British Journal of Haematology, 2000, **110**, 308–314

No impact of high-dose cytarabine on the outcome of patients transplanted for acute myeloblastic leukaemia in first remission

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Received 8 December 1999; accepted for publication 21 March 2000

Summary. High-dose cytarabine is currently used in combination with anthracycline in the treatment of acute myeloblastic leukaemia (AML). Moreover, high-dose cytarabine has been reported to produce long-term disease-free survival in a proportion of patients, especially in certain subtypes of AML. However, it remains unknown whether the outcome of patients undergoing allogeneic or autologous stem cell transplantation is influenced by previous treatment with high-dose cytarabine. To this end, 1672 patients with AML in first remission who were reported to the Acute Leukaemia Working Party registry of the European Group for Blood and Marrow Transplantation (EBMT) and who were transplanted between 1980 and 1995 were analysed according to the dose intensity of cytarabine given at induction and/or consolidation. Autologous stem cell transplantation (ABMT) was performed in 846 patients and allogeneic bone marrow transplantation (BMT) in 826 patients. This study shows that the dose of cytarabine (Ara-C) given at induction and/or consolidation did not influence the relapse incidence in patients subsequently allografted or autografted. In addition, it did not give any advantage in terms of overall outcome. Therefore, high-dose (HD) Ara-C may not be needed for patients who have a planned stem cell transplantation (SCT) as post-remission therapy. Nevertheless, HD Ara-C may be utilized in certain subtypes of AML that are believed to be curable by chemotherapy alone.

Keywords: cytarabine, bone marrow transplantation, acute myeloblastic leukaemia.

High-dose cytarabine (HD Ara-C) has been shown to be effective for both the induction and consolidation of complete remission (CR) in patients with acute myeloblastic leukaemia (AML) (Mayer *et al*, 1994; Mitus *et al*, 1995; Bishop *et al*, 1996; Weick *et al*, 1996; Cole & Gibson, 1997; Fopp *et al*, 1997; Rowe & Tallman, 1997). In patients below 60 years of age who were treated using chemotherapy alone without transplant, a randomized study of various doses of Ara-C administered for consolidation has shown that, in younger patients, the higher the dose of Ara-C the better the outcome. In the South-West Oncology Group–Eastern Cooperative Oncology Group–Cancer and Leukaemia Study Group B (SWOG–ECOG–CALGB) (Cassileth *et al*, 1998) intergroup randomized study that compared conventional chemotherapy using HD Ara-C with allogeneic (BMT) and autologous (ABMT) stem cell transplantations, consolidation with HD Ara-C led to a better outcome than the transplantations. This was as a result of salvage by autologous or allogeneic bone marrow transplantation in the patients who relapsed after HD Ara-C. Although both HD Ara-C and stem cell transplantation are effective therapeutic measures for curing AML, it is unknown whether the combination of the two, i.e. HD Ara-C in the pre-transplant period followed by transplant, would be of

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benefit or would increase toxicity. To answer the question, we retrospectively analysed results from transplants reported to the registry of the Acute Leukaemia Working Party of the European Co-operative Group for Blood and Marrow Transplantation (EBMT).

PATIENTS AND METHODS

Patients. The study included 1672 patients with AML in first complete remission (CR1). These patients were transplanted between 1980 and 1995 and were reported to the Acute Leukaemia Working Party of the EBMT. Eight hundred and forty-six were transplanted with autologous stem cells and 826 with BMT from an HLA-matched sibling. Patients and transplant characteristics are given in Table I. The dose intensity of Ara-C was defined as follows: standard dose (SD) for patients receiving 100–200 mg/m^2/d for 5–10 d, high dose (HD) for patients receiving 1·5–3 g/m^2/d for 4–6 d. Patients receiving doses falling between these two groups were included in an intermediate group (ID). Following these criteria, 820 patients among the autologous group received Ara-C for induction and 803 patients received Ara-C for post-remission therapy. For induction, 767 patients received SD and 31 patients received HD. For post-remission therapy, 358 patients and 284 patients received SD and HD respectively. Among the BMT group, 809 patients received Ara-C for induction and 670 patients received Ara-C for post-remission treatment. During induction, 733 patients were treated with SD and 45 patients with HD. For post-remission therapy, 393 patients received SD and 201 patients received HD.

