Bone Marrow Transplantation (2008) 41, S118–S127
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ORIGINAL ARTICLE

28 years of high-dose therapy and SCT for neuroblastoma in Europe: lessons from more than 4000 procedures

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Between 1978 and 2006, the European Group for Blood and Marrow Transplantation registered 4098 high-dose therapy (HDT) procedures followed by stem cell rescue (SCR) (3974 autologous/124 allogeneic) in patients with neuroblastoma. The 5-year rates for overall (OS) and event-free survival are 37 and 32%, respectively. The median age at diagnosis is 3.9 years (0.3–62 years) with 76 patients older than 18 years. Patients above 10 years carry a 2.5-fold higher risk. Younger patients cure significantly (<0.001) better with OS rates of 40 and 30% for age groups 2–4 years and 4–10 years, respectively. Their risks are about twofold higher than that of patients below 2 years with OS rates of 60%. The better the quality of remission status before HDT/SCT the better are the observed OS rates: 43% in CR1 (1199 patients) and 42% for CR2 (140 patients), and 36% for those in very good partial or partial remission (1413 patients) and 21% for those with sensitive relapse (134 patients). Patients reported with stable disease in first remission still had an OS rate of 30%. Multivariate analysis shows significantly better OS in the age group of less than 2 years (<0.0001), as well as a better quality of remission status before HDT/SCT ($P<0.0001$), with the use of peripheral stem cells ($P=0.014$), autologous SCT ($P=0.031$) and busulphan/melphalan HDT ($P<0.001$). Busulphan/melphalan HDT/SCT in first remission achieves an OS of 48%, while it is only 35% with other regimens ($P<0.001$), including melphalan alone, other melphalan-containing regimens, a variety of other drugs given as a single HDT as well as the addition of TBI or sequential HDT/SCT procedures. Further progress in the field may only be expected from large-scale international randomized trials.

Bone Marrow Transplantation (2008) **41,** S118–S127; doi:10.1038/bmt.2008.69

Keywords: neuroblastoma; high-dose treatment; stem cells; EBMT

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Introduction

The European Group for Blood and Marrow Transplantation (EBMT) data represent a selected cohort of high-risk neuroblastoma patients having been allocated for high-dose treatment (HDT) procedure followed by stem cell rescue. Hence registry-specific shortcomings need careful consideration including the wide variations in indications, age, lack of biological prognostic data, pre-treatment response status, type of HDT/SCT and source of stem cells used. Finally, there is no report on treatments following post transplant period, assuming that those would influence at least event-free survival (EFS) rates.

Although overall survival (OS) rates for high-risk neuroblastoma have improved only modestly over the past several decades,[1–4] there has been marked progress in the ability to recognize prognostic subgroups based on clinical and biological factors,[5] including age,[6–8] disease stage,[9] MYCN oncogene copy number (amplification),[10,11] DNA index (ploidy),[12,13] chromosomes 1 p36 and 11q23 deletions,[14] 17 q gain[15] and histology.[16,17]

Nowadays, patients with neuroblastoma are considered to be at high risk when presented with metastatic disease at an age above 12–18 months[7,8] as well as patients with MYCN-amplified tumours at any age. Therapeutic approaches have evolved over the past decades. Most recent treatment concepts foresee an intensive induction regimen; local control modalities including resection of the primary tumour eventually followed by postponed local radio-

therapy and finally HDT with SCT followed by treatments for minimal residual disease.

In this report, special attention will be given to current indications based on the messages coming from 28 years of European data collection for neuroblastoma within the EBMT registry and leading publications in the field.

Patients and methods

Since 1984, 3571 patients with neuroblastoma were registered on the EBMT database, out of which 3421 are currently evaluable for stage, remissions status and outcome. However, the EBMT registry did not capture prognostic biological data, that is, MYCN status. The median age at HDT/SCT is 3.9 years (range, 0.3–62 years) with 77 patients above the age of 18 years. Male patients account for 59% in this cohort. The median follow-up time from SCT is 9 years with a median observation time of 4.2 years.

Two thousand seven hundred and forty-one (89%) patients received HDT/SCT as consolidation of primary treatments, the vast majority presenting with stage 4 disease at diagnosis. Relapse was the indication in another 345 patients (11%), while, in 335 patients, the status before HDT was not specified so far.

