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High-dose infusional ifosfamide, etoposide plus methylprednisolone followed by dexamethasone, high-dose ara-C and cisplatinum and autologous stem cell transplantation for refractory or relapsed aggressive non-Hodgkin's lymphoma

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Background and Objectives. A salvage program including infusional high-dose ifosfamide plus etoposide (IFOVM) was evaluated in patients with refractory or relapsed aggressive non-Hodgkin's lymphoma.

Design and Methods. Forty-six patients were included. IFOVM consisted of ifosfamide (10 g/m^2 as a 72-hour continuous infusion), etoposide (900 mg/m^2) and methylprednisolone; responding patients underwent two cycles of DHAP and subsequently an autologous peripheral blood stem cell transplantation (APBSCT) with BEAM as the conditioning regimen.

Results. All but one patient showed tumor regression following IFOVM. Myelosuppression was brief but 26 patients developed neutropenic fever. All but two patients proceeded to DHAP. Overall response rate to IFOVM/DHAP was 59% (29% CR and 30% PR). Refractory patients had a significantly lower response rate than relapsed patients (39% vs. 85% p=0.002). All refractory patients with intermediate-high or high IPI progressed during IFOVM/DHAP. Twenty-seven patients proceeded to APBSCT. Two-year overall survival of patients with low or low-intermediate IPI was 47% [95% CI 25-69%], which was significantly better than that obtained in patients with intermediate-high or high IPI (11% [95% CI 0-22%] p=0.0001).

Interpretation and Conclusions. This sequential regimen of IFOVM, followed by DHAP and consolidated with BEAM is active in relapsed or refractory patients with low or low-intermediate IPI aggressive lymphoma. However, it has little activity in those patients with intermediate or high IPI, especially in refractory lymphomas.

Key words: lymphoma, salvage therapy, ifosfamide, transplantation.

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Most patients with aggressive non-Hodgkin's lymphoma who fail to respond to their first-line anthracycline-containing chemotherapy or who relapse from complete remission have a poor prognosis.[1-3] Many salvage regimens have been developed over the last two decades. These combinations have demonstrated activity against lymphoma but with varying effectiveness and no definite improvement in survival.[1–7] Ifosfamide-based regimens have been used in various dosages and in combination with other agents,[8,11] frequently etoposide,[11-24] in patients with relapsed or refractory aggressive lymphoma. These regimens have induced response rates that have ranged from 35% to 79%, but durable remissions are infrequent. High-dose therapy (HDT) followed by autologous stem-cell transplantation (ASCT) has been demonstrated to improve the long-term outcome of patients with relapsed aggressive lymphoma, especially in chemosensitive relapses.[25-28]

The objective of this study was to investigate the efficacy and toxicity of a salvage regimen including high-dose infusional ifosfamide plus high-dose fractionated etoposide and methylprednisolone (IFOVM), followed by DHAP chemotherapy and subsequent HDT with BEAM conditioning and autologous peripheral blood stem cell transplantation (APBSCT) for patients with refractory or relapsed aggressive lymphoma.

Design and Methods

Patients and staging

From November 1996 to August 2001, 46 consecutive patients with relapsed or refractory aggressive lymphoma were entered into the study

at 5 hospitals from the *Grup per l'Estudi de Limfomes de Catalunya i Balears* (GELCAB). Patients between 16 and 65 years were eligible and all gave signed informed consent. Patients had either relapsed or refractory lymphoma of the following histologies according to the REAL/WHO classification:[29,30] diffuse large B-cell lymphoma or peripheral T-cell lymphoma. Patients with transformed B-cell lymphoma were also eligible but not those with mantle-cell lymphoma. All patients had initially been treated with an anthracycline-containing regimen as front-line treatment: 36 patients (78%) with CHOP, 6 (13%) with high-dose CHOP/ESHAP and 4 (9%) with other regimens. Patients were required to have a performance status of < 3 on the ECOG scale, with a life expectancy of > 3 months, an absolute neutrophil count > 1.5×10^9/L, a platelet count > 100 $\times10^9$/L, and serum creatinine and serum bilirubin levels lower than twice the upper-normal values. Patients were excluded if they had CNS involvement, human immunodeficiency virus infection, active infection, a history of serious cardiac or lung disease, or a formal contraindication to HDT followed by ASCT. All patients underwent restaging procedures which included computed tomography scans and bone marrow biopsy. Gallium scans were optional. The preliminary results of this trial have been previously reported.[31]

