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High-Dose Therapy and Autologous Stem Cell Transplantation in First Relapse for Diffuse Large B Cell Lymphoma in the Rituximab Era: An Analysis Based on Data from the European Blood and Marrow Transplantation Registry

Nicolas Mounier,[1] Carmen Canals,[2] Christian Gisselbrecht,[3] Jan Cornelissen,[4] Roberto Foa,[5] Eulogio Conde,[6] John Maertens,[7] Michel Attal,[8] Alessandro Rambaldi,[9] Charles Crawley,[10] Jian-Jian Luan,[11] Mats Brune,[12] Sebastian Wittnebel,[13] Gordon Cook,[14] G. W. van Imhoff,[15] Michael Pfreundschuh,[16] Anna Sureda,[10,17] for the Lymphoma Working Party of the European Blood and Marrow Transplantation Registry (EBMT)

Autologous stem cell transplantation (ASCT) consolidation remains the treatment of choice for patients with relapsed diffuse large B cell lymphoma. The impact of rituximab combined with chemotherapy in either first- or second-line therapy on the ultimate results of ASCT remains to be determined, however. This study was designed to evaluate the benefit of ASCT in patients achieving a second complete remission after salvage chemotherapy by retrospectively comparing the disease-free survival (DFS) after ASCT for each patient with the duration of the first complete remission (CR1). Between 1990 and 2005, a total of 470 patients who had undergone ASCT and reported to the European Blood and Bone Transplantation Registry with Medical Essential Data Form B information were evaluated. Of these 470 patients, 351 (74%) had not received rituximab before ASCT, and 119 (25%) had received rituximab before ASCT. The median duration of CR1 was 11 months. The median time from diagnosis to ASCT was 24 months. The BEAM protocol was the most frequently used conditioning regimen (67%). After ASCT, the 5-year overall survival was 63% (95% confidence interval, 58%-67%) and 5-year DFS was 48% (95% confidence interval, 43%-53%) for the entire patient population. Statistical analysis showed a significant increase in DFS after ASCT compared with duration of CR1 (median, 51 months versus 11 months; $P < .001$). This difference was also highly significant for patients with previous exposure to rituximab (median, 10 months versus not reached; $P < .001$) and for patients who had experienced relapse before 1 year (median, 6 months versus 47 months; $P < .001$). Our data indicate that ASCT can significantly increase DFS compared with the duration of CR1 in relapsed diffuse large B cell lymphoma and can alter the disease course even in patients with high-risk disease previously treated with rituximab.

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From the [1]CHU de l'Archet, Nice, France; [2]Lymphoma Working Party, European Blood and Marrow Transplantation Registry Office, Barcelona, Spain; [3]Institut d'Hématologie, Hôpital Saint Louis, Paris, France; [4]Erasmus MC-Daniel den Hoed Cancer Centre, AE Rotterdam, the Netherlands; [5]Universita "La Sapienza," Rome, Italy; [6]Servicio de Hematología-Hemoterapia, Hospital U. Marqués de Valdecilla, Santander, Spain; [7]Department of Hematology, University Hospital Gasthuisberg, Leuven, Belgium; [8]Department de Hematologie, Hopital de Purpan CHU, Toulouse, France; [9]Divisione di Ematologia, Ospedali Riuniti di Bergamo, Bergamo, Italy; [10]Department of Haematology, Addenbrooke's Hospital, Cambridge, UK; [11]EBMT Data and Study Office, Faculté de Médecine Saint-Antoine, Paris, France; [12]Hematology Section, Sahlgrenska University Hospital Center for Hematopoietic Cell Transplantation, Göteborg, Sweden; [13]Institut Cancerologie Gustave Roussy, Villejuif, France; [14]Yorkshire Blood and Marrow Transplant Programme, Haematology Department, James Institute of Oncology, Leeds, UK; [15]Department of Hematology, University Medical Center Groningen, Groningen, the Netherlands; [16]Department of Internal Medicine, BMT Unit, University of Saarland, Homburg, Germany; and [17]Hematology Department, Hospital de la Santa Creu I Sant Pau, Barcelona, Spain.

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Correspondence and reprint requests: Anna Sureda, Addenbrooke's Hospital, Department of Haematology, Box 234, Hills Road, CB2 0QQ Cambridge, UK (e-mail: anna.sureda@addenbrookes.nhs.uk).

