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Massive Therapy and Autologous Bone Marrow Transplantation in Pediatric and Young Adults Burkitt's Lymphoma (30 courses on 28 patients: a 5-year experience)

T. PHILIP,* P. BIRON,* I. PHILIP,* M. FAVROT,* G. SOUILLET,† D. FRAPPAZ,‡ J. JAUBERT,‡ P. BORDIGONI,§ J. L. BERNARD,‖ J. P. LAPORTE,¶ A. LeMEVEL,** E. PLOUVIER,†† G. MARGUERITE,‡‡ R. PINKERTON,* C. P. BRIZARD,‡ F. FREYCON,‡ H. K. FORSTER,§§ N. PHILIPPE† and M. BRUNAT-MENTIGNY*

**Centre Leon Berard, Bone Marrow Transplant Team, 28 rue Laennec 69273 Lyon, Cedex 8; †Hôpital Debrousse, Service d'Hematologie Pediatrique et Unite de Greffe de Moelle, Lyon; ‡Hôpital Bellevue, Service de Pediatrie et CRTS Service d'Hematologie, Saint Etienne; §Hôpital CHU, Nancy; ‖Hôpital CHU, Marseille; ¶Hôpital Saint Antoine, Bone Marrow Transplant Team, Paris, France; **CAC – Nantes; ††Hôpital St Jacques et CRTS, Bone Marrow Transplant Team, Besançon; ‡‡Hôpital St Charles, Montpellier, France; §§Hoffmann–La Roche Laboratory, Basel, Switzerland*

Abstract—*A* 5-yr *experience of massive therapy and autologous bone marrow transplantation (ABMT) for Burkitt's lymphoma is reviewed. Thirty courses were given to* 28 *patients. Three patients were in resistant relapse and all three died before day* 54 *post ABMT. Thirteen patients were in non-resistant relapse and seven are alive with non-evidence of disease (NED). All three patients grafted in partial remission (PR) are alive NED including two with initial central nervous system (CNS) disease. Nine patients were grafted in 1st complete remission (CR) either because of long delay to achieve CR* [3] *or as consolidation in those with initial CNS involvement* [5] *or leukaemia* [1]. *Three of these nine are alive including* 2/3 *with a long delay to CR and* 1/5 *initial CNS. The overall survival NED for the* 28 *patients is* 46%. *The median observation time post ABMT,* 22 months.

Clear indications for ABM T in BL are in our opinion restricted to about 20% *of the patients: non-resistant relapses and PR after initial induction therapy. Massive therapy as consolidation of* 1st *CR after initial CNS involvement and in resistant relapses should still be considered as experimental. In* 14 *patients whose marrow was purged there is laboratory evidence suggesting that the purging procedures used in this study may have been incomplete. Purging techniques still require perfection at a laboratory level and their rationale should not be judged on the basis of incomplete procedures.*

INTRODUCTION

THE BACT massive chemotherapy regimen followed by autologous bone marrow rescue (ABM T) was first proposed in 1978 by Appelbaum for relapsed or resistant Burkitt's lymphoma (BL) [1,2] which is the commonest non-Hodgkin's malignant lymphoma (NHML) in childhood and at that time had a very bad prognosis [3–6]. Several teams, including ours, have confirmed the potential value of such a procedure [7–9]. Burkitt's lymphoma is, however, now curable by conventional chemotherapy regimens [10,11] in 75% of the cases and despite very good results with ABM T some controversy still persists on the precise indication of such a procedure in 1986.

We review here our 5-yr experience of massive therapy and ABM T for Burkitt's lymphoma. When we initiated this programme, overall survival in Lyon by conventional chemotherapy was 42% and CNS relapse was the major problem [4,5]. In addition, with regard to ABM T, purging procedures prior to ABM T were not ready for clinical use. At the present time, overall survival in Lyon by a conventional regimen is 77% [12] and CNS relapse is now a rare event in BL (less than 5% [10]). A purging procedure is now ready and was used for 14 of the 28 patients [13,14]. The increasing survival after conventional chemotherapy was observed in parallel with the progress of massive therapy regimens causing a problem in interpret-

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Address requests for reprints and correspondence to: Dr. T. Philip, Centre Leon Berard, 28 rue Laennec 69273 Lyon, Cedex 8, France.

ing the value of the latter.

Despite these difficulties in analysis we think that firm conclusions can now be drawn from the initial experience and that massive therapy is still indicated in 20% of Burkitt's lymphoma cases. The objective of this report is to use our background to define clearly the present indications for such a procedure in BL.

PATIENTS AND METHODS

Patients

A total of 30 courses in 28 patients are reviewed. Twenty-four courses were performed in Lyon–Saint Etienne group (15 at Centre Leon Berard, five at Hôpital Debrousse and four at Saint Etienne). Two patients are from Besançon, and four others from Nantes, Marseille, Nancy and Paris respectively. A summary of the 28 patients status at time of ABM T is shown in Table 1. All patients were children, except patients 16, 19 and 25 who were young adults, included in a pediatric protocol at initial presentation. Thirteen were stage III, 10 stage IV (eight CNS ± BM and two BM alone) and five were initially stage I or II. They all had received Adriamycin containing regimens prior to ABM T (Table 1). The median interval between diagnosis and ABM T was 5 months (range 1–26). At time of ABM T 13 patients (15 courses) were in relapse but still responding to rescue protocol (non-resistant relapse [15,16]). Three patients were in resistant relapse (2 pt) or progressive disease (1 pt). Three were in partial remission after first induction therapy and nine in 1st CR (three long delay to CR and five initial CNS disease and 1 L3 Burkitt leukaemia) (Table 1). All relapses were relapses on therapy (Table 1).

METHODS

Parents or patients were always fully informed of the protocol risks and they gave formal consent in presence of at least two physicians. The protocol was reviewed and accepted by the Comité d'Ethique des Hospices Civils de Lyon et de l'Université Claude Bernard. The cooperative group France Autogreffe de Moelle Osseuse also reviewed and accepted the protocol.

Bone marrow harvesting and freezing procedures were performed as previously reported [7,16]. In 2/30 courses no ABM T was performed after massive BACT therapy as previously reported and discussed [7]. Patients were always isolated in a sterile room under standardized gut decontamination, bacteriological and transfusion policies [7].