Chemotherapy

IFOVM induction salvage chemotherapy consisted of ifosfamide (10 g/m^2 as a 72-hour continuous intravenous infusion on days 1-3), etoposide (150 mg/m^2 every 12 hours as a 2-hour i.v. infusion on days 1 to 3), mesnum (20% of the total dose of ifosfamide 30 minutes before its infusion, 60% during the infusion of ifosfamide and 20% during the 12 hours after its completion) and methylprednisolone (60 mg/m^2 on days 1 to 5). Glycosylated granulocyte colony-stimulating factor (G-CSF) at a dose of 5 μg/kg daily was started on day 6 until granulocyte recovery and prophylaxis with oral quinolones was recommended. Seven days after full hematologic recovery, one or two cycles of the modified DHAP regimen[4] (dexamethasone 40 mg days 1-4, cisplatin 50 mg/m^2 by continuous infusion on days 1 and 2, and cytarabine 2 g/m^2 every 12 hours as a 2-hour infusion on days 3 and 4) were given as consolidation chemotherapy. Harvesting of peripheral blood stem cells (PBSC) was planned after either IFOVM or DHAP, both primed with G-CSF at a dose of 5 μg/kg daily. A total number of CD34$^+$ cells higher than 2×10^6/kg was recommended. Patients who achieved complete remission (CR) or partial remission (PR) proceeded to APBSCT with a modified BEAM[32] protocol: carmustine 300 mg/m^2 i.v. over 1 h on day -6, etoposide 200 mg/m^2 i.v. over 2 h on day -5, -4, -3, and -2, cytarabine 200 mg/m^2 i.v. over 2 h every 12 h on day -5, -4, -3, and -2 and melphalan 140 mg/m2 i.v. over 1 h on day -1. Patients received an infusion of PBSC on day 0. Isolation procedures, prophylactic antibiotic therapy and blood component management have been described elsewhere.[28] Colony-stimulating factors were not routinely used. Toxicity was assessed according to WHO criteria.

Study definitions

Refractory patients were those who failed to attain CR or PR with front-line therapy, patients with acquired refractory disease were those who attained CR or PR with front-line therapy but relapsed within 6 months, and relapsed patients were considered to be those who attained a CR lasting at least 6 months.[33] Response evaluation was determined according to the guidelines recently proposed by an international workshop.[34] Overall survival (OS) was defined as the time from the day of study entry until death from any cause or last date known to be alive. Event-free survival (EFS) was defined as the time from the day of study entry until relapse, death from any cause or last date known to be alive.

Statistical methods

Factors associated with response to IFOVM were analyzed and compared using the χ^2 test or Fisher´s exact test. Actuarial curves of EFS and OS were obtained according to the Kaplan-Meier method[35] and comparison between curves was performed using the log-rank test.[36] Factors examined for their correlation with response to IFOVM/DHAP and on outcome were: age (≤60 vs >60 years), sex, phenotype (B vs T), disease status at study entry (relapsed vs refractory), ECOG (0,1 vs ≥ 2), B-symptoms (present vs absent), LDH (≤1 vs >1 normal value), β_2-microglobulin (≤1 vs >1 normal value), number of extranodal sites (<2 vs ≥ 2), stage (I-II vs III-IV) and international prognostic index (IPI)[37] (<3 vs ≥ 3). Variables found to be associated with response (CR and PR) to IFOVM/DHAP in univariate analysis were examined in multivariate analysis with logistic regression. Variables associated with survival in univariate analysis were entered into a multivariate analysis that was performed according to the Cox model of multiple regression.[38] All *p*-values are two-sided and statistical significance was defined as a $p < 0.05$.

Results

Patients

The patients' characteristics at study entry are summarized in Table 1. The median age at progression was 46 years (range, 19-65). Twenty-three patients were male and 23 female. Disease status at study entry was as follows: relapsed lymphoma in 20 patients (44%), acquired refractory lymphoma in 8 (17%) and primary refractory lymphoma in 18 (39%). Thirty-three patients (72%) had been treated with one regimen of first-line anthracycline-containing chemotherapy, 12 (26%) with two types and one (2%) with three different regimens. At study entry, thirty patients (65%) had low/low-intermediate IPI and 14 (30%) intermediate-high/high IPI.

