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Published in:
European Journal of Haematology

DOI:
[10.1111/j.1600-0609.2004.00294.x](https://doi.org/10.1111/j.1600-0609.2004.00294.x)

2004

[Link to publication](#)

Citation for published version (APA):
Jerkeman, M., Leppä, S., Kvaløy, S., & Holte, H. (2004). ICE (ifosfamide, carboplatin, etoposide) as second-line chemotherapy in relapsed or primary progressive aggressive lymphoma--the Nordic Lymphoma Group experience. *European Journal of Haematology*, 73(3), 179-182. <https://doi.org/10.1111/j.1600-0609.2004.00294.x>

Total number of authors:
4

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ICE (ifosfamide, carboplatin, etoposide) as second-line chemotherapy in relapsed or primary progressive aggressive lymphoma – the Nordic Lymphoma Group experience

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Eur J Haematol 2004; 73: 179–182. © Blackwell Munksgard 2004.

Abstract: *Objective:* To evaluate ICE (ifosfamide, carboplatin, etoposide) as second-line chemotherapy in relapsed or primary progressive aggressive lymphoma, in terms of objective response rate (ORR) and peripheral blood stem cell (PBSC) harvest mobilization rate. *Patient population:* A total of 40 patients were included, with a median age of 57 yr. The major histopathological subgroup was diffuse large B-cell lymphoma ($n = 27$). The indication for ICE was relapse in 23 patients, primary progressive disease in 11, transformation in four and adjuvant primary chemotherapy in one patient. *Results:* After three cycles of ICE, the ORR was 59%. Among patients with primary progressive disease, ORR was 36% (four of 11). A PBSC harvest after ICE could be performed in 11 of 20 patients, and was sufficient for stem cell rescue in 10 of 20. The median number of collected CD34⁺ cells was 3.6×10^6 (range 1.4–12.5). In six of 10 patients, an adequate PBSC harvest could be performed with a second mobilization regimen. *Conclusion:* In this patient population, the rate of response to ICE was comparable with other second-line regimens used in aggressive lymphoma. The rate of harvest failure (45%) was disappointingly high, compared with previous reports, possibly because of patient selection or differences in granulocyte-colony stimulating factor (G-CSF) dosage.

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Key words: aggressive lymphoma; relapse; chemotherapy; stem cell mobilization

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Accepted for publication 13 March 2004

Aggressive lymphoma in relapse is a curable disease. After second-line induction chemotherapy and consolidating high-dose chemotherapy with stem cell support (HDSCT), about 40–50% of patients with chemosensitive disease obtain long-term progression-free survival (1).

A prerequisite for a favorable prognosis after HDSCT consolidation is response to second-line induction chemotherapy, reflecting a relative sensitivity to chemotherapy (2).

Patients with primary progressive aggressive lymphoma, refractory to primary chemotherapy, are associated with a significantly worse prognosis, as only a small minority respond to second-line chemotherapy (3).

The stem cell source of choice in HDSCT is peripheral blood stem cells (PBSC), as HDSCT with bone marrow stem cell support is associated with a significantly prolonged time to hematological recovery (4). In clinical practice, the use of bone marrow stem cells is restricted to patients in whom PBSC mobilization has failed.

Attempts to purge stem cells from tumor cell contamination, such as CD34⁺ selection, require even higher numbers of PBSC.

In summary, an ideal second-line chemotherapy regimen for use in aggressive lymphoma should be associated with a high response rate and a high PBSC mobilization capacity.

In addition, such a regimen should preferably be associated with a low level of non-hematological toxicity, as this may hamper tolerability to the consolidative high-dose chemotherapy.

In 1999, results regarding a novel second-line regimen, ICE (ifosfamide, carboplatin, etoposide) were reported (5). This study reports on 163 patients, 144 with aggressive lymphoma.

For patients treated at relapse ($n = 85$) objective response rate (ORR) was 80%, and for patients with primary progressive disease ($n = 78$), it was 58%. The median number of mobilized PBSC was 8.4×10^6 CD34⁺/kg, and harvest failure was observed in only 14%. The toxicity was mainly hematological (grade 3/4 thrombocytopenia in 29.4% of cycles) Non-hematological toxicity was uncommon. Stimulated by these promising results, a phase II trial with ICE was initiated in Scandinavia to evaluate in consecutively treated patients the efficacy of ICE in terms of ORR and PBSC harvest mobilization rate.

Patients and methods

Inclusion criteria

The protocol included transplant-eligible patients with relapsed or primary progressive aggressive lymphoma from the Southern Sweden Health Care Region (the Norwegian Radium Hospital, Oslo, Norway), and Helsinki University Hospital (Finland) between 2000 and 2002. The age limit was 18–70 yr. Relapse was defined as disease progression, verified by biopsy, after an initial complete remission (CR). Primary progressive disease was defined as progression in a patient without attaining CR. First-line chemotherapy should consist of an anthracyclin-based cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP)-like regimen. Aggressive lymphoma was defined according to Hiddemann *et al.* (6), including the following histopathological entities of the REAL classification: diffuse large B-cell lymphoma, mantle cell lymphoma, follicular lymphoma grade III, peripheral T-cell lymphoma, unspecified, anaplastic large T-cell lymphoma or transformed indolent lymphoma. Patients with central nervous system (CNS) relapse or severe concomitant disease were excluded. The primary endpoints were: ORR and peripheral stem cell harvest failure rate.

