Bone Marrow Transplantation (2007) 40, 1019–1025

www.nature.com/bmt

ORIGINAL ARTICLE

IGEV regimen and a fixed dose of lenograstim: an effective mobilization regimen in pretreated Hodgkin's lymphoma patients

M Magagnoli[1], M Spina[2], M Balzarotti[1], I Timofeeva[1], L Isa[3], M Michieli[2], R Capizzuto[1], E Morenghi[1], L Castagna[1], U Tirelli[2] and A Santoro[1]

[1]*Department of Medical Oncology and Hematology, Istituto Clinico Humanitas, Rozzano, Milan, Italy;* [2]*Department of Medical Oncology, Centro di Riferimento Oncologico, Aviano, Italy and* [3]*Division of Internal Medicine, San Luigi Hospital, Gorgonzola, Italy*

We explored the efficacy of the IGEV regimen (ifosfamide, gemcitabine, vinorelbine and prednisone) combined with a fixed dose of lenograstim (263 µg/day) to mobilize peripheral blood stem cells (PBSCs) in 90 Hodgkin's lymphoma patients. The median total CD34+ cells/µl peak, colony-forming units granulocyte–macrophage and white blood cells for all individual collection sets were 85/µl, 12×10^4/kg and 20 700/µl, respectively. An adequate number of CD34+ cells (more than 3×10^6 or 6×10^6 CD34+ cells/kg depending on whether single or tandem high-dose chemotherapy was used) were collected in 89 out of 90 (98.7%) mobilized patients, whereas the only failure reached 2.3×10^6 CD34+ cells/kg. The median CD34+ cell collections were 11×10^6/kg (range 2.3–39×10^6/kg) and 10×10^6/kg (range 6–22.0×10^6/kg) with a median of 1 and 2 leukapheresis for patients eligible for single high-dose treatment and for candidates for tandem transplant, respectively. Target yields were reached in 71.43 and 49.09% and additionally in 17.14 and 43.64% of cases after the first and second apheresis procedures, respectively. Hematological and non-hematological side effects were acceptable, and no toxic deaths occurred. Thirty-four patients received a single and 47 received tandem transplantation with rapid engraftment. These results confirm that the IGEV regimen with lenograstim support can be used successfully and safely to mobilize PBSCs.

Bone Marrow Transplantation (2007) **40,** 1019–1025; doi:10.1038/sj.bmt.1705862; published online 1 October 2007
Keywords: PBSC mobilization; CD34+ cells; combination chemotherapy; lenograstim; Hodgkin's lymphoma

Introduction

Despite high-dose chemotherapy (HDCT) with autologous peripheral blood stem cell (PBSC) support being universally recognized as the gold standard for recurrent/refractory Hodgkin's lymphoma (HL), the optimal induction regimen, has yet to be defined clearly.[1–4] An ideal salvage regimen should combine a high response rate with acceptable hematological and non-hematological toxicities, and the ability to mobilize a sufficient number of hematopoietic progenitors for rapid and stable engraftment after HDCT.

Most previous reports on HDCT do not provide data on CD34+ cell mobilization, and details on PBSC mobilization and collection are reported in a limited number of studies.[5–19]

Recently we completed a phase II trial of gemcitabine combined with ifosfamide, vinorelbine and prednisolone (IGEV) in patients with refractory or recurrent HL, and reported a high response rate.[20] The study objectives were to evaluate the mobilizing potential of IGEV chemotherapy in 90 patients, to explore issues related to stem cell yield and optimal timing for harvesting, and also to identify risk factors affecting collections. We also compared the IGEV regimen with the most common salvage chemotherapy combinations reported in the literature.

Patients and methods

Patients

From November 1997 to July 2006, 105 patients with relapsed or primary refractory HL after chemotherapy with or without radiotherapy were placed on a study protocol consisting of four cycles of combined ifosfamide, gemcitabine, vinorelbine and prednisone (IGEV). The protocol was approved by the ethics committee and written informed consent was obtained from all participants. Fifteen patients were not mobilized for various reasons, specifically progression before the third IGEV cycle in six cases, assignment to allogeneic transplantation in eight cases and because HDCT had not been planned in one case. All 90 mobilized patients had received at least one previous chemotherapy combination ranging from four to eight

Correspondence: Dr M Magagnoli, Department of Medical Oncology and Hematology, Istituto Clinico Humanitas, Via Manzoni 56, Rozzano (Milano), Milano 20089, Italy.
E-mail: massimo.magagnoli@humanitas
Received 24 April 2007; revised 13 July 2007; accepted 13 July 2007; published online 1 October 2007

courses as a function of the initial stage of the disease. Most patients (80%) had been treated with one regimen, the range being from one to four. All patients received an anthracycline-containing regimen.

