987; 1:5-16
16 Van der Ploeg RJO. Hand-held dynamometry. Medicine. Groningen: University of Groningen, 1992; 93
17 Horvat M. Reliability and objectivity of the Nicholas Manual Muscle Tester. Isokin Exc Science 1992; 2:175-181
18 Henderson S, Sugden D. Movement Assessment Battery for Children. Sidcup, England: The Psychological Corporation, 1992
19 Smits-Engelsman BC. Movement Assessment Battery for Children; Nederlandse bewerking. Lisse, Nederland: Swets & Zeitlinger, 1998
20 Croce RV, Horvat M, McCarthy E. Reliability and concurrent validity of the movement assessment battery for children. Percept Mot Skills 2001; 93:275-280
21 Whittle MW. Gait analysis; an introduction. 3rd ed. Oxford: Butterworth Heinemann, 2002
22 Macdonald DR. Neurologic complications of chemotherapy. Neurol Clin 1991; 9: 955-967
23 Olesen LL, Jensen TS. Prevention and management of drug-induced peripheral neuropathy. Drug Saf 1991; 6:302-314
24 Beenakker EA, van der Hoeven JH, Fock JM, et al. Reference values of maximum isometric muscle force obtained in 270 children aged 4-16 years by hand-held dynamometry. Neuromuscul Disord 2001; 11:441-446
25 Backman E, Odenrick P, Henriksson KG, et al. Isometric muscle force and anthropometric values in normal children aged between 3.5 and 15 years. Scand J Rehabil Med 1989; 21:105-114
26 Bohannon RW. Intertester reliability of hand-held dynamometry: a concise summary of published research. Percept Mot Skills 1999; 88:899-902
27 Wright MJ, Hanna SE, Halton JM, et al. Maintenance of ankle range of motion in children treated for acute lymphoblastic leukeamia. Ped Physiother 2003; 15:146-152
28 Watter P. Movement Assessment Battery for Children (Movement ABC). Aust J Physiother 2006; 52:68

CHAPTER 5

PERCEIVED AND ACTUAL MOTOR COMPETENCE OF CHILDREN TREATED FOR CANCER WITH VINCRISTINE CONTAINING CHEMOTHERAPY

A. Hartman [1,2], C. van den Bos [3], Th. Stijnen [4], R. Pieters [1]

[1]Department of Pediatric Oncology / Hematology, Erasmus MC Sophia Children's Hospital, Rotterdam, the Netherlands.
[2]Department of Pediatric Physiotherapy, Erasmus MC Sophia Children's Hospital, Rotterdam, the Netherlands.
[3]Department of Pediatric Oncology, Emma Children's Hospital Academic Medical Center, Amsterdam, the Netherlands.
[4]Department of Epidemiology and Biostatistics, Erasmus MC, Rotterdam, the Netherlands.

Pediatr Blood Cancer 2008; 51 (2) 306-307
Published in adapted form.

ABSTRACT

Background

Perceived athletic competence is an important factor in self-esteem of children. Motor problems have been described in children who were treated for cancer with protocols including vincristine. In the present study we investigated whether perceived motor competence of children was decreased following treatment for cancer and the relationship with actual motor performance.

Procedure

Fifty-three children (age 8-12 years), who had completed chemotherapy including vincristine for childhood cancer at least one year earlier, were asked to complete the m-CBSK questionnaire for perceived motor competence. Their actual motor performance scores were measured with the Movement Assessment Battery for Children (movement-ABC).

Results

The perceived motor competence score of the ex-patients did not significantly differ from the reference normal values (p=0.95). A moderate but significant correlation between perceived motor competence and actual motor competence was found (r_s = 0.375, p=0.006). In 77% of the cases the movement-ABC score was lower than the perceived competence score.

Conclusion

Children who had completed treatment with chemotherapy for cancer did not show an impaired perceived motor competence, but they had a tendency to overrate their performance.

INTRODUCTION

In children, self-esteem is thought to depend on a number of factors, one of which is athletic competence [1]. A child's perception of ' being like their peers', 'fitting in with the group' and 'not being any different' contributes to positive self-perception, which in its turn is an important factor for a child's ability to adjust to life situations [2]. Motor problems have been described in 30% to 100% of children with acute lymphoblastic leukemia (ALL), two to seven years after completion of treatment [3-6]. A recent study showed that children with other malignancies, who were treated with regimens which contained vincristine, had an impaired motor performance [7]. It is not known how children who have completed chemotherapy perceive their motor competence and whether this has a negative influence on their self-esteem.

The studies that analysed quality of life, body image and self-esteem after completion of treatment for childhood cancer have not answered this question. The subjects of some studies were adolescents and adults [8-12]. In one study parents were questioned, but not their children [13]. One study investigating opinions of children was carried out during treatment [14]. In another study that took place after completion of treatment, no difference in self-perception was found between 56 ex-patients aged 5-12 and a control group [15]. In this study the Self-Perception Profile for Children (SPPC) was used, which has a global self-worth domain and five various sub-domains, including 'athletic competence' [1]. However, as each domain is evaluated by only six questions, the athletic competence domain provides a limited view of the children's perception of their motor performance.

Vincristine, which is used in treatment protocols for various childhood malignancies, causes polyneuropathy which may lead to a decrease in muscle strength in upper and lower extremities [16]. We recently showed that children with malignancies demonstrated impaired motor performance after vincristine containing chemotherapy [7].The aim of the present study was to evaluate the perceived competence of children treated for cancer with chemotherapy including vincristine regarding motor skills. In addition, we analysed whether their perceived motor competence is related to actual motor performance.

METHODS

Patients

The study was conducted in the pediatric oncology departments of the Erasmus MC Sophia Children's Hospital, Rotterdam, and the Emma Children's Hospital, Amsterdam, in the Netherlands. Approval from the Medical Ethics Committees of both hospitals was obtained. Informed consent was obtained from the parents of all participating children. Eligibility criteria were as follows:

- being in complete remission after treatment for acute lymphoblastic leukemia, Wilms' tumor (WT), B-non Hodgkin lymphoma (B-NHL) or malignant mesenchymal tumor (MMT) i.e. soft tissue sarcomas.
- earlier chemotherapy contained vincristine
- at least one year after completion of therapy at time of testing
- age 8-12 years at time of testing (because the test used to measure self-perception is validated for this age category)
- attending regular primary school education

Children were excluded if they had a solid tumor whereby the location of the tumor itself could have contributed to motor problems, such as a tumor of the upper or lower limb or central nervous system.

Data on age at testing, age at diagnosis, cumulative vincristine dose, duration of chemotherapy and time since completion of chemotherapy were collected. The children took part in a larger study that investigated motor problems in children treated for childhood cancer [7].

Treatment

Children with ALL were treated according to the protocols of the Dutch Childhood Oncology Group: the Berlin-Frankfurt-Munster based ALL-8 [17] and protocol ALL-9, that is almost identical to the previously used protocol ALL-6 [18]. Children with WT and MMT were treated with protocols of the Societé Internationale d'Oncologie Pédiatrique (SIOP) [19-21] and children with B-NHL received DCOG-NHL-94 or LMB-96 protocol; the latter two protocols are very similar [22]. Maximum vincristine dose per administration varies by protocol: 2.0 –2.5 mg; cumulative vincristine doses in the above mentioned treatment protocols also vary as shown in Table I. Cumulative vincristine doses were obtained for each child from the medical records.

Table I Vincristine schedules

	ALL-8	ALL-9	WT	NHL	MMT
cumulative vincristine dose in mg/m^2	12-15	62-68	12-36	6-14	15-19.5
vincristine dose per administration in mg/m^2	1.5	2.0	1.5	2.0	1.5
maximum vincristine dose per administration in mg	2.0-2.5	2.5	2.0	2.0	2.0
cumulative prednisone dose in mg/m^2	1933-1957	-	-	1417-1605	-
cumulative dexamethasone dose in mg/m^2	236	1244-1370	-	-	-

ALL-8 = acute lymphoblastic leukemia treated with DCOG protocol 8, ALL-9 = acute lymphoblastic leukemia treated with DCOG protocol 9, WT = Wilms' tumor, NHL = non Hodgkin lymphoma, MMT = malignant mesenchymal tumor, mg/m^2 = milligrams per square meter body surface.

Assessment of motor performance

Motor performance was measured using the Dutch version of the Movement Assessment Battery for Children (movement-ABC) [23,24]. The movement-ABC consists of a series of eight standardized tasks divided in three subsections: hand function, ball skills and balance skills. The tasks vary with age and are designed to resemble every day activities of children. The total score of the movement-ABC is transformed by age-related norms into a percentile score. A score below the 5th percentile is indicative of a motor problem, between 5th and 15th percentile is borderline and higher than the 15th percentile is normal. The child's performance on each of the subsections is also expressed as either below or above the 15th percentile. The validity of the movement-ABC to test motor ability in children has been demonstrated [25].

All measurements were carried out by the same pediatric physiotherapist.

Assessment of perceived motor competence

Children were asked to complete the motor supplement of the 'Competentie BelevingsSchaal voor Kinderen' (m-CBSK) [26], which is an extension of the 'athletic competence' domain of the SPPC [1]. This test was developed specifically for Dutch children aged 8-12 years. Internal consistency and test-retest reliability of the m-CBSK have been shown to be satisfactory (Cronbach's alpha 0.77, r_p = 0.83) [26].

The questionnaire consists of 17 questions covering a range of motor skills needed for outdoor activities, physical education classes, and sports such as throwing and catching a ball, running and jumping. As in the SPPC, children are asked to rate their motor competence in relation to the motor performance of their peers. The construction of the questions is two-tiered. Children are first asked to choose which child is most like him or her: a child who performs well or a child who performs less well. They are then asked whether 'this is only sort of true' or 'really true'. An example of such a question is:

really true for me ☐	sort of true for me ☐	*some children are very good at jumping*	BUT	*other children are not so good at jumping*	sort of true for me ☐	really true for me ☐

The procedure was first explained to the child and his parents and then practiced with the child. The questionnaire was then completed at home. If necessary, parents were allowed to help with reading of the questions, providing they did not supply their child with an answer. The two-tiered construction discourages responses which are led by social desirability [26,27]. Total scores (ranging from 12-48 points) are transformed into decile scores, which differ for boys and girls.

On completing the questionnaire the child is asked to rate the importance of the motor competence domain in comparison to five other domains such as 'doing well at school', 'looking nice' etc. Each domain yields a score from 1- 4; a domain with a score ≥ 3 is considered important to the child.

Statistics

The SPSS statistical package (version 10.1) was used to analyse the data. A Wilcoxon signed rank test was used to analyze differences in perceived motor competence with the normal population. Group differences were analysed with the Mann Whitney and Kruskal-Wallis test. The Spearman correlation coefficient was calculated to investigate relationships between perceived motor competence and age at time of testing, age at diagnosis, duration of treatment, time since completion of treatment and motor performance on the movement-ABC.

RESULTS

Patients

The m-CBSK questionnaire, consisting of 'perceived motor competence' and 'importance of motor domain' was handed out to 61 children from our previous cohort, aged 8-12. Six children did not return the questionnaire; their patient characteristics did not differ from the rest of the group. Fifty-five children completed and returned the perceived motor competence questionnaire; two of those could not be used because more than one reply was given to a question. One of the children did not complete the 'importance of motor domain' part. Of the 53 remaining participants 34 were boys (64%) and 19 were girls (36%). They had been treated for various conditions: 26 for ALL (12 with ALL-8 and 14 with ALL-9 protocol), 4 for MMT, 15 for WT and 8 for NHL. One of the children treated for MMT received retroperitoneal radiation. Of the children treated for WT three received radiation to the abdominal area and one to the lungs. Mean age at testing was 10.2 years (± 1.3). The children's age at diagnosis ranged from 1.7-8.8 years (mean 5.2 ± 1.9), duration of chemotherapy ranged from 0.2-2.3 years (mean 1.3 ± 0.8), time since completion of treatment from 1.4-7.1 years (mean 3.6 ± 1.7) and cumulative vincristine dose from 5.0 – 68.0 mg/m^2 (mean 29.6 ± 24.0) (Table II).

Perceived motor competence

Total scores of perceived motor competence were transformed into decile scores. There was no significant difference in perceived motor competence between the study group and the reference values (p=0.95); median decile score was 6.0 for the ex-patients.

Table II Patient characteristics

	ALL-8 (n=12)	ALL-9 (n=14)	WT (n=15)	NHL (n=8)	MMT (n=4)	total group (n=53)
boys : girls	8 : 4	8 : 6	8 : 7	7 : 1	3 : 1	34 : 19
mean age at testing in years ± sd	10.2 ± 1.2	10.3 ± 1.5	10.3 ± 1.5	9.7 ± 0.9	10.3 ± 1.8	10.2 ± 1.3
mean age at diagnosis in years ± sd	3.3 ± 1.3	5.8 ± 1.7	5.5 ± 1.6	6.3 ± 1.6	5.5 ± 1.9	5.2 ± 1.9
chemotherapy duration in years ± sd	2.0 ± 0.02	2.1 ± 0.06	0.7 ± 0.4	0.4 ± 0.3	0.5 ± 0.3	1.3 ± 0.8
mean time since stop chemotherapy in years ± sd	5.0 ± 1.2	2.1 ± 0.5	4.0 ± 1.9	3.2 ± 1.2	4.4 ± 1.3	3.6 ± 1.7
mean cumulative vincristine dose in mg/m^2 ± sd	12.0 ± 0.0	66.0 ± 3.7	24.5 ± 10.5	8.3 ± 1.9	13.9 ± 2.8	29.6 ± 24.0

ALL-8 = acute lymphoblastic leukemia treated with DCOG protocol 8, ALL-9 = acute lymphoblastic leukemia treated with DCOG protocol 9, WT = Wilms' tumor, NHL = non Hodgkin lymphoma, MMT = malignant mesenchymal tumor, sd = standard deviation.

In the study group 24 children (45%) considered the motor domain of importance. There was no significant difference in perceived motor competence between children who considered the motor domain important and those who did not (p=0.34), with median decile scores of 6.5 and 5.5 respectively (Figure 1).

There was no difference in perceived motor competence between boys and girls (p = 0.56). Perceived motor competence was not affected by age at time of testing (r_s = -0.05, p = 0.71), age at diagnosis (r_s = 0.08, p = 0.59), duration of treatment (r_s =

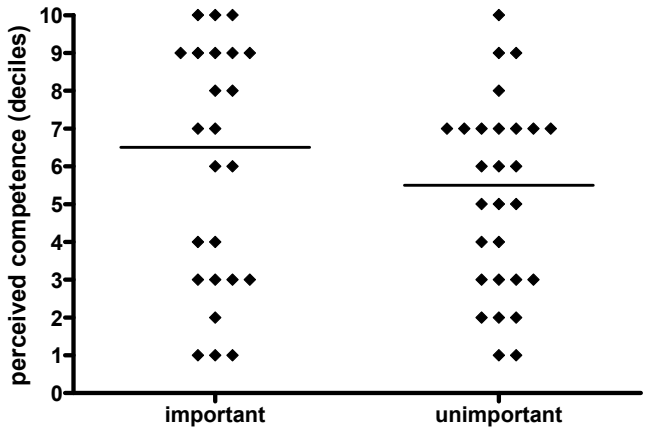

Figure 1 Perceived motor competence of children who considered the motor domain important and those who did not. The horizontal bars depict the median values.

-0.22, p = 0.12), time since completion of chemotherapy (r_s = 0.01, p = 0.96), time since completion of vincristine administration (r_s = 0.08, p=0.59), cumulative vincristine dose (r_s = -0.12, p=0.41) or type of malignancy (p=0.26).

Actual motor competence

Percentile scores of the ex-patients on the movement-ABC test were significantly lower than reference values (p < 0.001). The median percentile score of the ex-patients was 25.0. Scores below < 15th percentile were found in 32% of the children.

There was a weak but significant correlation between movement-ABC score and perceived motor competence (r_s = 0.38, p = 0.01). In 77% of the cases (n=41) the score on the movement-ABC was lower than the perceived competence score (Figure 2). There was no significant difference in movement-ABC score between children who considered the motor domain important and those who did not (p = 0.69).

Actual motor competence did not differ between boys and girls (p = 0.59). Actual motor competence was affected by age at time of testing (r_s = -0.33, p = 0.02), but not by age at diagnosis (r_s = -0.02, p = 0.91), duration of treatment (r_s = -0.17, p = 0.24, time since completion of chemotherapy (r_s = -0.14, p = 0.33), time since completion of vincristine administration (r_s = -0.15, p=0.29), cumulative vincristine dose (r_s =-0.14, p=0.34) or type of malignancy (p=0.54). Motor competence of children who had received corticosteroids did not differ from those who had not (p=0.62).

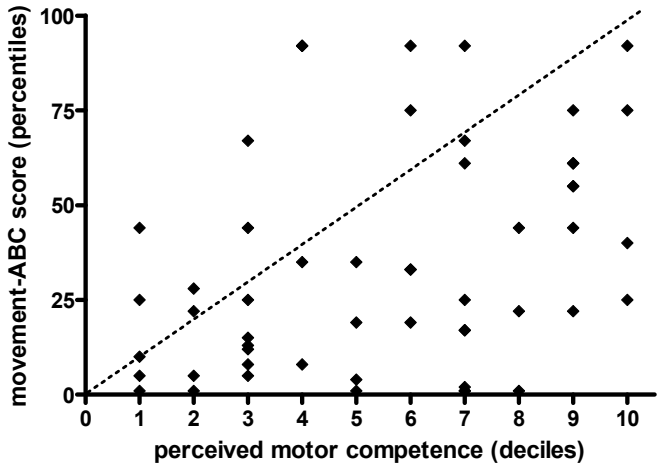

Figure 2 Perceived motor competence and actual motor performance. This figure represents all 53 cases; some children had identical scores. Scores below the dotted line (x = y) indicate overrating of motor performance.

DISCUSSION

Children with physical differences are suggested to be at risk for negative social perceptions and behaviours and loss of self-esteem [28,29] and during chemotherapy children show dissatisfaction with their athletic performance [30]. As impaired motor performance is one of the late effects of chemotherapy [7], we hypothesised that that children who had been treated with chemotherapy would have low perceived motor competence. However our results showed that their perceived motor competence did not differ from the reference values.

We found a weak but significant correlation between perceived competence and actual motor performance. This indicates that children who performed better on the motor test did rate themselves more highly than those with lower scores. However, in 77% of the cases the actual movement-ABC score was lower than the perceived competence score indicating that the majority of children were 'overrating' their performance. An explanation for this tendency to 'overrate' may be to try to avoid being pitied, or having their parents worry about them. Also they may wish to be 'normal', something that has been observed in a study of adolescent cancer survivors [31]. Ex-patients may also overrate their motor performance because they have known an earlier treatment period during which they felt less able, which changed their frame of reference.

The results on the perceived motor competence test and the actual motor performance test could have been a mere reflection of the treatment with vincristine. A higher cumulative vincristine dose might lead to impaired motor performance, which could subsequently result in a lower perception score. Our results show that neither was the case. Other variables related to vincristine treatment such as 'duration of treatment' and 'time since completion of treatment' also had no effect on perceived motor competence or actual motor performance.

Five children received radiation, but this was applied to areas that would have no effect on motor performance.