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INTRODUCTION

During the last decade, the addition of the anti-CD20 monoclonal antibody rituximab to various chemotherapies has dramatically improved overall survival (OS), progression-free survival (PFS), and response rates in patients with diffuse large B cell lymphoma (DLBCL), with complete responses ranging from 75% to 80% [1]. However, despite this major advance in first-line treatment, a significant proportion of patients experience relapse after the initial chemotherapy, especially patients with high-risk scores on the International Prognostic Index (IPI) [2,3].

Before the advent of rituximab, the standard therapeutic approach for relapsed DLBCL was to decrease the tumor burden and assess chemosensitivity with a second-line therapy, and then consolidate the remission status with high-dose therapy and autologous stem cell transplantation (ASCT). Using this approach, the 5-year OS was 53% [4]. The sole prospective randomized trial of patients with DLBCL in first relapse or primary refractory to first-line therapy in the rituximab era was the CORAL trial, which included 396 patients [5]. The patients were randomized between 2 widely used regimens, ICE (ifosfamide, carboplatin, etoposide) and DHAP (dexamethasone, high-dose ara-c, cisplatinum), both of which were combined with rituximab (R-ICE and R-DHAP). No difference in outcome between the R-ICE and R-DHAP groups was seen. However, various parameters greatly affected the results of ASCT, including chemotherapy sensitivity before ASCT, previous treatment with rituximab, and time from diagnosis to relapse of <12 months. Nevertheless, to date no comparative study has evaluated the efficacy of ASCT according to these subgroups. Moreover, the outcome of relapsed patients without ASCT is poor, with <10% of patients alive at 5 years [1].

The purpose of the present study was to evaluate the efficacy of ASCT in the rituximab era by retrospectively comparing the duration of disease-free survival (DFS) after ASCT with the duration of the last disease phase just before the phase that included ASCT in each patient studied. Only chemosensitive patients in complete remission (CR) before ASCT were eligible for the study, because these patients are the best candidates for a salvage strategy. The aim of this approach, which has been used to develop new drugs such as I-131 tositumomab [6] and to evaluate ASCT in indolent non-Hodgkin lymphoma [7], was to ascertain whether ASCT lengthens the disease-free period during the disease course and ultimately has the potential to cure the disease.

PATIENTS AND METHODS

Study Design

The European Blood and Marrow Transplantation registry (EBMT) is a voluntary organization comprising 525 transplantation centers located mainly in Europe. Member centers are required to submit minimal essential data (MED-A form; www.ebmt.org) from consecutive patients to a central lymphoma registry in which patients are identified by subtype of lymphoma and type of transplantation. Participating transplantation centers are subject to onsite audits to assess data accuracy and consecutive reporting. Informed consent was obtained locally according to regulations applicable at the time of transplantation. Since January 1, 2003, all EBMT centers have been required to obtain written informed consent before data registration according to the Declaration of Helsinki of 1975.

This study was designed to evaluate the benefit of this strategy in patients with DLBCL who achieved second CR (CR2) after salvage chemotherapy by retrospectively comparing the DFS after ASCT with the duration of the first CR (CR1) for each patient. Partial responders, stable patients, and patients with progressive disease were excluded. The EBMT database was used to identify adult patients with DLBCL treated with a first ASCT in CR2 between 1990 and 2005. The registry included a total of 1166 such patients, only 470 of whom had a fully documented ASCT with an EBMT MED-B form. To avoid any bias related to the analysis of the patients with a MED-B form, both populations were compared in terms of 4 major outcomes: nonrelapse mortality (NRM), relapse rate (RR), DFS, and OS. No significant differences between the 2 populations were seen, and the 470 patients with fully documented ASCT information were used in further studies.

Patient and Transplant Characteristics

Characteristics of the patients and transplants are summarized in Table 1. The median patient age was 52 years (range, 18-74 years). Of the 470 patients, 275 (59%) underwent ASCT before 2002, and 351 (74%) did not receive rituximab before undergoing ASCT. Among the remaining 119 patients (25%) who did receive rituximab, 114 were treated between 2002 and 2005, 15 received rituximab during first-line treatment, 26 received rituximab in the relapse setting, and 41 received rituximab both during first-line treatment and after relapse. Information was not available for 32 patients. The median time from diagnosis to ASCT was 24 months (range, 6-395 months). The median duration of CR1 was 11 months (range, 1-112 months), and CR1 lasted <12 months in 49% of cases.

