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Papers

High-dose Chemotherapy with Autologous Bone Marrow Rescue in Advanced Stage IV Neuroblastoma

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In order to better evaluate the role of bone marrow purging procedures in the treatment of stage IV neuroblastoma, two similar groups of patients, prospectively treated during the same period at Léon Bérard Center, Lyon, France, and at Giannina Gaslini Institute, Genova, Italy, were reviewed. 18 children were treated in Lyon with a protocol including induction chemotherapy, surgery and a single course of high-dose chemotherapy followed by purged autologous bone marrow rescue. 21 patients were treated in Genoa with a very similar protocol which did not include purging procedures. Progression-free survival at 6 years was 12% (95% confidence interval 0–24%), without any difference between the two series of patients. The only prognostic factor for long-term survival was the persistence (or not) of bone lesions and the presence of metastatic disease (bone or bone marrow) at graft. The small numbers in the two groups and the very poor outcome make it difficult to conclude on the efficacy of purging.
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INTRODUCTION

NEUROBLASTOMA is a neoplasm typical of childhood originating in the sympathetic ganglia and adrenal medulla. During the past decade remarkable progress has been made in the understanding of neuroblastoma natural history and biological characteristics [1, 2]. The continuous refinement of treatment modalities and the administration of increased doses resulted in a higher response rate and in a clear prolongation of survival; however, the prognosis of children with disseminated disease older than 1 year at diagnosis remains poor [3–7].

According to some phase II studies [8, 9], high-dose chemo-radiotherapy (HDCR) with autologous bone marrow transplantation (ABMT) has been recently used to improve survival rate [10–13]. Although the present data suggest that consolidation therapy plays a role in the improvement of overall and progression-free survival [14], a definitive statement regarding the true gain in cure rate cannot be made yet. In addition, a number of questions concerning specific aspects of HDCR with ABMT remain unanswered. Among them, the drugs to be used in high-dose regimens, the role of total body irradiation, the benefits of elective bone marrow purging or of allogeneic bone marrow graft.

In order to evaluate the role of purging, we analysed two comparable groups of patients treated during the same period in two institutions (Léon Bérard Center, Lyon, France and Giannina Gaslini Institute, Genoa, Italy) with similar HDCR consolidation regimens followed by purged (Lyon group) or unpurged ABMT (Genova group).

PATIENTS AND METHODS

Patients

This study reports on 39 children with disseminated stage IV neuroblastoma aged more than 1 year at diagnosis, who received a single course of HDCR followed by ABMT as consolidation of first line chemotherapy. 18 children were treated in Lyon (group A), 21 in Genova (group B). The main features of both groups are summarised in Table 1.

To obtain a significant follow-up, only patients treated between January 1983 and November 1987 were considered and the results are updated to February 1991.

Inductions regimens

Before ABMT, patients treated in Lyon received six to eight courses of chemotherapy alternating cisplatinum (CDDP), teniposide (VM26), with cyclophosphamide (CPM), doxorubicin (DOX) and vincristine (VCR), as previously reported [11]. Total doses were as follows: CDDP 400 mg/m^2, VM26 640 mg/m^2, CPM 6000 mg/m^2, DOX 240 mg/m^2, VCR 12 mg/m^2.

Patients treated in Genova received one course of peptichemio

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Table 1. Characteristics of the 39 patients

	Lyon	Genova
No. of patients	18	21
Sex: M/F	12/6	10/11
At diagnosis		
Median age, months	38	36
(range)	(15–94)	(16–70)
BM disease	17	20
Bone disease	16	14
Status at graft		
CR	3	8
VGPR	4	3
PR	11	10
BM+	6	9
Median time to graft, months	7	5
(range)	(4–11)	(4–15)

M, Male; F, female; BM, bone marrow; CR, complete remission; VGPR, very good partial remission; PR, partial remission.

