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Salvage chemotherapy with IAPVP-16 for advanced refractory or relapsed follicular lymphomas

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ABSTRACT

Background and Objectives. **Patients with follicular lymphoma (FL) who do not respond to first-line chemotherapy or those who relapse after obtaining a remission have a poor outcome with standard treatment. In an effort to obtain a high rate of responses we designed an intensive brief duration salvage chemotherapy regimen.**

Design and Methods. **Forty-four consecutive patients with advanced follicular lymphoma were treated. Nine had primary refractory disease, 13 had achieved a partial remission, 16 were in untreated relapse or progression and six were in chemosensitive relapse. The IAPVP-16 regimen consists in ifosfamide 5 g/m² iv on day 1, etoposide 100 mg/m² iv on days 1-3, Ara-C 1.2 g/m²/12 hours iv on days 1-2 and methylprednisolone, 80 mg/m² iv on days 1-5. Granulocyte colony-stimulating factor was used from day 6 in 68 of 114 courses.**

Results. **Eighteen patients (41%) achieved a complete remission and 17 (39%) a partial remission, for an overall response rate of 80%. There were no treatment-related deaths. All treatment courses were followed by severe neutropenia, and 66% also by severe thrombocytopenia, but there were no serious hemorrhagic events. Neutropenic fever occurred in 56% of the courses with only four severe infections. Non-hematologic toxicity was modest. Twenty-eight patients proceeded to a stem cell transplantation. After a median follow-up of 25 months (range 4-95), the median progression-free survival and overall survival are 32 and 58 months, respectively. The median PFS was 33 months for responders and 11 months for non-responders (p=0.05), while the median OS has not been reached in responders and is 23 months in non-responders (p=0.0005).**

Interpretation and Conclusions. **The IAPVP-16 regimen is an effective and well tolerated treatment for advanced FL, allowing most eligible patients to proceed with significant tumor reduction to high-dose therapy and SCT.**

Key words: salvage chemotherapy, follicular lymphomas, IAPVP-16

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Most patients with advanced follicular lymphoma (FL) are initially sensitive to first-line combination chemotherapy regimens, usually including an alkylating agent with or without an anthracycline. Patients who do not respond to front-line therapy or those who relapse following a first or subsequent remission have a relatively poor short-term prognosis with standard chemotherapy (CT).[1-3] Various salvage CT regimens have been studied in an effort to induce sustained remissions in such cases. The most effective traditional salvage protocols include combinations of ifosfamide plus etoposide[4,5] or Ara-C plus cisplatinum,[6,7] although more novel approaches with purine analogs or monoclonal-antibody based therapies are yielding promising results.[8-15]

We report the results of an intensive brief duration salvage regimen including ifosfamide, etoposide and high-dose Ara-C (IAPVP-16) for patients with refractory or relapsed FL.

Design and Methods

Patients

Patients with advanced FL defined according to the REAL classification[16] were eligible for treatment, with central histology review for referred patients. Histologic samples of cases treated before 1995 were reviewed to confirm the diagnosis of FL according to the REAL classification. Eight additional patients with mantle-cell lymphoma and four with small lymphocytic lymphoma were treated with IAPVP-16, but these cases are not included in this report.

Patients had to be refractory to a first-line anthracycline-containing combination CT (CHOP) or have relapsed or progressed after obtaining a remission. Eligible patients had to be between 18 and 70 years of age and have adequate organ function to tolerate intensive CT.

Forty-four consecutive patients were treated between October 1990 and January 1998. Patient characteristics are shown in Table 1. There were 24 men and 20 women, with a median age of 49 years (range 29-70). The median time from initial diagnosis to treatment was 18 months (range 2-133), and the median number of prior CT regimens was one

Table 1. Patient characteristics.

Characteristics	*No.*
All patients	44
Male/Female	24/20
Median age (range)	49 yrs. (29-70)
Histology	
Follicular, nodular	36
Follicular, diffuse	6
Follicular, transformed to DLCL	2
Stage	
III	10
IV	34
Chemosensitivity	
First PR	13
Untreated relapse	16
Sensitive relapse (<PR)	6
Resistant disease	9
Number of extranodal sites	
1	12
2	3
LDH	
Normal	37
High	7
Beta-2-microglobulin	
Normal	19
High	4
Unknown	21
Tumor mass > 10 cm	5
ECOG	
0-1	37
2	7
International Prognostic Index	
Low	30
Low-intermediate	7
High-intermediate	5
High	2
Median number of prior CT regimens (range)	1 (1-4)
Prior XRT	2
Median time from diagnosis to treatment (range)	18 mo.(2-133)

DLCL: Diffuse large cell lymphoma. PR: partial response. CT: chemotherapy. XRT: radiotherapy.

