Outpatient fractionated ifosfamide, carboplatin and etoposide as salvage therapy in relapsed and refractory non-Hodgkin’s and Hodgkin’s lymphoma

M. S. Hertzberg1*, C. Crombie2, W. Benson1, J. Taper2, D. Gottlieb1 & K. F. Bradstock1

1Department of Haematology, Westmead Hospital, Westmead NSW 2145, Australia; 2Cancer Care Centre Nepean Hospital, NSW, Australia

We have treated 75 transplant-eligible patients with relapsed or refractory lymphoma using an outpatient-based fractionated regimen of ifosfamide, carboplatin and etoposide (ICE) for both salvage and stem cell mobilisation. Patients included DLBCL (n = 33), follicular (n = 23), NK/T-cell (n = 3), mantle cell (n = 3) and Hodgkin’s lymphoma (n = 13). Cycles of outpatient ICE were given every 21 days and consisted of: ifosfamide 5000 mg/m² i.v. fractionated into three equally divided doses and infused over 2–3 h on days 1–3, carboplatin (mg dose = 5 · AUC) i.v. over 1 h on day 1; and etoposide 100 mg/m² i.v. daily on days 1–3, plus filgrastim 5 µg/kg/day. Most patients with indolent lymphoma also received rituximab. The median age of patients was 52 years (range 26–69 years). Patients received a mean of 2.8 cycles of ICE. Non-haematological toxicities included grade 1/2 CNS toxicity in four patients, cardiac toxicity in two, reversible renal impairment and haematuria in one each. Haematological toxicity included grades III/IV thrombocytopenia and neutropenia with at least one cycle of ICE in 71% and 72% of patients, respectively. The median time to PBSC harvest was 14 days (range 10–20 days), while the median CD34+ cell yield was 4.8 × 10⁶/kg (range 2.3–37.8). Five patients (7%) failed to mobilise PBSCs. The overall response rate to ICE was 89%, comprising 29% who achieved a CR and 60% who achieved a PR; for DLBCL, the overall response rate was 85% including 36% who achieved a CR and 49% who exhibited a PR. At a median follow-up of 24 months, the Kaplan–Meier estimates of the overall and event-free survival for all patients were 65% and 42%, respectively. For patients with DLBCL overall and event-free survival figures were 51% and 35%, respectively, at a median follow-up of 14 months. These data confirm the efficacy and tolerability of outpatient fractionated ICE as both a salvage and mobilisation regimen in relapsed/refractory lymphoma.

Key words: salvage, relapsed/refractory, lymphoma, transplant, mobilisation, toxicity

introduction

For patients with relapsed or refractory aggressive non-Hodgkin’s lymphoma (NHL) and Hodgkin’s lymphoma (HL) high-dose chemotherapy (HDCT) followed by stem cell transplantation (SCT) offers the potential for disease cure [1–4]. However, those who appear to benefit most from this approach have disease that is sensitive to second-line salvage chemotherapy [1–4]. A number of salvage regimens have been used in the treatment of patients with relapsed or refractory NHL and HL [5–7]. Although each of these is characterised by the ability to achieve significant cytoreduction, they differ with respect to their relative toxicities, both haematological and non-haematological, as well as their ability to mobilise sufficient numbers of peripheral blood stem cells (PBSCs). Some of the recently described salvage regimens in NHL and HL, in particular those incorporating ifosfamide, have enabled adequate numbers of PBSCs to be collected with minimal organ toxicity [8–11]. The ICE salvage regimen, which uses infusional ifosfamide together with carboplatin and etoposide, has been used successfully in transplant-eligible patients with relapsed/refractory NHL [9, 10] and HL [11]. More recently, lymphoma salvage regimens, including ICE, have incorporated the anti-CD20 monoclonal antibody rituximab with early encouraging results [12, 13].