(PTC) and two courses of CPM associated with VCR and CDDP, and one to two courses of VM26 and DOX as previously reported [14]. Total doses were as follows: PTC 450 mg/m^2, CDDP 400 mg/m^2, CPM 1200 mg/m^2, VCR 3 mg/m^2, VM26 750 mg/m^2, DOX 90 mg/m^2.

Surgical removal of the primary was attempted either at diagnosis, if possible, or most frequently after three to four courses of chemotherapy. Median time from diagnosis to ABMT was 7 months (range 4–11 months) in group A, and 5 months (range 4–15 months) in group B.

Definition of disease status

Disease was assessed by a full work-up regarding residual tumour size, urinary catecholamine excretion, bone lesions and bone marrow infiltration.

Bone marrow was evaluated by means of aspirates and trephine biopsies in at least two different sites 1–2 weeks before HDCR, 2–3 months after ABMT and whenever progression or relapse was suspected.

The following criteria were adopted: complete remission (CR) corresponded to a complete disappearance of all measurable tumour for at least 1 month; very good partial remission (VGPR) indicated a 90% removal of the primary tumour, normal catecholamines, normal bone marrow and improved results of TC99 or metaiodobenzylguanidine (MIBG) bone scan, occurring when no more than two lesions were detectable; partial remission (PR) occurred in case of a 50% reduction or more of all tumour lesions as well as abnormal catecholamine excretions. Minimal residual bone marrow infiltration, as defined below, was considered as a PR; stable disease (SD) indicated no significant change in any tumour lesion; finally, progressive disease (PD) indicated an increase in any tumour lesion, or the appearance of a new lesion. Progression of disease was defined either clinically or by computerised tomography, ultrasound imaging, bone marrow aspirates and TC99 or MIBG scanning.

Bone marrow evaluation, harvesting and purging

Bone marrow was extensively evaluated at least once before harvesting and at harvest on aspirates from four different sites and on trephine biopsies from four (Lyon) and two (Genova) different sites. In group B, aspirates were studied by traditional cytomorphology and indirect immunofluorescence, using UJ 13A monoclonal antibody (kindly provided by T.J. Kemshead, London, U.K.) [15, 16]; in group A, dual immunofluorescence analysis with UJ 13A immunostaining (Genova) [16] or, in case of absence of positive cells, double marker analysis (Lyon) were performed [17]. Any other bone marrow finding was considered as positive; however, the presence of few neoplastic cells in biopsy specimens or a single clump of neuroblastoma cells in smears with negative immunological analysis was defined as minimal residual bone marrow disease. Both evaluations showed a normal bone marrow in 24 patients. In the remaining 15 patients (6 in Lyon, 9 in Genova), bone marrow evaluation at harvesting showed minimal residual disease. The bone marrow was purged in group A using the Kemshead immunomagnetic procedure, as already reported [11, 18], whereas group B patients received untreated marrow. Freezing procedures were identical, as previously reported [11, 13].

Conditioning regimen

In both institutions all patients received a single course of HDCR including fractionated total body irradiation (TBI) and melphalan (L-PAM) before disease progression.

—VCR was administered with a bolus injection on day 1 and with a 24-h continuous infusion from day 1 to day 5 in both centres with the same dosage (total dose: 4 mg/m^2).
—Fractionated TBI was delivered in 3 days, either in six fractions of 2 Gy, starting lung protection at 10 Gy (Lyon), or in three fractions of 3.3 Gy without lung protection (Genova).
—L-PAM was used at 180 mg/m^2 (Lyon) or 140 mg/m^2 (Genova) on day 6 and was followed by ABMT after 24 h in both centres.

Supportive care, evaluation of toxicity and follow-up were performed with very similar methods, as previously described [11, 13].

Comparison between the two groups of patients and statistical methods

Various factors which could possibly influence the results were studied and are listed in Tables 1 and 2. Sites of metastases at diagnosis, quality and sites of response after induction therapy and status of disease before ABMT were compared. A comparison between group A and group B was made with regard to toxic deaths, duration of progression-free survival (PFS) and overall survival as well as sites and time of relapse.