Data were collected from 27 European countries: France (972 patients), Italy (553 patients), UK (484 patients), Germany (346 patients), Spain (203 patients), Austria (92 patients), Belgium (85 patients), Poland (85 patients), Finland (58 patients), Switzerland (52 patients), Sweden (51 patients), Ireland (32 patients), Czech Republic (32 patients), Hungary (31 patients), Greece (27 patients), Denmark (24 patients), Netherlands (21 patients), Portugal (15 patients), Slovakian Republic (12 patients), Croatia (10 patients), Serbia & Montenegro (8 patients), Lithuania (4 patients), Bulgaria (3 patients), Slovenia (3 patients), Romania (2 patients) and Belarus (1 patient).

In addition, Israel (116 patients), Australia (37 patients), Turkey (14 patients), Russia (13 patients), Saudi Arabia (11 patients), Jordan (10 patients), New Zealand (7 patients), South Africa (4 patients), Argentina (3 patients), have contributed to the EBMT registry.

A total of 4098 HDT procedures were registered. In 3974 patients, autologous stem cells were reinfused, while 124 patients were allocated for an allogeneic SCT.

Results and risk factors

Overall survival and EFS at 5 years were 37 and 32%, respectively. Further detailed outcome data are summarized in Table 1 for OS and EFS rates referring to age, stage, response, number of HDT courses, type of HDT regimens and stem cell source. All OS and EFS data refer to rates at 5 years.

Age influence

Patients with age under 12 months show a superior outcome in 32 infants with a 66% OS rate. Recently, the later age cut-off point at 18 months has gained importance. The registry finds 132 children in the age group from 12 to 18 months (about 90% are reported to with stage 4 disease) and their OS is 61%. In the age group of 18–24 months (277 patients), the OS rate is 58%. There is a significant drop in survival rates observed with increasing age. Within the EBMT data, one may observe children with an age below 2 years in the 60% OS range, while 2–4 years olds cluster around a 40% OS rate. Interestingly, age groups of 4–10 years are in the range of 30% while from 10 years onwards OS rates around 20% are observed. (Figures 1a and b). Survival data translate into increasing relative hazard rates of 1–1.3 below the age of 2 years, 1.8–2.3 for ages 2–10 years and they are 2.5-fold higher above the age of 10 years.

Stage

In the registry, the stage is currently reported only in 53% of the cohort but shows high prevalence for advanced disease with stage 4 in more than 90% in the reported cohort.

Response status

Response after primary treatments was reported as follows: first complete remission (CR1) in 1200 patients, partial response (VGPR/PR) in 1416 patients, stable disease in 53 patients and primary refractory disease in 72 patients (Figure 2).

After relapse, a total of 334 neuroblastoma patients received HDT. One hundred and thirty-two patients achieved a second complete remission, 132 had a sensitive relapse and 38 showed resistant relapse. Seventeen patients received no treatments before HDT (untreated relapse). The better the quality of remission status before HDT/SCT the better are the observed OS rates: 43% in CR1 (1199 patients) and 42% for CR2 (140 patients) and 36% for those in very good partial or partial remission (1413 patients) and 21% for those with sensitive relapse (134 patients). Interestingly, patients reported with stable disease in first remission still had an OS rate of 30%, suggesting a particular disease profile influenced by biology and/or histology.

Number of HDT courses

A single-HDT programme was used in 2985 patients, while 455 patients were part of sequential HDT programmes (Figure 3). One must consider here that many patients were submitted to sequential HDT designs within the frame of phase II settings.

Type of stem cell source

The use of peripheral stem cells has steadily increased and has contributed to lower the toxicity profile within the autologous SCT setting. So far, 1339 patients had received BMs, 113 had a combination of BM and PBSC, and, more recently, 1843 patients had PBSC. In the allogeneic setting, mainly BM was used. The outcome of patients with HDT in first remission according to stem cell source shows an OS rate of 36% for the BM group (1076 patients), 41% for the