Chemotherapy and stem cell collection

As already described,[20] IGEV (ifosfamide 2000 mg/m^2 intravenously (i.v.) on days 1–4 with mesna uroprotection, gemcitabine 800 mg/m^2 i.v. on days 1 and 4, vinorelbine 20 mg/m^2 i.v. on day 1, prednisolone 100 mg i.v. on days 1–4, of each 3-week course) was administered on an outpatient basis. Mesna was given at a dose of 900 mg/m^2 i.v. at 0, 2 and 4 h after ifosfamide.

A fixed dose of lenograstim (263 μg/day) was given from day 7 to day 12 of each course or up to apheresis during the mobilizing phase. Four courses of chemotherapy were planned, provided that at least partial remission was evidenced after the second cycle. Tumor manifestations were reassessed after the second and fourth treatment cycles using the same baseline imaging technique throughout the study. PBSC collection was performed after the first or second course in the first 11 patients, to test the mobilizing potential of the regimen, and thereafter after the third treatment course whenever an objective response was observed. A target yield of at least 3×10^6 CD34+ cells per kg of body weight was planned to support each high-dose chemotherapy. A PBSC yield below 3.0×10^6/kg was considered a failure. According to our protocols during different periods, patients were assigned to receive a single HDCT procedure with thiotepa–melphalan (thiotepa 600 mg/m^2 i.v. on day 1; melphalan 140 mg/m^2 i.v. on day 3) up to January 2001, and after that a tandem transplant procedure with melphalan 200 mg/mq[1] i.v. followed by BCNU, etoposide, cytarabine, melphalan (BCNU 300 mg/m^2 i.v. on day 1; Ara-C 400 mg/m^2 i.v. on days 2–5; VP-16 200/mg/m^2 i.v. on days 2–5; melphalan 140 mg/m^2 i.v. on day 5) within 90 days.[21]

Leukapheresis and stem cell cryopreservation

All patients underwent a routine complete blood count every other day starting from day 7 after each chemotherapy course. During the mobilization cycle, daily peripheral blood CD34+ monitoring was started when the ANC reached 1×10^9/μl, and apheresis was performed when the peripheral blood CD34+ cell count exceeded 10 cells/μl. CD34 cells were harvested using a COBE Spectra separator (COBE, Lakewood, CO, USA), software version 5.1 and 6.0, with a collection pump speed of 2400 g/min. Blood was collected via a central venous access device or from peripheral veins, and the patient's estimated blood volume was processed 2.7 times. Stem cells were cryopreserved using a Nicol Plus PC device (Air Liquide, DMC, Marne La Vallée, France) and a mixture of autologous plasma and DMSO (LiStarFISH; final concentration 10%), and then stored in liquid nitrogen.

CD34+ count

CD34+ count was performed on aliquots of apheresis samples using a single platform flow cytometric method based on International Society for Haematotherapy and Graft Engineering gating strategy: 100 μl of diluted cells was incubated in tubes containing antibodies against CD45-FITC/CD34-PE (Stem-kit Reagent, Immunotech, Beckman Coulter, Paris, France) and a viability dye 7-amino actinomycin D (7-AAD). Cells were lysed with NH_4Cl. All tubes were incubated for 20 min at room temperature, protected from light. Prior to acquisition of the sample, 100 μl of Stem-Count Fluorospheres or Flow-Count Fluorospheres was added to each tube. A Beckman Coulter Cytomics FC 500 flow cytometer with CXP software package was used for data acquisition and analysis. Alignment and calibration were performed daily by means of Coulter Flow-Check and Flow-Set fluorospheres. One hundred thousand CD45+ events were collected in the cytofluorimeter. The absolute count was expressed as number of cells per microliter. The absolute CD34+ cell number per apheresis pack was obtained by multiplying the absolute count per microliter by dilution factor, pack volume (in milliliters) and by 10^6 (to convert cell/μl to cell $\times 10^6$/pack).