Fifteen bone marrows were harvested either after relapse [14] or during disease progression [1]. Ten were harvested in 1st CR and three in PR after initial induction therapy.

Monoclonal antibody and complement purging procedures were used in 14 patients as shown in Table 1. Indications for and practical aspect of such procedures have been previously reported [13,14,17,18]. At time of relapse patients had been treated with the best rescue protocol available. If progressing or only stable on this rescue protocol patients were defined as 'resistant relapse'. All other patients were defined as 'non-resistant relapse'. At the time of CNS relapse intermediate dose Cytosine, high dose Methotrexate, VP16 and Lumbar puncture (MTX + Cytosine; twice weekly until CSF free of tumor cells) were used to induce remission. All patients with CNS relapse were irradiated cranially (18–24 grays) if not done previously. No patient received maintenance therapy after ABM T.

The massive regimens used in this study are shown in Table 2 and for each patient in Table 3. The Appelbaum BACT protocol was used in three courses, the Institut Gustave Roussy modified BACT (IGR BACT) [8] in 16 courses and the BEAM protocol [19] in 10 courses. Patient 10 received cyclophosphamide (CPM) alone (60 mg/kg × 5). Details of the drug infusion protocol have been previously published [7,16].

CR (Complete Remission), PR (Partial Remission), NR (Non Response) and PD (Progressive Disease) were defined at day 30 post ABM T according to the WHO recommendations [20]. Complications were defined as early (E) when observed before day 90 and as late (L) after day 90.

RESULTS

As shown in Table 3 and Fig. 1 only three patients were in resistant relapse or progressive disease at time of massive therapy (patients 14, 15 and 27). We observed only 1 PR and all three patients died before day 54 post ABM T. In non-resistant relapses (Tables 1 and 3, patients 1–26) as expected [15,16] results were good with an overall survival NED of 53.8% despite three therapy related deaths in CR in this group (Fig. 1). Median observation time for the survivors is 295 days post ABM T. All disease related deaths were observed before day 60. Only three patients were submitted to massive therapy when in PR after initial induction therapy (patients 2, 11 and 20). All three are alive NED 1455 +, 735 + and 460 + post ABM T. Nine patients were grafted in 1st CR either for long delay to CR (patients 8, 10 and 12) or consolidation of those with initial CNS involvement (patients 17, 18, 23, 24 and 28) or L3 leukaemia (patient 21). Of those only three are alive NED (33%) including 2/3 with a long delay to CR and only 1/5 with initial CNS disease. The L3 leukaemia relapsed day 35 and died day 73 post ABM T.

Seventeen patients were grafted either for iso-

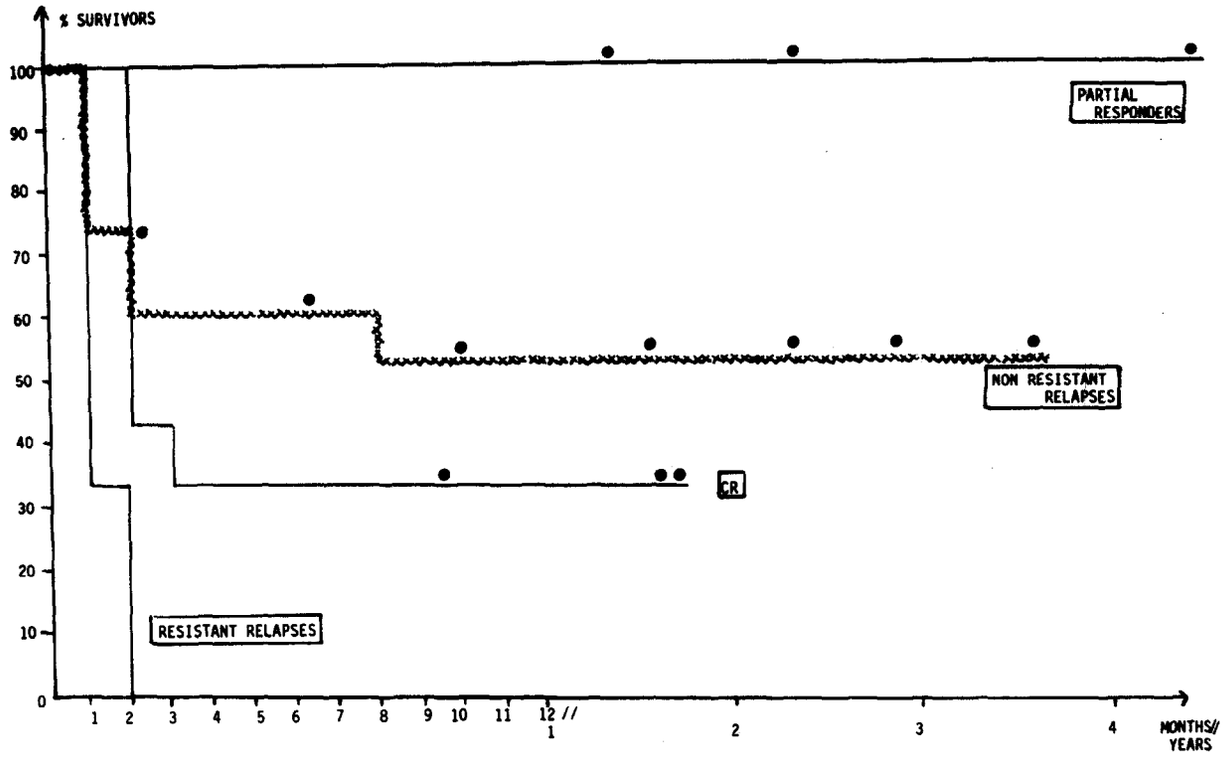

Fig. 1. Overall survival NED of the 28 patients according to status at ABM T.