The originally described ICE regimen requires the administration of ifosfamide as a 24-h continuous intravenous infusion in hospital [9, 10]. In large university teaching hospitals the pressure on bed availability can be a major impediment to the delivery of multiple cycles of chemotherapy on time, such that chemotherapy administered as an outpatient often proves to be a more practicable and cost-effective approach. Accordingly, we have used an outpatient-based regimen of fractionated ICE chemotherapy for both salvage and PBSC mobilisation in transplant-eligible patients with relapsed or refractory NHL and HL.

patients and methods

patients

Patients included in the study were transplant-eligible if they were >16 years but <70 years of age, had an ECOG performance status of <2 and were HIV
negative. They included individuals who were diagnosed with relapsed or refractory NHL and HL. Patients with diffuse large B-cell lymphoma (DLBCL) and NK/T-cell lymphoma were eligible if their disease was in first relapse or they had primary refractory disease to cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP)-like chemotherapy.

fractionated ICE chemotherapy regimen
Outpatient-based ICE chemotherapy consisted of: ifosfamide \(5000\, mg/m^2\) fractionated into three equally divided doses together with an equivalent dose of mesna as an intravenous (i.v.) infusion over 2–3 h daily for 3 consecutive days; carboplatin \(5 \times AUC\) on day 1 (max. 800 mg) as a 1-l i.v. infusion over 1 h; and etoposide \(100\, mg/m^2\) i.v. daily for days 1–3 over 30 min. Oral mesna 2000 mg was also given at 2 h and 6 h after each ifosfamide dose. Filgrastim 5 \(\mu g/kg\) daily was administered from day 4+5. Cycles of ICE chemotherapy were intended for administration every 21 days as an outpatient. It was planned to deliver three cycles of ICE to patients with NHL and at least two cycles to patients with HL. Of the 23 patients with follicular or small lymphocytic lymphoma, 18 patients also received rituximab 375 \(mg/m^2\) i.v. for four doses given at weekly intervals commencing with cycle one of their ICE therapy. It was intended for patients who were chemo-responsive to ICE to proceed to either autologous SCT or allogeneic transplantation with reduced-intensity conditioning (in follicular/SLL or mantle cell lymphoma patients only). Survival was calculated from the date of commencement of the first ICE cycle.

PBSC mobilisation
Peripheral blood stem cells were collected in chemo-responders after the second or third cycle of fractionated ICE. Initially, for stem cell mobilisation G-CSF (filgrastim) at a dose of 5 \(\mu g/kg\) was administered from day 4+5 until the completion of leukapheresis. More recently, filgrastim at a dose of 10 \(\mu g/kg/day\) has been used for the PBSC mobilisation. Leukapheresis was initiated when the CD34\(^+\) count in the peripheral blood was more than 20\(/l\) and continued until at least 2.0 \(\times 10^6\) CD34\(^+\) cells/kg were collected. For each apheresis, 12 l of blood were processed over a 3-h time frame using a Cobe Spectra.

high-dose chemotherapy and stem cell transplantation
Chemoresistant patients were transplanted as soon as possible after the completion of ICE therapy. ICE-refractory patients received either alternative protocols or palliation. For patients undergoing autologous SCT, the high-dose conditioning regimen was either BEAM for patients with NHL or CBV for those with HL. Seven patients with follicular and one with mantle cell lymphoma proceeded to a reduced-intensity allogeneic transplant from an HLA-compatible sibling and received conditioning therapy with fludarabine 25 mg/m\(^2\) i.v. daily for 5 days and cyclophosphamide 60 mg/kg i.v. daily for 2 days.

results
patient characteristics
A total of 75 transplant-eligible patients with relapsed or refractory lymphoma were included (Table 1). The study involved patients with DLBCL \(n = 33\), NK/T-cell lymphoma \(n = 3\), follicular (FL) or small lymphocytic lymphoma \(n = 23\), mantle cell lymphoma \(n = 3\) and HL \(n = 13\). Twenty-five per cent of patients \(n = 19\) were considered chemorefractory, including 36% \(12/33\) with DLBCL, 22% \(5/23\) with FL and 15% with HL \(2/13\). The remaining 56 patients had relapsed disease. The median age of patients was 52 years (range 26–69 years), while 20% of patients were \(\geq 60\) years of age. Sixty-five per cent of patients had advanced stage disease (stage III, \(n = 18\); stage IV, \(n = 31\)). Patients received a mean of 2.8 cycles (range 1–4) of ICE.

response to ICE
The overall response rate to ICE salvage therapy was 89% \(n = 67\), comprising 29\% \(n = 22\) who achieved a complete response (CR) and 60\% \(n = 45\) who achieved a partial response (PR); 11\% \(n = 8\) remained ICE-refractory. Among patients with DLBCL receiving ICE, 36\% \(n = 12\) achieved a CR, 49\% \(n = 16\) obtained a PR and 11\% \(n = 5\) remained ICE-refractory. Of the 19 patients refractory to prior chemotherapy, five (26\%) remained refractory to ICE salvage therapy and 14 (74\%) were ICE-responsive. Of these 14 responding patients, 13 achieved a PR and one had a CR to ICE therapy. Included among the 19 chemoresistant patients were 12 patients with DLBCL of whom nine (75\%) achieved a PR and three (25\%) remained refractory to ICE salvage. Two of the ICE-refractory patients with DLBCL achieved a partial response to alternate salvage therapy and proceeded to autologous transplantation, but relapsed soon afterwards and died.

