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Massive BACT Chemotherapy with Autologous Bone Marrow Transplantation in 17 Cases of non-Hodgkin's Malignant Lymphoma with a Very Bad Prognosis

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Abstract—*A group of 12 children and 5 adults, all with diffuse non-Hodgkin's malignant lymphoma (NHML), received massive chemotherapy regimens. The stages of the disease were as follows: 7 patients were in second complete remission; 6 in a progressive phase of the disease; and 4 in first complete remission which occurred late in the course of the disease. All patients received BACT (BCNU+aracytine+cyclophosphamide+thioguanine) or TACC (idem with CCNU) at different dose levels: 6/17 received 10 Gy total-body irradiation (TBI) after BACT treatment; 16/17 received autologous bone marrow transplantation (ABMT) previously stored in liquid nitrogen to combat the medullary effects of chemotherapy. Direct therapy-related deaths occurred in 4/17 patients (1 Aspergillus endocarditis; 1 Moskowitz syndrome; 1 veno-occlusive disease of the liver; and 1 Escherichia coli pneumopathy) and 6/17 patients relapsed between days 25 and 70 of treatment. Seven out of these 17 patients are still alive NED 102–900 days (mean, 475 days) after the beginning of therapy without receiving maintenance treatment. Massive chemotherapy could thus be the best treatment for NHML in relapse, but the high percentage of early therapy-related deaths is a strong limiting factor for patients before relapse.*

INTRODUCTION

THE PROGNOSIS of malignant non-Hodgkin's lymphoma after the first relapse is poor in both children and adults when treated with conventional therapy. Results published on intensive cytoreductive regimens followed by autologous bone marrow grafts are very impressive [1–9]. Until now, a total of 59 cases have been reported in the literature (76 including this report).

We investigated this type of treatment in 17 cases of NHML with very bad prognosis from February 1980 to June 1982. Our goal was to select patients with no chance of being cured with conventional therapy; the criteria for this selection were chosen using experience gained in our previous studies ([10, 11]; T. Philip, unpublished data), i.e. all diffuse NHML in relapse, patients with progressive disease under conventional therapy and patients who were not in complete remission (CR) after four courses of chemotherapy (usually CHOP).

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MATERIALS AND METHODS

Patients

The group of 13 male and 4 female patients consisted of 5 adults and 12 children aged from 3 to 36 yr (mean, 14.4 yr); 6 patients were in partial remission 2–28 months after diagnosis (mean 8 months, median 4 months), 7 were in their second CR less than 3 months after a relapse and 4 were in their first CR but with very bad prognosis (see

Table 1) because of the delay before CR occurred. The diagnosis for 14 of the patients was diffuse high-grade NHML (8 Burkitt's lymphomas, 4 T lymphoblastic lymphomas and 2 diffuse large cell lymphomas) according to the international classification [12]. Three patients had an intermediate-grade large non-cleaved diffuse NHML.

Methods

When patients relapsed BACT therapy was not given immediately and during a 2-month period conventional therapy was given in order to try and obtain a second CR. It should be noted that during the 2 yr of this study all the eligible patients of the participating institutions were included, except for 4 patients who died during the 2 months conventional therapy period. One patient received 2 courses of BACT therapy (first and second relapses; see Table 1). We thus report 18 courses of BACT therapy for 17 patients.

A second CR was obtained with conventional therapy before the end of the 2-month period in 7 cases but not in 5 other cases (12 cases, 11 patients). Two patients entered the study with progressive disease before first CR and 4 patients in the very bad prognosis group (see 'Patients') were in first CR (see Table 1).

In the case of the 12 children, parents were informed of the methods and emphasis was laid on the possibility of early therapy-related death, which was evaluated to be 20%. Oral consent was received by two collaborators. In the case of adults, the patients themselves were given the same information and oral consent received by a minimum of two collaborators.