Table 1 Summary of EBMT 2007 analysis for neuroblastoma

Factors	*Patients*	*5-years pSU*	P-*value*	*5-years pEFS*	P-*value*
HDT/SCT during primary treatment	2741	0.38 ± 0.01	<0.001	0.54 ± 0.06	<0.001
HDT/SCT after relapse	334	0.28 ± 0.03		0.31 ± 0.01	
Stage of disease					
Stage in primary treatment patients					
1–3, 4s	85	0.57 ± 0.06	0.002	0.28 ± 0.05	0.504
4	1365	0.36 ± 0.01		0.28 ± 0.04	
Initial stage in relapse patients					
1–3, 4s	103	0.35 ± 0.05	0.145 (NS)	0.34 ± 0.01	<0.001
4	128	0.27 ± 0.05		0.23 ± 0.03	
Response status prior HDT					
First remission	2741				
CR1	1200	0.43 ± 0.02	<0.001	0.39 ± 0.16	<0.001
PR, VGPR	1416	0.36 ± 0.02		0.31 ± 0.14	
SD	53	0.30 ± 0.07		0.28 ± 0.07	
PRD	72	0.19 ± 0.08		0.12 ± 0.04	
Relapse patients	334				
CR2	140	0.42 ± 0.05	<0.001	0.34 ± 0.04	<0.001
SR	134	0.21 ± 0.04		0.17 ± 0.04	
RR	40	0.14 ± 0.06		0.11 ± 0.05	
Relapse untreated	20	0.10 ± 0.07		0.05 ± 0.05	
Age at diagnosis					
<1 year	32	0.66 ± 0.09	<0.001	0.58 ± 0.01	<0.001
1–2 years	409	0.59 ± 0.03		0.57 ± 0.03	
12–18 months	132	0.61 ± 0.05		0.62 ± 0.05	
18–24 months	277	0.58 ± 0.03		0.54 ± 0.03	
⩾2–4 years	1337	0.40 ± 0.05			
⩾4–10 years	1391	0.30 ± 0.02			
⩾10–18 years	175	0.19 ± 0.04			
>18 years	77	0.27 ± 0.08		0.11 ± 0.05	
Type of stem cells					
HDT/autologous SCT	3350	0.37 ± 0.01	<0.001	0.32 ± 0.01	0.005
HDT/allogeneic SCT	71	0.25 ± 0.05		0.24 ± 0.05	
Autologous SCT					
Primary treatments	2698	0.39 ± 0.01	0.019	0.34 ± 0.07	<0.001
Relapse treatments	329	0.29 ± 0.03		0.31 ± 0.07	
Allogeneic SCT					
Primary treatments	43	0.29 ± 0.07	<0.001	0.31 ± 0.07	0.021
Relapse treatments	16	0.12 ± 0.08		0.13 ± 0.08	
Primary treatments					
HDT/autologous SCT	2698	0.39 ± 0.01	0.141 (NS)	0.34 ± 0.01	0.252
HDT/allogeneic SCT	43	0.29 ± 0.07		0.31 ± 0.07	
Relapse treatments					
HDT/autologous SCT	329	0.29 ± 0.03	0.016	0.23 ± 0.03	0.037
HDT/allogeneic SCT	16	0.12 ± 0.08		0.13 ± 0.08	
Autologous SCTs					
Number of HDT					
Single-HDT	2895	0.38 ± 0.01	0.105 (NS)	0.33 ± 0.01	0.187
Sequential-HDT	455	0.33 ± 0.03		0.27 ± 0.02	
SCT during primary treatments	2333				
Busulfan/melphalan	343	0.48 ± 0.03	<0.001	0.41 ± 0.03	0.004
Busulfan/melphalan with CYC/TTP	90	0.40 ± 0.05		0.39 ± 0.05	
Melphalan alone	234	0.34 ± 0.03		0.28 ± 0.03	
Melphalan+	287	0.36 ± 0.04		0.30 ± 0.03	
TBI	322	0.34 ± 0.03		0.29 ± 0.03	
Others	125	0.41 ± 0.05		0.33 ± 0.04	
Single MGT during primary treatments:					
TBI−	904	0.41 ± 0.02	0.004	0.36 ± 0.02	0.002
TBI+	318	0.34 ± 0.03		0.29 ± 0.03	

Abbreviations: EBMT = European Group for Blood and Marrow Transplantation; HDT = high-dose therapy; PRD = primary refractory disease.

