Ifosfamide, Etoposide, Cytarabine, and Methotrexate as Salvage Chemotherapy in Relapsed or Refractory Aggressive Non-Hodgkin's Lymphoma

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BACKGROUND. Patients with relapsed or resistant non-Hodgkin's lymphoma (NHL) have a poor prognosis and are rarely cured with usual salvage chemotherapy. Intensive treatment with the support of peripheral blood stem cells (PBSC) may be an effective therapy for these patients. We used a combination of ifosfamide, etoposide, cytarabine, and methotrexate (IVAM) with the intention both to reduce tumor burden and collect PBSC prior to transplantation.

METHODS. Thirty-one patients (17 with relapsed NHL and 14 with refractory NHL) were treated with 2 courses of chemotherapy: IVAM regimen (ifosfamide, 1500 mg/m^2 daily for 5 days plus mesna; etoposide, 150 mg/m^2 daily for 3 days; cytarabine, 100 mg/m^2 daily for 3 days; and methotrexate, 3 g/m^2 on Day 5, with leucovorin rescue). Twenty-three patients had an intermediate grade and 8 patients had a high grade lymphoma.

RESULTS. After IVAM therapy, 19 patients (61%) achieved complete response, 8 patients (26%) achieved partial response and 4 patients (13%) failed to respond. The major toxicity of IVAM was myelosuppression, but there were no toxic deaths. PBSC harvest could be performed in 29 patients (94%) with a median granulocyte-macrophage colony-forming unit count of 55 $\times$ 10^4/kg (range, 2–391 $\times$ 10^4/kg). Three patients could not undergo transplantation because of disease progression. One patient received a syngeneic transplant, 25 patients received PBSC transplantation, and 2 patients received a bone marrow transplant. In an intent-to-treat analysis, the overall survival rate at 4 years was 37% for the whole group (95% confidence interval: 22–55).

CONCLUSIONS. We conclude that IVAM is an effective salvage chemotherapy for refractory or relapsed NHL and permits PBSC collection in most of these patients. *Cancer* **1996; 77:2302–7.** © *1996 American Cancer Society.*

KEYWORDS: peripheral blood stem cells, stem cells collection, transplantation, autologous transplantation, lymphoma, lymphoma relapse, salvage treatment.

Half of the patients with non-Hodgkin's lymphoma (NHL) fail to achieve complete remission (CR) or experience a relapse after a standard chemotherapy.[1] Less than 10% of these patients obtain long term disease free survival with conventional-dose salvage chemotherapy.[1–3] Myeloablative cytotoxic chemotherapy followed by bone marrow transplantation is one form of treatment that uses a dose intensity that may overcome tumor cell resistance and seems to be the best way to obtain a durable CR in these patients.[1,2,4,5] Patients who undergo transplantation while in CR or with minimal tumor burden have a greater chance of long term disease free survival.[2,4,6,7] Results of a recently published prospective study demonstrate that intensive chemotherapy followed by autologous bone marrow transplantation, as compared with standard treatment, signifi-

cantly increases survival in patients with sensitive relapse of aggressive NHL.[8] Autologous peripheral blood stem cell (PBSC) transplantation is used in a manner analogous to bone marrow transplantation as a method to restore bone marrow functions,[9] with well known advantages.[7,10] PBSC are collected after chemotherapy such as high dose cyclophosphamide[11,12] and/or after hemopoietic growth factors.[12]

We used a salvage regimen consisting of ifosfamide, etoposide, cytarabine and high dose methotrexate (IVAM)[13] to treat 31 patients younger than 60 years with relapsed or resistant aggressive NHL, with the intention both to reduce tumor burden and collect PBSC prior to planned transplantation.

PATIENTS AND METHODS

Patients/IVAM Regimen

From January 1987 to December 1994, 31 patients younger than 60 years with relapsed or resistant aggressive NHL were included in this study. Relapse was defined as lymphoma recurrence at least 1 month after achieving a CR with front-line therapy. Refractory disease was defined as: 1) failure to obtain CR at anytime during the treatment; 2) disease progression during therapy or after achieving partial remission; or 3) early recurrence within the first month of CR.