Numerical data were compared using the *t*-test. Actuarial probability of survival without progression was analysed according to Kaplan–Meier method, and actuarial survival curves were compared using the log-rank test [19, 20].

Table 2. Haematological recovery after purged and unpurged ABMT

	Mean no. of days (±SD) to recovery		
	WBC > 1 × 10^9/l	ANC > 0.5 × 10^9/l	Plts > 50 × 10^9/l
Lyon	31 (±22)	30 (±10)	53 (±32)
Genova	14 (±4)	20 (±9)	45 (±24)
P value	0.003	0.002	0.43

WBC = White blood cells; ANC = absolute neutrophil count; Plts = platelets.

RESULTS

Overall results

The overall PFS of the 39 patients at 6 years is 12% [95% confidence interval (CI), 0–24%], and the median PFS after ABMT is 11 months (range 1–97 months). 6 patients are surviving and lead a normal life at 66 months from diagnosis (range 47–101 months) and at 58 months from ABMT (range 41–96 months).

Five toxic deaths were observed, all occurring during the first 100 days after ABMT: three were due to venocclusive disease (day 36, 52 and 86), one was due to multiorgan failure at day 5 and one was related to a septic shock at day 31 post ABMT.

28 of the 39 patients experienced relapse or progression 2–65 months post ABMT (median 10 months). The first site of relapse was bone marrow in 5 cases, skeleton in 3 cases, primary tumour in 2 cases, whereas multiple sites were involved in 17 cases (including the bone marrow in 15 cases).

1 patient developed an isolated relapse presenting as interstitial pneumonitis [21].

Disease status at ABMT (CR vs. VGPR vs. PR) did not significantly influence PFS.

The children who did not present any bone lesions fared better than those who did [PFS 25% (CI 0–55) vs. 16% (CI 3–29) $P = 0.05$]. The clearance of bone metastases before HDCR was followed by a significantly better outcome: none of the patients with residual bone disease survived as compared with 21% PFS (CI 3–40) of children with bone negative at graft ($P = 0.01$). PFS was 10% (CI 0–27) in patients with bone marrow infiltration at graft and 16% (CI 2–37) in patients without bone marrow disease. The PFS of 24 children with persistent metastatic disease at graft (bone 9, BM 12, both 3) was 6% (CI 0–17) vs. 27% (CI 4–49) of the 15 children without metastatic disease ($P = 0.02$).

Regarding the 27 children without bone metastases at graft, 12 had positive bone marrow and experienced 17% PFS (CI 0–37) compared with 27% PFS (CI 4–49) of the 15 children with negative bone marrow.

No significant difference in PFS has been observed between the children with negative bone at graft who received either purged or unpurged BM while being in complete remission or with minimal bone marrow disease.

Group A

Engraftment was obtained in all patients (Table 2). 3 patients died of venocclusive disease and 1 of septic shock. 3 patients received HDCR while in CR, 4 in VGPR, 11 in PR (6 with minimal bone marrow disease). Relapse or disease progression was documented in 12 patients and occurred at a median time of 8 months (range 2–65). 1 patient had recurrent primary disease, 2 patients relapsed with multiple bone lesions, 1 developed metastatic pneumonia and 8 presented a disseminated recurrence, including bone marrow disease. PFS at 60 months was 11% (CI 0–26) for all the 18 patients grafted in Lyon; 1 out of the 3 patients grafted in CR and one out of the 11 patients grafted in PR are surviving (Table 3).

Group B

1 patient died of multiple organ failure on day 5 postABMT, the remaining 20 patients had complete haematological recovery (Table 2). 8 patients received HDCR while in CR, 3 in VGPR, 10 in PR (9 with minimal bone marrow disease).