CFU-GM

Human clonogeneic progenitor assays were performed by plating stem cell populations at a concentration ranging between 1×10^4 cells and 1×10^5 cells into a methylcellulose formulation (MethoCult H4534, Stem Cell Technologies, Vancouver, British Columbia, Canada) containing 30% fetal bovine serum, 1% bovine serum albumin, 5% serum-containing phytohemagglutinin-stimulated human leukocyte conditioned medium, 10^{-4} M 2-mercaptoethanol, 2 mM L-glutamine, 2 U/ml erythropoietin, 100 U/ml penicillin, 0.4 mg/ml streptomycin and 1% methylcellulose in Iscove's MDM. Duplicate cultures were plated and incubated at 37 °C in a humidified atmosphere of 5% carbon dioxide. Differential colony counts were scored after 14 days by morphological characteristics using an inverted microscope.

Engraftment assessment

Engraftment was defined as the first day when ANC of 0.5×10^9/l was reached (lasting for at least 3 days) after the initial nadir post peripheral blood stem cell transplant.

Various definitions are used to describe platelet engraftment; we applied the International Bone Marrow Transplant Registry (IBMTR) criteria, according to which the day of platelet engraftment is defined as the first day of three consecutive complete blood counts with platelets of 20×10^9/l after the initial nadir post peripheral blood stem cell transplant in the absence of platelet transfusion.

Statistical analysis

Data were described as number and percentage or median and range where appropriate. Spearman's correlation test was used to compare CD34 cells/μl and CD34 leukapheresis products, and also CD34 μ/l and colony-forming units granulocyte–macrophage (CFU-GM)/kg. The Mann–Whitney *U*-test was applied to compare the influence of variables on CD34/kg, CFU-GM/kg and on the day of platelet and neutrophil recovery after high-dose

therapy. All calculations were performed with Stata 9 (www.stata.com).

Results

Stem cell collection

Leukapheresis was performed after the first, second, third and fourth cycles of chemotherapy in 4, 7, 71 and 8 patients, respectively. Patient characteristics are listed in Table 1. The time from the first day of IGEV to the first day of leukapheresis was 13 days (range 10–17). Seventy-six percent (69/90) of patients began the harvesting procedure between days 13 and 15. On the first day of apheresis, the following laboratory values were observed: median number of white blood cells 20 700/μl (range 1700–58 450), hemoglobin 11.8 g/dl (range 9.7–15.3) and platelet count 87 000/μl (range 29 000–289 000). The median total CD34+ cells/μl peak and CFU-GM for all individual collection sets were 85/μl (range 16.6–482) and 12×10^4/kg (range 9.6–385), respectively.

An adequate number of CD34+ cells were collected in 89 out of 90 (98.7%) mobilized patients, whereas the only failed attempt reached 2.3×10^6 CD34+ cells/kg (Table 2). The median CD34+ cell collections were 11×10^6/kg (range $2.3–39.0 \times 10^6$/kg) and 10×10^6/kg (range 6.0–22.0×10^6/kg) with a median of 1 (range 1–3) and 2 (range 1–3) leukapheresis for patients eligible for single high-dose treatment and for candidates to tandem transplant, respectively. Overall the target yields of 3×10^6 and 6×10^6 CD34+ cells/kg were reached in 71.43 and 49.09% of cases, and additionally in 17.14 and 43.64%, after the first and second apheresis procedure, respectively. There were no significant differences in the total number of CD34+ cells per leukapheresis and the total number of CD34+ cells in patients weighing $\leqslant$ or >70 kg (Table 3). Patients who had been pretreated with chemotherapy alone mobilized a significantly larger number of CD34+ cells, with 12.2 $(3.5–39) \times 10^6$ CD34+ cells/kg compared with 9.7 $(2.3–28) \times 10^6$ CD34+ cells/kg ($P = 0.003$) collected in the group of patients pretreated with chemotherapy and radiotherapy. None of the other factors considered (Table 4) significantly affected the mobilizing potential of the chemotherapy regimen.

