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Autologous Bone Marrow Transplantation in the Treatment of Poor Prognosis Non-Hodgkin's Lymphomas*

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Abstract—*Twelve patients with non-Hodgkin's lymphomas of poor prognosis were treated by TACC high-dose chemotherapy (cyclophosphamide* 45 mg/kg/day × 4, *cytosine arabinoside* 200 mg/m² *i.v. q* 12 hr × 7, 6-*thioguanin* 100 mg/m² *p.o.* × 7 *and CCNU* 200 *or* 250 mg/m² *p.o., single dose) followed by autologous bone marrow transplantation (ABMI) (infused dose:* 853–20,000 *CFU-c*/kg). *Patients were divided into* 2 *groups: those in primary therapy with high tumor load (group* 1; 3 *initial diagnoses,* 3 *relapses) and those in consolidation therapy for a low tumor load (group* 2; 5 *complete and* 1 *partial remissions). Results show that:* (1) *the aplasia following autologous bone marrow transplantation was short. Leukocyte* (>10^9/1) *and platelet* (>50 × 10^9/1) *recoveries were observed on day* 12 (*range,* 9–19) *and day* 14 (*range,* 8–27). (2) *In group* 1 *there were* 3 *complete remissions* (8, 21, 45+ months) *and* 3 *failures, including* 1 *death to toxicity of TACC. The* 3 *remissions occurred in patients in primary therapy and overall survival of these patients from the time of initial diagnosis was* 48+, 48+ *and* 60+ months. *In group* 2 *there were* 5 *persisting complete remissions* (12+ *to* 40+ months) *and* 1 *failure. Overall survival of these patients was* 23+, 24+, 27+, 42+ *and* 70+ months. *In both groups failures were associated with contamination of the frozen marrow by tumor. The toxicity of the association TACC + ABMT was acceptable and dominated by the risk of pericardial effusion and infection. The latter was absent in group* 2 *and occurred in* 5/6 *cases in group* 1. *These preliminary results indicate that autologous bone marrow transplantation has a possible role in the aggressive treatment of non-Hodgkin's lymphomas of high-grade malignancy and that its use should preferentially be in the consolidation mode.*

INTRODUCTION

RECENT reports demonstrating normal marrow recovery following infusions of cryopreserved stem cells have led to the conclusion that autologous bone marrow transplantation (ABMT) is practicable in the treatment of some selected severe malignancies with high-dose chemotherapy and/or total-body irradiation [1–11].

We report here our experience in the treatment of 12 cases of poor-prognosis non-Hodgkin's lymphomas with high-dose chemotherapy and/or total-body irradiation followed by autologous bone marrow transplantation.

We think these preliminary results may argue in favour of the use of autologous bone marrow transplantation in a more aggressive therapeutic strategy for NHL of high-grade malignancy.

MATERIALS AND METHODS

Patients

From April 1978 to February 1982, 12 patients selected on the basis of poor clinical and pathological prognostic criteria were entered into

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our study. They were divided into 2 groups. The first group consisted of 6 patients with a high tumor cell load (3 at presentation, 3 in relapse). These patients received high-dose chemotherapy followed by ABMT. The second group of 6 patients with a low tumor cell load (5 in complete remissions, 1 in partial) were consolidated with high-dose chemotherapy + ABMT. Preliminary data on 4 patients of group 1 have been already published [1].

Histological and cytological study

Tumor sections initially analysed between 1978 and 1982 using the Rappaport [12] or Lennert *et al.* [13] classifications were reviewed for the purposes of this study and reclassified by 2 hematopathologists, using the criteria recently proposed by Bethesda panel (NWF formulation) [14]. This review confirmed high-grade or intermediate malignancy in 10 cases. According to the reclassification, 2 patients had low-grade malignancies. However, they had poor prognosis clinical features (chemo-resistant relapse in 1 case, infradiaphragmatic location of a 15 cm tumor in 1 case).

