Parma International Protocol: Pilot Study of DHAP Followed by Involved-Field Radiotherapy and BEAC With Autologous Bone Marrow Transplantation

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Fifty patients with intermediate- or high-grade non-Hodgkin's lymphoma (NHL) who had relapsed after a complete remission induced by an Adriamycin-containing chemotherapy regimen participated in this prospective pilot study. The patients ranged in age from 16 to 60 years (median 42 years). All patients received dexamethasone, high-dose cytarabine, and cisplatin (DHAP) for two courses at 3- to 4-week intervals. Patients achieving a partial or complete response were scheduled to receive involved-field radiotherapy and high-dose carmustine, etoposide, cytarabine, and cyclophosphamide (BEAC), followed by autologous bone marrow transplantation (ABMT). Among 48 evaluable patients (ie, 1 was lost to follow-up and 1 had no measurable disease) 7 patients obtained a complete response (CR) and another 21 patients achieved partial response (PR), whereas the remaining 20 patients failed. One responder died of treatment-related toxicity, and six others declined ABMT. The patient with no measurable disease did not progress on DHAP and was submitted to ABMT. Twenty-two patients underwent ABMT [20 with BEAC and 2 with cyclophosphamide plus total body irradiation (TBI)] of whom 2 (9%) died of toxicity and 10 relapsed. One patient was a suicide at 28 months post-ABMT in CCR and 9 are alive disease-free 24 months to 32 months (median 30 months) post-ABMT. The actuarial 2-year event-free survival for patients undergoing transplantation is 40%. This prospective multicenter trial documents the ability of DHAP followed by ABMT to produce durable complete remission in a significant proportion of patients with relapsed aggressive NHL. Forty-four percent of all patients with relapsed lymphoma who entered the study actually underwent ABMT and 20% of the total group are projected to be long-term disease-free survivors.

PATIENTS WITH advanced diffuse non-Hodgkin's lymphoma (NHL) are rarely cured of their disease after conventional chemotherapy fails,[1] but experience gained in Burkitt's lymphoma has shown that these lymphomas may still be sensitive to intensive chemoradiotherapy after failing conventional dosage.[2-6] With bone marrow transplantation (BMT) providing hematologic support, administering intensive chemoradiotherapy and to cure some children or adults with disseminated aggressive NHL has been possible.[1,7-21] The appropriate place for high-dose chemoradiotherapy and BMT between front line and relapse has not yet been determined, despite encouraging results in numerous pilot studies.[22-28] Several groups of investigators using ABMT have suggested that response to preceding therapy may have prognostic importance in the outcome of ABMT in patients who have relapsed,[11,12] and confirmation of these findings was the major achievement of the 100-patient retrospective analysis reported in 1987.[29]

In 1986, an international multicentric study group called PARMA was organized, involving BMT centers from around the world, with the objective of testing the value of ABMT for patients with relapsed lymphoma in a prospective, randomized trial.[30] We review the pilot study of the PARMA protocol, which was performed in 1986 and 1987. We wished to confirm the response rate of the DHAP regimen[31] in patients with relapsed lymphoma, pilot the new conditioning regimen of involved-field radiotherapy and BEAC, and confirm the retrospective analysis[29] in a prospective international study.[30]

MATERIALS AND METHODS

Patients. Fifty patients aged 16 to 60 years at first relapse of intermediate (28 patients) or high-grade (22 patients) NHL were included in the study from 20 centers in the world. The 20 participating centers are Centre Leon Berard, Lyon, France; Hôpital Jean Minjoz, Besançon, France; Hôpital de l'Hotel-Dieu, Paris, France; C.H.U. La Miletrie, Poitiers, France; Institut Jules Bordet, Brussels, Belgium; St Vincent Hospital, Sydney, Australia; The Dr Daniel Den Hoed, Rotterdam, The Netherlands; Hôpital Jules Courmont, Pierre-Benite, France; M.D. Anderson Hospital,

