

IFOSFAMIDE, EPIRUBICINE, AND ETOPOSIDE (IEV) THERAPY IN RELAPSED AND REFRACTORY HIGH GRADE NON-HODGKIN'S LYMPHOMA AND HODGKIN'S DISEASE

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ABSTRACT

Background. A fundamental principle in the therapeutic strategy for recurrent lymphomas is the employment of agents that do not form part of the usual front line combination regimens. The cytotoxic agents should ideally lack complete cross resistance with those utilized up front.

Patients and Methods. A three-drug combination with ifosfamide, epirubicine, and etoposide (IEV) was utilized for the treatment of 20 patients with relapsing or refractory high-grade non-Hodgkin's lymphoma (HG-NHL) or Hodgkin's disease (HD).

Results. Of 14 patients with HG-NHL, 5 (36%) achieved a complete response (CR) and 4 partial remission (PR), giving an overall response rate of 64%. To date, all the complete responders are still in CR at +5, +5, +6, +7, and +9 months, respectively. Of 6 patients with HD, 4 (66%) obtained CR and 2 PR, giving an overall response rate of 100%. The 4 CRs are still in remission after +4, +5, +9, and +13 months, respectively. Clinical and hematologic toxic effects were moderate: in 6 patients, neutropenia was responsible for a temporary delay of 1 week of the treatment.

Conclusions. These results confirm the efficacy of IEV regimen in induction a good remission rate with moderate side effects in relapsing/refractory HG-NHL and HD patients and warrant further investigations.

Key words: high-grade non-Hodgkin's lymphoma, Hodgkin's disease, IEV regimen, relapsed/refractory patients

Although the significant progress made over the last 20 years in the treatment of high grade non-Hodgkin's lymphomas (HG-NHL) and Hodgkin's disease (HD) achieved with the introduction of third generation combination chemotherapy regimens,¹⁻⁴ autologous bone marrow transplantation (ABMT),⁵⁻⁷ and the combination with radiotherapy,⁸⁻¹⁰ approximately 30% of the patients will not achieve complete response. In addition, another 20% to 40% of the complete responders will eventually relapse. These patients failing on or relapsing following first-line treatment require effective second-line or salvage therapy.

The two major options now available consist of either megadose chemotherapy, with ABMT, or standard-dose chemotherapy salvage regimens. Even though the use of high-dose chemotherapy and ABMT has been associated with 20% long-term disease-free survival, whereas standard-dose chemotherapy has only yielded 10% disease-free survival, the patients treated in these studies are widely different.¹¹⁻¹⁴

They have often received the principal active agents as initial induction chemotherapy and this limits the therapeutic possibilities. Ifosfamide, an analogue of cyclophosphamide has been shown to produce responses in lym-

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phoma even when patients have been previously treated with cyclophosphamide.¹⁵⁻¹⁶

Responses to ifosfamide-containing combinations, in particular with etoposide with/without anthracyclines, have been documented in several reports.¹⁷⁻²²

We report here the results obtained with a salvage regimen including ifosfamide, epirubicin and etoposide (IEV) in patients with refractory or relapsed HG-NHL or HD.

Patients and Methods

Between March, 1993, and January, 1994, 20 patients with HG-NHL or HD completed three cycles of IEV regimen. The main protocol requirement was that patients should have had initially advanced (bulky stage II or stage III or IV) disease, as outlined by the Ann Arbor Conference²³ where first-line treatment had failed to produce complete response or where relapse had occurred. Criteria for entry into the study included: for the HG-NHL the histologic diagnosis according to the Updated Kiel classification;²⁴ the presence of measurable disease; and patients with normal hepatic, renal, cardiac functions. Staging reevaluation included bone marrow biopsy, hematologic and chemical survey in addition to chest radiograms, abdominal ultrasonography and computerized tomography of chest and abdomen in all patients.

Patients characteristics (Table 1)

The 20 patients comprised 14 with HG-NHL (mean age 38 years, range 19-57; males 10, females 4) and 6 HD (mean age 27 years, range 20-47; males 3, females 3). Among the patients with HG-NHL, 11 had disease relapsing or progression between 3 and 18 months after initial complete (5 pts, 3 in first and 2 in second complete response) or partial response (6 pts). These patients had previously received one (6 pts) or two (5 pts) chemotherapeutic regimens. Three patients were considered to be primarily refractory to first-line treatment. Among the HD patients, 5 had disease relapsing between 6-10 months after the complete response and 1 had a partial response after two lines of chemotherapy.

