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Treatment of Malignant Lymphoma with High Dose of Chemo or Chemoradiotherapy and Bone Marrow Transplantation

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Abstract—*Twenty-eight patients with malignant lymphoma were treated with high dose chemo or chemoradiotherapy and allogeneic or autologous bone marrow transplantation. They can be divided in two groups: Group* 1 : (19 *pts) consisted in patients in relapse or in* n *complete remission* (n > 2) (*high risk patients*); *Group* 2 (9 *pts) consisted in patients in first or second complete remission at time of bone marrow graft* (*standard risk patients*). *Complete remission was achieved in* 11/17 *patients evaluable for response* (65%). *Duration of response is very different for two groups: in group* 1, *all patients relapsed within a median of* 2 months (*range*: 1–12) *and died within a median of* 7 months (*range*: 2.5–15). *In group* 2, 7/9 *are alive and well in unmaintained CCR in a median of* > 18 months (*range* : > 15–> 36) (P < 0.01). *This experience shows the feasibility of this approach, the obvious antitumoral activity of these conditioning regimens and invited us to use such therapy at an earlier stage of the disease.*

INTRODUCTION

RECENT advances in the treatment of lymphoma have produced complete remission in most patients with disseminated Hodgkin's disease [1] or aggressive non-Hodgkin's lymphoma [2,3–5]. However the prognosis of patients who do not respond to first line therapy or relapse during treatment remains extremely poor [6–10]. Marrow transplantation has made it possible to treat such patients with a more aggressive approach using high dose radiochemotherapy [11–22].

The rationale behind high dose chemotherapy is that a dose/response relationship has been demonstrated with alkylating agents in several malignancies [23–26].

In the past 2 yr we used different high dose combination chemotherapies followed by bone marrow transplantation : melphalan (L.Phenyl Alanine Mustard), cyclophosphamide and TBI, BACT and BAVM based on the fact that these drugs are active against lymphomas [19, 20, 22, 28, 31–36, 38, 39], and have documented activity and toxicity in poor prognosis malignant lymphoma [27–30].

We report here our experience of 28 patients with Hodgkin's and non-Hodgkin's lymphomas using these high dose radiochemotherapy regimens followed by autologous or allogenic bone marrow transplantations.

In reviewing these results we attempt to determine the place of this approach in the treatment of lymphomas.

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PATIENT CHARACTERISTICS

Between September 1981 and July 1984, 28 patients (19 male and 9 female), median age: 31 yr (range : 6–60) with malignant lymphoma were treated using high dose chemotherapy followed by autologous or allogenic marrow transplantation.

Histologic subtypes [40], initial staging (Ann Arbor criterias) [41], previous therapy and status at the time of marrow transplantation are detailed in Tables 1 and 2. Prior to transplantation all patients had received chemotherapy and 23 had received radiotherapy. Lymphoblastic lymphomas were managed as ALL. Patients with diffuse histiocytic lymphomas received regimen with doxorubicin in various schedules: CHOP or M BACOD [3]. Nineteen patients had experienced complete remission, however 12 were in resistant relapse when they received transplant. Ten had a history of bone marrow involvement and three had previously meningeal involvement. Bulky disease (> 5cm) was present at the time of transplant in 10 patients.

Table 1. *Group* 1 *patient data and response to high-dose radiochemotherapy (high risk)*

UPN	Age/ Sex	Histology[a]	Initial staging[b] (disease site)	Previous therapy[c]	Duration of 1st CR (months)	Interval Δ g-BMT (months)	Patient status at time of[d] marrow aspiration transplantation (disease site)	Conditioning regimen	Response[d]	Response duration (months)	Survival (months)	Comments (relapse site)[b]
Allogeneic												
AL 17	29 F	L.L.	IV B (BM)	ADR–CY–VCR–PDN–MTX–L ASP–VDS–RT	3	5	1st REL (ABD + BONE)	CY–TBI	CR	4	7	Dead from REL (ABD + BONE)
AL 24	23 M	Burkitt L.	IV B (BM)	ADR–CY–VCR–PDN–MTX–L ASP–ARAC–RT	1,5	4	RESIST REL. (BM + CNS)	CY + TBI	PR	2	3	Dead from REL (BM + CNS)
AL 35	17 M	L.L.	IV B (BM)	RBM–CY–VCR–PDN–MTX–L ASP–ARAC–RDZ–RT	39	44	RESIST REL (BM)	CY–TBI	CR	2,5	2,5	Dead from Acute GVHD
AL 07	7 M	L.L.	IV A (BM)	ADR–CY–VCR–PDN–MTX–RBM–L ASP–ARAC–6MP	34	38	2nd PARTIAL REL (BM)	CY–TBI	CR	1,5	3	Dead from REL (BM)
AL 13[e]	11 M	L.L.	IV A (BM)	ADR–CY–VCR–PDN–MTX–L ASP– ARAC–VDS–6MP–VM26–RT	24	51	5e CR	CY–TBI	NE	3	3	Dead from acute GVHD
AL 40[e]	20 M	HD TYPE 2	IV B (bone, liver, lung)	ADR–MH–VCR–PDN–NAT–VDS–BLEO–VLB–DTIC–CCNU–CDPP–RT	3	21	RESIST REL (Bone-fever)	BU–CY	PR	3	3	Dead from REL (ABD)
AL 45	22 M	HD TYPE 3	III B	ADR–MH–VCR–PDN–NAT–BLEO–VLB–DTIC	0	7	RESIST REL (IV BM)	CY–TBI	CR	3	3	Dead from pneumonia + acute GVHD
Autologous												
AU 30[f]	41 M	D.H.L.	IV A (Cranial T.)	ADR–CY–VCR–PDN–VLB–RT	0	11	REL/RESIST REL	MPH	PR	1,5	9	Dead from relapse (Cranial)
AU 37	25 M	Burkitt L.	IV B (CNS+BM)	ADR–CY–VCR–PDN–MTX–L ASP–ARAC–6TG–RT	0	5	PR/PR (CNS)	BAVM	SD	1,5	2	Dead from relapse (CNS)
AU 34	53 M	D.H.L.	IV B (meningeal, bones)	ADR–CY–VCR–PDN–MTX–CCNU–BLEO–RT	0	6	REL/RESIST REL	BAVM	CR	2	8	Dead from relapse (CNS)
AU 27	44 M	D.H.L.	IV B (ABD)	ADR–CY–VCR–PDN–MTX–BLEO–VDS	0	12	PR/REL	MPH	CR	2	10	Dead from relapse (ABD.)
AU 27[g]	44 M	D.H.L.	IV B (ABD.)	ADR–CY–VCR–PDN–MTX–BLEO–VDS–ACL–1stMPH+ABMT–RT	0	16	REL/RESIST REL	BAVM	CR	2	5	Dead from relapse (ABD.)