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Houston, TX; Antonie Van Leeuwenhoek Hospital, Amsterdam, The Netherlands; Hospital de la Princesa, Madrid, Spain; Hôpital des Sablons, Grenoble, France; Università Degli Studi di Parma, Italy; Hôpital de l'Hotel-Dieu, Nantes, France; Ospedale di Pesaro, Italy; Ospedale S Martino, Genova, Italy; University Hospital "Dijkzigt," Rotterdam, The Netherlands; University of Nebraska Medical Center, Omaha; Hôpital Paul Brousse, Villejuif, France; and Centre Claudius Regaud, Toulouse, France. All patients had obtained a previous complete response (CR) with an Adriamycin-containing regimen. Fifteen were females and 35 were males. Normal BM was documented in all patients, and presence of CNS relapses was not considered for this study. A signed informed consent according to the PARMA protocol and each institution's rules was obtained. All but one patient were evaluable for response to the rescue regimen. Details of these 50 patients are shown in Table 1.

Methods. All patients were submitted to the DHAP regimen as reported by Velasquez et al.[31] After course 1 of DHAP, with the exception of clearly progressive disease (n = 14), BM was harvested under general anesthesia and frozen as previously described[4,5] unless the marrow had been stored previously. All patients had normal BM biopsies at time of harvest. A second course of DHAP was given beginning 1 day after harvest. At day 20 after second DHAP, patients were restaged according to previous involved sites of disease at initiation of study. CR was defined as complete disappearance of all previously involved sites. Partial response (PR) was defined as at least 50% reduction of all previously involved sites with no new lesion. CR and PR were defined as sensitive relapses and eligible for autologous BMT (ABMT).

Patients who had shown a response were then included in an involved-field radiotherapy (if bulky disease was present at relapse) and BEAC protocol (all patients) as shown in Table 2 (two patients previously irradiated at site of bulky disease did not receive radiotherapy according to the PARMA protocol). Two were grafted with cyclophosphamide and total body irradiation (TBI) as reported by the Seattle group[10,16] by individual patient decision with the authorization of the chairman and seven were not grafted (one toxic death, six refusals). ABMT was performed as previously reported.[29] Histologic material was reviewed centrally by a reference pathologist (D.W.) using the working formulation for classification of NHL.[32]

Statistical method. Comparisons of categorical data were performed using the chi-square and Ficher's exact test. Survival curves were computed according to the method of Kaplan-Meier. An event was defined as a relapse, evidence of progression, or death whatever the cause. In the event-free survival curve, the date of the first event is taken into account.

RESULTS

Response to DHAP regimen. Forty-eight patients are evaluable. One was in complete remission before DHAP (complete surgical excision), and one was lost to follow-up. Twenty-eight were responders (58.5%), including 7 CR (25% of responders); 21 patients achieved a PR. No difference was observed between intermediate-grade and high-grade patients (10 of 22 PR, 2 of 22 CR high grade; 11 of 26 PR, 5 of 26 CR, and 2 nonevaluable intermediate grade) (Table 1).

Toxicity to DHAP regimen. Severe neutropenia (<500 polynuclears) was observed in 22 courses (22 of 50 = 44%). Thrombocytopenia with less than 50,000 platelets was recorded in 19 (34%). Seven had marked renal impairment, 7 (14%) had severe gastrointestinal toxicity, 2 (4%) had cytosine-related neurologic disorders (ie, weakness and headache), and 8 (16%) had sepsis. One reversible myocardiopathy was also observed. One responding patient died of toxicity (hemolytic uremic syndrome) after DHAP 2.

Treatment of sensitive-relapse patients after DHAP 2. Twenty of the 29 patients (28 responding and the 1 already in CR) received the involved-field radiotherapy and BEAC protocol as scheduled (Table 2). Twelve still had evaluable disease (PR to DHAP). Among them, 11 of 12 were converted to CR after ABMT (91% response rate to BEAC). Median time to reach 1,000 WBC was 15 days; to reach 500 polynuclears, it was 15 days, to reach 200 polynuclears, 13 days; and to reach 50,000 platelets, it was 25 days. Two toxic deaths were recorded (hepatic and early renal failure and pulmonary bleeding), and 17 were in CR after ABMT. Ten patients subsequently relapsed (9 CR an 1 PR post ABMT), 1 committed suicide in CCR 28 months post-ABMT, and 7 of 20 are still alive disease-free with a median follow-up of 30 months from inclusion (24 to 32 months).