Statistical Methods

DFS was measured from the date of ASCT to the date of disease relapse or death. OS was measured from the date of ASCT to the date of death from any cause. DFS and OS curves were generated using the

Table 1. Characteristics of Patients at ASCT

Characteristic	n (%)	5-Year OS, %	*P* Value	5-Year DFS, %	*P* Value
Sex					
Male	262 (56)	62		47	
Female	208 (44)	63	.80	46	.90
Age					
<50 years	209 (45)	69		54	
≥50 years	261 (55)	56	.002	39	.003
Relapse before ASCT					
<12 months	240 (51)	61		47	
≥12 months	230 (49)	62	.30	44	.50
Previous rituximab therapy					
Yes	119 (25)	74		60	
No	351 (75)	63	.10	49	.05
Number of chemotherapy regimens					
2	412 (88)	62		47	
3	37 (8)	57		42	
4	8 (2)	53		38	
5 or 6	13 (3)	53	.20	38	.40
Conditioning regimen					
TBI/VP16/cyclophosphamide	20 (4)	52		40	
BEAM	314 (66)	60		44	
CBV	10 (2)	59		48	
BuCy	4 (1)	70		50	
Other protocol	132 (27)	52	.40	40	.70
Stem cell source					
Bone marrow	60 (13)	60		44	
Peripheral blood	399 (85)	63		46	
Both	11 (2)	62	.70	45	.80

BEAM indicates BCNU, VP16, cytarabine, and cyclophosphamide; BuCy, busulfan and cyclophosphamide; CBV, cyclophosphamide, BCNU, and VP16; TBI, total body irradiation.

Kaplan-Meier method, and NRM and RR were determined using cumulative incidents to account for competing risks. The primary endpoint of the study was DFS after ASCT, and the log-rank test was used to compare groups. The study's main objective was to evaluate the benefit of ASCT in CR2 by comparing DFS with the duration of CR1, using each patient as his or her own control. This approach is illustrated in Figure 1.

The duration of DFS and duration of CR1 were compared using the paired Wilcoxon signed rank test in the entire series and in defined subsets of patients. If a patient had not relapsed by the time of follow-up and if the duration of follow-up after ASCT was longer than the duration of CR1, then the impact of ASCT on DFS was considered positive for that patient. Some patients could not be included in the paired test because they had been censored because of having a shorter duration of follow-up than the duration of CR1.

All statistical analyses were performed using the SPSS 15.0 statistical package (SPSS, Inc., Chicago, IL) and NCSS97 software (Number Cruncher Statistical System, Kaysville, UT). A *P* value <.05 was considered significant.

RESULTS

Patient and transplant characteristics are summarized in Table 1. All of the patients were in CR2 after salvage chemotherapy before ASCT, and 88% of them received 2 regimens. The BEAM conditioning regimen was used in 67% of patients, with peripheral stem cell support in 85% of cases. At diagnosis, age-adjusted IPI (aaIPI) was available in 141 patients; values were 0-1 in 40% of the patients and 2-3 in 60%; bulky disease was present in 13%. At relapse, the aaIPI was 0-1 in 63% and 2-3 in 37%.

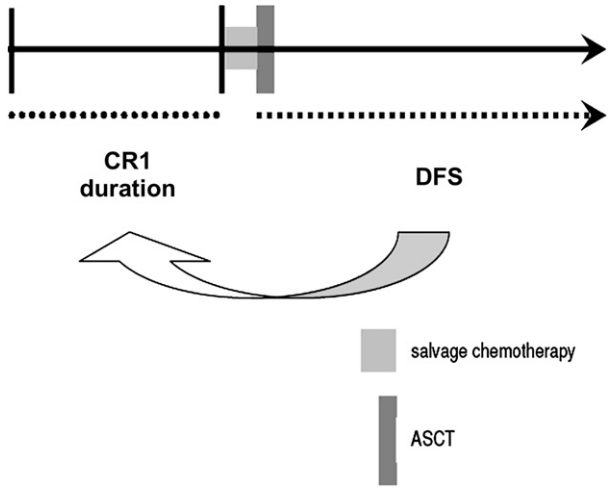

Figure 1. Disease course of relapsed patients with DLBCL. Each patient is considered his or her own control.