Chemotherapy regimen

Three cycles of ICE chemotherapy were planned to be administered at 2-wk intervals. The ICE regimen was administered according to the original protocol from the Memorial Sloan-Kettering Cancer Center

(MSKCC) (5): (i) etoposide 100 mg/m²/d i.v. on days 1–3; (ii) carboplatin administered on day 2 and dosed to an AUC of 5, calculated using the Calvert formula [$5 \times (\text{iohexol clearance} + 25)$]; (maximum dose: 800 mg); and (iii) ifosfamide 5000 mg/m² mixed with 3000 mg/m² mesna, 24 h continuous infusion beginning on day 2. G-CSF was administered on days 5–12. The G-CSF dose was not specified in the protocol. Dose reductions were not allowed, but treatment was delayed until the absolute neutrophil count was more than 1000 / μ L and the platelet count was more than 50 000 / μ L. CT scans of the neck, chest, abdomen, and pelvis were performed before the initiation of ICE and 2–4 wk after cycle 3 of ICE to evaluate the initial extent of disease and response to ICE. A bone marrow examination, including biopsy, was performed before start of therapy and, if positive, after cycle 3. Off protocol, four patients at one center received rituximab, 375 mg/m² i.v. on day 1 in each cycle of ICE.

Stem cell harvesting

PBPCs were mobilized after the third cycle of ICE chemotherapy using G-CSF (filgrastim or lenograstim). A dose of 10 μ g/kg was used in six patients, in the remaining eight, the dose ranged between 4 and 8 μ g/kg (median 7), beginning on day 5 and continuing until the completion of leukapheresis. Leukapheresis was initiated when the CD34⁺ count was more than 20 000 /mL and was continued daily until more than 2×10^6 CD34⁺ cells/kg were collected.

Statistical methods

Complete remission (CR) was defined as no evidence of disease as documented by restaging 2–4 wk after completion of the third cycle of ICE. A partial remission (PR) was defined as a $\geq 50\%$ decrease in the sum of the products of the diameters of each measurable lesion. Progressive disease (PD) was defined as the appearance of a new lesion or an increase of $> 50\%$ of the sum of the products of the diameters of a pre-existing lesion. If the criteria for CR, PR or PD were not fulfilled, the response was classified as no change (NC).

Analysis of differences between groups was performed by Mann–Whitney's test.

Results

Patients

A total of forty patients were included in the study (southern Sweden: 15; Norwegian Radium Hospital: 15; Helsinki University Hospital: 10). The

Table 1. Patient characteristics (*n* = 40)

	<i>n</i> (%)
Gender	
Male	25 (62.5)
Female	15 (37.5)
Histology	
Diffuse large B-cell	27 (62.5)
Follicular grade III	7 (17.5)
Follicular, unspecified	2 (5.0)
Aggressive B-cell unspecified	1 (2.5)
Mantle cell	1 (2.5)
Peripheral T-cell unspecified	2 (5.0)
Indication for ICE	
Relapse	23 (57.5)
Primary progression	11 (27.5)
Transformation	5 (12.5)
Primary treatment	1 (2.5)

patient median age was 57 years (range 25–73). A total of 22% of the patients were older than 60 yr. The majority were classified as diffuse large B-cell lymphoma (DLBCL) (27 patients). Two patients presented with relapse of a clinically aggressive follicular lymphoma, grade unspecified, and were thus enrolled into the protocol.

The indication for ICE was relapse in 23 patients, and primary progressive disease in 11. In five patients, ICE was administered as induction chemotherapy for transformed follicular lymphoma prior to HDSCT. One patient, previously treated for Hodgkin lymphoma, received ICE + rituximab as adjuvant primary chemotherapy after complete surgical resection of DLBCL. This patient was excluded from analysis of response. For other baseline data see Table 1.

Toxicity and dose intensity

In total, 137 cycles of ICE were administered. The median number per patient was 4 (range 1–6). Eighty-one of 137 (59%) cycles were given as planned with 14 day interval. In patients older than 60 yr, 15 of 27 (55%) were administered according to schedule.

The majority of patients experienced grade III–IV neutropenia and thrombocytopenia (90%), but grade III–IV infection was seen in only five patients.

Non-hematological toxicity was mainly secondary to high-dose ifosfamide, reversible grade III–IV CNS toxicity was observed in four patients. In two patients, grade III–IV nephrotoxicity (acute tubular necrosis) led to the cessation of ICE chemotherapy. For other toxicity data see Table 2.