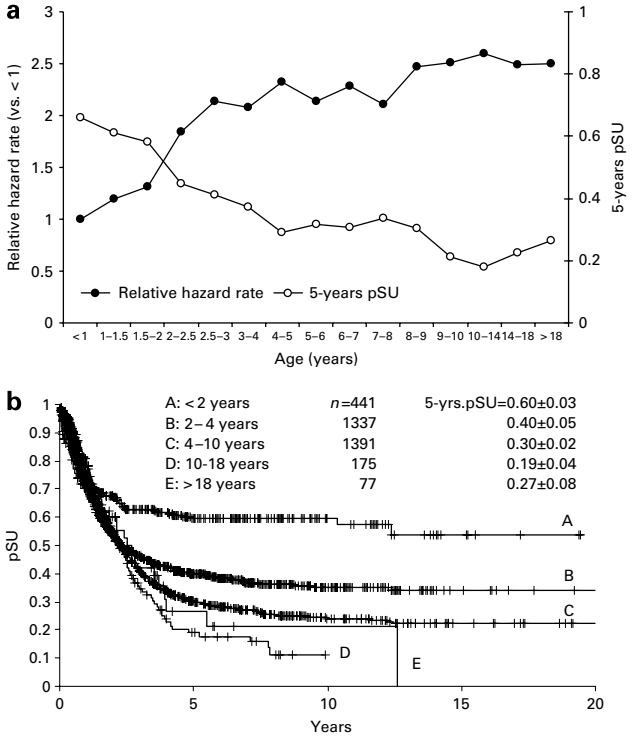


Figure 1 (**a**) Association of age and outcome. (**b**) Outcome according to age.

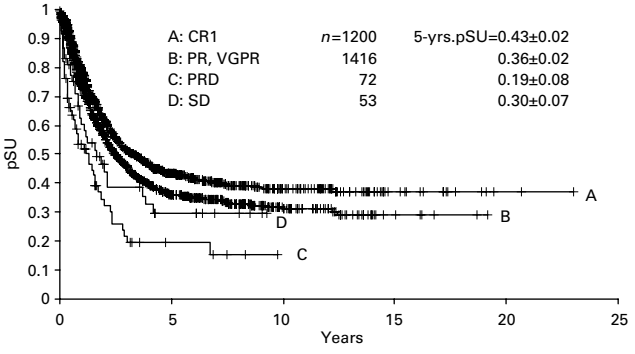


Figure 2 Outcome according to response status in first remission.

PBSC group and 41% for the group receiving both PBSC and BM.

Influence of HDT regimens

With the help of the EBMT data set, it was possible to demonstrate a superior outcome related to the type of HDT. This could be shown in a cohort of 2333 patients receiving HDT during primary treatments followed by autologous stem cell reinfusion. The busulphan/melphalan regimen used in 343 patients produced a significantly superior outcome with a 5-year OS rate of 48% (Figure 4). busulphan/melphalan combined with cyclophosphamide and thiotepa in addition was used in 90 patients resulting in a 5-year OS of 40%. Notably, the oldest cohort of 234 patients that received melphalan alone had the same result

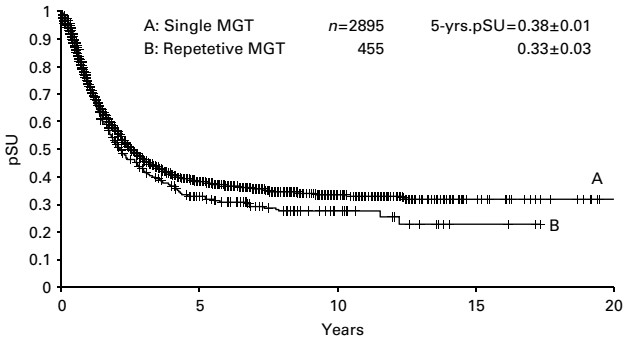


Figure 3 Outcome according to the number of HDT procedures.

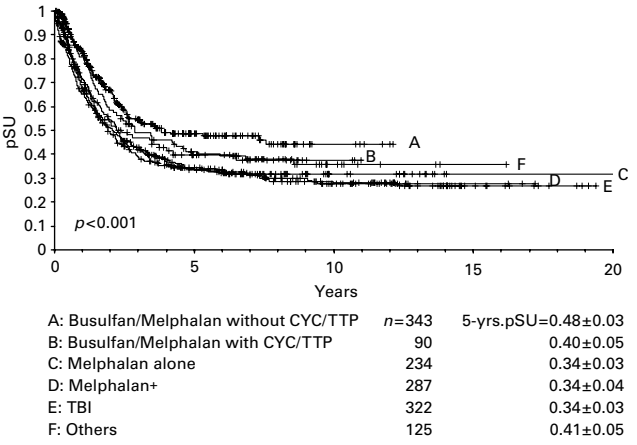


Figure 4 Outcome according to type of high-dose therapy for patients in first remission.

as regimens combining melphalan and other high-dose chemotherapy producing both an OS rate of 34%. TBI-containing regimens used in 322 patients produced equal results with the burden of TBI late effects. One hundred and twenty-five patients had various other HDT combinations resulting in an OS rate of 41%.