Treatment delivery and toxicity

Treatment compliance during chemotherapy was good, and no patient refused to complete the treatment program. Only one treatment toxicity-related admission to the hospital occurred. No treatment-related deaths have been documented so far. Out of 313 cycles evaluated, 13 (4.2%) were delayed and 27 (8.6%) reduced (75% of doses) mainly for neutropenia and thrombocytopenia. IGEV-related toxic effects were mild with a relatively low incidence of grade 3 and 4 toxicity according to WHO Common Toxicity

Table 1 Characteristics of mobilized patients before starting IGEV

Characteristics	*No. of patients*	*%*
Total	90	
Histology		
Nodular sclerosis	69	76.67
Others	21	23.33
Symptoms		
Yes	48	53.33
No	42	46.67
No. of involved sites		
$\leqslant 3$	46	51.11
>3	44	48.89
Extranodal involvement		
Yes	41	45.56
No	49	54.44
Previous regimen		
1	78	86.67
$\geqslant 2$	12	13.33
Bulky disease		
No	48	53.33
Yes	42	46.67
Disease status		
Refractory	33	36.67
Relapse	57	63.33
Previous radiotherapy		
Yes	56	62.22
No	34	37.78

Abbreviation: IGEV = ifosfamide, gemcitabine, vinorelbine and prednisone.

Table 2 Peripheral blood stem cell collection

Patients mobilized, total	90
Adequate CD34+ collection, total	89
Collection failure, total[a]	1
Day from IGEV, median (range)	13 (10–17)
CFU-GM cells, median (range)	12 (9.6–385)
WBC on first day of apheresis, median (range)	20 700 (1700–58 540)
CD34+ cell peak/μl, median (range)	85 (16.6–482)
Single HDCT	35
Median CD34+ cells collected (range)	11 (2.3–39)
Median apheresis procedures (range)	1 (1–3)
Tandem HDCT	55
Median CD34+ cells collected (range)	10 (6.0–22)
Median apheresis procedures (range)	2 (1–3)

Abbreviations: CFU-GM = colony-forming unit granulocyte–macrophage; HDCT = high-dose chemotherapy; IGEV = ifosfamide, gemcitabine, vinorelbine and prednisone.
[a]2.3×10^6 CD34+ cells/kg.

Table 3 Median CD34+ cells collected (range) according to weight

Weight	*Number of patients*	*CD34+ median*	P
$\leqslant 50$ kg	2	14.45 (12.6–16.3)	
>50–60 kg	22	10.5 (2.3–28)	
>60–70 kg	25	9.8 (3.22–29)	
>70 kg	41	10.2 (5.6–39)	
$\leqslant 70$ kg as a group	49	10 (2.3–29)	0.6726

Table 4 Median CD34+ cells/kg collected (range) as a function of several parameters

Parameter	*Number of patients*	*CD34+/kg, median (range)*	P
Prior radiotherapy			
Yes	56	9.7 (3–28)	**0.003**
No	34	12.2 (2.3–39)	
Number of chemotherapy regimens before IGEV			
1	78	10 (2.3–39)	0.92
>1	12	11.05 (5.9–28)	
Age			
<40 years	66	10.25 (3–28)	0.76
⩾40 years	24	10 (2.3–39)	
Chemotherapy at first line			
ABVD	34	10 (4.9–23)	0.69
Other regimens	56	10.4 (2.3–39)	
Time elapsed from last chemoradiotherapy			
<6 months	33	10.7 (3.5–39)	0.52
⩾6 months	57	10 (2.3–29)	

Abbreviations: ABVD = adriamycin, bleomycin, vincristine, dacarbazine; IGEV = ifosfamide, gemcitabine, vinorelbine and prednisone.
Significant *P*-value is in bold.

Criteria. Neutropenia was the most common hematologic toxicity, with grades 3–4 in 28% of courses. Platelet transfusion support was required in 15 cycles (4.4%), and red blood cells were transfused in 27 cycles (7.9%). Nausea and vomiting were mild and stomatitis occurred in 2% of patients. Peripheral neurotoxicity never exceeded grade II. Eleven grade II infections (3.0%) were documented, but all patients recovered rapidly.