IEV regimen

The treatment schedule was as follows: ifosfamide 2500 mg/sqm i.v. on days 1 to 3 (plus Mesna given i.v. 800 mg at 0, 4, 8, 10 hours following ifosfamide), epirubicin 100 mg/sqm i.v. on day 1, etoposide 150 mg/sqm i.v. on days 1 to 3.

Courses were repeated every 21 days utilizing antiemetic prophylaxis; in case of myelosuppression, the next course was delayed and given at the full dose on day 28. Treatment was given in hospital and all the patients received at least 3 cycles of IEV regimen.

Patients were restaged after completion of 3 cycles. Clinical and pathologic evaluations were made by repeating radiographic investigations and bone marrow and/or liver biopsies if previous results had been positive. Standard Eastern Cooperative Oncology Group (ECOG) toxicity criteria were used.²⁵

Dose intensity was evaluated according to Hryniuk and Bush's model;²⁶ relative dose intensity was the ratio between dose intensity received and protocol dose intensity.

Table 1. Patient characteristics.

	HG-NHL	HD
Number of patients	14	6
Age (years):		
• mean	38	27
• range	19-57	20-47
Symptoms (no/yes)	10/4	3/3
Stage:		
• II	6/4	1/6
• III	/	3/6
• IV	8/14	2/6
Histology*		
• Cb pol	8/14	4/6 NS
	2/6 LP	
• Ib	2/14	/
• ALC	3/14	/
• Lb	1/14	/
Status		
• I relapse	3/14	2/6
• ≥ II relapse	2/14	3/6
• refractory	3/14	/
• in PR	6/14	1/6

* Cb pol: centroblastic polymorphous; Ib: immunoblastic; ALC: anaplastic large cell; Lb: lymphoblastic; NS: nodular sclerosis; LP: lymphocyte predominant.

Evaluation response

Complete response (CR) was defined as the complete disappearance of signs and symptoms due to lymphoma and maintained for at least 6 weeks; partial response (PR) was defined as a reduction of at least 50% in the product of the two largest perpendicular diameters of all measurable lesions for a duration of at least 6 weeks. Progression of disease (PD) was used where there was unequivocal evidence of advancing disease, despite continuation of the treatment.

Survival and relapse-free survival were calculated according to the method of Kaplan and Meier.²⁷

Results

Response

Tables 2 and 3 depict the responses to initial IEV treatment. Major responses (CR+PR) were seen in 9 HG-NHL and 6 HD cases (75%).

In particular, among the 14 HG-NHL patients we had 4 CR, 4 PR, and 3 PD in the subset of 11 patients relapsed following first-line therapy. Of the three patients with primarily or secondarily refractory disease, 1 achieved CR and the remaining 2 did not respond to therapy and were considered to have disease progression.

The overall response rate (CR+PR) for HG-NHL was 64%. Two PR patients have relapsed after IEV regimen and both died. Three PR patients went on to additional treatment with radiotherapy and all of them obtained a CR. The 5 patients who achieved a CR are still in remission after 5, 5, 6, 7, and 9 months. None of the CRs have been maintained. The overall mean survival of all HG-NHL patients was 6 months (range, 2 to 12 mo).

The overall response rate (CR+PR) for HD patients was 100%; 4 patients (1 in PR after ABVD-MOPP regimen, 1 in first relapse and 2 at the second relapse of the HD) obtained a CR. The remaining 2 patients (1 in fourth relapse, 1 in first relapse) achieved a PR. Two CRs underwent to additional autologous bone marrow transplantation in order to consolidate the response. Actually, the 4 CRs are still in remission after 4, 5, 9, and 13 months. Both PRs did not relapse with a follow-up of 4 and 9 months, respectively. The overall mean survival of all HD patients was 7 months (range, 4 to 13 mo).

Toxic effects

A total of 66 courses of IEV regimen were administered in 20 patients, with a median number of 3 cycles per patient (range 3-5); 11 (16%) courses were administered at a reduced

Table 2. Details of patients with HG-NHL obtaining a complete response with IEV regimen.

