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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

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ABSTRACT

To achieve long-term disease-free survival, high-dose therapy and autologous stem cell transplantation (ASCT) is the current standard approach in patients with relapsed or refractory Hodgkin disease (HD) or non-Hodgkin lymphoma (NHL). Because chemosensitivity is a significant factor in determining transplantation eligibility, it is critical to select a salvage chemotherapy regimen that has the potential to induce a high response rate with low nonhematologic toxicity. In this phase II study, 49 patients with relapsed or refractory HD (n = 22) and NHL (n = 27) with a median age of 42 years were treated with an IIVP salvage regimen consisting of ifosfamide, idarubicin, and etoposide. Twenty-seven percent of the patients had primary refractory disease, whereas 22% and 51% had early and late relapses, respectively. As analyzed by intention to treat, 16 patients (33%) achieved complete remission and 21 patients (43%) achieved a partial response, leading to an overall response rate of 76% (63% in NHL and 91% in HD). In the univariate analysis, diagnosis (HD versus NHL), remission duration before the initiation of IIVP, disease bulk, increased lactate dehydrogenase, and the presence of "B" symptoms were significant factors affecting the response achieved by the IIVP regimen. Of 37 responders, 31 (84%) underwent high-dose therapy and transplantation. The probability of 4-year overall survival (OS) and event-free survival (EFS) in this group of patients who underwent ASCT was 67.7% and 49.1%, respectively. When compared with the patients who achieved a partial response, patients who achieved complete remission with the IIVP regimen had a significantly higher probability of 4-year EFS (67.3% versus 30%; $P = .016$) and 4-year OS (92.3% versus 39.2%; $P = .003$). In patients with HD, 4-year EFS and 4-year OS were 54.9% and 70.6%, respectively, without a significant difference with respect to the survival rates obtained in patients with NHL (43.6% and 63.6%, respectively). Common side effects observed during 102 cycles of therapy were grade 3 to 4 neutropenia (62%) and thrombocytopenia (58%). The IIVP regimen is a highly effective salvage regimen for patients with relapsed or refractory HD or NHL who are candidates for ASCT. Furthermore, the degree of response to IIVP predicts the posttransplantation outcome. However, close follow-up is necessary because of a high incidence of grade 3 to 4 hematologic toxicity.

KEY WORDS

Salvage • Lymphoma • Autologous transplantation

INTRODUCTION

Despite advances in therapy, 40% to 60% of patients with non-Hodgkin lymphoma (NHL) will not achieve a complete remission (CR) or will relapse after standard first-line therapy. Although most patients with Hodgkin disease (HD) will be cured with initial therapy, 10% to 20% will not achieve a CR, and 20% to 30% will relapse after standard therapy [1]. High-dose chemotherapy (HDC) followed by autologous stem cell transplantation (ASCT) is the treatment of choice for patients with relapsed or primary resistant HD or NHL [2-5]. The high rates of toxicity and costs associated with HDC/ASCT demand that it be

reserved for patients in whom it clearly increases the chance for cure compared with standard-dose therapy. Many studies have defined chemosensitivity to conventional salvage chemotherapy as the most important predictor of long-term event-free survival [4-6]. At least a partial response (PR) to the salvage regimen is required to proceed with HDC and ASCT, to increase the chance of achieving long-term survival [7,8]. Most commonly used salvage regimens—including DHAP (dexamethasone, cytarabine, and cisplatin), ESHAP (etoposide, methylprednisolone, cytarabine, and cisplatin), and ICE (ifosfamide, carboplatin, and etoposide)—can induce overall response rates (ORRs) ranging between 40% and 60% [9-12]. The IIVP regimen, consisting of ifosfamide, idarubicin, and etoposide, was previously reported as a salvage regimen with an acceptable toxicity profile for patients with relapsed or refractory NHL or in small numbers of patients with relapsed or refractory HD [13,14]. However, the effect of the IIVP regimen on transplantation has not been reported.

An ideal pretransplantation salvage regimen is still being investigated to improve transplantation eligibility and outcome. In this study, the IIVP regimen was administered to patients with relapsed or refractory lymphoma. The aims of this study were to determine the efficacy and toxicity of the regimen, to determine the proportion of patients who would be able to proceed with HDC/ASCT, and, finally, to determine the outcome of ASCT on the basis of the response obtained after the IIVP salvage regimen.