The massive chemotherapy regimens used were Appelbaum BACT in 10 cases, TACC in 1 case and a modification of BACT regimen in 7 cases (i.e., IGR BACT) [9]. Details of these protocols are given in Table 2. BCNU was given i.v., infused slowly over 10 min, Ara-C in continuous infusion q. 12 hr, cyclophosphamide dissolved in 250 ml 5% dextrose i.v. for 30 min and thioguanine *per os* q. 12 hr. In 6 cases the patient received 10 Gy TBI after BACT therapy (Tables 1 and 2).

In 16/18 courses an autologous bone marrow graft was performed in order to combat chemotherapy-induced aplasia. In 2 cases (see Table 1) aplasia was left to run its course naturally, due to suspicion of bone marrow contamination by malignant cells. Bone marrow was harvested prior to relapse and before day 80 after diagnosis in 7/16 cases and after relapse from another site (usually central nervous system or local recurrence) in 9/16 cases. In all cases 4 bone marrow smears and 4 bone marrow biopsies were analyzed at the time of aspiration for contamination by malignant cells. For B cell lymphomas (10/16) a personal culture test was used [13].

A previously described freezing procedure was used [14]; briefly, dimethyl sulfoxide (Me_2So) in plasma (2200 mosm) was added to the cell suspension at a final concentration of 10%. The marrow suspension was transferred into Teflon-Kapton freezing bags, which were cooled from 6 to −140°C at predetermined rates of 2 and 5°C/min in an electronic freezer equipped with a programmer (SFPO, France). At the end of the procedure the bags were rapidly transferred to liquid nitrogen (−196°C). Thawing of stem cells was carried out in a 42°C water bath. Me_2So was removed by centrifugation; the marrow cell pellet was resuspended in fresh frozen plasma plus saline 9/1000 and infused without delay.

All patients were treated in a sterile care unit under systematic parenteral nutrition. After oral decontamination sterile enteral nutrition was allowed. The minimum stay in the sterile care unit was 20 days and the maximum 47 (day 0 is always the day of ABMT or, in the absence of ABMT, the theoric day of reinjection). The special bacteriological monitoring of the patients has previously been reported [15]. Folinic acid and vitamin B_{12} were systematically administered during aplasia.

No further chemotherapy or radiotherapy was administered after this treatment and the patients were discharged without treatment.

RESULTS

Details of observations on the 17 patients are given in Table 1. Patient 6, who received 2 courses of BACT therapy, received an autograft only after the second course and patient 3 did not receive an autograft after typical Appelbaum BACT treatment. Details of bone marrow recovery in the 16/17 patients receiving autografts are also given in Table 1 and of the numbers of cells and CFU that were frozen and grafted in Table 3. However, the number of grafts [16] is not high enough to obtain statistically significant conclusions, although several points can be outlined: (a) hospitalization in the sterile care unit lasted for 20–47 days (mean, 27.7 days; median = 25); (b) the mean duration of white blood corpuscle (WBC) levels <1000 lasted for 5–28 days (mean, 15.1 days; median = 14); (c) the mean duration of polynuclear cell (PN) levels <500 lasted for 8–43 days (mean, 19.3 days; median = 17); (d) the mean duration of polynuclear cell levels <200 lasted for 2–29 days (mean, 13.8 days; median = 14); and (e) the mean duration of platelet levels $<50{,}000/mm^3$ (without platelet transfusion) lasted for 3–70 days (mean, 25 days; median = 21).