Patients	Age/Sex	Histology	Previous treatment	Status before IEV	Response	Duration of response (mos)
1	22/M	ALC	F-MACHOP + RT	I relapse	CR	6
2	42/M	Cb pol	MACOP-B	I relapse	CR	5
3	30/F	Cb pol	MACOP-B	Refractory	CR	9
4	31/M	Ib	MACOP-B + RT	I relapse	CR	7
5	40/F	Cb pol	M-BACOD + RT	II relapse	CR	5

Table 3. Details of patients with HD obtaining a complete response with IEV regimen.

Patients	Age/Sex	Previous treatment	Status before IEV	Response	Duration of response (mos)
1	22/F	MOPP-ABVD + RT + ABMT	II relapse	CR	4
2	17/F	ABVD + RT	I relapse	CR	9
3	47/M	MOPP-ABVD	PR	CR	13
4	32/M	MOPP-ABVD + CEP	II relapse	CR	5

dosage due to myelosuppression. In addition, 7 courses (6 patients) were given with a delay of one week over the 3 weeks planned because of neutropenia. The main toxicity of IEV was myelosuppression; grade 3-4 neutropenia was recorded following 17 (25%) of a total of 66 cycles, and grade 3-4 thrombocytopenia occurred in only 9/66 (7%) courses.

The relative dose intensities for the regimen drugs are as follows: ifosfamide 0.92, epirubicin 1.0, and etoposide 0.98; none statistically significant difference between responders and non responders groups and by age was recorded.

Non hematologic toxicity was minimal. Only mild nausea and vomiting (10%) and alopecia (50%) were seen in several patients. Cardiac, liver and renal toxic effects were not observed, and no fatalities due to drug side effects were recorded.

Discussion

Despite the progress observed with the newest first line chemotherapy regimens¹⁻⁴ for HG-NHL, at least 30 to 50% of patients will not achieve remission. These patients have a poor prognosis, and almost all will die of progressive lymphoma without effective second line salvage therapy. About HD, patients who do not respond after a second treatment with a standard program or after high-dose chemotherapy in the setting of bone marrow are candidates for various alternative (*third-line*) programs. Treatment under these circumstances is rarely curative and should be given as part of a formal clinical trial, since it is largely a way to identify new drugs that can improve the treatment of newly diagnosed HD.⁸⁻¹⁰

The poor results are due to primary drug resistance following failure of first/second-line therapy and to the inability of patients to tolerate full doses of chemotherapy salvage regimens. Furthermore, these salvage regimens can play an important role reducing the tumor burden before the eventual ABMT or in the patients who are ineligible for the ABMT.

In the present study, where the majority of HG-NHL patients had received third-generation regimens as first-line treatment and all HD

patients underwent to combined therapy including MOPP-ABVD chemotherapy and radiotherapy, we obtained 9 (45%) CR (5 pts, 36% for HG-NHL and 4 pts, 66%, for HD) with an overall response rate (CR+PR) of 75%. Among HG-NHL, complete responses to IEV were seen more frequently in patients who had achieved a CR with front-line treatment (4/5, 80%) than in those who had failed first-line chemotherapy (1/3, 33%). IEV regimen appears to be equally active in all histologic subtypes treated. In addition, considering the few cases of reversible hematologic toxicity, IEV therapy was well tolerated and there was no evidence of severe or permanent toxic effects.

A series of salvage regimens have been tested during the last decade.^{17-22,28-32} The first series of regimens were developed using Ifosfamide and Etoposide as the backbone like MIME and MINE regimens or MIME-like regimens.

Subsequently, DHAP and new ARA-C/platinum-based combinations showed interesting results as second- or third-line treatment. Now, in view of the activity and potential for non-cross resistance of the ifosfamide/etoposide-based regimens and the ARA-C/platinum combination, there is a trend to explore the use of these two regimens in sequence or in alternating fashion. A major advantage of these two regimens, alone or both, is the lack of cross-resistance with other front-line protocols such as MACOP-B and CHOP.

Our data confirm the real efficacy of a ifosfamide-etoposide combination containing regimen in HG-NHL and HD patients relapse or refractory to the conventional first- or second-line treatments. Clearly, additional multicenter randomized trials that include growth factors as components of therapy are requested to determine whether toxicity can be reduced further without sacrificing efficacy.

This regimen represents an available opportunity in the strategy of treatment including the consolidation of the response, in the prospect of prolonged disease-free survival, with mega-dose chemotherapy and ABMT.

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