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Original Paper

1070 Myeloablative Megatherapy Procedures Followed by Stem Cell Rescue for Neuroblastoma: 17 Years of European Experience and Conclusions

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1070 myeloablative procedures followed by stem cell rescue for neuroblastoma are reviewed. These 1070 procedures are part of the European Group for Blood and Marrow Transplant (EBMTG) registry from the last 17 years (in 4536 patients). In 1070 neuroblastoma patients, survival at 2 years was 49%, at 5 years, 33% and relapses were observed as late as 7 years post-BMT (bone marrow transplant). However, 5-year survivors after megatherapy with BMT for stage 4 disease do have an 80% chance of becoming a long-term survivor. When BMT had been used in first complete response (CR1) no salvage was possible, whereas 15% survivors may be seen if BMT is used for the first time at relapse. Infants with stage 4 neuroblastoma had a 17% toxic death rate and indication in this group is exceptional and not recommended. In a matched cohort (17 allogeneic and 34 autologous), autologous stem cell rescue (SCR) was shown to be at least equal to allogeneic SCR. Multivariate analysis of clinical prognostic factors in children with stage 4 disease over 1 year showed that event-free survival was mainly influenced by two adverse factors before the megatherapy procedure: persisting skeleton lesions (^{99}Tc and/or mIBG scan positive) as well as persisting bone marrow (BM) involvement. © **1997 Elsevier Science Ltd.**

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INTRODUCTION

THE FIRST report of the EBMTG (European Group for Blood and Marrow Transplant) experience in the field of intensification with autologous marrow transplantation in solid tumours was in Granada in 1984 at the 10th Annual Meeting of the European Cooperarive Group for Bone Marrow Transplantation. Only 105 patients were recorded from all over Europe. The solid tumour working party was able to collect 1000 patients in 1990 [1] and the 1996 report was based on 4536 cases of solid tumours [2]. The objective of this report is to summarise the status of our knowledge in neuroblastoma based on 17 years of retrospective analysis in Europe using a registry of 1070 grafts where median follow-up from graft is 75 months (range 2–216 months) [3–16].

PATIENTS AND METHODS

Patients

4536 patients were registered from January 1984 to January 1996 using the EBMT forms devoted to solid tumours. 1985 patients were under 16 years of age at time of diagnosis. Among the 4536 patients registered, 1070 were neuroblastoma, 319 soft tissue sarcoma, 327 Ewing's tumour, 400 glioma, 83 Wilms' tumour, 572 germinal tumour and 62 peripheral neuroectodermic tumours (PNET). Various other tumours were recorded in 309 patients (59 medulloblastomas, 30 retinoblastoma, 36 osteosarcoma, 32 ependymoma, 14 other brain tumours, 8 malignant histiocytosis, 18 renal cell carcinoma and 112 miscellaneous).

Methods

All reports were sent annually by means of paper forms or floppy disks to the coordinating centre in Lyon. Follow-up was requested from various centres by the coordinating centre every year before the annual EBMT congress. Since 1990, there has been systematic on-site quality control of the data for neuroblastoma and missing data have been verified and added to the registry by clinical monitors.

RESULTS

Since 1984, 1070 patients who had neuroblastoma and received stem cell rescue were collected (Table 1). Median age at diagnosis was 3 years (1 day to 30 years) and median observation time was 16 months (1 day to 168 months). 905 patients were consolidation of CR1, partial response (VGPR1/PR1) or SD (stable disease/first minor response) and 129 were relapses or progressions (36 unknown). Eight hundred and eighty-three patients had a single graft programme and 187 a double graft programme. As shown in Figure 1, with a median follow-up of 75 months, a 33% overall survival was observed at 5 years. 49% of the patients are alive after 2 years and 10% of the relapses were observed between 24 and 48 months postgraft. 20% of the patients are still at risk of relapses after 48 months as shown in Figure 2.