Influence of autologous vs allogeneic stem cell grafts

Currently, outcome compared on the basis of source of stem cells is still in favour of the autologous approach as used in 3350 patients with a 5-year OS rate of 37% as opposed to 25% only in the allogeneic setting (Figure 5).

Transplant-related mortality

For the autologous patients' cohort, a steady significant decrease in transplant-related mortality was observed. The 1-year cumulative incidence was 11%, whereas before 1995, it was of only 4% from 1995 onwards. Such a decrease in TRM over time is not observed in the registry for the allogeneic setting (1-year cumulative incidence of 16% in both periods) (Figure 6).

Here, it is of particular interest to compare the autologous and the allogeneic group as mortality rates evolve over time. The cumulative incidence is 4, 6 and 8%, respectively, at day 100, after 1 year and after 5 years for

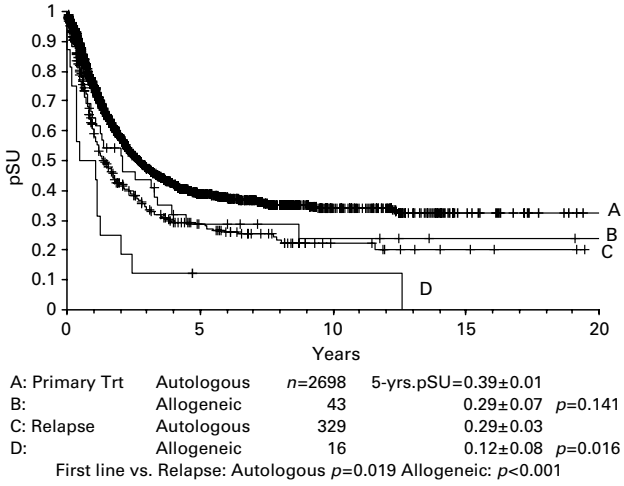


Figure 5 Outcome according to stem cell source and remission status.

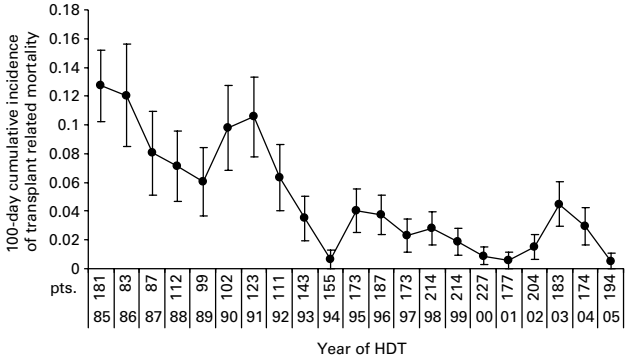


Figure 6 Transplant-related mortality and years of HDT procedures.

the autologous setting, whereas, for the allogeneic setting, it is 13, 16 and 18%, respectively.

Multivariate analysis

The MVA of EBMT data clearly demonstrate the significantly better prognosis for children with an age below 2 years, as well as the advantage of autologous peripheral stem cells and the use of busulphan/melphalan for patients in complete remission before HDT/SCT (Table 2).

Table 2 Multivariate analysis on EBMT neuroblastoma data 2007

	P-*value*	*HR*	*95% CI*
Age above 2 vs below 2	<0.0001	1.6	1.4–1.9
Status at transplant (vs CR1)	**<0.0001**		
PR, VGPR	0.001	1.2	1.1–1.4
SD	0.018	1.5	1.1–2.2
PRD	<0.001	2.5	1.9–3.3
CR2	0.350	1.1	0.9–1.4
Sens. relapse	<0.001	2.1	1.7–2.6
Res. relapse	<0.001	3.2	2.3–4.6
RU	<0.001	4.2	2.6–6.7
Type allogeneic vs autologous	**0.031**	1.4	1.0–1.8
Stem cell source (vs pB)			
BM	0.014	1.1	1.0–1.3
Other	0.889	1.0	0.7–1.3
Conditioning regimen vs BUMEL	**0.001**		
Busulfan/melphalan + CYC-TTP	0.458	1.1	0.8–1.5
Melphalan alone	0.003	1.4	1.1–1.8
Melphalan ±	0.025	1.3	1.0–1.6
TBI	<0.001	1.5	1.2–1.9
Others	0.514	1.1	0.8–1.6
Sequential	0.020	1.3	1.0–1.6

Abbreviations: EBMT = European Group for Blood and Marrow Transplantation; PRD = primary refractory disease.
Bold values are the *P*-values of the global test.