Patients with HL were highly responsive to salvage therapy with the fractionated ICE regimen. Of the 13 patients with HL, 10 had relapsed after first-line therapy, one after second-line treatment and two were refractory to induction therapy. All 13 patients responded to ICE therapy, of whom 31\% achieved a CR and 69\% obtained a CR. One patient who had relapsed after second-line treatment experienced a PR after ICE therapy, had a delayed autograft due to non-compliance and relapsed at 10 months following HDCT and ASCT. Two patients have relapsed post-transplant and are currently alive in partial remission following further salvage therapy. An additional patient died in CR of a post-transplant pneumonitis. The remaining nine

<table>
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(69%) ICE-responsive patients are alive in CR at a median follow-up of 30 months.

**toxicity to ICE**
The mean number of ICE cycles delivered was 2.8. Forty-seven patients received three cycles and 19 patients received two cycles of ICE therapy; one patient received one cycle, while eight received four cycles of ICE. There were no toxic deaths while non-haematological toxicities secondary to the ICE therapy included three patients with grade 1 and one with grade 2 CNS toxicity, one with gross haematuria and one with significant but reversible nephrotoxicity. Two patients exhibited cardiac toxicity including one who developed atrial fibrillation and one with congestive cardiac failure who had an already impaired left ventricular ejection fraction of 35% prior to ICE. The major toxicity experienced was haematological and included thrombocytopenia grades III (20%) or IV (51%) and neutropenia grades III (17%) or IV (55%) with at least one cycle of ICE. Febrile neutropenia necessitating admission to hospital occurred in 18 patients. Neutropenia was brief and tended to have a nadir which occurred around days 9–11 after treatment.

**PBSC harvest**
PBSCs were collected following the second or third cycle of ICE therapy in 61 patients. In two patients, PBSCs had been collected previously. A total of five patients (7%) failed to mobilise sufficient numbers of stem cells, of whom four required a bone marrow harvest (one progressed on ICE). The median time to PBSC harvest was 14 days (range 10–20 days), while 78% of patients were harvested between days 13 and 15 after ICE. The median CD34+ cell yield was $4.8 \times 10^6$/kg (range 2.3–37.8 $\times 10^6$/kg). Among the 61 patients in whom PBSCs were collected, 55 patients required one leukapheresis, five required two leukaphereses while one patient required three leukaphereses. The yield of CD34+ cells/kg using G-CSF at a daily dose of 10 μg/kg/day ($n = 35$, including five failures) versus 5 μg/kg/day ($n = 23$) were similar at $4.3 \times 10^6$ and $5.0 \times 10^6$, respectively. The mobilisation-adjusted response rate (overall response rate minus mobilisation failures) was 82%.

**transplantation**
Of the 67 patients responding to ICE, 59 underwent an autologous SCT and eight had a reduced-intensity allogeneic SCT from an HLA-compatible sibling (one also had an autograft). Nine patients did not proceed to transplant including six ICE-refractory patients and three responding patients, one of whom progressed just prior to SCT. In addition, one 69-year-old patient exhibited cardiac and renal toxicity precluding transplantation and one 68-year-old responding patient did not proceed to SCT because of a poor performance status. There was one transplant-related death, while the 100-day peri-transplant mortality was 7.6% (5/66) including three patients with early disease progression post-transplant.

**event-free and overall survival**
The median follow-up period for the entire patient cohort is approximately 24 months. Kaplan–Meier estimate of the proportion of patients alive and event-free at 24 months is 65% and 42%, respectively (Figure 1). The median follow-up period for the group with DLBCL is 14 months, while the Kaplan–Meier estimate of the proportion of patients alive and event-free is 51% and 35%, respectively (Figure 2). Altogether,
there have been 31 deaths, including disease progression on or after ICE ($n=5$), post-transplant disease progression ($n=21$), infection ($n=3$), graft versus host disease ($n=1$) and intra-abdominal bleeding ($n=1$).