AU 38	44 F	D.H.L.	IV B (Ethm.+ Subcut. nod.)	ADR–CY–VCR–PDN–MTX–BLEO–RT	4	6	CR/REL	BAVM	CR	4	5	Dead from relapse (Ethm.)
AU 47	26 M	L.L.	II B (Mediast.)	ADR–CY–VCR–PDN–MTX–L ASP– VM26–CDDP–RT	1	7	2nd PR/2nd PR	BAVM	CR	2	9	Dead from relapse (mediast.)
AU 42	32 F	D.H.L	IV A (Mediast. +Sternum)	ADR–CY–VCR–PDN–MTX–BLEO–RT	0	5	PR/PR	BAVM	NE	–	1	Dead from penumonia +VOD
AU 02	60 F	PINKUS L	IV B (Maxillar)	ADR–CY–VCR–5FU–CDDP–PDN–RT	6	15	REL/RESIST REL	MPH	CR	12	14	Dead from relapse (Multiple subut. nod.)
AU 05	59 F	D.H.L.	IV B (ABD.)	ADR–CY–VCR–PDN–RT	0	9	PR/RESIST REL	MPH	NE	–	0,3	Dead from sepsis
AU 75	42 F	D.H.L.	IV B (ABD.)	ADR–CY–VCR–PDN–MTX–BLEO	0	9	RESIST REL/ RESIST REL	MPH	PR	5	7	Dead from relapse (ABD)
AU 24	27 M	H.D.	IV Bb (lung)	MH–VCR–PDN–NAT–CCNU–VLB–VDS–RT	0	41	RESIST REL/RESIST REL	BACT	PR	1	15	Dead from relapse (lung)
AU 21	34 F	H.D.	II Aa (Thymus)	ADR–VCR–PDN–MH–NAT–BLEO–VLB–DTIC–RT	19	37	2nd RESIST REL/2nd RESIST REL	BACT	CR	4	12	Dead from relapse (thymus)

a — L.L.: Lymphoblastic lymphoma
D.H.L.: Diffuse histiocytic lymphoma
Pinkus L.: Pinkus lymphoma (42)

b — BM: bone marrow; ABD: abdominal; Cranial T.: cranial tumour; CNS: central nervous system: Mediast.: mediastinal; ethm.: ethmoïdal; subcut. nod.: subcutaneous nodules; VOD: veno-occlusive disease; GVHD: graft versus host disease.

c — RT: radiation therapy; ADR: doxorubicin; CY: cyclophosphamide; VCR: vincristine; 5FU: 5–FU; CDDP: cisplatin; PDN: predisone; VM 26: teniposide; VDS: vindesine; MTX: methotrexate; Bleo: bleomycin; VLB: vinblastine; ACL: aclacynomycine; MPH + ABMT: melphalan + autologous bone marrow transplant; CCNU: lomustine; L. asp: L. asparaginase; ARA C: cytosine arabinoside; 6 TG: 6 thioguanine; MP: mercaptopurine; RDZ: rubidazone; RBM: cerubidin; DTIC: deticene; NAT: procarbazine; MH: mechlorethamine hydrochloride.

d — CR: complete remission; PR: partial remission; SD: stable disease; REL: relapse; RESIST. REL: resistant relapse; NE: not evaluable.

e — mismatched transplantation.

f — diffuse phase after 7 years of nodular lymphoma.

g — second course of high dose chemotherapy in this patient.

Table 2. Group 2 patient data and response to high-dose radiochemotherapy (standard risk)

