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Salvage Chemotherapy with Dexamethasone, Etoposide, Ifosfamide and Cisplatin (DVIP) for Relapsing and Refractory Non-Hodgkin's Lymphoma

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ABSTRACT: **Background:** There is currently no standard salvage chemotherapy for the 40–50% of patients with non-Hodgkin's lymphoma who fail first-line treatment.
Objectives: To review the experience of a major tertiary medical center with DVIP (dexamethasone, etoposide, ifosfamide and cisplatin) salvage therapy for primary refractory/relapsing NHL.
Methods: We reviewed the records of all patients with NHL who received DVIP salvage therapy during the period 1993 to 2005.
Results: We identified 37 adult patients (mean age 56.3 years): 29 with aggressive lymphoma and 8 with indolent lymphoma. Mean event-free survival was 13.5 months (range 0–82 months), mean time between diagnosis and DVIP treatment 18.5 months (range 2–101), and mean number of DVIP cycles 1.9. Four patients (11%) achieved a complete response and 9 (24%) a partial response (overall response 35%). Consolidation with stem cell transplantation was used in 14 patients with aggressive lymphoma and 4 with indolent lymphoma; 14 patients, all with aggressive lymphoma, responded (12 complete, 2 partial). Of the 10 patients who underwent SCT despite no response to salvage DVIP, 6 achieved a complete response. Five year overall survival since the diagnosis for the whole sample was 39.4 ± 8.7%, and 5 year post-DVIP overall survival 37.6 ± 8.0%. On multivariate analysis, SCT was the strongest predictor of survival (relative risk 0.73, $P < 0.0001$) followed by a high score on the International Prognostic Index (RR 3.71, $P = 0.032$).
Conclusions: DVIP salvage therapy for NHL was associated with a low response rate of 35% but a 5 year post-DVIP survival rate of 37.6%. Patients who are refractory to salvage treatment with DVIP might still be salvaged with SCT.
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KEY WORDS: non-Hodgkin's lymphoma, relapse, salvage chemotherapy, stem cell transplantation

Aggressive non-Hodgkin's lymphomas are potentially curable malignant disorders. The established first-line chemotherapy regimen consists of doxorubicin combined with cyclophosphamide, vincristine and prednisone (CHOP). Nevertheless, about 40–50% of patients either fail to respond (primary refractory disease) or have relapsing disease [1].

The currently used conventional-dose programs for relapsing NHL are associated with a very low rate of response in patients with primary refractory disease. Various second-line regimens were proposed for refractory or recurrent NHL in the 1980s [2-9], but they proved curative in less than 15% of patients with aggressive disease who had failed upfront CHOP-based therapy [2-6]. The chances of success were higher for patients with a partial response to first-line therapy and highest for patients with complete remission after initial therapy, especially if the remission lasted more than one year [9-11]. In 1995, the PARMA trial [12] compared in relapsing patients the effectiveness of salvage with six courses of DHAP (dexamethasone, cisplatin, cytarabine) to two courses of DHAP followed by high dose therapy and autologous bone marrow transplantation in responders to DHAP. The 5 year overall survival rates significantly favored the addition of high dose therapy followed by autologous bone marrow transplantation (53% vs. 32%, $P = 0.038$), and it was consequently adopted by many centers as the second-line approach to patients with relapsed or primary refractory chemosensitive aggressive NHL. Since then, most centers offer stem cell transplantation to patients who achieve a partial or complete response to initial chemotherapy. The expected 5 year event-free survival rate is 40–45%.