Statistical methods. Data were analysed from December 1998. All analyses were performed using the SPSS statistical package software. Leukaemia-free survival (LFS), relapse incidence (RI) and transplant-related mortality

Table I. Patient characteristics.

	Autograft	Allograft
Induction		
No	26	17
LD	2	5
SD	767	733
ID	20	26
HD	31	45
Consolidation		
No	43	156
LD	3	8
SD	358	393
ID	158	68
HD	284	201
Induction and/or consolidation		
No	3	6
LD	2	3
SD	351	493
ID	174	89
HD	301	230
Median age (range)	35 years (< 1–69)	29 years (< 1–53)
Year of SCT (median)	1991 (80–95)	1990 (80–95)
Delay diagnosis to CR1	39 d (10–921)	42 d (15–491)
Delay CR1 to SCT	129 d (10–1245)	92 d (10–554)
Sex, male/female	430/416	435/390
Purge, yes/no	172/674	–
TBI, yes/no	355/381	521/132
FAB, M1/M2/M3/M4/M5/M6/M7	147/230/109/184/126/15/9	132/259/94/195/80/20/7
WBC ($\times 10^9$/l), median (range)	13·8 (0·3–474)	11·7 (0·2–336)
Donor age		27 (< 1–57)
Donor sex, male/female		425/359
GVHD prevention CSA/MTX/both/T-cell depletion		72/69/298/167
aGVH, yes/no		426/262
aGVHD score (I/II/III/IV)		138/134/43/47
Delay SCT to aGVHD		21 d (3–92)
cGVHD, yes/no		306/322

No, no Ara-C; LD, low-dose Ara-C; SD, standard-dose Ara-C; ID, intermediate dose Ara-C; HD, high-dose Ara-C; SCT, stem cell transplantation; CR1, first complete remission; TBI, total body irradiation; WBC, white blood cells at diagnosis; GVHD, graft-versus-host disease; CSA, cyclosporin A; MTX, methotrexate; aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease.

Table II. Autografts: 5-year results in relation to the dose of Ara-C at induction and/or consolidation.

Dose Ara-C	Patients	LFS (means ± SE)	RI (means ± SE)	TRM (means ± SE)
Induction				
No	26	38 ± 10	56 ± 10	12 ± 6
SD	765	46 ± 2	47 ± 2	12 ± 1
ID	20	50 ± 11	30 ± 11	27 ± 10
HD	31	44 ± 9	47 ± 9	17 ± 8
P-value		0·76	0·77	0·2
Consolidation				
No	43	36 ± 8	55 ± 8	21 ± 9
SD	357	46 ± 3	47 ± 3	13 ± 2
ID	158	50 ± 4	47 ± 4	6 ± 2
HD	283	46 ± 3	47 ± 3	14 ± 3
P-value		0·63	0·91	0·39
Induction and/or consolidation				
SD		44 ± 3	49 ± 3	22 ± 2
ID		51 ± 4	44 ± 4	9 ± 2
HD		46 ± 3	46 ± 3	14 ± 3
P-value		0·65	0·67	0·85

LFS, leukaemia-free survival; RI, relapse incidence; TRM, transplant-related mortality; SE, standard error of the mean; No, no Ara-C; SD, standard dose Ara-C; ID, intermediate dose Ara-C; HD, high-dose Ara-C.

(TRM) were calculated using the Kaplan–Meier product limit method.

Comparison of these data was based on results from log rank tests. The Cox regression model was applied to assess the prognostic value of both patient and treatment characteristics in relation to relapse, LFS and TRM. Variables tested with the doses of Ara-C were age, gender, white blood cell count (WBC) at diagnosis, French–American–British (FAB) classification, cytogenetics, interval between diagnosis and CR, interval between diagnosis and BMT, conditioning

Table III. Allografts: 5-year results in relation to the dose of Ara-C at induction and/or consolidation.