UPN	Age/ Sex	Histology[a]	Initial staging[b] (disease site)	Previous therapy[c]	1st CR duration (months) at time of trans-plantation	Interval Δ g-BMT (months)	Patient status at time of[d] marrow aspiration transplantation (disease site)	Con-ditioning regimen	Response[d]	Response duration after trans-plantation (months)	Survival (months)	Comments (relapse site)[b]
Allogeneic												
AL 08	35 M	L.L.	IV B (BM)	ADR–CY–VCR–PDN–MTX–L ASP–VDS	2+	4	1ST CR	CY–TBI	NE	36+	36+	Alive and well
AL 33	16 M	L.L.	IV A (Skin)	ADR–CY–VM26–PDN MTX	5+	6	1ST CR	CY–TBI	NE	18+	18+	Alive and well
AL 37	6 F	L.L.	IV A (BM)	ACL–CY–VDS–PDN–RDZ–VM26–L ASP ARAC–HYDREA–6TG–RT	23+	25	1ST CR	CY–TBI	NE	16+	16+	Alive and well
AL 25	31 M	L.L.	IA (Mediast.)	ADRCY–VCR–PDN–MTX–L ASP–VDS–ARAC–RT	6+	7	1ST CR	CY–TBI	NE	21+	21+	Alive and well
Autologous												
AU 29	31 M	D.H.L.	II B (Mediast.)	ADR–CY–VCR–PDN–VM26–VDS–RT	7	12	2rd CR/2nd CR	MPH	NE	2	2,5	Dead from relapse (Mediast.)
AU 63	40 F	L.L.	IV A (BM)	ADR–CY–VCR–PDN–MTX–ARAC–6TG–MP–RT	12+	13	1ST CR /1STCR	BEAM	NE	15+	15+	Alive and well.
AU 62	29 M	D.H.L.	IV A (bone)	ADR–CY–VCR–PDN–MTX–BLEO–RT	4+	6	1STCR/1STCR	BEAM	NE	15+	15+	Alive and well
AU 45	47 M	L.L.	II A	ADR–CY–VCR–PDN–MTX–ARAC–6TG–MP–RT	7	PR /2nd	CR	BAVM	NE	23+	23+	Alive and well
AU 67	46 M	D.H.L.	III A (Cavum, spleen)	ADR–CY–VCR–PDN–MTX–BLEO–RT	8+	10	1ST CR/1ST CR	BEAM	NE	3	13	Dead from relapse (cavum, BM)

a — L.L.: Lymphoblastic lymphoma D.H.L.: Diffuse histiocytic lymphoma

b — BM: bone marrow; ABD: abdominal; Cranial T.: cranial tumour; CNS: central nervous system; Mediast.: mediastinal; ethm.: ethmoïdal; subcut. nod.: subcutaneous nodules; VOD: veno-occlusive disease; GVHD: graft versus host disease.

c — RT: radiation therapy; ADR: doxorubicin; CY: cyclophosphamide; VCR: vincristine; 5FU: 5 FU; CDDP: cisplatin; PDN: predisone; VM 26: teniposide; VDS: vindesine; MTX: methotrexate; Bleo: bleomycin; VLB: vinblastine; ACL: aclacynomycine; MPH + ABMT: melphalan + autologous bone marrow transplant; CCNU: lomustine; L. asp: L. asparaginase; ARA C: cytosine arabinoside; 6 TG: 6 thioguanine; MP: mercaptopurine; RDZ: rubidazone; RBM: cerubidin; DTIC: deticene; NAT: procarbazine; MH: mechlorethamine hydrochloride.

d — CR: complete remission; PR: partial remission; SD: stable disease; REL: relapse; RESIST. REL: resistant relapse; NE: not evaluable.

Twenty-eight patients were studied and analysed in 29 different courses, one patient (AU27) received a second treatment and graft 4 months after the first.

The patients can be divided in two groups:

High risk patients

Consisted of patients in relapse or in *n* complete remission ($n > 2$). Patients in this group had a very poor chance of survival. Nineteen grafts were performed in relapse-patients: 12 in relapse resistant to all therapy at time of transplantation; seven in non-resistant relapse.

One patient was in 5th complete remission (CR).

Standard risk patients

Consisted of patients in first or second CR at time of bone marrow graft. They will be considered for transplantation as part of a pilot study. Eligibility was considered if they had the following risk factors: (1) for diffuse histiocytic lymphoma: systemic symptoms (B symptoms), bulk disease, involvement of marrow, CNS or mediastinum; (2) for lymphoblastic lymphoma: 2nd CR, initial bulky disease, obtention of CR after more than 4 weeks of therapy.

In this group there were nine patients, seven were in first CR and two in 2nd CR.

METHODS

(A) *Bone marrow procedures*

Eighteen patients received autologous marrow transplantation. The technique of harvesting cryopreservation, colony forming cells control, thawing procedure and reinfusion has been reported previously [28]. The median yield of nucleated marrow cells was 2.6×10^8/kg (range 1–3.4).

The marrow was harvested 0–7 months before the graft. At this time it was cytologically normal in all patients. Two patients received fresh-marrow grafts (AU02, AU30) and 16 received cryopreserved marrow.

Eleven patients received allogeneic marrow transplantation. From an HLA histocompatible sibling [9] or from an HLA mismatched donor (2 : AL13; AL40). The median of infused nucleated cells was 2.8×10^8 kg (range : 2.2–3.8).

(B) *High dose radiochemotherapy*

(1) *Allogeneic marrow transplantation regimens (11 patients).* Ten patients were conditioned with cyclophosphamide 60 mg/kg for 2 days and TBI from linear-accelerator source.

One patient (AL40) who was irradiated before transplantation for Hodgkin's lesions was prepared with Busulfan and cyclophosphamide [43].

Prophylaxis against graft-versus-host disease (GVHD) was done using Methotrexate [45] in nine patients and cyclosporine A in 2 [46, 47].

(2) *Autologous transplantation regimens.* (a) High dose Melphalan alone (140 mg/m^2): Melphalan was given as an intravenous bolus into six patients hydrated (3000 ml/m^2/d) with continuous intravenous fluids started 6–12 hr before and continued for 24 hr after chemotherapy. (b) Combination chemotherapy with high-dose melphalan: The first six patients received the BAVM protocol* [28]. One patient (AU34) with central nervous system involvement, received BCNU 300 mg/m^2 IV on day 1; Procarbazin 200 mg/m^2 IV on days 1, 2, 3 and 4: VEHEM (VM26) 200 mg/m^2 IV on days 2, 3 and 4; melphalan 140 mg/m^2 IV on day 5.

