Haematologica 1998; 83:323-328 original paper

Efficacy of a combination of idarubicin, etoposide and intermediate-dose cytosine arabinoside as salvage therapy in relapsing or resistant unfavorable lymphoma

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ABSTRACT

Background and Objective. **Idarubicin, an anthracycline analogue, is active in non-Hodgkin's lymphoma. This study evaluates the efficacy and toxicity of a combination of idarubicin, etoposide and intermediate-dose cytarabine (IVA) in unfavorable lymphoma in relapse or resistant to prior doxorubicin- or novantrone-based regimens.**

Design and Methods. **Thirty patients with relapsing or resistant unfavorable lymphoma received a combination of idarubicin 12 mg/m² i.v. on day 1, etoposide 60 mg/m² i. v. every 12 hours for 3 days, and Ara-C 1 g/m² i. v. every 12 hours for 3 days (3-hour infusion). Median age was 39 years (range: 22-60). All patients had been given prior doxorubicin or novantrone; 54% of them had received 2 or more chemotherapy regimens; 67% of total were in clinical relapse (30% in their second relapse), and 23% had resistant disease.**

Results. **The overall response rate to IVA was 60% (18 of 30 patients). Complete remission rate was 20% (6 of 30) in the whole group, 45% (5 of 11) among patients in their first relapse. Remission median duration was 9 months (range: 1-18), with a 3-year relapse-free and overall survival of 20% and 15%, respectively. Severe neutropenia occurred in 13 patients (43%) and severe thrombocytopenia in 11 patients (37%), with a median duration of 9 and 13 days, respectively. No cardiac toxicity developed; sepsis during neutropenia was documented in four instances and two patients (7%) died of therapy-related events (septic shock).**

Interpretation and Conclusions. **Idarubicin combined with etoposide and intermediate-dose cytarabine proved to be an active salvage therapy in unfavorable lymphoma given prior doxorubicin or novantrone; the best results were obtained among patients in their first relapse, with low tumor burden.**

Key words: idarubicin, salvage therapy, unfavorable lymphoma; relapsed lymphoma, resistant lymphoma

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Salvage therapy in relapsed or resistant unfavorable non-Hodgkin's lymphoma usually includes drugs non cross-resistant with first-line doxorubicin-based regimens; the most frequently used agents in this setting have been novantrone, ifosfamide, etoposide, cisplatin and high-dose cytarabine.[1-4] Several different combinations of these drugs have demonstrated remarkable antitumor activity with tolerable toxicity; the ultimate results are, however, rather disappointing and long-term survival can only be offered to a small proportion of patients.[5-11] Trying to improve on survival after relapse in unfavorable non-Hodgkin's lymphoma, high-dose chemotherapy with hematopoietic stem cells support is also being used, with results that are largely dependent upon patient selection;[12-15] however, this procedure can only be applied to a minority of patients. The search for new active combinations of conventional-dose therapy is therefore strongly warranted.

In the last decade, idarubicin, a new anthracycline derivative of daunorubicin,[16-18] has been the subject of several studies in non-Hodgkin's lymphomas. As a single agent, this drug has been given both orally or intravenously and demonstrated to be active in relapsed or refractory patients with advanced stage favorable and unfavorable histology.[19-24] When used in combination, idarubicin has been associated with high-dose cytarabine,[25] with ifosfamide and etoposide,[26,27] and with fludarabine.[28] The activity of these different regimens was dependent upon the response of lymphoma to prior chemotherapy and upon the number and type of previous regimens; an overall response rate of about 50-60% was obtained in patients who had been sensitive to prior treatment versus about 15-30% among patients who were refractory. Interestingly, a proportion of patients relapsing after doxorubicin still responded to idarubicin,[29] demonstrating a lack or minimal cross-resistance between the two anologues. The major toxicity of idarubicin was myelosuppression, and no apparent cumulative cardiotoxicity was demonstrated in patients pretreated with doxorubicin.[25, 26] In our previous experience, intermediate- and high-dose cytarabine was active in unfavorable non-Hodgkin's lymphoma, with particular reference to

therapy of meningeal disease.[30] Accordingly, we combined idarubicin with intermediate-dose cytarabine and etoposide (IVA regimen) as salvage therapy for relapsing or refractory unfavorable (large cell) lymphoma who had received prior treatment with doxorubicin- or novantrone-based regimens. This study was aimed at determining the efficacy and toxicity of this regimen.