MATERIAL AND METHODS

Patients

Forty-nine consecutive adult patients with relapsed or refractory NHL or HD were treated with the IIVP salvage regimen at Hacettepe University Institute of Oncology between December 1999 and July 2004. Eligibility criteria included patients between 16 and 65 years of age, an Eastern Cooperative Oncology Group performance status of <3, and adequate organ function, defined by a serum creatinine level <2 mg/dL, serum transaminases <3 times the normal value, a bilirubin level of <2 mg/dL, a cardiac ejection fraction $>50\%$ as determined by echocardiography, an absolute neutrophil count $>1.5 \times 10^9$/L, and a platelet count of $>100 \times 10^9$/L. Patients were required to be free of central nervous system (CNS) involvement, active infection, and human immunodeficiency virus infection. Patients with a histology of mantle cell lymphoma or Burkitt or lymphoblastic lymphoma were excluded. Also, patients with low-grade histology, such as small lymphocytic lymphoma or follicular lymphoma grade I and grade II, were excluded. A tumor size of ≥ 7 cm was classified as bulky disease. All patients underwent staging procedures before IIVP that included chest radiograph, computed tomography scans, and bone marrow biopsy. Gallium scanning was optional.

Primary refractory disease was defined as disease progression or failure to attain a CR during first-line chemotherapy. CR was defined as the disappearance of all detectable clinical and radiographic evidence of disease for >1 month. Early relapse required a CR lasting ≤ 12 months, and late relapse was defined as a CR lasting >12 months.

All responding patients proceeded to stem cell mobilization and collection if they were eligible for HDC and stem cell transplantation. Eligibility criteria for HDC/stem cell transplantation were age ≤ 60 years, Eastern Cooperative Oncology Group performance status <3, adequate pulmonary function (defined as a forced expiratory volume in the first second and diffusing capacity of carbon monoxide $>60\%$ of predicted), and adequate cardiac, liver, and renal function. All patients signed informed consent forms before proceeding with HDC and ASCT.

Salvage Protocol

The salvage regimen consisted of ifosfamide (1 g/m^2/d as a 1-hour infusion on days 1-5), mesna (200 mg/m^2 30 minutes before the infusion of ifosfamide and 4 and 8 hours after completion of ifosfamide on days 1-5), idarubicin (10 mg/m^2/d as a 30-minute infusion on days 1-2), and etoposide (150 mg/m^2/d infused over 2 hours on days 1-3), administered every 28 days. The regimen was administered on an inpatient basis, and after completion of the regimen, patients were followed up on an outpatient basis. Patients were closely followed up for infectious, hematologic, and nonhematologic toxicities. Antibacterial prophylaxis consisting of ciprofloxacin 500 mg twice daily was given to patients with an absolute neutrophil count $<0.5 \times 10^9$/L. Patients were hospitalized if febrile neutropenia did not resolve within 48 hours with oral antibiotics or if they had symptoms or signs of septicemia. As supportive measures, platelet and red blood cell transfusions and empirical intravenous antibiotic therapy for neutropenic fever were promptly commenced.

Patients who had a 50% to 75% reduction in tumor size after the second cycle received a third cycle of the IIVP regimen, to achieve maximal cytoreduction before high-dose therapy and stem cell collection. Patients with progressive disease after the first cycle were switched to an alternative salvage protocol.

Use of Growth Factors

Because of the high incidence of neutropenic fever episodes observed in the first 18 patients, primary prophylaxis with granulocyte colony-stimulating fac-

tor (G-CSF) at a dose of 5 μg/kg/d was started 48 hours after the last dose of the salvage regimen until granulocyte recovery in the remaining 31 patients. The median duration of G-CSF administration was 9 days.

Assessment of Response

The response to therapy was assessed by physical examination of all palpable lymph node regions before each cycle and by computed tomography scans of the involved sites after the second and third cycles of IIVP. Bone marrow biopsy was repeated if it was positive at baseline. Patients who underwent transplantation were assessed on posttransplantation day +100 and every 3 months thereafter. Standard response definitions previously defined by the International Working Group were used [15].