(range 1-4). Nine patients had primary refractory disease, 13 had achieved a partial remission, 16 were in untreated relapse or progression after an initial complete or partial remission and six were in chemosensitive relapse but their response had not reached a partial remission. Thirty patients had a low (0-1) international prognostic index (IPI) before IAPVP-16, and two cases had histologic signs of transformation to large-cell lymphoma.

Treatment schedule

The IAPVP-16 regimen consists in ifosfamide, 5 g/m^2 as a 2-hour intravenous (iv) infusion on day 1, etoposide (VP-16), 100 mg/m^2 iv over 1 hour on days 1, 2 and 3, Ara-C, 1.2 g/m^2 every 12 hours iv over 2 hours on days 1 and 2 and methylprednisolone, 80 mg/m^2 iv on days 1 to 5. Granulocyte colony-stimulating factor (G-CSF) was used from day 6 until neutrophil recovery in 68 of 114 courses. Supportive care consisted in antiemetics, allopurinol, acyclovir, and most patients received antibacterial prophylaxis. Treatment cycles were repeated at 28 to 35-day intervals. Treatment-related toxicity was graded according to the World Health Organization criteria.

Since all patients with relapsed or refractory FL will ultimately progress and die of their disease irrespective of the response to salvage therapy, from 1992 onward the protocol was amended so that all patients under the age of 55 years were to proceed to an autologous or allogeneic stem cell transplant (SCT) following IAPVP-16. Chemosensitive patients were candidates for autologous SCT, while for patients not reaching a partial response, allogeneic SCT was preferred if a sibling donor was available.

Response criteria

Before and after treatment disease response was assessed clinically and by standard radiologic and histologic methods. Complete remission (CR) was defined as no measurable disease including no bone marrow (BM) involvement by conventional cytology and histology. Partial response (PR) consisted of at least a 50% reduction in the sum of the products of perpendicular diameters of all measurable lesions before treatment, with BM involvement of less than 20%. Response less than a PR was considered as no response (NR), and progressive disease (PD) reflected involvement of new sites after treatment, recurrence in originally involved sites, increase by more than 25% in original tumor masses and/or reappearance of BM involvement.

Statistical considerations

The main parameters analyzed were treatment-related toxicity, disease response, progression-free survival (PFS), defined as the interval from the first day of treatment until relapse, disease progression, death or last follow-up, and overall survival (OS), defined as the interval from the first day of treatment until death or last follow-up. Since SCT was the planned therapy for most patients in our protocol, follow-up was not censored at transplant. The closing date for analysis was June 15, 1998. PFS and OS were calculated by the Kaplan-Meier method, and the log-rank test was used to establish differences in these parameters for different variables. Fisher's exact test was used to compare proportions such as response rates according to various parameters, and the Student's t-test was used to compare means.

Results

Toxicity

Forty-four patients received a total of 114 courses of IAPVP-16, with a median of two courses per patient (range 1-6). There were no treatment-related deaths. All treatment courses were followed by severe

neutropenia (neutrophils < 0.5×10^9/L), and 66% also by severe thrombocytopenia (platelets < 20×10^9/L). The mean duration of neutropenia was 5 days (range 2-10) in patients treated with G-CSF and 9 days (range 5-13) in those not ($p < 0.001$). The mean duration of severe thrombocytopenia was 4 days (range 1-13), and there were no serious hemorrhagic events. Neutropenic fever occurred in 64 cycles (56%). Most (n=43) were fevers of unknown origin, with eight uncomplicated bacteremias, nine minor respiratory or mucocutaneous infections and four severe infections (two Gram-negative septic shocks and two pneumonias of unknown cause). Non-hematologic toxicity was modest, and only three courses were complicated by grade 3-4 hepatic toxicity. Mild nausea and vomiting occurred in 62% of the patients, and 15% developed grade 1 neurotoxicity, usually manifested as somnolence immediately after the infusion of ifosfamide.

