Ifosfamide, gemcitabine, and vinorelbine: a new induction regimen for refractory and relapsed Hodgkin's lymphoma

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ABSTRACT

Background and Objectives

Response to pre-transplant salvage chemotherapy remains the most important prognostic factor for outcome in refractory or relapsed Hodgkin's lymphoma. Results of a new induction regimen are reported in terms of response rates, toxicity, and stem cell mobilization.

Design and Methods

Ninety-one patients with refractory or relapsed Hodgkin's lymphoma were treated prospectively with a salvage regimen consisting of ifosfamide 2000 mg/m^2 on days 1 to 4, gemcitabine 800 mg/m^2 on days 1 and 4, vinorelbine 20 mg/m^2 on day 1, and prednisolone 100 mg on days 1 to 4 (IGEV).

Results

Forty-nine patients (53.8%) achieved a complete remission and 25 (27.5%) a partial response for an overall response rate of 81.3%. In the multivariate analysis response to the last chemotherapy (p<0.0001) and involvement of ≥3 sites (p<0.049) were the most important prognostic factors for response. Adequate CD34$^+$ cell collection was achieved in 78 out of 79 (98.7%) mobilized patients. So far, no treatment-related death has been documented. Thirteen (4.2%) and 27 (8.6%) out of 313 evaluated cycles had to be delayed or reduced, respectively, mainly because of neutropenia and thrombocytopenia. No grade 4 non-hematologic toxicity was observed, except for one episode of mucositis.

Interpretation and Conclusions

The high response rate, in particular the complete remission rate, the low toxicity profile, and the very high mobilizing potential of the IGEV regimen strongly suggest that patients with relapsed/refractory Hodgkin's lymphoma may benefit from the use of this salvage induction regimen.

Key words: Hodgkin's lymphoma, salvage chemotherapy, complete remission, CD34$^+$ cell mobilization.

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Since the early 1990s, salvage chemotherapy followed by high dose chemotherapy with autologous bone marrow or peripheral blood stem cell (PBSC) support has become the gold standard treatment for patients with refractory or relapsed Hodgkin's lymphoma, as clearly shown by several retrospective or phase II studies,[1,2] as well as by two prospective randomized trials.[3,4] This treatment approach can produce long-term remissions in approximately 40–50% of relapsed patients,[5-7] and in up to 25–30% of those with primary refractory disease.[8–11] The possibility of a cure depends strongly on several prognostic factors, including duration of the initial remission, extent of disease, prior chemotherapy regimen, presence of B symptoms, and the number of previous chemotherapy lines.[2,5,12–15] However, in almost all series, the disease status before high-dose chemotherapy with PBSC support remains the most important factor predicting outcome for these patients.[2,4–5, 13–15]

Very few studies reported data relating to which standard-dose salvage regimen is the best to induce a good clinical response and shrinkage of bulky disease[16–25] before high-dose therapy. Hence, the identification of new active regimens, combining therapeutic activity and CD34$^+$ stem cell mobilizing potential, is of the utmost importance to increase pre-transplant response rates and, possibly, the final outcome.

In November 1997, following initial experiences with single-agent vinorelbine[26] and gemcitabine,[27] as well as with a combination of vinorelbine and ifosfamide,[24,28] we designed a new chemotherapy regimen including gemcitabine, vinorelbine, and ifosfamide for patients with refractory or relapsed Hodgkin's lymphoma. This combination was used in a multicenter study whose results with regards to response rates, toxicity, and stem cell mobilization are reported here.

Design and Methods

Study design

From November 1997 to September 2005, 91 patients with relapsed or primary refractory Hodgkin's lymphoma after chemotherapy with or without radiotherapy were entered in a study protocol consisting of four cycles of combined ifosfamide, gemcitabine, and vinorelbine (IGEV).The protocol was approved by the Ethics Committee and written informed consent was obtained from all participants. Patients who had failed to achieve complete remission with previous chemotherapy were defined as refractory, those who relapsed after an initial complete remission were classified as having relapsed.

All patients were staged according to the Cotswolds modification of the Ann Arbor system and all underwent at least computed tomography of the thorax and abdomen, and bone marrow biopsy. Starting from 2002, many patients underwent positron emission tomography (PET)-scanning as part of thier staging procedure. Other criteria for eligibility were World Health Organization (WHO) performance status ≤2, and adequate pulmonary, cardiac, renal, and liver function. Human immunodeficiency virus-positive patients were excluded.