Response and toxicity to IFOVM/DHAP

All but one patient showed dramatic tumor regression following the first cycle of IFOVM. No clinical differences were noted between relapsed or refractory patients. Treatment was well-tolerated and all patients were evaluable for toxicity. The main toxicity was myelosuppression with neutropenia (<0.5×10^9/L) lasting for a median of 5 (range, 2-10) days and thrombocytopenia (< 20 ×10^9/L) for a median of 4 (range, 0-32) days. Twenty-six patients (57%) developed neutropenic fever with 6 uncomplicated bacteremias and two patients had urinary tract infection. All patients recovered successfully. Non-hematologic toxicity according to the WHO scale was modest. Four patients had grade 3 toxicity of pulmonary or hepatic origin and two patients grade 2 neurologic toxicity, with full recovery in all cases. Alopecia occurred in all patients. All but two patients were consolidated with DHAP. One patient who showed rapid progression after IFOVM was withdrawn from the study and one patient received two cycles of IFOVM. The other 44 patients received DHAP (in 9 cases only one cycle, in 31 two cycles and in 4 three cycles). Hematologic toxicity was milder than with IFOVM, as were the infectious complications. Seven patients developed neutropenic fever, 6 uncomplicated bacteremias and one septic shock.

Following IFOVM and DHAP, 13 patients achieved CR (28% [95% CI 15-41%]) and 14 PR (30% [95% CI 17-43%]) for a total response rate of 59% [95% CI 32-60%]). Tumor progression during DHAP was noted in 18 patients. Patients with relapsed lymphoma had a significantly better overall response rate (85% [95% CI 70-100%]) than those with refractory disease (39% [95% CI 20-58%]) (p=0.002) (Table 2). Overall response was not significantly different between patients with primary (33% [95% CI 11-55%]) versus acquired refractory disease (50% [95% CI 15-85%]). Compared to refractory patients, those with relapsed lymphoma had a relative risk of response to IFOVM/DHAP of 9.1 [95% CI 2.1-39]. Univariate analysis identified as favorable factors at study entry predicting response: male sex, relapsed disease, absence of B symptoms, ECOG 0-1, normal LDH and low/low-intermediate IPI (Table 3). In the multivariate

Table 1. Patients' characteristics at study entry prior to IFOVM.

	N (%)
Stage	
I-II	16 (35)
III-IV	30 (65)
B symptoms	
Absent	30 (65)
Present	16 (35)
LDH	
≤ 1 n. v.	20 (44)
> 1 n. v.	25 (54)
Not done	1 (2)
β2-microglobulin	
≤ 1 n. v.	29 (63)
> 1 n. v.	12 (26)
Not done	5 (11)
Performance status	
0-1	31 (67)
2-4	14 (30)
Not known	1 (2)
IPI	
0-2	30 (65)
3-5	14 (30)
Not available	2 (5)
Histology	
DLBCL	36 (78)
PTCL	9 (20)
Transformed follicular	1 (2)
No. of prior chemotherapies	
1	33 (72)
2	12 (26)
≥ 3	1 (2)
Type of chemotherapy	
CHOP	36 (78)
MegaCHOP/ESHAP	6 (13)
MACOP-B	1 (2)
Others	3 (7)
Previous response to therapy	
Primary refractory	18 (39)
Acquired refractory	8 (17)
Relapsed	20 (44)

IFOVM: ifosfamide, etoposide, methylprednisolone; n. v.: normal value; IPI: international prognostic index; CHOP: cyclophosphamide, vincristine, doxorubicin, prednisone; Mega-CHOP: high-dose cyclophosphamide, vincristine, doxorubicin, prednisone; ESHAP: etoposide, cisplatin, cytarabine, methylprednisolone; MACOP-B: methothrexate, adriamycin, cyclophosphamide, vincristine, prednisone, bleomycin; DLBCL: diffuse large B-cell lymphoma; PTCL: peripheral T-cell lymphoma.

Table 2. Response to IFOVM / DHAP and to IFOVM / DHAP / ASCT according to disease status at study entry.

	Response to IFOVM/DHAP		Response to IFOVM/DHAP/ASCT	
	CR	OR	CR	OR
All patients (n=46)	13 (28%)	27 (59%)	17 (37%)	21 (46%)
Refractory (n=26)	3 (12%)	10 (39%)*	7 (27%)	9 (35%)
Relapsed (n=20)	10 (50%)	17 (85%)*	10 (50%)	12 (60%)

*IFOVM: ifosfamide, etoposide, methylprednisolone; DHAP: dexamethasone, cytarabine, cisplatin; CR: complete remission; OR: overall response; *p=0.002 in Fisher's exact test.*

Table 3. Univariate analysis of factors prognostic of response to IFOVM / DHAP and survival.