Relapse or disease progression was documented in 16 patients and occurred at a median time of 9 months after bone marrow transplantation (4–23). 1 patient had recurrent primary disease, one relapsed with multiple cortical bone lesions, while bone marrow was the first site of relapse in the remaining 14 patients (the only site in 5). PFS at 60 months is 19% (CI 2–36) for all the 21 patients grafted in Genova; in detail, there are 2 patients surviving out of the 8 grafted in CR, 1 out of the 3 in VGPR, and 1 out of the 10 in PR (Table 3).

DISCUSSION

The use of HDCR as consolidation in stage IV neuroblastoma has been investigated by several teams and more than 500 grafted patients have been reported in the European Bone Marrow Solid Tumour Registry [22]. Our results in the two reported patient groups with high-risk neuroblastoma, grafted before disease progression, did not differ from those obtained in most centres and showed a 12% PFS at 6 years from diagnosis. These results compare favourably with the previous experience with traditional approaches in terms of duration of PFS [3–5, 7]. Nevertheless, long-term survival remains poor [23]. Improved results may also be due to intensified first line chemotherapy, even if data from the randomised study of the European Neuroblastoma Study Group show that consolidation with high-dose L-PAM and ABMT in responding stage IV patients is more useful than no further therapy [14]. In analogy with the reports of the European Bone Marrow Transplantation Solid Tumor Registry [22], no significant difference in PFS was observed between patients grafted in CR or VGPR or PR in the Lyon–Genova patient cohort. However, PFS of children with persistent metastatic disease was poorer than that of children without metastatic disease at graft, and, among factors influencing the final outcome of these patients, the pattern of metastatic disease seems to play a relevant role [23]. Patients without bone lesions at diagnosis did only slightly better than children with positive bone (PFS 25 vs. 16%; $P = 0.05$); however, in case of a complete clearance of bone metastases after induction regimen, a significantly better PFS was observed (21% vs. 0; $P = 0.01$). The presence or not of residual bone marrow disease did not modify the survival of this group of patients.

We have studied these two small groups of consecutive patients, simultaneously treated in two different institutions, to evaluate the role of purging in ABMT. The limited number of patients reflects the rarity of neuroblastoma and in particular of advanced stage IV neuroblastoma, eligible for HDCR and ABMT. There are some differences between these two groups, mainly depending on the different strategies adopted by the two centres. Both TC99 and MIBG have been used more frequently for the detection of bone metastases in group A patients. Furthermore, different induction regimens were given in the two groups but the length of pre-ABMT chemotherapy as well as the total dose of the single drugs are very similar. The methods to evaluate bone marrow disease are also similar, including cytology, histology at different sites as well as immunostaining with the same highly sensitive and specific monoclonal antibody. A comparison between the two methods was not made, however, dual immunofluorescence and double marker analysis seem to be more precise. Patients treated in Lyon received a slightly intensified conditioning regimen. However, outcome after ABMT (PFS at 5 years 11% in group A and 19% in group B), incidence of relapses (12 out of 18 patients in group A and 16 out of 21 in group B) and time to relapse (median time 8 months in group A and 9 months in group B) were similar and so poor that differences, if they exist at all, are difficult to find. Sites of relapse were also similar in the two groups, except for an excess

Table 3. Details of remission status before ABMT, site-time of relapse and outcome after ABMT