Survival

The median follow-up time after ASCT for the 305 surviving patients was 52 months. A total of 196 cases (42%) relapsed after ASCT, at a median of 10 months (range, 1-172 months). The 5-year cumulative incidence of relapse was 45% (95% confidence interval [CI], 40%-50%) (Figure 2A). Thirty-five patients (7%) experienced NRM (cumulative incidence of 6% at 3 years; 95% CI, 4%-9%) (Figure 2A). A total of 239 patients (51%) were alive and disease-free after ASCT at the time of follow-up. The estimated 5-year DFS and OS were 48% (95% CI, 43%-53%) and 63% (95% CI, 58%-67%), respectively (Figure 2B).

The association between the main patient characteristics and DFS calculated by univariate analysis showed that age at ASCT (≤50 years versus >50 years) was a significant prognostic factor (3-year DFS, 60% versus 48%; $P = .004$). The DFS curves according to CR1 duration showed nonproportional hazards over time. In this regard, the impact of this variable was investigated by separating the posttransplantation course into several different periods. A short duration of CR1 (<12 months versus ≥12 months) was associated with a worse DFS in the initial period after ASCT, with a DFS of 52% versus 67% at 2 years ($P = .003$) and no differences at longer follow-up periods. Finally, previous treatment with rituximab was associated with a better DFS after ASCT, with borderline significance (DFS at 3 years, 68% versus 55%; $P = .05$). This factor was investigated in patients who underwent ASCT

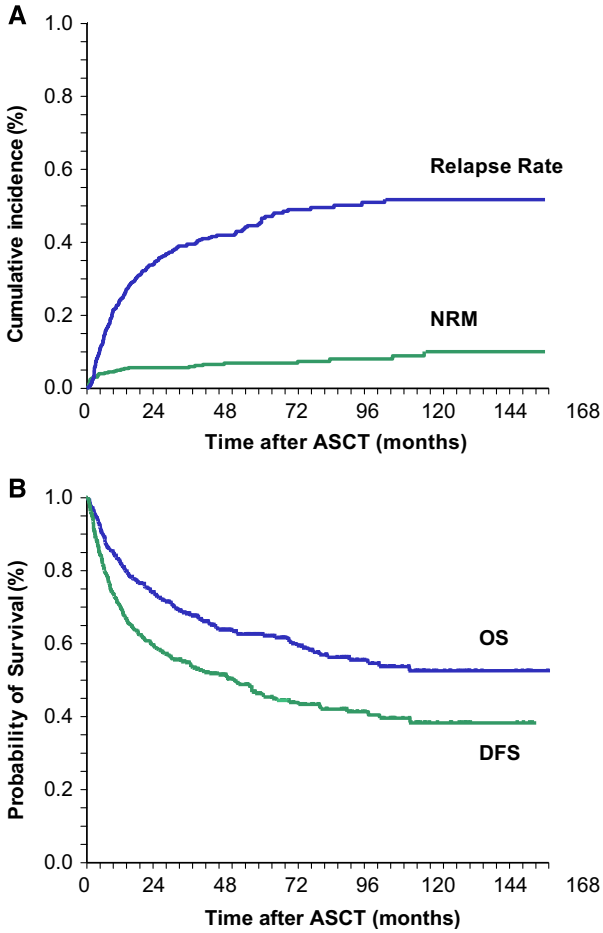

Figure 2. Overall outcome of the entire series (n = 470). (A) Relapse rate and nonrelapse mortality. (B) DFS and OS.

between 2002 and 2005. The absence of significant differences between the 81 patients who underwent ASCT after 2002 and never received rituximab versus the 270 patients who never received rituximab (TRM, 4% versus 3%; male sex, 56% versus 54%; IPI 2-3, 66% versus 67%; age >50 years, 45% versus 44%; DFS at 5 years, 43% versus 41%).

In summary, in patients with DLBCL, duration of CR1, previous treatment with rituximab, and age at ASCT were identified as prognostic factors for DFS after ASCT in CR2.

