Malignant Lymphomas

research paper

haematologica 2002; 87:816-821
http://www.haematologica.ws/2002_08/816.htm

Ifosfamide, epirubicin and etoposide (IEV) regimen as salvage and mobilizing therapy for relapsed/refractory lymphoma patients

PIER LUIGI ZINZANI, MONICA TANI, ANNA LIA MOLINARI,* VITTORIO STEFONI, ELIANA ZUFFA,* LAPO ALINARI, ANNALISA GABRIELE, FRANCESCA BONIFAZI, PATRIZIA ALBERTINI, MARZIA SALVUCCI,* SANTE TURA, MICHELE BACCARANI

Institute of Hematology and Medical Oncology "L. e A. Seràgnoli", University of Bologna; *Division of Hematology, Ravenna Hospital, Ravenna, Italy

Background and Objectives. Therapy for relapsed/refractory lymphomas should be based only on drugs not included in the front-line chemotherapy regimens. We adopted the strategy of using salvage chemotherapy to debulk disease and simultaneously mobilize stem cells, using a regimen based on ifosfamide and etoposide, (drugs not usually used for front-line treatment).

Design and Methods. A three-drug combination of ifosfamide, epirubicin and etoposide (IEV) was used to treat 62 patients with relapsing or refractory aggressive non-Hodgkin's lymphoma (NHL; n=51) or Hodgkin's disease (HD; n=11). Forty-five of the patients were studied for the feasibility of peripheral blood stem cell (PBSC) harvest.

Results. The overall and complete response (CR) rates were, respectively, 77% and 32% in the NHL subset and 81% and 45% in the HD subset. Among the 17 patients who achieved CR after IEV but did not have a subsequent transplantation, the median duration of the response was 9 months (range, 2 to 14 months). Mobilization was successful in 33 of 45 (71%) patients. Among the 45 who proceeded to autotransplantation, 27 (60%) were in CR status after the autograft; 23/45 (51%) patients are currently in continuous CR with a median follow-up of 25 months (range, 10-68 months); the relapse-free survival curve shows 83% in this state at 60 months. Twenty-three (37%) patients are currently in continuous CR with a median follow-up of 25 months. Clinical and hematologic toxic effects were mild.

Interpretation and Conclusions. Our results indicate the efficacy of the IEV regimen in inducing a good remission rate. IEV is a predictable and highly effective mobilization regimen in relapsed/refractory patients with aggressive NHL or HD.

Key words: IEV regimen, HD, aggressive NHL, relapse/refractory patients, PBSC mobilization.

Correspondence: Pier Luigi Zinzani, M.D., Istituto di Ematologia e Oncologia Medica "L. e A. Seràgnoli", Policlinico S.Orsola, via Massarenti 9, 40138 Bologna, Italy. Phone: international +39.051.6363680. Fax: international +39.051.6364037. E-mail: plzinzo@med.unibo.it

Although advanced stage Hodgkin's disease (HD) and some aggressive non-Hodgkin's lymphomas (NHL) are potentially curable with standard chemotherapy, many patients either relapse or never achieve remission.[1,2] One way of improving this situation could be to intensify front-line chemotherapy, either by dose-escalation of conventional therapy[3] or by adding high-dose chemotherapy with peripheral blood stem cell (PBSC) rescue.[4,5] Whereas treatment of relapsing disease with conventional chemo- and/or radiation therapy is unsatisfactory, especially in those patients who have had an early relapse,[6,7] high-dose chemotherapy and stem cell rescue may improve prognosis.[8,9] Although high-dose chemotherapy can also be effective as a salvage strategy for HD patients who do not respond to induction treatment,[10] the approach fails with many refractory primary lymphomas.[11] So, despite our current ability to cure almost half of all aggressive NHL and the majority of HD, effective second-line therapies are needed for both resistant and relapsing disease. These second-line therapies could serve both for re-induction prior to high-dose chemotherapy with PBSC rescue, and for patients who are not candidates for transplantation.