Response and outcome

Eighteen patients (41%) achieved CR and 17 (39%) PR following IAPVP-16, for an overall response rate of 80% (95% CI, 67-92). Response rates according to various patient features are shown in Table 2. Of nine primary resistant patients, four achieved a CR and two a PR. The maximal response occurred in all patients after two or three cycles of IAPVP-16. Seven patients received one to three further courses (total four to six) since they were not eligible to receive a SCT. Variables analyzed for their predictive value for achieving a response (CR+PR) to IAPVP-16 were age, sex, proven chemosensitivity, IPI, time from diagnosis to IAPVP-16 and number of prior CT regimens. As shown in Table 2, only the IPI (low/low-intermediate vs high-intermediate high) was associated with the chance of obtaining a response (86% vs 43%, respectively, $p = 0.02$). Twenty-eight patients proceeded to a SCT at a median time of 4 months (range 1-7) from treatment.[17] Ten of these patients were in CR, 11 in PR and seven had not responded to IAPVP-16. Twenty-three patients received an autologous SCT. Four received a bone marrow transplant and nineteen a peripheral blood stem cell transplant; two bone marrow transplants and six peripheral blood stem cell transplants were purged by an immunomagnetic method using anti-B antibodies, and five patients received an allogeneic SCT. Early transplant-related mortality occurred in one autologous and two allogeneic SCT recipients, and five responder patients have relapsed after an autograft.

The PFS and OS curves are shown in Figure 1. After a median follow-up of 25 months (range 4-95), 10/35 responders have progressed (five after SCT). The median PFS and OS are 32 and 58 months, respectively, and the estimated 3-year PFS and OS are 43% (95% CI, 24-62) and 66% (95%CI, 49-84), respectively, for all patients (Figure 1). Although these intervals were certainly influenced by the SCT that most patients received after salvage therapy with IAPVP-16, comparison of the PFS and OS between responders and non-responders showed significant differences. The median PFS was 33 months for responders and 11 months for non-responders ($p = 0.05$), while the median OS has not been reached in responders and is 23 months in non-responders ($p = 0.0005$). Overall, nine patients have died from progressive lymphoma at 6-58 months (median 27 months) from the start of IAPVP-16. Of the 35 responders, 14 did not proceed to SCT and their median PFS and OS were 32 and 43 months, respec-

Table 2. Patient features and response.

Feature	*N[a] of patients*	*% CR + PR*	*p*
All patients	44	80	–
Age			
< 50 years	24	83	NS
≥ 50 years	20	75	
Sex			
Male	24	75	NS
Female	20	85	
Proven chemosensitivity			
Yes*	19	89	NS
No°	25	72	
International Prognostic Index			
Low/low-intermediate	37	86	0.024
High/high-intermediate	7	43	
Time from diagnosis			
< 18 months	23	87	NS
≥ 18 months	21	71	
N° of prior CT regimens			
1	30	87	NS
>1	14	64	

*CT: chemotherapy. *First PR + sensitive relapse; °untreated relapse + resistant disease.*

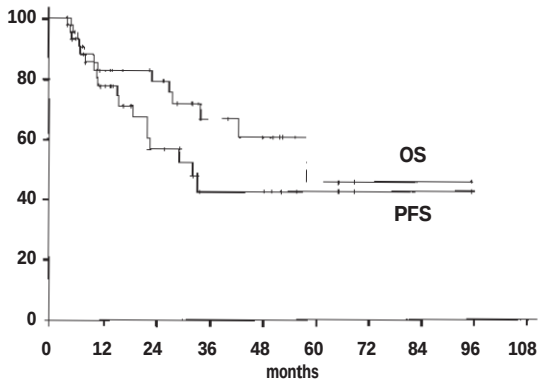

Figure 1. Overall survival and progression-free survival from start of IAPVP-16 for all 44 patients.

tively, while these intervals have not been reached in the 21 responders who were transplanted (p=0.44 and p = 0.02 for PFS and OS between transplanted and non-transplanted responders) (Figures 2 and 3).