The m-CBSK test does not contain items that ask children to specify who they consider to be their peers, which would affect the way they rate their own performance. It is unknown whether children who have had cancer are different from the general population in choosing their peer group. Whether the relationship between perceived and actual motor competence of the children in the present study is different from the general population is also unknown. There are no other studies where children have been examined with both the m-CBSK and the movement-ABC.

Interestingly, the percentage of children in this study who rated the motor domain as 'important' (45%) seems noticeably lower than the 70% found in the general population [26].

The m-CBSK is validated for children aged 8-12 years. Whether our results hold true for younger or older children is therefore uncertain. Particularly older children may have a different view on body image and social quality of life.
A potential source of bias in this study is the fact that parents were allowed to assist their child in completing the survey, in case of reading difficulties. Although parents were instructed only to assist their child in case he or she did not know the meaning of a word, their assistance may still have altered the child's response.
Although the children in this study may find motor competence of less importance then their peers and they have a tendency to overrate their competence, the results could still be considered positive, as the majority of children appeared to be satisfied with their motor performance.
In conclusion, the perceived motor competence of children who had completed treatment with chemotherapy for cancer did not differ from the general population. However, the ex-patients had a tendency to overrate their actual motor performance.

Acknowledgment
We would like to thank Dr. A. E. Darlington-Molkenboer for her valuable comments on the manuscript.

REFERENCES

1 Harter S. Manual for the self-perception profile for children. Denver: University of Denver, 1985
2 Rutter M. Resilience in the face of adversity. Protective factors and resistance to psychiatric disorder. Br J Psychiatry 1985; 147:598-611
3 Harten G, Stephani U, Langermann H-J, et al. Slight impairment of psychomotor skills in children after treatment of acute lymphoblastic leukemia. Eur J Pediatr 1984; 142: 189-197
4 Vainionpaa L. Clinical neurological findings of children with acute lymphoblastic leukaemia at diagnosis and during treatment. Eur J Pediatr 1993; 152:115-119.
5 Reinders-Messelink H, Schoemaker M, Goeken L, et al. Handwriting and fine motor problems after treatment for acute lymphoblastic leukemia. In: Simner ML, Leedham CG, Thomassen AJWM, eds. Handwriting and drawing research: basic and applied issues. Amsterdam: IOS Press, 1996; 215-225
6 Wright MJ, Halton JM, Barr RD. Limitation of ankle range of motion in survivors of acute lymphoblastic leukemia: a cross-sectional study. Med Pediatr Oncol 1999; 32:279-282.
7 Hartman A, van den Bos C, Stijnen T, et al. Decrease in motor performance in children with cancer is independent of cumulative vincristine dose. Cancer 2006; 106:1395-1401
8 Kopel SJ, Eiser C, Cool P, et al. Brief report: assessment of body image in survivors of childhood cancer. J Pediatr Psychol 1998; 23:141-147
9 Olivo EL. Body image satisfaction and schema of young adult men and women successfully treated for cancer in childhood. Columbia: Columbia Univeristy, 2001
10 Seitzman RL, Glover DA, Meadows AT, et al. Self-concept in adult survivors of childhood acute lymphoblastic leukemia: a cooperative Children's Cancer Group and National Institutes of Health study. Pediatr Blood Cancer 2004; 42:230-240
11 Langeveld NE, Grootenhuis MA, Voute PA, et al. Quality of life, self-esteem and worries in young adult survivors of childhood cancer. Psychooncology 2004; 13: 867-881
12 Nathan PC, Ness KK, Greenberg ML, et al. Health-related quality of life in adult survivors of childhood wilms tumor or neuroblastoma: A report from the childhood cancer survivor study. Pediatr Blood Cancer 2006
13 Noll RB, MacLean WE, Jr., Whitt JK, et al. Behavioral adjustment and social functioning of long-term survivors of childhood leukemia: parent and teacher reports. J Pediatr Psychol 1997; 22:827-841

14 Hockenberry-Eaton M, Dilorio C, Kemp V. The relationship of illness longevity and relapse with self-perception, cancer stressors, anxiety, and coping strategies in children with cancer. J Pediatr Oncol Nurs 1995; 12:71-79
15 Spirito A, Stark LJ, Cobiella C, et al. Social adjustment of children successfully treated for cancer. J Pediatr Psychol 1990; 15:359-371
16 Gidding CE, Kellie SJ, Kamps WA, et al. Vincristine revisited. Crit Rev Oncol Hematol 1999; 29:267-287
17 Kamps WA, Bokkerink JPM, Hakvoort-Cammel FGAJ, et al. Results of the DCLSG-study ALL8 (1991-1997): BFM oriented treatment without cranial irradiation (CI) and comparing conventional oral and high-doses intravenous 6-mercaptopurine. Med Pediatr Oncol 1999; 33:O-109 (abstract)
18 Veerman AJ, Hahlen K, Kamps WA, et al. High cure rate with a moderately intensive treatment regimen in non-high-risk childhood acute lymphoblastic leukemia. Results of protocol ALL VI from the Dutch Childhood Leukemia Study Group. J Clin Oncol 1996; 14:911-918
19 D'Angio GJ. SIOP (International Society of Paediatric Oncology) and the management of Wilms' tumor. J Clin Oncol 1983; 1:595-596
20 Graf N, Tournade MF, de Kraker J. The role of preoperative chemotherapy in the management of Wilms' tumor. The SIOP studies. International Society of Pediatric Oncology. Urol Clin North Am 2000; 27:443-454
21 Rousseau P, Flamant F, Quintana E, et al. Primary chemotherapy in rhabdomyosarcomas and other malignant mesenchymal tumors of the orbit: results of the International Society of Pediatric Oncology MMT 84 Study. J Clin Oncol 1994; 12:516-521
22 Patte C, Gerrard M, Auperin A, et al. Final results and prognostic factors of the randomised international trial FAB LMB 96 for the 'intermediate risk' in childhood and adolescent b-cell lymphoma (abstract). Pediatric Blood Cancer 2004; 43:348
23 Henderson S, Sugden D. Movement Assessment Battery for Children. Sidcup, England: The Psychological Corporation, 1992
24 Smits-Engelsman BC. Movement Assessment Battery for Children; Nederlandse bewerking. Lisse, Nederland: Swets & Zeitlinger, 1998
25 Croce RV, Horvat M, McCarthy E. Reliability and concurrent validity of the movement assessment battery for children. Percept Mot Skills 2001; 93:275-280
26 Van Rossum JHA, Vermeer A. Handleiding motorische competentie-zelfbeoordeling. Lisse: Swets & Zeitlinger, 2000
27 Harter S. The perceived competence scale for children. Child Development 1982; 53:87-97
28 Varni JW, Rubenfeld LA, Talbot D, et al. Determinants of self-esteem in children with congenital/acquired limb deficiencies. J Dev Behav Pediatr 1989; 10:13-16

29 Varni JW, Katz ER, Colegrove R, Jr., et al. The impact of social skills training on the adjustment of children with newly diagnosed cancer. J Pediatr Psychol 1993; 18: 751-767
30 Noll RB, Gartstein MA, Vannatta K, et al. Social, emotional, and behavioral functioning of children with cancer. Pediatrics 1999; 103:71-78
31 Madan-Swain A, Brown RT, Sexson SB, et al. Adolescent cancer survivors. Psychosocial and familial adaptation. Psychosomatics 1994; 35:453-459

CHAPTER 6

POLYMORPHISMS IN GENES INVOLVED IN VINCRISTINE PHARMACOKINETICS OR PHARMACODYNAMICS ARE NOT RELATED TO IMPAIRED MOTOR PERFORMANCE IN CHILDREN WITH LEUKEMIA

A. Hartman [1,2], R.H.N van Schaik [3], I.P. van der Heiden [3], M. J.C. Broekhuis [1], M.Meier [1], M.L. den Boer [1], R. Pieters [1]

[1]Department of Pediatric Oncology / Hematology, Erasmus MC Sophia Children's Hospital, Rotterdam, the Netherlands.

[2]Department of Pediatric Physiotherapy, Erasmus MC Sophia Children's Hospital, Rotterdam, the Netherlands.

[3]Department of Clinical Chemistry[3], Erasmus MC, Rotterdam, the Netherlands.

Submitted

ABSTRACT

Background

Impaired motor performance has been demonstrated in children treated with vincristine containing chemotherapy for cancer, but there was no relationship with the dose-schedule of vincristine. We analysed whether genetic variation of the drug metabolising gene *CYP3A5*, and VCR–toxicity related genes *MDR-1* and *MAPT* is related to impaired motor performance in children with acute lymphoblastic leukemia (ALL).

Methods

In 34 children, aged 4-12, who had completed treatment for ALL for at least one year, motor performance was measured with the movement Assessment Battery for Children (m-ABC). DNA, extracted from mononuclear peripheral blood cells, was genotyped for *CYP3A5*3/*3* and **1/*3*, *MDR-1* (C1236T, G2677T, C3435T) and *MAPT* polymorphisms.

Results

There was no significant difference in m-ABC percentile scores between cases with *CYP3A5 *3/*3* and *CYP3A5*1*3* genotypes. Percentile scores were also not significantly affected by *MDR-1* C1236T, C3435T, or G2677T single nucleotide polymorphisms (SNP) nor was the difference between carriers of 3435C/2677G, 3435T/2677G and others significant. In addition, no significant difference was found between *MAPT* haplotype A and haplotype B.

Conclusion

Our data do not provide evidence that *CYP3A5*, *MDR-1* or *MAPT* genetic polymorphisms are linked with impaired motor performance in children who had been treated with vincristine containing chemotherapy for ALL.

INTRODUCTION

Survival of children treated for cancer has increased dramatically since the 1950's amongst others by improvements in chemotherapy. However, chemotherapy can give rise to a number of side effects, which may remain present after completion of treatment. Impaired motor performance has been described in children treated for acute lymphoblastic leukemia (ALL) with chemotherapy protocols containing vincristine (VCR) [1-4]. A known complication of treatment with VCR is the development of polyneuropathy, which can result in loss of peripheral muscle power in upper and lower extremities [5]. It has often been assumed that there is a positive relationship between cumulative VCR dose and the severity of motor problems [5-7]. However, a recent study showed that impaired motor performance was not related to frequency, dose, or cumulative dose of VCR. Also, in children treated with identical protocols motor performance varied greatly [8]. The cause of differences in susceptibility for disturbances in motor performance is yet unknown.

VCR belongs to the group of vinca-alkaloid drugs metabolised by the cytochrome P450 system in the liver [9]. Isoforms of this system expressed in humans are *CYP3A4* and *CYP3A5*. Polymorphisms of *CYP3A4* exist but are rare [10]. In contrast, *CYP3A5* polymorphisms are relatively common in the Caucasian population. Reports on the expression of *CYP3A5* vary from 10% - 40%, which is caused by the A6986G genetic polymorphism (*CYP3A5*3* variant allele) in the *CYP3A5* gene [11,12]. The estimated hepatic clearances of VCR were 5-fold higher for *CYP3A5* high expressers compared to *CYP3A5* non-expressers [13]. As VCR is known to cause polyneuropathy, which can subsequently give rise to motor problems, a link may exist between the presence of a *CYP3A5* polymorphism and the level of motor performance of children treated with vincristine as part of their chemotherapy.

The multi drug resistance (*MDR-1* or *ABCB1*) gene is also involved in the pharmacokinetics of VCR. Upregulation of the *MDR-1* gene encoding for P-glycoprotein (P-gp), an efflux pump, results in a decrease in intracellular concentration of VCR and an increase in biliary clearance [14,15]. So far, at least 29 single nucleotide polymorphisms (SNPs) have been described of the *MDR-1* gene. Two of these, C3435T and G2677A/T influence the pharmacokinetics of P-gp substrates [16-18]. No association was observed between C3435T or G2677T and vincristine pharmacokinetics, but when haplotypes as described by Johne [19] were assigned, haplotype 1/1 carriers (3435C/2677G) showed a longer elimination half-life for vincristine than non-carriers [20]. Haplotype 1/2 carriers (3435T/2677G) may have a shorter elimination half-life. Another SNP, C1236T has been linked to C3435T and G277T/A, although no effect on pharmacokinetics has been described [21].

Thirdly, genetic variation in the microtubule-associated protein tau (*MAPT*) gene may influence VCR effects at the tissue level. *MAPT* promotes the assembly and stabilisation of

microtubules, which form a target for VCR. When VCR damages microtubules, apoptosis occurs. MAPT abnormalities have been linked to a number of neurodegenerative disorders e.g. Parkinson's disease, progressive supranuclear palsy, and Alzheimer's disease [22-24].

The purpose of our study was to investigate whether the variation in motor performance in children treated with VCR for ALL, was related to the presence of polymorphisms in genes involved in the metabolism of VCR, i.e. *CYP3A5* and the toxicity of VCR i.e. *MDR-1* and *MAPT*.

METHODS

Patients

The study was conducted at the paediatric oncology department of the Erasmus MC Sophia Children's Hospital in the Netherlands. Approval of the Medical Ethical Committee was obtained. Written informed consent according to the Helsinki agreement was obtained from all parents.

Eligibility criteria were as follows:

- being in complete remission after treatment for acute lymphoblastic leukemia
- at least one year after completion of therapy at time of testing
- aged 4-12 years at time of testing (because the test used to measure motor performance is validated for this age category)

Children who attended special education were excluded, as cognitive impairment is known to influence results of the motor performance test.

DNA isolation

DNA was isolated from EDTA blood using the Magnapure LC system (Roche).

CYP3A5 and MDR-1 analysis

For a 50-µl PCR, we used about 10 ng of genomic DNA. The PCR mixture contained 1X buffer [10 mM Tris-HCl, pH 8.3, 1.5 mM $MgCl_2$, 50 mM KCl, and 10 mg/L gelatin (Perkin-Elmer)], 0.2 mM each of the deoxynucleotide triphosphates (Roche), and 1.25 U of Amplitaq Gold (Perkin-Elmer). For the *CYP3A5*3* analysis, 40 pmol of primers P1 (5'-CATGACTTAGTAGACAGATGAC-3') and P2 (5'-GGTCCAAACAGGGAAGAAA-TA-3') was used, with the underlined nucleotide presenting a mismatch with the *CYP3A5* sequence, creating a restriction site in the PCR product. PCR conditions were: 7 min at 94°C; 40 cycles of 1 min at 94°C, 1 min at 57°C and 1 min at 72°C; and finally 7 min at 72°C. The 2936 bp PCR product (10 µl) was digested with Ssp1 (New England

Biolabs) in a total volume of 15 µl for 2 h at 37°C and subsequently analyzed on a 3% agarose/Tris-borate-EDTA gel with ethidium bromide staining.
The fragments obtained for the *CYP3A5*1* allele were 148, 125 and 20 bp; for the *CYP3A5*3* variant allele, the fragments obtained were 168 and 125 bp.
For the *MDR-1* C3435T genotyping, 40 pmol of primers P3 (5'-CATGCTCCCAGGCT-GTTTAT-3') and P4 (5'-GTAACTTGGCAGTTTCAGTG-3') were used. PCR conditions were: 7 min at 94°C; 35 cycles of 1 min at 94°C, 1 min at 60°C and 1 min at 72°C; and finally 7 min at 72°C. The 340 bp PCR product (10 µl) was digested with DpnII (New England Biolabs) in a total volume of 15 µl for 2 h at 37°C and subsequently analyzed on a 3% agarose/Tris-borate-EDTA gel with ethidium bromide staining. The fragments obtained for the 3434C allele were 172, 90, 78 bp, for the 3435T variant allele the fragments were 262 and 78 bp. For the *MDR-1* C1236T genotyping, 40 pmol of primers P5 (5'-CCTGACTCACCACACCAATG -3') and P6 (5'-TATCCTGTGTCTGT-GAATTGCC-3') were used. PCR conditions were: 7 min at 94°C; 35 cycles of 1 min at 94°C, 1 min at 55°C and 1 min at 72°C; and finally 7 min at 72°C. The 370 bp PCR product (10 µl) was digested with HaeIII (New England Biolabs) in a total volume of 15 µl for 2 h at 37°C and subsequently analyzed on a 3% agarose/Tris-borate-EDTA gel with ethidium bromide staining. The fragments obtained for the 1236C allele were 272, 63, 35 bp, for the 1236T variant allele the fragments were 272, and 98 bp. The *MDR-1* G2677A/T genotyping was performed using Taqman allelic discrimination assays on the ABI Prism 9700 HT Sequence detection system. For this tri-allelic variant, two separate assays were designed, one detecting G2677A and one detecting G2677T. Each assay consisted of two allele-specific minor groove binding (MGB) probes, labeled with the fluorescent dyes VIC and FAM. The primer and probe sequences, designed by Applied Biosystems by their Assay-by-Design service are listed in Table I. Polymerase

Table I Taqman primer and probe sequences for MDR-1 G2677A/T

SNP	Sequence	
MDR-1 G2677A	Forward primer	AATACTTTACTCTACTTAATTAATCAATCATATTTAGTTTGACTCA
	Reverse primer	GTCTGGACAAGCACTGAAAGATAAGA
	VIC probe	TTCCCAG<u>C</u>ACCTTC
	FAM probe	CTTCCCAG<u>T</u>ACCTTC
MDR-1 G2677T	Forward primer	CTTAGAGCATAGTAAGCAGTAGGGAGT
	Reverse primer	GAAATGAAAATGTTGTCTGGACAAGCA
	VIC probe	TTCCCAG<u>C</u>ACCTTC
	FAM probe	TTCCCAG<u>A</u>ACCTTC

The positions of the SNPs are underlined.

chain reactions (PCR) were performed in a reaction volume of 10µl, containing assay-specific primers, allele-specific Taqman MGB probes, Abgene Absolute QPCR Rox Mix and genomic DNA (1 ng). The thermal profile consists of an initial denaturation step at 95°C for 15 minutes, followed by 40 cycles of denaturation at 92°C for 15 seconds and annealing and extension at 60°C for 1 minute. Genotypes were scored by measuring allele-specific fluorescence using the SDS 2.2.2 software for allelic discrimination (Applied Biosystems).

MAPT mutation analysis

The 13 coding exons including intron-flanking regions of the microtubule-associated protein *MAPT* gene were amplified using PCR primers designed in Oligo 6.22 (Molecular Biology Insights) and listed in Table II. PCR conditions were optimized per exon, but in general samples were heated to 95°C for 5 min and amplified for 14 cycles at 94°C for 20 s, 63°C for 60 s (decrease of 0.5°C per cycle) and 72°C for 60 s. Subsequently, a second amplification was initiated for 20 cycles at 94°C for 20 s, 56°C for 60 s and 72°C for 60 s, the program is completed by a final extension step of 5min 72°C. PCR reactions were performed in 30 µl volumes containing 36 ng genomic DNA, 1x PCR buffer (Integro), 2 mM $MgCl_2$ (Applied Biosystems), 200 µM of each dNTP (Promega), 300 µM of forward and reverse primer (Eurogentec) and 0.75 U ThermoPerfect Taq polymerase (Integro). Samples were denatured at 95°C for 5 min and slowly cooled down to 4°C to facilitate heteroduplex formation. Aliquots of 10µl of each PCR product were injected under temperature and acetonitrile gradient conditions, optimized per exon (listed in Table III) and subsequently analysed for the presence of mutations by DH-PLC (WAVE™-system 2100/3500HT, Transgenomic). Abnormal products were identified by examination of the WAVE patterns using Wavemaker™ software (Transgenomic). PCR products suspected to be abnormal were subjected to bidirectional sequence analysis as described by the protocol of BigDye terminator v1.1 (Applied Biosystems) followed by automated sequencing on the ABI PRISM® 3100 Genetic Analyzer (Applied Biosystems). Polymorphism A68504G (exon 1), A80659G (intron 3), C90092T (exon 5), T96360C (intron 7), T96214C (exon 7), T102787C (exon 9) were defined as haplotype A, based on linkage analysis in Haploview 3.32. Linkage was defined as $r^2 \geq 0.8$. The other polymorphisms found were not linked to the previous mentioned are defined as haplotype B.