Response

Response could be evaluated in 39 patients (Table 2). The total ORR was 59% (23 of 39). In

Table 2. Efficacy (39 patients) and toxicity data (40 patients)

	<i>n</i> (%)
Response to ICE	
CR	7 (17.9)
PR	16 (41.0)
CR + PR	23 (59.0)
NC	9 (23.0)
PD	7 (18.0)
Attempt to mobilize PBSC with ICE	
No	20 (50.0)
Yes	20 (50.0)
Successful mobilization with ICE	
No	9 (45.0)
Yes	11 (55.0)
Successful mobilization with other regimen	
No	6 (50.0)
Yes	6 (50.0)
Grade III–IV toxicity	
Neutropenia	
Grade III	25 (62)
Grade IV	11 (28)
Thrombocytopenia	
Grade III	8 (20)
Grade IV	28 (70)
Renal	
Grade IV	2 (5)
Infectious	
Grade III	4 (10)
Grade IV	1 (2)
Nausea	
Grade III	2 (5)
Cardiac	
Grade III	1 (2)
Liver	
Grade III	1 (2)
Neurological	
Grade III	4 (10)

patients with relapse, the ORR was 78% (18 of 23). In patients with primary progressive disease, the ORR was 36% (four of 11). Among patients with DLBCL, the ORR was 74% (17 of 23). Among patients older than 60, six of nine (67%) responded.

Three patients who received ICE + rituximab could be evaluated for response. All three responded (one CR, two PR). The median time to progression among responding patients was 12 months.

Stem cell harvesting

In 20 patients, an attempt was made to mobilize PBSC after ICE. Among these, PBSC could be harvested in 11, causing a harvest failure rate of 45%. In patients > 60 years, one of six failed mobilization. For one of the patients where PBSC harvest was performed, the harvest yield (1.4×10^6 CD34⁺/kg) was insufficient for stem cell rescue, and was supported with bone marrow stem cells. Thus, an adequate PBSC harvest was obtained in only 50%. In six of 10 patients, PBSC could be harvested after a second mobilization regimen (high-dose cyclophosphamide: four; MIME: two).

The median number of collected PBSC was 3.6×10^6 CD34⁺/kg (range 1.4–12.5). There was no significant difference in G-CSF dose between patients that were successfully harvested compared with patients with harvest failure after ICE (median dose 8.1 vs. 7.5, $P = 0.39$).

Discussion

In Scandinavia, the most commonly used second-line regimen for aggressive lymphoma during the last 10 yr has been MIME (mitoguazone, ifosfamide, methotrexate, etoposide) (7).

In a Swedish series, the ORR was 59% (20 of 34) in relapsed and 44% in primary progressive disease with this regimen (8).

A recent report from Oslo (Norway), describes results regarding stem cell mobilization with MIME. In this series, a PBSC harvest $> 2 \times 10^6$ CD34⁺/kg was obtained in 83% (90 of 108) (9).

In comparison, the results of the present study demonstrate a response rate after ICE that is similar to MIME, both in relapsed and primary progressive disease. In contrast, the results regarding PBSC mobilization are clearly inferior, with only 50% obtaining a PBSC harvest $> 2 \times 10^6$ CD34⁺/kg.

Furthermore, our results are noticeably worse both in terms of ORR and stem cell mobilization compared with the original report by Moskowitz *et al.* (5).

One explanation for this may be the higher median age in our series of patients, 57 vs. 48 yr. However, the results in patients > 60 yr were not inferior compared with younger patients in our series. Another possible explanation for the inferior harvest yield may be related to the PBSC mobilizing G-CSF dose. Moskowitz *et al.* (5) used consistently a dose of 10 μ g/kg, whereas the dose in our series ranged between 4 and 10 (median 7.0). However, we found no significant difference in G-CSF dose between harvested patients and harvest failures.

Alternative second-line regimens in aggressive lymphoma are DHAP (dexamethasone, cytarabine, cisplatin), ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin), and dexa-BEAM (dexamethasone, carmustine, etoposide, cytarabine, melphalan). Response rates to dexa-BEAM have been reported to be lower compared with other regimens, and exposure to stem cell toxic drugs (carmustine, melphalan) is associated with inferior PBSC harvest results (10). In a small series with DHAP ($n = 14$), the ORR was 86% and median PBSC harvest results was 2.6×10^6 CD34⁺/kg (11). A potential disadvantage with cisplatin-based regimens (DHAP, ESHAP) is nephrotoxicity, which may complicate the high-dose chemotherapy.

As no randomized trials have been performed in this setting, differences in outcome and PBSC harvest results may be due to differences in patient populations, previous therapy, and indication for second-line therapy. At the moment, there are two ongoing phase III trials in relapsed patients, one comparing ICE and DHAP, both in combination with rituximab, named the CORAL trial, by the GELA group and others, one comparing ESHAP and ESHAP + rituximab, by the Spanish National Lymphoma Group.

Awaiting results from randomized trials, our results do not support the use of ICE as a standard second-line regimen in aggressive lymphoma.

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