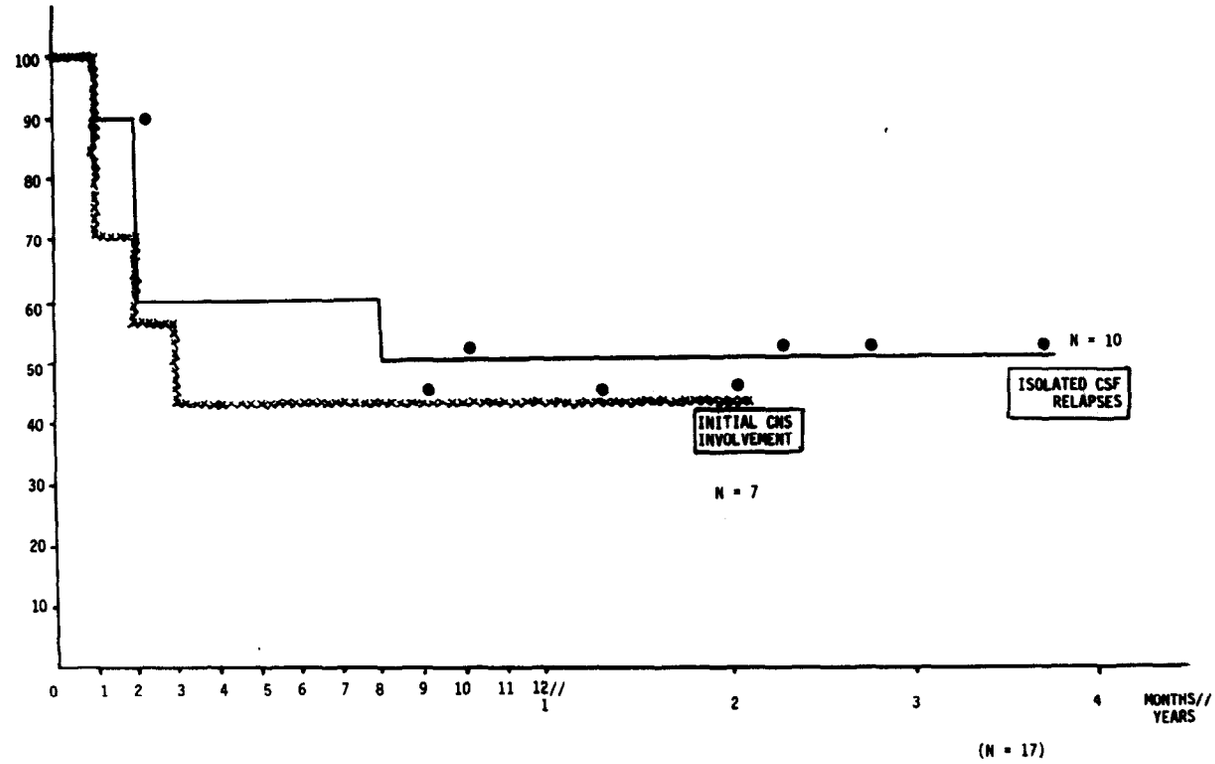

Fig. 2. Overall survival NED of patients with initial CNS involvement or isolated CNS relapses (no statistical difference).

lated CNS relapses (10 cases, see Table 1) or after initial CNS involvement who achieved only PR or CR (seven cases, see Table 1). No clear difference is observed as shown in Fig. 2 in the results between CNS relapse and initial CNS involvement. This group of patients with initial CNS involvement does very badly with conventional therapy [10]. 3/7 are alive NED 277 +, 466 + and 735 + post ABM T.

No major difference was observed between patients grafted with a marrow harvested in 1st CR and the others.

Table 1. Clinical status prior ABM T for the 28 patients.

PATIENT	AGE	SEX	DIAGNOSIS AND STAGING (Murphy) AT DIAGNOSIS	PREVIOUS THERAPY	INTERVAL DIAGNOSIS MASSIVE THERAPY	TIME OF BM COLLECTION (Purge if done)	STATUS PRIOR MASSIVE THERAPY
MARS 1 14 BER	9	M	BL STAGE III	VCR-CPM-ADR PRED-CYT-ASP HD MTX-TG	10 MONTHS	AFTER RELAPSE	PROGRESSIVE DISEASE (abdominal relapse) AFTER RELAPSE RR
DEB 5 15 BEC	11	F	BL STAGE III	VCR-CPM-ADR HDMTX-PRED	1 MONTH	PROGR.DISEASE PURGE Y 29/55	PROGRESSIVE DISEASE CNS RR
CLB 27 ORL	14	M	BL STAGE III	VCR-CPM-ADR HDMTX-ITMTX-CYT CDDP-VP 16-ASP	3 MONTHS	AFTER RELAPSE PURGE Y 29/55 + AL2	PROGRESSIVE DISEASE AFTER LOCAL (Head &Neck) and ABDOMINAL RELAPSE RR
CLB 3683 1 VUI	3	M	BL STAGE III	VCR-CPM-ADR MTX-IT-ASP PRED-CNS-X RAY	5 MONTHS	AFTER RELAPSE	2nd CR AFTER CSF RELAPSE NRR
CLB 3433 3 DEB	11	M	BL STAGE III	VCR-CPM-ADR MTX IT-MTX HD ASP-PRED	7 MONTHS	AFTER RELAPSE	2nd CR AFTER CSF AND CNS RELAPSE NRR
CLB 2054 4 MUZ	7	M	BL STAGE III	VCR-CPM-ADR-MTX IT&HD-ASP-PRED CNS-X RAY	3 MONTHS	NO ABMT	2nd CR AFTER ABDOMINAL RELAPSE NRR
			2 nd COURSE BL	30 GRAYS CNS VCR-CPM-ADR	12 MONTHS	AFTER RELAPSE	PR AFTER CNS RELAPSE NRR
BES 1 5 SAN	10	F	BL STAGE IV CNS	VCR-CPM-ADR MT IT-PRED CNS-X RAY	4 MONTHS	AFTER RELAPSE	PR AFTER CNS AND CSF RELAPSE NRR
BES 1 6 DEB	14	M	BL STAGE III	VCR-CPM-ADR MTX IT-PRED CNS-X RAY	11 MONTHS	AFTER RELAPSE	2nd CR AFTER CSF RELAPSE NRR
DEB.1 7 JAC	4	M	BL STAGE II	VCR-CPM-ADR MTX IT-MTX HD ASP-PRED	4 MONTHS	AFTER RELAPSE	PR AFTER CSF AND CNS RELAPSE NRR
MARS 2 9 DJE	4	M	BL STAGE II	VCR-CPM-ADR MTX IT-MTX HD CYT-ASP-TG	11 MONTHS	1st CR	2nd CR AFTER CSF RELAPSE NRR
CLB			2nd course		26 MONTHS	AFTER RELAPSE PURGE Y29/55 + AL 2	3rd CR AFTER CSF RELAPSE NRR
DEB 2 13 BOU	14	M	BL STAGE II	VCR-CPM-ADR HDMTX	3 MONTHS	AFTER RELAPSE	PR AFTER EARLY LOCAL RELAPSE (HEAD and NECK) NRR
NANT 1 16 GIL	32	M	BL STAGE III	VCR-CPM-ADR HDMTX-ARAC CNS-X RAY-VM-26	12 MONTHS	PR BEFORE RELAPSE	PR AFTER THORACIC RELAPSE NRR
SE 5 19 BAR	24	F	BL STAGE I	CPM-ADR-VCR PRED-BLEO.	7 MONTHS	AFTER RELAPSE PURGE Y29 55+AL2	2nd CR OF ABDOMINAL AND BM RELAPSE NRR
CLB 2766 22 BAL	14	M	BL STAGE I	CPM-ADR-VCR-PRED HD MTX-CNS-X RAY	7 MONTHS	AFTER RELAPSE	2nd CR OF CNS RELAPSE NRR