Table 1. Clinical details concerning the 17 patients

Patient	Age	Sex	Pathological diagnosis	Interval *diagnosis/* massive therapy	Previous therapy	*Status* prior BACT	Type of therapy	TBI	No. of days: Stay in sterile care	No. of days: <1000 WBC	No. of days: <500 PN	No. of days: <200 PN	No. of days: <50 000 platelets	Complications: E = early L = late	Status on 1.9.82
No. 1 3683 CLB	3	M	BL	5 months	VCR, CPM, ADR, MTX-IT ASP, PRED	2nd CR	BACT Appelb.	no	25 days	13	16	14	NE		died day 25 progression (reinjected bone marrow contaminated)
No. 2 HEH 1	30	M	intermediate-grade large non-cleaved	2 months	VCR, CPM, ADR, PRED, BLM	PR	BACT Appelb.	10 Gy	23 days	14	15	11	32		CR 900 days +
No. 3 3176 CLB	4	F	BL	3 months	VCR, CPM, ADR, MTX-IT, PRED	PR	BACT Appelb.*	no	45 days	9	16	11	11	E: toxic agranulocytosis (duration 17 days) L: interstitial pneumopathy	CR 600 days +
No. 4 3530 CLB	32	F	intermediate-grade large non-cleaved	7 months	VCR, CPM, ADR, MTX-IT, PRED, BLM CYT, TG	first CR obtained at 3 months	BACT Appelb.	10 Gy	20 days	16	16	12	15	L: Moskowitz	died day 147 (lymphoma at autopsy)
No. 5 3433 CLB	11	M	BL	7 months	VCR, CPM, ADR, MTX-IT, MTX-HD, ASP, PRED	2nd CR	BACT IGR	no	25 days	20	22	16	25	L: leucoencephalitis	CR 480 days +
No. 6 2054 CLB	7	M	BL	3 months	VCR, CPM, ADR, MTX-IT, PRED, MTX-HD, ASP, 24 Gy CNS	2nd CR	BACT Appelb.*	no	24 days	9	11	3	3		relapse day 210 *Intracranial* Burkitt tumor with normal CSF
				12 months	30 Gy CNS	PR	BACT IGR	no	21 days	11	11	9	13		3rd CR 454 days +
No. 7 3529 CLB	27	M	high-grade immunoblastic	12 months	VCR, CPM, ADR, MTX-IT, MTX-HD, ASP, PRED, CYT, TG, BCNU	2nd CR	BACT Appelb.	10 Gy	31 days	11	20	14	NE	E: *Aspergillus* endocarditis	died day 23 (no lymphoma at autopsy)

Table 1. Continued

Patient	Age	Sex	Pathological diagnosis	Interval diagnosis/ massive therapy	Previous therapy	Status prior BACT	Type of therapy	TBI	Stay in sterile care	No. of days <1000 WBC	No. of days <500 PN	No. of days <200 PN	No. of days <50 000 platelets	Complications: E = early L = late	Status on 1.9.82
No. 8 4477 CLB	36	M	intermediate-grade large non-cleaved	8 months	VCR, CPM, ADR, MTX-IT, MTX-HD, ASP, BLM, PRED	1st CR obtained after 5 months	BACT Appelb.	10 Gy	27 days	14	16	16	17		CR 401 days +
No. 9 SE 1	9	M	T lymphoblastic	39 months	VCR, CPM, ADR, MTX-IT, MTX-HD, ASP, PRED, CYT, TG	2nd CR	BACT Appelb.	10 Gy	47 days	5	8	2	NE	E: veno-occlusive disease	died day 47 CR
No. 10 SE2	10	M	T lymphoblastic	28 months	VCR, CPM, ADR, MTX-IT, MTX, HD, ASP, PRED, CYT, TG	PR (relapse)	BACT IGR	no	35 days	14	24	16	32		died day 90 (relapse day 70)
No. 11 BE1	10	F	BL	4 months	VCR, CPM, ADR, MTX-IT, MTX-HD, PRED	PR (relapse)	BACT IGR	no	21 days	14	19	12	NE	E: cyclophosphamide myocardiopathy (R) cyclophosphamide cystitis (R)	died day 45 (relapse day 35)
No. 12 BE2	16	M	BL	11 months	VCR, CPM, ADR, MTX-IT, PRED, CNS irradiation	2nd CR	BACT IGR	no	30 days	24	43	29	70		CR 102 days +
No. 13 HCL DEB1	4	M	BL	4 months	VCR, CPM, ADR, MTX-IT, MTX-HD, ASP, PRED	PR (relapse)	BACT IGR	no	30 days	28	32	27	NE day 35 >100 000	L: reinjected bone marrow contaminated	died day 83 (relapse day 60)
No. 14 HCL DEB2	3	M	T lymphoblastic	6 months	VCR, CPM, ADR, MTX-IT, MTX-HD, ASP, PRED, BLM, CYT, TG	PR (relapse)	BACT Appelb.	no	25 days	15	25	15	21	E: hypokalaemia with tubulopathy	died day 40 progression