Ideally, second-line therapy should not share any mechanism of action or toxicity with the initial induction regimen. In pratical terms, since most primary induction chemotherapy regimens contain anthracyclines and tend to be myelosuppressive, second-line combinations that avoid cardiac toxicity and excessive stem cell damage would be particularly useful. In multiple trials in which combination chemotherapy has been used to treat relapsed lymphoma patients following treatment with CHOP, most of the regimens have included cisplatin, methotrexate, mitoxantrone, and ifosfamide.[12-14] The *MINE* (ifosfamide, mitoxantrone, etoposide) regimen was one of the first to include ifosfamide, and several investigators have used variants of this combination to treat patients with

relapsed lymphomas.[15-23] All these studies have indicated that ifosfamide-based regimens incorporating etoposide and other agents can induce responses in transplanted patients and, when used in high doses in combination with growth factors, can act as excellent mobilizers of PBSC.

We previously reported[20] on the use of *IEV* (ifosfamide, epirubicin, and etoposide) alone in a group of resistant or relapsing lymphoma (HD and aggressive NHL) patients. Herein, we report an extended follow-up of a larger series of patients treated with IEV either alone or prior to autologous bone marrow transplantation (ABMT).

Design and Methods

Patients' characteristics

The present study regards 62 consecutive, previously treated patients (37 males, 25 females; median age, 42 years, range 14-62) with either NHL (n=51) or HD (n=11) diagnosed between January 1995 and September 2000 (Table 1).

Eligibility criteria included a confirmed histologic diagnosis of aggressive or indolent NHL or HD according to the REAL classification;[24] disease stage II to IV according to the Ann Arbor staging system;[25] Eastern Cooperative Oncology Group (ECOG)[26] performance status less than 3; human immunodeficiency virus negativity; and normal renal, hepatic, and cardiac functions [including a baseline resting left ventricular ejection fraction (LVEF) greater than 50%]. In all cases, staging evaluation included initial hematologic and chemical surveys, in addition to chest X-rays, abdominal ultrasonography, computed tomography of the chest and abdomen, and bone marrow biopsy. Other studies included lymphography (in 2 HD patients), and liver biopsy when appropriate.

No patient underwent staging laparotomy. Bulky disease was defined as a tumor mass ≥6 cm. Twenty-three patients had stage II, 15 had stage III, and 24 had stage IV disease. Twenty-two patients presented bulky disease. Thirty-eight patients had elevated serum lactate dehydrogenase (LDH) level and 29 patients had at least an extranodal involvement.

The performance status was 0-1 in 40 patients and 2 in the remaining 22 patients; according to the stage, 5 patients had stage II, 29 stage III, and 28 stage IV disease. Histologically, all 51 NHL patients had aggressive disease. Informed consent was always provided according to the Declaration of Helsinki.

Table 1. Patients' characteristics [n=62].

Age (years)	Median	42
	Range	14-62
Sex	M/F	37/25
Histology		
Hodgkin's disease		11
Follicular grade III		3
Peripheral T-cell		2
Diffuse large B-cell		44
Anaplastic large B-cell		2
Response status at time of treatment:		
PR		12
Relapse		33
Refractory		17
Elevated LDH level	Yes	38
	No	24
Performance status	0-1	40
	2	22
Extranodal sites	Yes	29
	No	33
Stage	II	5
	III	29
	IV	28
IPI	0-2	45
	≥ 3	17

Treatment protocol

The IEV schedule was as follows: ifosfamide 2,500 mg/m^2/day i.v. over 4 hours followed by mesna (3 g/m^2) and hydration over 10 h. daily to protect against urothelial toxicity on day 1 to 3, epirubicin 100 mg/m^2 i.v. on day 1; etoposide 150 mg/m^2 i.v. on days 1 to 3. Courses were repeated every 21 days, with a target total of three courses; chemotherapy was given in an outpatient setting. In the 45 patients for whom PBSC harvest was feasible only 2 conditioning courses were given in order to reduce tumor volume before high-dose chemotherapy and PBSC reinfusion. For these patients, subcutaneous administration of granulocyte colony-stimulating factor (G-CSF) (5 μg/kg, once daily) was commenced on day 6 and continued until completion of the PBSC harvest. The remaining 17 patients, who were considered unsuitable for myeloablative therapy, all received 3-4 cycles; G-CSF was administered at the same dose from day 6 to 14 of each cycle.