Patients and Methods

From October 1992 to December 1994, thirty patients with relapsed or refractory intermediate- or high-grade non-Hodgkin's lymphoma according to the Working Formulation[31] were treated with the IVA chemotherapy. Idarubicin was administered intravenously at the dose of 12 mg/m^2 on day 1; etoposide was given at the dose of 60 mg/m^2 twice a day for 3 consecutive days as intravenous infusion of 30 minutes; Ara-C was administered at the dose of 1 g/m^2 twice a day for 3 consecutive days as intravenous infusion of 3 hours. Patients were hospitalized and the cycles were repeated every 21 days; cycle deferral was generally preferred to dose adjustment in presence of hematopoietic and/or non-hematopoietic toxicity. Since January 1994, to maximize dose-intensity and reduce hematopoietic toxicity, patients with severe neutropenia after the first cycle of IVA were elegible to receive granulocyte colony-stimulating factor (G-CSF) after subsequent cycles; G-CSF was given subcutaneously at the dose of 5 μg/kg/day until the polymorphonucleated cells were more than 1×10^9/L for two consecutive days.

Due to the heavy pretreatment of our group of patients, the therapy plan consisted of four cumulative cycles of IVA in patients responding to therapy, whereas those who did not respond or progress after the first cycle of therapy were withdrawn from the program.

Pretreatment features before IVA and previous treatment history were assessed for each patient. Disease extension before IVA was evaluated through physical examination, chest X-ray, bone marrow biopsy and chest and abdomen computed tomography, when appropriate. All patients were negative for human immunodeficiency virus and had measurable disease; tumor burden was assessed according to the M. D. Anderson Hospital criteria.[32] Cardiac ejection fraction was measured with bidimensional echocardiography before the initiation and after the end of IVA chemotherapy.

Complete remission (CR) was defined by the disappearance of any evidence of active lymphoma for at least 1 month; partial response by a decrease of at least 50% and minor response by a decrease less than 50% of the largest tumor mass; partial and minor responses are referred to in the text as objective responses. The duration of remission was calculated from the time of documented response, usually after the second cycle of therapy. Overall survival was calculated from the time of treatment to death or to the last follow-up. Overall and relapse-free survival were calculated with the actuarial analysis.

Results

Patient characteristics

Patient pretreatment features and prior chemotherapy data are illustrated in Table 1. The median age was 39 years (range: 22-60), the M/F ratio was 17/13. The large majority of patients had diffuse large cell lymphoma (70%); 23% had large cell immunoblastic lymphoma and two patients (7%) had a large cell lymphoma evolving from a low-grade histology. All patients had advanced-stage disease; tumor burden was present in 37% and LDH serum levels were above the normal values in 77% of total.

All patients had received prior combination chemotherapy; 54% of total had been pretreated with two or more different CT regimens. Prior CT regimens con-

Table 1. Patient characteristics.

Features	*Number of patients (%)*
Total	30
Median age (yrs)	39
Range (yrs)	22-60
Men/women ratio	17/13
Histology (WF)	
Diffuse large cell	21 (70%)
Immunoblastic	7 (23%)
Histologic progression	2 (7%)
LDH ≤ 450 UI/L	7 (23%)
LDH > 450 UI/L	23 (77%)
Tumor burden	11 (37%)
Number of prior CT regimens	
1	14 (46%)
2	12 (41%)
> 2	4 (13%)
Type of prior CT regimens	
CHOP/CNOP	12 (40%)
MACOP-B/VACOP-B	20 (66%)
HDAra-C+Novantrone	9 (30%)
Disease status at IVA regimen	
First relapse	11 (37%)
Second relapse	9 (30%)
Late relapse	3 (10%)
Resistant disease	7 (23%)
Patients given prior doxorubicin	28 (93%)
mean dose in mg/m^2	310
dose range in mg/m^2	100-470
Patients given prior novantrone	13 (43%)
mean dose in mg/m^2	48
dose range in mg/m^2	30-72

CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; CNOP: cyclophosphamide, novantrone, vincristine, prednisone; CT: chemotherapy; HDAra-C: High dose cytarabine; LDH: lactic dehydrogenase; MACOP-B: methotrexate, doxorubicin, cyclophosphamide, vincristine, bleomycin; VACOP-B: etoposide, doxorubicin, cyclophosphamide, vincristine, bleomycin; WF: Working Formulation.