Table 1. Continued

Patient	Age	Sex	Pathological diagnosis	Interval diagnosis/ massive therapy	Previous therapy	Status prior BACT	Type of therapy	TBI	Stay in sterile care	No. of days <1000 WBC	No. of days <500 PN	No. of days <200 PN	No. of days <50 000 platelets	Complications: E = early L = late	Status on 1.9.82
No. 15 3826 CLB	16	F	T lymphoblastic	11 months	VCR, CPM, ADR, MTX-IT, MTX-HD, ASP, PRED, BLM, CYT, TG	2nd CR	BACT Appelb.	10 Gy	24 days	18	20	16	NE	E: veno occlusive disease syndrome (regression) L: pneumopathy *E. coli*	died day 46 no lymphoma at autopsy
No. 16 4560 CLB	4	M	BL	8 months	VCR, CPM, ADR, MTX-IT, MTX-HD, ASP, PRED, CYT, TG	1st CR obtained after 5 months	BACT IGR	no	25 days	18	17	13	30		died day 47 (relapse day 46)
No. 17 NANTES	23	M	high-grade immunoblastic	11 months	Irradiation VM26, ADR	1st CR obtained after 3 months	TACC modified Appelb.	No	22 days	19	17	14	22	E: infectious hepatitis L: thoracic Herpes zoster	CR 433 days +

CR = complete response; PR = partial response; NE = non-evaluable; ABMT = autologous bone marrow transplantation; VCR = vincristine; CPM = cyclophosphamide; ADR = adriamycin; MTX = methotrexate; IT = intrathecal; HD = high dose; ASP = asparaginase; PRED = prednisone; BLM = bleomycin; CYT = cytosine; TG = thioguanine; WBC = white blood corpuscles; * = no ABMT; PN = polynuclear; BACT = see definition in Table 2; TBI = total-body irradiation; CLB = Centre Leon Berard, Lyon; HEH = Hôpital Edouard Herriot, Lyon; SE = Saint Etienne; BE = Besançon; HCL DEB = Hôpital Debrousse, Lyon.

Table 2. Protocols used

Drugs	Days 1	2	3	4	5	6	7	8
BACT protocol (Appelbaum)								
BCNU, 200 mg/m²	●							
Cytosine arabinoside, 200 mg/m²		●	●	●	●			
Cyclophosphamide, 50 mg/kg		●	●	●	●			
6-Thioguanine, 200 mg/m²		●	●	●	●			
ABMT							●	
Modified BACT protocol (IGR)								
BCNU, 200 mg/m²	●	●	●					
Cytosine arabinoside, 200 mg/m²		●	●	●	●			
Cyclophosphamide, 50 mg/kg		●	●	●	●			
6-Thioguanine, 200 mg/m²		●	●	●	●			
ABMT							●	
BACT protocol + TBI								
BCNU, 200 mg/m²	●							
Cytosine arabinoside, 200 mg/m²		●	●	●	●			
Cyclophosphamide, 50 mg/kg		●	●	●	●			
6-Thioguanine, 200 mg/m²		●	●	●	●			
TBI							●	
ABMT								●

TACC is identical to BACT except that CCNU replaces BCNU.