Treatment

Children with ALL were treated according to the ALL-9 protocol of the Dutch Childhood Oncology Group: this is almost identical to the previously used protocol ALL-6 [25]. The VCR dose is 2.0 mg/m^2 with a maximum of 2.5 mg; cumulative VCR doses in the above

Table II Primers microtubule-associated protein tau (MAPT)

Exon	Primer	Sequence	Temp. (°C) used for dHPLC
1	forward	5′- CAGGGAGGCTGAGATCTG -3′	62
	reverse	5′- GTGCATGGCTGTCCACTA -3′	
2	forward	5′- CCACAGGGAGCGATTTT -3′	63
	reverse	5′- AAGCACGGCTAAGCACA -3′	
3	forward	5′- GGTGGATCTCGGTGGTT -3′	62
	reverse	5′- GCCCCACAGGAGGATAA -3′	
4	forward	5′- ACCCCCCTTCATTTGC -3′	57
	reverse	5′- TCCCAGGCTGGACAAG -3′	
5-1	forward	5′- CACCACTGCGTATCTCCAC -3′	64
	reverse	5′- CTGGGATCTCTGTGGAAACT -3′	
5-2	forward	5′- CTCCCTGTGGATTTCCTC -3′	64
	reverse	5′- AGGCCTGGAAGCTCAGT -3′	
6	forward	5′- GCTGGCTTTCTGTGAACA -3′	57
	reverse	5′- AACCTGCCAACTGCTCTT -3′	
7	forward	5′- CCTCCATGTGCTGACTTTTAT -3′	58
	reverse	5′- CTTAGGAGCTGCTGCTATGAG -3′	
8	forward	5′- AGCCACGTTTTGAGTCAAG -3′	60
	reverse	5′- GGACTGAGAAGGCAATGAA -3′	
9	forward	5′- CCACCCACTCGAGTCCT -3′	64/65
	reverse	5′- AGGGGACTGGGGTGTTA -3′	
10	forward	5′- TGCCAATGCCGAAAGTG -3′	60
	reverse	5′- TTCACCCAGAGGTCGC -3′	
11	forward	5′- GGCCTGGGCTTACACA -3′	58
	reverse	5′- GCTCCCGCAAGTTTCA -3′	
12	forward	5′- TGGCAAGATGCTCTTGTG -3′	60
	reverse	5′- GACCAGCCTTTGTCCACT -3′	
13	forward	5′- GGCAGGGCTGGTCTTT -3′	61
	reverse	5′- GGGCCGGGTCATTATT -3′	

mentioned treatment protocol varies from 62.0 mg/m^2 in the high-risk protocol to 68.0 mg/m^2 in the non high-risk protocol.

Assessment of motor performance

Motor performance was measured using the Dutch version of the Movement Assessment Battery for Children (movement-ABC) [26,27]. The movement-ABC consists of a series of eight standardized tasks divided in three subsections: hand function, ball skills and balance skills. Tasks vary with age and are designed to resemble every day activities

Table III Aberrations found in MAPT

exon/ intron	SNP[a] position	alteration	position on chromosome 17	amino acid substitution	% in patient group	corrected for extra patients *based on rs1800547*[c]	dbSNP number[d]
missense							
5	89673	A>G	41416697	Q230R	10,8% (4/37)		unknown
5	89837	G>A	41416860	D285N	38,5% (15/39)		unknown
5	89850	T>C	41416873	V289T	38,5% (15/39)		unknown
5	90092	C>T	41417115	R370W	38,5% (15/39)	36,4% (24/66)	**rs17651549**
7	96196	T>C	41423219	H441Y	66,7% (26/39)		rs2258689
7	96124	T>C	41423237	S447F	38,5% (15/39)	36,4% (24/66)	**rs10445337**
silent							
1	68504	A>G	41395527	no translation[b]	38,5% (15/39)	36,4% (24/66)	**rs17650901**
5	89839	C>T	41416862	D285D	30,7% (12/39)		unknown
9	102787	T>C	41429810	N572N	35,1% (13/37)	36,4% (24/66)	**rs17652121**
9	102832	G>A	41429855	P587P	5,4% (2/37)		rs11568305[e]
intronic							
3	80659	A>G	41407682		36,4% (24/66)	36,4% (24/66)	**rs1800547**
7	96322	A>G	41423345		28,2% (11/39)		unknown
7	96360	T>C	41423383		28,2% (11/39)	36,4% (24/66)	**rs17651754**
9	102947	G>A	41429970		8,1% (3/37)		unknown
11	120594	G>A	41447623		33,3% (13/39)		unknown

mutation which could not be identified by sequencing
amplicon of exon 2
amplicon of exon 9
amplicon of exon 13
a position relative to Ensembl entry: ENSG00000186868 genomic sequence
b this SNP was located in 3'UTR, no amino acid translation
c extra 27 patients were tested for rs1800547, because linkage was proven between: rs17651549/ rs10445337/rs17652121/rs1800547 and rs17651754, they were all subjected for analysis
d reference number in dbSNP database, numbers in bold are linked together based on haploview, r^2=1,0
e was not shown in haploview and was not analyzed for linkage

of children. The total score of the movement-ABC is transformed into a percentile score by age-related norms. A score below the 5th percentile indicates impaired motor performance, between 5th and 15th percentile is borderline and higher than the 15th percentile is normal. The child's performance on each of the subsections is also expressed as either below or above the 15th percentile. Validity of the movement-ABC to test motor ability in children has been shown before [28].

Statistics

The SPSS statistical package (version 12.0.1) was used to analyse the data. Group differences were calculated using the Mann Whitney and Kruskal-Wallis tests. Comparison of ordinal categorical scores between individuals with *MAPT* haplotype A and B was carried out with the linear-by-linear association test.

RESULTS

Patients

A total number of 34 survivors of ALL, 18 boys (53%) and 16 girls (47%), participated in the study. Mean age at follow-up was 7.8 years (sd ± 2.2), mean age at diagnosis 3.7 years (± 2.1) and mean time since completion of treatment 1.9 years (± 0.5). Nine children had been treated with the ALL high-risk protocol, the other 25 children with the protocol for non high-risk patients.

Distribution of individual SNPs and haplotypes

Thirty-four patients were genotyped for the *CYP3A5*3* allele, detecting twenty-two individuals with *CYP3A5 *3/*3* (65%) and 12 individuals *1/*3 (35%).

For the *MDR-1* analysis at position 3435, we found 11 individuals 3435TT (32%); 19 individuals 3435CT (56%) and 4 individuals 3435CC (12%). For the SNP at position 2677, both the G2677T and the G2677A substitutions were determined, yielding 9 patients 2677 TT (27%), 14 patients 2677GT (43%), 2 patients 2677GA (6%), 8 patients 2677GG (24%); one result was inconclusive. These genotypings resulted in 2 carriers of haplotype 1/1 (6%) and 5 carriers of haplotype 1/2 (15%) as described by Johne [19].

For the C1236T SNP of the *MDR-1* gene, 8 patients were 1236TT (25%), 14 patients were 1236CT (44%) and 10 patients were 1236CC (31%). Two results were inconclusive.

The *MAPT* analysis revealed a similarity in results for a number of patients (Table III). Haploview linkage analysis revealed that SNP's in exon 1,2,3,4,5 and 7 were closely linked (r^2 =1.0) and hence we defined this as haplotype A. The other SNP's were labelled as haplotype B. Ten patients were haplotype A carriers (29%) and 24 haplotype B (71%); one result was inconclusive. The distribution of individual SNPs and haplotypes is shown in Table IV.

Table IV Distribution of SNPs

Case number	CYP3A5 C1236T	MDR-1 G2677A/T	MDR-1 C3435T	MDR-1	MAPT haplotype
1	*1/*3	CC	GG	CC	B
2	*3/*3	CT	TT	TT	B
3	*1/*3	CC	GA	CC	B
4	*3/*3	TT	TT	TT	B
5	*3/*3	CT	GT	TT	A
6	*3/*3	TT	TT	TT	A
7	*3/*3	CC	GG	CT	B
8	*1/*3	CT	GT	CT	A
9	*3/*3	CT	GT	CT	B
10	*3/*3	-	-	CT	A
11	*3/*3	CC	GG	CT	A
12	*1/*3	TT	TT	TT	A
13	*3/*3	CC	GG	CT	A
14	*3/*3	CT	GT	CT	B
15	*3/*3	TT	TT	TT	B
16	*3/*3	CT	GT	CT	B
17	*1/*3	TT	TT	TT	B
18	*3/*3	CC	GG	CT	B
19	*3/*3	CC	GA	CC	B
20	*3/*3	CT	GT	CT	B
21	*3/*3	CT	GT	CT	B
22	*3/*3	CC	GG	CT	B
23	*3/*3	CT	TT	TT	B
24	*3/*3	CC	GG	TT	B
25	*1/*3	-	GT	CT	B
26	*3/*3	CC	GG	CC	A
27	*1/*3	TT	TT	CT	B
28	*1/*3	TT	GT	CT	B
29	*3/*3	TT	TT	TT	A
30	*1/*3	CT	GT	CT	B
31	*1/*3	CT	GT	TT	B
32	*1/*3	CT	GT	CT	B
33	*1/*3	CT	GT	CT	B
34	*3/*3	CT	GT	CT	B

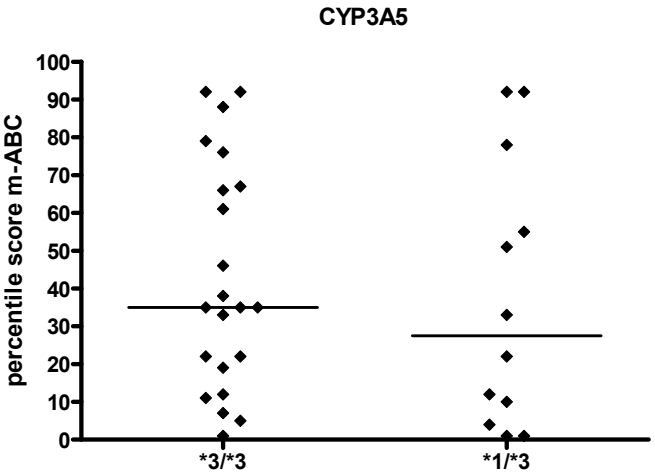

Figure 1 Movement-ABC scores of motor performance, in percentiles, of children with CYP3A5 *3/*3 and CYP3A5 *1/*3 genotypes. The horizontal bars depict the median values.

Motor performance scores

The scores on the movement-ABC test for motor performance (m-ABC) were converted into percentiles. The median percentile score of the total group was 35.

The difference in percentile scores on the m-ABC between *CYP3A5 *3/*3* and *CYP3A5*1/*3* genotypes was not statistically significant (p= 0.49, Figure 1).

Percentile scores on the m-ABC were not significantly affected by the *MDR-1* SNPs C3435T (p= 0.87, Figure 2a), G2677A/T (p=0.28, Figure 2b) or C1236T (p=0.66, Figure 2c). The data were also analysed using haplotypes as defined by Johne [19]. There was no significant difference in percentiles score between 3435C/2677G carriers (haplotype 1/1), 3435T/2677G carriers (haplotype 1/2) and others (p=0.56).

There was no significant difference in percentile scores on the m-ABC between *MAPT* haplotype A and haplotype B carriers (p=0.47, Figure 3).

DISCUSSION

This study did not provide evidence that *CYP3A5*, *MDR-1* or *MAPT* genetic polymorphisms affect motor performance in children who have been treated for ALL with VCR containing chemotherapy.

We hypothesised that the presence of *CYP3A5*3/*3* would increase VCR toxicity and result in lower scores on the movement-ABC motor performance test, but our data did not support this. However, because our patient cohort only had *CYP3A5*1/*3* expressers, no conclusions about the effect of *CYP3A5*1/*1* individuals could be made. This pro-

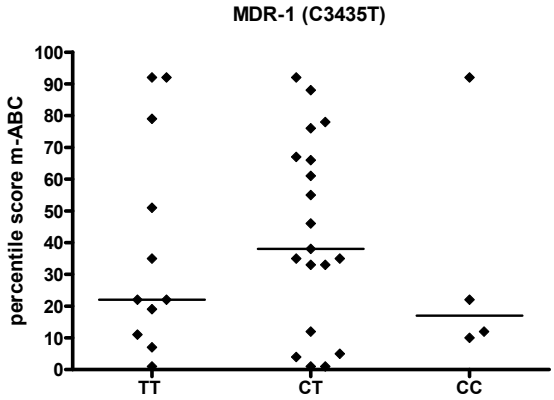

Figure 2a Movement-ABC scores of motor performance, in percentiles, of children with MDR-1 3435TT, 3435CT, and 3435CC genotypes. The horizontal bars depict the median values.

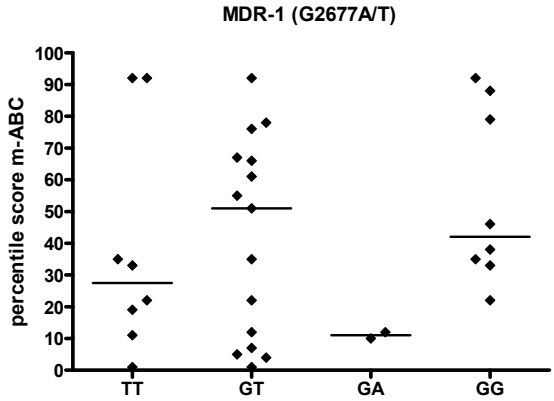

Figure 2b Movement-ABC scores of motor performance, in percentiles, of children with MDR-1 2677TT, 2677GT, 2677GA, 2677GG genotypes. The horizontal bars depict the median values.

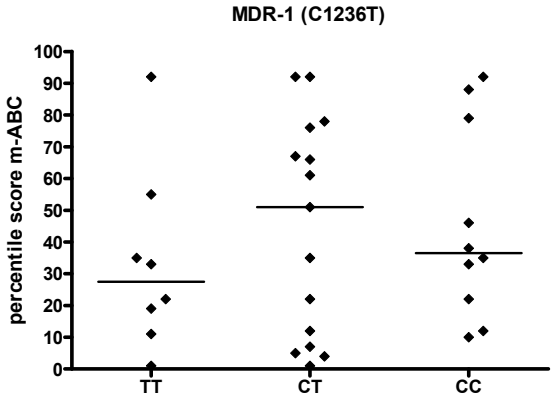

Figure 2c Movement-ABC scores of motor performance, in percentiles, of children with MDR-1 1236TT, 1236CT and 1236CC genotypes. The horizontal bars depict the median values.

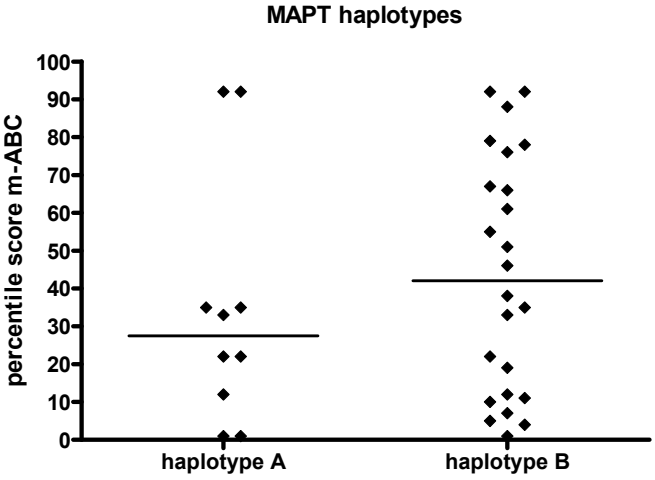

Figure 3 Movement-ABC scores of motor performance, in percentiles, of children with MAPT haplotype A and haplotype B. The horizontal bars depict the median values.

hibited us of comparing motor performance between the two extremes of the spectrum, i.e. *CYP3A5 *3/*3* versus *CYP3A5*1/*1*.

The *MDR-1* gene, encoding the efflux pump P-glycoprotein (P-gp), affects the distribution of drugs such as VCR. P-gp has been shown to influence biliary clearance of VCR [14,15,29]. P-gp is located in the blood-nerve barrier and can limit VCR exposure of the nerves [30,31]. If P-gp is under-expressed or has lower activity, nerve exposure to VCR and the incidence of polyneuropathy may increase and affect motor performance outcome. MDR-1 SNPs associated with VCR pharmacokinetics are C3435T and G2677T/A, but in our patients we did not find an effect on motor performance. Plasschaert et al described a negative effect of 3435C/2677G carriers and a possible positive effect of 3435T/2677G carriers on the elimination half-life of VCR [20]. We hypothesised that these haplotypes would affect motor performance in a similar way, but our data did not support this. However, as there were only two 3435C/2677G and five 3435T/2677G carriers in our cohort, numbers might have been too small to reach a definite conclusion.

Polyneuropathy as a side effect of VCR occurs because it damages microtubules in the axonal part of the nerves, resulting in impaired axonal transport and loss of nerve function. The *MAPT* promotes microtubule assembly and stability in the axonal compartments of neurons [32]. Theoretically, under-expression of *MAPT* may compromise microtubule stability thereby increasing the incidence and severity of polyneuropathy. Our hypothesis was that *MAPT* haplotype A carriers would perform less well on the movement-ABC test compared to haplotype B, but this was also not supported by our data.

In conclusion, our study did not show that polymorphisms of *CYP3A5*, *MDR-1* or the *MAPT* gene influenced motor performance in children who had been treated for ALL with VCR.
However, the number of cases studied was relatively small limiting the power to study the effect of combinations of polymorphisms in different genes. Very large studies would be needed to analyse such a multifactorial cause of differences in motor performance.

REFERENCES

1 Harter S. The perceived competence scale for children. Child Development 1982; 53:87-97

2 Vainionpaa L. Clinical neurological findings of children with acute lymphoblastic leukaemia at diagnosis and during treatment. Eur J Pediatr 1993; 152:115-119.

3 Reinders-Messelink H, Schoemaker M, Goeken L, et al. Handwriting and fine motor problems after treatment for acute lymphoblastic leukemia. In: Simner ML, Leedham CG, Thomassen AJWM, eds. Handwriting and drawing research: basic and applied issues. Amsterdam: IOS Press, 1996; 215-225

4 Wright MJ, Halton JM, Martin RF, et al. Long-term gross motor performance following treatment for acute lymphoblastic leukemia. Med Pediatr Oncol 1998; 31:86-90.