Event-free survival of patients with DLBCL appeared to vary with the response to ICE salvage therapy. At a median follow-up time of 14 months, the event-free survival for DLBCL patients who achieved a CR and PR after ICE was 49% and 35%, respectively, although this difference was not statistically significant (Figure 3). There was no difference in overall survival for patients with DLBCL who achieved a CR after ICE (58%) and those who achieved a PR after ICE (55%) (Figure 4). The few patients with DLBCL who failed to respond to ICE had a median survival duration of approximately 6 months.

**discussion**

In the present study, we confirm the efficacy and tolerability of an outpatient-based fractionated ICE chemotherapy regimen for both salvage and stem cell mobilisation for relapsed/refractory NHL and HL. Such an approach has enabled all patients to receive salvage chemotherapy in an outpatient setting, circumventing the frequently encountered difficulties in ensuring inpatient admission to large haematology units and transplant centres on a regular and predictable basis. In contrast, alternative salvage chemotherapy such as DHAP, ESHAP, EPOCH, dexamethasone-BEAM and infusional ifosfamide-containing regimens all require inpatient administration with the attendant disadvantages of cost, inconvenience and pressure on bed availability [2–7].

Response rates to commonly used second-line regimens for patients with relapsed or refractory aggressive lymphoma vary between 35% and 80% [3, 5–7]. In the present study of fractionated ICE, rates of CR and PR for the entire cohort were 29% and 60%, respectively, while rates of CR and PR for the group of patients with DLBCL were 36% and 49%. These results are similar to those reported in the original ICE study in patients with aggressive NHL, in which the rates of CR and PR were 23% and 44%, respectively [9]. Furthermore, although the median follow-up time for patients with DLBCL is relatively short at 14 months, overall and event-free survival rates of 51% and 35%, respectively, are similar to those reported in the original ICE study at a similar early stage of follow-up [9].

Patients with aggressive NHL who achieve a CR to salvage therapy appear to exhibit a more favourable outcome following transplantation than those who achieve a PR to salvage [9]. In the original ICE study, for NHL patients proceeding to HDCT and SCT, the OS for those in CR (65%) was significantly better than that for patients in PR (45%), at a median follow-up of 40 months [9]. Updated results of that study indicate that overall survival differences between those patients achieving a CR and those achieving a PR after ICE are no longer statistically significant [14]. In the present study, for DLBCL patients, there was also a non-significant trend towards an improved EFS for those who achieved a CR after ICE (49%) compared with those who achieved a PR after ICE (35%), at a median follow-up time of 14 months. Furthermore, at this early stage there is no difference in overall survival for patients with DLBCL who achieved a CR after ICE (58%) and those who achieved a PR after ICE (55%).

Recently, salvage regimens have incorporated monoclonal antibody therapy using rituximab in patients with aggressive NHL [12, 13]. Rituximab when added to ICE in patients with relapsed or primary refractory DLBCL appears to double CR.
rates from 27% to 53% when compared with historical controls receiving ICE, while the overall response rates are similar [12].

The critical question is whether improving the CR rate will translate into improved outcomes after ASCT. Notably, the ‘CORAL’ randomised study initiated by the Groupe d’Etudes des Lymphomes Adultes (GELA), which is comparing rituximab plus either ICE or DHAP salvage therapy administered every 21 days, will address this issue as well as whether disease status and secondary age-adjusted IPI affect response rates to rituximab-containing salvage therapy.

In HL, ICE therapy is a particularly effective salvage therapy since in a recent study among 65 patients with relapsed/ refractory HL, infusional ICE therapy resulted in CR and PR rates of 26% and 58%, respectively [11]. Although the present study included relatively small numbers of patients with HL, nevertheless, the remission rates of 31% (CR) and 69% (PR) are similar to those reported previously for the infusional ICE regimen. At a median follow-up of 30 months, 11 patients (85%) are alive, of whom nine are in ongoing CR, and two are in PR following further salvage treatment.