In 1989, Haim and co-workers [13,14] initiated a Phase II trial of 4 days treatment with DVIP (dexamethasone, etoposide, ifosfamide, cisplatin) in patients with primary refractory or recurrent aggressive NHL [Table 1]. Thereafter, several hematology centers in Israel introduced it as their salvage regimen. In the present report, we summarize the long-term results of the DVIP protocol in an unselected

NHL = non-Hodgkin's lymphoma
SCT = stem cell transplantation
RR = relative risk

CHOP = cyclophosphamide, adriamycin, vincristine and prednisone
DHAP = dexamethasone, cisplatin, cytarabine
DVIP = dexamethasone, etoposide, ifosfamide and cisplatin

Table 1. Schedule of DVIP regimen given every 3 weeks

Drug	Daily dose*	Mode of administration	No. of days
Cisplatin	20 mg/m²	IV in saline (250 ml) over 30 min	1–4
Etoposide	75 mg/m²	IV in saline (500 ml) over 1 hr	1–4
Ifosfamide	1200 mg/m²	IV in saline (300 ml) over 2 hrs	1–4
Dexamethasone	40 mg	IV bolus, 20 mg before cisplatin and 20 mg after ifosfamide infusion	1–4

DVIP = dexamethasone, etoposide, ifosfamide, cisplatin.
*Maximum daily doses of cisplatin, etoposide, ifosfamide.

group of patients with refractory or recurrent aggressive or indolent lymphoma treated at our institution over a 12 year period.

PATIENTS AND METHODS

We reviewed the hospital records of all consecutive patients who received DVIP salvage therapy for NHL between 1993 and 2005. Clinical and laboratory data were retrieved from the hospital databases. The diagnosis of NHL was established by tissue biopsy and reclassified according to the World Health Organization classification of tumors [15]. The International Prognostic Index score was calculated for patients with aggressive lymphoma [16] and the Follicular IPI score for patients with indolent lymphoma [17] at diagnosis and before DVIP treatment. The DVIP schedule was given over 4 consecutive days, as shown in Table 1 [13,14]. For analysis, patients were divided into subgroups as follows:

- **Disease stage:** group I (stages I and II), group 2 (stages III and IV)
- **Nodal status:** group 1 (0–3), group 2 (≥ 4)
- **Extranodal status:** group 1 (0, 1), group 2 (> 1)
- **IPI score:** group 1 (0–2), group 2 (3–5)
- **FLIPI score:** group 1 (0–2), group 2 (> 2)

Time to DVIP administration was calculated from the date of diagnosis to the date of the first DVIP treatment. DVIP-associated overall survival was calculated from the date of DVIP treatment to death or end of the study. Event-free survival and overall survival were calculated from the date of diagnosis to the date of disease progression, relapse, or death.

STATISTICAL ANALYSIS

Statistical analysis was performed using the SPSS 12.1 software program (SPSS Inc., Chicago, IL, USA). Student's t-test was used to identify associations between infectious complications and mean nadir blood counts, and between patient age and response to DVIP treatment. The Kaplan-Meier product-limit method was used to calculate EFS and overall survival. The log rank test was used to compare survival rates between subgroups of patients. The relative influence of different variables on survival was studied by multivariate survival analysis using Cox regression.

IPI = International Prognostic Index
FLIPI = follicular IPI

RESULTS

PATIENT CHARACTERISTICS AT DIAGNOSIS [TABLE 2]

Our file review identified 37 patients who received DVIP as salvage therapy. Age range of the sample was 21–78 years (mean 56.3 years); 21 (57%) were female. Twenty-nine patients had aggressive lymphoma: diffuse large B cell lymphoma in 26, and peripheral T cell lymphoma in 3. The other eight were diagnosed with follicular lymphoma. First-line treatment in the patients with aggressive lymphoma consisted of adriamycin-based protocols [Table 2]; in four cases rituximab was included in the regimen. Fourteen patients with aggressive disease (49%) achieved complete remission after primary treatment, 4 (13%) achieved a partial response and 11 (38%) had refractory disease at presentation.

PATIENT CHARACTERISTICS BEFORE DVIP TREATMENT

The mean EFS time before DVIP treatment was 13.5 months (range 0–82), and the mean interval between diagnosis and DVIP treatment was 18.5 months (range 2–101).