Bulky disease was defined as a mediastinal mass larger than one third of the maximum thoracic diameter and/or any node over 10 cm. Disease evaluation was performed after two and four chemotherapy cycles by repeating all examinations that had given an initial positive response. Bone marrow biopsy was repeated when initially positive.

Therapy

The IGEV regimen was administered in an outpatient setting. This regimen consists of ifosfamide 2000 mg/m^2 on days 1 to 4 as a 2-hour infusion/day with 2,000 mL saline solution hyperhydration, MESNA 2600 mg/m^2 on days 1 to 4, gemcitabine 800 mg/m^2 on days 1 and 4, vinorelbine 20 mg/m^2 on day 1, and prednisolone 100 mg on days 1 to 4, of each 3-week course. Granulocyte colony-stimulating factor (G-CSF) was administered from day 7 to day 12 of each course or up to apheresis in the course of mobilization. Four courses of chemotherapy were planned, provided there was evidence of at least partial remission after the second cycle. PBSC were collected after the first or second course in the first 11 patients, in order 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 3.0×10^6 CD34$^+$ cells/kg of body weight was planned to support each high-dose chemotherapy. The mobilization procedure was considered to have failed when the target yield was not achieved. Apheresis, CD34$^+$ analysis, and cryopreservation procedures have been reported previously.[27] Patients with complete or partial remission after four IGEV courses received single or tandem high-dose chemotherapy.

Monitoring and toxicity assessment

Just 3 weeks before entering the study, each patient underwent a clinical assessment that included evaluation of B symptoms and WHO performance status score, recording of weight, height, blood pressure, and pulse rate, and measurement of palpable or visually identified tumor lesions. All patients underwent the following tests: complete blood cell counts, blood chemistry, coagulation tests, urine analyses, electrocardiography and echocardiography. During therapy, WHO performance status, weight, blood pressure, pulse rate, and a complete blood cell count were obtained before each course. The toxic effects were evaluated according to the WHO Common Toxicity

Table 1. Response rate as a function of the patients' characteristics before IGEV chemotherapy.

Characteristics	Patients N	%	Response in % CR (49)	PR (25)	IF (17)	p value*
Total	91	100	53.8	27.5	18.7	
Histology						
Nodular sclerosis	68	74.7	50.0	27.9	22.1	0.3
Other	23	25.3	65.2	26.1	8.1	
Symptoms						
Yes	54	59.3	51.8	24.1	24.1	0.28
No	37	40.7	56.8	32.4	10.8	
Bulky disease						
Yes	41	45.1	43.9	31.7	24.4	0.158
No	50	54.9	63.3	24.5	12.2	
No. of involved sites						
≤3	50	54.9	64.0	24.0	12.0	0.076
>3	41	45.1	41.5	31.7	26.8	
Extranodal involvement						
Yes	43	47.2	49.2	25.5	26.3	0.635
No	48	52.8	56.2	29.2	14.6	
Previous regimens						
1	70	76.9	52.9	28.6	18.6	0.944
≥2	21	23.1	57.1	23.8	19.0	
Disease status						
Refractory	36	39.6	33.3	27.8	38.9	<0.001
Relapse	55	60.4	67.3	27.3	5.4	
Relapse						
CR ≤12 months	28	30.8	60.7	28.6	10.7	0.279
CR >12 months	27	29.7	74.1	25.9	0.0	
Previous radiotherapy						
Yes	55	60.4	60.0	30.9	9.1	<0.019
No	36	39.6	44.4	22.2	33.3	

*IGEV: ifosfamide, gemcitabine, and vinorelbine. *complete remission (CR) vs. partial remission (PR) vs. induction failure (IF). Due to rounding off to the nearest digit, percentages may not sum up to 100%.*

Criteria. Tumor manifestations were reassessed after the second and fourth treatment cycles using the same baseline imaging technique throughout the study. Bidimensional tumor measurements and response evaluation were based on WHO standard criteria.[29] Responses were confirmed on two separate measurements made at least 4 weeks apart. PET negativity was mandatory to define complete remission in those patients initially staged by PET. Time to best response and time to disease progression were measured from the start of IGEV treatment to the time of documentation of response or tumor progression. Survival was calculated from the beginning of therapy to the time of death from any cause.

Statistics

Our analysis included all patients who completed IGEV treatment before November 2005. Data are described as numbers and percentages, or means and standard deviations, when appropriate. The prognostic factors were subjected to univariate logistic regression analysis to determine whether they also influenced the response to IGEV. All variables showing a p value <0.1 were considered as candidates for a stepwise logistic regression procedure. All calculations were performed using Stata 9 software (*www.stata.com*).