Comparative Survival Analysis by Patient

We then compared DFS duration and CR1 duration using each patient as his or her own control. The duration of CR1 and DFS after ASCT are shown in Figure 3. When each patient was assessed as his or her own control, the statistical analysis showed a significant increase in the duration of DFS after ASCT ($P < .001$). Fifty-eight patients could not be included in the paired analyses because of insufficient follow-up. In the remaining 412 patients, the duration of DFS after ASCT was longer than the duration of previous

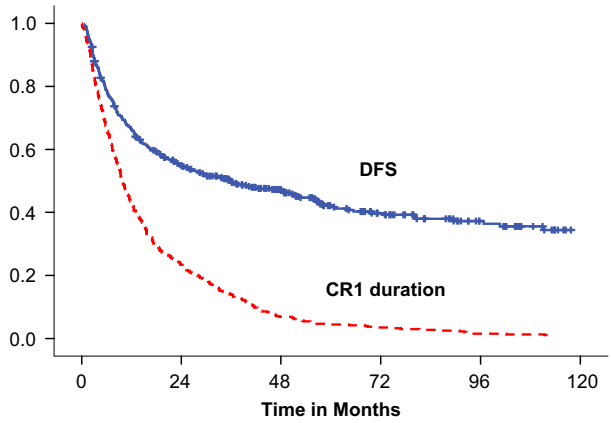

Figure 3. Duration of first complete remission and DFS after the ASCT for the entire series (n = 470).

CR1 for 291 patients (71%) and shorter for 121 patients (29%).

To better evaluate the benefit of ASCT consolidation for each patient, we analyzed several subgroups of patients. Follow-up duration was sufficient for inclusion in paired analysis in 228 patients with a CR1 shorter than 12 months and 184 patients with a CR1 longer than 12 months. The duration of DFS after ASCT was longer than the duration of previous CR1 in 80% of the patients in the first group ($P < .001$) and in 58% of the patients in the second group ($P = .002$). The duration of DFS exceeded that of previous CR1 in 66% of the 313 patients not previously treated with rituximab ($P < .001$), compared with 88% of the 99 patients previously treated with rituximab ($P < .001$). We also looked for potential differences between the groups "CR2 shorter than CR1" and "CR2 longer than CR1," considering clinical characteristics and rituximab administration. The only difference between these 2 groups was in the rate of previous rituximab treatment (15% versus 27%; $P = .001$), which persisted in the 2 subsets: CR1 duration <1 year (16% versus 31%; $P = .04$) and CR1 duration >1 year (14% versus 21%; $P = .20$).

To examine the effect of age at ASCT, 192 patients age <50 years and 220 patients age ≥50 years were included in the paired analyses. These analyses showed that ASCT significantly increased DFS after CR2 in both subgroups compared with the duration of CR1 (74% and 66% of the cases, respectively; $P < .001$ for both groups).

DISCUSSION

In response to the dramatic improvement in the treatment of DLBCL with rituximab therapy, several questions have been raised regarding the role of consolidation with ASCT in relapsed patients and whether the introduction of rituximab has changed the situation. The role and the quality of salvage chemotherapy

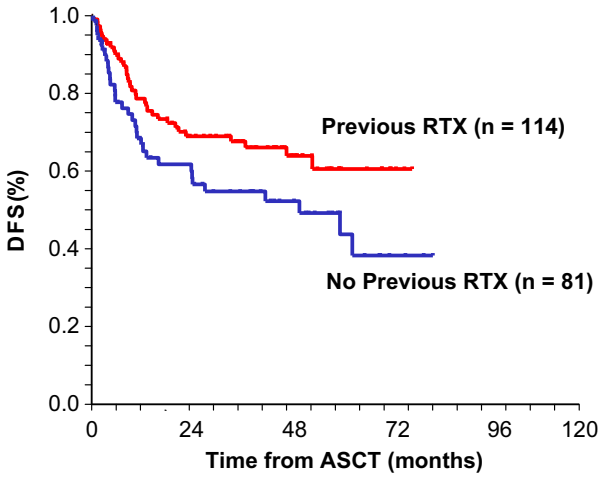

Figure 4. Impact of rituximab administration before ASCT on DFS in patients who underwent autografting between 2002 and 2005.

before ASCT remain the major determinants. The addition of rituximab to second-line chemotherapy followed by ASCT has significantly improved PFS in patients not exposed to rituximab as part of their first-line treatment [8]. However, previous exposure to rituximab during first-line treatment was an adverse prognostic factor for response to salvage treatment with rituximab in the CORAL trial [5], with only one-half of the patients responding.