Factor	Response (%)	p	RR (95% CI) (months)	Survival	p	RR (95% CI)
Sex						
Male	72	–	–	19	–	–
Female	43	0.05	3.4 (1.0-11.7)	6	0.05	2.2 (1-4.6)
Age						
≤ 60	63	–	–	12	–	–
> 60	38	NS	–	4	NS	–
Stage						
I-II	69	–	–	19	–	–
III-IV	53	NS	–	5	NS	–
B symptoms				NR	–	–
Absent	73	–	–	–	–	–
Present	31	0.008	6.1 (1.6-22.9)	4	0.01	2.6 (1.2-5.6)
LDH						
≤ 1 n. v.	75	–	–	19	–	–
> 1 n. v.	44	0.04	3.8 (1.1-13.8)	5	NS	–
β2-microglobulin						
≤ 1 n. v.	62	–	–	8	–	–
> 1 n. v.	42	NS	–	5	NS	–
PS-ECOG						
0-1	74	–	–	19	–	–
2-4	29	0.006	7.2 (1.8-29.5)	3	0.0005	3.7 (1.7-8.2)
Histology						
DLBCL	61	–	–	11	–	–
PTCL	50	NS	–	5	NS	–
IPI			19	–	–	
0-2	77	–	–	–	–	–
3-5	21	0.001	12 (2.6-55.7)	3	0.0001	5.2 (2.3-11.9)
Status study entry						
Relapsed	85	–	–	19	–	–
Refractory	39	0.002	9.1 (2.1-39)	5	0.05	2.1 (1-4.7)

N. v.: normal value; NR: not reached; NS: not significant; PS: performance status; DLBCL: diffuse large B-cell lymphoma; PTCL: peripheral T-cell lymphoma; IPI: international prognostic index.

analysis, relapsed disease at study entry and absence of B symptoms were factors associated with a significantly higher probability of response to IFOVM/DHAP (p=0.01 and p=0.036, respectively). Of note, all refractory patients with intermediate-high or high IPI progressed during IFOVM/DHAP. On the contrary, all relapsed patients with low or low-intermediate IPI responded. Overall response rate to IFOVM/DHAP in refractory patients with low or low-intermediate IPI and in relapsed patients with intermediate-high or high IPI were 56% [95% CI 32-80%] and 50% [95% CI 10-90%], respectively.

In 8 patients no attempt was made to collect PBSC. In the remaining 38 cases PBSC were collected after IFOVM in 16 patients and after DHAP in 22. In the former group the median number of $CD34^+$ cells harvested was 9.2×10^6/kg (range, 1.2-30) with a median of 1.4 aphereses (range, 1-2) (only one apheresis in 75% of cases), while in the DHAP group a median of 8×10^6/kg $CD34^+$ cells (range, 2.2-27.5) were harvested with 1 to 3 aphereses (median 2; one apheresis in 27%, two in 55% and three in 18% of cases).

High-dose therapy

Twenty-seven patients proceeded to high-dose BEAM followed by APBSCT (12 in CR, 13 in PR and 2 with progressive disease). Time from study entry to transplant was 3.6 months (range, 1-7). Toxicity of HDT was mainly due to myelosuppression, but two cases of transplant-related mortality were registered: one patient in CR suffered sudden death on day +5 and one with progressive lymphoma had fatal refractory septic shock. The other patient with progressive disease did not respond to BEAM. Of the 13 patients autografted in PR, six patients achieved CR, 4 maintained their status of PR and three progressed shortly after transplant. All evaluable patients conditioned in CR maintained this status at 3 months. Therefore, in an intent-to-treat basis, overall response to IFOVM/DHAP/BEAM was 46% [95% CI 32-60%], with 37% [95% CI 23-51%] CR and 9% [95% CI 1-17%] PR.

Survival

With a median follow-up after transplant of 12 months (range, 3-56), 3 additional patients progressed (2 died rapidly and 1 is alive after allogeneic transplantation with reduced intensity conditioning), 1 died in PR due to neurologic complications and 17 are still in CR. The two-year OS and EFS were 36% [95% CI 22-50%] and 34% [95% CI 20-

48%], respectively. Univariate analysis identified favorable factors at study entry predicting survival: male sex, relapsed disease, absence of B symptoms, ECOG 0-1, low/low-intermediate IPI, response to IFOVM/DHAP (Table 3). According to the Cox model, the probability of OS was significantly better in the group of patients who responded to IFOVM/DHAP (relative risk 21.4 [95% CI 4.3-106.1] p=0.0002). If we exclude in multivariate analysis response to IFOVM/DHAP, relapsed patients at study entry had a higher probability of OS than those with refractory lymphoma (RR 3.2 [95% CI 1.3-7.6] p =0.01). A second predictive factor for OS in multivariate analysis was IPI (RR 6.8 [95% CI 2.5-18.9] p=0.0002).