Response

All patients were restaged after completion of IEV chemotherapy. Clinical and pathologic evaluations were made by repeating radiographic investigations and bone marrow and/or liver biopsies

whenever previous results had been positive. Complete response (CR) and partial remission (PR) were defined according to international criteria.[27] No response (NR) was anything less than PR. Standard ECOG toxicity criteria were used.[26]

Statistical methods

Overall survival was measured from the time of entry into the protocol until death; the relapse-free interval was calculated from the date of response after autograft until relapse or death; event-free survival was measured from the autograft to the first event (resistance to treatment, relapse, death, last follow-up). Overall, relapse-free survival, and event-free survival curves were calculated according to the method of Kaplan and Meier.[28] Deaths from lymphoma, secondary to lymphoma treatment or to any disease (related or unrelated) were considered an event. Analyses of prognostic factors [including the International Prognostic Factor Index, (IPI)][29] were performed with log-rank tests, Cox's analysis,[30] and logistic regression analysis.

Leukaphereses and cryoconservation

Aphereses began during recovery from myelosuppression when the peripheral blood $CD34^+$ cell count was $>20\times10^6$/L. Cells were collected using a COBE cell separator. Leukapheresis was performed on consecutive days, aiming for a minimum target dose of 2×10^6/kg $CD34^+$ cells. All PBSC products were cryopreserved with a final dimethyl sulfoxide concentration of 10% and stored at –190°C in liquid nitrogen. Patients who subsequently proceeded to autograft received conditioning therapy with either the BEAM (BCNU, etoposide, aracytin, melphalan) regimen (for HD patients) or with BAVC (BCNU, aracytin, etoposide, cyclophosphamide) regimen (for NHL patients), followed by reinfusion of the thawed PBSC product.

Results

Response

Of the 62 patients studied, 21 (34%) fulfilled the criteria for CR and 27 (44%) for PR after IEV therapy, giving an overall response rate of 78%. The remaining 14 patients were considered as having NR to the treatment. Table 2 summarizes the responses with respect to histology and status before treatment.

The overall response rates for HD and aggressive NHL were 81% and 77%, respectively, the CR rates being 45% and 32%, respectively. Among the 12 patients who were in PR before the IEV regimen, 5 (42%) achieved CR and 4 (33%) had an improved PR (a good PR; GPR). Among the patients treated with IEV after relapse, 14 (43%) achieved CR and 19 (57%) PR. Among the 19 patients with primary refractory disease, 2 (11%) achieved CR and 4 (23%) PR.

Table 2. Responses according to disease status prior to IEV therapy of all 62 patients.

		HD (n=11) response			*NHL (n=51) response*		
Disease status at time of treatment	No. pts	CR	PR	NR	CR	PR	NR
During PR	12	3	1	0	2	3	.3
Relapsed	33	2	1	0	12	18	0
Refractory	17	0	2	2	2	2	9

Seventeen patients were not considered available for response evaluation because of rapid disease progression (6 patients), lost to follow-up (3 patients), transplant refused (2 patients), shifting to allogeneic transplant (2 patients), or sudden disease progression with fatal outcome. Among the 17 patients who received only IEV, the 9 responders had a median duration of response of 9 months (range, 2 to 14 months).

On the other hand, 27 (60%) of the 45 patients who proceeded to autotransplantation were in CR status after grafting and 23 (51%) of them are currently still in continuous CR with a median follow-up of 25 months (range, 10-68 months). Figure 1 shows the relapse-free survival curve in patients who were in CR after the ABMT (83% at 60 months). The overall survival (Figure 2) at 60 months was 58% and event-free survival (Figure 3) was 42% at 60 months. At present, 31/62 (50%) patients are still alive and 23/62 (37%) are in continuous CR with a median follow-up of 25 months.

PBSC mobilization

Mobilization of PBSC with the IEV regimen was successful in 33/45 (74%) patients, each of whom achieved the defined minimum transplant dose of 2×10^6 $CD34^+$ cells/kg. Of these, 19 had relapsed after front-line treatment (prior to IEV), 9 were refractory to the first-line therapy, and 5 were in PR. Among the 12 patients who failed to mobilize PBSC there were 7 pretreated (with chemotherapy regimens and mediastinal radiation therapy) refractory patients. Bone marrow was harvested from these 12 patients (7 refractory, 3 relapsed and 2 in PR). In 30/33 (91%) of the PBSC transplanted

patients, leukapheresis commenced between 13 and 15 days after starting IEV chemotherapy. The harvest of PBSC was completed after either one (n=20) or two (n=13) leukaphereses.