Transplantation Protocol

The ASCT protocol consisted of 3 sequential phases of HDC. Phase 1 consisted of cyclophosphamide (4.5 g/m^2 given over two 1-hour administrations at 3-hour intervals) followed by G-CSF (10 μg/kg/d) and peripheral blood stem cell (PBSC) collection. Stem cell collection was initiated when the leukocyte count was >5000/μL and was continued daily for 2 to 3 days until more than 2×10^6 CD34$^+$ cells per kilogram were collected. Phase 2 consisted of etoposide (2 g/m^2 over 12 hours) with G-CSF support at 5 μg/kg/d. The transplantation phase consisted of mitoxantrone (60 mg/m^2 given over three 1-hour administrations at 1-hour intervals on day −4) and melphalan (180 mg/m^2 given over two 1-hour administrations at 1-hour intervals on day −1) followed by PBSC infusion (day 0). G-CSF was initiated 4 hours after PBSC infusion. The interval between the phases was a minimum of 21 days.

Statistical Analysis

Responses to the IIVP regimen were analyzed by intention to treat, but only patients who achieved at least a PR to the IIVP regimen were eligible for ASCT. The primary end points of this study were response rate (CR plus PR), ability to proceed with transplantation, and toxicity of the regimen. The secondary end points were the success rate of mobilization and the outcome of transplantation. The outcome variables examined were (1) response rate to IIVP; (2) overall survival (OS), defined from the time of initiation of IIVP chemotherapy to last follow-up evaluation or death; and (3) event-free survival (EFS), defined as achievement of a CR or PR from the time of initiation of IIVP chemotherapy until progression, relapse, or death from any cause.

Statistical analysis was performed by using StatView for Windows (SAS Institute, Inc., Cary, NC) version 5.0. Survival curves were estimated by using the method of Kaplan and Meier [16]. Outcomes of different clinical and prognostic groups were compared by using the 2-sided log-rank test [17]. Differences in response rates were analyzed by Fisher exact test with the Yates continuity correction [18]. Because of the small sample size, multivariate analysis was not performed. All probability values were 2 sided and statistically significant when $P < .05$.

RESULTS

Patient Characteristics

Patient characteristics before the initiation of IIVP are listed in Table 1. The median age of the patients was 42 years (range, 16-65 years), and 7 (14%) patients were older than 60 years of age.

Among NHL patients, diffuse large B-cell lymphoma was the most common histology (n = 22; 81%), followed by follicular lymphoma grade III (n = 1), anaplastic large cell lymphoma (n = 1), peripheral T-cell lymphoma (n = 1), and natural killer/T-cell lymphoma (n = 2). Of the 27 NHL patients, 4 (15%) had a T-cell phenotype. Most patients with HD had either nodular sclerosis (n = 10) or mixed cellularity (n = 10) histology. All patients had experienced treatment failure with at least 1 anthracycline-based regimen. Half of the patients had primary refractory disease (27%) or early relapse (22%). Of patients with relapsed disease (n = 36), 67% were at their first relapse, and 33% were beyond first relapse. Eighty-six percent of patients (n = 42) received either 2 or 3 cycles of IIVP. Three patients with progressive disease after the first cycle of IIVP had to switch to an alternative salvage regimen.

Response to Chemotherapy and Factors Influencing Response

Response to the IIVP regimen was not evaluable in 3 patients because of toxic death (n = 2) and a serious adverse event leading to discontinuation of the therapy after the first cycle. Nine patients did not respond to IIVP. As analyzed by intention to treat, 16 patients (33%) achieved CR and 21 patients (43%) achieved PR, leading to an ORR of 76% (Figure 1). Factors predicting response to IIVP are depicted in Table 2. Remission duration (late relapse, early relapse, and primary refractory disease) before the initiation of IIVP was found to be a significant factor for response to IIVP ($P < .0001$; χ^2 for independence, 18.6). The best ORR was achieved in patients with late relapse (100%), followed by early relapse (64%) and primary refractory disease (38%; Figure 2). In addition, patients with nonbulky disease ($P = .022$), without "B" symptoms ($P = .011$), with normal lactate dehydrogenase ($P = .035$), and with HD ($P = .043$)