Table 3. Number of nucleated cells and GMCFUC: harvesting data

Case No.	Volume collected (ml)	Nucleated cells collected (×10⁸/kg)	Total CFUGM frozen (×10⁴/kg)	Nucleated cells grafted (×10⁸/kg)	CFUGM grafted (×10⁴/kg)
No. 1	190	7.8	3.6	1.5	1.0
No. 2	820	3.8	2.4	0.6	0.66
No. 4	790	6.4		0.97	0.4
No. 5	350	2.7	1.5	1.4	
No. 6	240	3.0	7.2	1.6	3.7
No. 7	780	1.4	5.6	1.3	5.3
No. 8	930	1.3	4.4	1.0	
No. 9	500	2.8	9.2	2.5	8.0
No. 10	480	4.1		1.1	6.1
No. 11	640	3.3	13.7	2.1	8.9
No. 12	600	0.9	10.0	0.6	7.2
No. 13	230	5.3	8.0	2.0	4.6
No. 14	250	4.0	24.0	2.0	7.0
No. 15	500	2.1	15.6	1.3	13.0
No. 16	210	4.9	30.0	2.5	27.0
No. 17	1000	2.0	8.8	0.5	2.2

Only 6 patients received 10 Gy TBI and no significant conclusions could be drawn, although no differences were observed in recovery (number of days duration of levels of: <1000 WBC: mean, 15.1, TBI group, 13; <500 PN: mean 19.3, TBI group, 12.5; <200 PN: mean 13.8, TBI group, 11.8; <50,000 platelets/mm³: mean 25, TBI group, 21).

No correlation could be established between the number of GMCFUC/kg and recovery nor between the number of nucleated cells injected and recovery. Patients 3 and 6, who received Appelbaum BACT treatment but no autologous bone marrow, recovered very quickly (Table 1).

Overall survival of all patients is given in Fig. 1. However, the results can be summarized as follows:

(a) Four patients died from direct therapy-related complications, i.e. Moskowitz syndrome (patient No. 4), *Aspergillus* endocarditis (patient No. 7), veno-occlusive disease (patient No. 9) and *E. coli* pneumopathy (patient No. 15). At autopsy 2 patients were in complete remission and 2 were in relapse.

(b) Six patients died from progression or relapse, which could be considered as a BACT failure. It should nevertheless be emphasized that BACT treatment was prescribed for 7 patients with a tumor target and CR obtained in 6/7. The 5

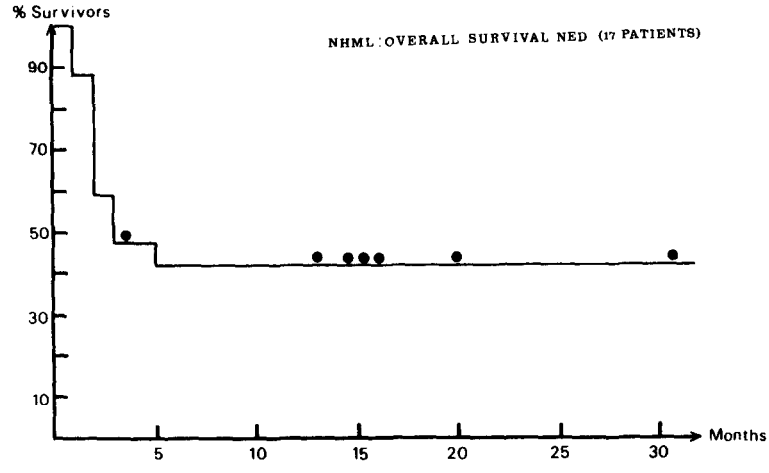

Fig. 1. Overall survival of the whole group (Kaplan–Meier).

relapses occurred between days 16 and 70 (mean, day 46). It is impossible to know whether the post-transplant relapse resulted because of BACT failure to clear the tumor or because of a tumor cell reinfusion with ABMT [13].