Discussion and future perspectives

Although widely used, the role of HDT as first-line treatment for neuroblastoma in first remission was a matter of debate over the last 20 years. A very large number of HDT regimens have been employed, as this therapeutic modality was introduced in the early 1980s.[18] The large variety and, consequently, the limited number of patients treated with each individual regimen hindered for a long time the possibility of reaching firm conclusions on their respective antitumour effect and toxicity.

EBMT data may be a valuable source of information, in particular, in view of more than 4000 HDT/SCT procedures performed for neuroblastoma. However, some restraints need to be acknowledged upfront. EBMT data represent a selected patient cohort, as the data do not reflect patients suffering early progressions during front-line treatments. Thus, EBMT results tend to show a superior outcome for patients in first remission as compared with data generated from large prospective trials. On the other hand, EBMT data also capture second-line indications in poor responding, primary refractory or relapse patients including local only as well as metastatic recurrences, all having nevertheless survived long enough to be allocated to HDT/SCT. The latter may explain the quite favourable OS rates of 28%, which is otherwise not seen in relapsing stage 4 disease.[19] In addition, the change in sensitivity and accuracy of methods while evaluating metastatic disease including BMs (morphology/immunohistochemistry/reverse transcription-PCR methods) and skeletal disease (Tc99 scans and/or metaiodobenzylguanidine (MIBG) scans) needs to be considered. For this reason, PR and VGPR data were pooled in the current analysis. Only 5% of patients have non-stage 4 disease within the EBMT registry when allocated to a HDT/SCT programme in the first remission. MYCN amplification is nowadays generally accepted as major adverse factor in local/locoregional disease, and patients with this biological feature are in need of intense treatment including HDT/SCT. However, as the EBMT registry did not capture biological data or prognostic histological subgroups,[16,17] one may not specify retrospectively if the indication in this group was based on the histobiological profiles or on unsatisfactory clinical response.

Over the past 28 years, lessons from the EBMT registry for neuroblastoma include the following major messages.