These two protocols have been evaluated in a previous study [28]. The last three patients received the BEAM protocol (as a part of a multicentric study): BCNU 300 mg/m^2 IV on day 1; etoposide (VP16) 100 mgm/m^2 IV on days 2, 3, 4, and 5; ARA-C 100 mg/m^2 IV q.12hr on days 2, 3, 4 and 5; melphalan 140 mg/m^2 IV on day 6. Autologous bone marrow was infused 24 hr or 48 hr after IV melphalan. (c) The BACT regimen [44] was used on two patients with Hodgkin's Disease†: Autologous bone marrow was infused 48 hr after the last dose of chemotherapy.

(C) *Supportive care*

All allogeneic marrow transplantations were conducted under sterile conditions in laminar air flow rooms with decontamination of the gastrointestinal tract. Autologous marrow transplantations were managed in single rooms with conventional hospital reverse isolation except patients AU21, AU24, AU29, who were treated in laminar air flow rooms. They received prophylactic Bactrim. Blood components except marrow were irradiated with 15 Gray and were given as needed to maintain the hemoglobin level above 10 g/100 ml and the platelet count above 20,000/μl.

(D) *Evaluation of response and toxicity*

Patient's response was evaluated 1 month after bone marrow transplantation. Complete remission (CR) was defined as complete disappearance of all signs related to tumor at least for 1 month; partial response (PR) was used to define a decrease of greater than 50% in all measurable tumor at least

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* BAVM: BCNU: 300 mg/m^2 IV D1
ARA-C: 200 mg/m^2 c.i. D2, 3, 4, 5, 6
VDS: 1.3 mg/m^2 c.i. D2, 3, 4, 5, 6
MPH: 140 mg/m^2 IV D7

† BACT: BCNU: 200 mg/m^2 IV D1
CY: 50 mg/kg IV D2, 3, 4, 5
ARA-C: 200 mg/m^2 c.i. D2, 3, 4, 5
6 TG: 200 mg/m^2 p.o. D2, 3, 4, 5

for one 1 month. Stable disease (SD) was defined as no evidence of disease progression at least for 1 month.

RESULTS

Overall results

Seven patients were alive and free of disease from 15 + to 36 + months after transplantation. All are standard risk patients. All the other patients died: 16 from progression of the disease, two from GVHD, three from infection.

Antitumor response and survival

Tables 1 and 2 summarise the outcome of each patient after BMT.

High risk group. 17/20 patients were evaluable for response after transplantation. Three are not evaluable: two patients (AU05, AU42) died early from infection; the last one received high dose radiochemotherapy in 5th CR. 11/17 patients (65%) had 2nd complete remission; five patients had a partial remission. Only one patient was considered as non responder (AU37). Out of 17 responders after transplantation, three died early from bone marrow graft complications (AL13, AL35, AL45). All the remaining patients relapsed within a median of 2 months (range 1–12) and died within a median of 7 months (range 2.5–15).

Standard risk group. 7/9 patients are alive and well in unmaintained continuous complete remission in a median of > 18 months (range: > 15 to > 36). The two other patients relapsed at 2 and 3 months.

Patterns of relapse

Sixteen patients relapsed after complete or partial remission. In 14/16 cases, relapse occurred predominantly at sites of prior lymphomatous involvement. In all but one case, patient relapse was observed within the first 5 months after transplantation.

Hematological suppression

Hematological toxicity is detailed in Table 3. Severe marrow aplasia occurred in all cases with leucocyte counts of less than $0.1 \times 10^9/l$ and platelet counts of less than $20 \times 10^9/l$.

Twenty-eight patients survived for at least 30 days and were evaluable for hematologic recovery: blood neutrophil counts reached 500 per microlitre in a median of 22 days (range 16–43) after allogeneic transplantation and 14 days (range 8–24) after autologous ($P < 0.01$). Platelet counts reached 50,000/μl in a median of 36 days (range 13–96 after allogeneic graft and 25 days (range 13–52) after autologous.

Delay of hematologic recovery was longer in allogeneic than in autologous grafts; this is related with use of fractionated TBI and methotrexate for prevention of GVH.

Toxicity (Table 3)

(a) *Infection.* 28 patients developed fever during aplasia: median duration of hyperthermia > 38°C was 5 (range 0–21). The number of days under IV antibiotics ranged from 0 to 67 days (median : 19).

One patient (AU05) died from sepsis by day 12; three developed acute respiratory distress syndrome overwhelming gram positive sepsis (AU38, AU42, AL45).

(b) *GVHD.* 7/11 patients developed acute GVHD with grading > 2. Two patients died directly from the consequences of severe GVHD (AL13, AL35).

(c) *Fifteen cases of moderate or severe mucostitis were observed.* Twelve patients suffered from moderate or severe nausea and six from moderate or severe diarrhea.

(d) *Other extra-hematological complications were:* One veinous occlusive disease (AU42). One cardio-myopathy with pericarditis (AU24) which, fortunately, resolved. One pancreatitis with perforated duodenal ulcer (AL40). One hemorrhagic

Table 3. Hematologic recovery and toxicity

	Allogenic grafts		Autologous grafts
Total number of patients	11		17
Infused nucleated cells/kg $\times 10^8$ mean ± S.D.	2.77 ± 0.53	NS	2.32 ± 0.85
Number of days with G¢ $< 0.5 \times 10^9/l$ mean ± S.D.	25.45 ± 8.79	$P < 0.01$	13.60 ± 4.30
Number of days with Pl $< 50 \times 10^9/l$ mean ± S.D.	37.80 ± 23.24	NS	26.41 ± 11.75
Number of days of fever > 38°C mean ± S.D.	11.09 ± 10.4	NS	4.71 ± 5.35
Number of days under antibiotics mean ± S.D.	28.09 ± 16.88	NS	16.35 ± 11.79

G¢ = granulocytes

cystitis clearly attributable to the cyclophosphamide (AL45).