Table 1. *Patient Characteristics*

Characteristic	NHL (n = 27)	HD (n = 22)	Total (n = 49)
Median age, y (range)	48 (26-64)	36 (16-65)	42 (16-65)
Sex			
Male	17 (63%)	15 (68%)	32 (65%)
Female	10 (37%)	7 (32%)	17 (35%)
Stage			
I, II	16 (59%)	7 (32%)	23 (47%)
III	5 (19%)	9 (41%)	14 (28%)
IV	6 (22%)	6 (27%)	12 (25%)
Increased serum LDH	13 (54%)	10 (48%)	23 (51%)
Remission duration before initiation of IIVP			
Primary refractory	8 (30%)	5 (23%)	13 (27%)
Relapse	19 (70%)	17 (77%)	36 (73%)
Duration of previous response			
Early relapse (≤12 mo)	9 (33%)	2 (9%)	11 (22%)
Late relapse (>12 mo)	10 (37%)	15 (68%)	25 (51%)
No. relapses			
First relapse	17 (63%)	7 (32%)	24 (49%)
Second relapse	2 (7%)	7 (32%)	9 (18%)
Third relapse and beyond	0 (0%)	3 (13%)	3 (6%)
Prognostic score for NHL*			
Low	9 (33%)	—	
Low-intermediate	8 (30%)	—	
High-intermediate	9 (33%)	—	
High	1 (4%)	—	
No. IIVP cycles administered			
1	6 (22%)	1 (5%)	7 (14%)
2	14 (52%)	17 (77%)	31 (63%)
3	7 (26%)	4 (18%)	11 (23%)

LDH indicates lactate dehydrogenase.

*According to an age-adjusted International Prognostic Index.

had a better response to IIVP. There was no statistically significant difference between the response rates of patients with a single relapse and patients with more than 1 relapse.

Patients with NHL. Eight (30%) patients achieved CR, and 9 (33%) patients achieved PR, corresponding to an ORR of 63%. Factors predicting the response to IIVP were remission duration, disease bulk, lactate dehydrogenase level, presence of B symptoms, and age-adjusted International Prognostic Index (Table 3). Except for 3 patients, all responding patients proceeded to stem cell transplantation. In addition, 1 patient who was refractory to IIVP responded to an alternative salvage regimen and underwent ASCT.

Patients with HD. Twenty-two patients with HD had an ORR of 91%, consisting of 36% CR and 55% PR. The only significant factor that influenced response to IIVP was remission duration (primary refractory versus relapse, $P = .043$; odds ratio, 25; 95% confidence interval, 0.97-642). Whereas all relapsed patients responded to the IIVP salvage regimen, 40% of primary refractory patients remained resistant. All but 3 responding patients proceeded to ASCT.

Transplantation Data

Of the 37 responders, 31 (84%) underwent HDC and transplantation. Two responding patients refused high-dose therapy; 2 patients were ineligible for ASCT because of their concomitant systemic diseases, and 1 patient was ineligible because of age >60 years. One responding patient relapsed before initiation of the third phase of the high-dose sequential chemotherapy protocol. Of the 6 patients who did not undergo transplantation, none is alive. The median EFS and OS of these patients were 5.2 and 8 months, respectively. Of the 9 patients refractory to IIVP, 1 responded to a second-line salvage therapy and eventually proceeded to ASCT. This patient is currently alive and free of disease.

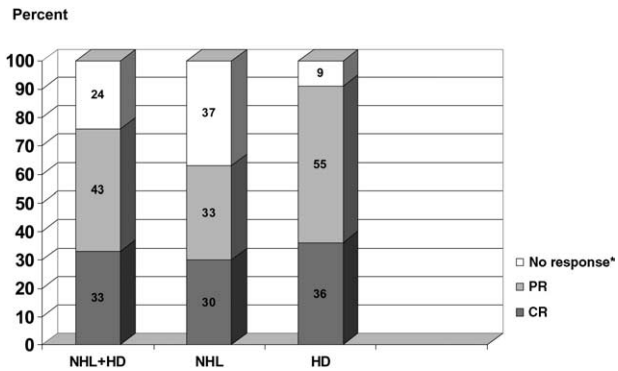

Figure 1. Response to the IIVP regimen in the entire group and in patients with NHL and HD. CR indicates complete response; PR, partial response. No response* includes treatment-resistant and unevaluable patients.