SA 1 25 ORY	20	M	BL STAGE III	VCR-CPM-ADR HDMTX-IT MTX CYT	7 MONTHS	AFTER RELAPSE PURGE Y29/55+AL2	2nd CR AFTER ABDOMINAL RELAPSE (3 MONTHS) NRR
CLB 26 JOZ	7	M	BL STAGE III	VCR-CPM-ADR HDMTX-IT MTX	4 MONTHS	AFTER RELAPSE PURGE Y29/55 + AL2	2nd CR AFTER CSF RELAPSE NRR
CLB 3176 2 COR	4	F	BL STAGE IV BM	VCR-CPM-ADR MTX-IT-ASP PRED-CNS-X RAY	3 MONTHS	NO ABMT	PR AFTER INITIAL INDUCTION THERAPY (MONOCLONAL GAMMA- PATHY AND PARTIAL BM INVOLVEMENT) PR
CLB 3571 11 BOU	4	M	BL STAGE IV CNS	VCR-CPM-ADR MTX IT-MTX HD ASP-PRED-CYT	5 MONTHS	INITIAL PR	PERSISTANT FACIAL PALSY AFTER 5 MONTHS OF THERAPY PR
NANC 1 20 LES	4	M	BL STAGE IV CNS	CPM-ADR-VCR-PRED HD MTX-ASP-CYT HD CYT-CNS-X RAY	4 MONTHS	PR PURGE Y29/55	PR OF INITIAL CNS : PERSISTANT FACIAL PALSY PR
CLB 4560 8BEN	4	M	BL STAGE III	VCR-CPM-ADR MTX IT-MTX HD ASP-PRED-CYT-TG	8 MONTHS	1st CR	1st CR OBTAINED AFTER 5 MONTHS OF CONVENTIONAL THERAPY CR
SE 3 10 CRO	10	M	BL STAGE III	VCR-CPM-ADR HDM TX-IT MTX	7 MONTHS	1st CR	1st CR (see text) CR
CLB 278 12 RAH	4	F	BL STAGE III	VCR-CPM-ADR MTX IT-MTX HD ASP-PRED-CYT	5 MONTHS	1st CR PURGE Y 29/55	1st CR OBTAINED AFTER 4 MONTHS OF CONVENTIONAL THERAPY CR
SE 4 17 TAY	14	M	BL STAGE IV CNS + BM	VCR-CPM-ADR HD MTX-IT MTX PRED-CYT	3 MONTHS	1st CR PURGE Y 29/55	CR(INITIAL ABDOMEN + CNS + BONE MARROW) CR
DEB 6 18 MAB	10	M	BL STAGE IV CNS + BM	VCR-CPM-ADR HD MLTX-IT MTX PRED-CYT	3 MONTHS	1st CR PURGE Y 29/55	CR(INITIAL ABDOMEN + CNS + BONE MARROW) CR
CLB 656 23 PAS	10	M	BL STAGE IV CNS + BM	VCR-CPM-ADR HD MTX-IT MTX	5 MONTHS	1st CR PURGE Y29/55+AL2	CR (INITIAL CNS + BM) CR
CLB 1768 24 DAL	6	M	BL STAGE IV CNS + BM	VCR-CPM-ADR HD MTX-IT MTX	3 MONTHS	1st CR PURGE Y29/55+AL2	CR (INITIAL CNS + BM + JAW) NRR
SE 6 28 BRE	6	M	BL STAGE IV CNS + BM	VCR-CPM-ADR HDMTX-IT MTX CYT	3 MONTHS	1st CR PURGE Y29/55 + AL 2	1st CR (INITIAL BM + CNS) CR
DEB 7 21 DUR	9	F	BL STAGE IV LEUKAEMIA	CPM-ADR-VCR-PRED HD MTX-CYT-CNS CNS-X RAY	5 MONTHS	1st CR PURGE Y 29/55+AL2	1st CR (leukaemia) CR

CLB: Centre Léon Bérard, Lyon: BES: Besançon; DEB: Hôpital Debrousse, Lyon; MARS: Marseille; SE: Hôpital Bellevue, Saint Etienne; Nant: Nantes; Nanc: Nancy; SA: Hôpital Saint Antoine, Paris; M: Mâle; F: Female; VCR: Vincristine; CPM: Cyclophosphamide; ADR: Adriamycine; MTX IT: Intra Thecal Methotrexate; MTX HD: High dose Methotrexate; ASP: Asparaginase L; Pred: Prednisone; CNS X ray: Radiotherapy cranium to C2; CYT: Cytosine Arabinoside; TG: Thioguanine; CDDP: Cisdichloroaminoplatinum; VP 16: Etoposide.