Table 2. Multivariate analysis for response.

Prognostic factor	OR	SE	Multivariate
CR vs. PR vs. IF			
Refractory/relapsed (baseline=relapsed)	0.636	0.151	<0,0001
Involved sites (baseline=≤3)	0,295	0.148	0,049
Prior RT (baseline=no RT)	1.141	0.164	n.s.

OR: odds ratio; SE: standard error; CR: complete remission; PR: partial remission; IF: induction failure; RT: radiotherapy; n.s: not significant.

Results

Patients' characteristics

Ninety-one patients with primary refractory or relapsed Hodgkin's lymphoma were enrolled and evaluated for response to and toxicity of IGEV. The patients' main characteristics before the initiation of IGEV chemotherapy are listed in Table 1. There were 52 males and 39 females; their median age was 30 years (range 17–59 years). Nodular sclerosis was the most frequent histological subtype (74.7%). A high percentage of patients had B symptoms (59.3%), extranodal involvement (47.2%), more than three involved sites (45.1%), and/or bulky disease (45.1%). As regards response to the last chemotherapy before IGEV administration, 36 patients (39.6%) were refractory, whereas the remaining 55 patients (60.4%) achieved a complete remission, which lasted less than 12 months in 28, and over 12 months in 27 cases.

According to the initial stage of their disease, all patients had received from four to eight courses of at least one previous chemotherapy combination. The majority of patients (76.9%) had received only one regimen, with a range from one to four. All patients had been treated with an anthracycline-containing regimen: 38 with adriamycin, bleomycin, vinblastine, dacarbazine (ABVD); 18 with mechlorethamine, oncovin, procarbazine, prednisolone (MOPP) alternated with ABVD; 29 with epidoxorubicin, cyclophosphamide, vinorelbine, bleomycin, prednisone (VEBEP); and 6 with other regimens. Four patients had relapsed after high-dose chemotherapy with PBSC support.

Table 3. Main toxicity according to WHO Common Toxicity Criteria.

	No.	*%*
Number of cycles	313	100
Number of delayed cycles	13	4.2
Number of reduced cycles	27	8.6
Infection (documented)	11	3.5
Treatment-related death	0	0
Hematologic toxicity		
Neutropenia (grade 3/4)	71/18	22.7/5.7
Thrombocytopenia (grade 3/4)	48/15	15.3/4.8
Anemia (grade 3/4)	52/5	16.6/1.6
Platelet transfusion	15	4.8
Red blood cell transfusion	25	8.0
Non-hematologic toxicity		
Mucositis (grade 3/4)	6/1	1.9/0.3
Nausea/vomiting (grade 3/4)	10/0	3.2/0
Cystitis (grade 3/4)	1	0.3/0
Neurological (grade 3/4)	0	0
Hepatic (grade 3/4)	0	0
Cardiac (grade 3/4)	0	0
Renal (grade 3/4)	0	0

Table 4. Peripheral blood stem cell collection.

Patients mobilized, total	79
Adequate $CD34^+$ collection, total	78 (98.7%)
Collection failure, total	1*(1.3%)
Days from IGEV, median (range)	13 (10–17)
$CD34^+$ cell peak, median (range), $\times 10^6$/kg body weight	68.5 (16.6–482.0)
Single HDCT scheduled	
median $CD34^+$ cells collected (range), $\times 10^6$/kg body weight	10.5 (3.0–39.0)
median apheresis procedures (range)	1 (1–3)
Tandem HDCT scheduled	
median $CD34^+$ cells collected (range), $\times 10^6$/kg body weight	10.3 (6.0–22.0)
median apheresis procedures (range)	2 (1-3)

*HDCT: high-dose chemotherapy; *2.3×10⁶ $CD34^+$ cells/kg.*

Fifty-five patients had received radiotherapy as part of their previous treatment program for Hodgkin's lymphoma. The median follow-up time was 26 months, with a range from 5 to 94 months.

Response to IGEV

Forty-nine patients (53.8%) achieved complete remission and 25 (27.5%) partial remission with an overall response rate of 81.3% (Table 1). Prognostic factors influencing the likelihood of patients achieving a response were disease status at accrual (relapsed vs refractory, $p<0.001$), and previous radiotherapy ($p<0.019$), while a trend was observed for number of involved sites ($p=0.076$). All other prognostic factors such as age, B symptoms, histology, extranodal involvement, bulky disease, number of previous chemotherapy regimens, duration of previous complete remission (≤12 months vs >12 months), and previous high-dose chemotherapy with PBSC support, did not influence the response rate significantly.