Table 2. *Factors Influencing Response to IIVP (n = 49)*

Factor	Response, n (%)		*P* value	Odds Ratio	95% CI
	CR + PR	Resistance			
Sex					
Male	24 (75)	8 (25)	1.00†	—	—
Female	13 (76)	4 (24)			
Diagnosis					
HD	20 (91)	2 (9)	.043	5.9	1.13-30.65
NHL	17 (63)	10 (37)			
Remission duration					
Primary refractory	5 (38)	8 (62)	<.0001	18.6*	
Early relapse	7 (64)	4 (36)			
Late relapse	25 (100)	0 (0)			
Bulky disease					
No	29 (88)	4 (12)	.022	6.3	1.48-27.23
Yes	8 (53)	7 (47)			
"B" symptoms					
Absent	18 (90)	2 (10)	.011	9.0	1.55-52.29
Present	8 (50)	8 (50)			
LDH					
Normal	20 (91)	2 (9)	.035	6.4	1.20-34.42
High	14 (61)	9 (39)			
Stage					
I-III	30 (81)	7 (19)	.14	—	—
IV	7 (58)	5 (42)			

LDH indicates lactate dehydrogenase; CI, confidence interval.
*Chi-square for independence.
†Identical results in both groups leads to a *P* value of 1.

Analysis of ASCT

One patient who was refractory to IIVP but underwent ASCT after responding to second-line salvage therapy was not included in the analysis. None of the patients experienced mobilization failure during stem cell collection. A median of 8.3 $\times$ 10^6 $CD34^+$ cells per kilogram (range, 2-18) was collected.

After ASCT, 7 patients relapsed or progressed, and 8 patients died. Mortality was secondary to relapsed or progressive disease (n = 4), ASCT toxicity (n = 2), congestive heart failure (n = 1), and secondary acute myeloblastic leukemia (AML; n = 1).

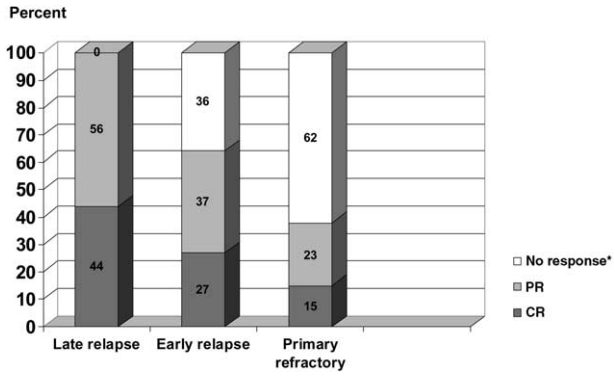

Figure 2. Response to the IIVP regimen according to remission duration before the initiation of IIVP. CR indicates complete response; PR, partial response. No response* includes treatment-resistant and unevaluable patients.

Survival Analysis of ASCT

The median follow-up time for patients who responded to IIVP and underwent ASCT was 31 months. The probability of 4-year OS and 4-year EFS was 67.7% and 49.1%, respectively. When compared with patients who achieved PR, patients who attained CR to IIVP had a significantly higher probability of 4-year EFS (67.3% versus 30%; $P = .016$) and 4-year OS (92.3% versus 39.2%; $P = .003$; Figure 3). Patients who experienced treatment failure with IIVP had a median survival of only 5 months. In patients with HD, 4-year EFS and 4-year OS were 54.9% and 70.6%, respectively, without a significant difference with respect to survival rates obtained in patients with NHL (43.6% and 63.6%, respectively). Remission duration before IIVP did not predict the outcome of ASCT.

Toxicity

Patients received a total of 102 cycles of IIVP. The toxicity profile of the regimen is summarized in Table 4. The toxicity profile was not different between patients with HD and NHL. The most common side effects were grade 3 to 4 neutropenia (observed in 62% of the cycles) and grade 3 to 4 thrombocytopenia (in 58%). Febrile neutropenia was observed in 38% of the cycles. Only 1 patient developed grade 4 infection. Hospitalization due to febrile neutropenia was necessary in 31% of the cycles. The administration of sec-