Patients 14, 15 and 27 are resistant relapses (RR), patients 1 to 26 are non-resistant relapses (NRR). Patients 2, 11 and 20 were grafted in 1st PR (Partial Remission). Patients 8 to 21 were grafted in 1st CR (Complete Remission); CNS: Central Nervous System; CSF: Cerebro Spinal Fluid; BM: Bone Marrow.

Table 2. Massive chemotherapy regimen used in this study (legends as Table 1)

		Days								Number of courses
Drugs		1	2	3	4	5	6	7	8	
				Appelbaum BACT						
BCNU	200 mg/m^2	•								
Cytosine arabinoside	200 mg/m^2		•	•	•	•				
Cyclophosphamide	50 mg/kg		•	•	•	•				3
6 Thioguanine	200 mg/m^2		•	•	•	•				
ABMT								•		
				IGR BACT						
BCNU	200 mg/m^2	•	•	•						
Cytosine arabinoside	200 mg/m^2		•	•	•	•				
Cyclophosphamide	50 mg/kg		•	•	•	•				16
6 Thioguanine	200 mg/m^2		•	•	•	•				
ABMT							•			
				Beam protocol						
BCNU	300 mg/m^2	•								
Cytosine arabinoside	200 mg/m^2		•	•	•	•				
Melphalan	140 mg/m^2						•			10
VP 16	200 mg/m^2		•	•	•	•				
ABMT								•		
1 patient received high dose cyclophosphamide alone – see Table 1 and 3 (Patient 10)										1

During the 30 courses of massive therapy morbidity was observed in 11 (36%), i.e. 5/30 (17%) of pneumonitis (two candida pneumonitis patients 2 and 26; one idiopathic pneumonitis patient 23, and two CMV pneumonitis, patients 9 and 13). All patients recovered completely including patients 9 and 24 who subsequently died of other complications (Table 3). Cystitis was observed in two cases (despite Uromitexan i.e. Mesna prophylaxis in all cases) and was transient in both. One cardiomyopathy occurred but regressed with Digitalis and Frusemide (patient 9 first course). One leucoencephalopathy was observed and patient 3 is alive, but with neurological sequelae.

Four patients (cases 9, 16, 19 and 21 Table 3) died of therapy related complications in CR (one 1st CR, two 2nd CR, one 3rd CR): one myocardiopathy, one acute pulmonary oedema, one candida sepsis and one unexplained brain complication, producing a 14% mortality rate for these 30 courses of massive therapy in 28 patients.

As shown in Fig. 3, the overall survival NED for the 28 patients is 13/28, i.e. 46%. The median observation time post ABM T is for the survivors of 22 months (655 days +). If patients transplanted in 1st CR are excluded the overall survival is 52% i.e. 10 out of 19 patients. It is well known that in such a group (13 relapses on therapy, three progressive disease, three PR) survival is very unlikely with conventional chemotherapy regimens [4].

Comparison between the purged and unpurged group is difficult because of the predominance of initial CNS in the purged group. However, as shown in Fig. 4, the overall survival NED for the two groups are comparable (46% vs. 50%). An alternative way to look at this small group is shown in Table 4. If we exclude those in 1st CR and compare the 5/12 relapses in the unpurged group and the two relapses out of seven patients grafted with purged marrow, all relapses were early relapses. Four relapses in group 1 were observed first in the marrow, whereas the two relapses in group 2 are clearly non-marrow relapses. In the group of patients grafted in 1st CR of initial bone marrow involvement, however, 3/4 relapses were in bone marrow despite purging of a cytologically normal marrow in all cases (Table 4).

DISCUSSION

During this experience of 5 yr using massive therapy and ABM T we have been involved in the French SFOP protocol of conventional chemotherapy which has increased the cure rate for BL from 42 to 77% [4,5,10,11]. At present, 100% of our patients with BL are included at diagnosis in the conventional regimen but 20% still remain candidates for ABM T. Based on an analysis of the progress which was achieved over recent years with massive therapy and new conventional regimen,

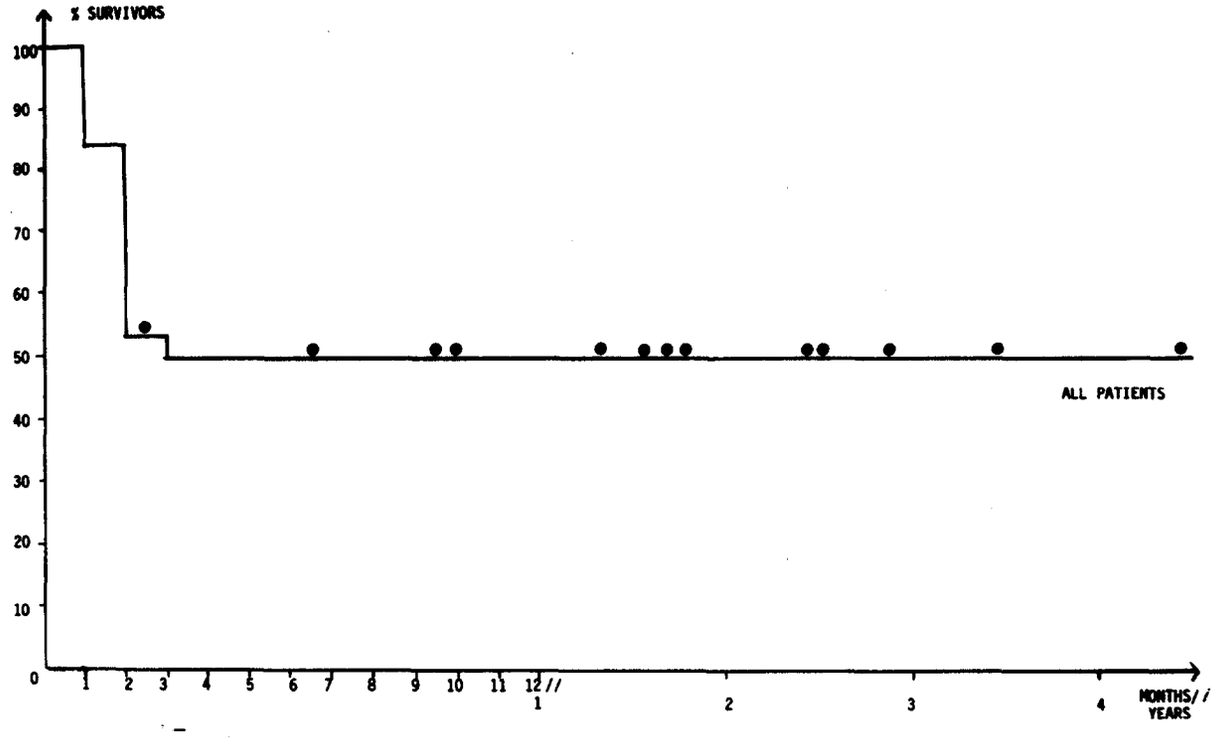

Fig. 3. Overall survival NED of the 28 patients.