Toxicity

The toxicity due to IEV therapy was similar among the HD and NHL patients. The main form of toxicity was myelosuppression; grade 3-4 neutropenia was recorded following 36 (25%) of a total of 145 cycles, and grade 3-4 thrombocytopenia occurred in 25 (17%) courses. Clinically relevant infections were recorded in only 5 (8%) patients; eight (13%) required blood transfusions and 3 (5%) patients needed platelet transfusions. Although ECOG grade 3 alopecia was universal, no cardiac (monitored with LVEF), liver or renal toxicity was observed, and there were no fatalities due to side effects.

Statistical analysis

Among the ten factors (age, sex, presence/absence of bulky disease, presence/absence of B symptoms, stage, LDH level, extranodal sites, response to the front-line treatment, performance status, and IPI) investigated by Cox multivariate analysis, those most significantly associated with longer overall or relapse-free survival were good performance status (p= 0.001), the response to the front-line treatment (p= 0.001), and IPI (p= 0.026).

Discussion

The prognosis of patients with relapsed or resistant aggressive NHL and HD treated with conventional regimens remains poor. Response rates to salvage combinations generally range from 50% to 70%, with CR rates of 25 to 45%. Despite investigation of ifosfamide-etoposide or cytarabine-cisplatin-based regimens[31-33] such as DHAP and ESHAP, the 2-year event-free survival rate of these patients remains at best only 10 to 15%, with less than 10% surviving for as long as 3 years. In order to increase the number of patients who could benefit from autologous bone marrow transplantation (ABMT), these forms of chemotherapy might be administered at an early time point, following an abbreviated induction therapy. There are several reports[12-23] showing that ifosfamide-etoposide-containing regimens can induce responses in a wide variety of lymphoid neoplasms, both in the relapsed setting and as initial therapy, and that they can be administered with minimal toxicity. Such combinations, which use varying doses of ifosfamide, can also act as excellent stem cell mobilizers, especially when co-administered with

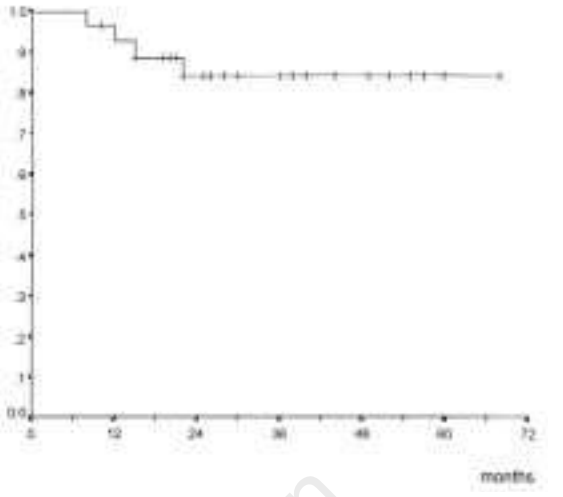

Figure 1. Relapse-free survival curve of patients who achieved CR after IEV regimen plus ABMT.

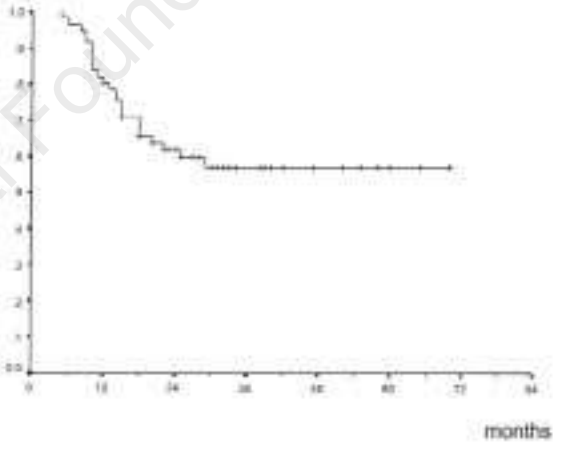

Figure 2. Overall survival curve of all 62 patients.