Table 3. *Factors Predicting Response to IIVP in NHL Patients (n = 27)*

Factor	Response, n (%)		*P* Value	Odds Ratio	95% CI
	CR + PR	Resistance			
Remission duration					
Late relapse	10 (100)	0 (0)	.003	29.4	1.48-583.78
Primary refractory or early relapse	7 (41)	10 (59)			
Bulky disease					
No	15 (83)	3 (17)	.008	15.0	1.98-113.61
Yes	2 (25)	6 (75)			
LDH					
Normal	10 (91)	1 (9)	.013	16.0	1.54-166.14
High	5 (38)	8 (62)			
"B" symptoms					
Absent	9 (90)	1 (10)	.006	31.5	2.35-422
Present	2 (22)	7 (78)			
AA-IPI					
Low and low-intermediate	14 (82)	3 (18)	.013	10.9	1.73-68.6
High-intermediate and high	3 (30)	7 (70)			

CI indicates confidence interval; LDH, lactate dehydrogenase; AA-IPI, age-adjusted International Prognostic Index.

ond and third cycles was delayed in 4 patients because of febrile neutropenia. There was no evidence of increasing rates of febrile neutropenia during the consequent cycles. Because a high incidence of febrile neutropenia was observed (72%) in the first 18 patients, primary prophylaxis with G-CSF in the remaining patients was initiated. All of the first 18 patients who did not receive growth factor support stayed on schedule. The mean number of single-donor platelet and erythrocyte transfusions for each cycle was 1.5 (range, 0-7) and 0.8 (range, 0-5), respectively.

None of the patients experienced a decrease in cardiac ejection fraction or arrhythmia associated with anthracycline use during or after IIVP. No hemorrhagic cystitis or renal toxicity was observed throughout the study period. Three patients developed CNS toxicity (posterior leukoencephalopathy syndrome, confusion, and nonconvulsive status epilepticus) related to ifosfamide. CNS toxicity was reversible in 2 patients. Two toxic deaths (4%), 1 due to CNS toxicity (posterior leukoencephalopathy syndrome) and another due to tumor lysis syndrome, occurred after IIVP. Compared with the first cycle, no increase in the incidence or severity of toxicities was observed throughout the consequent cycles.

As a posttransplantation complication, 3 patients developed congestive heart failure (1 was severe), mainly because of high cumulative doses of anthracyclines during the previous treatments coupled with high-dose mitoxantrone exposure in the conditioning regimen, although the contribution of idarubicin in the IIVP regimen could not be excluded. One of the patients who developed congestive heart failure had a diagnosis of thalassemia intermedia, and transfusion-related hemochromatosis contributed to congestive heart failure. Other complications of the transplantation procedure were myeloid engraftment failure in 1 patient, leading to sepsis and death; delay in platelet engraftment in 1 patient; myelodysplastic syndrome in 1 patient; and secondary AML in 1 patient. None of the patients developed veno-occlusive disease.

DISCUSSION

The grave prognosis in patients with relapsed or refractory NHL or HD who do not receive or are

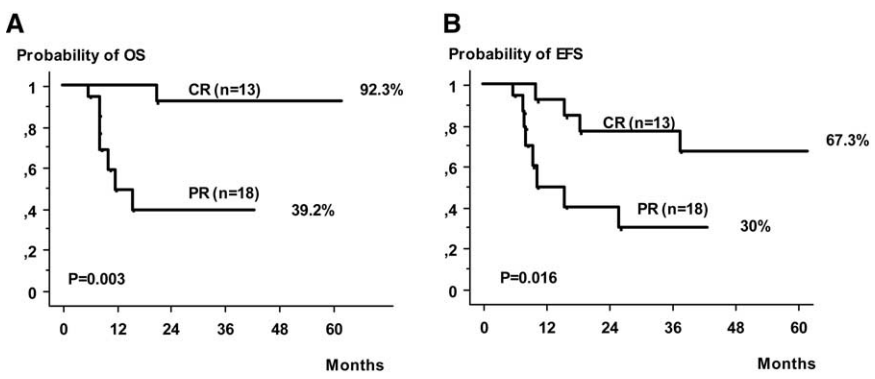

Figure 3. Probability of overall survival (A) and event-free survival (B) separated by IIVP response in patients undergoing ASCT.