Two-year OS and EFS of patients with relapsed disease were 44% [95% CI 22-66%] and 39% [95% CI 18-60%], respectively, which were significantly better than in those with refractory disease (both 29% [95% CI 12-46%]). Figure 1 shows the survival curves according to disease status and IPI at study entry. In this series, two-year OS of low/low-intermediate IPI patients with relapsed disease (60% [95% CI 31-89%]) was better than that in refractory lymphoma (53% [95% CI 20-86%]), and was significantly better than that obtained in intermediate-high/high IPI with either relapsed or refractory lymphoma (29% [95% CI 0-58%] and 13% [95% CI 0-30%], respectively) (p=0.016 and p=0.0005, respectively).

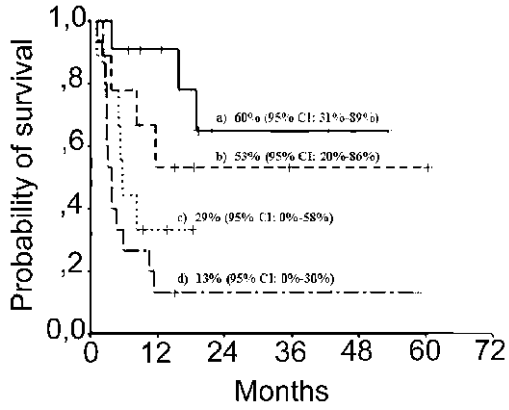

Figure 1. Overall survival at 2 years according to disease status and International Prognostic Index at study entry: a) relapsed low/low-intermediate IPI, 11 patients; b) refractory low/low-intermediate IPI, 9 patients; c) relapsed intermediate-high/high IPI, 9 patients; d) refractory intermediate-high/high IPI, 15 patients.

Discussion

During the last two decades, several salvage regimens for relapsed or refractory aggressive lymphoma have been developed. Most of these regimens are either cytarabine/platinum-based[4-7] or ifosfamide-based.[7-24] Used alone, ifosfamide has been reported to induce clinical remission in 29-47% of patients with relapsed or refractory aggressive lymphoma, but durations of responses have been only 6-8 weeks.[8,9] Various combinations of ifosfamide with other agents have obtained response rates between 36% and 70% (8-37% CR). Based on these data, we combined high-dose infusional ifosfamide and high-dose etoposide as an induction regimen in patients with relapsed or refractory aggressive lymphoma, trying to obtain a higher number of responses that would allow more patients to reach HDT, since the poor outcome of those patients with relapsed or refractory aggressive lymphoma who do not receive HDT with ASCT is well known.[25-28,39-44]

IFOVM represents a considerable dose escalation of ifosfamide and etoposide with respect to previously reported regimens and the entire treatment sequence is relatively short, a fact that represents an increase in the dose-intensity. In the present trial, the IFOVM/DHAP combination induced responses in 85% of our patients with relapsed aggressive lymphoma, including 50% CR. Even patients treated with high-dose CHOP/ESHAP as front-line therapy and those who had received more than one regimen responded to IFOVM. In a recent study,[24] van Besien used high-dose infusional ifosfamide combined with either etoposide or mitoxantrone for recurrent aggressive lymphoma obtaining an overall response rate of 79% (41% CR). Although a formal comparison cannot be made, our response rate in the group of relapsed patients is similar to that reported by van Besien and seems to be slightly more favorable than those reported in series using a variety of different regimens.[4-6,11,17,22] Although the vast majority of patients with primary refractory aggressive lymphoma do not respond to salvage therapy, in our study IFOVM/DHAP achieved a response rate of 39% (9% CR) in this group of patients. Similarly, Cortelazzo[44] reported a response rate of 34% using a high-dose sequential regimen in a population of patients similar to those in our series and excluded from other studies, such as the PARMA trial. Of note, a substantial number of primary refractory patients, including cases with bone marrow infiltration and histologic transformation, responded to our salvage program, which allowed them to reach the planned APBSCT with chemosensitive

disease. It is likely that as a result of this the survival of these patients is eventually improved.