Seven patients received two lines of chemotherapy before DVIP treatment (three with aggressive lymphoma and four with indolent lymphoma); one patient (aggressive lymphoma) received three lines of treatment, and one patient (indolent lymphoma) received four lines. Twenty patients underwent repeated biopsy study, of whom 15 showed the same histological diagnosis and 5 showed a histological transformation – 4 from indolent to aggressive lymphoma and 1 from aggressive to indolent lymphoma. Before DVIP treatment 13 patients (35%) had localized disease (stages and II), and 24 patients (65%) had disseminated disease (stages III and IV). B symptoms were recorded in 52% of patients, bulky disease (> 10 cm) in 22%, bone marrow involvement in 18%, extranodal disease in 64% and elevated lactate deyhydrogenase in 46%. Of the patients with aggressive lymphoma 58% had a low IPI score of 0–2, while 62.5% of patients with follicular lymphoma had a low FLIPI score.

DVIP THERAPY AND STEM CELL COLLECTION AND TRANSPLANTATION

Patients received between one and four DVIP cycles (mean 1.9). Granulocyte colony-stimulating factor was administered

EFS = event-free survival

Table 2. Patient characteristics at diagnosis and first-line treatment

	All patients	Aggressive lymphoma	Indolent lymphoma
No. of patients	37	29	8
Mean age (yrs, range)	56.3 (21–79)	56.1 (21–78)	57.0 (41–79)
Gender: M/F	1/1.3 (16/21)	1/1.9 (10/19)	1/3 (2/6)
Stage			
I	5 (13.5%)	4 (14%)	1 (12.5%)
II	8 (22%)	7 (24%)	1 (12.5%)
III	9 (24%)	8 (28%)	1 (12.5%)
IV	15 (40.5%)	10 (34.5%)	5 (62.5%)
Histology			
Aggressive	29 (78%)	29 (100%)	
Diffuse large B cell	26 (70%)	26 (90%)	
Peripheral T cell	3 (8%)	3 (10%)	
Indolent	8 (22%)		8 (100%)
Follicular (grade I-III)	8 (22%)		8 (100%)
Grade I	4 (11%)		4 (50%)
Grade II	3 (8%)		3 (37.5%)
Grade III	1 (3%)		1 (12.5%)
B symptoms	22 (59.5%)	17 (59%)	5 (62.5%)
Bulky disease	12 (32%)	10 (34%)	2 (25%)
5–10 cm	6 (16%)	5 (18%)	1 (12.5%)
› 10 cm	6 (16%)	5 (18%)	1 (12.5%)
Bone marrow involvement	11 (30%)	5 (18%)	6 (75%)
Extranodal disease	25 (76%)	20 (69%)	5 (62.5%)
Elevated serum LDH	14 (39%)	12 (41%)	2 (28.6%)
IPI			
0–2		16 (55%)	
3–5		11 (38%)	
Unknown		2 (7%)	
FLIPI			
0–2			3 (37.5%)
3–4			5 (62.5%)

	All patients	Aggressive lymphoma	Indolent lymphoma
First-line treatment			
Chlorambucil	1		1
Fludarabine	1		1
R-COP	2		2
Irradiation	1		1
CHOP	23	20	3
R-CHOP	4	4	
MACOP-B	3	3	
ProMACE-CytaBOM	1	1	
CNOP	1	1	
Response to first-line treatment			
Overall response	23 (62%)	18 (62.1%)	5 (62.5%)
Complete response	18 (49%)	14 (48.3%)	4 (50%)
Partial response	5 (13%)	4 (13.8%)	1 (12.5%)
No response	14 (38%)	11 (37.9%)	3 (37.5%)
Second-line treatment		3	4
≥ Third-line treatment		1	1
Irradiation treatment	8 (21.6%)	6 (21%)	2 (25%)

R-COP = chlorambucil, fludarabine, rituximab, cyclophosphamide, vincristine, prednisone; CHOP = cyclophosphamide, adriamycin, vincristine, prednisone; R-CHOP = rituxumab+CHOP; MACOP-B = methotrexate, adriamycin, cyclophosphamide, vincristine, prednisone, bleomycin; ProMACE = cytaBOM-prednisone, adriamycin, cyclophosphamide, etoposide, cytarabine, bleomycin, vincristine, methotrexate; CNOP = cyclophosphamide, mitoxantrone, vincristine, prednisone, LDH = lactate dehyrogenase.