Table 4. *WHO Grade 3/4 Hematologic Toxicity of the IIVP Regimen (Total of 102 Courses)*

Toxicity (WHO Grade 3-4)	NHL (n = 55)	HD (n = 47)	Total (n = 102)
Neutropenia	34 (62%)	29 (62%)	63 (62%)
Febrile neutropenia	21 (38%)	12 (26%)	33 (32%)
Treated inpatient	17 (31%)	10 (21%)	27 (26%)
Thrombocytopenia	32 (58%)	26 (55%)	58 (57%)
Anemia	9 (16%)	7 (15%)	16 (16%)

NHL indicates non-Hodgkin lymphoma; HD, Hodgkin disease; WHO, World Health Organization.

not eligible for HDC and ASCT is well known [4,5,8,19,20]. In this study, a combination of ifosfamide, etoposide, and idarubicin was utilized as the salvage regimen to obtain high response rates in order to improve eligibility for ASCT. Because chemosensitivity is a prerequisite for transplantation eligibility in most patients with relapsed or refractory lymphoma, an important variable affecting outcome in patients with relapsed or refractory lymphoma is the cytoreductive capacity of the salvage regimen before ASCT. Because of the lack of randomized studies comparing salvage regimens, it is not possible to interpret one as superior to another. Thus, it is critical to select a salvage regimen that has the potential to induce a high response rate with low nonhematologic toxicity, without cumulative myelosuppression that may subsequently impair stem cell collection.

Salvage regimens are designed in anticipation of resistance to previously used chemotherapy regimens. Anthracyclines are one of the most effective drug groups against lymphoma. Because of a lack of cross-resistance between idarubicin and other anthracyclines, patients who develop resistance to doxorubicin may still respond to subsequent idarubicin therapy [21]. The mdr-1 gene overexpression is strongly associated with the development of a high level of resistance to doxorubicin, but not to idarubicin [22]. In previously untreated lymphoma patients, regimens containing idarubicin 10 mg/m^2 were shown to have the same efficacy as regimens containing doxorubicin, with slightly lower toxicity [23]. In patients with relapsed or refractory lymphoma who had prior anthracycline exposure, idarubicin combinations proved to be active salvage therapies, with response rates ranging between 47% and 72% [13,24,25]. Ifosfamide can elicit responses in patients refractory to cyclophosphamide and has been shown to be active in experimental tumor models resistant to anthracyclines or cyclophosphamide [26-28].

The following findings emerge from this phase II trial. (1) IIVP is an effective salvage chemotherapy regimen with acceptable nonhematologic toxicity before high-dose sequential chemotherapy and ASCT in patients with relapsed or refractory HD or NHL. (2) Acute hematologic toxicity is manageable and reversible but warrants close follow-up. (3) The regimen is effective, with a satisfactory ORR of 76% (63% in NHL and 91% in HD). (4) Remission duration before the initiation of IIVP (primary refractory versus early relapse versus late relapse) is a major factor in predicting response. (5) Response to IIVP (CR versus PR) predicts OS and EFS in patients undergoing ASCT, so efforts should be taken to increase the rate of CR achieved with IIVP. (6) The response in patients with primary refractory disease is 38%, which alerts us to the urgent need for the development of novel strategies in this group of patients.

The high response rate to IIVP compares favorably to the results obtained with the commonly used pretransplantation salvage regimens, including DHAP, Mini-BEAM/Dexa-BEAM (carmustine, etoposide, cytarabine, and melphalan with or without dexamethasone), and ICE [12,29-34]. ICE yields response rate of 66% and a CR rate of 24% [12]. In addition to ICE, several ifosfamide/etoposide-based regimens have been used as salvage therapy. The ORRs and CR rates achieved with dexamethasone, ifosfamide, carboplatin, and etoposide are 73% and 41% in patients with NHL [35]; with ifosfamide, epirubicin, etoposide, they are 77% and 32% in patients with NHL and 81% and 45% in patients with HD [36]; and with dexamethasone, ifosfamide, idarubicin, and etoposide, they are 58% and 26% in patients with NHL/HD [24]. One of the most important factors predicting response to IIVP was prior remission duration. The response rate was 100% in late relapse, 64% in early relapse, and 38% in primary resistance disease. Similarly, several studies have reported remission duration as the predictive factor for response to salvage regimens [30,34,37-39]. However, in contrast to the literature [32,39-41], this was not a prognostic factor for survival in our transplantation patients. Although this study was not powered to detect modest differences, it can be speculated that the poor prognostic effect of remission duration may disappear among patients who respond to IIVP salvage therapy.