5 Gidding CE, Kellie SJ, Kamps WA, et al. Vincristine revisited. Crit Rev Oncol Hematol 1999; 29:267-287

6 Vainionpaa L, Kovala T, Tolonen U, et al. Vincristine therapy for children with acute lymphoblastic leukemia impairs conduction in the entire peripheral nerve. Pediatr Neurol 1995; 13:314-318

7 Verstappen CC, Koeppen S, Heimans JJ, et al. Dose-related vincristine-induced peripheral neuropathy with unexpected off-therapy worsening. Neurology 2005; 64: 1076-1077

8 Hartman A, van den Bos C, Stijnen T, et al. Decrease in motor performance in children with cancer is independent of cumulative vincristine dose. Cancer 2006; 106:1395-1401

9 Zhou-Pan XR, Seree E, Zhou XJ, et al. Involvement of human liver cytochrome P450 3A in vinblastine metabolism: drug interactions. Cancer Res 1993; 53:5121-5126.

10 Van Schaik RH, de Wildt SN, Brosens R, et al. The CYP3A4*3 allele: is it really rare? Clin Chem 2001; 47:1104-1106

11 Kuehl P, Zhang J, Lin Y, et al. Sequence diversity in CYP3A promoters and characterization of the genetic basis of polymorphic CYP3A5 expression. Nat Genet 2001; 27:383-391

12 Hustert E, Haberl M, Burk O, et al. The genetic determinants of the CYP3A5 polymorphism. Pharmacogenetics 2001; 11:773-779

13 Dennison JB, Jones DR, Renbarger JL, et al. Effect of CYP3A5 Expression on Vincristine Metabolism with Human Liver Microsomes. J Pharmacol Exp Ther 2007

14 Song S, Suzuki H, Kawai R, et al. Effect of PSC 833, a P-glycoprotein modulator, on the disposition of vincristine and digoxin in rats. Drug Metab Dispos 1999; 27: 689-694

15 Watanabe T, Miyauchi S, Sawada Y, et al. Kinetic analysis of hepatobiliary transport of vincristine in perfused rat liver. Possible roles of P-glycoprotein in biliary excretion of vincristine. J Hepatol 1992; 16:77-88
16 Hoffmeyer S, Burk O, von Richter O, et al. Functional polymorphisms of the human multidrug-resistance gene: multiple sequence variations and correlation of one allele with P-glycoprotein expression and activity in vivo. Proc Natl Acad Sci U S A 2000; 97:3473-3478
17 Chowbay B, Cumaraswamy S, Cheung YB, et al. Genetic polymorphisms in MDR1 and CYP3A4 genes in Asians and the influence of MDR1 haplotypes on cyclosporin disposition in heart transplant recipients. Pharmacogenetics 2003; 13:89-95
18 Siegmund W, Ludwig K, Giessmann T, et al. The effects of the human MDR1 genotype on the expression of duodenal P-glycoprotein and disposition of the probe drug talinolol. Clin Pharmacol Ther 2002; 72:572-583
19 Johne A, Kopke K, Gerloff T, et al. Modulation of steady-state kinetics of digoxin by haplotypes of the P-glycoprotein MDR1 gene. Clin Pharmacol Ther 2002; 72: 584-594
20 Plasschaert SL, Groninger E, Boezen M, et al. Influence of functional polymorphisms of the MDR1 gene on vincristine pharmacokinetics in childhood acute lymphoblastic leukemia. Clin Pharmacol Ther 2004; 76:220-229
21 Goto M, Masuda S, Saito H, et al. C3435T polymorphism in the MDR1 gene affects the enterocyte expression level of CYP3A4 rather than Pgp in recipients of living-donor liver transplantation. Pharmacogenetics 2002; 12:451-457
22 Scott WK, Nance MA, Watts RL, et al. Complete genomic screen in Parkinson disease: evidence for multiple genes. Jama 2001; 286:2239-2244
23 Pastor P, Ezquerra M, Perez JC, et al. Novel haplotypes in 17q21 are associated with progressive supranuclear palsy. Ann Neurol 2004; 56:249-258
24 Tanahashi H, Asada T, Tabira T. Association between tau polymorphism and male early-onset Alzheimer's disease. Neuroreport 2004; 15:175-179
25 Veerman AJ, Hahlen K, Kamps WA, et al. High cure rate with a moderately intensive treatment regimen in non-high-risk childhood acute lymphoblastic leukemia. Results of protocol ALL VI from the Dutch Childhood Leukemia Study Group. J Clin Oncol 1996; 14:911-918
26 Henderson S, Sugden D. Movement Assessment Battery for Children. Sidcup, England: The Psychological Corporation, 1992
27 Smits-Engelsman BC. Movement Assessment Battery for Children; Nederlandse bewerking. Lisse, Nederland: Swets & Zeitlinger, 1998
28 Croce RV, Horvat M, McCarthy E. Reliability and concurrent validity of the movement assessment battery for children. Percept Mot Skills 2001; 93:275-280

29 Watanabe T, Suzuki H, Sawada Y, et al. Induction of hepatic P-glycoprotein enhances biliary excretion of vincristine in rats. J Hepatol 1995; 23:440-448
30 Saito T, Zhang ZJ, Shibamori Y, et al. P-glycoprotein expression in capillary endothelial cells of the 7th and 8th nerves of guinea pig in relation to blood-nerve barrier sites. Neurosci Lett 1997; 232:41-44
31 Saito T, Zhang ZJ, Ohtsubo T, et al. Homozygous disruption of the mdrla P-glycoprotein gene affects blood-nerve barrier function in mice administered with neurotoxic drugs. Acta Otolaryngol 2001; 121:735-742
32 Goedert M. Neurofibrillary pathology of Alzheimer's disease and other tauopathies. Prog Brain Res 1998; 117:287-306

CHAPTER 7

A RANDOMISED TRIAL INVESTIGATING AN EXERCISE PROGRAMME TO PREVENT REDUCTION OF BONE MINERAL DENSITY AND IMPAIRMENT OF MOTOR PERFORMANCE DURING TREATMENT FOR CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA

A. Hartman MSc[1,2] / M.L. te Winkel MD[1], R.D. van Beek MD[1], S.M.P.F. de Muinck Keizer-Schrama MD PhD[3], H.C.G. Kemper PhD[4], W.C. J. Hop PhD[5], M.M. van den Heuvel-Eibrink MD PhD[1], R. Pieters MD PhD[1]

Department of Paediatric Oncology / Haematology[1], Paediatric Physiotherapy[2], Paediatric Endocrinology[3], Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands, EMGO Institute VU University Medical Center[4], Amsterdam, the Netherlands, Department of Biostatistics[5] Erasmus MC, Rotterdam, the Netherlands.

Submitted

ABSTRACT

Reduced bone mineral density (BMD), altered body composition, impaired motor performance and passive ankle dorsiflexion are side effects of acute lymphoblastic leukemia (ALL) treatment.

At diagnosis we randomised 51 ALL patients (median age: 5.4 years) into a group receiving a two-year exercise programme or a control group, to investigate whether exercise could prevent these side effects. BMD of total body (BMD_{TB}), lumbar spine (BMD_{LS}) and body composition were measured using dual energy X-ray absorptiometry, motor performance with Bayley Scales of Infant Development or Movement-ABC, and passive ankle dorsiflexion with a goniometer. The investigator was blinded to the randomisation. Repeated measurements analysis (ANOVA) was used.

Body-fat increased equally during treatment in both groups. One year after cessation of therapy more rapid decline of excessive body fat was observed in the intervention group than in the controls ($p=0.01$). Lean body mass, BMD_{TB} and BMD_{LS} of both groups decreased equally during treatment and increased equally thereafter. Both groups showed a similar decrease in passive ankle dorsiflexion and motor performance during treatment. Adherence to the intervention programme varied considerably.

The exercise programme was not more beneficial in preventing reduction in BMD, motor performance and passive ankle dorsiflexion than standard care, most likely due to unsatisfactory compliance.

INTRODUCTION

Because the survival rate of ALL has improved, preventing side effects of chemotherapy has become increasingly important. Several studies have shown that motor performance, peripheral muscle strength and passive ankle dorsiflexion in children treated for ALL was impaired during treatment and also after cessation of chemotherapy[1-4]. These problems were mainly attributed to vincristine-induced neuropathy. Moreover, treatment protocols for ALL contain a considerable amount of prednisone and/or dexamethasone. This may cause steroid-associated myopathy with weakness of proximal musculature and muscle atrophy leading to a decreased lean body mass (LBM) [5]. In addition, corticosteroids and methotrexate (MTX) are known to cause reduction of bone mineral density (BMD). Several studies have shown that BMD is already lower at diagnosis of ALL and decreases further during the two-year treatment period[6,7]. Although a decreased BMD is unlikely to affect motor performance directly, it is associated with an increased fracture risk[8]. Studies investigating BMD in long-term survivors of childhood ALL show conflicting results[9-13]. In general, BMD of patients treated without cranial irradiation shows a tendency to improve after cessation of therapy[8,14]. Several animal studies in which mechanical loads were applied showed that the crucial factor in stimulation of bone acquisition is the magnitude rather than the number of repetitions of the load applied[15,16]. Therefore, short-burst high-intensity activities might be effective to enhance BMD during childhood[17-20]. However, no studies have been performed to investigate this effect of exercise on BMD during treatment of childhood ALL.

Because vincristine-related neuropathy causes weakness in the dorsiflexors of the foot, children are at risk for developing a plantigrade contracture of the ankle. Wright et al. found positive effects of preventative education and physiotherapy consisting of stretching and strengthening exercises on passive ankle dorsiflexion during treatment for ALL[21]. Another study reported positive effects of physical exercises on ankle dorsiflexion mobility and strength of knee extensors, but no improved functional outcome was found[22].

In the current prospective randomised study in childhood ALL we investigated whether an exercise programme starting at onset and continued during 2-year treatment for ALL has a beneficial effect on BMD, body composition, motor performance and passive ankle dorsiflexion.

MATERIALS AND METHODS

Patients

Between April 2001 and September 2004 the study was conducted in Erasmus MC-Sophia Children's Hospital Rotterdam, the Netherlands. Children with ALL aged 1-18 years

that did not have cognitive impairment and had good command of the Dutch language were eligible. Clinical data (age, gender, immunophenotype of leukemia, fractures) were obtained from the medical records. The Medical Ethical Committee approved the study. Written informed consent according to the Helsinki agreement was obtained from all parents and from patients ≥ 12 years.

Chemotherapy treatment

Patients were treated according to the ALL-9 protocol of the Dutch Childhood Oncology Group (DCOG), which was identical to the previously used ALL-6 protocol for the non-high-risk (NHR) patients[23]. The ALL-9-NHR protocol started with induction therapy including dexamethasone and vincristine, followed by high-dose MTX courses and maintenance therapy with 6-mercaptopurine/MTX plus vincristine/dexamethasone pulses. Patients were treated according to the high-risk (HR) protocol when they met one of the following criteria: white blood cell count ≥50x10^9, T-cell immunophenotype, mediastinal mass, involvement of the central nervous system, infiltration of the testes, t(9;22) or BCR-ABL gene rearrangement, t (4;11) or translocations involving 11q23 with *MLL* gene-rearrangements. High-risk ALL patients received anthracyclines during induction treatment, higher doses of MTX during central-nervous-system prophylaxis and they received two additional intensification courses before start of maintenance therapy.

Randomisation

Randomisation into the intervention or the control group was carried out in randomly permuted blocks of randomly chosen size, using sealed envelopes prepared by the statistician. The research nurse informed parents into which group their child was randomised. The investigators and treating physicians were blinded for the randomisation.

Intervention and standard care

The intervention group received an initial session and 6-weekly follow-up sessions with the hospital-based paediatric physiotherapist, throughout the two-year treatment period. The initial session comprised of education regarding possible motor problems resulting from chemotherapy and general measures to ensure an optimum level of motor functioning. In addition an exercise programme was introduced, consisting of exercises to maintain hand and leg function, stretching exercises to maintain ankle dorsiflexion mobility and short-burst high-intensity exercises (e.g. jumping) to prevent reduction in BMD. Exercises to maintain hand and leg function had to be performed once a day and stretching and jumping exercises twice daily. The 6-weekly follow-up sessions involved an evaluation of the child's main motor skills (walking, running, jumping), discussion and adjustment of the exercise programme if necessary. Passive ankle dorsiflexion was monitored and if < 5° beyond the neutral position, patients received plaster of Paris splints overnight. In case

of concern regarding a child's motor ability they would be referred to a local paediatric physiotherapist for additional treatment. Follow-up sessions with the hospital-based physiotherapist always coincided with regular visits to the oncology outpatient department.
Standard care for the control group included neither an initial session nor any pre-scheduled follow-up sessions with the hospital-based physiotherapist. If child or parents reported motor problems to the treating physician a referral to a local paediatric physiotherapist was allowed.
On cessation of chemotherapy parents of children in both groups received a short questionnaire. All parents were asked whether they had valued testing of motor performance by the investigator. Parents of children in the intervention group were questioned about adherence to the exercise programme.

End points

At diagnosis, 32 weeks after diagnosis, one year after diagnosis, on cessation of treatment (two years after diagnosis) and one year after cessation of therapy the following end points were measured: anthropometric data (height, weight, body mass index (BMI)), body composition (LBM and percentage body fat), BMD (primary end point) of the total body (BMD_{TB}), and lumbar spine (BMD_{LS}). Motor performance (primary end point) and passive ankle dorsiflexion were assessed at diagnosis, following induction therapy (six weeks after diagnosis), one year after diagnosis and on cessation of treatment.

Anthropometry, body composition and BMD

Height was measured using a Harpenden stadiometer and weight using a standard clinical balance. Body mass index (BMI) was calculated as weight/height^2. In patients aged 4-19 years body composition parameters, BMD_{TB}, and BMD_{LS} were measured using dual energy X-ray absorptiometry (DEXA; Lunar DPX-L, Madison, WI). To correct for bone size, bone mineral apparent density of the lumbar spine ($BMAD_{LS}$) was calculated as $BMAD_{LS}= BMD_{LS}*[4/(\varpi*\text{width})]$. The DEXA of total body provided estimates of body composition: lean body mass (LBM) which consists mainly of muscle mass and percentage of body fat. All results were compared with those of Dutch healthy children and expressed as standard deviation scores (SDS) [24,25].

Skeletal complications

Fractures had to be confirmed on X-ray and symptomatic osteonecrosis by magnetic resonance imaging.

Motor performance

For children < 3.5 years motor performance was measured using the motor scale of the Dutch Bayley Scales of Infant Development (BSID-II) and for children aged ≥ 4 years the

Dutch version of the Movement Assessment Battery for Children (movement-ABC) was used[26,27]. The motor scale of the BSID-II consists of several motor tasks and the total number accomplished by the child is converted into a SDS. The movement-ABC has eight standardized tasks divided in three subsections: hand function, ball skills and balance skills. The total score of the movement-ABC is transformed by age-related norms into a percentile score.

Passive ankle dorsiflexion

To measure passive ankle dorsiflexion a standardised position was used: supine position, with the knee extended. A range of motion past neutral position had a positive notation and less than neutral was negative. The lower of the two passive ankle dorsiflexion values (preferred and non-preferred side) will determine the level of impairment and was therefore used for analysis.

Statistical analysis

The Mann-Whitney U-test/χ^2-test was used to compare patient characteristics of the intervention and control groups. Motor performance of the whole study group was compared with reference values using the one-sample T-test. Within-group differences in motor performance and passive ankle dorsiflexion mobility were analysed using a paired T-test. These statistical analyses were carried out with SPSS for Windows version 11.0.1 (SPSS Inc., Chicago, IL, USA). Differences between the two groups in changes of endpoints during the two-year treatment period (Δ1) and from cessation of chemotherapy during the first year after cessation (Δ2) were analysed using repeated measurements analysis (SAS PROC MIXED SAS Institute Inc., Cary, North Carolina, USA), with an unstructured repeated covariance type. P-values less than 0.05 (two-sided) were considered statistically significant. Power calculations resulted in entering 50 children in the study. All analyses were carried out according to the intention-to-treat principle; for children who did not complete the study data prior to elimination were included.

RESULTS

Patients

During the inclusion period 67 children were eligible of which 12 declined and 4 were not randomised. There were no significant differences in age at diagnosis (median age: 5.4 vs. 4.8 year, p=0.41), gender (50% vs. 59% male, p=0.53) and immunophenotype of ALL (80% vs. 75% B-lineage ALL, p=0.73) between patients who did or did not enter the randomised study.

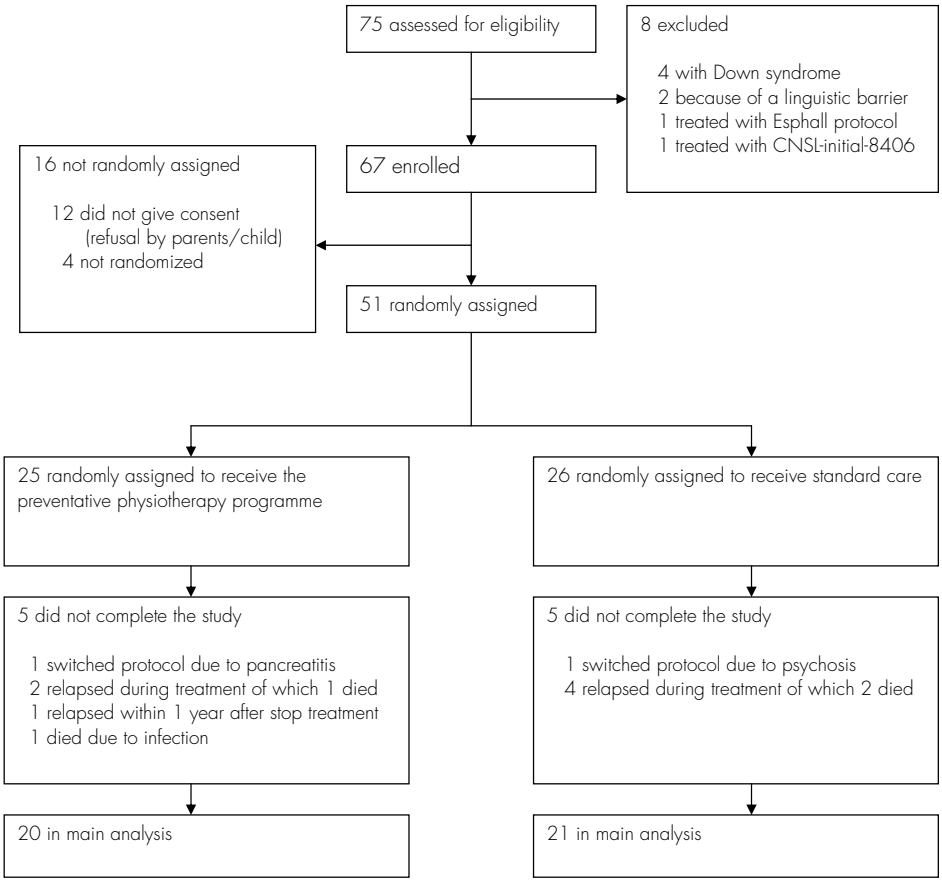

Figure 1. Study profile

Figure 1 shows the study profile. Patient characteristics of the intervention and the control group at diagnosis are shown in Table I.

Anthropometry and body composition

Height, weight and BMI

At diagnosis, height, weight and BMI were not significantly different between the two groups (Table II). BMI significantly increased during the two years of chemotherapy in the intervention group (Δ_1BMI = 1.53 SDS) and in the control group (Δ_1BMI = 1.38 SDS); this increase did not significantly differ between both groups (p=0.69). One year after cessation of treatment, BMI had decreased towards normal values of healthy peers in both intervention and control group (Δ_2BMI = -0.95 SDS vs. Δ_2BMI = -0.47 SDS), but this change was significantly more pronounced in the intervention group (p=0.026) (Figure

Table I Patient characteristics of the intervention group and the control group at diagnosis.