to 28 patients. After the first cycle of DVIP, the mean nadir platelet count was 118,000/μl (range 9000–496,000), mean nadir hemoglobin level 10.5 g/dl (range 7–14), and mean nadir neutrophil count 1381/μl (range 0–8395). After the second cycle of DVIP, the mean nadir values were as follows: platelet count 125,318/μl, hemoglobin level 9.73 g/dl, and neutrophil count 1610/μl. Corresponding values after the third cycle were 53,750/μl, 9.3 g/dl and 715/μl. Infectious complications were recorded in 13 patients (35%), including 9 with aggressive lymphoma at diagnosis. There was no significant association of mean patient age, nadir values of white blood cell count, neutrophil count or platelet count, with occurrence of infection.

The overall rate of response to DVIP was 35%. Four patients (11%) showed complete response, 9 (24%) partial response, and 16 (43%) no response; in the remaining 8 patients (22%) the disease progressed. Stem cell collection was performed in 23 patients (62%). The mean number of CD34 cells collected (known in 12 patients) was 6.8 x 106/kg (range 1.64–20 x 106). Eighteen patients, 14 with aggressive lymphoma at diagnosis and 4 with indolent lymphoma, received consolidation with SCT after DVIP: 17 autologous SCT and 1 (with indolent lymphoma) allogeneic SCT. Three of the 18 patients, all with aggressive lymphoma, had shown complete response to DVIP, and all 3 also showed complete response to SCT and are currently alive. Five of the 18 patients had a partial response to DVIP, of whom 3 achieved a complete response to SCT and are currently alive, 1 achieved a partial response, and 1 died during the procedure. The other 10 patients underwent SCT despite no previous response to DVIP: 6 achieved a complete response and are currently alive, and 4 had a partial (1 patient) or no response and died thereafter.

Overall, of the 14 patients with aggressive lymphoma who underwent SCT, 12 (86%) had a complete response and 2 (14%) a partial response, for an odds ratio of response to SCT of 100%. Only 1 of the 12 patients who achieved a complete response relapsed later. Of the four patients with indolent lymphoma who underwent SCT, only one achieved complete response and two progressed soon after transplantation. The disease later relapsed in the patient with the complete response.

Nineteen patients in the series did not undergo SCT for the following reasons: indolent lymphoma and good response to DVIP (one patient), prolonged complete response after two salvage consolidation courses of DVIP (one patient with aggressive lymphoma), older age (eight patients) and progressive active disease with bone marrow involvement (nine patients).

Eighteen patients received treatment other than SCT after DVIP: 6 received more than one protocol or mode of therapy, 5 received radiation treatment, and 3 received rituximab and other salvage protocols.

SURVIVAL

All patients: Twenty-two patients (59.5%) died by the end of the study period: 17 with aggressive lymphoma and 6 with indolent lymphoma at diagnosis. The 5 year overall survival rate for the 37 patients was 39.4 ± 8.7%, and the 10 year survival rate 27.6 ± 9.4%. The mean survival time was 64.4 ± 9.9 months and the median 51 ± 20.1 months. The mean overall EFS time (after diagnosis) was 13.5 ± 3.3 months: 50.6 ± 10.3 months in the patients with localized disease (stage I, II) at diagnosis (median 51 ± 25.6) and 11.8 ± 3.5 months (median 6) in the patients with advanced disease (stage III, IV) ($P = 0.0005$). The mean EFS time after DVIP therapy in the 18 patients who achieved a complete response to the first-line treatment was 40.3 ± 7.8 months (median 37 ± 10.9). The overall 5 year post-DVIP survival rate was 37.6 ± 8.0% (mean survival time 52.4 ± 9.7 months, median 11 ± 4.2 months).