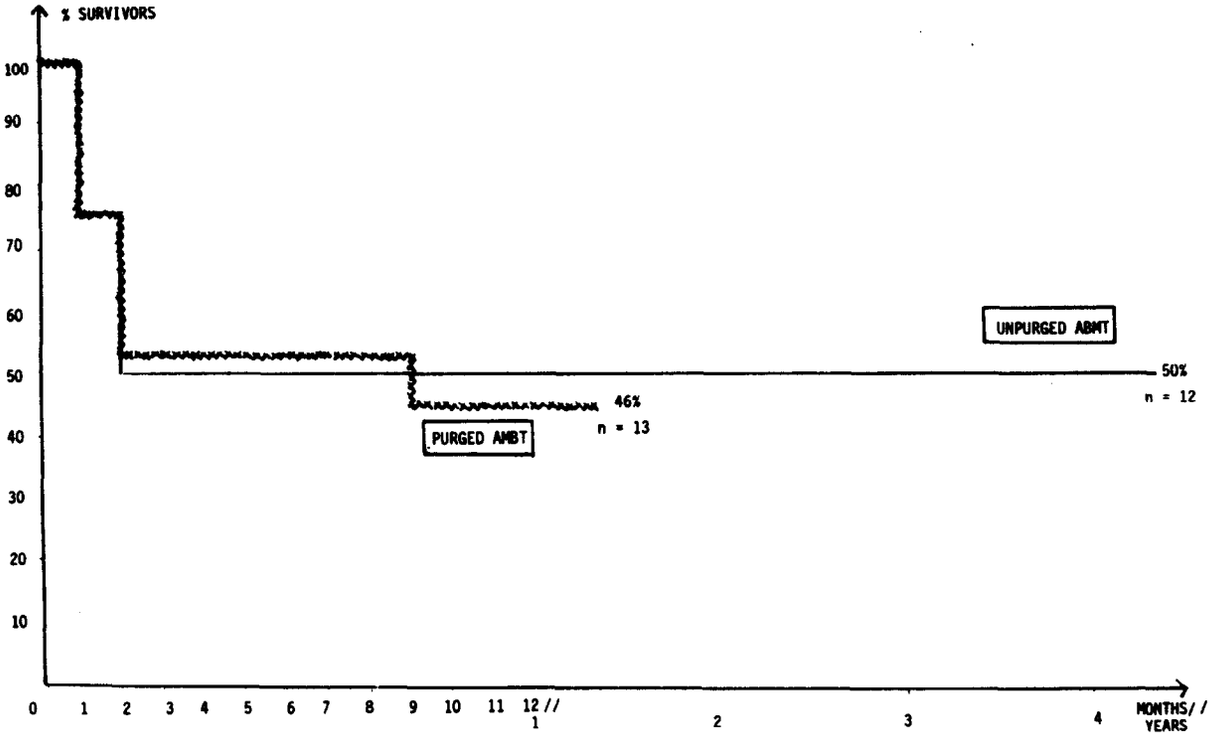

Fig. 4. Overall survival NED purged vs. unpurged group (no statistical difference).

simultaneously, we think it is possible to make several conclusions:

The group of BL with progressive disease, relapses and PR after initial induction therapy is still a group of patients where survival is very rare with conventional therapy [10,11]. In this group we report here 10/19 survivors NED, i.e. 52%. This is clearly considerable progress for patients with Burkitt's lymphoma. It is of interest to note that therapy related deaths in this group (14%) is not

Table 3. Response to massive therapy and ABM T for the 28 patients.

PATIENT	TYPE OF THERAPY	STAY IN STERILE UNIT(DAYS)	NUMBER OF DAYS <1000 WBC	<500 PN	<200 PN	<50.000 Platelets	STATUS AFTER MASSIVE THERAPY	COMPLICATIONS E : EARLY L : LATE	STATUS
MARS 1 14 BER	BACT IGR	22	17	20	11	15	PD	--	DIED DAY 39
DEB. 5 15 BEC	BACT IGR	10	6	5	3	13	PD	--	DIED DAY 54
CLB 27 ORL	BEAM	25	18	20	15	40	PR	--	RELAPSE DAY 30 DIED DAY 40
CLB 3683 1 VUI	BACT APPELBAUM	25	13	16	14	NE	PD	--	RELAPSE DAY 17 DIED DAY 25
CLB 3433 3 DEB	BACT IGR	25	20	22	16	25	CR	LEUCOENCEPHALITIS(L)	CR 1335 +
CLB 2054 4 MUZ	BACT APPELBAUM	24	9	11	3	3	CR	--	RELAPSE DAY 210 CNS
	BACT IGR	21	11	11	9	13	CR	--	CR 1019 +
BES 1 5 SAN	BACT IGR	21	14	19	12	NE	CR	CPM MYOCARDIOPATHY AND CYSTITIS (E)	RELAPSE DAY 35 DIED DAY 45
BES 2 6 DEB	BACT IGR	30	24	43	29	70	CR	--	CR 837 +
DEB.1 7 JAC	BACT IGR	30	28	32	27	NE	CR	--	RELAPSE DAY 60 DIED DAY 83
MARS 2 9 DJE	BACT IGR	34	19	21	9	23	CR	INTERSTITIAL PNEUMONITIS (E) LEUCOENCEPHALITIS(E)	CSF RELAPSE DAY 60 DIED IN CR DAY 223
	BEAM	24	24	20	19	24	CR	MYOCAR- DIOPATHY (E)	DIED IN CR MYOCARDIOPATHY D24 (D223 post 1st ABMT)
DEB. 2 13 BOU	BACT IGR	25	12	21	11	23	CR	INTERSTITIAL VIRAL PNEUMONITIS (E)	CR 605 +
NAN 1 16 GIL	BEAM	> 7	>7	>7	>7	>7	NE	ACUTE PULMO-. NARY OEDEMA (E)	Died in clinical CR DAY 7
SE 5 19 BAR	BACT IGR	15	10	13	10	NE	CR	CANDIDA SEPSIS (E)	DIED DAY 15 in CR