Engraftment data

At present, engraftment data on 81 patients are available. Thirty-four patients received a single high-dose therapy procedure with thiotepa–melphalan, and 47 received tandem transplantation. One patient died from septic shock during the aplasia period following BCNU, etoposide, cytarabine, melphalan. Another patient died for unknown reasons the day after discharge from the bone marrow unit. After thiotepa—melphalan, the median number of reinfused $CD34^+$ cells was 11 (range 3–39) $\times 10^6$/kg, whereas in patients treated with tandem transplant the median number of reinfused $CD34^+$ cells was 4.5×10^6/kg (range 3–8.9) and 5×10^6/kg (range 3–12) after MEL200 and BEAM, respectively. Following thiotepa–melphalan, neutrophil recovery and platelet recovery were achieved after a median time interval of 10 (range 8–28) and 8 days (range 6–38), respectively. As for tandem HDCT, following both HDCT courses, the median time period to ANC $>0.5 \times 10^9$/l was 11 days (range 3–28), whereas a platelet count $>20 \times 10^9$/l was reached after 7.5 and 8 days following MEL200 and BCNU, etoposide, cytarabine, melphalan, respectively. The mean number of transfused platelets, red cell units and duration of fever following thiotepa and melphalan administration, and after the first and second HDCT of a tandem transplant were similar. No correlation was found between the number of CFU-GM or CD34+ cells reinfused, prior radiotherapy, the number of chemotherapy cycles and other factors, on the one hand, and the number of days to engraftment, on the other.

Costs

The mean cost of IGEV administered for four cycles was approximately 2800 Euros (700 Euros per course). This cost included the cost of the drugs, as well as their preparation and administration, and it is not much more than the common chemotherapy regimen used in relapsed/progressing HL (see Table 5). Furthermore therapy was administered on an outpatient basis and the very low hematological and non-hematological toxicity profile resulted in low toxicity-related costs.

Discussion

The current standard approach for relapsed/refractory HL consists of induction salvage therapy followed by HDCT plus PBSC support.[1,4] However, the best approach in terms of response rate and PBSC mobilization is still under investigation. Several platinum (DHAP, ASHAP or ESHAP) and ifosfamide-based (ICE, MIME, VIP, IIVP) combinations have been explored with superimposable results in terms of response rate ranging from 8 to 69% (Table 5). Recently, a high CR rate has been reported with a combination of ifosfamide, vinorelbine and gemcitabine,[20] supporting the use of this combination as pretransplant regimen in this patient subset.

The IGEV regimen was based on the results of previous trials including vinorelbine, gemcitabine and ifosfamide as single agents and ifosfamide plus vinorelbine. In various phase II studies, vinorelbine, as a single agent, showed response rates ranging from 35 to 90% even in patients already given vinca alkaloids and/or epipodophyllotoxins,[22] and ifosfamide given at high doses circumvented resistance to conventional doses of alkylating agents.[23] The efficacy of the combination of ifosfamide and vinorelbine as salvage and mobilizing stem cell regimen for poor prognosis lymphoma has been demonstrated.[7,8,24] Furthermore, several studies have suggested the efficacy of gemcitabine as single-agent therapy in patients with recurrent or refractory HL.[25,26] A multicenter trial of 23 patients demonstrated an overall response rate of 39%, with a very low toxicity profile.[27]

The mobilizing potential of the IGEV regimen has been investigated in this report, and the following findings have emerged.

The IGEV regimen followed by a fixed dose of lenograstim is an effective method for mobilization of CD34+ cells. In the present series, a successful harvest was obtained in 99% of patients, with only one failed attempt that reached 2.3×10^6 CD34+, which is considered sufficient to support an HDCT procedure.

The use of this regimen resulted in the successful collection of an adequate number of CD34+ cells (11×10^6/kg, range 2.3–39.0 $\times 10^6$/kg and 10×10^6/kg, range 6.0–22.0 $\times 10^6$/kg, with a median number of 1, range

Table 5 Overview of salvage regimens in Hodgkin's lymphoma (costs are expressed in Euros)