Dose Ara-C	Patients	LFS (means ± SE)	RI (means ± SE)	TRM (means ± SE)
Induction				
No	17	76 ± 10	13 ± 8	13 ± 8
SD	726	55 ± 2	23 ± 2	28 ± 2
ID	24	50 ± 10	21 ± 9	47 ± 11
HD	44	45 ± 8	42 ± 9	21 ± 7
P-value		0·14	0·02*	0·98
Consolidation				
No	154	51 ± 4	27 ± 4	29 ± 4
SD	393	56 ± 3	24 ± 3	26 ± 3
ID	68	54 ± 6	21 ± 6	28 ± 6
HD	193	56 ± 4	23 ± 4	27 ± 3
P-value		0·88	0·72	0·92
Induction and/or consolidation				
SD	493	55 ± 2	24 ± 2	27 ± 2
ID	87	51 ± 6	22 ± 5	34 ± 6
HD	222	55 ± 3	26 ± 3	25 ± 3
P-value		0·72	0·41	0·81

* Among the 45 patients having received HD at induction 16 received HD Ara-C twice and the delay between diagnosis and CR1 was prolonged in this restricted population (median, 61 d vs. 42 d for the remaining patients).

LFS, leukaemia-free survival; RI, relapse incidence; TRM, transplant-related mortality; SE, standard error of the mean; No, no Ara-C; SD, standard-dose Ara-C; ID, intermediate-dose Ara-C; HD, high-dose Ara-C.

regimen, bone marrow purging, source of stem cells, graft-versus-host disease (GVHD) prophylaxis, acute and/or chronic GVHD and the year of transplantation. The characteristics of the three groups of patients who received standard dose (SD), intermediate dose (ID) or HD Ara-C were compared using the χ^2 test for qualitative variables and the Kruskall–Wallis test for continuous variables. All variables that were associated with outcome and that showed a *P*-value less than 0·2 and/or that had a different distribution between groups were included in the Cox model.

RESULTS

Outcome of autografted patients

For ABMT, the dose intensity of Ara-C, whether evaluated at induction or after remission, did not influence LFS, RI or TRM at 5 years (Table II).

Outcome of allografted patients

After BMT, relapse incidence was more important for patients induced with HD Ara-C than for patients induced with SD Ara-C. There was no statistical difference between TRM and LFS. No difference was found among the three groups of Ara-C prescribed as post-remission therapy in terms of probability of LFS, RI or TRM at 5 years (Table III).

Prognostic factors other than dose of Ara-C: univariate analysis

In the ABMT patients, age, date of transplant, FAB M3, purging and interval between diagnosis and remission all had a prognostic value for relapse and LFS.

In the BMT patients, age, interval between diagnosis and

Table IV. (A) Cytogenetics at diagnosis.

Autografts: patient distribution	
Good(n = 49)	t(15;17), t(8;21), inv(16)
Poor (n = 23)	abn 5 and/or 7, hypodiploidy, abn 11q
Standard (n = 140)	All others
Allografts: patient distribution	
Good(n = 53)	t(15;17), t(8;21), inv(16)
Poor (n = 20)	abn 5 and/or 7, hypodiploidy, abn 11q
Standard (n = 139)	All others

(B) Dose of Ara-C at induction and/or consolidation by cytogenetic group.

	SD (%)	ID (%)	HD (%)
Autografts			
Good	25 (22)	5 (22)	18 (24)
Standard	75 (69)	16 (70)	46 (61)
Poor	9 (8)	2 (9)	11 (15)
Allografts			
Good	33 (27)	10 (33)	10 (18)
Standard	77 (62)	19 (63)	42 (75)
Poor	14 (11)	1 (3)	4 (7)

(C) Outcome (5 years) according to cytogenetic cytostratification

	LFS (means ± SE)	RI (means ± SE)	TRM (means ± SE)
Autografts			
Cyto good	46 ± 7	46 ± 7	15 ± 6
Cyto standard	46 ± 4	49 ± 5	10 ± 3
Cyto poor	26 ± 9	73 ± 9	4 ± 4
P-value	0·15	0·05	0·74
Allografts			
Cyto good	62 ± 7	12 ± 5	29 ± 6
Cyto standard	58 ± 4	24 ± 4	24 ± 4
Cyto poor	27 ± 11	62 ± 14	24 ± 4
P-value	0·02	0·0004	0·93

SD, standard dose Ara-C; ID, intermediate dose Ara-C; HD, high-dose Ara-C; LFS, leukaemia-free survival; RI, relapse incidence; TRM, transplant-related mortality; SE, standard error of the mean.

Table V. Autografts: multivariate analysis.