DISCUSSION

Patients suffering from malignant lymphomas not responding to first line conventional chemotherapy or in relapse present a therapeutic challenge: Prolonged disease-free survival after secondary therapy is unusual in this poor prognostic group. For example: Cabanillas reports a 21% remission rate and only a 7% disease-free in his study involving 243 patients recurrent non-Hodgkin's lymphoma treated in five different chemotherapeutic regimens [6]. Santoro reports a better result with a 22% disease free survival rate 5 yr after treatment in patients with Hodgkin's disease resisting primary chemotherapy with MOPP who were treated with ABVD, a regimen designed to avoid cross-resistance with MOPP [10].

Both experimental and clinical studies suggest greater efficacy of intensive cytotoxic therapy for hematologic cancers [48] [23]. Using autologous, syngenic or allogeneic marrow transplantation to limit myelosuppression it has been possible to cure 15–20% of patients with resistant non-Hodgkin's lymphoma [11], [19], [49].

Our results confirm that using high dose cytoreductive therapy and BMT, it is possible to achieve a high response rate (65%) in patients with advanced Hodgkin's disease and non-Hodgkin's lymphoma who have been extensively treated prior to progression of their disease (high risk group).

In this population of multi-resistant patients with malignant lymphomas our response and remission rates are similar to other published high dose chemoradiotherapy regimens. Using autologous bone marrow grafting, Appelbaum reported a 10/14 response rate (70% CR and PR) [44] and Philip obtained 7/10 (70% CR) using BACT [18]; Hartmann obtained 11/16 (68% CR) using modified BACT on children [15]; Gorin obtained 4/6 (66% CR) with TACC [14]; Tannir gave 5/8 (62% CR) with CBV or CY-TBI [20]. Using CY-TBI, Phillips presented 23 CR/34 evaluable patients (65%) [50, 51] and Appelbaum reported 7 CR/8 patients with twin donors [11] and 14 CR/20 patients (70%) with allogenic transplantation [12]. Using CRAB regimen and allogenic grafting O'Leary obtained CR in three relapsed lymphomas [17].

One potential disadvantage of autologous marrow transplanation is the reinfusion of malignant cells and many clinicians have been reluctant to use this technique as part of an otherwise possibly curative approach.

However we observed that most relapses were localized to sites that had previously been involved with lymphoma and were not widely disseminated as might have been anticipated if the infused marrow had contained viable tumour cells.

This demonstrates that our regimens, CY-TBI[1] melphalan alone of BAVM are not completely lymphoma ablative in refractory lymphomas. That the CY-TBI regimen is inadequate is suggested by the high relapse rate reported after its use in allogeneic marrow and syngeneic marrow transplantation [49] or after autologous [19]. The same was observed with BACT regimen [49] except for Burkitt's lymphoma. It will be important to define the sensitivity of the different forms of lymphoma to the different preparative regimens.

It is also interesting to note that prolonged remissions were achieved and reported, even following transplantation of marrow that was initially involved with lymphoma and cleared with conventional chemotherapy before marrow storage [49].

Nevertheless, regimen-related failure may obscure a high relapse rate due to reinoculated lymphoma cells, and it would appear logical to prefer a HLA identical sibling to an autograft whenever possible, or in the latter case to minimize the possibility of infusing tumor cells with the use of techniques more sensitive than histologic studies to identify occult malignant cells [52, 53] and methods to purge occult tumor cells from the marrow before storage [54–58].

On the other hand intensive therapy associating boost radiotherapy to sites of bulky disease can be safely given with substantial anti-lymphoma activity. Preliminary study suggests the possibility that the intensification with boost will reduce the relapse but follow up has yet been insufficient for us to be able to draw any conclusions [51].

Potential disadvantages of allogeneic marrow transplantation include the immunologic problems of rejection: graft-versus host disease and prolonged immunodeficiency status. Although more complications are associated with allogeneic than with autologous bone marrow transplantation, there are situations in which the former is preferable especially in the case of marrow involvement with lymphoma at time of diagonsis. Whether GVHD has any beneficial antitumor effect in lymphoma patients, as has been suggested in acute leukemia, remains to be established.

The short duration of response of high risk group patients is relatively predictable in such a selection of resistant patients and has been observed as well with other regimens in malignant lymphomas and in other malignancies. The only feature associated with prolonged disease-free survival was patient status at time of transplantation: in high risk group 14/14 patients evaluable for duration of response relapsed. Amongst the nine standard risk patients, two relapsed and seven are in unmaintained CR