Regimen (ref.)	*Cost of cycle in Euros/m²*	*No. of patients*[a]	*Overall response (CR) %*	*CD34+ × 10⁶ (target)*	*CD34+ × 10⁶ collected (median)*	*Collection in a single apheresis (%)*	*No. of apheresis (median)*	*Succesfull collection (%)*	*G3-G4 toxicity % Neut/PLT*	*Engraftment ANC<0.5/PLT<20 in days (Median)*
DHAP[19]	300	105	NR	2.0	13.0	63	1	97	NR	NR
DHAP[10]	300	102	89 (21)	NR	6.1	NR	NR	96	68/69	NR
MINE[8]	350	100	75 (34)	NR	NR	NR	NR	NR	NR	NR
GVD[18]	1300	91	70 (19)	NR	NR	NR	NR	NR	63/14	NR
ESHAP[22]	280	78	52 (41)	NR	7.6	58	1	97	NR	9/9
ICE[14]	700	66	88 (26)	2.5	7.0	NR	3	86	NR	NR
ASHAP[17]	360	56	70 (34)	NR	NR	NR	NR	NR	100/NR	NR
Mini-BEAM[12]	200	55	84 (51)	NR	NR	NR	NR	NR	86/60	13/15[b]
MVC[5]	300	45	91 (44)	NR	NR	NR	NR	NR	61/47	NR
VIP[16]	300	42	67 (38)	NR	NR	45	1	NR	87/NR	NR
Mini-BEAM[11]	200	34	68 (20)	2.0	NR	NR	NR	NR	NR	NR
GDP[11]	590	34	62 (8)	2.0	NR	NR	NR	NR	NR	NR
IVE[13]	530	28	NR	2.5	5.4	NR	1	88	NR	NR
IFO-VNR[7]	460	26	77 (38.5)	NR	NR	NR	NR	NR	61/2	NR
PEND[9]	220	19	69 (16)	NR	NR	NR	NR	NR	100/NR	NR
GDP[6]	590	23	69.5 (17)	2.0	NR	NR	NR	NR	9/13	NR
IGEV[20]	700	90	83.4 (53)	3.0	11/10	71[c]/49[a]	1[c]/2[a]	98.7	28[c]/20[a]	10–11[c]/8–7.5[a]

Abbreviations: ASHAP = adriamicyn, solumedrol, cytosine arabinoside, cisplatin; DHAP = dexamethasone, cytarabine, cisplatin; DTIC = dacarbazine; ESHAP = etoposide, cisplatin, aracytin; GDP = gemcitabine, dexamethasone, cisplatin; GVD = gemcitabine, vinorelbine, pegylated doxorubicin; ICE = ifosfamide, carboplatin, etoposide; IFO-VNR = ifosfamide, vinorelbine; IGEV = ifosfamide, gemcitabine, prednisone, vinorelbine; IVE = ifosfamide, etoposide, epirubicin; MINE = mitoguazone, ifosfamide, vinorelbine, etoposide; MVC = mitoxantrone, vinblastine, CCNU; Mini-BEAM = BCNU, etoposide, cytarabine, melphalan; NR = not reported; PEND = prednisone, etoposide, mitoxantrone, DTIC; VIP = etoposide, ifosfamide, cisplatinum.

[a]Tandem transplant.

[b]PLT > 50 000 × mmc.

[c]Single transplant.

1–3 and 2, range 1–3) per apheresis procedure for patients eligible for single high-dose treatment, and for candidates to tandem transplant, respectively.

The required number of CD34+ cells were harvested after a single leukapheresis in about two-thirds of the patients.

Furthermore, IGEV and a fixed dose of lenograstim produced good mobilization results even in patients >70kg.

These high levels of stem cell mobilization are comparable to the results obtained with DHAP regimen with over 95% successful stem cell mobilizations reported;[10,19] however, these involved higher doses of G-CSF and patients who were able to receive only one transplant procedure. In the largest series reported in the literature, Smardova *et al*.[19] achieved a 97% rate of successful CD34+ collection in 105 patients after DHAP, but by mobilizing patients with a high dose of G-CSF (10 μg/kg/day), after the first cycle of chemotherapy, and requiring a minimum CD34+ harvest of 2×10^6/kg.[19]

In our study, PBSC collection was performed after the first or second course in only 11 patients, in order to test the mobilizing potential of the regimen. It was subsequently performed after a third course in the other patients, whenever an objective response was observed.

With reference to a fixed dose of G-CSF, to our knowledge, only one study in the literature has so far been reported on the use of chemotherapy plus a fixed dose of G-CSF for mobilizing HL patients. Akhtar *et al*.[28] achieved a 97% mobilization rate by using ESHAP plus G-CSF 300 μg s.c. b.i.d in 131 HL and non-HL patients. In this study, less than half of the patients weighed ⩾60 kg, and as a result most of them received over 10 μg/kg/day of G-CSF.[28]

In conclusion, our results strongly support the use of IGEV as a salvage induction regimen in patients with refractory or relapsed HL because of its high mobilizing potential associated with a favorable toxicity profile and a high response rate.