Bone marrow collection was performed only after multiple bone marrow examinations failed to show any evidence of involvement on either biopsy or aspiration. Similarly, transplantations were undertaken only after the integrity of the harvested marrow was verified by a smear and by biopsies taken at the time of marrow collection in the OR. In one case (No. 12), however, since a small percentage of suspicious cells had been found on aspiration at time of diagnosis (but not later at time of collection when the patient was in CR), the marrow was incubated in the presence of 4-hydroperoxycyclophosphamide (4-HC) before cryopreservation. For the purposes of this publication, bone marrow smears taken in all patients before collection and taken from the harvested marrow itself were examined again.

Bone marrow harvesting, freezing and storage

Techniques of collection, freezing, storage and thawing have been described in detail elsewhere [1, 6]. Briefly, collection was carried out under general anesthesia and a minimum volume of 800 ml was harvested in every case. The richness of the marrow was evaluated both by cell count and by the absolute number of myeloid progenitor cells GM CFU-c. The cooling programme was essentially the same as the one we tested previously on canine marrow [6]. Additional modifications to diminish the third slope of the freezing curve were introduced in January 1981, when it was discovered that there was an inverse relationship between the recovery of CFU-c and cooling rate beyond the heat of fusion [8, 15]. Test bags were routinely thawed after freezing and again before transplantation for CFU-c assay. Overall recovery was around 75% [16].

Retrospective study of individual freezing curves for each marrow sample revealed that optimal conditions were met in 11 cases (of 12), and were lacking in case No.1, where the quantity of injected CFU-c was under what we presently consider to be the minimum dose for a successful transplantation (approx. 800 CFU-c/kg) [16].

Chemotherapy, irradiation and transplantation

All patients in this study received the TACC protocol (in use in our department since 1976) which is a slight modification of the BACT, previously used as a conditioning regimen for allogeneic transplantation by the Bethesda group [17], as follows: 6-thioguanine 100 mg/m^2 p.o. q 12 hr on days 1–4 for 7 doses, cytosine arabinoside 200 mg/m^2 i.v. q 12 hr on days 1–4 for 7 doses, cyclophosphamide 45 mg/kg/day i.v. days 1–4 and, CCNU 200 mg/m^2 p.o. on day 2.

An alkaline forced diuresis (3 l/m^2) was instituted along with chemotherapy and was continued up through the infusion of autologous marrow. In addition, 2 patients received local or regional irradiation and 1 received total body irradiation at a total dose of 8 Gy.

All available bags of marrow were thawed and reinfused (2 per day for 3–4 days), starting 48 hr after the last dose of cyclophosphamide or 24 hr after total-body irradiation. In most cases the CFU-c content of the injected bags was assayed and the exact quantity of CFU-c administered was calculated. In 2 cases the dose of erythroblast progenitor cells (BFU-e) injected was also calculated.

While aplastic, patients were supported with frozen packed red cells and platelets. Only 3 patients received leukocyte transfusions. All blood products were irradiated at 25 Gy.

All patients received hyperalimentation. None received maintenance chemotherapy following ABMT.

Kinetics of ABMT were studied through daily peripheral blood counts, bone marrow aspirates and biopsies, routine CFU-c cultures on days 5, 9, 14, 19 and 25, and occasional BFU-e and CFU-e studies. Curves were established with day 0 being the first day of marrow infusion.

These kinetics were analyzed for correlation with the dose of bone marrow infused and the duration of marrow storage. Also, in an effort to detect any functional alteration of infused stem cells, the patients were subdivided according to

whether marrow collection occurred before or after conventional chemotherapy.

Patients were staged prior to treatment, at time of hematologic recovery and every 3 months thereafter. Complete remission was defined as the disappearance of any clinically or investigatively detectable tumor (CT scanning, second-look laparotomy included). Post-mortem examination was performed on all deceased patients.

RESULTS

Autologous bone marrow transplantation (*Fig.*1, *Table* 1)

Case No.1, who received a low dose of CFUc and did not engraft, was excluded from the study.