Two of the 29 patients were grafted after a cyclophosphamide and TBI regimen. Both are alive disease-free with 26 months and 28 months of follow-up. Nine of 22 of the grafted patients are alive disease-free (40% overall survival at 24 months), as shown in Fig 1, with no difference between patients grafted in CR (3 of 6) or in PR (6 of 16).

The seven other responders were not grafted because of toxic death (n = 1) or individual decision (n = 6). One refused treatment and died. Five had received four to six additional courses of DHAP. None of them are alive disease-free at present (one is still alive but has progressive disease).

DISCUSSION

High-dose therapy and ABMT can cure patients with relapsed, aggressive NHL.[2-22] The results of this prospective multicenter pilot study provide the only available prospective data for estimation of the impact of this treatment approach on such patients. Fifty-eight percent of all patients treated consecutively in this study after relapse from an Adriamycin-containing induction regimen were chemotherapy sensitive and thus represented good-risk patients for ABMT. Two percent (1 of 50) of the patients for whom this strategy was intended died of treatment-related toxicity from the DHAP, however, and 20% (6 of 29) declined to undergo BMT despite a good response to conventional rescue therapy. Forty-four percent of all patients with relapsed lymphoma who entered the study actually underwent ABMT, and 40% of these patients (ie, 20% of the total who entered the study) are projected to be long-term, disease-free survivors.

The 58% total response rate observed in this study confirms the original report by Velasquez et al on the activity of DHAP for relapsed lymphomas.[31] In both studies, a few of the responding patients actually achieved complete remissions. We found no difference in the response rate between intermediate-grade and high-grade lymphomas.

Table 1. Characteristics of the 50 Patients

Patient No./ Age/Sex	Working Formulation	Karnofsy Score (%)	Stage Ann-Arbor	Duration of First CR (mo)	Response to DHAP	Status Post-BEAC
001/46/F	IG:Diffuse large cell	50	3	5	PD	Not grafted
002/29/M	HG: Diffuse immunoblastic	90	2	3	CR	Not grafted
003/43/M	IG: Follicular large cell	70	3	7	PD	Not grafted
004/21/M	HG: Diffuse immunoblastic	100	3	6	PR	CR
005/27/F	IG: Diffuse large cell	100	3	8	PR	CR*
006/35/F	IG: Diffuse large cell	80	2	3	PD	Not grafted
007/33/F	IG: Diffuse mixed	90	3	1	CR	CR
008/27/F	HG: Diffuse large cell	80	4	5	PD	Not grafted
009/22/F	HG: Diffuse lymphoblastic	70	4	19	PD	Not grafted
010/53/M	IG: Diffuse mixed	50	4	7	PD	Not grafted
011/25/M	HG: Diffuse immunoblastic	60	3	21	PR	CR
012/22/M	HG: Diffuse immunoblastic	80	4	4	PD	Not grafted
013/53/F	HG: Diffuse immunoblastic	90	3	2	CR	Not grafted
014/17/M	HG: Diffuse lymphoblastic	100	1	12	PD	Not grafted
015/27/F	IG: Diffuse large cell	90	2	8	PD	Not grafted
016/28/M	IG: Diffuse large cell	90	3	5	NC	Not grafted
017/42/M	IG: Diffuse mixed	100	3	3	PD	Not grafted
018/51/M	IG: Diffuse mixed	90	4	6	PD	Not grafted
019/21/M	IG: Diffuse large cell	90	2	1	PD	Not grafted
020/39/M	IG: Diffuse mixed	80	4	15	PR	Not grafted
021/38/F	HG: Diffuse immunoblastic	70	3	3	PR	Not grafted
022/30/M	IG: Diffuse large cell	80	4	7	PR	Not grafted
023/20/F	HG: Diffuse immunoblastic	60	3	1	PD	Not grafted
024/26/F	IG: Diffuse mixed	80	2	8	NE	CR
025/54/M	IG: Diffuse large cell	40	2	3	PD	Not grafted
026/54/M	IG: Diffuse small cleaved cell	80	2	5	PR	CR
027/51/M	HG: Diffuse small noncleaved cell	50	2	2	PD	Not grafted
028/40/M	IG: Diffuse mixed	90	4	4	PR	Not grafted
029/45/M	IG: Diffuse large cell	80	3	8	PR	CR
030/45/M	HG: Diffuse lymphoblastic	90	3	7	PR	CR
031/46/M	IG: Diffuse large cell	100	3	6	CR	CR
032/55/M	IG: Diffuse large cell	90	2	3	PR	Not grafted
033/42/M	HG: Diffuse immunoblastic	80	2	2	PD	Not grafted
034/39/F	HG: Diffuse immunoblastic	90	3	6	PD	Not grafted
035/45/M	HG: Diffuse immunoblastic	100	2	5	PR	NE
036/53/M	IG: Diffuse mixed	50	4	8	CR	CR
037/50/M	IG: Diffuse large cell	100	2	5	CR	CR
038/56/F	IG: Diffuse mixed	80	4	9	CR	CR
039/43/M	HG: Diffuse immunoblastic	80	4	5	PR	CR
040/16/F	HG: Diffuse lymphoblastic	80	2	2	PR	NE
041/47/M	IG: Follicular large cell	80	3	1	PR	CR
042/22/M	HG: Diffuse lymphoblastic	80	1	8	PR	PR
043/33/M	IG: Diffuse unclassified	80	4	5	PR	CR*
044/43/F	HG: Diffuse immunoblastic	80	3	4	PR	CR
045/35/M	HG: Diffuse immunoblastic	80	3	6	NR	Not grafted
046/54/M	IG: Diffuse mixed	80	4	5	PR	CR
047/34/M	IG: Diffuse small cleaved cell	80	3	6	PR	CR
048/46/M	HG: Diffuse immunoblastic	80	3	5	NR	Not grafted
049/45/M	HG: Diffuse immunoblastic	90	3	7	PR	CR
050/37/M	IG: Diffuse large cell	100	4	6	NE	Not grafted