The treatment intended in these patients was comprised of two courses of the IVAM regimen followed by intensive myeloablative therapy and autologous PBSC transplantation, with PBSC being collected during hemopoietic regeneration after chemotherapy. The IVAM regimen consisted of ifosfamide, 1500 mg/m^2 daily, from Day 1 to Day 5 plus mesna, 1500 mg/m^2 daily, from Day 1 to Day 5; cytabarine, 100 mg/m^2 daily, from Day 1 to Day 3; etoposide, 150 mg/m^2 daily, from Day 1 to Day 3; and methotrexate, 3 g/m^2, at Day 5 plus leucovorin rescue, 100 mg/m^2, from Day 6 to Day 8. The second course was begun at Day 28.

The main characteristics of the 31 patients are listed in Table 1. All patients had intermediate or high grade lymphoma and had previously been treated in the same institution with only one first-line regimen containing anthracyclin in the studies from the Groupe d'Etudes des Lymphomes de l'Adulte (GELA).[14]

TABLE 1
Patient Characteristics before IVAM

		No. of patients
		31
Age (yrs)	Median	40
	Range	22–56
Sex	Female	10
	Male	21
Disease status	Resistant	14
	Relapse	17
First-line treatment	ACVBP	23
	NCVBP	4
	CHOP	2
	m-BACOD	2
First remission duration	0–6 mos	23
	6–12 mos	5
	> 12 mos	3
Histology	Intermediate grade	
	Follicular, large cells	2
	Diffuse mixed	5
	Diffuse, large cels	20
	High grade	
	Immunoblastic	2
	Lymphoblastic	1
	Burkitt's	1
Ann Arbor Stage	I	3
	II	4
	III	4
	IV	20
Performance status	0–1	23
	2–4	8
BM involvement		7
LDH level > N		17

IVAM: ifosfamide, etoposide, cytarabine, and methotrexate. ACVBP: doxorubicin, cyclophosphamide, vindesine, bleomycine, prednisolone; NCVBP: mitoxantrone, cyclophosphamide, vindesine, bleomycine, prednisolone; CHOP: doxorubicin, cyclophosphamide, vincristine, prednisolone; m-BACOD: methotrexate, doxorubicin, cyclophosphamide, vincristine, bleomycine, dexamethasone, BM: bone marrow; LDH: lactate dehydrogenase; N: normal.

Peripheral Blood Stem Cell Collection, Storage, and Reinfusion

When the leukocyte count reached 1 × 10^9/L after IVAM chemotherapy, apheresis were performed with a CS 3000 plus blood separator (Fenwall Laboratories, Baxter, Deerfield, IL) using procedures "1 modified" and "8 special." Patients were anticoagulated with acid citrate dextrose A (ACD A), using a whole blood ACD A, ratio of 8/1. The small volume collect chamber was chosen as collection chamber. For each collection, 10 liters of whole blood were processed. After collection, cells were suspended in dimethylsulfoxide (DMSO) 20% albumin 80% solution added volume to volume and frozen at 2 °C/minute in 2 DF 700 Gambo bags (Gambo, Hechingen, Germany) (100 to 120 mL per bags) using a preprogrammed controlled freezer (Nicool st 20, Compagnie) with prior storage in liquid nitrogen. At reinfusion, cells were rapidly thawed in a water bath at 37 °C, washed once using the Cobe 2991 (Cobe France, Rungis, France) cell washer, and immediately reinfused.

In recent years, 12 patients received recombinant human granulocyte-colony stimulating factor (G-CSF) at a dose of 5 μg/kg/day from Day 8 of the IVAM course until leukaphereses were completed.