Among the 905 patients with consolidation as first-line treatment, no difference was found between CR and PR and between very good partial response (VGPR) and CR at time of BMT. Patients who received a single graft programme (746 patients) did as well as double-graft programmes (159 patients). Patients who received total body irradiation (TBI) (346 patients) did as well but not better than those who received chemotherapy alone (559 patients).

Age at diagnosis, involvement of marrow at time of transplantation and status of bone metastasis at graft were the only significant prognostic factors on univariate analysis [6]. Multivariate analysis showed that persisting skeletal lesions prior to BMT, defined by ^{99}Tc or mIBG scans, appeared as the major risk factor in predicting outcome ($P = 0.0018$) and persisting BM involvement prior to BMT was also significant ($P = 0.0237$).

Patients who were treated after relapse (129 patients) had an overall survival rate at 5 years of 24%, with a significant difference for patients still sensitive to rescue protocols and without previous record of intensification as first-line therapy [7].

Infants

Eighteen infants (14 boys and 4 girls) with carefully documented stage 4 neuroblastoma were reported to the EBMT Registry for Solid Tumours by six major European transplant centres between December 1981 and August 1992 [6]. All these patients showed bone metastases on plain radiographs, most confirmed with ^{99}Tc or mIBG scans. 12 patients (67%) had BM involvement and all had other metastases at distant sites. Tumour cell *MYC*N and DNA ploidy studies were not available. The median age at diagnosis was 9 months (range 1–12 months) and, at the time of high-dose consolidation chemotherapy (HDCHT), 20 months (range 13–27 months). Patients were treated with multi-agent induction chemotherapy according to the various national protocols with a median duration of 9 months (range 5–19 months). After induction treatment, 7 patients achieved CR, 3 VGPR and 7 PR, while 1 patient had primary refractory disease [6]. BM infiltration cleared in all patients, but 5/18 still had positive bone lesions on plain radiographs. None of the latter was in the VGPR group. HDCHT regimens were melphalan-based

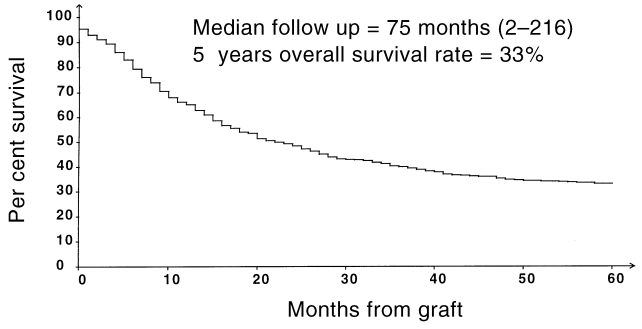

Figure 1. 1070 neuroblastoma patients grafted (overall survival from graft).

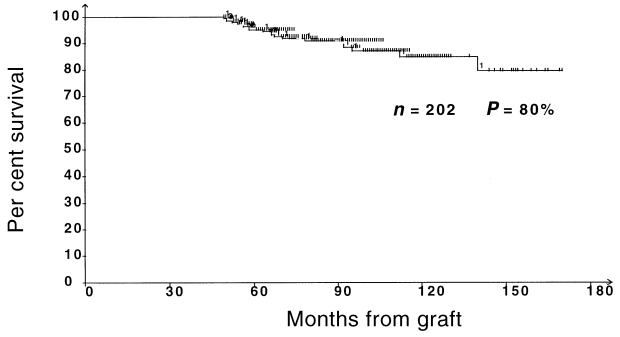

Figure 2. 202 neuroblastoma patients alive at 48 months postgraft (overall survival from graft).

in 16/18 and bichloronitrosurea-based in 2/18 patients and were followed by autologous bone marrow rescue (ABMR).

The median follow-up time after HDCHT was 79 months (range 9–127 months). The overall survival from diagnosis at 5 years was 55% for infants and 29% for stage 4 patients older than 1 year of age at diagnosis ($P = 0.01$). For the 10 CR and VGPR patients, the survival rate at 5 years was 77%. HDCHT toxic death rate was 17% [6].