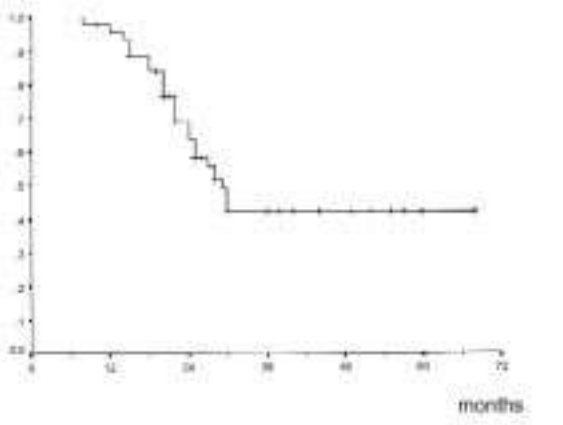

Figure 3. Event-free survival curve of all 45 patients after IEV regimen plus ABMT.

growth factors, thereby increasing the value of these regimens as relapse therapies.

In our study, the response rate after IEV was 78% (CR 34%, PR 44%) with no significant difference of response being found between HD patients and patients with aggressive NHL (overall response rates, 81% vs. 77%; CR rates 45% vs. 32%). Forty-five patients were studied for the feasibility of PBSC harvest, and in 33 (74%) an adequate collection was obtained. This subset of patients also included refractory cases. In addition, most of the mobilizers needed only one leukapheresis. Following the complete sequence of second-line treatment (i.e. IEV reinduction and transplantation with PBSC) 23/62 (37%) of the patients are currently in continuous CR after a median follow-up of 25 months. IEV therapy was well tolerated and there was no evidence of severe or permanent toxic effects.

Even in the refractory subset, IEV provided a relatively encouraging overall response rate (34%). Not surprisingly, the best target was the subset of relapsed patients in whom the overall response rate was 100%. The patients treated while in PR obtained an intermediate overall response rate (75%).

All the patients who received only IEV relapsed rapidly (within 14 months) after obtaining CR. In the subgroup of patients who were eligible for myeloablative treatment, we performed initial tumor debulking with IEV in order to increase the possibity of eradicating the lymphoma in the subsequent ABMT phase. Therefore, the role of subsequent ABMT with PBSC rescue seems to be pivotal in relapsed or refractory lymphoma patients. Successful mobilization of PBSC is essential for delivery of dose-intensive chemotherapy. An effective mobilization regimen forming an integral part of a planned therapeutic program should include antitumor activity, possibly in an outpatient setting, a consistently high yield of $CD34^+$ cells, a predictable time to leukapheresis and minimal toxicity. Our experience indicates that the IEV regimen can meet these criteria. Combinations that include ifosfamide and new drugs, especially those with novel mechanisms of action (e.g. carboplatin),[31,32] or novel biological agents (e.g. rituximab),[33,34] may ultimately improve the responses of these patients and, hopefully, their eventual chances of cure.

Contributions and Acknowledgments

PLZ designed the study. MT, ALM, VS, EZ, LA, AG, PA, MS were responsible for the care of patients and data collection. FB was responsible for the statistical analyses. All authors contributed to revising the manuscript. They are listed according to a criterion of decreasing individual contribution to the work, with the exception of the last two authors (ST, MB) who had a major role as senior authors in interpreting the data.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