(c) Seven patients (41.2% of the total group) are still alive without treatment 102–900 days after massive chemotherapy. The average observation time of NED patients is 16 months (Fig. 1). Of these patients, 6 had B cell lymphomas and the remaining patient (No. 8) was not typed immunologically. Except for patient No. 5, who is paraplegic due to a leucoencephalitis, it should be emphasized that the quality of life of these patients appears to be normal, in view of the absence of therapy or hospitalization.

DISCUSSION

Our results show a high response to BACT therapy (6/7 patients treated with a tumour target), a high proportion of early therapy-related deaths (4/17) with this treatment and a high proportion of long-term survivors (7/17) and are in agreement with those in the literature (summarized in Table 4 and [16]), where the feasibility of ABMT was demonstrated. However, no treatment other than BACT reported so far can be compared with this procedure in relapsed diffuse lymphoma. The absence of early death in 16 patients treated with a non-BACT regimen (see Table 4) is not significant, but merits further trials since this is a major problem in both our studies and those of others (Table 4).

In our study 5 patients died from relapse and 1 from progression and in all 6 cases bone marrow involvement with lymphoma cells was noted at death. Details of these cases are published elsewhere [13], although it should be noted that bone marrows were collected after a first relapse of the lymphoma in 4/6 of these patients and that this practice should be avoided in the future. Thus the time of bone marrow collection is a capital point in this procedure and should be carried out as soon as possible in high risk to relapse groups, followed by immediate storage [13]. At the present time, in our group, collection is made systematically in high risk patients after the first two courses of chemotherapy. Our patients 3 and 6 (first treatment) did not receive ABMT and the clinical outcome was similar to the 16 courses followed by ABMT. This fact did not confirm Appelbaum's findings in 22 patients, in which 12 received ABMT and recovered significantly faster than the controls [1]. This point is of great concern to us. We have ethical resistance to begin a randomized study, especially for patients who received 600 mg/m^2 BCNU. Nevertheless, we think that in the case of a suspicion of bone marrow

Table 4. Massive chemotherapy and ABMT: review of the literature concerning non-Hodgkin's malignant lymphoma (from [16])

Protocols	No. of patients	Response	Early deaths	Alive NED at 1 yr
BACT ± TBI	60	64.7% CR 26.4% PR 8.8% NR	18%	31%
CP + TBI	10	80.0% CR 20.0% NR	0%	37.5% 5/8
Others	6	62.5% CR	0%	37.5%

contamination by malignant cells, BACT should be used without bone-marrow rescue. In Table 3 there is considerable variability in the ratio of cells or CFUC collected and reinfused. This variability is explained by the difference in time of collection and confirms that in the future bone marrow has to be collected earlier and at the same time for each patient.

In this group of patients 6/7 survivors had B cell lymphomas and the 4 patients with T cell lymphomas died (2 with relapse). The fact that BACT treatment is more efficient on B cell lymphoma should be tested in future in randomized trials.

Of the 8 patients with Burkitt's lymphoma, 4 are still alive between 102 and 600 days after the end of treatment (mean, 409 days, i.e. 13.6 months). This is one of the best results ever reported in relapse patients with Burkitt's lymphoma [16] and could support the hypothesis that BACT regimen is first of all a B lymphoma therapy.

The early therapy-related deaths appear to be the major limiting factor of this procedure. Table 1 shows that this effect is very rapid (between 23 and 147 days; mean, 66 days) and, as can be seen in Fig. 1, reaches a plateau at 5 months of evolution. TBI seems to enhance iatrogenic risk in our study, but this has not been confirmed by others (Table 4).

This risk factor, therefore, prevents the use of this intensive therapy in the earlier stages of the disease and further studies should be set up to try to diminish these complications, possibly by reducing the quantities of BCNU. At present, BACT therapy followed by autologous bone marrow graft is the best treatment for diffuse non-Hodgkin's lymphoma in relapse and further trials should be carried out on patients with this stage of the disease.

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