Table 2. Response to the IVA regimen.

	Number of patients (% of total)
Evaluable patients	30
Complete remission	6 (20%)
Objective response	12 (40%)
Median duration of CR (range)	9 mos (1-18)
CR in patients treated in their 1st relapse	5/11 (45%)
CR in patients refractory to prior therapy	1/7 (14%)
CR in patients with low tumor burden	5/19 (26%)
CR in patients with high tumor burden	1/11 (9%)

CR: complete remission.

Table 3. Hematopoietic toxicity of the IVA regimen.

	No. of patients (% of total)	*No. of cycles (% of total)*
Total	30	77
Severe neutropenia (PMN $\leq 0.5\times10^9$/L)	13 (43%)	43 (56%)
Severe thrombocytopenia (Plts $\leq 15\times10^9$/L)	11 (37%)	42 (55%)
Median day of nadir after the end of IVA	10th	
Median value of PMN at nadir	0.6×10^9/L	
Median value of Plts at nadir	11×10^9/L	
Median duration of neutropenia	9 days	
Median duration of thrombocytopenia	13 days	

PMN: polymorphonucleated cells; Plts: platelets.

sisted of CHOP or CNOP (substituting novantrone for doxorubicin) in 12 patients (40%), of MACOP-B or VACOP-B (substituting etoposide for methotrexate) in 20 patients (66%), of novantrone and high-dose cytarabine in 9 patients (30%). All prior regimens included anthracycline and/or anthracenedione derivatives; doxorubicin had been given in 93% of cases with a mean dose of 310 mg/m^2 and a range from 100 and 470 mg/m^2; novantrone had been given in 43% of cases with a mean dose of 48 mg/m^2 and a range from 30 to 72 mg/m^2. As for disease status at the initiation of IVA, 37% of patients were in their first relapse, 30% in second relapse and 10% were relapsing after more than two years of complete remission (late relapses). All together, 8 patients (27%) were relapsing after one year of complete remission, while 7 patients (23%) had resistant disease, having failed to achieve remission at any time.

Response to treatment

All 30 patients were evaluable for response and toxicity; the cumulative number of cycles of chemotherapy was 77, with a mean of 2.6 cycles per patient. The type of response is illustrated in Table 2. The overall response rate to the IVA protocol was 60% (18 of 30 patients) and included 20% (6 patients) of complete remissions and 40% (12 patients) of objective responses (partial and minor responses). The response was analyzed according to the responsiveness to previous combination chemotherapy; patients relapsing from a prior treatment were significantly ($p < 0.01$) more likely to respond to IVA than patients refractory to prior therapy. In particular, the patients treated at their first relapse achieved the complete remission in 45% of cases (5 of 11 patients), whereas the CR rate was only 14% (1 of 7 patients) among the cases resistant to primary chemotherapy. No significant differences in response to IVA were found according to the type of previous chemotherapy, with particular reference to prior doxorubicin versus prior novantrone. The probability of attaining a complete remission was also directly correlated with the tumor burden; the CR rate in patients with low tumor burden was 26% (5 of 19) compared to 9% (1 of 11) among patients with high tumor burden ($p < 0.01$). The median number of cycles required to achieve complete remission was 2, and the median CR duration was 9 months (range: 1-18). The 3-year relapse-free and overall survival were 20% and 15%, respectively.

Toxicity

The hematopoietic toxicity encountered after the IVA regimen is illustrated in Table 3. Episodes of severe neutropenia (PMN $\leq 0.5\times10^9$/L) occurred in 13 patients (43% of patients) after 43 of 77 cumulative cycles of therapy (56%), while episodes of severe thrombocytopenia (Plts $\leq 15\times10^9$/L) occurred in 11 patients (37%) after 42 of 77 cycles of therapy (55%). G-CSF was used in 10 patients for a total of 25 cycles of therapy. The median values of PMN and platelets at their nadir were 0.6×10^9/L and 11×10^9/L, respectively. The median day of nadir was the 10th day after the end of therapy; the median duration of neutropenia and thrombocytopenia was of 9 and 13 days, respectively. Fever during neutropenia developed in 17 patients (57%), after 36 of 77 cumulative cycles of therapy (47%). Sepsis during neutropenia occurred in four patients (13%) and in two instances (7%) was fatal; microbiological cultures were positive for *Escherichia coli* in two cases, for *Pseudomonas aeruginosa* and *Candida spp.* in one case, each.