References

1. Canellos GP, Anderson JR, Propert KJ, Nissen N, Cooper MR, Henderson ES, et al. Chemotherapy of advanced Hodgkin's disease with MOPP, ABVD, or MOPP alternating with ABVD. N Engl J Med 1992; 327:1478-84.
2. Fisher RI, Gaynor ER, Dahlberg S, Oken MM, Grogan TM, Mize EM, et al. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. N Engl J Med 1993; 328:1002-6.
3. Diehl V, Franklin J, Hasenclever D, Tesch H, Pfreundschuh M, Lathan B, et al. BEACOPP, a new dose-escalated and accelerated regimen, is at least as effective as COPP/ABVD in patients with advanced-stage Hodgkin's lymphoma: interim report from a trial of the German Hodgkin's Lymphoma Study Group. J Clin Oncol 1998; 16:3810-21.
4. Carella AM, Pollicardo N, Pungolino E, Frassoni F, Giordano D, Bruni R, et al. Autologous stem cell transplantation as adjuvant treatment vs no further therapy for poor-risk Hodgkin's disease in first complete remission after MOPP/ABVD. Leuk Lymphoma 1995; 15 Suppl 1:59-61.
5. Haioun C, Lepage E, Gisselbrecht C. Survival benefit of high dose therapy over sequential chemotherapy in poor risk aggressive non-Hodgkin's lymphoma: final analysis of the prospective LNH 87-2 protocol. A GELA study. Blood 1999; 94 Suppl 1:a2711[abstract].
6. Longo DL, Duffey PL, Young RC, Hubbard SM, Ihde DC, Glatstein E, et al. Conventional-dose salvage combination chemotherapy in patients relapsing with Hodgkin's disease after combination chemotherapy: the low probability for cure. J Clin Oncol 1992; 10:210-8.
7. Salles G, Shipp MA, Coiffier B. Chemotherapy of non-Hodgkin's aggressive lymphomas. Semin Hematol 1994; 31:46-69.
8. Philip T, Guglielmi C, Hagenbeek A, Somers R, Van der Lelie H, Bron D, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. N Engl J Med 1995; 333:1540-5.
9. Schmitz N, Sextro M, Pfistner B, Hasenclever D, Tesch H, Carella A, et al. High-dose therapy (HDT) followed by hematopoietic stem cell transplantation (HSCT) for relapsed chemosensitive Hodgkin's disease (HD): final results of a randomized GHSG and EBMT Trial (HD-R1). Proc Am Soc Clin Oncol 1999; 18:a5[abstract].
10. Sweetenham JW, Carella AM, Taghipour G, Cunningham D, Marcus R, Della Volpe A, et al. High-dose therapy and autologous stem-cell transplantation for adult patients with Hodgkin's disease who do not enter remission after induction chemotherapy: results in 175 patients reported to the European Group for Blood and Marrow Transplantation. Lymphoma Working Party. J Clin Oncol 1995; 17: 3101-9.
11. Mills W, Chopra R McMillan A, Pearce R, Linch DC, Goldstone AH. BEAM chemotherapy and autologous bone mar-