	Covariate	*P*-value	RR	95% CI
LFS	Interval diagnosis to CR1 > 39 d	0·04	1·25	1·02–1·55
	Adult	0·0035	1·60	1·17–2·2
	Year SCT > 1987	0·014	0·71	0·54–0·93
	M3 FAB	0·03	0·66	0·46–0·95
RI	Interval diagnosis to CR1 > 39 d	0·033	1·29	1·02–1·62
	Adult	0·03	1·46	1·05–2·02
	Year SCT > 1987	0·004	0·66	0·49–0·9
	M3 FAB	0·005	0·54	0,36–0,83
TRM	Adult	0·03	3·65	1·13–11·7

Covariates: Ara-C at induction and/or consolidation, SD vs. ID vs. HD; age, children vs. adults; Year of SCT, ≤ 1987 vs. > 1987; purge, yes vs. no; FAB, M3 vs. M5 vs. other; interval diagnosis to CR1, ≤ 39 d vs. > 39 d (median).

SCT, stem cell transplantation; CR1, first complete remission; RR, relative risk; CI, confidence interval.

CR1, WBC at diagnosis and T-cell depletion influenced LFS. WBC at diagnosis, T-cell depletion and cytogenetics influenced relapse. TRM was influenced by age, year of transplant, total body irradiation (TBI) and interval between diagnosis and CR1.

Acute GVHD was associated with a lower relapse incidence, a higher TRM and a lower LFS. Chronic GVHD was not analysed owing to a lack of data.

Results of cytogenetics were available for 425 patients. Table IVA shows the distribution of patients within the good, standard and poor risk categories according to the modified Chicago classification. The distribution of the cytogenetic categories in relation to the dose of Ara-C did not show any unbalance (Table IVB). As previously shown by the EBMT (Ferrant *et al*, 1997), the outcome after either autografting or allografting was worse in the poor risk category patients (Table IVC). The distribution of the cytogenetic subgroups was identical between the three doses of Ara-C, but it was not possible to include cytogenetics in the multivariate analysis owing to the small number of patients in each subgroup.

Prognostic factors: multivariate analysis

Variables differing significantly or recognized as potential prognostic factors were included as covariates in the multivariate analysis. The dose of Ara-C given at induction or after remission had no influence on the outcome of ABMT in terms of LFS, RI or TRM. Other independent

Table VI. Allografts: multivariate analysis.

	Covariate	*P*-value	RR	95% CI
LFS	Interval diagnosis to CR1 > 42 d	0·034	1·50	1·03–2·17
	T depletion	0·01	1·63	1·12–2·39
RI	Interval diagnosis to CR1 > 42 d	0·02	1·99	1·11–3·59
	No TBI	0·008	2·56	1·26–5
	WBC > 11·7 ($\times 10^9$/l)	0·03	1·93	1·07–3·5
	T depletion	0·007	2·37	1·27–4·43
	No aGVHD	0·014	2·13	1·16–3·84
TRM	Adult	0·03	3·70	1·15–12
	aGVHD	0·0002	3·21	1·75–5·9

Covariates: Ara-C at induction and/or consolidation, SD vs. ID vs. HD; age, children vs. adults; age donor, children vs. adults; year of SCT, ≤ 1987 vs. > 1987; TBI, yes vs. no; FAB, M3 vs. M5 vs. other; interval diagnosis to CR1, ≤ 42 d vs. > 42 d (median); WBC at diagnosis, ≤ 11·7 vs. > 11·7 ($\times 10^9$/l); T depletion; aGVHD (time-dependent covariate). SCT, stem cell transplantation; TBI, total body irradiation; CR1, first complete remission; WBC, white blood cell at diagnosis; aGVHD, acute graft-versus-host disease; LFS, leukaemia-free survival; RI, relapse incidence; TRM, transplant-related mortality; RR, relative risk; CI, confidence interval.

factors are shown in Table V. In the BMT patients, no influence of SD or HD Ara-C (Table VI) was observed.

DISCUSSION

Uncertainty remains about optimal remission and post-remission Ara-C regimens for *de novo* AML outside the context of stem cell transplantation (SCT). Although pilot studies suggested a significant improvement with higher doses, there have been only two prospective randomized trials using HD Ara-C as part of the standard induction. In the SWOG study (Weick *et al*, 1996), patients were randomized for induction between SD or HD Ara-C and both groups received daunorubicin (DNR). Complete responders to HD Ara-C received an additional course of HD Ara-C and DNR. Complete responders to SD were randomized to receive SD plus DNR or HD plus DNR.There was no advantage for HD Ara-C in terms of CR rates. The LFS was better in patients treated with HD Ara-C, but was associated with significantly more lethal toxicities. Similar findings were reported by the Australian Leukaemia Study Group (Bishop *et al*, 1996) in a study that compared HD Ara-C plus daunorubicin and etoposide with SD Ara-C plus daunorubicin and etoposide. Patients in CR tended to survive longer with HD Ara-C, but there was no statistical difference between the two arms in terms of overall survival.