	Intervention group	Control group	P-value
Gender			0.69
Boys	14 (56%)	16 (62%)	
Girls	11 (44%)	10 (38%)	
Age (years)			0.52
Median	5.3	6.2	
Minimum	1.3	1.7	
Maximum	15.6	17.1	
Immunophenotype			0.73
B-lineage	21 (84%)	20 (77%)	
T-lineage	4 (16%)	6 (23%)	
Protocol			0.17
Non high risk	19 (76%)	15 (58%)	
High risk	6 (24%)	11 (42%)	

Table II Anthropometry and body composition at diagnosis, on cessation of chemotherapy and 1 year after cessation of chemotherapy

	Diagnosis			Cessation of chemotherapy			1 Year after cessation of chemotherapy		
Median SDS	Intervention group	Control group	P-value	Intervention group	Control group	P-value	Intervention group	Control group	P-value
Height	-0.11	0.10	0.66	-0.87	-0.27	0.16	-0.47	-0.07	0.92
Weight	-0.40	-0.09	0.76	0.54	0.51	0.93	-0.10	0.36	0.51
Body mass index	-0.33	-0.38	0.86	1.20	1.00	0.52	0.26	0.54	0.4
Percentage of body fat	0.47	-0.22	0.12	1.51	1.34	0.6	0.44	0.85	0.32
Lean body mass	-0.46	-0.66	0.57	-1.07	-0.78	0.37	-0.78	-0.56	0.48

2A). On cessation of chemotherapy and one year after cessation of therapy there were no significant differences between the groups in height, weight and BMI (Table II).

Body fat

At diagnosis there was no significant difference between the groups in percentage of body fat. During treatment there was no significant difference in the change of body fat percentage between the intervention group and that in the control group ($\Delta_1$fat% = 1.04 SDS vs. $\Delta_1$fat% = 1.56 SDS, p=0.25). One year after cessation of chemotherapy the percentage of body fat had decreased in the intervention group ($\Delta_2$fat% = -1.08 SDS, p<0.001) and in the control group ($\Delta_2$fat% = -0.49 SDS, p=0.001). The decrease was more prominent in the intervention group than in the control group (p=0.013) (Figure 2B).

LBM

At diagnosis there was no significant difference in LBM between the intervention group and the control group. We found no differences between the two groups in decline of LBM from start to cessation of treatment (intervention group: Δ_1LBM = -0.61 SDS vs. control group: Δ_1LBM = -0.12 SDS, p=0.16). One year after treatment LBM had increased equally in both groups (intervention group: Δ_2LBM = 0.29 SDS vs. control group: Δ_2LBM = 0.22 SDS, p=0.66) (Figure 2C).

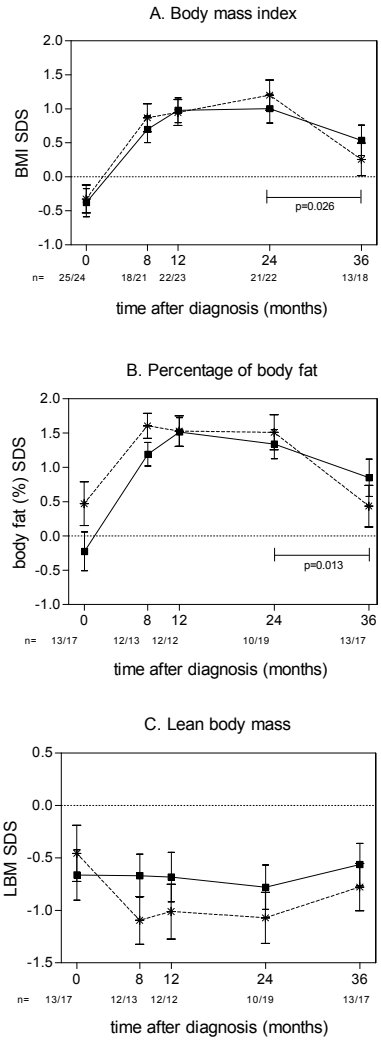

Figure 2. Development of body composition of the intervention and the control group.
Values are expressed as mean +/− standard error of the mean. Abbreviations: SDS = standard deviation score, BMI = body mass index, LBM = lean body mass. Results of the intervention group: dotted line. Results of the control group: continuous line.

Bone mineral (apparent) density

At diagnosis there were no significant differences between the intervention group and the control group in BMD_{TB} (-0.10 SDS vs. –0.18 SDS, p=0.87), BMD_{LS} (-0.42 SDS vs. -0.96 SDS, p=0.22) and $BMAD_{LS}$ (0.14 SDS vs. –0.48 SDS, p=0.09).

Between start and cessation of treatment BMD_{TB} decreased significantly in both groups (intervention group: $\Delta_1 BMD_{TB}$ = -0.75 SDS, p=0.03 and control group: $\Delta_1 BMD_{TB}$ = -0.96 SDS, p=0.003). The decrease of BMD_{TB} did not differ between both groups (p=0.65). One year after discontinuation of treatment BMD_{TB} had recovered in both groups (intervention group: $\Delta_2 BMD_{TB}$ = 0.42 SDS, p=0.004 and control group: $\Delta_2 BMD_{TB}$ = 0.35 SDS, p=0.002). This recovery of BMD_{TB} was not different between both groups (p=0.70) (Figure 3A).

BMD_{LS} did not change in either group during treatment (intervention group: $\Delta_1 BMD_{LS}$ = -0.15 SDS, p=0.69 vs. control group: $\Delta_1 BMD_{LS}$ = -0.04 SDS, p=0.90) nor one year after cessation of chemotherapy (intervention group: $\Delta_2 BMD_{LS}$ = 0.10 SDS, p=0.54 vs. control group: $\Delta_2 BMD_{LS}$ = 0.14 SDS, p=0.30) (Figure 3B). In addition, after correction for bone size, we found no difference between the intervention and control group in the development of the BMD of the lumbar spine during chemotherapy ($\Delta_1 BMAD_{LS}$ = -0.66 SDS vs. $\Delta_1 BMAD_{LS}$ = -0.36 SDS, p=0.47) or during the year after cessation of therapy ($\Delta_2 BMAD_{LS}$ = 0.12 SDS vs. $\Delta_2 BMAD_{LS}$ = 0.04 SDS, p=0.77) (Figure 3C).

Skeletal complications

During the study period seven children in the intervention group and three controls sustained fractures (29% vs. 12%, p=0.17). Each group contained one patient with 2 fractures.

Motor performance

At diagnosis motor performance of the patients was significantly impaired compared to healthy peers (-1.41 SDS, p<0.001). There was a trend to improvement in motor performance of both groups combined from -1.41 SDS at diagnosis to -1.00 SDS at cessation of treatment (p=0.055). There was no significant difference between the intervention and control group in change of motor performance during the course of chemotherapy treatment (Δ_1= 0.37 SDS vs. Δ_1= 0.68 SDS, p=0.44) (Figure 4).

Passive ankle dorsiflexion

Mean passive ankle dorsiflexion of both groups combined changed significantly from 9.1° (SD 4.6) at diagnosis to 4.2° (SD 5.8) at cessation of treatment (p=0.001). However, there was no significant difference in decrease in passive dorsiflexion mobility during the course of treatment between the intervention and control group (Δ_1= -5.2° vs. Δ_1= -4.6°, p=0.76) (Figure 5). In the intervention group five children had been supplied

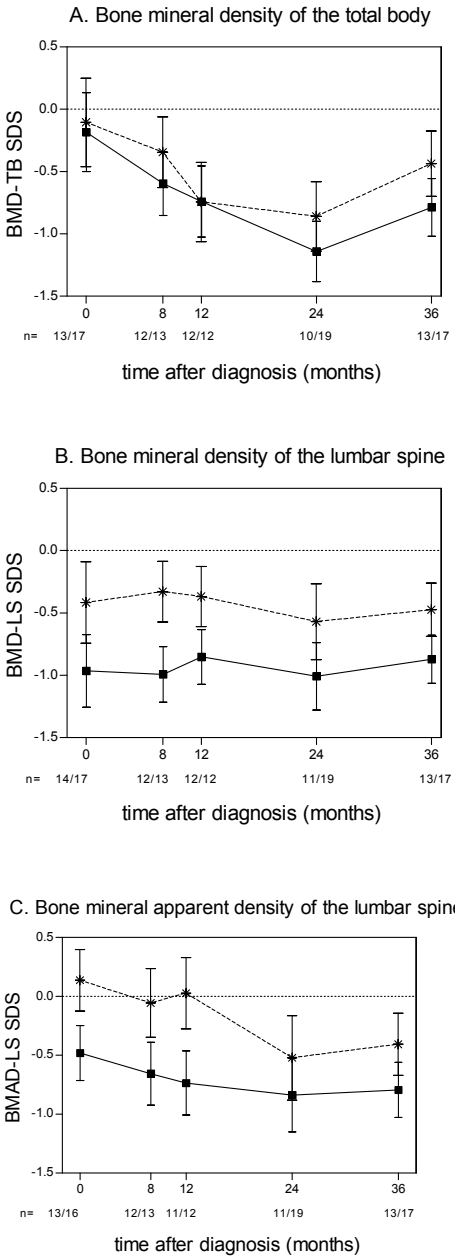

Figure 3. Development of bone mineral density of total body and lumbar spine and of bone mineral apparent density of the lumbar spine of the intervention and control group.
Values are expressed as mean +/– standard error of the mean. Abbreviations: SDS = standard deviation score, BMD-TB = bone mineral density of the total body, BMD-LS = bone mineral density of the lumbar spine, BMAD = bone mineral apparent density.
Results of the intervention group: dotted line. Results of the control group: continuous line.

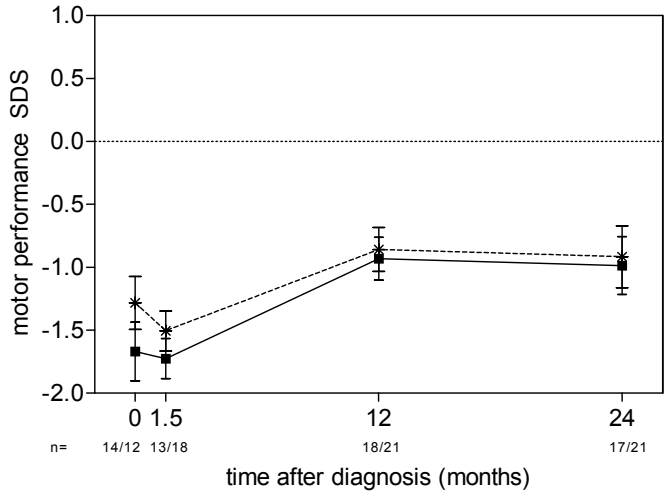

Figure 4 Development of motor performance scores of the intervention and the control group
Values are expressed as mean +/– standard error of the mean. Abbreviation: SDS = standard deviation score. Results of the intervention group: dotted line. Results of the control group: continuous line.

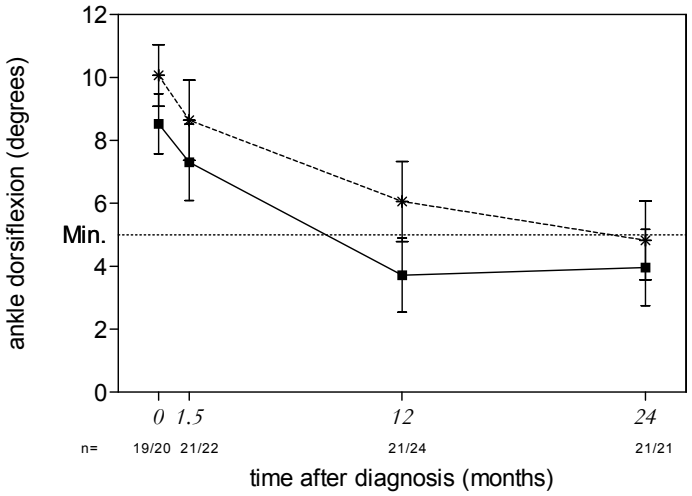

Figure 5 Development of passive ankle dorsiflexion of the intervention and the control group.
Values are expressed as mean +/– standard error of the mean. The horizontal dotted line indicates the lower limit of normal mobility. Results of the intervention group: dotted line. Results of the control group: continuous line.

with night splints to maintain ankle dorsiflexion mobility versus none in the control group (p=0.017).

Questionnaires

On completion of chemotherapy forty-two questionnaires were sent out: four were not returned leaving 38 available for analysis (19 in the intervention group, 19 controls). Ninety-five percent of all parents stated that they had appreciated the regular testing of motor performance and 84% of the parents in the intervention group appreciated the physiotherapy follow-up sessions. Adherence to the exercise programme in the intervention group varied considerably: 11% of the parents performed exercises daily with their child, 37% more than once a week, 16% once weekly, and the other 36% less than once a week. Eight children in the intervention group (42%) and seven children in the control group (37%) had been referred to a local physiotherapist (p=0.52).

DISCUSSION

The present study showed no difference in change of BMI, body fat, LBM, BMD, motor performance or passive ankle dorsiflexion between childhood ALL patients who received the exercise programme and those who received standard care. Therefore, we conclude that the exercise programme was not more beneficial than standard care to prevent motor problems and reduction in bone mass during ALL treatment. However, increased BMI and body-fat of ALL patients in the intervention group did recover faster than in the control group during the year after cessation of chemotherapy, which may point to an educational effect of the intervention programme.

The results maybe explained by several reasons. First, although the study was based on a reasonable concept, it may not be possible to maintain a continuous 2-year exercise programme during childhood ALL treatment. In our cohort, disappointing adherence to the exercise programme seems to underscore this and may be important for the lack of impact on the primary end points. Another explanation might be that the intervention and control group were not well matched. However, the similarity of the groups in age, gender, body weight and immunophenotype or risk-group stratification does not support this hypothesis.

Scarce information is available in the literature on the value of regular exercise to prevent reduction in BMD, fractures, altered body composition, and impairment of motor performance and passive ankle dorsiflexion during childhood ALL. The exercise programme aimed to diminish loss of BMD, muscle power and ankle mobility. According to the retrospectively filled out questionnaires the adherence to the exercise programme was low. In order to promote adherence we ensured that parents - and if possible children - were educated regarding the side effects of chemotherapy, difficulties that could arise and the need for exercises. A large number of exercises were provided to make variation possible and the exercises had been constructed to fit into children's normal daily activities.

The 6-weekly visits to the hospital-based paediatric physiotherapist always coincided with other appointments, but were missed regularly. Adherence to long-term programmes tends to be lower than to short-term interventions[28] and exercising throughout the treatment duration of 2 years may have been too long to remain motivated. Marchese et al. reported a positive effect of an exercise programme on active ankle dorsiflexion and knee extension strength. This may be explained by the fact that the intervention in their study lasted for four months only[22]. Whether this effect was maintained for the remainder of the treatment period is unknown. Progression of symptoms may have affected adherence negatively[29]. Another important consideration is that also 37% of the children in the control group had received physiotherapy, albeit locally. It may well be that children who develop motor problems are referred on time and that standard care is already adequate.

Finally, because parents met regularly in the outpatient department, some exchange of information about the exercise programme between parents of children in the intervention group and of the controls cannot be ruled out.

Several animal studies showed that mechanical loads are a crucial factor in the stimulation of bone acquisition[15,16]. In addition, studies in postmenopausal women[30] and in healthy children[17-20] have shown that exercise (including short-burst high-intensity activities) is an effective way to increase BMD. Therefore, we hypothesized that an exercise programme with short-burst high-intensity activities might impede the reduction in BMD in childhood ALL. However, the reduction of BMD was not prevented in our intervention group. Furthermore, we found no difference in number of patients with fractures between both groups.

Both BMI and body fat are in inverse relation to physical activity in healthy children[31]. We found no influence of the exercise programme on BMI or body fat during the treatment period of two years, but the increased body fat was lost faster after cessation of chemotherapy in the intervention group. We cannot rule out an educational effect of the intervention, which may have resulted in a lifestyle change.

Motor performance of children with ALL was already decreased at diagnosis and was still decreased at cessation of chemotherapy. It is known that although motor performance improves, it is still lower than in healthy peers two years after cessation of treatment[2]. Ankle mobility in the current study decreased during the first year of therapy and remained stable in the second year, but we do not know whether improvement occurred after cessation of chemotherapy. It is therefore recommended to monitor mobility and motor performance not only during treatment but also after therapy is completed.

In conclusion, effects of the exercise programme on body composition, BMD, motor performance and passive ankle dorsiflexion were not beneficial over standard care. Low adherence to the intervention programme or adequate standard care may have influenced the results. Increased BMI and body-fat of ALL patients in the intervention group

recovered faster after cessation of chemotherapy, which may be due to the educational effect of the intervention programme. Further studies are necessary to analyse physical activity intervention programmes of shorter duration in order to improve adherence.

REFERENCES

1 Wright MJ, Halton JM, Martin RF, Barr RD. Long-term gross motor performance following treatment for acute lymphoblastic leukemia. Med Pediatr Oncol. 1998;31: 86-90.

2 Hartman A, van den Bos C, Stijnen T, Pieters R. Decrease in motor performance in children with cancer is independent of cumulative vincristine dose. Cancer. 2006; 106:1395-1401.

3 Marchese V, Chiarello L, Lange B. Strength and functional mobility in children with acute lymphoblastic leukemia. Med Pediatr Oncol. 2003;40:230-232.

4 Hartman A, van den Bos C, Stijnen T, Pieters R. Decrease in peripheral muscle strength and ankle dorsiflexion as long-term side effects of treatment for childhood cancer. Pediatr Blood Cancer. 2008;50:833-837.

5 Salehian B, Kejriwal K. Glucocorticoid-induced muscle atrophy: mechanisms and therapeutic strategies. Endocr Pract. 1999;5:277-281.

6 Boot AM, van den Heuvel-Eibrink MM, Hahlen K, Krenning EP, de Muinck Keizer-Schrama SM. Bone mineral density in children with acute lymphoblastic leukaemia. Eur J Cancer. 1999;35:1693-1697.

7 Atkinson SA, Halton JM, Bradley C, Wu B, Barr RD. Bone and mineral abnormalities in childhood acute lymphoblastic leukemia: influence of disease, drugs and nutrition. Int J Cancer Suppl. 1998;11:35-39.

8 Van der Sluis IM, van den Heuvel-Eibrink MM, Hahlen K, Krenning EP, de Muinck Keizer-Schrama SM. Altered bone mineral density and body composition, and increased fracture risk in childhood acute lymphoblastic leukemia. J Pediatr. 2002; 141:204-210.

9 van der Sluis IM, van den Heuvel-Eibrink MM, Hahlen K, Krenning EP, de Muinck Keizer-Schrama SM. Bone mineral density, body composition, and height in long-term survivors of acute lymphoblastic leukemia in childhood. Med Pediatr Oncol. 2000;35:415-420.

10 van Beek RD, de Muinck Keizer-Schrama SM, Hakvoort-Cammel FG, et al. No difference between prednisolone and dexamethasone treatment in bone mineral density and growth in long term survivors of childhood acute lymphoblastic leukemia. Pediatr Blood Cancer. 2006;46:88-93.