Discussion

Follicular lymphomas is the most frequent of the low-grade or indolent non-Hodgkin's lymphomas. Despite initial response to first line therapy with an alkylating agent and/or an anthracycline-containing combination regimen in most advanced cases, disease progression will eventually occur. With the classic CHOP (cyclophosphamide, adriamycin, vincristine and prednisone) regimen, the response rate (CR + PR) ranges from 70-80%, but the median progression-free survival from remission is only two to three years and the median overall survival from five to seven years. Following a first progression, patients treated with conventional single-agent or combination regimens have an overall median survival of 4.5 years and a median failure-free survival of 1.7 years.[3] However, advanced disease at relapse and the duration of the response are major determinants of short-term outcome. In any case, for young patients the predicted overall survival is exceedingly short and novel salvage approaches should be pursued. Unfortunately, in low-grade lymphomas in general, and in FL in particular, there has been no clear-cut survival advantage of achieving a very good remission, even CR, following either first-line or salvage regimens. This is mostly due to the long survival seen in many patients with active disease and the continuous pattern of progression in patients in remission. Recent evidence, however, suggests that the quality of the remission obtained may have an impact on overall survival. Thus, molecular remissions following either hematopoietic SCT[18] or prolonged multidrug salvage chemotherapy[19] have translated into a prolongation in overall survival. These data suggest that obtaining the best remission possible may be a first step in reaching prolonged DFS and even the possibility of cures in FL in young patients with advanced disease.

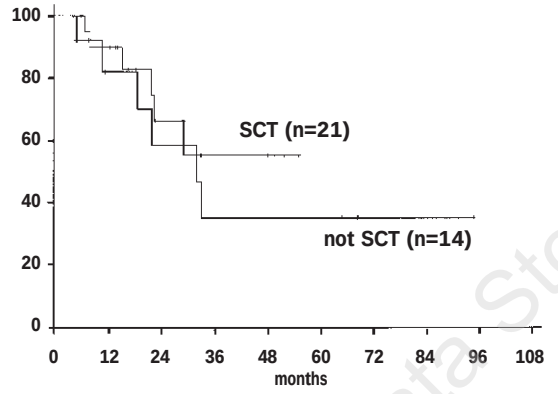

Figure 2. Progression-free survival in responders (n=35) submitted (n=21) or not submitted (n=14) to stem cell transplantation (log rank, p=0.44).

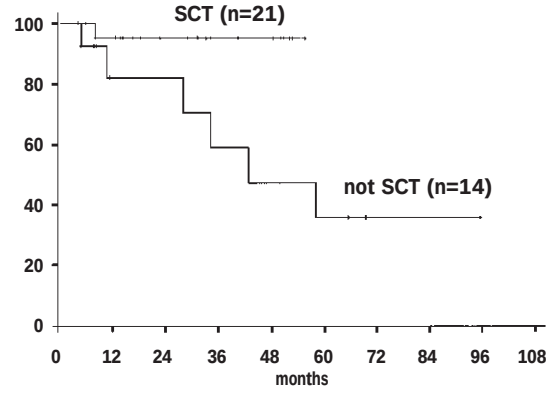

Figure 3. Overall survival in responders (n=35) submitted (n=21) or not submitted (n=14) to stem cell transplantation (log rank, p=0.02).

We have studied a novel salvage regimen which combines drugs active against FL in previous studies. The IAPVP-16 regimen produces a high rate of responses over a relatively brief treatment period; thus, the median time to achievement of remission was only three months. Since inclusion criteria and response definitions vary somewhat from one study to another, we cannot definitively compare our response rates to those in other previously published studies[8-15] (Table 3), although they appear to be similar if not higher. In an effort to prolong disease-free survival following the excellent antitumor responses obtained after IAPVP-16, the protocol was amended in 1992 so that all responding patients were to proceed to SCT within three months after IAPVP-16. In this respect, we previously showed that IAPVP-16 followed by G-CSF is an excellent mobilization regimen in patients with lymphoid malignancies,[20,21] obtaining a mean of 13.3×10^6/kg $CD34^+$ cells with 1-3 leukaphereses. The excellent yield obtained with this regimen allows the concurrent treatment of the underlying lymphoma and the harvesting of sufficient cells for *ex vivo* purging of the stem cells in most patients.[17] Current data, however, have somewhat blunted the initial enthusiasm forautologous SCT in FL, since there appears to be no plateau in DFS after the procedure.[22]

The IAPVP-16 regimen produces significant hematologic toxicity with few extrahematologic side effects. Indeed, severe neutropenia lasted a median of five days with G-CSF, and 66% of treatment cycles were complicated by severe thrombocytopenia. Neutropenic fevers led to hospital readmission following 60% of treatment cycles, a rate that was reduced to 25% by intensifying the antibacterial prophylaxis.[23] Most patients with relapsed or refractory advanced

Table 3. Studies of different regimens in patients with relapsed or primary refractory follicular and other low-grade lymphomas.