More frequently, schedules including HD Ara-C have been included as post-remission intensification therapy. The Cancer and Leukaemia Study Group B (CALGB) (Mayer *et al*, 1994) randomized patients in remission between three groups in order to compare the dose intensity of Ara-C. The three different groups received 6 g/m^2/d at days 1, 3 and 5, 400 mg/m^2/d for 5 d and 100 mg/m^2/d for 5 d respectively. At 4 years, the disease-free survival rate (DFS) was significantly in favour of the higher dose in patients less than 60 years of age. The patients also experienced significant dose-related toxicities. The Swiss Group for Clinical Cancer Research (Fopp *et al*, 1997) has recently published results suggesting that Ara-C dose intensity might be more important than the total cumulative dosage. The question of the type of chemotherapy given before SCT has never been analysed in terms of dose intensity. Several studies have investigated the optimal interval between CR1 and SCT. This approach has always been limited by biases such as relapse with time, complications that delay transplant or poor haematological recovery for autologous stem cell harvest (Gorin, 1998). The best chemotherapy regimen available is not necessarily the best option before transplantation. More frequently now, BMT is performed quickly after achieving CR1, whereas the therapies between CR1 and ABMT are quite heterogeneous in length and intensity. In some studies, ABMT can be considered as an additional treatment, whereas in others it takes the place of another intensification.These could be the major explanations for the differences observed between randomized trials (Zittoun *et al*, 1995; Reiffers *et al*, 1996; Harousseau *et al*, 1997; Burnett *et al*, 1998; Cassileth *et al*, 1998) showing various differences between chemotherapy and ABMT according to different designs and timing of transplantation. Apart from the dose of Ara-C, the type and dose of anthracycline used, both in induction and after remission, may be important, especially when considering idarubicin. From the data reported here, we can speculate that high-dose therapy administered with SCT could abrogate the advantage of previous intermediate or HD Ara-C.

HD Ara-C improves LFS in chemotherapy-treated AML patients despite higher toxicity, including Ara-C-related mortality. Patients who died as a result of Ara-C toxicity could not proceed to BMT and therefore the present study has focused on a selected group of patients that should have favoured the appearance of a possible beneficial effect of Ara-C after BMT. However, no such effect was found.

Because *in vivo* purging with HD Ara-C has been used in several trials (Zittoun *et al*, 1995; Harousseau *et al*, 1997; Schiller *et al*, 1997; Burnett *et al*, 1998; Pavlovsky *et al*, 1998) and has a major disadvantage in prolonging the delay to platelet recovery, its use before ABMT should be avoided. Presently, the choice between conventional chemotherapy and BMT is being approached in a different way, according to the prognostic factors at diagnosis, such as cytogenetics (Ferrant *et al*, 1997; Bloomfield *et al*, 1998; Grimwade *et al*, 1998). Some current trials are now stratifying treatment approach by using cytogenetics and by considering HD Ara-C as the option of choice for core binding factor-type cytogenetic abnormalities in adult AML with BMT being reserved for relapse. However, we did not analyse patients with inv(16) and t(8;21) at diagnosis separately because of their low number and also to avoid the statistical problems associated with subgroup analysis.

In conclusion, to analyse the impact of HD Ara-C given at induction or post-remission therapy before subsequent intensification with SCT, we have retrospectively studied data reported to the EBMT. Three subgroups have been compared. This study clearly shows that increasing the dose of Ara-C before SCT does not give any advantage in terms of outcome. HD Ara-C does not seem to be the gold standard before BMT or ABMT and probably should be dedicated to certain subtypes of AML that can be treated using chemotherapy alone.

ACKNOWLEDGMENTS

The authors are greatly indebted to Patricia Palut for help in preparing the statistical analysis. This study was supported by EBMT funds, Etablissement Français Des Greffes (EFG, Paris, France), Association Claude Bernard (Paris, France) and Ligue Régionale Contre le Cancer du Doubs (Besançon, France).

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