Prognostic factors associated with response, according to the univariate $p<0.1$ criterion, were entered into a multivariate logistic regression model (Table 2). The significant predictive factors were response to the last chemotherapy before IGEV (complete remission vs. partial remission vs. induction failure; $p<0.0001$), and number of involved sites (≤3 vs >3 sites, $p=0.049$), whereas previous radiotherapy lost significance in multivariate analysis.

Overall, 64 out of 74 patients in complete or partial remission after IGEV proceeded to single (29 cases) or tandem (35 cases) high-dose chemotherapy with PBSC support. Another five responsive patients who had been treated with IGEV following relapse after previous high-dose chemotherapy with PBSC were allocated to receive non-myeloablative allogeneic transplants. The remaining five patients refused high-dose therapy. The 3-year freedom from progression and overall survival rates were 52.98% and 70.03%, respectively, for the entire series. However long-term results were influenced by response to previous chemotherapy as well as to the IGEV regimen. Details on freedom from progression and overall survival require a longer follow-up.

Treatment delivery and toxicity

The details on treatment delivery and toxicity are reported in Table 3. No treatment-related deaths have been documented so far. Only one treatment toxicity-related admission to the hospital occurred. Out of 313 cycles evaluated, 13 (4.2%) were delayed and 27 (8.6%) reduced mainly because of neutropenia and thrombocytopenia. Overall, the IGEV-related toxic effects were mild with a relatively low incidence of grade 3 and 4 toxicity according to WHO Common Toxicity Criteria. In particular, grade 4 hematologic toxicity was recorded in a very limited number of cycles. Platelet transfusion support was required in 15 cycles (4.8%), and red blood cells were transfused in 25 cycles (8.0%). As regards non-hematologic toxicity, no grade 4 effects were recorded except for one case of mucositis. No grade 3 or 4 renal, neurological, hepatic, or myocardial function toxicity was observed. Eleven infections (3.5%) were documented; however, all patients recovered quickly. Grade 3 ifosfamide-related cystitis occurred in one case and promptly recovered with hyperhydration and mesna supplementation. In no case was ifosfamide stopped or reduced because of cystitis.

Table 5. Summary of results with pre-transplant salvage regimens

Regimen	N. of patients	Response (%)		Grade 3-4 toxicity (%)		Toxic deaths (%)	Ref.
		CR+PR	CR	Neutrophilis	Platelets		
DEXABEAM	144	81	27	NR	NR	5	16
DEXABEAM	55	60	31	90	87	4	4
MiniBEAM	55	82	32	86	60	0	20
MiniBEAM	44	84	32	NR	90	0	21
DHAP	102	89	21	88	69	0	17
MINE	100	75	34	NR	NR	0	25
ICE	65	85	26	NR	NR	0	11
ASHAP	56	70	34	100	NR	0	19
GDP	34	62	10	NR	NR	0	23
IGEV	91	81	54	38	20	0	This study

NR: not reported.

Stem cell collection

Seventy-nine patients underwent stem cell mobilization with G-CSF (236 μg/kg per day) from day 7 to leukapheresis after one (4 patients), two (7 patients), three (60 patients) and four (8 patients) IGEV cycles (Table 4). Twelve patients did not undergo stem cell mobilization because of disease progression before the third IGEV cycle (9 cases) or allocation to allogeneic transplantation (3 cases). Leukapheresis was performed when the number of $CD34^+$ cells/mL was at least 12 and conducte daily possibly until over 3×10^6 or 6×10^6 $CD34^+$ cells/kg were collected according to whether single or tandem high-dose chemotherapy procedures were planned. In all cases harvesting started from between day 11 and 17 (median, day 13) following the beginning of IGEV chemotherapy. An adequate $CD34^+$ cell collection (i.e. over 3×10^6 $CD34^+$ cells/kg for each high-dose chemotherapy procedure) was achieved in 78 out of 79 (98.7%) mobilized patients, the only failure pooling 2.3×10^6 $CD34^+$ cells/kg.

The median number of $CD34^+$ cells collected was 10.5×10^6/kg (range, 3.0–39.0$\times10^6$/kg) with a median of one (range 1–3) apheresis procedure for patients elegible for single high dose treatment, whereas the median number of $CD34^+$ cells was 10.3×10^6/kg (range, 6.0-22.0$\times10^6$/Kg) with a median of two (range, 1-3) apheresis procedures for candidates for tandem transplant. Overall the target yields of 3×10^6 and 6×10^6 $CD34^+$cells/kg were reached in 69.0% and 44.0% of cases, respectively, after the first apheresis procedure and in 20.7% and 50.0%, after the second apheresis.