row transplantation for patients with relapsed or refractory non-Hodgkin's lymphoma. J Clin Oncol 1995; 13:588-95.
12. Spinolo JA, Cabanillas F, Dixon DO, Khorana SM, McLaughlin P, Velasquez WS, et al. Therapy of relapsed or refractory low-grade follicular lymphomas: factors associated with complete remission, survival and time to treatment failure. Ann Oncol 1992; 3:227-32.
13. Velasquez WS, McLaughlin P, Tucker S, Hagemeister FB, Swan F, Rodriguez MA, et al. ESHAP: an effective chemotherapy regimen in refractory and relapsing lymphoma: a 4-year follow-up study. J Clin Oncol 1994; 12: 1169-76.
14. Velasquez WS, Cabanillas F, Salvador P, McLaughlin P, Fridrik M, Tucker S, et al. Effective salvage therapy for lymphoma with cisplatin in combination with high-dose Ara-C and dexamethasone (DHAP). Blood 1988; 71:117-22.
15. Rodriguez MA, Cabanillas FC, Hagemeister FB, McLaughlin P, Romaguera JE, Swan F, et al. A phase II trial of mesna/ifosfamide, mitoxantrone and etoposide for refractory lymphomas. Ann Oncol 1995; 6:609-11.
16. Hagemeister FB, Tannir N, McLaughlin P, Salvador P, Riggs S, Velasquez WS, et al. MIME chemotherapy (methyl-GAG, ifosfamide, methotrexate, etoposide) as treatment for recurrent Hodgkin's disease. J Clin Oncol 1987; 5:556-61.
17. Cabanillas F. Experience with ifosfamide combinations in malignant lymphomas. Semin Oncol 1989; 16:78-81.
18. Aurlien E, Holte H, Pharo A, Kvaloy S, Jakobsen E, Smeland EB, et al. Combination chemotherapy with mitoguazon, ifosfamide, MTX, etoposide (MIME) and G-CSF can efficiently mobilize PBPC in patients with Hodgkin's and non-Hodgkin's lymphoma. Bone Marrow Transplant 1998; 21:873-8.
19. Proctor SJ, Taylor PR, Angus B, Wood K, Lennard AL, Lucraft H, et al. High-dose ifosfamide in combination with etoposide and epirubicin (IVE) in the treatment of relapsed/refractory Hodgkin's disease and non-Hodgkin's lymphoma: a report on toxicity and efficacy. Eur J Haematol 2001; Suppl 64:28-32.
20. Zinzani PL, Barbieri E, Visani G, Gherlinzoni F, Perini F, Neri S, et al. Ifosfamide, epirubicin and etoposide (IEV) therapy in relapsed and refractory high-grade non-Hodgkin's lymphoma and Hodgkin's disease. Haematologica 1994; 79:508-12.
21. Bonfante V, Viviani S, Santoro A, Devizzi L, Di Russo A, Zanini M, et al. Ifosfamide and vinorelbine: an active regimen for patients with relapsed or refractory Hodgkin's disease. Br J Haematol 1998; 103:533-5.
22. Engert A, Schnell R, Kupper F, Reiser M, Engelhard M, Wilhelm M, et al. A phase-II study with idarubicin, ifosfamide and VP-16 (IIVP-16) in patients with refractory or relapsed aggressive and high grade non-Hodgkin's lymphoma. Leuk Lymphoma 1997; 24:513-22.
23. Garay G, Dupont J, Dragosky M, Nucifora E, Cacchione R, Schnidrig P, et al. Combination salvage chemotherapy with MIZE (ifosfamide-mesna, idarubicin and etoposide) for relapsing or refractory lymphoma. Leuk Lymphoma 1997; 26:595-602.
24. Harris NL, Jaffe ES, Stein H, Banks PM, Chan JK, Cleary ML, et al. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. Blood 1994; 84:1361-92.
25. Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M. Report of the Committee on Hodgkin's Disease Staging Classification. Cancer Res 1971; 31:1860-1.
26. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5:649-55.
27. Cheson BD, Horning SJ, Coiffier B, Shipp MA, Fisher RI, Connors JM, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. J Clin Oncol 1999; 17:1244-51.
28. Kaplan EL, Meier P. Non-parametric estimation from incomplete observations. JAMA 1958; 53:457-81.
29. Cox DR. Regression models and life tables (with discussion). J R Stat Soc B 1972; 34:187-90.
30. Anonymous. A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. N Engl J Med 1993; 329:987-94.
31. Moskowitz CH, Bertino JR, Glassman JR, Hedrick EE, Hunte S, Coady-Lyons N, et al. Ifosfamide, carboplatin, and etoposide: a highly effective cytoreduction and peripheral-blood progenitor-cell mobilization regimen for transplant-eligible patients with non-Hodgkin's lymphoma. J Clin Oncol 1999; 17:3776-85.
32. Kingreen D, Beyer J, Kleiner S, Reif S, Huhn D, Siegert W. ICE-an efficient drug combination for stem cell mobilization and high dose treatment of malignant lymphoma. Eur J Haematol 2001; 66 Suppl 64:46-50.
33. Joyce RM, Kraser CN, Tetrealt JC, Giallombardo N, McDermott D, Levine J, et al. Rituximab and ifosfamide, mitoxantrone, etoposide (RIME) with Neupogen support for B-cell non-Hodgkin's lymphoma prior to high-dose chemotherapy with autologous haematopoietic transplant. Eur J Haematol 2001; Suppl 64:56-62.
34. Kewalramani T, Zelenetz A, Bertino J. Rituximab significantly increases the complete rate in patients with relapsed or primary refractory DLBCL receiving ICE as second-line therapy (SLT). Blood 2001; 98 Suppl 1:a1459 [abstract].

Peer Review Outcomes

Manuscript processing

This manuscript was peer-reviewed by two external referees and by Professor Gilles Salles, who acted as an Associate Editor. The final decision to accept this paper for publication was taken jointly by Prof. Salles and the Editors. Manuscript received February 5, 2002; accepted June 5, 2002.

What is already known on this topic

Salvage chemotherapy for relapse or refractory lymphoma patients should allow a high rate of tumor response in order to proceed with subsequent autologous stem cell transplantation. Several regimens based on the use of ifosfamide plus etoposide have been developed over the years.

What this study adds

This study describes the association of epiribucin with ifosfamide plus etoposide (IEV) with a high response rate and a manageable toxicity. A substantial proportion of patients received autologous stem cell transplant, three quarters of them with PBSC collected after IEV.

Potential implications for clinical practice

This regimen can be used as a salvage regimen for relapsing or refractory patients, allowing a good mobilization of hematopoietic stem cells.

Gilles Salles, Associate Editor