Myeloablative Therapy

Among the 31 patients, 28 subsequently underwent transplantation. Nineteen patients received a BEAM regimen

(BCNU, 300 mg/m^2, at Day 7; cytarabine, 100 mg/m^2 twice a day, from Day 6 to Day 3; etoposide, 100 mg/m^2 twice a day, from Day 6 to Day 3; and melphalan, 140 mg/m^2 at Day 2) prior to transplantation,[15] and 9 patients were treated with fractionated total body irradiation (TBI) at a total dose of 12 Gray and chemotherapy (cytarabine, 150 mg/m^2 daily, for 4 days; etoposide, 250 mg/m^2 daily, for 4 days, and cyclophosphamide, 1 g/m^2 daily, for 4 days). The regimen containing TBI was chosen in 2 patients with large cell follicular lymphoma, in the patients with bone marrow involvement, and in a patient who received a syngeneic transplant. Eleven patients who received the BEAM regimen were given involved fields irradiation after transplantation.

Response Criteria and Statistics

Complete response was defined as the complete disappearance of all evidence of disease. A partial response (PR) was defined as a reduction of >50% in tumor volume. A reduction of <50% in tumor volume was considered to be a failure. Statistical analyses were performed by the chi-square test with Yates corrections. Overall survival was measured from the first day of the first IVAM course to the day of death. Time to treatment failure was calculated from first day of the first IVAM course to the first adverse event including failure, relapse, or death from any cause.[16] Survival was determined by the method of Kaplan and Meier.[17] Comparison of survival curves was performed by the log rank test. Analyses were performed with use of JPSI statistical software (developed by P. Kwiatkowski, Centre Jean Perrin, Clermont-Ferrand, France).

RESULTS

IVAM Regimen Toxicity

Myelosuppression was the most important toxicity after the IVAM regimen. Severe neutropenia (<0.5 × 10^9/L) was observed in all patients during the first course with a median duration of 9 days (range, 2–19 days) and in all patients but 3 after the second course with a median duration of 7 days (range, 0–20 days). Thrombocytopenia (<20 × 10^9/L) appeared in 21 patients after the first IVAM course and in 26 patients after the second course. Patients who received G-CSF after IVAM had a significantly shorter period of neutropenia (Table 2). One episode of severe infection (pulmonary aspergillosis) occurred after the first IVAM course (World Health Organization [WHO][36] grading toxicity 4). There were no toxic deaths and no severe bleeding (WHO grading toxicity 3 and 4).

PBSC Collection

Among the 31 patients treated with IVAM, 29 patients underwent PBSC collection. Two patients could not because of disease progression. The median number of mononuclear cells collected was 9.7 × 10^8/kg (range, 1.7–25 × 10^8/kg) and the median number of granulocyte-macrophage colony-forming unit (GFU-GM) was 55 × 10^4/kg (range, 2–391 × 10^4/kg). Patients who received G-CSF after IVAM had a significantly higher yield of CFU-GM (Table 2).

TABLE 2
Characteristics of Hemopoietic Reconstitution and PBSC Collection According to the Administration of G-CSF after IVAM

	Without G-CSF (n = 17)	With G-CSF (n = 12)
First course of IVAM		
Days with neutrophils < 0.5 × 10^9/L	10 (7–19)	7 (2–10)[a]
Days with platelets < 20 × 10^9/L	1 (0–7)	1 (0–7)[b]
Second course of IVAM		
Days with neutrophils < 0.5 × 10^9/L	8 (0–20)	3 (0–10)
Days with platelets < 20 × 10^9/L	1 (0–13)	1 (0–4)
Cytaphereses		
No.	5 (2–9)	3 (3–6)
Day of first cytapheresis	20 (8–27)	16 (14–31)
Mononuclear cells (×10^8/kg)	8.4 (2–25)	13 (1;7–25)
CFU-GM (×10^4/kg)	42 (2–56)	99 (4–391)[b]
Transplantation		
Days with neutrophils < 0.5 × 10^9/L	16 (9–25)	14 (7–22)
Days with platelets < 50 × 10^9/L	15 (6–510)	12 (6–100)

PBSC: peripheral blood stem cells; G-CSF: granulocyte colony-stimulating factor; IVAM: ifosfamide, etoposide, cytarabine, and methotrexate; CFU-GM: granulocyte-macrophage colony-forming unit. Median values.

[a] $P < 0.01$.

[b] $P < 0.05$.