Abbreviations: IG, intermediate grade; HG, high grade; PD, progressive disease; CR, complete response; PR, partial response; NC, no change; NE, nonevaluable; NR, nonresponse.

*Cyclophosphamide and total body irradiation (instead of BEAC).

These data suggest that DHAP is as active as other reported regimens in patients with relapsed aggressive lymphomas.[1] Toxicity of the DHAP regimen must be considered. The myelosuppression we observed was severe and perhaps more than might have been expected with the doses of the agents delivered, but only one patient died of a constellation of symptoms that suggested the hemolytic uremic syndrome. As a regimen to reduce tumor preceding ABMT, however, the most important side effect was renal toxicity. Significant renal impairment occurred in 14% of the pa-

Table 2. Conditioning Regimen Schedule

Protocol Regimen	Monday, Day 1	Tuesday, Day 2	Wednesday, Day 3	Thursday, Day 4	Friday, Day 5	Saturday, Day 6	Sunday, Day 7
Week 1*							
IFXRT	X	X	X	X	X	—	—
	X	X	X	X	X	—	—
Week 2							
IFXRT	X	X	X	X	X	—	—
	X	X	X	X	X	—	—
Week 3†							
BCNU 300 mg/m²/24 h† (30 minutes IV)	X	—	—	—	—	—	—
Etoposide 200 mg/m²/24 h (100 mg/m² IV twice daily)	—	X	X	X	X	X	X
ARA-C 200 mg/m²/24 h (100 mg/m² IV twice daily)	—	X	X	X	X	—	—
Cyclophosphamide 35 mg/kg/24 h (as short infusion in 60 minutes)	—	X	X	X	X	—	—
MESNA 50 mg/kg/24 h (optional)	—	X	X	X	X	—	—
Week 4							
ABMT (at least 48 hours after etoposide)	—	—	—	—	—	—	X

Abbreviations: DHAP, dexamethasone, high-dose cytarabine, and cisplatin; — no treatment; IFXRT, involved-field radiotherapy; ABMT, autologous bone marrow transplantation; BCNU, bichloro nitrosourea; MESNA, N-acetylcystein.