Discussion

The response rates to pre-transplant induction chemotherapy regimens and/or their mobilizing potential, as well as their impact on outcome have been assessed accurately in only a small number of studies (Table 5). Usually induction chemotherapy has produced an overall response rate of around 70-80% and the complete remission rate has been lower than 30-35%.

Our study outlines the results of a prospective program evaluating a new chemotherapy regimen (IGEV) for the treatment of 91 patients with refractory/relapsed Hodgkin's lymphoma. The study regimen, which was based on the results of previous protocols including vinorelbine,[26] gemcitabine,[27] and ifosfamide plus vinorelbine,[24,28] induced an overall response rate of 81.3%, which is comparable to rates reported in the past. However, the incidence of complete remission induced by four courses of IGEV, was very high (53.8%) compared with previous data (Table 5). The complete remission rate in refractory patients (33.3%) is also noteworthy even though it is lower than that observed in relapsed patients (67.3%). As a consequence disease status (i.e. relapsed vs. refractory) disease extent (i.e., number of involved sites before IGEV) remain the most important predictors of response in multivariate analysis.

With regard to toxicity, IGEV was very well tolerated with one hospitalization and no treatment-related deaths. Only a very limited number of cycles had to be delayed because of hematologic or non-hematologic toxicity, and from a general viewpoint toxicity was mild. Grade 4 hematologic toxicity was recorded in a very low number of cycles. Furthermore, no grade 4 extrahematologic toxicity was observed, except for one episode of mucositis, and no patient developed grade 3 toxicity apart from mucositis (1.9% of cycles), cystitis (0.3% of cycles) and nausea and vomiting (3.2% of cycles). These data compare very favorably

Table 6. Summary of stem cell collection with induction chemotherapy.

Regimen (Ref)	*N. of patients*	*CD34⁺×10⁶ (target)*	*CD34⁺×10⁶ collected (median)*	*Collection in a single apheresis (%)*	*No. of aphereses (median)*	*Successful collection (%)*
DHAP[30]	105	2.0	13.0	63	1	97
ESHAP[31]	78	NR	7.6	58	1	97
ICE[11]	66	2.5	7.0	NR	3	86
MiniBEAM[23]	34	2.0	5.5	36	1	82
GDP[23]	34	2.0	11.1	73	1	97
IVE[32]	28	2.5	5.4	NR	1	88
IGEV (this study)	79	3.0/6.0	10.5/10.3	69/44	1/2	99

NR: not reported.

with those from other series in which a higher incidence of side-effects was documented (Table 5).

Finally the capacity to mobilize PBSC is a critical requirement for a pre-transplant induction regimen. In the majority of previous reports on high-dose chemotherapy, data on $CD34^+$ cell mobilization are lacking and details on PBSC mobilization and collection are reported in a limited number of studies[11,23,30-32] (Table 6). An adequate stem cell collection (>2×10^6 $CD34^+$ cells/kg) was observed in over 80% of patients. In the present series, the target yield of 3×10^6 or 6×10^6 $CD34^+$ cells/kg after IGEV was reached in almost all patients (98.7%), with a failed harvest of 2.3×10^6 $CD34^+$ cells in only one patient. Furthermore, a single apheresis procedure was sufficient to achieve the target yield in a high percentage of cases. These data confirm our previous experience with ifosfamide plus vinorelbine[28] and are better than those attained with the two widely used regimens: ICE[11] and miniBEAM.[23]

In conclusion, our results strongly suggest the benefit of IGEV as a salvage induction regimen in patients with refractory or relapsed Hodgkin's lymphoma. This is clearly supported by the high response rate, in particular the complete remission rate, the very favorable toxicity profile, and also the very high mobilizing potential.

Author Contributions

AS acted as principal investigator: he designed the protocol, co-ordinated the study, and wrote the report. MM, MB, MS, GP, LS, AN, and UT participated in the data collection, analysis and interpretation. IC, MM, and BS provided guidance regarding the interpretation of the study results; EM analyzed the data. The study sponsor had no role in the study design, in the data collection, analysis, and interpretation, or in the writing of the report. The corresponding author had full access to the data and took final responsability to submit this report for publication.

Conflict of Interest

The authors reported no potential conflicts of interest.

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