Patients with indolent disease at diagnosis (n=8): The mean EFS time for the eight patients with indolent disease at diagnosis was 11.5 ± 4.5 months. Their mean 5 year survival rate was 25 ± 15.3% (mean 54.6 ± 18.9 months, median 23 ± 20.5 months), and their mean 5 year post-DVIP survival rate 25 ± 15% (mean time 36 ± 16 months, median 11 ± 3.5 months).

Patients with aggressive lymphoma at diagnosis (n=29): Mean EFS time in the 29 patients with aggressive lymphoma was 32.1 ± 7.4 months (median 17.0 ± 14 months). There was a statistically significant correlation of EFS and IPI score at diagnosis. Patients with a low IPI score (0–2) had a mean EFS of 48.5 ± 9.6 months (median 51 ± 13.9) compared to 6.9 ± 2.2 months (median 6) in the patients with a high IPI score (3–5, $P = 0.0013$). The mean 5 year survival rate in the aggressive lymphoma group was 43.8 ± 10.2% (mean time 63.1 ± 10.4 months, median 55 ± 22.6 months). There was a statistically significant correlation of overall survival with overall response (complete + partial) to first-line treatment. Patients who responded to first CHOP or CHOP-like treatment had a mean survival time of 76.5 ± 11.7 months (median 76 ± 17.6 months) compared to 23.8 ± 6.9 months (median 8 ± 1.1 months) for the patients with no response or progressive disease ($P = 0.016$).

A significant correlation was found between overall survival and complete response to DVIP therapy: all four patients who achieved a complete response were alive at the end of the study (follow-up time 41, 80, 94, and 105 months), whereas of those who did not show a complete response 17 died and 8 are alive with a 5 year survival of 33.8 ± 10.8% ($P = 0.022$). A correlation was also found in the aggressive lymphoma group between overall survival and IPI score at diagnosis. In patients with a low IPI score (group 1, 0–2, n=16), the 5 year survival rate was 62.4 ± 13.7% (mean time 85.45 ± 12.5 months, median 76 ± 25.26 months) compared to zero (mean time 19.3 ± 5.0 months, median 14 ± 6.6 months) in those with a high IPI score (group 2, 3–5; n=10) ($P < 0.0001$).