In this study, the degree of response (CR versus PR) achieved with the IIVP regimen before the initiation of HDC showed a significant effect on post-transplantation outcome. Similarly, in several studies, patients who underwent transplantation in CR were demonstrated to have better outcomes than patients who underwent transplantation in PR [8,12,40]. This

observation suggests that (1) the quality of response to salvage chemotherapy is an expression of degree of chemosensitivity of lymphoma, and a lymphoma induced into CR by salvage chemotherapy inherently is more likely than a lymphoma induced into PR to be eradicated by high-dose therapy; (2) the efficacy of high-dose therapy may be affected by tumor burden; thus, the potentiating response to the salvage regimen may improve the outcome of HDC.

In patients with relapsed or refractory NHL, CR rates obtained with commonly used salvage chemotherapy regimens (DHAP, ESHAP, Mini-BEAM, and ICE) range from 25% to 35% [9,29,37,42,43]. Rituximab, in addition to its antitumor effect that leads to responses in approximately 30% to 35% of patients with relapsed or primary refractory NHL [44], sensitizes tumor cells to the effects of chemotherapy. The addition of rituximab to the cyclophosphamide, doxorubicin, vincristine, and prednisone regimen significantly increases the CR rate among patients with previously untreated diffuse large B-cell lymphoma [45]. When added to ICE, rituximab doubles the CR rate in patients with relapsed or primary refractory diffuse large B-cell lymphoma [30]. Therefore, adding rituximab to IIVP may augment both overall response and CR rates. Currently, a phase II study of rituximab and IIVP in patients with B-cell NHL has been initiated at our institution to answer this question.

In the light of these results, our future goals while designing a salvage regimen should be to increase the ORR for more patients to be eligible for HDC and to increase the CR rate to obtain a better outcome after ASCT. At present, these goals can be accomplished by combining biotherapy (monoclonal antibodies) with chemotherapeutics.

The treatment-related toxicity of IIVP was mainly hematologic and reversible. Myelosuppression was profound but relatively brief. Despite the use of antibiotic prophylaxis and G-CSF support, neutropenic fever and uncomplicated bacteremias frequently occurred. However, no life-threatening complications or deaths due to infectious complications were observed in this study. The grade 4 thrombocytopenia and grade 4 neutropenia reported with ICE were 47% and 53%, respectively, which were not much different from those with the IIVP regimen [46]. Cumulative myelosuppression that might subsequently impair the harvesting of sufficient stem cells was not seen. The major life-threatening toxicity of IIVP was ifosfamide-induced encephalopathy, and this was fatal in 1 patient. We think that this risk can be minimized by the administration of ifosfamide as a 24-hour infusion [12]. Some currently used salvage regimens can produce severe and irreversible nonhematologic toxicities that might prevent patients from proceeding to ASCT. DHAP and ESHAP may cause renal insufficiency, defined as a doubling of the patient's serum creatinine level, in nearly 20% of patients [4,47] and life-threatening hypomagnesemia. In addition, both regimens were associated with toxic deaths of more than 5% [9,10,48]. Stem cell mobilization after regimens containing high-dose cytarabine (DHAP) or containing stem cell–toxic chemotherapeutic agents such as carmustine and melphalan (Mini-BEAM or Dexa-BEAM) may adversely affect stem cell collections [48-50].

Two patients with HD developed secondary malignancy during follow-up. One had a treatment history of 22 years, including radiotherapy, experienced 3 relapses before the IIVP salvage regimen, and eventually developed myelodysplastic syndrome. The second patient, who developed AML, had had 2 relapses before IIVP and has received radiotherapy. Thus, use of HDC/ASCT earlier, at the time of first relapse, rather than after multiple recurrences may reduce the risk of secondary malignancies.

In conclusion, IIVP is an effective salvage chemotherapy regimen with acceptable toxicity and without adverse effects on PBSC mobilization in patients with relapsed or refractory NHL and HD. In addition to determining patients who qualify for ASCT, the degree of response to IIVP predicts long-term outcome after autologous transplantation.

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