In the remaining 11 patients peripheral blood recovery was similar, with a very small range of values. As can be seen in Fig. 1, the median day of recovery of leukocytes ($>10^9/1$) was day 12 (range, 9–19; mean, 14). The median day of recovery of platelets ($>5 \times 10^{10}/1$) was day 14 (range, 8–27; mean, 15).

An initial transitory leukocyte peak, corresponding to a partial recovery from aplasia (or 'false' leukocytic peak), was observed in 3 cases (Nos. 7, 10, 12) during the first week.

No significant correlation was found between either the dose of marrow infused or the length of marrow storage and the kinetics of peripheral blood recovery. Interestingly, however, the slowest leukocyte recovery rates, 'false peaks' with oscillations and delayed white cell recovery beyond the critical value of $10^9/1$, were observed only in those patients who received a marrow dose less than 3600 CFU-c/kg. These observations were not statistically significant.

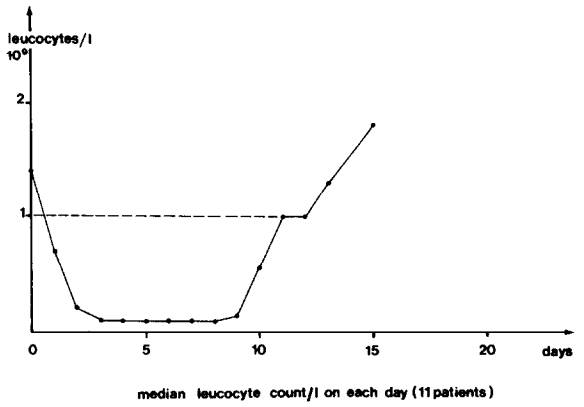

Fig. 1. *Recovery of leukocytes after TACC chemotherapy in patients with NHL receiving autologous bone marrow infusion.*

Anti-tumor effectiveness

Results were quite different in group 1 (high tumor load) and group 2 (low tumor load).

Group 1 (*Table* 2). Three of the 6 patients in this group appeared to receive a beneficial anti-tumor effect and are still alive 45+ to 58+ months later, at the time of writing. These patients enjoyed complete remissions of 8, 21 and 45+ months following their therapy. Of the 2 patients that relapsed, the first one presented 8 months after TACC + abdominal irradiation + ABMT, with multiple recurrences including 3 well-defined intracranial localizations by Tc scintigraphy. He failed to respond to CHOP and was put into complete remission by crude interferon therapy, which was discontinued 2 yr later. The second patient relapsed in the original infra-diaphragmatic location and was put again into CR by the CHOP induction regimen. The overall

Table 1. *Hematopoietic recovery as a function of the dose and length of storage of bone marrow*

Case No.	Infused dose of marrow (CFU-c/kg)	Storage (months)	Hematopoietic recovery Leukocytes $>10^9/1$ (days)	Platelets $>5 \times 10^{10}/1$
8	853	6	11	9
7	936	7	17	19
12	1160 (after 4-HC)	1 week	19	22
3	2500	27	13	—
4	2800	2 weeks	12	10
10	3350	1	18	21
6	3600	2 weeks	11	10
9	10,000	3 weeks	12	14
2	11,200	3 weeks	9	27
11	20,000	8	13	14

Cases are listed in ascending order of administered doses of marrow (CFU-c/kg). The line between cases 10 and 6 indicates the threshold in CFU-c/kg, above which no aberration in the kinetics of recovery of leukocytes was observed (no statistical significance).