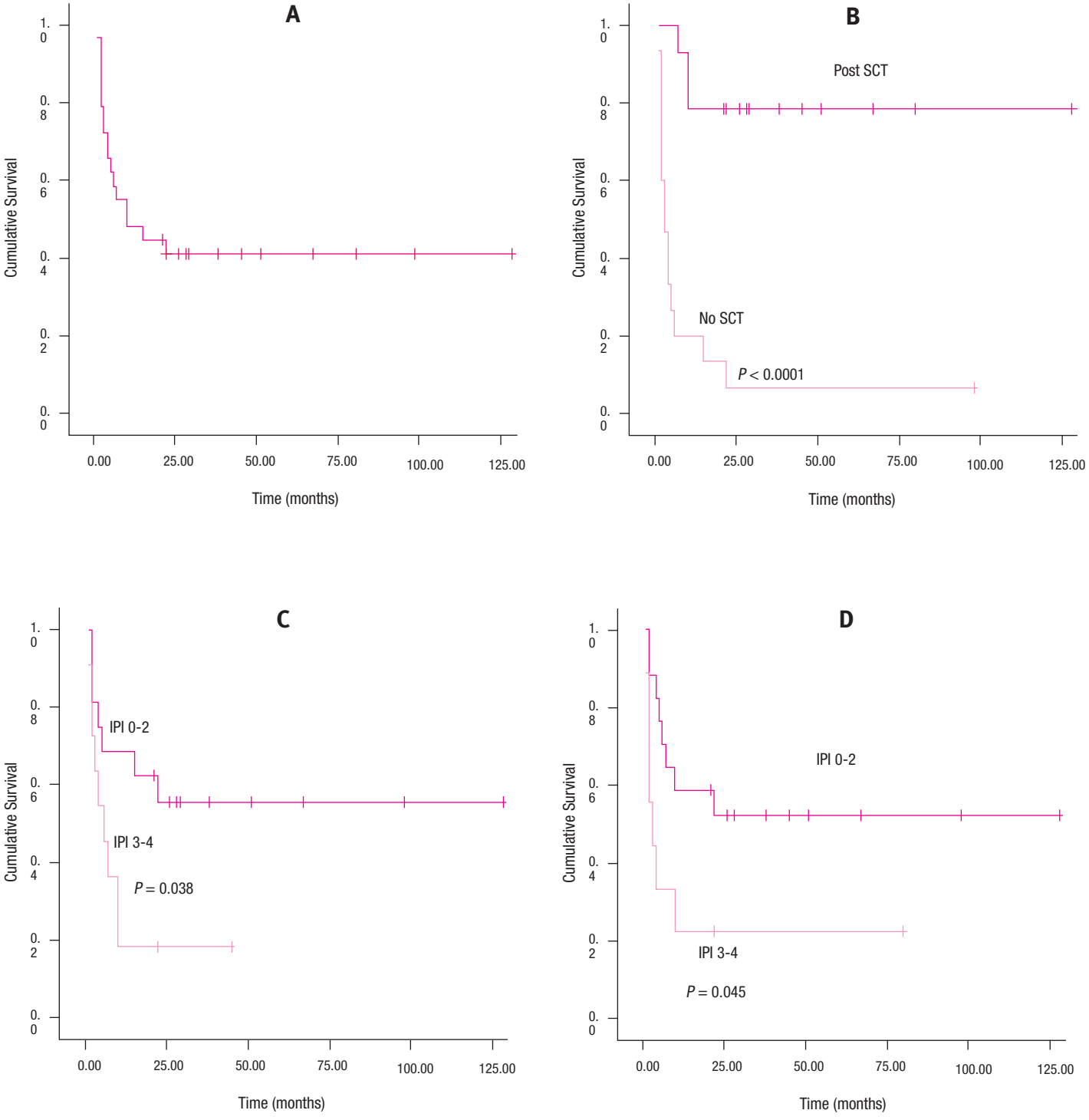
Post-DVIP survival and prognostic parameters [Table 3, Figure 1]. The 5 year post-DVIP overall survival rate was 41.1 ± 9.2%. The mean survival time was 56.1 ± 11.2 months and the median 10 ± 7.2 months [Figure 1A]. Several factors correlated significantly with post-DVIP survival on univariate analysis [Table 3]: consolidation with or without SCT ($P < 0.0001$) [Figure 1B], IPI at diagnosis ($P = 0.038$) [Figure 1C], IPI before DVIP ($P = 0.045$) [Figure 1D], disease stage before DVIP ($P = 0.051$), and response to DVIP (complete response vs. other, $P = 0.033$). No correlation was found between post-DVIP survival and lactate dehydrogenase level before onset of DVIP treatment. On multivariate analysis with Cox regression, SCT was found to have the strongest predictive value for post-DVIP survival (relative risk 0.73, $P < 0.0001$). Of the 14 patients with aggressive disease who underwent SCT, 11 were alive at the end of follow-up, with a 5 year survival rate of 78.6 ± 11% and mean survival time of 102.5 ± 13 months (median not reached). By contrast, of the 15 patients with aggressive disease who did not undergo SCT, 14 died by the end of the study, with a 5 year survival rate of only 7.8 ± 11% and mean survival time of 11.4 ± 6.1 months (median 3 ± 1 months) ($P < 0.0001$) [Figure 1B]. Response to DVIP did not add to the significance of these findings. A high IPI was significantly associated with poor prognosis (RR 3.71, $P = 0.032$).