Factors predictive of response to IFOVM/DHAP were disease status at study entry, B-symptoms and IPI. The current trial showed that all patients with relapsed aggressive lymphoma and low or low-intermediate IPI responded. On the contrary, no patient with refractory intermediate-high or high IPI had a clinical response and all progressed within a short time. In this group of patients IFOVM/DHAP appears to have little activity, and such patients should receive alternative investigational therapies. The response rate of patients with either intermediate-high/high IPI relapsed aggressive lymphoma or low/low-intermediate IPI refractory lymphoma were 50% and 56%, respectively. Recently, a combination of rituximab (anti-CD20) with CHOP has been reported to increase the response rate in elderly patients with *de novo* aggressive lymphoma.[45] It could be speculated, therefore, that the addition of rituximab to IFOVM/DHAP would significantly increase the proportion of responding patients.

IFOVM was well-tolerated and the toxicity was primarily hematologic. Myelosuppression was profound, but relatively brief. Despite the use of antibiotic prophylaxis and G-CSF support, neutropenic fever and uncomplicated bacteremias frequently occurred. However, no life-threatening complications or deaths were reported. Stem cell progenitors were collected from peripheral blood after IFOVM or DHAP. Both regimens showed high mobilization efficiency. Responding patients proceeded to high-dose BEAM with APBSCT. Several studies of ASCT in patients with aggressive lymphoma have shown that the strongest prognostic factor for outcome is the status of the disease prior to transplantation.[25-28,39-44] In our series, all but two patients were autografted in chemosensitive disease or complete remission. The predicted OS of these patients was 64% at 2 years, which is similar to that reported by other groups.[26-28,39-44]

Several variables have been found to be prognostic factors for survival in this study. Of these clinical features, IPI at study entry was the most important prognostic factor. Recent reports suggest that IPI at diagnosis and at progression identify patients with a different outcome following transplantation.[46] Of note, disease status at study entry was associated with a lower relative risk for survival than IPI. A recently reported series using high-dose ifosfamide concluded that no major survival benefit derived from the use of the more intensive ifosfamide regimen compared to MINE/ESHAP followed by BEAC.[24] In our series, the predicted OS at 2 years in relapsed patients with low or low-intermediate IPI was 60% (95% CI 31-89%) which is similar to that reported in the PARMA trial. However, the OS at 2 years of 53% (95% CI 20-86%) in primary refractory aggressive lymphoma with low or low-intermediate IPI seems promising and slightly superior to the best available results in this category of patients.[44,47-48] These figures suggest that our sequential regimen produces prolonged survival in a substantial proportion of patients. Unfortunately, our results regarding refractory patients with intermediate or intermediate-high IPI are poor and demonstrate that this regimen is ineffective in this group of patients.

In summary, the data in this study indicate that IFOVM is well tolerated and allows adequate PBSC mobilization. This sequential salvage treatment consisting of IFOVM followed by DHAP and consolidation with BEAM and ASCT is active in relapsed or refractory patients with low or low-intermediate IPI aggressive lymphoma. However, it has little activity in those patients with intermediate or high IPI, especially in refractory lymphomas and, in consequence, alternative approaches are needed in such patients.

Contributions and Acknowledgments

AS and RM contributed to the conception and design of the study, and carried out the analysis and interpretation of the results. AS, RM, GP, JMR, ALG, RG, LE and AA were involved in the clinical management of the patients. JS and EM critically corrected the manuscript. AS: responsible for the writing of the manuscript: AS, RM; responsibles for the Tables and Figures.

Disclosures

Conflict of interest: none.

Redundant publications: yes, ≤ 50%. The result of a pilot phase of this study appeared in Haematologica 2000; 85:217-9 as a paper by Salar A, Martino R, Altés A, Sureda A, Brunet S, Sierra J. High-dose ifosfamide and etoposide plus methylprednisolone for refractory or relapsed aggressive non-Hodgkin's lymphoma.

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Peer Review Outcomes

Manuscript processing

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What is already known on this topic

Most patients with aggressive non-Hodgkin's lymphoma who fail to respond to their first-line anthracycline-containing chemotherapy or who relapse from complete remission have a poor prognosis.

What this study adds

This sequential salvage regimen may induce complete response in a portion of patients with low or low-intermediate International Prognostic Index (IPI).

Potential implications for clinical practice

Patients with refractory or relapsed aggressive non-Hodgkin's lymphoma and intermediate or high IPI are very unlikely to benefit from this salvage regimen, whereas a portion of those with low or low-intermediate IPI may achieve complete remission.

Mario Cazzola, Editor-in-Chief (Pavia, Italy)