There is evidence that rapid progression is associated with *MYCN* amplification [13, 17]. Thus, the role of early HDCHT in infants with *MYCN* amplification has still to be defined, but could be considered for infants with initial PR (persistent, biopsy-proven bone metastases) or non-responding patients. In view of actuarial survival rates up to 75% [18, 19] with conventional dose chemotherapy and surgery, these data suggest strongly that there is no advantage in terms of survival when HDCHT and ABMR are given to good responding (bone negative) stage 4 neuroblastoma patients of less than 1 year at diagnosis. Thus, the toxicity risks of such an approach would be avoided in these patients.

Toxic deaths

The toxic death rate of the whole group (i.e. all stages) was 12.4% for CR, 14% for PR-VGPR and 14% for relapses (non-significant difference). Patients who had received TBI (346 patients) had significantly more toxic death (18%) than those who had received a chemotherapy conditioning regimen (11%) ($P < 0.005$) [9–14]. Single and double graft programmes produced equivalent toxic death rates.

Table 1. *Summary of the* 1070 *neuroblastoma patients by stage*

Stage	Number	Median age at diagnosis	Treatment before megatherapy (from diagnosis to graft)		Status of disease at time of megatherapy	
I	6	33 months (1 month–7 years)	CT + S	4	CR1 =	1
			CT + RT	1	CR2 =	2
			CT + RT + S	1	SR =	3
II	12	4 years (13 months–30 years)	S	1	CR1 =	1
			CT + S	6	VGPR1 =	1
			CT + RT + S	5	PR1 =	2
					RD =	1
					CR2 =	4
					SR =	1
					RR =	2
III	78	2 years (7 days–17 years)	CT	12	CR1 =	11
			CT + S	42	VGPR1 =	17
			CT + RT	1	PR1 =	9
			CT + RT + S	22	SD =	2
			UKN	1	RD =	5
					R =	1
					CR2 =	12
					SR =	13
					RR =	7
					UKN =	1
IV	912	3 years (4 days–24 years) 2 unknown	CT	142	CR1 =	277
			CT + S	636	VGPR1 =	210
			CT + RT	17	PR1 =	308
			CT + RT + S	97	SD =	18
			RT + S	1	RD =	13
			S	1	R =	8
			UKN	18	CR2 =	27
					SR =	19
					RR =	2
					UKN =	30
IVs or V	6	17 months (1 month–23 years)	CT	1	CR1 =	1
			CT + S	5	PR1 =	3
					SD =	1
					CR2 =	1
UKN	56	2 years (6 days–24 years)	CT	5	CR1 =	23
			CT + S	5	VGPR1 =	12
			CT + RT + S	2	PR1 =	8
			S	1	RD =	1
			UKN	43	R =	1
					CR2 =	2
					SR =	3
					RR =	1
					UKN =	5

Treatment before megatherapy: CT = chemotherapy; S = surgery; RT = radiotherapy. Status of disease at time of megatherapy: CR1 = first complete remission; VGPR1 = first very good partial response; PR1 = first partial response; SD = first minor response or stable disease; RD = primary refractory disease; R = relapse (untreated): CR2 = second or subsequent complete response; SR = sensitive relapse; RR = resistant relapse. UKN = unknown.

Stage 3 neuroblastoma

Between May 1978 and January 1994, 78 children presenting with stage 3 neuroblastoma at diagnosis were elected to receive megatherapy followed by autologous SCR in 23 European centres. Five children were not evaluable. There were 53 males and 20 females with a median age of 29 months at diagnosis (range 7 days to 17 years). The most common primary tumour site was the abdominal region. A surgical attempt was performed in 80% of patients as part of first-line treatment, radiotherapy was added in 16%, whereas second-line chemotherapy had to be given in 56% of the children. 44/73 patients were elected for megatherapy in first remission (status before graft) and 29 had already experienced a relapse. The median follow-up time since megatherapy was 69 months (range 4 months to 17 years).