1. In 2007, a total of 4098 HDT/SCTs procedures are registered within the EBMT database. For 3421 evaluable patients, the OS at 5 years is 37%. The OS is 38% for patients in first remission and less favourable with 28% for patients after relapse. Late relapses do occur beyond the 5th year. However, 5-year survivors do have an 80% chance of becoming a long-term survivor.
2. Age is a major predictor for outcome after HDT/SCT approaches with a significant decrease of prognosis with increasing age. In the EBMT registry, children with an age below 2 years are in the 60% OS range, while 2–4 years olds cluster around a 40% OS rate. Interestingly, ages from 4 to 9 years are in the range of 30%, whereas from 10 years onwards OS rates around 20% are observed. Infants with stage 4 disease reported to the EBMT had a 17% toxic death rate.[20] In 2007, only this fragile age group should be submitted to HDT/SCT on the basis of an adverse biological profile considering the peculiarities of this disease at very young age capable of undergoing spontaneous regression even with wide-spread disease (stage 4 and 4s). In addition, the favourable outcome of children with stage 4 neuroblastoma in the age group of 12–18 months has recently been described with and without association of biological factors.[6–8] In view of the good prognosis of patients less than 18 months, the results from INRG (International Neuroblastoma Risk Grouping) suggest that patients with stage 4, MYCN non-amplified neuroblastoma with hyperdiploid tumours should not receive HDT, but their outcome should be very carefully monitored to ensure that the good outcome of this group with over 60% OS is not compromised.[12] Stage 4 disease under the age of 18 months, therefore, needs careful evaluation of currently accepted risk profiles prior being submitted to HDT/SCT procedures.[8]
3. The quality of response before HDT/SCT is a significant predictor for ultimate outcome underlining the importance of effective induction regimens. Multivariate analysis of clinical prognostic factors in children with stage 4 disease over the age of 1 year showed that EFS was mainly influenced by two adverse factors before HDT/SCT: persisting skeletal involvement (99 Tc and/or MIBG positive) as well as persisting BM disease.[21] The advantage of the lack of skeletal involvement at diagnosis (50 vs 5%) as well as the disappearance of all detectable metastatic disease before HDT was clearly described in children treated with intense induction treatments.[9,21] The lack of uniform criteria to document the regression of skeletal and BM disease has made it difficult over the last decades to compare results.[22–24] However, the upcoming revised INRG criteria and international standardization[25] will help future trials to be more comparable on the international level.
4. Once local relapse with an adverse biological profile or disseminated relapse occurs, only patients responding after 12 months from diagnosis and having not been treated by HDT/SCT previously may benefit from salvage HDT/SCT. Relapse patients who do not fulfil these criteria gain no advantage from this intensive procedure. In particular, none of the survivors of patients with a HDT/SCT procedure carried out after relapse had previously received a HDT/SCT. This message is of particular importance for decision-making processes in relapsing stage 4 patients.[20]
5. One of the most interesting merits of the EBMT registry was the identification of a significantly superior HDT regimen for neuroblastoma in Europe. With growing statistical power, the busulphan/melphalan HDT approach resulted in a significantly improved survival rate of 48% in first remission patients in comparison with the other reported HDT regimens. The SIOP Europe Neuroblastoma Group (SIOPEN) currently randomizes busulphan/melphalan in comparison with CEM (carboplatin, melphalan, melphalan) within the ongoing European HR-NBL-1/SIOPEN study. Combinations of busulphan/melphalan combined with cyclophosphamide and/or thiotepa in addition resulted in a 5-year OS of 40%. Notably, the cohort receiving melphalan alone achieved a result similar to that of regimens combining melphalan with two to three drugs out of the following, that is, adriamycin, BCNU, cisplatin, carboplatin, etoposide (VP16), vumon (VM26), thiotepa, vincristine,[21,26–32] with an OS rate of 34%. Various other HDT combinations resulted in an OS rate of 41%.
6. TBI-containing regimens were developed for the predicted capacity of TBI to achieve a cell kill likely to eradicate micro-metastases. TBI regimens produced comparable results as high-dose chemotherapy combinations alone with an OS rate of 34% in first-line patients with the burden of TBI late effects. When the population of patients in the first remission with a single-HDT procedure was analysed, results were even clearer, showing a significantly worse OS rate of 34% ($P = 0.004$) for TBI-containing regimens in comparison with an OS of 41% for regimens not including TBI. As there is no convincing evidence for benefits of TBI, it should be spared in children.
7. Of notice, the EBMT analysis does not show any significant difference in the overall toxic death rate between different regimens, but TBI may produce more long-term complications. TBI was still included in pre-transplant regimens (up to a total dose of 14 Gy) until quite recently.[1,33,34] A further development is the use of high doses of MIBG either alone or in addition to TBI and local radiotherapy, which may increase the chance of eradicating small tumour deposits.[35]
8. The use of MIBG in place of TBI has been proposed in pilot studies[36,37] and was used in trial settings.[38] Preliminary results of the association of melphalan with TBI and MIBG demonstrate the feasibility of such a regimen.[39–41] High doses of MIBG alone or in combination with topotecan[42] or other radiosensitizing agents such as CDDP[43,44] followed by PBSCR have been piloted with early promising results in poor responding or relapse patients.
9. Within the EBMT data, the sequential HDT/SCT programmes were performed in 455 patients showing an OS of 33% as compared with 38% in single-HDT/

SCT procedures. Sequential tandem HDT has been developed in view of the frequency of early relapse following BMT.[45] The LMCE2 pilot study used a double-HDT procedure including TBI in the latter, reporting survivors up to 5 years.[46] Quite promising results were recently published with tandem cycles of HDT and SCR with a 5-year EFS rate of about 50%.[47] Based on this, the next COG study will explore the impact of single- vs sequential HDT through randomization.