The non-hematopoietic toxicity of the IVA regimen is illustrated in Table 4. Mild (grade I-II according the WHO criteria) gastrointestinal toxicity occurred in 14 patients (47%), after 32 of 77 cycles of therapy (42%); severe gastrointestinal toxicity (grade III) developed in five patients (17%). Insignificant changes of ventricular ejection fraction occurred during therapy; no episodes of congestive cardiac failure were documented. Three patients (10%) developed renal failure

Table 4. Non-hematopoietic toxicity of the IVA regimen.

Type of toxicity	*No. of patients (% of 30 patients)*	*No. of episodes (% of 77 cycles)*
Gastrointestinal		
grade I-II	14 (47%)	32 (42%)
grade III	5 (17%)	8 (10%)
Fever during neutropenia	17 (57%)	36 (47%)
Sepsis during neutropenia	4 (13%)	4 (5%)
Renal	3 (10%)	3 (4%)
Therapy-related deaths	2 (7%)	

Grading according to the WHO criteria.

after therapy; this event, however, occurred in a setting of progressive disease and general deterioration of clinical status along with the lymphoma progression.

Therapy-related deaths occurred in two patients (7%); the cause of death in both instances was a septic shock developing during severe neutropenia.

Discussion

The prognosis of patients with intermediate- or high-grade non-Hodgkin's lymphoma not achieving complete remission with primary chemotherapy or relapsing after complete remission is usually poor; the most important prognostic indicator in these situations is whether a complete remission was achieved and the duration of this remission.[2,3] A number of salvage regimens have been developed for relapsing or resistant patients and consist of combinations of newer drugs that are active in non-Hodgkin's lymphoma and may be non cross-resistant with front-line drugs. Such drugs include anthracycline and anthracenedione derivatives, ifosfamide, cisplatin, etoposide and nitrosureas used at conventional doses and high-dose cytarabine.

Idarubicin is a good candidate for salvage therapy in non-Hodgkin's lymphoma because of its activity as single agent, the lack of cross-resistance with doxorubicin and novantrone and the lower cardiotoxicity compared to doxorubicin documented in experimental models.[16] The IVA regimen which combines idarubicin with etoposide and intermediate-dose cytarabine proved to be active as salvage therapy in relapsing and refractory lymphoma allowing an overall response rate of 60% and a complete remission rate of 20%. The most important factors influencing the probability of attaining a complete remission were the low tumor burden and the prior sensitivity to chemotherapy; indeed, the complete remission rate was significantly higher (45%) in patients treated with IVA at their first relapse compared to resistant patients (14%), and among patients with low tumor burden compared to those with high tumor burden ($p < 0.01$). No differences in the response rate to IVA were encountered according to whether prior chemotherapy contained doxorubicin or novantrone; this may suggest a substantial lack of cross-resistance between idarubicin and doxorubicin.

Table 5. Salvage therapy with idarubicin in non-Hodgkin's lymphoma.

Regimen (ref.#)	*Drugs*	*Schedule of idarubicin*	*CR %*	*OR %*	*CR median duration*	*OS*
Single agent (24)	Idarubicin	15 mg/m^2, day 1	10	43	10 mos	NA
(25)	Idarubicin HDAra-C	7 mg/m^2 × 3 days	59	64	11 mos	43% at 4 yrs
MIZE (26)	Idarubicin Ifosfamide Etoposide	12 mg/m^2, day 1	56*	80	NA	39% at 18 mos
IIVP-16	Idarubicin	10 mg/m^2 × 2 days	20	49	10 mos	37% at 1 yr
IVA (this paper)	Idarubicin Etoposide HDAra-C	12 mg/m^2, day 1	20	60	9 mos	15% at 3 yrs

*CR: complete remission; NA: not available; OR: overall response; OS: overall survival; *the study includes patients with low-grade lymphoma and Hodgkin's disease.*

Our results are comparable to those achieved in malignant lymphoma with different salvage protocols including idarubicin, which are summarized in Table 5. The CR rate varied from 10% (with idarubicin as a single agent) to 59%; however, in all the series the median duration of complete remission was between 9 and 11 months and the overall survival range from 15% at 3 years to 43% at 4 years. Table 6 summarizes the results obtained in non-Hodgkin's lymphoma with different salvage regimens containing newer drugs at conventional dosage; the IVA results are comparable to those obtained with MIME[6] and DHAP[7] regimens and are apparently inferior to those of EPOCH[10] and ESHAP[11] therapies. However, the series of patients treated with the latter protocols included a substantial proportion of low-grade lymphomas (24% in EPOCH and 28% in ESHAP) which, at variance, were excluded from our study; that may have influenced the overall results in term of response rate. Furthermore, in our series, 54% of patients had been given two or more prior regimens (all of them doxorubicin- or novantrone-based), 66% had received third-generation regimens and 30% prior high-dose cytarabine; in the ESHAP study, the percent of heavily pretreated patients was substantially lower (40%) and that again may account for the difference in the overall survival after salvage therapy.