The overall survival (OS) of the whole group after megatherapy was 32% at 5 years. There were 11 infants who had a 5-year OS rate of 62%. Results in patients over 12 months at diagnosis were related to the response status prior to megatherapy. Patients in CR1 achieved a 5-year OS rate of 61%, whereas it was 41% in those with more than 50% tumour reduction prior to megatherapy (VGPR + PR) and 53% for relapse patients in second CR prior to megatherapy. However, the outcome of patients with less than 50% response after all primary treatments prior to megatherapy or relapsed patients not achieving a second CR was extremely poor and the majority of these patients died within 2 years. 54/73 patients had measurable disease prior to megatherapy followed by stem cell rescue (SCR). The overall response rate was 35%, i.e. 19/54 showed a response of more than 50% after megatherapy. The complete remission rate was 20%: however, CR was mainly achieved in patients already showing a 90% tumour reduction prior to megatherapy. The early and late transplant-related toxic death rate (before and after day 100) was 5.5% each.

On the basis of this analysis, only a limited number of patients with unresectable stage 3 neuroblastoma should be considered for this type of dose-escalating strategy: first remission patients over 12 months at diagnosis with a response of more than 50% but not in CR prior to megatherapy as well as patients with sensitive relapse.

Stage 4 neuroblastoma

Multivariate analysis for prognostic factors (on stage 4) related to survival showed that only age at diagnosis and bone status at marrow transplant are of significance with treatment duration before ABMT [3].

Allogeneic versus autologous BMT

A case–control study was performed to investigate the potential advantage of allogeneic bone marrow transplantation (BMT) in advanced or poorly responding neuroblastoma first remission patients using the EBMT Solid Tumour Registry [8]. Seventeen allogeneic and 34 autologous BMT cases were matched based on a number of prognostic factors including age, sex, prior treatment durations, pregraft response status and bone and BM involvement before BMT. Only single BMT procedures were included. The median age at diagnosis was 47 months (range 18–113 months). The median follow-up time since BMT was 58 months (range 13–133 months).

The only significant prognostic factor within the allogeneic BMT ($P = 0.012$) and autologous BMT groups ($P = 0.025$) was residual skeletal disease before BMT, detected by mIBG in 86% of the cases. However, the progression-free survival was not significantly different: 35% and 41% at 2 years, respectively. Only half of the allogeneic BMT patients had developed graft-versus-host disease (GVHD): 7 of 9 grade I-II and only 2 of 9 grade IV. The median donor age was very young at 74 months (range 20–240 months) and 10 of 17 were sex matched [8].

Thus, the lower incidence of GVHD in young children could be a major obstacle in achieving an antitumour effect with allogeneic BMT in neuroblastoma.

DISCUSSION

It is clear from these 17 years of experience that in a number of situations, intensification with BMT is inappropriate i.e. neuroblastoma in infants, stage 3 or relapse after BMT. In summary:

(1) For the 1070 neuroblastoma patients, survival at 2 years is 49%, at 5 years is 33% and relapses are observed as late as 7 years BMT. However, 5-year survivors after megatherapy followed by BMT for stage 4 disease do have an 80% chance of becoming a long-term survivor.
(2) Seventy-three evaluable children had stage 3, 11 were infants and 29 had relapsed. Only sensitive relapse patients should receive BMT.
(3) Forty-eight patients were in second or subsequent relapse of stage 4. When BMT had been used in first CR no salvage was possible, whereas 15% survivors may be seen if BMT is used for the first time at relapse [7].
(4) Infants with stage 4 neuroblastoma had a 17% toxic death rate and indication in this group is exceptional and not recommended [6].
(5) In a matched cohort (17 allogeneic and 34 autologous), autologous SCR was shown to be at least equal to allogeneic SCR [8].
(6) Multivariate analysis of clinical prognostic factors in children with stage 4 disease over 1 year showed that event-free survival was mainly influenced by two adverse factors before the MGT procedure: persisting skeleton lesions (^{99}Tc and/or mIBG scan positive) as well as persisting BM involvement.

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APPENDIX

Participating centres in the EBMT for neuroblastoma

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