References

1 Linch DC, Winfield D, Goldstone AH, Moir D, Hancock B, McMillan A *et al*. Dose intensification with autologous bone marrow transplantation in relapsed and resistant Hodgkin's disease: results of a BNLI randomised trial. *Lancet* 1993; **341**: 1051–1054.

2 Magagnoli M, Castagna L, Balzarotti M, Demarco M, Santoro A. What is the best option to cure patients with resistant/relapse Hodgkin's disease? *Curr Stem Cell Res Ther* 2006; **1**: 419–424.

3 Schmitz N, Pfistner B, Sextro M, Sieber M, Carella AM, Haenel M *et al*. German Hodgkin's lymphoma Study group; lymphoma working party of the European group for blood and marrow transplantation. Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem cell transplantation for relapsed chemosensitive Hodgkin's disease: a randomized trial. *Lancet* 2002; **359**: 2065–2071.

4 Seyfarth B, Josting A, Dreyling M, Schmitz N. Relapse in common lymphoma subtypes: salvage treatment options for follicular lymphoma, diffuse large cell lymphoma and Hodgkin disease. *Br J Haematol* 2006; **133**: 3–18.

5 Alexandrescu DT, Karri S, Wiernick PH, Duthcher JP. Mitoxantrone, vinblastine and CCNU: long-term follow-up of patients treated for advanced and poor-prognosis Hodgkin's disease. *Leuk Lymphoma* 2006; **47**: 641–656.

6 Baetz T, Belch A, Couban S, Imrie K, Yau J, Myers R *et al*. Gemcitabine, dexamethasone and cisplatin is an active and non-toxic chemotherapy regimen in relapsed or refractory Hodgkin's disease: a phase II study by the National Cancer Institute of Canada Clinical Trials Group. *Ann Oncol* 2003; **14**: 1762–1767.

7 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**: 533–535.

8 Ferme C, Bastion Y, Lepage E, Berger F, Brice P, Morel P *et al*. MINE regimen as intensive salvage chemotherapy for relapsed and refractory Hodgkin's disease. *Ann Oncol* 1995; **6**: 543–549.

9 Ibrahim D, Smith MR, Varterasian M, Karanes C, Millenson M, Yeslow G *et al*. Phase II study of PEND chemotherapy in patients with refractory/relapsed Hodgkin lymphoma. *Leuk Lymphoma* 2004; **45**: 2079–2084.

10 Josting A, Rudolph C, Reiser M, Mapara M, Sieber M, Kirchner HH *et al*. Time-intensified dexamethasone/cisplatin/cytarabine: an effective salvage therapy with low toxicity in patients with relapsed and refractory Hodgkin's disease. *Ann Oncol* 2002; **13**: 1628–1635.

11 Kuruvilla J, Nagy T, Pintilie M, Tsang R, Keating A, Crump M. Similar response rates and superior early progression-free survival with gemcitabine, dexamethasone, and cisplatin salvage therapy compared with carmustine, etoposide, cytarabine, and melphalan salvage therapy prior to autologous stem cell transplantation for recurrent or refractory Hodgkin lymphoma. *Cancer* 2006; **106**: 353–360.

12 Martin A, Fernandez-Jimenez MC, Caballero MD, Canales MA, Perez-Simon JA, Garcia de Bustos J *et al*. Long-term follow-up in patients treated with mini-BEAM as salvage therapy for relapsed or refractory Hodgkin's disease. *Br J Haematol* 2001; **113**: 161–171.

13 McQuaker I, Haynes A, Stainer C, Byrne J, Russell N. Mobilisation of peripheral blood stem cells with IVE and G-CSF improves CD34+ cell yields and engraftment in patients with non-Hodgkin's lymphomas and Hodgkin's disease. *Bone Marrow Transplant* 1999; **24**: 715–722.

14 Moskowitz CH, Kewalramani T, Nimer SD, Gonzalez M, Zelenetz AD, Yahalom J. Effectiveness of high dose chemoradiotherapy and autologous stem cell transplantation for patients with biopsy-proven primary refractory Hodgkin's disease. *Br J Haematol* 2004; **124**: 645–652.