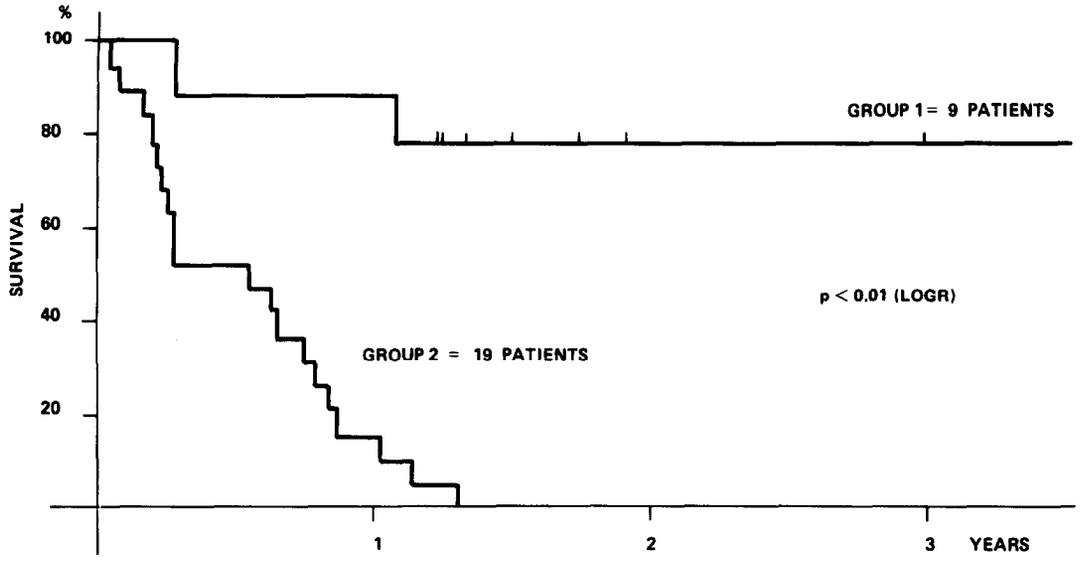

Fig. 1. Product limit estimate of survival (Kaplan Meier method) in "High Risk" and "Standard Risk" patients (statistical method = Log Rank Test).

from > 15 to > 36 months (Fig. 1). Identical results are seen in the preliminary study of O'Leary [17].

The feasibility of this approach and the obvious antitumoral activity of these conditioning regimens (very high response rate in patients resistant to conventional chemotherapy) invited us to use such therapy at an earlier stage of the disease in first or second complete remission, in selected patients known to have poor prognosis under conventional chemotherapy.

In conclusion bone marrow transplantation provides an alternative to conventional chemotherapy for the patients with poor risk lymphomas when the graft is performed before the adverse conditions of high tumour burden and drug resistance are. Consolidation therapy with autologous BMT during the first remission has been successful in canine lymphomas and these results are supported by our study; transplantation of allogeneic or syngeneic marrow during the first remission has proved to be a successful strategy in reducing the incidence of relapse in acute leukemia [22] and lymphomas [17].

However a high risk of relapse is required to justify the morbidity of intensive therapy during the first remission.

Reliable prognosis factors have not been identified for patients with lymphoma in the first CR after newer primary chemotherapy.

Salvaging patients who have previously received aggressive first line chemotherapy and subsequently relapsed is obviously much more difficult; and it is to be expected that the response rate is low and the duration of response short.

All these factors make it difficult to determine which categories of patients should be treated with conventional or with high dose chemotherapy.

We are currently performing high dose chemotherapy intensification:

1. On children with lymphoblastic or Burkitt's lymphomas in early relapse, in partial or in second remission, or in 1st CR when there are these risk factors: CNS or bone marrow involvement, bulk disease; unobtained CR after 4 weeks of induction therapy.

2. On adults: (a) with diffuse histiocytic lymphomas, with clinical stage 3 or 4 and responding or not to initial chemotherapy (restaging after 4 M-BACOD); (b) with lymphoblastic lymphoma stage 3 or 4 (Murphy classification) who were or not in complete remission at the end of the consolidation phase of the LSA2 L2 protocol; (c) with relapsed or resistant lymphomas for other histologies.

Despite the known risk of GVHD with allogeneic BMT our results should encourage the use of allogeneic BMT for those patients who have sibling donors.

REFERENCES

1. de Vita VT, Simon RM, Hubbard SM *et al.* Curability of advanced Hodgkin's disease with chemotherapy: long-term follow up of MOPP treated patients at the National Cancer Institute. *Ann Intern Med* 1980, **92**, 587–595.