Table 3. Prognostic factors: correlation between various parameters and survival post-DVIP treatment in 29 patients with aggressive lymphoma at diagnosis

Prognostic parameter	Mean survival (mos)	Median survival (mos)	5 yrs survival (%)	*P* value
IPI at diagnosis 0–2 (n=16) IPI at diagnosis 3–5 (n=11)	74.5 ± 15.2 12.3 ± 4.7	Not reached 6 ± 2.2	55.6 ± 12.6 0	0.038
IPI before DVIP 0–2 (n=17) IPI before DVIP 3–5 (n=9)	70.5 ± 14.8 20.4 ± 10.6	Not reached 3 ± 1.5	52.3 ± 12.3 22.2 ± 13.9	0.045
Stage before DVIP I-II (n=12) III-IV (n=17)	 77.6 ± 17.2 26.47 ± 8.4	 Not reached 4 ± 1	 57 ± 14.6 29.4 ± 11.1	 0.051
Age before DVIP ≤ 60 yrs (n=12) › 60 years (n=17)	 78.7 ± 16.9 31.8 ± 10.4	 Not reached 5 ± 1.5	 58.3 ± 14.2 29.4 ± 11.1	 0.07
OR to DVIP (CR+PR) (n=9) No response to DVIP (n=20)	67 ± 14.6 41 ± 12.6	Not reached 5 ± 4.4	66.7 ± 16 29.2 ± 10	0.083
CR to DVIP (n=4) No CR to DVIP (n=25)			100% 31.5 ± 9	0.033
Stem cell transplantation yes (n=14) no (n=15)	 102.5 ± 13 11.4 ± 6.1	 Not reached 3 ± 0.9	 78.6 ± 11 6.7 ± 6.4	 ‹ 0.0001

IPI = International Prognostic Index, DVIP = dexamethasone, etoposide, ifosfamide, cisplatin, OR = overall response, CR = complete response, PR = partial response

Figure 1. Post-DVIP survival in patients with aggressive lymphoma. **[A]** All 29 patients, **[B]** Patients consolidated with or without SCT, **[C]** Patients with low vs. high IPI at diagnosis, **[D]** Patients with low vs. high IPI before DVIP.



DISCUSSION

In this study we review our experience with DVIP salvage therapy in an unselected group of patients with refractory (38%) or relapsing (62%) NHL. Almost half the patients were further consolidated with SCT.

We found an overall response rate to DVIP of only 35% (13 patients), and a complete response rate of only 11% (4 patients). Although these results are poor, it is very interesting that SCT can salvage so many patients. Consolidation SCT was administered to 18 patients. Of the 10 patients who underwent SCT despite a lack of response to salvage DVIP, 6 achieved a complete response and all of them are still alive. The 5 year survival rate of the whole sample was 39.4% and the 10 year survival rate 27.6%. However, for the 14 patients with aggressive lymphoma who underwent SCT after DVIP, the 5 year survival rate was considerably higher, at 76.5% compared to only 7.8% for those who did not receive SCT consolidation. Univariate analysis identified several factors predictive of post-DVIP survival in patients with aggressive lymphoma, namely IPI at diagnosis, IPI before DVIP treatment, stage before DVIP treatment, complete response to DVIP treatment, and SCT consolidation after DVIP treatment. When these factors were entered into a multivariate model, SCT proved to be the strongest predictive factor ($P < 0.0001$), followed by high IPI ($P = 0.032$). Achieving a complete response to DVIP did not add to the statistical significance.

The salvage treatment for patients with refractory and relapsing NHL includes different drugs from those in the initial regimen in order to prevent cross-resistance and cumulative toxicity. It generally consists of platinum-based or ifosfamide-based chemotherapy, usually in combination with etoposide and sometimes with other drugs, such as mitoxantrone or methotrexate. Commonly used pre-SCT second-line regimens for relapsed DLBCL are dexamethasone, cisplatin, cytarabine (DHAP) or etoposide, methylprednisone, cisplatin and cytarabine (ESHAP), or ifosfamide, carboplatin, etoposide (ICE). The DHAP protocol has been the most frequently used for decades, but it incorporates only two drugs and has dose-limiting renal toxicity.