Table 2. High-dose chemotherapy, irradiation and autologous bone marrow transplantation in the treatment of non-Hodgkin's lymphomas—I. High tumor load (group 1: 6 patients)

Case No.	Pathology	Patient status (previous therapy)	Treatment	Dose of marrow (CFU-c/kg)	Antitumor effectiveness	Survival from ABMT (overall survival*)	Comments
1	Lymphoblastic (T)	1st relapse (liver spleen, mediastinum, bone marrow) (CHOP)	TACC	<100	persistence of systemic and leukemic infiltration	4.5 months (12.5 months)	contaminated marrow; faulty cryopreservation dose of marrow insufficient in CFU-c
2	Lymphoblastic	1st relapse (GI tract and brain) (CHOP)	TACC + total-body irradiation	11,200	failure—disease progression and leukemic infiltration	1.5 months (12 months)	contaminated marrow (2%); reversible pericardial effusion
3	Follicular small cells	1st relapse (infra-diaphragmatic: CAT scan) (CHOP)	TACC	2500	death on day 13 renal failure (pre-existing involvement)	13 days (39 months)	persistence of tumor infiltrate on post-mortem examination; myocardial lesion linked to TACC
4	Burkitt-like lymphoblastic	initial diagnosis (none)	TACC + abdominal irradiation (10 Gy)	2800	CR 8 months	45+ months (48+ months)	2nd complete remission induced by interferon: 37+ months
5	Mixed diffuse	initial diagnosis (none)	TACC + local irradiation	ND	CR 21 months	58+ months (60+ months)	
6	Follicular centroblasto-centrocytic (Bennett–Millet)	initial diagnosis (none)	TACC	3600	CR 45+ months	45+ months (48+ months)	

*Since initial diagnosis.
†CHOP: cyclophosphamide, hydroxyrubidomycine, oncovin, prednisone.
‡Complete remission.

survival of the 3 patients from initial diagnosis has been 48+, 48+ and 60 + months.

One patient (No. 3) died on day 13 as he was coming out of aplasia due to acute renal failure imposed on lymphomatous renal infiltration and heart failure. Post-mortem examination revealed the persistance of high tumor cell load. In 2 cases (Nos. 1 and 2), treatment by TACC or TACC + total-body irradiation failed to stop tumor progression and leukemic marrow invasion. In the first case the reinfused dose of autologous marrow was below our dose threshold, and in both cases an in-depth retrospective analysis of the frozen marrow revealed tumoral cell contamination that has been missed.

Group 2 (*Table* 3). Five patients treated while in first complete remission (from 2 to 7 months) or in second complete remission (for 9 months) were still in unmaintained complete remission after 12+, 24+, 27+, 42+ and 70+ months. One patient (No.7), in CR for 8 months, developed recurrent leukemia 1 month after transplantation and expired 5 months later. Retrospective analysis of the frozen marrow failed to reveal any tumor infiltration.

Thus, though 5 out of 6 patients in group 2 seem to have benefited from the antitumor effect associated with ABMT, in group 1 only 3 out of 6 received a beneficial effect: the 3 that were treated in primary therapy.

Toxicity

Toxic effects were observed in bone marrow, and liver.

Marrow toxicity. Marrow aplasia induced by TACC with or without total-body irradiation was constant. The minimum leukocyte value ($<0.1 \times 10^9/l$) was observed between days 3 and 8 (median duration, 5 days) and minimum platelet values ($<4 \times 10^{10}/l$) were observed between days 5 and 18 (median duration, 13 days). All patients had fever. In the 11 successfully transplanted patients there were 94 febrile days (>38.5°C). The median duration of each febrile episode was 6 days (range, 3–16 days) in these patients, but was 24 days in the 1 case with transplantation failure.

Five proven cases of septicemia (1 *Pseudomonas aeruginosa,* 1 *E. coli,* 1 *Moraxella* sp., 1 *Klebsiella* sp., 1 *Staphylococcus sepsis*) were observed in group 1; no positive blood cultures were found in group 2. No noteworthy haemorrhagic complications were observed.

Other toxicities. Metabolic disorders resulted from the forced diuresis, the chemotherapy-induced hypersecretion of ADH, cardiotoxicity and the volemic overload caused by parenteral feeding. Apart from the necessary ionic equilibration in response to hypocalcemia, hypokalemia, and hypophosphoremia, the principal side-effect was weight gain in every case, corrected by water restriction and furosemide.