2. Fisher RI, de Vita VT, Hubbard SM *et al.* Diffuse aggressive lymphomas: Increased survival after alternating flexible sequences of PRO-MACE and MOPP chemotherapy. *Ann Intern Med* 1983, **98**, 304–309.
3. Horwich A, Pekham M. 'Bad risk' non Hodgkin lymphomas. *Semin Hematol* 1983, **20**, 35–36.
4. Levine AM, Forman SJ, Meyer PR *et al.* Successful therapy of convoluted T-lymphoblastic lymphoma in the adult. *Blood* 1983, **61**, 92–98.
5. Skarin A, Canellos G, Rosenthal D, Case D, Moloney W, Frei E. Therapy of diffuse histiocytic and undifferentiated lymphoma with high dose Methotrexate and citrovorum factor rescue, Bleomycin, Adriamycin, Cyclophosphamide, Oncovin and Decadron (M-BACOD). *Proc Am Soc Clin Oncol* 1980, **21**, 463 (abstract n° C-568).
6. Cabanillas F. Hagemeister FB, Bodey GP, Freireich EJ. IMVP-16: An effective regimen for patients with lymphoma who have relapsed after initial combination chemotherapy. *Blood* 1982, **60**, 693–697.
7. Cabanillas F, Hagemeister FB, McLaughlin P. *et al.* Long term outcome of complete responders to salvage chemotherapy for recurrent or refractory lymphoma. *Proc Am Soc Clin Oncol* 1983, **2**, 213 (abstract n° C-833).
8. Fisher RI, de Vita VT, Hubbard SP, Simon R, Young RC. Prolonged disease-free survival in Hodgkin's disease with MOPP reinduction after first relapse. *Ann Intern Med* 1979, **90**, 761–763.
9. Harker WG, Kushlan P, Rosenberg SA. Combination chemotherapy for advanced Hodkin's disease after failure of MOPP: ABVD and B-CAVE. *Ann Intern Med* 1984, **101**, 440–446.
10. Santoro A, Bonfante V, Bonadonna G. Salvage chemotherapy with ABVD in MOPP-resistant Hodgkin's disease. *Ann Intern Med* 1982, **96**, 139–143.
11. Appelbaum FR, Fefer A, Cheever MA *et al.* Treatment of non Hodgkin's lymphoma with marrow transplantation in identical twins. *Blood* 1981, **58**, 509–513.
12. Appelbaum FR, Sullivan K, Thomas ED *et al.* Treatment of non Hodgkin's lymphoma with chemoradiotherapy and allogeneic bone marrow transplantation. *Proc Am Soc Clin Oncol* 1983, **2**, 220 (abstract n° C-859).
13. Douer D, Champlin RE, Ho WG *et al.* High dose combined modality therapy and autologous bone marrow transplantation in resistant cancer. *Am J Med* 1981, **71**, 973–976.
14. Gorin NC, David R, Stachowiak J *et al.* High dose chemotherapy and autologous bone marrow transplantation in acute leukemias, malignant lymphomas and solid tumors. A study of 23 patients. *Eur J Cancer* 1981, **17**, 557–568.
15. Hartmann O, Pein F, Philip T, Biron P, Lemerle J. The effects of high dose polychemotherapy with autologous bone marrow transplantation (ABMT) in 18 children with relapsed lymphoma. *Eur J Cancer Clin Oncol* 1982, **18**, 1044. (*Proceedings of the XIVth Annual Meeting of International Society of Pediatric Oncology* – abstract n° 26.)
16. Kaizer H, Leventhal BG, Wharam MD *et al.* Cryopreserved autologous bone marrow transplantation in the treatment of selected pediatric malignancies: A preliminary report. *Transplant Proc* 1979, **11**, 208–211.
17. O'Leary M, Ramsay NKC, Nesbit ME *et al.* Bone marrow transplantation for non-Hodgkin's lymphoma in children and young adults: A pilot study. *Am J Med* 1983, **74**, 497–501.
18. Philip T, Biron P, Herve P *et al.* Massive BACT chemotherapy with autologous bone marrow transplantation in 17 cases of non-Hodgkin's malignant lymphoma with a very bad prognosis. *Eur J Cancer Clin Oncol* 1983, **19**, 1371–1379.
19. Phillips GL, Herzig RH, Lazarus HM, Fay JW, Wolff SN, Mill WB, Lin H, Thomas PRM, Glasgow GP, Shina DC, Herzig GP. Treatment of resistant malignant lymphoma with cyclophosphamide, total body irradiation, and transplantation of cryopreserved autologous marrow. *N Engl J Med* 1984, **310**, 1557–1561.
20. Tannir NM, Spitzer G, Zander AR *et al.* High dose chemoradiotherapy and bone marrow transplantation in patients with refractory lymphoma. *Eur J Cancer Clin Oncol* 1983, **19**, 1091–1096.
21. Spitzer G, Dicke KA, Litam J *et al.* High dose combination chemotherapy with autologous bone marrow transplantation in adult solid tumors. *Cancer* 1980, **45**, 3075–3085.
22. Thomas ED. Marrow transplantation for malignant diseases. *J Clin Oncol* 1983, **1**, 517–531.
23. Frei E III, Canellos GP. Dose: a critical factor in cancer chemotherapy. *Am J Med* 1980, **69**, 585–594.
24. Maraninchi D, Pico JL, Hartmann O *et al.* High dose melphalan with or without marrow transplantation: a study of dose effect in patients with refractory and–or relapsed acute leukemias. *Cancer Treat Rep* (in press).
25. Rustin GIS, Cornbleet MA, Hedley DW, McElwain TJ. High dose melphalan in advanced malignant melanoma. *Br J Cancer* 1981, **43**, 719–720.
26. Skipper HE, Schmidt LH. A manual on quantitative drug evaluation in experimental tumor systems. *Cancer Chemother Rep* 1962, **17**, 1–143.
27. Dumont J, Philip T, Maraninchi D *et al.* High dose chemotherapy and bone marrow