Response to the IVAM Regimen

Among the 31 patients treated, 19 patients achieved CR (61%), 8 patients achieved PR (26%), and 4 failed to respond (13%). Response after IVAM was not significantly influenced by age, sex, histology, performance status, stage, bone marrow involvement, lactate dehydrogenase level, or disease status before salvage therapy.

Transplantation

Twenty-eight patients underwent transplantation (19 in CR, 8 in PR, and 1 in progression); the remaining 3 could not because of disease progression. One patient had an identical twin donor and received a syngeneic bone marrow transplant. Twenty-five patients underwent transplantation with PBSC. Two patients received a bone marrow transplant because of a CFU-GM yield < 1 × 10^4/kg in the peripheral blood, in spite of G-CSF mobilization for one patient. These patients had stage III and IV intermediate grade NHL[37] without bone marrow involvement. After transplantation, neutrophil engraftment (>0.5 × 10^9/L) occurred at a median of Day 15 (range, 7–25 days) and the platelet count (>50 × 10^9/L) rose at a median of

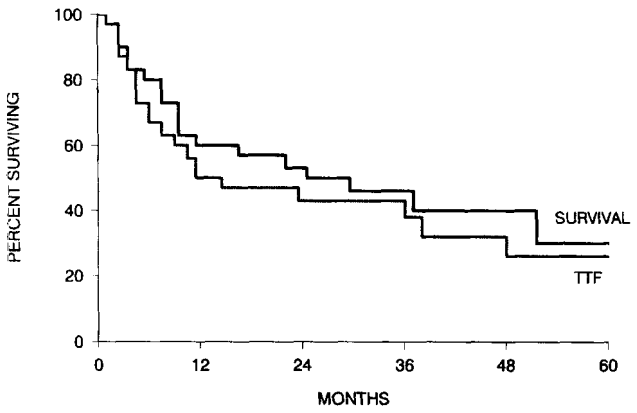

FIGURE 1. Overall survival and time to treatment failure from the beginning of treatment with ifosfamide, etoposide, cytarabine, and methotrexate for the 31 patients.

Day 15 (range, 6–510 days). Bone marrow recovery was correlated to conditioning regimen, with patients treated with TBI having a delayed engraftment as compared with those receiving chemotherapy only. Neutrophil engraftment occurred on Day 13 (range, 7–22 days) after BEAM and on Day 18 (range, 12–25 days) after TBI ($P < 0.05$). Platelet count ($>50 \times 10^9$/L) rose on Day 12 (range, 6–80 days) after BEAM and on Day 17 (range, 11–510 days) after TBI ($P < 0.02$). Neutrophil and platelet engraftment were not influenced by G-CSF mobilization after IVAM (Table 2).

Twenty-four patients achieved CR after transplantation (6 of whom were in PR after IVAM), 1 patient achieved PR, and 1 patient progressed despite therapy. Two patients died shortly after transplant, one from intraalveolar bleeding and the other from pulmonary aspergillosis.

Survival

At the time of this analysis, with a median follow-up of 38 months for living patients, 10 patients are alive with 8 in continuing CR, and 2 who relapsed at 33 and 9 months, respectively, after achieving CR. The overall survival rate at 4 years for the whole group is 37% (95% confidence interval [CI] 22–55%) (Fig 1). The overall survival was not influenced by age, sex, histology, performance status, stage, bone marrow involvement, lactate dehydrogenase level, first remission duration, or disease status before IVAM. No significant difference in survival could be found between patients who received a BEAM regimen (44% at 4 years; 95% CI, 21–63%) and those who received a TBI regimen (40% at 4 years; 95% CI, 19–73%). The only determinant of survival was response to IVAM therapy, with responders to salvage therapy having a greater chance of long term survival (42.5% at 4 years; 95% CI, 26–61%) ($P < 0.01$). Nevertheless, the subgroup of patients in PR after IVAM did not have a different survival than those in CR.