The toxicity of the IVA protocol was mostly

Table 6. Conventional salvage chemotherapy in non-Hodgkin's lymphoma.

Regimen (ref. #)	*Drugs*	*CR %*	*OR %*	*CR median duration*	*OS*
MIME (6)	Mitoguazone Ifosfamide Methotrexate Etoposide	24	60	15 mos	22% at 2 yrs
DHAP (7)	Dexamethasone High-dose Ara-C Cisplatin	31	56	12 mos	10% at 4 yrs
EPOCH (10)	Etoposide Prednisone Vincristine Cyclophosphamide Doxorubicin	27	87	NA	30% at 2 yrs
ESHAP (11)	Etoposide Solumedrol High-dose Ara-C Cisplatin	37	64	20 mos	31% at 3 yrs

NA: not available.

hematopoietic, with severe neutropenia and/or thrombocytopenia in more than half of patients and a median duration of neutropenia of 9 days; neutropenia-related fever occurred in 57% of patients and sepsis was documented in 4 patients (13%). The incidence of therapy-related death after IVA was 7%; this figure is comparable with that of other salvage regimens ranging from 3%[10] to 6%.[6]

High-dose chemotherapy with hematopoietic precursors rescue, either from bone marrow and/or from peripheral blood, is being extensively used in relapsing or resistant unfavorable lymphoma; the results of this approach are largely dependent upon the patient characteristics.[12-15] Although a high remission rate can be attained with high-dose chemotherapy followed by hematopoietic rescue, relapses are frequent and the 5-year disease-free survival remains at about 20%.[12] A direct relationship has been found between favorable outcome, chemosensitive disease and low tumor burden; indeed, the best results are achieved in chemosensitive relapses with a 2-year overall survival rate ranging from 35% to 50%.[33-37]

In patients with chemotherapy-sensitive disease, the superiority of high-dose chemotherapy followed by autologous hematopoietic rescue over conventional chemotherapy has been suggested in retrospective analyses of the GELA group[38] and demonstrated by the prospective randomized PARMA study.[39] Any reliable comparison of high-dose chemotherapy results with those of the present study is impossible due to the bias of different inclusion criteria; only one third of the IVA patients were in their first relapse and more than half had been treated before IVA with two or more CT regimens; furthermore, about one fourth of the patients had a chemotherapy-resistant disease.

In conclusion, the IVA regimen proved to be of some efficacy as salvage therapy in a particularly bad-risk group of patients; the toxicity of therapy was substantial and this may have been conditioned, at least in part, by the heavy pretreatment.

Prospectively, the IVA regimen could be integrated into a mega-therapy program as a chemosensitivity test before conditioning with high-dose CT and hematopoietic rescue. We are evaluating the capacity of IVA therapy to mobilize hematopoietic precursors (PBSC) into peripheral blood; should IVA permit a good PBSC collection, this regimen could be used as debulking and mobilizing procedure, as well.

Finally, a proportion of patients with relapsing or resistant unfavorable lymphoma can not undergo a high-dose chemotherapy approach because of advanced age and/or poor performance status; in this setting, the IVA regimen could be a suitable candidate for salvage therapy.

Contributions and Acknowledgments

EB and CB formulated the design of the IVA protocol. All the authors participated in the clinical work and followed the patients. EB was responsible for data handling, analysis, interpretatrion and writing of the paper. The criteria for the order in which the authors' names appear were as follows: first name for the protocol conception, data handling and paper writing; last name for the major clinician involved as responsible for the study design, intermediate names for all the authors who followed the patients clinically. All authors critically revised the paper and approved this final version.

Disclosures

Conflict of interest: none

Redundant publications: no overlapping with previous papers.

Manuscript processing

Manuscript received October 16, 1997; accepted January 15, 1998.

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