Given the infeasibility of conducting a randomized study comparing salvage chemoimmunotherapy followed by ASCT with no ASCT, we decided to examine the outcomes of patients who had undergone ASCT while in first relapse and to compare the duration of the CR before ASCT with the duration of CR after ASCT in each patient. To avoid investigator bias in the definition of partial responders, only patients in CR2 or with a MED-B form available were included.

Before the rituximab era, the 5-year OS for relapsed DLBCL was 53% after high-dose chemotherapy and ASCT [4]. In the present study, our entire series of 470 patients had a projected 5-year OS of 63%. This 10% improvement since the 1980s might be attributed to better supportive care measures during the immediate post-ASCT period and the use of rituximab combined with salvage chemotherapy. The CORAL trial's 3-year OS of 68% for 206 patients who underwent ASCT [5] was similar to our finding. For those patients who achieve CR before ASCT, a clear benefit is seen in the reduction of RR compared with elderly patients not consolidated with an ASCT. No data are available for relapsed patients age <65 years treated with chemotherapy only. In one study, elderly patients who experienced disease progression after R-CHOP chemotherapy had a median OS of 0.6 year and a 3-year survival rate of 18% [1]. Nevertheless, several factors adversely affect outcome after ASCT, including age >50 years and CR1 duration of <12 months. However, the positive effect of previous rituximab exposure may reflect the quality of response before ASCT in all of these responding patients (Figure 4). In addition, this impact was seen mostly in patients treated with rituximab after relapse, and was not seen in patients treated up front and at relapse with rituximab chemotherapy or in patients who never received rituximab (data not shown). The underlying biology of the disease cannot be ascertained from clinical parameters alone; genomic profiles are needed as well [9]. Consequently, the finding that a patient who had experienced one relapse did not relapse again after salvage chemotherapy and ASCT implies that the new treatment is efficient. Similarly, an increase in the disease-free duration after ASCT can lead to the same conclusion.

In the present study, when each patient was assessed as his or her own control, the duration of PFS after ASCT exceeded that of CR1, demonstrating that ASCT can alter the course of disease. This difference in favor of the post-ASCT period was significant in patients with previous exposure to rituximab and relapse before 1 year. Overall, the 5-year DFS of 48% suggests that ASCT can change the disease course even in high-risk relapsed DLBCL patients. These results can be extrapolated to relapsed patients who achieve partial response after salvage chemotherapy, as shown in the CORAL trial. Our results must be viewed with caution, however, given the retrospective nature of our analysis, the inclusion of some inherent selection bias, and the fact that the quality of tumor response was not investigated in more detail by positron emission tomography using [18F]-fluoro-2-deoxy-D-glucose [10].

In conclusion, the quality of salvage chemotherapy must be improved, and the most appropriate treatment should be identified by considering the characteristics of those patients who experience relapse after chemoimmunotherapy. Because approaches to predicting outcome after treatment using microarray genome-wide techniques are still not available in the clinical setting, ASCT remains a good therapeutic option for patients with chemosensitive relapsed DLBCL. Specific efforts aimed at identifying those patients with refractory disease at early stages are crucial. In this context, new approaches, including allogeneic transplantation [11,12] and novel targeted therapies developed as a result of a better understanding of the biology of the disease [13], will play key roles.

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APPENDIX: EBMT PARTICIPATING CENTERS