The weight gain was associated in 4 cases with: a pericardial effusion between days 2 and 7 (Nos. 2, 3, 9 and 10) which regressed spontaneously except in 1 case (No. 3—where it was complicated by cardiac–renal failure contributing to death on day 13). Post-mortem examination disclosed hemaorrhagic lesions in the myocardium compatible with direct TACC toxicity; a moderate increase in transaminases (×2–5) and/or bilirubin, was constant; however, an increase in alkaline phosphatases (×2–3) was observed only twice. These alterations were transitory and reversible in every case.

Other toxic effects included 2 cases of hemorragic cystitis due to cyclophosphamide and one case of autoimmune hemolytic anemia in the immediate post-transplantation period that regressed spontaneously.

DISCUSSION

Numerous preliminary therapeutic trials have demonstrated the usefulness of ABMT in hematologic support [1–11, 18–20]. In the present set of patients this beneficial effect was again confirmed. White cell recovery kinetics were quite homogeneous, with a short (12 days) median duration of leukopenia. Platelet recovery kinetics showed greater dispersion and, due to the routine use of platelet supports, were of less significance. Nevertheless, the median duration of the thrombocytopenic phase was also short (14 days).

These kinetics are identical to those of Appelbaum *et al.* concerning 22 patients with non-Hodgkin's lymphomas [10] and our own concerning 23 patients with hematologic malignancies and various solid tumors [1]. They confirm the ABMT reduces the duration of aplasia induced by high-dose chemotherapy such as TACC by half. Spitzer *et al.* [20] have established a relationship between the injected dose evaluated in terms of CFU-c/kg and the kinetics of white cell recovery. The small number of patients in our study prevented us from establishing a similar statistical relationship. However, it is probable that the kinetic anomalies such as 'false' peaks, oscillations and slowing in the white cell count recovery in those patients who received a low dose of marrow (3600 CFU-c/kg) have the same significance.

The benefit in terms of antitumor effect and survival of high-dose chemotherapy and/or total-body irradiation with ABMT is now under study in numerous institutions.

Table 3. High-dose chemotherapy, irradiation and autologous bone marrow transplantation in the treatment of non-Hodgkin's lymphomas—II. Low tumor load (group 2: 6 patients)

Case No.	Pathology	Patient status (previous induction chemotherapy)*	Treatment	Dose of marrow CFU-c/kg (BFU-e/kg)	Antitumor effectiveness	Overall survival†	Comments
7	diffuse large	1st CR‡ at 8 months (COP)	TACC	936	recurrent leukemia 1 month after transplantation	16 months (5 months post-ABMT)	marrow harvested before chemotherapy
8	mixed diffuse	2nd CR at 9 months (COP, CHOP)	TACC	853	persistent CR 26+ months	70+ months	
9	Burkitt-type lymphoblastic (EBNA > 1/1280)	Partial remission (CHOP)	TACC	10,000 (3500)	CR 16+ months	23+ months	reversible pericardial effusion related to TACC?
10	immunoblastic	1st CR* at 2 months (following surgery) (none)	TACC	3350	persistent CR* 40+ months	42+ months	reversible cardiac failure related to TACC?
11	diffuse large cells	1st CR at 9 months (CHOP)	TACC	20,000 (8200)	persistent CR 16+ months	27+ months	
12	lymphoblastic (T)	1st CR at 7 months (AMACOP following resistance to CHOP)	TACC	(incubation with 4-HC), 1160 after incubation	persistent CR 12+ months	24+ months	

*CHOP: cyclophosphamide, hydroxyrubidomycine, oncovin, prednisone; AMACOP: CHOP + ARAC + methotrexate.
†Since initial diagnosis.
‡Complete remission.