transplantation in poor prognosis Hodgkin's disease. Second International Conference on malignant lymphoma Lugano June 13–16, 1984.
28. Mascret B, Maraninchi D, Gastaut JA *et al.* Phase I–II study of high dose melphalan and autologous marrow transplantation in adult patients with poor risk non Hodgkin's lymphomas. *Cancer Chemother Pharmacol* 1985, **14**, 216–222.
29. Philip T, Biron P, Herve P *et al.* Massive cytoreductive regimen and autologous bone marrow transplantation in 32 cases of bad prognosis malignant lymphomas. *Exp Hematol* 1983, **11** (suppl. 14), 69 (abstract n° 125).
30. Philip T, Biron P, Maraninchi D *et al.* Role of massive chemotherapy and autologous bone marrow transplantation in non Hodgkin's malignant lymphoma. *Lancet* 1984, **i**, 391.
31. Bender RA, Anderson T, Fisher RI, Young RC. Activity of the epipodophyllotoxin VP-16 in the treatment of combination chemotherapy resistant non Hodgkin's lymphoma. *Am J Hematol* 1978, **5**, 203–209.
32. Dobbs HJ, Barret A, Rostom AY, Peckham MJ. Total body irradiation in advanced non Hodgkin's lymphoma. *Brit J Radiol* 1981, **54**, 878–881.
33. Fleishman GB, Velasquez WS, Butler JJ *et al.* Lymphoblastic lymphoma: the MD Anderson Hospital experience. *Proc. AACR/ASCO* 1981, **22**, 515.
34. Kantarjian H, Barlogie B, Plunkett W *et al.* High dose cytosine arabinoside in non Hodgkin's lymphoma. *J Clin Oncol* 1983, **1**, 689–694.
35. Maraninchi D, Abecassis M, Gastaut JA *et al.* High dose Melphalan and autologous bone marrow transplant for relapsed acute leukaemia. *Cancer Chemother Pharmacol* 1983, **10**, 109–111.
36. Phillips GL, Fay JW, Herzig GP *et al.* Intensive 1,3 bis (2 choroéthyl) 1 nitrosourea (BCNU), NSC = 4366650 and cryopreserved autologous marrow transplantation for refractory cancer. A phase I–II study. *Cancer* 1983, **52**, 1792–1802.
37. Spitzer G, Dicke KA, Verma DS, Zander A, McCredie KB. High dose BCNU therapy with autologous bone marrow infusion: Preliminary observations. *Cancer Treat Rep* 1979, **63**, 1257–1264.
38. Sullivan MP, Ramirez I, Pullen J *et al.* Use of Cytosar in pediatric non Hodgkin's lymphoma. *Med Pediatr Oncol* (suppl.) **1**, 251–257.
39. Radice PA, Bunn PA, Ihde DC. Therapeutic trials with VP16-213 and VM26: active agents in small cell lung cancer, non Hodgkin's lymphomas and other malignancies. *Cancer Treat Rep* 1979, **63**, 1231–1239.
40. Rappaport H. Tumors of the hematopoietic system in Atlas of Tumor Pathology. Washington, D.C., U.S. Armed Forces Institute of Pathology, 1966, sect. 3, Fascicle 8.
41. Rosenberg SA. Validity of the Ann Arbor staging classification for the non Hodgkin's lymphoma. *Cancer Treat Rep* 1977, **61**, 1023–1028.
42. Pinkus GS, Said JW, Hargreaves H. Malignant lymphoma, T-cell type: a distinct morphologic variant with large multilobated nuclei, with a report of four cases. *Am J Clin Pathol* 1979, **72**, 540–550.
43. Santos GW, Tutschka PJ, Brookmeyer RS *et al.* Marrow transplantation for acute non lymphocytic leukemia after treatment with busulfan and Cyclophosphamide. *N Engl J Med* 1983, **309**, 1347–1353.
44. Appelbaum FR, Deisseroth AB, Grauw RG, Herzig GP, Levine AS, Magrath IT, Pizzo PA, Poplack DG, Ziegler JL. Prolonged complete remission following high dose chemotherapy of Burkitt's lymphoma in relapse. *Cancer* 1978, **41**, 1059.
45. Thomas ED, Storb R, Clift RA *et al.* Bone marrow transplantation. *N Engl J Med* 1975, **292**, 832–843, 895–902.
46. Bertault-Peres P, Maraninchi D, Carcassone Y, Cano JP, Barbet J. Clinical pharmacokinetics of Cyclosporin A in bone marrow transplantation patients. *Cancer Chemother Pharmacol* 1985 (in press). 1985, **15**: 76–81.
47. Tutschka PJ, Beschorner WE, Hess, AD. Santos GW. Cyclosporin A to prevent graft versus host disease: A pilot study in 22 patients receiving allogeneic marrow transplants. *Blood* 1983, **61**, 318–325.
48. Bruce WA, Meeker BE, Valeriote FA. Comparison of the sensitivity of normal hematopoietic and transplanted lymphoma colony-forming cells to chemotherapeutic agents administered in vivo. *J Natl Cancer Inst* 1966, **32**, 233–245.
49. Appelbaum FR, Thomas ED. Review of the use of marrow transplantation in the treatment of non Hodgkin's lymphoma. *J Clin Oncol* 1983, **1**, 440–447.
50. Phillips GL, Herzig GP, Herzig RH, Lazarus HM, Wolff SM, Fay JW. Cyclophosphamide, total body irradiation and autologous bone marrow transplantation for refractory malignant lymphoma. *Proc Am Soc Hematol* 1981, 175a (abstract).
51. Phillips GL, Herzig RH, Wolff SN *et al.* Cyclophosphamide total body irradiation with and without boost radiotherapy in autologous bone marrow transplantation for relapsed lymphoma. *Exp Hematol* 1983 (suppl. 14), **11**, 69 (abstract n°126).
52. Benjamin D, Magrath IT, Douglass EC, Corash LM. Derivation of lymphoma cell lines from microscopically normal bone marrow in patients with undifferentiated lymphomas: evidence of occult bone marrow involvement. *Blood* 1983, **61**, 1017–1019.

53. Philip I, Philip T, Lenoir GM. *In vitro* outgrowth of malignant Burkitt's lymphoma cell clones following cultivation of cytologically normal bone marrow: Application to autologous bone marrow transplantation. *Exp Hematol* 1983, **11** (suppl. 13), 169 (abstract).
54. Baumgartner C, Brun Del Re G, Bucher U *et al.* Autologous bone marrow transplantation for stage IV abdominal non Hodgkin's lymphoma: *In vitro* marrow purging with the monoclonal antibody anti Y29/55 and complement. *Exp Hematol* 1983, **11** (suppl. 13), 169 (abstract).
55. Kaizer H, Levy R, Brovall C *et al.* Autologous bone marrow transplantation in T-cell malignancies: A case report involving in vitro treatment of marrow with a pan-T-cell monoclonal antibody. *J Biol Res Mod* 1982, **1**, 233–243.
56. Jansen J, Falkenburg JHF, Stepan DE, Lebien W. Removal of neoplastic cells from autologous bone marrow grafts with monoclonal antibodies. *Semin Hematol* 1984, **21**, 164–181.
57. Nadler LM, Ritz J, Hardy R, Pesando JM, Schlossman SF, Stashenko P. A unique cell surface antigen identifying lymphoid malignancies of B-cell origin. *J Clin Invest* 1981, **67**, 134–140.
58. Nadler LM, Takvorian T, Botnick L *et al.* Anti-B1 monoclonal antibody and complement treatment in autologous bone marrow transplantation for relapsed B-cell non Hodgkin's lymphoma. *Lancet* 1984, **ii**, 427–431.