CLB 2766 22 BAL	BEAM	25	20	20	14	33	CR	MYCOPLASMA PNEUMONITIS (E)	CR 295 +
SA 1 25 ORY	BEAM	28	28	24	21	30	CR	--	CR 200 +
CLB 26 JOZ	BEAM	25	23	25	22	56	CR	CANDIDA PNEUMONITIS (E)	CR 65 +
CLB 3176 2 COR	BACT APPELBAUM	45	9	16	11	11	CR	TOXIC AGRANULO-CYTOSIS (E) INTERSTITIAL PNEUMONITIS (L)	CR 1455 +
CLB 3571 11 BOU	BACT IGR	28	20	22	17	25	CR	CSF BLEEDING (E)	CR 735 +
NANC 1 20 LES	BACT IGR	40	27	29	20	44	CR	--	CR 460 +
CLB 4560 8 BEN	BACT IGR	25	18	17	13	30	CR	--	RELAPSE DAY 46 DIED DAY 47
SE 3 10 CRO	CPM60mg/kg X 5	25	6	11	6	0	CR	--	CR 655 +
CLB 278 12 RAH	BACT IGR	24	17	20	17	16	CR	--	CR 657 +
SE 4 17 TAY	BACT IGR	27	17	11	10	27	PD	SEPSIS (E) CPM CYSTITIS (E)	RELAPSE D30 DIED DAY 90
DEB. 6 18 MAB	BACT IGR	22	14	19	14	23	CR	--	RELAPSE DAY 60 DIED DAY70
CLB 656 23 PAS	BEAM	22	23	23	15	39	CR	NON DOCUMENTED Pneumonitis (L)	CR 277 +
CLB 1768 24 DAL	BEAM	20	18	21	12	45	CR	PYOCYANIC-SEPSIS CMV INFECTION (E) BRAIN ? (E)	DIED IN CR DAY 80
SE 6 28 BRE	BEAM	30	14	17	14	33	CR	- - -	RELAPSE DAY 37 ALIVE DAY 60 PD
DEB.7 21 DUR	BEAM	30	26	21	7	39	CR	--	RELAPSE DAY 35 DIED DAY 73

very different from that associated with most modern conventional chemotherapy [10,21,22]. It is also of interest to consider all patients treated in Lyon during this period who were potential candidates for ABM T (Fig. 5). In our group six such patients out of 25 were not included either because of early death after relapses (two cases), resistant relapses on progression under rescue protocol (one case), bone marrow involvement at relapse (one case), or progressive disease early after reinduction of remission (two cases). If we considered this total experience of Burkitt's lymphoma the overall survival between 1980 and 1985 in Lyon for patients with indication for ABM T in BL is then 40%. The selections for ABM T of 19 patients out of 25 with clear indications does not modify the conclusion (Fig. 5). In our previous experience, such a group had 0% survivors [4]. As previously shown, patients with BL who stay in CR more than 8 months can be considered as cured [4] and 80% of our survivors belong to this group (see Table 3).

The patients with a long delay to CR were in 1980 clearly a group of very bad prognosis [4–6]. 2/3 patients grafted in this situation are long-term survivors. However, with the new conventional regimen, this prognostic factor has disappeared and this is not now an indication for ABM T in our group.

The patients treated with ABM T in responding relapse after a CNS or CSF relapse are encouraging with 5/10 long-term survivors. The only CSF relapse observed by us under the new SFOP conventional regimen was easily induced into 2nd CR and is still in CR 107 days post ABM T. The question of whether these particular relapses can be cured by conventional regimens (like ALL) must now be addressed.

Our very preliminary experience of massive therapy as consolidation for initial CNS involvement in 1st CR is disappointing perhaps because the drugs used do not penetrate the CNS particularly well. The numbers are small but the observed survival of 3/7 is not clearly better than the 25% survival produced with a conventional regimen [5].

Table 4. Comparison between purged and unpurged marrow prior to ABMT (patients in CR with no initial CNS and the two courses with no ABMT excluded)

Cases	Unpurged			Cases	Purged Not in 1st CR			Cases	Purged In 1st CR		
	Initial BM	BM at harvesting	Site of relapses		Initial BM	BM at harvesting	Site of relapses		Initial BM	BM at harvesting	Site of relapses
1	–	–	Bone marrow CSF abdomen Day 17	9	–	–	Died in CR Day 223	17	+	–	CSF Day 30
3	–	–	–	15	–	–	CNS Day 30	18	+	–	Bone marrow + CSF Day 60
4	–	–	–	19	–	–	Died in CR Day 15				
5	–	–	Bone marrow Day 35								
6	–	–	–								
7	–	–	Bone marrow Day 60	20	–	–	–	23	+	–	–
9	–	–	CSF Day 60	25	–	–	–	24	+	–	Died in CR Day 80
11	–	–	–	26	–	–	–	28	+	–	Bone marrow + CSF Day 37
13	–	–	–								
14	–	–	Bone marrow + abdomen Day 30								
16	–	–	Died in CR								
22	–	–	–	27	–	–	Head & neck Day 30	21	+	–	Bone marrow + CSF Day 35