15 Oyan B, Koc Y, Ozdemir E, Kars A, Turker A, Tekuzman G *et al*. Ifosfamide, idarubicin, and etoposide in relapsed/refractory Hodgkin disease or non-Hodgkin lymphoma: a salvage regimen with high response rates before autologous stem cell transplantation. *Biol Blood Marrow Transplant* 2005; **11**: 688–697.

16 Ribrag V, Nasr F, Bouhris JH, Bosq J, Brault P, Girinsky T *et al*. VIP (etoposide, ifosfamide and cisplatinum) as a salvage intensification program in relapsed or refarctory Hodgkin's disease. *Bone Marrow Transplant* 1998; **21**: 969–974.

17 Rodriguez J, Rodriguez MA, Fayad L, McLaughlin P, Swan F, Sarris A *et al*. ASHAP: a regimen for cytoreduction of refractory or recurrent Hodgkin's disease. *Blood* 1999; **11**: 3632–3636.

18 Bartlett N, Niedzwiecki D, Johnson J, Friedberg J, Johnson K, van Besien K *et al*. Gemcitabine, vinorelbine, and pegylated liposomal doxorubicin (GVD), a salvage regimen in relapsed

Hodgkin's lymphoma: CALGB 59804. *Ann Oncol* 2007; **18**: 1071–1079.
19 Smardova L, Engert A, Haverkamp H, Raemakers J, Baars J, Pfistner B *et al*. Successful mobilization of peripheral blood stem cells with the DHAP regimen (dexamethasone, cytarabine, cisplatinum) plus granulocyte colony-stimulating factor in patients with relapsed Hodgkin's disease. *Leuk Lymphoma* 2005; **46**: 1017–1022.
20 Santoro A, Magagnoli M, Spina M, Pinotti G, Siracusano L, Michieli M *et al*. Ifosfamide, gemcitabine, and vinorelbine (IGEV): a new induction regimen for refractory and relapsed Hodgkin's lymphoma. *Haematologica* 2007; **92**: 35–41.
21 Castagna L, Magagnoli M, Balzarotti M, Sarina B, Siracusano L, Nozza A *et al*. Tandem high-dose chemotherapy and autologous stem cell transplantation in refractory/relapsed Hodgkin's lymphoma: a monocenter prospective study. *Am J Haematol* 2007; **82**: 122–127.
22 Devizzi L, Santoro A, Bonfante V, Viviani S, Balzarini L, Valagussa P *et al*. Vinorelbine: an active drug in the management of patients with heavily pre-treated Hodgkin's disease. *Ann Oncol* 1994; **5**: 817–820.
23 La Cesne A, Antoine E, Spielmann M, Le Chevalier T, Brain E, Toussaint C *et al*. High-dose ifosfamide: circumvention of resistance to standard dose ifosfamide in advanced soft tissue sarcomas. *J Clin Oncol* 1995; **13**: 1600–1608.
24 Magagnoli M, Sarina B, Balzarotti M, Castagna L, Timofeeva I, Nozza A *et al*. Mobilising potential of ifosfamide/vinorelbine-based chemotherapy in pretreated malignant lymphoma. *Bone Marrow Transplant* 2001; **28**: 923–927.
25 Lucas JB, Horwitz SM, Horning SJ, Sayegh A. Gemcitabine is active in relapsed Hodgkin's disease. *J Clin Oncol* 1999; **17**: 2627–2628.
26 Zinzani PL, Bendandi M, Stefoni V, Albertini P, Gherlinzoni F, Tani M *et al*. Value of gemcitabine treatment in heavily pretreated Hodgkin's disease patients. *Haematologica* 2000; **85**: 926–929.
27 Santoro A, Bredenfeld H, Devizzi L, Tesch H, Bonfante V, Viviani S *et al*. Gemcitabine in the treatment of refractory Hodgkin's disease: results of a multicenter phase II study. *J Clin Oncol* 2000; **18**: 2615–2625.
28 Akhtar S, Tbakhi A, Humaidan H, El Weshi A, Rahal M, Maghfoor I. ESHAP + fixed dose G-CSF as autologous peripheral blood stem cell mobilization regimen in patients with relapsed or refractory diffuse large cell and Hodgkin's lymphoma: a single institution result of 127 patients. *Bone Marrow Transplant* 2006; **37**: 277–282.