	Lyon				Genova			
Disease status at ABMT	Patient no.	Residual disease prior to ABMT	Site of relapse (months post ABMT)	Outcome (months post ABMT)	Patient no.	Residual disease prior to ABMT	Site of relapse (months post ABMT)	Outcome (months post ABMT)
CR	1	—	—	ADF (90)	1	—	BM (9)	DWD (17)
	2	—	BM, B, N (7)	DWD (19)	2	—	—	ADF (54)
	3	—		TD (2)	3	—	BM (7)	DWD (9)
					4	—	BM (19)	DWD (23)
					5	—	Pr (24)	DWD (32)
					6	—	B (11)	DWD (12)
					7	—	—	ADF (52)
					8	—	BM, N (4)	DWD (6)
VGPR	4	B	BM, B (4)	DWD (7)	9	Pr	Pr, N (5)	DWD (8)
	5	B	—	TD (1)	10	Pr	Pr, N	DWD (6)
	6	B	BM, C (5)	DWD (21)	11	Pr	—	ADF (48)
	7	B	—	TD (1)				
PR	8	BM, B, Pr	BM, N (7)	DWD (16)	12	BM	BM, B (18)	DWD (24)
	9	BM, Pr	BM, Pr, B (4)	DWD (20)	13	BM, Pr	BM (4)	DWD (3)
	10	B	L	DWD (6)	14	BM, Pr	—	—
	11	BM, B	B (64)	AWD (87)	15	BM, Pr	—	TD (1)
	12	BM, B, Pr	BM, B (2)	DWD (44)	16	BM, Pr	BM, Pr (15)	DWD (22)
	13	B	BM, B (8)	DWD (15)	17	BM	BM, B (12)	DWD (13)
	14	BM	—	TD (2)	18	BM	BM, B (12)	DWD (27)
	15	BM	—	ADF (67)	19	Pr	BM, N (5)	DWD (6)
	16	B, Pr	B (3)	DWD (9)	20	BM, Pr	BM, B, N (4)	DWD (8)
	17	B	BM, B (2)	DWD (6)	21	BM	BM (11)	DWD (20)
	18	B	Pr (4)	DWD (5)				

CR, Complete remission; VGPR, very good partial remission; PR, partial remission; BM, bone marrow; B, bone; N, nodes; Pr, primary site; C, cerebral; L, lung; ADF, alive disease free; DWD, death with disease; TD, toxic death.

of isolated bone marrow relapses in group B (5 patients vs. none in group A); only 1 patient (in group A) relapsed with a metastatic interstitial pneumonitis suggesting a reinfusion of malignant cells with the bone marrow [21].

The pattern of recurrence usually mimicked the appearance of disease at diagnosis or before graft and a comparable pattern and relapse rate have been observed in patients treated similarly and grafted with allogeneic bone marrow [24]. This seems to suggest strongly that induction protocol and conditioning regimens fail to eradicate the disease, and that reinfusion of neuroblastoma cells is probably not the immediate cause of most relapses, as also confirmed by the poor outcome of the overall group and in particular of the patients with residual bone metastases. Only at that time the consolidation with megatherapy and ABMT seems to eradicate minimal residual bone marrow disease and a purged graft could be helpful, particularly in case of residual metastatic disease.

The significant delay in white blood cell and polymorphonuclear leukocyte recovery after reinfusion of manipulated bone marrow suggests some toxicity of the procedure for the stem cell pool, resulting in a prolongation of the period at risk for infection and of hospitalisation. However, the higher dosage of L-PAM could also contribute to the higher incidence of toxic deaths in the purged group. Platelet recovery was similar in both groups and, as usual, longer than myeloid recovery.

Summarising these clinical observations, several suggestions seem to be reasonable. First of all, induction regimens should be rendered more effective, and able to clear all but the minimal disease. Only at that time a consolidation with megatherapy could be able to eradicate the residual disease and the infusion of a purged marrow will be safe.

Secondly, a careful and comparable evaluation of disease status at graft and of bone marrow harvest is crucial to clarify the pathogenesis of failures and the role of purging. Thirdly, a definitive conclusion on the value of purging could require a large randomised multicentre trial with unselected and homogeneously treated patients. However, such a kind of trial is probably difficult and can be inconclusive. Thus, we have relied for the moment on observations emerging from pooled data of the major transplant centres to study the impact of residual bone marrow or bone marrow disease or contaminated bone marrow harvest on long term disease-free survival, while being aware of the possible biases in such a patient cohort.

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