Considerations that led us to the undertaking of the present therapeutic trial are: (1) non-Hodgkin's lymphomas (NHL) are a set of heterogeneous tumors from which a recent pathological classification [14] has singled out a group with a high degree of malignancy. Nevertheless, for this group of tumors chemosensitivity remains high [14] and aggressive therapy seems justified; and (2) a direct dose–response (antitumor) relationship [21–23] has been established for the majority of drugs (cyclophosphamide, cytosine arabinoside and CCNU) in the TACC and BACT protocols, which are already proven to be efficacious in NHL [1, 10]. An increase in dose above the threshold of marrow toxicity could possibly greatly enhance tumor cell kill.

In our study antitumor effect of this therapy was evaluated in 2 groups: the first, who were patients with a high tumor load, by reduction in tumor burden; the second, patients with immeasurable tumour, by the duration of remission.

Analysis of results is not of statistical significance given the small number of patients. Our results, however, do lead to several observations which could be of possible future use.

(1) The TACC regimen was directly responsible for the death of one patient. Apart from widespread tumor infiltration, post-mortem examination showed hemorrhagic lesions of the myocardium similar to those previously described by Appelbaum *et al.* [24] and attributed to direct toxicity of BACT.

In this series, immediate mortality imputable to antineoplastic agents was 8%. This figure is almost identical to that which we observed in a set of 35 patients treated from July 1976 to July 1981 (9%) [15]. Morbidity was dominated by pericardial effusion (4 cases, 32%) and septicemia (5 cases, 40%). Of interest is that all cases of septicemia occurred in the group of patients with tumor load (group 1) and the 4 caused by Gram-negative organisms were in patients suffering massive infra-diaphragmatic involvement with invasion of the digestive tract. Not a single case of septicemia occurred in group 2.

Whereas mortality and infectious morbidity were appreciable in group 1, they were practically absent in group 2, where TACC and ABMT were carried out during a period of complete or partial remission.

(2) Our results confirm the effectiveness of TACC in treatment of NHL with poor prognosis [1, 25, 26]. It was more effective in group 2, where TACC was given to consolidate remissions (1 failure, 5 persistent complete remissions of 12+, 16+, 16+, 26+ and 40+ months), than in group 1, where it was used as primary therapy (3 failures, 3 complete remissions of 8, 21 and 45+ months). In addition, since many patients are still alive, the overall survival of patients treated by TACC and ABMT at any time in the course of the disease (groups 1 + 2) may yet prove to be superior to that of conventionally treated patients with NHL of high-grade malignancy. The most ominous consideration with this procedure is the risk of reinfusing malignant cells along with the autologous marrow. This cannot be ignored, since 3 of our patients presented with recurrent leukemia in the immediate post-transplantation period.

For these 3 patients routine checks failed to reveal evidence of medullary infiltration before cryopreservation. Although retrospective analysis was able to demonstrate this involvement in 2 cases, it failed to do so in the third. Thus the chronology of marrow collection should be given great attention, so as to balance 2 competing desires, i.e. to obtain marrow that is rich in stem cells, thus shortening the period of aplasia (collection preferable before chemotherapy), but is free from malignant cells (collection preferable after several cycles of chemotherapy). In making this decision the pathologic nature of the tumor and the likelihood of marrow involvement should play a large part.

Given the dismal prognosis of NHL of high-grade malignancy treated by conventional methods in our department, the preliminary results of our study lead us to the following conclusions: (1) autologous bone marrow transplantation following TACC results in a short period of aplasia (median 12 days); (2) the toxicity of this therapeutic regimen is acceptable and is considerably reduced if the treatment is used in consolidation; (3) we think that trials combining TACC and ABMT in complete remission should be pursued. In view of the risk of reinfusing tumor cells, we think that the marrow should be collected early, after several courses of chemotherapy and establishment of the first complete remission, and carefully checked for tumor contamination; and (4) to assess the potential benefit of TACC + ABMT in the overall therapy of NHL of poor prognosis and, alternatively, the potential hazards of this technique including the risk of reinfusion of clonogeneic tumor cells, randomized trials comparing conventional therapy delivered alone to the same regimen combined with TACC + ABMT in the consolidation mode might be of value. A multicentric randomized study with this aim is at present being performed in numerous institutions, including ours.

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