Patients with primary chemorefractory lymphoma, particularly DLBCL, have poor prognoses. The role of HDCT and ASCT is less clear in these patients, however, recent data indicates that for those patients displaying chemosensitivity to the salvage regimen HDCT/ASCT may be effective [10, 15]. Indeed, among patients with chemoresistant disease, EFS is equivalent for patients with primary refractory disease or relapsed disease [10]. In the present study, of the 19 patients refractory to prior chemotherapy, five (26%) remained refractory to ICE salvage therapy and 14 (74%) were ICE-responsive. Included among the 19 refractory patients were 12 patients with DLBCL of whom nine (75%) achieved a PR and three (25%) remained refractory to ICE salvage.

Notwithstanding the small numbers in this cohort, these results are similar to those reported for infusional ICE in primary refractory patients with aggressive NHL [10].

Organ toxicity associated with both the 24-h infusional and outpatient fractionated ICE regimens is quite low in comparison with other salvage regimens incorporating cisplatin and cytarabine, such as DHAP and ESHAP [5–7]. In the present study, one patient exhibited gross haematuria, while reversible nephrotoxicity was also seen in one patient. Two patients developed cardiac toxicity, including atrial fibrillation in one patient and cardiac failure in one patient who had an already impaired left ventricular ejection fraction. ICE-related toxicity precluded transplantation in two patients, including a 69-year-old patient who developed cardiac and renal toxicity. Ifosfamide-induced encephalopathy has been observed previously among patients receiving bolus administration [16, 17]. Reassuringly, the incidence of CNS toxicity seen with fractionated outpatient ifosfamide was low, since only four patients experience grade I/II confusion. This incidence is similar to that reported in association with the infusional ICE regimen [9–11].

Mobilisation of PBSCs is a critical requirement for salvage chemotherapy regimens. The outpatient fractionated ICE regimen proved to be highly effective at mobilising sufficient numbers of CD34+ PBSCs. The median number of CD34+ cells/kg collected after ICE and G-CSF was 4.8 × 10⁶/kg, with the vast majority of patients (55 of 61) requiring only onepheresis procedure. Moreover, only five patients (7%) failed to mobilise sufficient numbers of PBSCs. The above yields of PBSC are slightly less than those associated with the infusional ICE or RICE regimens, in which CD34+ cell yields were 7.0 and 8.4 × 10⁶/kg, respectively, although the median number ofpheresis procedures was three for each regimen [9–12].

The frequency of administration of cycles of fractionated ICE in the present study differed from that in the original studies of infusional ICE [9–11]. In the modified fractionated ICE regimen, the three courses are delivered as an outpatient every 21 days, i.e. the three cycles are completed within a total of 45 days. In the original infusional ICE regimen the aim was to deliver the three courses of therapy within a period of 31 days, i.e. at cycle intervals of 2 weeks. However, for the patients who received all three cycles of ICE, the actual achieved median time for completion of treatment in the study was 38–39 days due to dosage delays [9]. Notably, in the study using R-ICE the median time to completion of three cycles was 45 days (range 35–59) primarily because of grade 3 or 4 haematological toxicity [12].

In the current outpatient-based fractionated ICE regimen the delivery of three cycles of ICE over a total of 45 days represents a potential mild reduction in relative dose-intensity. Nevertheless, the frequency of haematological toxicity appeared to be slightly greater than that seen with the infusional ICE regimen, since grade IV neutropenia and thrombocytopenia were each experienced on at least one occasion by 55% and 51% of patients, respectively, versus less than 15% of ICE cycles in the original study [9]. Furthermore, the neutrophil nadir was perhaps slightly more delayed in the outpatient-based ICE regimen occurring at around days 9–11 versus days 7–9 with the infusional regimen [9]. Accordingly, it is possible that the dose-intensity of the fractionated ICE regimen, as reflected in the increased haematological toxicity, is slightly greater than that associated with the infusional ICE regimen and so compensates for the effect of the cycle interval change. The cause of the differences in haematological toxicity between the two studies may relate to the pharmacokinetics of ifosfamide when administered in a fractionated schedule over 3 days. To date, the few studies comparing a short versus a long infusional ifosfamide regimen in cancer patients have failed to show convincing evidence of a difference in either pharmacokinetics, response rates or haematological toxicity [17]. However, recent preliminary data suggests that the AUC for ifosfamide given as a brief infusion on consecutive days may be greater than that for the same total dosage infused over 24 h [18].

In summary, an outpatient-based fractionated ICE chemotherapy regimen is both effective and tolerable in patients with relapsed/refractory NHL and HD and enables successful mobilisation of peripheral blood stem cells in the vast majority of patients.

references