11 Brennan BM, Mughal Z, Roberts SA, et al. Bone mineral density in childhood survivors of acute lymphoblastic leukemia treated without cranial irradiation. J Clin Endocrinol Metab. 2005;90:689-694.

12 Kaste SC, Rai SN, Fleming K, et al. Changes in bone mineral density in survivors of childhood acute lymphoblastic leukemia. Pediatr Blood Cancer. 2006;46:77-87.

13 Warner JT, Evans WD, Webb DK, Bell W, Gregory JW. Relative osteopenia after treatment for acute lymphoblastic leukemia. Pediatr Res. 1999;45:544-551.
14 Kadan-Lottick N, Marshall JA, Baron AE, Krebs NF, Hambidge KM, Albano E. Normal bone mineral density after treatment for childhood acute lymphoblastic leukemia diagnosed between 1991 and 1998. J Pediatr. 2001;138:898-904.
15 Rubin CT, Lanyon LE. Regulation of bone formation by applied dynamic loads. J Bone Joint Surg Am. 1984;66:397-402.
16 Lanyon LE. Control of bone architecture by functional load bearing. J Bone Miner Res. 1992;7 Suppl 2:S369-375.
17 Jones G, Dwyer T. Bone mass in prepubertal children: gender differences and the role of physical activity and sunlight exposure. J Clin Endocrinol Metab. 1998;83: 4274-4279.
18 Lehtonen-Veromaa M, Mottonen T, Irjala K, Nuotio I, Leino A, Viikari J. A 1-year prospective study on the relationship between physical activity, markers of bone metabolism, and bone acquisition in peripubertal girls. J Clin Endocrinol Metab. 2000;85:3726-3732.
19 Fuchs RK, Bauer JJ, Snow CM. Jumping improves hip and lumbar spine bone mass in prepubescent children: a randomized controlled trial. J Bone Miner Res. 2001;16: 148-156.
20 Kemper HC, Twisk JW, van Mechelen W, Post GB, Roos JC, Lips P. A fifteen-year longitudinal study in young adults on the relation of physical activity and fitness with the development of the bone mass: The Amsterdam Growth And Health Longitudinal Study. Bone. 2000;27:847-853.
21 Wright MJ, Hanna SE, Halton JM, Barr RD. Maintenance of ankle range of motion in children treated for acute lymphoblastic leukeamia. Ped Physiother. 2003;15: 146-152.
22 Marchese VG, Chiarello LA, Lange BJ. Effects of physical therapy intervention for children with acute lymphoblastic leukemia. Pediatr Blood Cancer. 2004;42:127-133.
23 Veerman AJ, Hahlen K, Kamps WA, et al. High cure rate with a moderately intensive treatment regimen in non-high-risk childhood acute lymphoblastic leukemia. Results of protocol ALL VI from the Dutch Childhood Leukemia Study Group. J Clin Oncol. 1996;14:911-918.
24 van der Sluis IM, de Ridder MA, Boot AM, Krenning EP, de Muinck Keizer-Schrama SM. Reference data for bone density and body composition measured with dual energy x ray absorptiometry in white children and young adults. Arch Dis Child. 2002;87:341-347; discussion 341-347.
25 Fredriks AM, van Buuren S, Burgmeijer RJ, et al. Continuing positive secular growth change in The Netherlands 1955-1997. Pediatr Res. 2000;47:316-323.

26 Henderson S, Sugden D. Movement Assessment Battery for Children. Sidcup, England: The Psychological Corporation; 1992.
27 Bayley N. Manual for the Bayley Scales of Infant Development, 2nd ed. San Antonio: The Psychological Corporation; 1993.
28 Sackett D, Snow J. The magnitude of compliance and noncompliance. In: Haynes R, Taylor D, Sackett D, eds. Compliance in health care. Baltimore: Johns Hopkins Press; 1979:11-22.
29 Prasad SA, Cerny FJ. Factors that influence adherence to exercise and their effectiveness: application to cystic fibrosis. Pediatr Pulmonol. 2002;34:66-72.
30 Wolff I, van Croonenborg JJ, Kemper HC, Kostense PJ, Twisk JW. The effect of exercise training programs on bone mass: a meta-analysis of published controlled trials in pre- and postmenopausal women. Osteoporos Int. 1999;9:1-12.
31 White J, Flohr JA, Winter SS, Vener J, Feinauer LR, Ransdell LB. Potential benefits of physical activity for children with acute lymphoblastic leukaemia. Pediatr Rehabil. 2005;8:53-58.

CHAPTER 8

SUMMARY

SUMMARY

The survival rate of childhood cancer has improved tremendously over the last decennia. This is mainly due to the introduction of combination chemotherapy. With the improvement in survival, the attention for side effects has increased. One of the drugs renowned for it side effects is vincristine (VCR). Vincristine has proven its effectiveness in the treatment of acute lymphoblastic leukemia (ALL), Wilms' tumor (WT), B-non Hodgkin lymphoma (B-NHL) and malignant mesenchymal tumors (MMT). However, VCR is almost invariably neurotoxic. The use of VCR causes a polyneuropathy with peripheral muscle weakness in upper and lower limbs and sensory disturbances in a 'glove and stocking' distribution. Motor performance of children receiving VCR containing chemotherapy is likely to be adversely affected by development of the above symptoms. The main aim of this thesis was to study the long-term effects of VCR containing chemotherapy on motor performance and handwriting in children, to investigate underlying impairment (peripheral muscle strength and joint mobility) and other contributing factors (self-perceived motor competence) and to determine whether an intervention programme may diminish VCR induced side effects.

In Chapter 2 we investigated motor performance level in children aged 4 to12 years who had completed VCR containing chemotherapy for at least one year. They had been treated for ALL, WT, B-NHL or MMT. We found that motor performance levels varied greatly and were impaired in comparison to healthy peers. Surprisingly, there was no relationship between motor performance levels and cumulative dose of VCR, number of VCR administrations, or elapsed time since completion of chemotherapy. Other drugs that may affect motor performance are corticosteroids as they can cause myopathy. The effect of corticosteroids was therefore investigated. No association between cumulative dose of corticosteroids and motor performance was detected and corticosteroids were excluded as a determining factor in impairment of motor performance.

In Chapter 3 we examined the often-heard comments of parents and teachers regarding deteriorating hand writing skills of children treated with VCR. A standardized writing test was administered to children who participated in the motor performance study as described in Chapter 2 and attended group 4 or 5 of regular education. Both writing speed and quality of handwriting (i.e. legibility) were measured and compared to age and gender matched healthy controls. An investigator who was blinded to whether the writing was produced by a case or a control assessed all handwriting samples. The data showed that there was no difference in writing speed or quality of handwriting between children who had received chemotherapy and healthy peers. Cumulative VCR dose,

number of administrations and time since completion of VCR treatment did not affect handwriting skills.

In Chapter 4 a study on peripheral muscle strength and passive ankle mobility in children treated with VCR is reported. In the children who participated in the motor performance study and had completed chemotherapy at least one year previously, we measured muscle strength of dorsiflexors of hand and feet and also full grip and pinch grip strength, with a hand held dynamometer. Children attending a local school for primary education were invited to participate as controls.
Weakness of foot dorsiflexors produces an altered gait pattern because the ankle is not put through its full range of motion. Children with foot drop are at risk for developing a contracture of the ankle in plantigrade position. Therefore we also investigated passive ankle dorsiflexion mobility. Results showed that strength of the foot dorsiflexors was reduced compared to healthy peers, as was passive ankle dorsiflexion mobility. In the upper limb pinch grip was reduced bilaterally and wrist dorsiflexors of the non-dominant side were also weakened. The loss of muscle strength or ankle mobility did not fully explain the impaired motor performance described in Chapter 2.

In Chapter 5 we investigated children's perceived motor competence. We examined how children who had been treated for cancer rated their motor performance in comparison to healthy peers and whether they rated themselves reliably. Children aged 8 to 12 years from the cohort in the motor performance study described in Chapter 2, completed a standardised questionnaire on perceived motor competence. Survivors appeared satisfied with their motor performance and did not rate themselves differently in comparison to healthy children. However, if we took their actual motor performance scores into consideration they did have a tendency to overrate themselves. Also, the percentage of children who considered motor performance important was noticeably lower than in the healthy population.

As mentioned, variation in motor performance level was not related to cumulative VCR dose. This raised the question whether the underlying mechanism could be genetic variation in genes involved in VCR metabolising genes or VCR toxicity related genes. In Chapter 6 we further explored this hypothesis. Vincristine belongs to the group of vinca-alkaloid drugs metabolised by the cytochrome P450 system in the liver. Isoforms of this system expressed in humans are *CYP3A4* and *CYP3A5*. Polymorphisms of *CYP3A4* exist but are rare. In contrast, *CYP3A5* polymorphisms are relatively common in the Caucasian population. The multi drug resistance (*MDR-1*) gene is also involved in VCR pharmacokinetics. Genetic variation in the microtubule-associated protein tau (*MAPT*)

gene may influence VCR effects at tissue level. *MAPT* promotes the assembly and stabilisation of microtubules, which form a target for VCR.
We analysed whether genetic variation of *CYP3A5*, *MDR-1* and *MAPT* were related to motor performance level of children with ALL who had been treated with the ALL-9 protocol of the Dutch Childhood Oncology Group. The data did not provide any evidence that a link existed between polymorphisms in the aforementioned genes and impaired motor performance. However, numbers were relatively small – 34 samples were analysed – and not every variety in expression of *CYP3A5* was present in our cohort. The small number also limited the power of studying the effect of combinations of polymorphisms in different genes.

In Chapter 7 we report on a randomised controlled trial examining the effect of an exercise programme during treatment for ALL on impaired motor performance, decrease in passive ankle dorsiflexion and bone mineral density (BMD). Children diagnosed with ALL were randomised into a group receiving intervention starting at diagnosis or into a control group receiving standard care, which includes referral to a local pediatric physiotherapist if considered necessary by the treating physician. The intervention started with a pediatric physiotherapist explaining the potential side effects of chemotherapy in relation to motor performance. In addition an exercise programme was introduced, consisting of exercises to maintain hand and leg function, stretching exercises to maintain ankle dorsiflexion mobility and short-burst high-intensity exercises (e.g. jumping) to prevent reduction in BMD. Throughout the treatment for ALL children were seen at six weekly intervals to monitor gross motor skills and ankle mobility and also to adjust the exercise programme if necessary. BMD, motor performance and ankle mobility were outcome parameters. Children were measured at diagnosis, after induction therapy (6 weeks after diagnosis) half way during treatment (54 weeks after diagnosis), at completion of chemotherapy (109 weeks after diagnosis) and one year after completion of chemotherapy. The investigator was blinded to the randomisation.
The study showed no difference in change of motor performance, passive ankle dorsiflexion and BMD between ALL patients who received the exercise programme and those who received standard care. However, adherence to the exercise programme - reported by parents - was low and may have affected the results. We concluded that the exercise programme did not prevent motor problems and reduction in bone mass during ALL treatment.

CHAPTER 9

DISCUSSION AND FUTURE PROSPECTS

DISCUSSION AND FUTURE PROSPECTS

The main aim of this thesis was to study the long-term effects of vincristine (VCR) containing chemotherapy on motor performance and handwriting in children, to investigate underlying impairment (peripheral muscle strength and joint mobility) and other contributing factors (self-perceived motor competence) and to determine whether a two-year exercise programme as intervention may have a positive effect on outcome. In this chapter the results and future perspectives are discussed.

Motor performance

VCR induced polyneuropathy is a well known side effect, which sometimes leads to dose adjustment or even omitting of the drug [1]. The occurrence of motor problems found in children treated for ALL has been attributed to the use of VCR [2-7]. The functional outcome parameters used in the published series varied, making it difficult to compare results. Furthermore, no results on children treated with VCR for malignancies other than ALL were available and therefore none of the studies gave insight into motor performance of children who had been treated with relatively small cumulative VCR doses.

This thesis made clear that motor performance of children aged 4-12 years who had been treated with VCR-containing chemotherapy for ALL, WT, B-NHL and MMT was still impaired three years after completion of chemotherapy. This implies that the motor performance of these children does not recover fully and that motor problems do not only occur in children treated for ALL but also in other patient groups.

It was hypothesised that motor performance would depend on cumulative VCR dose and that children treated with the highest cumulative dose (ALL protocol with VCR/steroid pulses during maintenance therapy) would show poorer results, but our data did not support this. There was no difference in motor performance between children with ALL who had received pulses of VCR and steroids during maintenance therapy and those who had not. Similar results on the effect of VCR/steroid pulses were found by Reinders-Messelink et al [5] who tested 18 survivors of ALL and also found that the use of pulses during maintenance treatment did not affect motor performance. The use of steroids may also have an adverse effect on motor performance as known side effects of these drugs are myopathy [8], osteoporosis [9] and avascular necrosis (AVN) [10]. Corticosteroids – prednisone and dexamethasone - are used in the treatment of ALL and B-NHL but not in the treatment of WT and MMT. However, no difference was found in motor performance scores between children treated with or without steroids. Differences in motor performance could therefore not be explained by the use of steroids.

As impaired performance was found in all patient groups and could not be related to cumulative dose of VCR or steroids, nor to follow up time or age at testing, interindividual differences in sensitivity to VCR was thought to be a possible underlying mechanism.

Future prospects

Children in our cohort were aged 4-12 years at the time of the study and therefore relatively young when receiving chemotherapy. However, AVN as a side effect of treatment with steroids tends to be most profound in adolescents [11,12]. AVN may result in joint swelling, pain, limited range of motion[13] and has been shown to affect functional mobility[14]. Up to 38% of children receiving treatment for ALL have been reported to develop AVN, albeit often without
symptoms [10,15]. Further studies that include older children are needed to investigate the impact of AVN on motor performance.

Although chemotherapy in our study had been completed at least one year before, a number of children treated with VCR still had complaints of pain and cramps in the lower limbs when walking a prolonged distance (data not reported). Their capacity for long-duration activities may be affected. However, this is not measured by the movement-ABC as its motor tasks are short-duration activities. It would therefore need to be investigated separately. Peak oxygen uptake and thus fitness level was shown to be reduced in studies of ALL survivors and may be related to myocardial damage or to muscle atrophy [16]. Future studies should explore these issues, because a reduced fitness level is known to have an adverse effect on quality of life[17].

Handwriting ability

Handwriting is a motor task and could therefore be affected by VCR polyneuropathy. Parents and teachers of children treated with VCR often report that the handwriting is difficult to read, untidy or lacking consistency [18,19]. We investigated Handwriting of children attending group 4 or 5 of regular education who had completed VCR treatment more than three years before. There appeared to be no difference in writing speed or in quality (i.e. legibility) of handwriting compared to healthy peers. These results conflicted with a study using the same BHK writing test [20], which also showed that writing speed did not differ from matched controls, but that quality of writing was significantly lower [5]. However, those results may have been affected by the fact that children were asked to write as fast as possible whereas instructions of the BHK stipulate to write at normal speed. In addition, children had been included who were older than the BHK guidelines specify and the investigator was not blinded to whether handwriting had been produced by a case or by a control.

The results of our study raise the question why handwriting complaints are reported when handwriting was found to be no different from healthy peers. Reinders-Messelink reported that children who had been treated for ALL increased their pen-to-paper pressure when performing a drawing task, probably in order to compensate for VCR-related sensory loss [21]. A significant decrease in amplitude of sensory evoked potentials of the median nerve, suggesting axonal injury, was found in children with ALL two years after the last

VCR injection [22]. If neurological damage persists in the longer term it may explain the handwriting difficulties reported by children treated with VCR. Although children who have been treated with VCR apparently succeed in producing the same handwriting at the same speed as healthy children, they may require more effort to do so.

Future prospects

The data showed that handwriting in this cohort did not differ from healthy peers. However, as in the previous study, these children received chemotherapy at an early age. Whether children who received VCR when they were already skilled writers, experience problems is not known and warrants further investigation. The nature of handwriting difficulties in children treated with VCR has not yet been documented. Patients treated with VCR complain of muscle cramp in upper and lower limbs [23]. Whether writer's cramp also occurs in this group is not known.

Muscle strength

The research in this thesis aimed to investigate the effect of chemotherapy on motor performance but also to understand possible underlying mechanisms of impairment. Reduction of muscle strength is a known side effect of VCR polyneuropathy [1] and likely to adversely affect motor performance. Muscle strength had only been investigated in children with ALL and predominantly through performance on motor tasks [4,6]. In one study using standardised measurements with a dynamometer chair, reduced muscle strength in upper and lower limbs in survivors of ALL was found [24]. However, the subjects were adolescents and adults whose height was significantly shorter than the controls, which may have contributed to the reduction in strength. Using a hand held dynamometer has now become a wide spread method for assessment of muscle strength. Marchese et al found reduced strength of knee extensors and ankle dorsiflexors in eight children during treatment for ALL [25]. Data on long-term muscle strength had not been reported.

We found evidence for long-term reduced peripheral muscle strength in lower and upper limbs in children treated for ALL, B-NHL, WT and MMT. No relationship between impaired strength and cumulative VCR dose or steroid was found. Long-term axonal damage due to use of VCR seems to be the underlying cause. The lack of relationship between level of impairment and cumulative VCR dose supports the earlier mentioned hypothesis of variety in sensitivity to VCR on the basis of genetic variation.

Although muscle strength was reduced in upper as well as lower limbs, only pinch grip strength could be related to impaired motor performance (this thesis). When testing strength with a hand held dynamometer maximum generated force is measured. However, maximum force is not needed in the motor tasks of the movement-ABC, which may explain the lack of further relationships. Loss of muscle strength may prove to have a greater impact on long-duration activities, such as going for a walk or running.

Passive dorsiflexion

Due to the development of VCR polyneuropathy children become unable to adequately lift their feet whilst walking. Heel strike is lost and a high stepping gait may even develop. This altered gait pattern increases the risk for a plantigrade contracture of the ankle. Mobility of the ankle joint is an important factor in motor performance as it affects walking, running and jumping. Passive ankle mobility appeared to be significantly less on the dominant and non-dominant side in cancer survivors treated with VCR more than three years after completion of chemotherapy compared to healthy peers (this thesis). Similar results were found in another study of ALL survivors [7]. Using < 5° of passive ankle dorsiflexion on either side as the criterion to define impairment [26], one third of the children in our cohort were impaired, indicating that the problem is considerable. Although impaired ankle mobility did not affect to motor performance score (this thesis) it may affect long-duration activities. Once a contracture has developed, regaining dorsiflexion mobility through exercise and stretching is difficult [27]. Serial plaster casting or surgical release are other options. However, both are rather drastic measures and rarely applied. Prevention would appear to be the most useful strategy and was investigated in another study, which will be discussed later in this chapter.