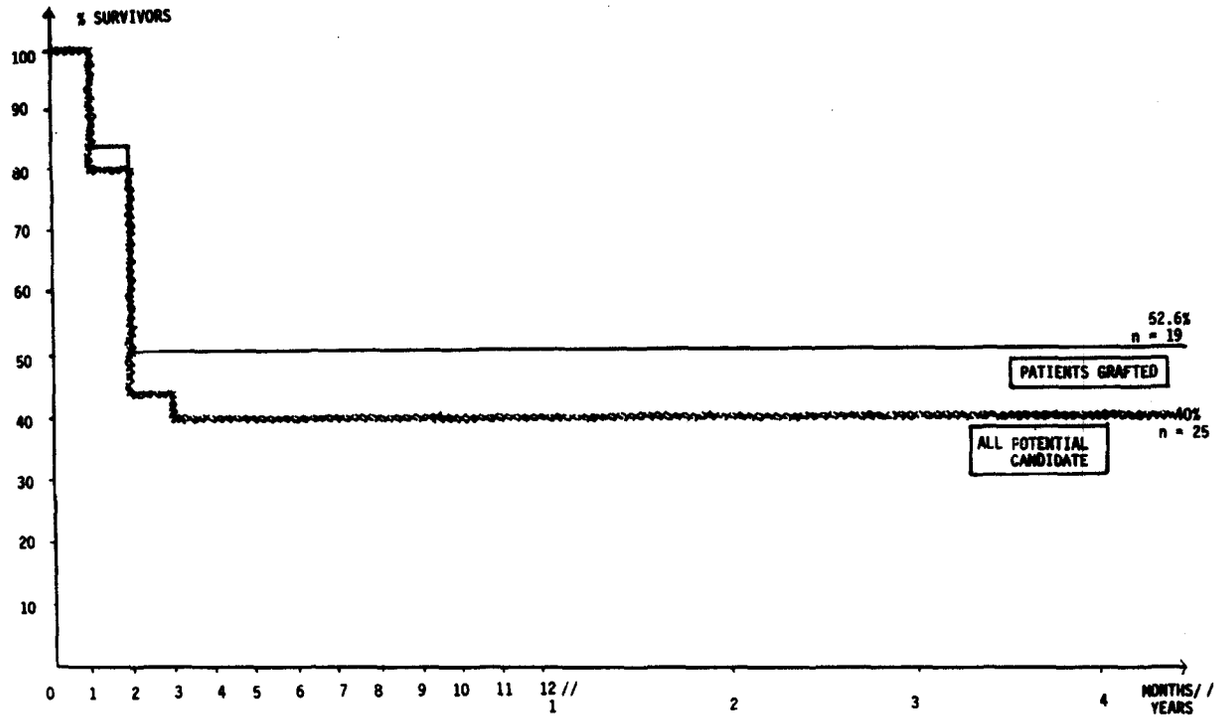

Fig. 5. Overall survival NED for the 'good indication' patients grafted vs. all putative indication (no statistical difference).

The question of a possible adverse effect of massive therapy followed by ABM T must be considered. Cases 17 and 28 are of particular interest, both had initial CNS and abdominal BL with more than 80% BM involvement and normal WBC. They both reached a quick CR under the SFOP protocol. Twenty grays were given to the CNS before ABM T and they received IGR BACT (case 17) or BEAM (case 28) when in well defined CR and received histologically normal marrow purged by monoclonal antibodies and complement. CNS relapses occurred very early (day 30 and day 37) after a quick recovery following massive therapy which did not produce major complications. In case 17 the marrow was clearly normal at time of relapse and the role of immunodepression due to massive therapy in the explosive relapse is questionable. In case 28 the relapse occurred at the same time in the marrow and in the CSF and it is possible that BL cells contaminated as *in vitro* data showed that in this case the addition of B_7 would have been necessary to effectively purge the marrow. Unfortunately, we were not able to use this antibody for *ex vivo* treatment at that time.

We have previously shown *in vitro* that Burkitt's lymphoma cells could grow in a liquid culture system from cytologically and histologically normal marrow [17,23,24]. On the basis of this test, we show that apparent normal BM at time of harvesting grew in culture [14,18,23]. However whether cells that grow out in liquid culture are capable of reestablishing a malignancy when reintroduced into the human is as yet unknown. We, nevertheless, have selected a cocktail of three monoclonal antibodies which would react with virtually all Burkitt lymphoma and developed a purging procedure using complement lysis [13,25]. We believe however that ultimately a number of different techniques will have to be associated for *in vitro* purging [26]. The feasibility of purging is clearly demonstrated here in our patients and in addition, case 23 is encouraging with regard to the toxicity of multiagent purging procedures even after TBI. The continued occurrence of marrow relapse despite purging might lead to the conclusion that such procedures have little to contribute. However we have laboratory evidence that purging procedure with Y29/55 alone or with AL_2 without B_7 are incomplete [18,25]. Only case by case analysis, using a clonogenic or liquid culture assay, can clarify in the future the need and efficacy of the purging procedure. Our preliminary conclusion is that purging techniques still require perfection at a laboratory level and the rationale for their use should not be judged on the basis of incomplete procedures.

The indications for ABM T in BL are in our opinion restricted to 20% of patients and should be divided in 2 groups:

Massive therapy and ABM T are currently the best treatment for BL in PR after initial induction therapy or in relapse still responding to rescue protocols. The only question which remains unclear is whether the high efficacy of second line

rescue protocols will still be observed when relapses follow more aggressive initial therapy. Massive therapy and ABM T is still an experimental treatment for BL with initial CNS involvement, a group which results remain disappointing with conventional regimens [10].

Massive therapy such as BACT or BEAM are clearly not able to cure patients with progressive disease [15]. For this group of patients new phase II studies are urgently needed and should be set up as a multicenter cooperative trial. These studies could be based on conventional chemotherapy regimens tested with ABM T to define if a dose–effect relationship can improve the results. New massive therapy combinations included high dose CDDP, Melphalan, Ifosfamide, BCNU, Cytosine and high dose Methotrexate should be explored. Combinations of various alkylating agents as proposed by the Baltimore group may be a useful avenue to explore [27]. The role of TBI remains unclear in BL despite poor results reported in other lymphomas [28]. However it is clear that such phase II studies will be the basis of any future progress in Burkitt's lymphoma either in conventional or massive therapy regimens.

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