The following EBMT centers and principal investigators contributed patients to the study: Hôpital St. Louis, Paris, France (C. Gisselbrecht), n = 35; Erasmus Medical Center–Daniel den Hoed Cancer Center, Rotterdam, the Netherlands (J. J. Cornelissen), n = 19; University "La Sapienza", Rome, Italy (R. Foa), n = 18; Hospital of the University of Marqués de Valdecilla, Santander, Spain (E. Conde), n = 17; University Hospital Gasthuisberg, Leuven, the Netherlands (J. Maertens), n = 16; Hopital de Purpan, Toulouse, France (M. Attal), n = 13; Ospedali Riuniti di Bergamo, Bergamo, Italy (A. Rambaldi), n = 13; Addenbrooke's Hospital, Cambridge, UK (C. Crawley), n = 11; Sahlgrenska University Hospital, Göteborg, Sweden (M. Brune), n = 10; Yorkshire Blood and Marrow Transplant Programme, Leeds, UK (G. Cook), n = 9; University Medical Center Groningen, Groningen, the Netherlands (G. W. van Imhoff), n = 9; University of Saarland, Homburg, Germany (M. 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Cortelazzo), n = 6; Ospedale di Careggi, Firenze, Italy (A. Bosi), n = 6; Azienda Ospedaliera, Reggio Calabria, Italy (G. Irrera), n = 6; VU University Medical Center, Amsterdam, the Netherlands (J. Janssen), n = 6; University Hospital, Basel, Switzerland (J. Passweg), n = 5; Ospedale San Martino, Genoa. Italy (A. Bacigalupo), n = 5; Radboud University–Nijmegen Medical Centre, Nijmegen, the Netherlands (A. Schattenberg), n = 5; CHU Nantes, Nantes, France (M. Mohty), n = 5; Ospedale Maggiore di Milano, Milano, Italy (A. Cortelezzi), n = 5; Service D'Hématologie Clinique Adulte et Pédiatrie, Clermont-Ferrant, France (J.-O. Bay), n = 5; University Hospital, Lund, Sweden (S. Lenhoff), n = 5; Helsinki University Central Hospital, Helsinki, Finland (L. Volin), n = 5; Hôpital de l'ARCHET, Nice, France (J. P. Cassuto), n = 5; ICO–Hospital Duran i Reynals, Bellvitge, Spain (R. F. Duarte), n = 5; St. Bartholomew's and The Royal London NHS Trust, London, UK (J. Gribben), n = 5; Centro di Riferimento Oncologico, Aviano, Italy (M. Michieli), n = 4; Leiden University Hospital, Leiden, the Netherlands (J. H. Veelken), n = 4; Cliniques Universitaires St. Luc, Brussels, Belgium (X. Poire), n = 4; University Medical Center, Utrecht, the Netherlands (E. Petersen), n = 4; Bologna University, S Orsola-Malpighi Hospital, Bologna, Italy (M. Baccarani), n = 4; Belfast City Hospital, Belfast, Northern Ireland (M. F. McMullin), n = 4; Kuopio University Hospital, Kuopio, Finland (E. Jantunen), n = 4; Haga Hospital (Leyenburg), The Hague, the Netherlands (P. W. Wijermans), n = 4; University Hospital Maastricht, Maastricht, the Netherlands (H. Schouten), n = 4; Klinikum Nürnberg, Nürnberg, Germany (H. Wandt), n = 4; Institut Gustave Roussy, Villejuif Val de Marne, France (J. H. Bourjuis), n = 4; Hospital Clinico Universitario, Salamanca, Spain (D. Caballero), n = 4; Sezione di Ematologia, Perugia, Italy (M. F. Martelli), n = 4; Institut Jules Bordet, Brussels, Belgium (D. Bron), n = 3; Centre Leon Berard, Lyon, France (P. Biron), n = 3; Hospital de la Santa Creu i Sant Pau, Barcelona, Spain (A. Sureda), n = 3; American University of Beirut, Beirut, Lebanon (A. Bazarbachi), n = 3; Centre for Clinical Haematology, Queen Elisabeth Hospital, Birmingham, UK (C. Craddock), n = 3; St. István and St. Laszlo Hospital of Budapest, Budapest, Hungary (T. Masszi), n = 3; L'Hôpital Erasme, Brussels, Belgium (B. Bailly), n = 3; University College London Hospital, London, UK (K. Thompson), n = 2; Hospital de la Princesa, Madrid, Spain (A. Alegre), n = 2; The Great Western Hospital, Swindon, UK (N. E. Blesing), n = 2; Chaim Sheba Medical Center, Tel-Hashomer, Israel (A. Nagler), n = 2; Royal Bournemouth Hospital, Bournemouth, UK (R. Hall), n = 2); Rigshospitalet, Copenhagen, Denmark (H. Sengeloev), n = 1; Hopital Jean Minjoz, Besancon, France (E. Deconinck), n = 1; Hopital La Miletrie, Poitiers, France (F. Guilhot), n = 1; CHU Angers, Angers, France (N. Ifrah), n = 1; Hôpital Percy, Clamart, France (T. De Revel), n = 1; Charles University Hospital, Pilsen, Czech Republic (V. Koza), n = 1; Hospital Universitari Son Dureta, Palma de Mallorca, Spain (J. Besalduch), n = 1.