*Day 20 post-DHAP 2.

†Day 35 post-DHAP 2.

tients and will certainly make some patients ineligible for BMT.

Previous reports of ABMT in patients with relapsed lymphomas have suggested that sensitivity to preceding chemotherapy is the most important prognostic factor.[11,12,29] Patients with chemotherapy-resistant disease have been long survivors only approximately 10% of the time,[29] but patients who are still chemotherapy sensitive (ie sensitive relapses) have been reported to have durable complete remissions from 20% to 40% of the time.[1] In one study of 100 patients undergoing autologous transplants on whom 44 were sensitive relapses, 36% of the patients had long-term, disease-free survival.[29] The results from this first prospective study, with 40% long-term, disease-free survival in sensitive relapsed patients undergoing ABMT, are similar to these reports. Local, hyperfractionated radiotherapy followed by the BEAC regimen produced a significant long-term, disease-free survival with a low proportion (ie, 10%) of treatment-related deaths. This is the first prospective study to confirm that sensitive-relapse patients are curable with conventional rescue protocol and consolidation with high-dose therapy and ABMT. This prospective pilot study confirms the high response rate of platinum-based salvage therapy and the ability to intensify these responses with involved-field irradiation and high-dose combination chemotherapy with ABMT support.

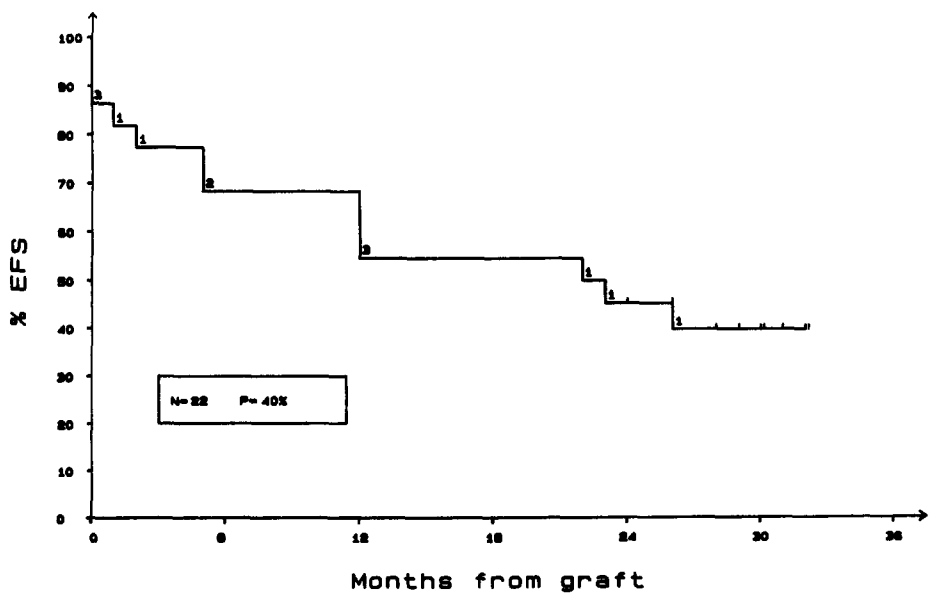

Fig 1. Event-free survival of the 22 grafts.

The major conclusion of this pilot study is that DHAP is active and of tolerable toxicity to induce response after relapses from an Adriamycin-containing front-line regimen for diffuse lymphomas. Also of major importance is the confirmation in a prospective international study that 40% of sensitive relapsed patients can be long-term survivors after ABMT with no more than 10% toxic death. This is not sufficient evidence, however, to prove that consolidation with BMT is the best available therapy for sensitive-relapse NHL because this stategy affects only the few NHL patients considered for such treatment. The ongoing prospective and randomized PARMA study based on these very encouraging results is now in the process of comparing consolidation with involved-field radiotherapy and ABMT *v* continuation on the DHAP regimen to consolidate sensitive-relapse patients after two induction courses with DHAP. As of June, 1990, more than 130 patients had been included in this still ongoing study and results with at least 24 months of follow-up are expected for 1992.

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