Perceived motor competence

Children with physical differences are at risk for negative social perceptions and loss of self esteem [28,29]. Athletic competence contributes to positive self-perception in children [30]. Noll et al demonstrated lower satisfaction with athletic competence in children receiving chemotherapy for various childhood cancers matched to healthy class room peers [31]. However, children were still receiving treatment at the time of the study and their lower satisfaction could be a reflection of low energy and chronic fatigue, which are common symptoms during chemotherapy. Poorer self-perception of adequacy in physical activity was found in children and adolescents five years after completing treatment for ALL [32]. Neither study investigating self-perceived athletic competence reported on the relationship with actual motor performance level. This was analysed in the present thesis and no difference was found between perceived motor competence of children who had completed VCR containing chemotherapy and reference values, but their actual motor performance scores were significantly lower. There was a weak but significant correlation between perceived competence and actual motor performance scores. Interestingly, a large majority of the children 'overrated' themselves; they perceived themselves to function more adequately than their motor performance scores indicated. Norm values of perceived motor competence exist for Dutch children aged 8-12, but the relationship to their actual motor performance is not known. Therefore it is unknown whether healthy children also have a tendency to overrate. A difference with the healthy population

was the lower level of importance survivors attributed to motor performance (this thesis). Underreporting of feelings has been described in children with
cancer [33]. This was explained either by use of denial or by a coping style avoiding conflict/feelings [34]. Attributing a lower level of importance to motor performance may be a coping strategy in survivors of childhood cancer.

Future prospects

Investigating self-perceived motor competence in relation to actual motor performance is needed in order to establish whether children treated for cancer are truly satisfied with their motor performance, are in denial or displaying a coping strategy.

Intervention

The effect of a two-year exercise programme was investigated in a randomised study in children with ALL. Outcome measures were bone mineral density, body composition, motor performance and passive ankle mobility, of which only the latter two will be discussed further. On completion of chemotherapy after two years, no difference in motor performance or passive ankle mobility between the intervention and control group could be demonstrated.

The lack of difference in motor performance between the intervention and control group is in accordance with the results of Marchese et al. A randomised study in children on maintenance therapy for ALL showed that motor performance measured by time up and down stairs and
9 minute run-walk test had not changed compared to the control group after a four month period of intervention [35]. Passive ankle mobility was not an outcome measure in this study; active ankle dorsiflexion improved in their intervention group. No deterioration in passive ankle mobility during treatment for ALL was shown by Wright et al [36] whereas in our cohort passive ankle mobility decreased significantly. Maintenance of passive ankle mobility as achieved in the study by Wright et al may be explained by the fact that their intervention was solely targeted at ankle mobility. Furthermore, only children whose passive ankle mobility decreased to < 10 degrees were required to perform the exercises. Both factors may have improved compliance.

In our study only 11% of the children in the intervention group had exercised daily as requested. Moreover, 36% had exercised less than once a week. Lack of compliance may have had an adverse effect on the outcome. Marchese et al also reported that compliance was lower than expected: children had exercised three times a week instead of five. However, their study showed positive results, which may be due to the fact that the intervention lasted for four months only and children had been involved in designing their own programme. Whether the results could be maintained until completion of chemotherapy was not reported [35].

Future prospects

Redesigning our exercise programme is supported by the positive results reported in the two aforementioned studies. Simplifying the exercises and shortening the duration of the intervention could be considered. Furthermore, commencing stretching exercises only when deterioration in ankle mobility has started to occur, may improve compliance. Starting exercises to improve general condition after completion of the two-year treatment period may prove to be more successful than during chemotherapy when repeated medication tends to impede progress.

Genetic variation

Impaired motor performance was found in children treated with VCR containing chemotherapy and was not related to cumulative VCR, cumulative steroid dose, follow-up time or age at testing. Furthermore, motor performance of children treated with identical protocols varied highly. Variation in sensitivity to VCR due to genetic variation was thought to be the possible underlying mechanism. Vincristine belongs to the group of vinca-alkaloid drugs metabolised by the cytochrome P450 system in the liver. Isoforms of this system expressed in humans are *CYP3A4* and *CYP3A5*. Polymorphisms of *CYP3A4* exist but are rare. In contrast, *CYP3A5* polymorphisms are relatively common in the Caucasian population and have been linked to the pharmacokinetics of VCR[37]. A recent study found that Afro-Americans who commonly express CYP3A5 experience significantly less VCR-associated neurotoxicity than Caucasians who commonly do not express functional CYP3A5[38]. The multi drug resistance (*MDR-1*) gene is also involved in VCR pharmacokinetics[39,40]. Genetic variation in the microtubule-associated protein tau (*MAPT*) gene may influence VCR effects at tissue level as *MAPT* promotes the assembly and stabilisation of microtubules, which form a target for VCR. It was hypothesised that variation in motor performance in children treated with VCR, was related to the presence of polymorphisms in the aforementioned genes. In children who had completed treatment with the ALL-9 protocol two years before, motor performance level appeared not to be related to the presence of these polymorphisms (this thesis). However, as the number of cases studied was relatively small the power of the study to detect single polymorphisms or combinations of polymorphisms as factors contributing to motor performance disturbances was limited.

An alternative explanation for the variety in motor performance may be gene mutations leading to an increased tendency towards hereditary neuropathies. A patient with Wilms' tumor had been reported with a strong adverse response to VCR that was due to underlying but asymptomatic Charcot-Marie-Tooth (CMT) disease, type 1A [41]. In contrast, a recent report described uneventful administration of VCR to a child with proven CMT type 1X [42]. In the majority of cases however, CMT is related to a duplication of the

17p11.2-12 region, known as type 1A [43]. Whether there is a link between this duplication and VCR related problems in children treated with chemotherapy is not yet known.

Future prospects

Large studies would be needed to analyse such genetic variations as a multifactorial cause of differences in motor performance. The relationship between duplication of the 17p11.2-12 region and adverse responses to VCR warrants specific further investigation.

General conclusions and recommendations

The research described in this thesis showed that impaired motor performance in children receiving VCR containing chemotherapy does not fully recover. Furthermore, muscle strength and passive ankle dorsiflexion were still found to be impaired a number of years after completion of chemotherapy. Although childhood cancer survivors rate their motor performance similarly to healthy children this may be a coping strategy.

Regular monitoring of motor performance would be beneficial in identifying children who develop severe disturbances during therapy and who have not made a full recovery after completion of chemotherapy. Intervention to prevent impairment did not prove more successful than standard care, but compliance was low. Prevention of reduction in ankle mobility seems a realistic aim and adjusting the exercise programme may prove to be effective. Starting exercises after chemotherapy treatment has been completed may be more successful in improving motor performance.

REFERENCES

1 Gidding CE, Kellie SJ, Kamps WA, et al. Vincristine revisited. Crit Rev Oncol Hematol 1999; 29:267-287

2 Eiser C, Lansdown R. Retrospective study of intellectual development in children treated for acute lymphoblastic leukaemia. Arch Dis Child 1977; 52:525-529.

3 Harten G, Stephani U, Langermann H-J, et al. Slight impairment of psychomotor skills in children after treatment of acute lymphoblastic leukemia. Eur J Pediatr 1984; 142: 189-197

4 Vainionpaa L. Clinical neurological findings of children with acute lymphoblastic leukaemia at diagnosis and during treatment. Eur J Pediatr 1993; 152:115-119.

5 Reinders-Messelink H, Schoemaker M, Goeken L, et al. Handwriting and fine motor problems after treatment for acute lymphoblastic leukemia. In: Simner ML, Leedham CG, Thomassen AJWM, eds. Handwriting and Drawing Research: Basic and Applied Issues: IOS Press, 1996; 215-225

6 Wright MJ, Halton JM, Martin RF, et al. Long-term gross motor performance following treatment for acute lymphoblastic leukemia. Med Pediatr Oncol 1998; 31:86-90.

7 Wright MJ, Halton JM, Barr RD. Limitation of ankle range of motion in survivors of acute lymphoblastic leukemia: a cross-sectional study. Med Pediatr Oncol 1999; 32:279-282.

8 Salehian B, Kejriwal K. Glucocorticoid-induced muscle atrophy: mechanisms and therapeutic strategies. Endocr Pract 1999; 5:277-281

9 Kamps WA, Bokkerink JPM, Hakvoort-Cammel FGAJ, et al. Results of the DCLSG-study ALL8 (1991-1997): BFM oriented treatment without cranial irradiation (CI) and comparing conventional oral and high-doses intravenous 6-mercaptopurine. Med Pediatr Oncol 1999; 33:O-109 (abstract)

10 Wei SY, Esmail AN, Bunin N, et al. Avascular necrosis in children with acute lymphoblastic leukemia. J Pediatr Orthop 2000; 20:331-335

11 Arico M, Boccalatte MF, Silvestri D, et al. Osteonecrosis: An emerging complication of intensive chemotherapy for childhood acute lymphoblastic leukemia. Haematologica 2003; 88:747-753

12 Nachman JB. Adolescents with acute lymphoblastic leukemia: a new "age". Rev Clin Exp Hematol 2003; 7:261-269

13 Pavelka K. Osteonecrosis. Baillieres Best Pract Res Clin Rheumatol 2000; 14:399-414

14 Marchese VG, Connolly BH, Able C, et al. Relationships among severity of osteonecrosis, pain, range of motion, and functional mobility in children, adolescents, and young adults with acute lymphoblastic leukemia. Phys Ther 2008; 88:341-350

15 Ojala AE, Lanning FP, Paakko E, et al. Osteonecrosis in children treated for acute lymphoblastic leukemia: a magnetic resonance imaging study after treatment. Med Pediatr Oncol 1997; 29:260-265
16 Van Brussel M, Takken T, Lucia A, et al. Is physical fitness decreased in survivors of childhood leukemia? A systematic review. Leukemia 2005; 19:13-17
17 Foster C, Cadwell K, Crenshaw B, et al. Physical activity and exercise training prescriptions for patients. Cardiol Clin 2001; 19:447-457
18 Cousens P. Specific learning problems among children treated for acute lymphoblastic leukemia. J Ped Hematology/Oncology 1997; 4:353-362
19 Reinders-Messelink H. Motor performance of children treated for acute lymphoblastic leukemia. Medical Faculty. Groningen, the Netherlands: University of Groningen, 2000; 93
20 Hamstra-Bletz L, De Bie J, Den Brinker BPLM. Beknopte beoordelingsmethode voor kinderhandschriften (A brief evaluation method for for children's handwriting). Lisse: Swets & Zeitlinger, 1987
21 Reinders-Messelink HA, Schoemaker MM, Snijders TA, et al. Analysis of handwriting of children during treatment for acute lymphoblastic leukemia. Med Pediatr Oncol 2001; 37:393-399.
22 Harila-Saari AH, Vainionpaa LK, Kovala TT, et al. Nerve lesions after therapy for childhood acute lymphoblastic leukemia. Cancer 1998; 82:200-207.
23 Haim N, Barron SA, Robinson E. Muscle cramps associated with vincristine therapy. Acta Oncol 1991; 30:707-711
24 Hovi L, Era P, Rautonen J, et al. Impaired muscle strength in female adolescents and young adults surviving leukemia in childhood. Cancer 1993; 72:276-281
25 Marchese V, Chiarello L, Lange B. Strength and functional mobility in children with acute lymphoblastic leukemia. Med Pediatr Oncol 2003; 40:230-232
26 Whittle MW. Gait analysis: an introduction. Oxford: Butterworth Heinemann, 2002
27 Moseley AM, Herbert RD, Nightingale EJ, et al. Passive stretching does not enhance outcomes in patients with plantarflexion contracture after cast immobilization for ankle fracture: a randomized controlled trial. Arch Phys Med Rehabil 2005; 86: 1118-1126
28 Varni JW, Rubenfeld LA, Talbot D, et al. Determinants of self-esteem in children with congenital/acquired limb deficiencies. J Dev Behav Pediatr 1989; 10:13-16
29 Varni JW, Katz ER, Colegrove R, Jr., et al. The impact of social skills training on the adjustment of children with newly diagnosed cancer. J Pediatr Psychol 1993; 18: 751-767
30 Harter S. Manual for the self- perception profile for children. Denver: University of Denver, 1985

31 Noll RB, Gartstein MA, Vannatta K, et al. Social, emotional, and behavioral functioning of children with cancer. Pediatrics 1999; 103:71-78
32 Wright MJ, Galea V, Barr RD. Self-perceptions of physical activity in survivors of acute lymphoblastic leukemia in childhood. Ped Exc Science 2003; 15:191-201
33 Canning EH, Canning RD, Boyce WT. Depressive symptoms and adaptive style in children with cancer. J Am Acad Child Adolesc Psychiatry 1992; 31:1120-1124
34 Phipps S, Fairclough D, Mulhern RK. Avoidant coping in children with cancer. J Pediatr Psychol 1995; 20:217-232
35 Marchese VG, Chiarello LA, Lange BJ. Effects of physical therapy intervention for children with acute lymphoblastic leukemia. Pediatr Blood Cancer 2004; 42:127-133.
36 Wright MJ, Hanna SE, Halton JM, et al. Maintenance of ankle range of motion in children treated for acute lymphoblastic leukeamia. Ped Physiother 2003; 15:146-152
37 Dennison JB, Jones DR, Renbarger JL, et al. Effect of CYP3A5 expression on vincristine metabolism with human liver microsomes. J Pharmacol Exp Ther 2007; 321: 553-563
38 Renbarger JL, McCammack KC, Rouse CE, et al. Effect of race on vincristine-associated neurotoxicity in pediatric acute lymphoblastic leukemia patients. Pediatr Blood Cancer 2008; 50:769-771
39 Watanabe T, Miyauchi S, Sawada Y, et al. Kinetic analysis of hepatobiliary transport of vincristine in perfused rat liver. Possible roles of P-glycoprotein in biliary excretion of vincristine. J Hepatol 1992; 16:77-88
40 Song S, Suzuki H, Kawai R, et al. Effect of PSC 833, a P-glycoprotein modulator, on the disposition of vincristine and digoxin in rats. Drug Metab Dispos 1999; 27: 689-694
41 Schiavetti A, Frascarelli M, Uccini S, et al. Vincristine neuropathy: neurophysiological and genetic studies in a case of Wilms' tumor. Pediatr Blood Cancer 2004; 43: 606-609
42 Ajitsaria R, Reilly M, Anderson J. Uneventful administration of vincristine in Charcot-Marie-Tooth disease type 1X. Pediatr Blood Cancer 2008; 50:874-876
43 Timmerman V, Nelis E, Van Hul W, et al. The peripheral myelin protein gene PMP-22 is contained within the Charcot-Marie-Tooth disease type 1A duplication. Nat Genet 1992; 1:171-175

CHAPTER 10

NEDERLANDSE SAMENVATTING

SAMENVATTING

De overlevingskansen van maligniteiten op de kinderleeftijd zijn de laatste decennia sterk verbeterd. Dit is met name te danken aan de introductie van chemotherapie waarbij diverse cytostatica in combinatie worden toegediend. Nu er een betere kans bestaat op overleven is de aandacht voor bijwerkingen van de chemotherapie toegenomen. Een van de cytostatica welke bekend is om zijn bijwerking is vincristine (VCR). Vincristine is een effectief middel gebleken in de behandeling van acute lymfoblastische leukemie (ALL), Wilms' tumor (WT), B-non Hodgkin lymfoom (B-NHL) en maligne mesenchymale tumoren (MMT). Echter, bij behandeling met VCR treedt vaak neurotoxiciteit op. Gebruik van VCR veroorzaakt frequent een polyneuropathie, gekenmerkt door perifere krachtsvermindering in bovenste en onderste extremiteiten en sensorische uitval in een 'sok en handschoen' distributie. Chemotherapie die VCR bevat, heeft daarom een mogelijk negatief effect op de motorische ontwikkeling van kinderen.
De doelen van dit proefschrift waren enerzijds om de lange termijn effecten van VCR bevattende chemotherapie zowel op het motorisch prestatieniveau als op het handschrift van kinderen te bestuderen. Anderzijds om onderliggende oorzaken zoals vermindering van spierkracht en gewrichtsmobiliteit en verdere factoren zoals zelf-waargenomen motorische competentie te onderzoeken. Tot slot om vast te stellen of een interventieprogramma de motorische prestaties en enkelmobiliteit zou kunnen verminderen.

In Hoofdstuk 2 onderzochten wij het motorisch prestatieniveau van kinderen in de leeftijd van 4 tot en met 12 jaar, die waren behandeld voor ALL, WT, B-NHL of MMT. De chemotherapeutische behandeling was tenminste één jaar voor aanvang van de studie afgerond. Het motorische prestatieniveau varieerde sterk en was verminderd ten opzichte van de Nederlandse normwaarden. Een verassende bevinding was het ontbreken van een relatie tussen motorisch prestatieniveau en cumulatieve dosis VCR, aantal VCR giften, of de tijd verstreken sinds het afronden van de chemotherapie. Vervolgens werd daarom ook het effect van corticosteroïden, die gebruikt worden bij de behandeling van ALL en B-NHL en een myopathie kunnen veroorzaken, onderzocht. Er werd echter geen associatie gevonden tussen cumulatieve dosis corticosteroïden en motorisch prestatieniveau.

In Hoofdstuk 3 inventariseerden wij de regelmatig gehoorde klacht van ouders en onderwijzers over een verslechterd handschrift bij kinderen die behandeld werden met VCR. Bij de kinderen die in groep 4 of 5 van het regulier onderwijs zaten en die hadden deelgenomen aan de motorische studie beschreven in Hoofdstuk 2 werd een gestandaardiseerde schrijftest afgenomen. De snelheid en de kwaliteit ofwel de leesbaarheid van het handschrift werden gemeten en vergeleken met die van het handschrift van op leeftijd en geslacht gematchte controle kinderen.

Alle handschriften werden beoordeeld door dezelfde onderzoeker. Het was aan de onderzoeker niet bekend of het handschrift van een patiënt was, of van een controle. Er bleek geen verschil te zijn in schrijfsnelheid of kwaliteit van het handschrift tussen de patiënten en de controles. Cumulatieve VCR dosis, aantal VCR giften en verstreken tijd sinds het afronden van de chemotherapie hadden geen effect op de schrijfsnelheid of op de kwaliteit van het handschrift.

In Hoofdstuk 4 wordt een studie beschreven naar perifere spierkracht en passieve enkelmobiliteit bij kinderen die werden behandeld met VCR en waarbij de chemotherapie tenminste een jaar voor aanvang van de studie was afgerond. De data werden vergeleken met die van een cohort gezonde schoolkinderen.
Spierkracht van de dorsaalflexoren van voeten en dorsaalflexoren, knijpkracht en driepunts-knijpkracht van de handen werd gemeten met een hand-held dynamometer. Er werd gebruik gemaakt van de 'break' techniek waarbij het kind zolang mogelijk weerstand biedt tegen de toenemende kracht die de onderzoeker uitoefent. Verminderde kracht van de dorsaalflexoren van de voeten veroorzaakt een veranderd looppatroon waarbij een zogenaamde 'omgekeerde' afwikkeling van de voet optreedt. Kinderen met een dergelijk looppatroon lopen het risico een spitsvoet te ontwikkelen, omdat de 'range of motion' van de enkel tijdens het lopen onvolledig is. In verband hier mee werd ook de passieve dorsaalflexie van de enkel onderzocht, met behulp van een goniometer.
In de onderste extremiteiten bleek de kracht van de dorsaalflexoren van de voet verminderd te zijn bij de kinderen die met VCR behandeld waren. In de bovenste extremiteiten werd verminderde kracht gevonden in de dorsaalflexoren van de pols van de niet-voorkeurskant en de driepuntsgreep beiderzijds. De krachtsvermindering kon de in Hoofdstuk 2 gerapporteerde afname in motorisch prestatieniveau echter slechts gedeeltelijk verklaren. De passieve dorsaalflexie van de enkels bij de kinderen die met VCR waren behandeld was verminderd vergeleken met gezonde kinderen. De verminderde enkelmobiliteit had geen effect op het motorische prestatieniveau.