The reported response rates to all three regimens are similar: overall 60–70%, complete 25–35%. They are associated with a 2 year survival rate of 25–60% and a 5 year survival rate of 7–30% [2,6,8,9]. Although one retrospective analysis suggested a greater efficacy for ESHAP than DHAP [9], in the absence of a randomized study comparing two salvage regimens in relapsing DLBCL the optimal second-line regimen remains unclear.

The benefit of autologous SCT is thought to be limited to chemosensitive relapsed or primary refractory aggressive NHL [12,18,19], although about 20% of patients with chemoresistant disease achieve long-term survival [18]. To maximize the number of patients who achieve a complete response to SCT, many investigators have attempted to develop more effective second-line pre-SCT regimens. Others have sought to determine prognostic factors to identify the patients most likely to benefit from SCT, so that the other patients will be spared unnecessary interventions and can be offered alternative, often experimental, therapies.

In the earlier PARMA [12] trial, only patients less than 60 years old with a complete response to previous therapy and absence of bone marrow or central nervous system involvement were included. Of the initial 215 patients enrolled, only 109 were ultimately randomized; the others failed to respond to salvage therapy with DHAP. Further analyses showed that the IPI at the time of relapse was highly correlated with overall survival in the conventional therapy arm, but not in the SCT arm [20]. In addition, time to relapse (< 12 months vs. > 12 months) strongly correlated with EFS and overall survival irrespective of the DHAP response or the type of further treatment after DHAP (high dose therapy, autologous bone marrow transplantation or continuation of DHAP) [21]. Hamlin et al. [22] reported the outcome of a homogeneous population of 150 patients with relapsed or refractory DLBCL receiving ICE chemotherapy followed by high dose treatment and autologous SCT. They confirmed the predictive value of the IPI, showing that patients with a score of 2 or 3 at the time of relapse, when analyzed by intent to treat, had 4 year progression-free survival and overall survival rates of only 16% and 18%, respectively, compared with 70% and 74% for patients with an IPI score of 0.

In a recent study, Kewalramani and team [23] added rituximab to the salvage ICE regimen in patients with relapsed DLBCL and found a 15% improvement in response rate. The phase II CORAL study of rituximab-containing second-line regimens (rituximab-DHAP or rituximab-ICE) in patients with relapsed DLBCL is currently ongoing in centers in Europe, the USA, Australia and Israel.

The emergence of new, more effective first-line therapies for aggressive NHL also raises questions about the most effective salvage strategies. The addition of rituximab to CHOP and other first-line regimens for aggressive NHL has been shown to improve response and survival rates in patients with DLBCL [24]. Similar improvements were reported for dose-dense regimens, including CHOP-14 [25]. It is unclear whether high dose treatment and autologous SCT will prove to be effective salvage strategies for patients who relapse after these regimens.

This report has many limitations that are common in studies describing salvage protocols for NHL. First, it is a

DLBCL = diffuse large B cell lymphoma
ESHAP = etoposide, methylprednisone, cisplatin and cytarabine
ICE = ifosfamide, carboplatin, etoposide

retrospective analysis. Second, it describes a relatively small number of unselected patients diagnosed with heterogeneous lymphoma subtypes and most of them were treated a long time ago (since 1993) – before the improvements in diagnostic procedures and supportive care and the addition of rituximab to the chemotherapy regimens. Third, it should be noted that most of the patients in the present study were treated before PET/CT (positron emission tomography - computed tomography) became available to confirm complete remission in patients with residual masses on CT. It is therefore possible that some of the patients with no response to DVIP according to the CT examination were indeed already in complete remission.

However, it is important to emphasize that until now the best second-line therapy in relapsed/refractory lymphoma is unclear and we are awaiting the results of the international CORAL trial that compares R-ICE with R-DHAP.

CONCLUSIONS

The DVIP regimen in patients with refractory or relapsing NHL is associated with an overall response rate of only 35% but a 5 year post DVIP survival rate of 37.6%. Patients refractory to salvage treatment with DVIP might still be salvaged with SCT.

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