DISCUSSION

Relapsing or resistant NHL has a poor prognosis and only a small fraction of patients can be cured with conventional salvage chemotherapy.[1] Nevertheless, myeloablative therapy with autologous hemopoietic rescue using bone marrow or PBSC support has been used with better results in response and survival.[2,3,4,5,10] Furthermore, patients who are responsive to salvage therapy before transplant with minimal tumor burden do better than patients who are transplanted with resistant disease or high tumor burden.[1,2,3,8,18]

To reduce tumor burden and induce a response before transplantation, we used IVAM chemotherapy as a salvage regimen as previously described by Brice et al.[13] This regimen was derived from the IMVP 16 regimen described in 1982 by Cabanillas et al.[19] but contained additional cytarabine and higher doses of etoposide, ifosfamide, and methotrexate. None of the drugs in IVAM was used in first-line chemotherapy. Ifosfamide has been demonstrated to be effective in patients who relapsed after cyclophosphamide treatment, suggesting an incomplete cross-resistance between the two drugs.[20–22] Additionally, a possible synergistic effect between etoposide and methotrexate has been reported.[23] Moreover, each drug had independent activity against lymphoma.[24–27] We observed a 87% total response rate, including a 61% CR rate and 26% PR rate. This total response rate appears to compare favorably with other regimens such as IMVP 16,[19] which contains the same drugs as IVAM but with a different dosage and schedule, dexamethasone, high-dose cytarabine and cisplatin (DHAP)[28–30] or a mitoxantrone-based regimen.[27,31] The major toxicity observed was severe myelosuppression with 1 of 30 patients demonstrating WHO Grade 4 infection after the first course. However, there were no treatment-related deaths after IVAM.

The second purpose of the study was to evaluate the feasibility of PBSC collection to perform intensification. PBSC has been used in the same way as bone marrow and offers certain advantages: general anesthesia is avoided, collection can be performed in an outpatient setting, risk of contamination with malignant cells can be reduced, harvest can be done even if bone marrow is involved, and the recovery of bone marrow function is more rapid.[1,12] PBSC rise and can be collected during hemopoietic recovery after myelosuppression induced by high dose chemotherapy such as high dose cyclophosphamide with or without colony stimulating factors.[11,12,32] The magnitude of PBSC rebound depends on the intensity of previous myelosuppression,[33] bone marrow abnormalities such as hypocellularity or malignant involvement,[10] agents of

chemotherapy,[11] and growth factors.[9,12] IVAM induces myelosuppression; we took advantage of this to collect PBSC. Indeed, among the 31 patients, 29 patients could undergo PBSC collection. Only 2 patients had an insufficient CFU-GM yield and a bone marrow harvest was necessary to obtain a sufficient quantity of stem cells to successfully restore bone marrow functions. More recently, 12 patients were treated with G-CSF after IVAM, which dramatically increased CFU-GM counts. The median time for platelet and neutrophil recovery occurred on Day 15. As described by Brice et al.[13] we observed a delay of engraftment in patients who received TBI, perhaps because irradiation induces damage of the microenvironment that is necessary for bone marrow growth.

The overall survival rate of the whole patient group is about 37%, influenced only by the response to IVAM therapy, as has been demonstrated before by others.[2,5] No other significant correlation could be established between survival and prognostic factors, such as performance status, tumor size, lactate dehydrogenase level or age. Eleven patients in CR received posttransplant radiotherapy and 7 of these patients are still alive. Involved field irradiation may prolong the survival of patients with residual disease after transplantation. This approach could perhaps allow better tumor control for patients in CR who have a localized disease and a high tumor burden. The main posttransplant failure is caused by lymphoma recurrence.[18,34,35] Our results concerning response and survival are similar to previous reports of PBSC transplantation in patients with refractory or relapsed NHL.

We conclude that the IVAM regimen is an effective salvage chemotherapy with acceptable toxicity for patients with resistant or relapsed NHL. At the present time, this regimen is being studied by the Groupe d'Etudes des Lymphomes de l'Adulte (GELA) as a consolidation treatment during primary management of patients with adverse prognostic factors. Furthermore, the IVAM regimen functions as a mobilization regimen and allows PBSC collection prior to transplantation in most patients. Growth factors dramatically enhance peripheral hemopoietic stem cells mobilization.

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