In Hoofdstuk 5 wordt een studie beschreven naar de zelf-waargenomen motorische competentie van kinderen die met VCR waren behandeld. Bovendien werd onderzocht in hoeverre de zelf-waargenomen competentie overeen stemde met het daadwerkelijke motorische prestatieniveau.
Kinderen in de leeftijd van 8 tot en met 12 die hadden deelgenomen aan de motorische studie beschreven in Hoofdstuk 2, vulden een gestandaardiseerde vragenlijst in over zelf-waargenomen motorische competentie. De resultaten toonden aan dat de kinderen tevreden waren over hun motorische prestaties en dat hun zelf-waargenomen motorische competentie niet afweek van de Nederlandse normwaarden. Echter, als de zelf-waargenomen motorische competentie werd gerelateerd aan het daadwerkelijke

motorische prestatieniveau bleek er een neiging tot overwaardering te bestaan. Met andere woorden: de kinderen schatten hun motorische prestaties hoger in dan ze daadwerkelijk waren. Tevens was het percentage kinderen dat aangaf motorische prestaties niet zo belangrijk te vinden aanmerkelijk lager dan in de gezonde populatie. Mogelijk is hier sprake van coping strategieën.

Zoals eerder genoemd, bleek het motorische prestatieniveau niet gerelateerd te zijn aan de cumulatieve VCR dosis. Hierdoor ontstond de vraag of er mogelijk verschillen zouden zijn in gevoeligheid voor VCR op basis van een onderliggende genetische variatie in genen betrokken bij VCR metabolisme of bij VCR toxiciteit. In Hoofdstuk 6 wordt deze hypothese getoetst. VCR hoort tot de vinca-alkaloïden, welke worden gemetaboliseerd door het cytochroom P450 systeem in de lever. Isoformen van dit systeem zijn *CYP3A4* en *CYP3A5*. Polymorfismen van *CYP3A4* komen voor, maar zijn zeldzaam. Daarentegen komen *CYP3A5* polymorfismen in de Kaukasische populatie frequent voor. Het multi-drug resistance gen (*MDR-1* gen) is ook betrokken bij de farmacokinetiek van VCR. Genetische variatie in het Microtubuli-Associated Protein Tau gen (*MAPT*-gen) zou het effect van VCR op weefselniveau kunnen beïnvloeden. MAPT bevordert namelijk de constructie van microtubuli, welke beschadigingen oplopen door de behandeling met VCR.
Geanalyseerd werd of genetische variatie van *CYP3A5*, *MDR-1* en *MAPT* een relatie had met het motorische prestatieniveau van kinderen die behandeld waren met het ALL-9 protocol van de Stichting Kinderoncologie Nederland (SKION). De data toonden geen verband aan tussen polymorfismen in de genoemde genen en motorisch prestatieniveau. Echter, het aantal kinderen in de studie was beperkt en niet alle varianten van *CYP3A5* waren vertegenwoordigd in het cohort. Het aantal kinderen in de studie beperkte ook de mogelijkheid om het effect van combinaties van polymorfismen in diverse genen te analyseren.

In Hoofdstuk 7 wordt een gerandomiseerde studie beschreven naar het effect van een oefenprogramma tijdens de behandeling voor ALL, op het motorische prestatieniveau, de enkelmobiliteit en de botdichtheid. Kinderen met ALL werden na het stellen van de diagnose gerandomiseerd in een interventiegroep of in een controlegroep. De interventie bestond uit een toelichting, door een kinderfysiotherapeut betrokken bij het onderzoek over de te verwachten bijverschijnselen van de chemotherapie en een oefenprogramma, bestaande uit oefeningen om de spierkracht van de armen en benen te onderhouden, rekkingsoefeningen voor de enkels en springoefeningen ter verbetering van de botdichtheid. De kinderen uit de interventiegroep werden iedere 6 weken door de kinderfysiotherapeut terug gezien om de motoriek en de mobiliteit van de enkels te beoordelen. Indien nodig kon het oefenprogramma worden aangepast. De controlegroep kreeg

standaardzorg, dat wil zeggen de mogelijkheid te worden verwezen naar een 1e lijns-kinderfysiotherapeut wanneer zich motorische problemen voordeden.
De uitkomstparameters van de studie waren motorisch prestatieniveau, enkelmobiliteit en botdichtheid. Bij beide groepen werden metingen verricht ten tijde van de diagnose, na de inductie therapie (6 weken na diagnose), halverwege de behandelperiode (54 weken na diagnose), bij het afronden van de chemotherapie (109 weken na diagnose) en een jaar na het afronden van de chemotherapie. De onderzoeker was geblindeerd voor de randomisatie. Er bleek geen verschillen te zijn in verandering in motorisch prestatieniveau, passieve enkelmobiliteit en botdichtheid tussen de interventiegroep en de controles. De therapietrouw in de interventiegroep bleek echter gering te zijn, wat een negatief effect op de resultaten kan hebben gehad. Geconcludeerd werd dat afname van het motorisch prestatieniveau, de enkelmobiliteit en de botdichtheid niet werden voorkomen door het oefenprogramma.

Conclusies en aanbevelingen

Het onderzoek in dit proefschrift toont aan dat het verminderde motorische prestatieniveau van kinderen na afloop van behandeling met vincristine bevattende chemotherapie, niet volledig herstelt. Bovendien waren spierkracht en passieve enkelmobiliteit een aantal jaren na het beëindigen van de chemotherapie nog verminderd. Hoewel kinderen die werden behandeld voor kanker hun motorische prestaties na afloop van de chemotherapie net zo hoog aanslaan als gezonde kinderen, is dit in de meeste gevallen niet overeenstemming met hun daadwerkelijk motorische prestatieniveau. Mogelijk is hier sprake van een 'coping' strategie.
Tijdens de behandeling voor ALL nemen het motorisch prestatieniveau, de enkelmobiliteit en de botdichtheid af. Dit kon niet worden voorkomen met een oefenprogramma. Echter, de therapietrouw was onvoldoende. Een oefenprogramma wat alleen gericht is op het behouden van de passieve enkelmobiliteit is mogelijk meer succesvol. Het verdient aanbeveling het motorische prestatieniveau en de enkelmobiliteit van kinderen tijdens de chemotherapie voor ALL regelmatig te evalueren. Verder wordt aanbevolen een oefenprogramma om het motorisch prestatieniveau te verbeteren te starten na afronding van de chemotherapeutische behandeling.

DANKWOORD

Recent las ik in het NRC Handelsblad dat het promoveren al zo'n achthonderd jaar bestaat. In de 16e en 17e eeuw werden hier nog nauwelijks wetenschappelijke eisen aan gesteld en was het eenvoudig een kwestie van betalen. Het proefschrift werd ook niet noodzakelijkerwijs geschreven door de kandidaat zelf. Sinds die tijd is er echter veel veranderd en wordt van de kandidaat verwacht dat deze zelf onderzoek verricht. Zoals zo velen voor mij al hebben opgemerkt, is hierbij de hulp van anderen essentieel.
Mijn dank gaat dan ook in de eerste plaats uit naar mijn promotor. Prof. Dr. R. Pieters, beste Rob, tijdens de jaren van onze samenwerking heb ik heel wat gesprekken met je gevoerd. Geleidelijk nam mijn zelfvertrouwen toe, met name door jouw manier van begeleiden. Vanaf de start van het onderzoek in 2000 heb je je commentaar zonder uitzondering als positief en opbouwend weten te formuleren. Ik neem mijn petje daarvoor af en ben blij dat ik na deze promotie verder mag gaan als onderzoeker in jouw team. Dank voor alles wat ik van je heb geleerd.
Het onderzoek in dit proefschrift had niet kunnen worden uitgevoerd zonder de bereidheid van de kinderen en ouders. Hartelijk dank aan alle ouders die hun toestemming gaven en voor het enthousiasme en de inzet van de kinderen die hebben meegedaan. Bijzondere dank aan Derk Over en zijn ouders voor de toestemming voor het gebruiken van de foto voor de omslag van dit proefschrift.
Monique Flierman, Aad Barendregt en Karin Schrage, collega's van de afdeling fysiotherapie Erasmus MC Sophia, wil ik graag bedanken voor het behandelen van de kinderen die deelnamen aan de studie beschreven in hoofdstuk 7. De eisen die aan een dergelijk geblindeerd onderzoek worden gesteld namen jullie alle drie uiterst serieus. Dit was niet altijd eenvoudig omdat ik als onderzoeker op dezelfde afdeling werk. Hierin zijn jullie echter zeer goed geslaagd.
Eric Benda, hoofd afdeling fysiotherapie Erasmus MC, ik bedank je voor je steun en interesse in het onderzoek van start tot finish. Verder bedank ik alle andere collega's voor het meedenken en het – herhaaldelijk – luisteren naar voordrachten over mijn onderzoek. In het bijzonder dank aan Lianne van der Giessen die altijd voor mij klaar stond om mee te lezen en advies te geven. Ook de collega's van Transfergroep Rotterdam wil ik bedanken voor hun interesse en steun.
Zonder de hulp en medewerking van iedereen op de polikliniek kinderoncologie had dit onderzoek niet gerealiseerd kunnen worden. Organisatorisch vormden zij voor mij een belangrijke schakel.Ook Frederik Nijland in het Groene Hart ziekenhuis Gouda, Pieter Naterop in het Amphia ziekenhuis Breda, Harm Haas in ziekenhuis Walcheren locatie Vlissingen, Inge Schoonus in het Reinier de Graaf ziekenhuis Delft en Elly Meier

in het Ruwaard van Putten ziekenhuis Spijkenisse hebben mij allemaal hun medewerking verleend door te zorgen dat ik op hun afdeling kinderen kon onderzoeken, vaak meer dan eens. Zo ook collega's in fysiotherapiepraktijken in Gouda, Nieuwerkerk aan de IJssel en Lekkerkerk. Daardoor werden veel ouders en kinderen extra ritjes naar het Sophia Kinderziekenhuis bespaard, waarvoor mijn dank.
Diverse basisscholen hebben hun deuren voor mij geopend. Op de Juliana van Stolbergschool in Kapelle, basisschool D'n Overkant in Etten-Leur en basisschool De Hoeksteen in Spijkenisse mocht ik in diverse groepen schrijftesten afnemen. Op basisschool Open Vensters in Vlaardingen en basisschool De Hoeksteen in Spijkenisse werd ik in de gelegenheid gesteld mobiliteit en spierkracht te onderzoeken bij kinderen uit groep 3 t/m 8. Dat betekende voor deze scholen organisatorisch flink wat werk, niet alleen vooraf maar ook op de dagen dat het onderzoek werd uitgevoerd. Door iedereen werd alle medewerking verleend, nooit was er een bezwaar of werd het lastig gevonden. Tenminste niet voor zover ik heb gemerkt… De grote hoeveelheid gegevens die ik op die manier heb kunnen verzamelen was essentieel voor het onderzoek. Ik heb deze enthousiaste medewerking bijzonder gewaardeerd.
Veel dank gaat ook uit naar mijn mede-auteurs. Dr. C. van den Bos, beste Cor, hartelijk dank voor het meedenken, meelezen en voor het openen van de deuren van het AMC waar ik een gedeelte van het onderzoek mocht uitvoeren. Voor het onderzoek naar schrijfproblematiek was iemand nodig die bereid was 66 handschriften te beoordelen. Die persoon vond ik in collega kinderfysiotherapeut Nienke van Dartel. Jij ging hier enthousiast mee aan de slag en leverde met grote regelmaat de resultaten aan. Het zal af en toe een zenuwslopende taak zijn geweest, veel dank voor je hulp.
In het kader van dit proefschrift kwam ik ook in aanraking met het begrip genetische variatie. Nog niet eerder had ik mij gerealiseerd dat zoveel zaken in de oncologie hier nauw mee zijn verweven. Dr. R. van Schaik en Dr. M.L. den Boer, beste Ron en Monique, jullie waren beiden goed in staat deze ingewikkelde materie voor mij als fysiotherapeut toegankelijk te maken. De woorden van Ron 'dan kom je het toch gewoon nog een keer vragen' en van Monique 'zo moeilijk is het niet' hebben er voor gezorgd dat ik het hoofd koel kon houden. Niettemin ben ik nog steeds onder de indruk als ik hoofdstuk 6 lees.
Bij ieder onderzoek zijn er gelukkig altijd mensen die met je mee willen denken en schrijven. Ik heb de bijdragen van Ilse van der Heiden, Mathilde Broekhuis, Marrit Meier, Robert ten Beek, Sabine de Muinck Keizer, professor Han Kemper en Marry van den Heuvel erg op prijs gesteld. Een aparte vermelding voor Lizet te Winkel, die samen met mij eerste auteur was van het artikel in hoofdstuk 6. Beste Lizet, nog niet eerder had ik samen met iemand een manuscript geschreven. Twee weten meer dan één is mij nu heel duidelijk geworden. Ik heb het als erg plezierig ervaren hoop dat hier in de toekomst nog meer gelegenheid voor zal zijn. Ook je geduldige uitleg over het werken met GraphPad Prism, heb ik erg op prijs gesteld.

Prof. T. Stijnen, beste Theo, vanaf het eerste uur heb je mij met raad en dat terzijde gestaan op het gebied van de statistiek. De meeste analyses gingen mij aardig af, als het erg ingewikkeld werd was je altijd bereid de data samen ter plekke te analyseren. Enige tijd geleden vertrok je naar het LUMC en werd de fakkel overgenomen door Dr. W. Hop. Beste Wim, jouw werkwijze was weer anders en juist daardoor heb ik veel van je geleerd. Je enthousiasme en betrokkenheid waardeer ik zeer.

A special word of thanks to Professor Barbara Wilson. You first introduced me to the world of research. During completion of my thesis for the Master of Rehabilitation Studies in Southampton you acted as my mentor. Your encouragement and enthusiasm no doubt laid the foundation for returning to research at a later stage.

Jane, Jan and Joanna, we met during our studies 1988. Since then we have been close friends, you have truly become my honorary 'sisters'. You have called me 'Dr. Hartman' on and off ever since the word PhD was first mentioned. I treasure the interest and support you have shown me throughout the years. Also thanks to Ed Walsh for volunteering to read the entire manuscript and produce mock questions to prepare me for the real event.

Het onderzoek beschreven in dit proefschrift werd gefinancierd door het Zorgonderzoek Erasmus MC. Om vooral paramedici en verpleegkundigen aan te moedigen te promoveren worden jaarlijks voor drie personen financiën beschikbaar gesteld om hun onderzoek uit te kunnen voeren. Ik prijs mij gelukkig dat ik in dienst ben van een organisatie met deze visie op promotieonderzoek.

Jacqueline Dito en Jeanine Arnolds, secretaresses Prof. Pieters, hartelijk dank voor het regelmatig zoeken naar een plaats in zijn agenda. Dank aan Wilma Willemse, secretaresse afdeling fysiotherapie Erasmus Mc Sophia, voor je ondersteuning

Er zijn nog vele anderen die er aan hebben bijgedragen dat dit proefschrift uiteindelijk is voltooid. Frank Rijkee voor zijn goede zorgen, Andrea Dingemans en Astrid Schölvinck voor hun vriendschap en interesse. Rendie Leder en Rob Kroes meldden zich tot mijn groot plezier acht jaar geleden spontaan aan voor de functie van paranimf. Hun enthousiasme is al die tijd onveranderd gebleven ook al was de wachttijd toch tamelijk lang.

Mijn dank gaat ook uit naar mijn naaste familie en vrienden en alle anderen die mij lief zijn, maar die niet met name zijn genoemd.

LIST OF PEER REVIEWED PUBLICATIONS

Hartman A, Pickering RM, Wilson BA.
Is there a central executive deficit after severe head injury?
Clinical Rehab 1992; 6: 133-140

Hartman A, van der Cammen-van Zijp M.
De zuigeling met een vergrote buikomvang.
Ned TS Fysiother 1998;108 (3): 70-74

Bruning MFMT, **Hartman A**, Weisglas-Kuperus N, Stijnen T.
Een vergelijkende studie van de BOS 2-30 en de AIMS: twee motorische ontwikkelingstests die worden gebruikt bij prematuur geborenen.
Ned TS Fysiother 2000; 110 (6): 132-136

Van der Giessen LJ, Liekens D, Rutgers JM, **Hartman A**, Mulder GH, Oranje AP.
Validation of Beighton score and prevalence of connective tissue symptoms in 773 Dutch children.
J Rheumatol 2000; 28 (12): 2726-2730

Hartman A, van den Bos C, Stijnen T, Pieters R.
Decrease in motor performance in children with cancer is independent of cumulative vincristine dose.
Cancer, 2006;106 (6): 1395-1401

Hartman A, van Dartel N, van den Bos C, Stijnen T, Pieters R.
No adverse effect of vincristine on handwriting in children after completion of therapy.
Pediatr Blood Cancer 2007;49 (6): 841-845

Fleuren KMW, Smit LS, Stijnen T, **Hartman A**.
New reference values for the Alberta Infant Motor Scale need to be established.
Acta Paediatr 2007; 96 (3) 424-427

Hartman A, van den Bos C, Stijnen T, Pieters R.
Decrease in peripheral muscle strength and ankle dorsiflexion as long-term side effects of treatment for childhood cancer.
Ped Blood Cancer 2008 ; 50 (4) 833-837

Hartman A, van den Bos C, Stijnen T, Pieters R.
Perceived and actual motor competence of children treated for cancer with vincristine containing chemotherapy.
Pediatr Blood Cancer 2008; 51(2) 306

Douma-van Riet DCM, Engelbert RHH, van Genderen FR, ter Horst-de Ronde MTM, de Goede-Bolder A, **Hartman A**.
Physical fitness in children with haemophilia and the effect of overweight.
Haemophilia; accepted for publication

CURRICULUM VITAE

Annelies Hartman werd op 9 april 1956 geboren in Leidschendam. Na het behalen van haar VWO diploma aan het Veurs College in Leidschendam begon zij in Leiden in 1974 aan de opleiding fysiotherapie en ontving zij in 1978 haar Bewijs van Bevoegdheid. In 1982 vertrok zij naar Engeland en legde zich toe op de behandeling van neurologische patiënten, eerst in het National Hospital for Nervous Diseases en vervolgens in het Charing Cross Hospital, beide in Londen. In 1989 behaalde zij een Master of Science degree in Rehabilitation Studies (cum laude) aan de Universiteit van Southampton. Na terugkeer in Nederland startte zij in 1993 bij de afdeling fysiotherapie in het Eramus MC Sophia. In 1995 werd zij door Transfergroep Rotterdam gevraagd haar medewerking te verlenen aan het ontwikkelen van de opleiding Kinderfysiotherapie, welke vervolgens in 1996 van start ging. Zij is sindsdien als programmaleider en docent aan de opleiding verbonden. In 1998 werd zij door Elsevier gevraagd als mede-redacteur voor het boek Kinderfysiotherapie. Hiervan verscheen de 1e druk in 2000 en de 2e herziene druk in 2006. Sinds 2000 is zij coördinator van de vakgroep Kinderen van de afdeling fysiotherapie in het Erasmus MC. In 2000 startte zij onder begeleiding van Prof. Dr. Pieters het onderzoek beschreven in dit proefschrift.