10. In a matched EBMT cohort, autologous SCT was shown to be at least equal to allogeneic SCT.[48] The Children's Cancer Group reported a similar outcome for patients with neuroblastoma given this same induction therapy followed by autologous purged marrow to that with allogeneic marrow.[49] Also in the 2007 update, no advantage for allogeneic SCT is visible and the significantly higher burden of toxicities associated with allogeneic SCT is clearly documented. Any potential antitumour effect was probably lost through the increased toxicity observed resulting in no progression-free or survival advantage in the allogeneic SCT group. More recent allogeneic approaches, including haploidentical/matched unrelated donor programmes, may offer new aspects to develop a scenario to translate the observed graft vs tumour effects into remissions of longer durations.[50–54]
11. The use of peripheral stem cells has steadily increased and has contributed to lower the toxicity profile within the autologous SCT setting.[9,55–57]
12. The role of purging procedure also has been in question over the past decades.[58] Although gene-marking studies suggested that reinfused tumour cells at least contribute to relapse,[59] the disclosure of the most recent COG trial[60] showed no benefit for purging tested in a randomized trial setting in first line patients.
13. Transplant-related mortality significantly improved over time in the autologous setting. Although the 1-year cumulative incidence was 11% before 1995, it was of only 4% from 1995 onwards. Such a decrease in TRM over time is not observed in the registry for the allogeneic setting (1-year cumulative incidence of 16% in both periods).

The value of HDT/SCT for neuroblastoma patients in the first remission has been questioned over many years. So far, three randomized studies have reported prolongation of EFS rates and only the smallest series showed a benefit for OS. In 48 randomized patients with stages 3–4 neuroblastoma achieving at least partial remission after a standardized cisplatin-containing induction regimen, a prospective randomized study of high-dose melphalan followed by unpurged BM compared with no further treatment demonstrated a significant advantage for the melphalan group at 5 years for EFS (38 vs 17%) and OS (46 and 21%) rates.[3]

The CCG 3891 trial by Matthay *et al*.[1] investigated the advantage of a TBI-containing HDT followed by autologous purged BM compared with continued therapy. Evaluating 379 patients randomly assigned to standard continuation therapy or HDT/SCT, the study confirmed the superiority of HDT/SCT over continuous consolidation chemotherapy (EFS at 3 years 34 vs 22%, respectively; $P = 0.034$).

Finally, the GPOH–NB97 Study randomized 295 patients with high-risk neuroblastoma either to HDT (melphalan, etoposide, carboplatin) with autologous SCT ($n = 149$) or to oral maintenance chemotherapy with cyclophosphamide ($n = 146$). The intent-to-treat analysis showed that patients allocated HDT/SCT had increased 3-year EFS compared with those allocated maintenance therapy (47 vs 31%; $P = 0.0221$), but did not have significantly increased 3-year OS (62 vs 53%; $P = 0.0875$). The study showed that HDT/SCT improved the outcome for children with high-risk neuroblastoma despite the raised risk of treatment-associated death.[2]

The treatment of minimal residual disease has gained increasing importance. Its significant influence on outcome was shown by Matthay *et al*.[1] in randomizing for 13 *cis* retinoid acid, which has now become a gold standard after HDT/SCT in neuroblastoma. Refinement of this concept is under evaluation with fenretinide as one of the promising agents.[61,62]

Previous attempts to treat minimal residual disease after MGT with interleukin-2, so far, have not been convincing and were associated with major toxicities.[63–67]

A novel and innovative approach recently published by the COG may well be the hu14.18-IL2 the antibody. It consists of the humanized 14.18 antibody genetically linked to a molecule of human IL2. A phase I trial has demonstrated its clinical safety, while its capacity to eradicate residual neuroblastoma cells more effectively awaits further confirmation.[68]

MRD treatment with AntiGD2 ch14.18 in children in a non-randomized study has shown an advantage for the antibody group when OS was considered.[69,70]

Two major study groups, the COG and the SIOPEN Group are currently both investigating the ch14.18 antibody in prospective randomized clinical trial settings to ultimately establish the capacity of the antibodies to overcome MRD.

Further refinement of strategies in immunotherapy for MRD as well as the introduction of treatment with a new generation of drugs and antibodies based on the specific interaction at molecular level raises, in addition, hope for improved future outcome.

In summary, the prognosis for high-risk neuroblastoma has steadily improved over the past decades and numerous risk factors and groups are known today. Large-scale studies through international cooperation will help to further refine diagnostic and treatment strategies to further improve the outlook for these patients.

Conflict of interest

None of the authors declared any financial interests.

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