First author (year)[ref]	*N° of patients*	*Regimen*	*Patients responding – no. (%)*		
			CR	*PR*	*Total*
Rodriguez-Monge (1997)[6]	35	DHAP	4	12	16 (45)
Rodriguez-Monge (1997)[6]	36	ESHAP	13	14	27 (75)
Cabanillas (1987)[5]	91	MIME	11	39	50 (55)
Rodriguez (1995)[7]	36	MINE-ESHAP	20	9	29 (81)
McLaughlin (1996)[8]	51	FMD	24	24	48 (94)
Zinzani (1995)[9]	18	FMP	4	9	13 (72)
Pigaditou (1993)[10]	45	Fludarabine	4	16	20 (44)
Hochster (1992)[11]	25	Fludarabine	5	8	13 (52)
Saven et al (1996)[12]	23	2CdA-mitoxantrone	5	11	16 (70)
Hoffman (1994)[13]	21	2CdA	3	6	9 (43)
Kay (1992)[14]	40	2CdA	8	9	17 (43)
McLaughlin (1998)[15]	166	IDEC-C2B8	8	70	78 (48)

DHAP: dexamethasone, cytarabine and cisplatin. ESHAP: etoposide, methylprednisolone, cytarabine and cisplatin. MIME: methylprednisolone, ifosfamide, methotrexate and etoposide. MINE: methylprednisolone, ifosfamide, mitoxantrone and etoposide. FMD: fludarabine, mitoxantrone and dexamethasone. FMP: fludarabine, mitoxantrone and prednisone. 2CdA: 2-chlorodeoxyadenosine.

low-grade lymphoma are above the age of 60-65 years, and this may partly explain why most salvage regimens for these disorders are only mildly myelotoxic. Hematologic toxicity of IAPVP-16 is undoubtedly the major factor limiting its use in elderly patients.

In summary, the IAPVP-16 regimen obtains a high rate of complete and partial remissions in refractory or relapsed FL, allowing most eligible patients to proceed with significant tumor reduction to high-dose chemo-radiotherapy and a hematopoietic transplant.

Contributions and Acknowledgments

RL designed the study, was responsible for data management and prepared the manuscript. RM performed the data analysis and participated in writing the paper. SB collaborated in patient care and data management. AS collaborated in patient care and in preparation of the manuscript. AD designed the IAPVP-16 regimen. JS is the head of the Clinical Hematology Division and participated in writing the paper.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

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References

1. Horning SJ, Rosenberg SA. The natural history of initially untreated low-grade non-Hodgkin's lymphoma. N Engl J Med 1984; 311:1471-5.
2. Gallagher CJ, Gregory WM, Jones AE, et al. Follicular lymphoma: Prognostic factors for response and survival. J Clin Oncol 1986; 4:1470-80.
3. Johnson PWM, Rohatiner AZS, Whelan JS, et al. Patterns of survival in patients with recurrent follicular lymphoma: a 20-year study from a single center. J Clin Oncol 1995; 13:140-7.
4. Cabanillas F, Hagemeister FB, Bodey GP et al. IMVP-16, an effective regimen for patients with lymphoma who have relapsed after initial combination chemotherapy. Blood 1982; 60:693-7.
5. Cabanillas F, Hagemeister FB, McLaughlin P, et al. Results of MIME salvage regimen for recurrent or refractory lymphoma. J Clin Oncol 1987; 5:407-12.
6. Rodriguez-Monge, Cabanillas F. Long-term follow-up of platinum-based lymphoma salvage regimens. Hematol Oncol Clin N Am 1997; 11:937-47.
7. Rodriguez FC, Cabanillas F, Velasquez WS, et al. Results of a salvage treatment program for relapsing lymphoma: MINE consolidated with ESHAP. J Clin Oncol 1995; 13:1734-41.
8. McLaughlin P, Hagemeister FB, Romaguera JE, et al. Fludarabine, mitoxantrone, and dexamethasone: an effective new regimen for indolent lymphoma. J Clin Oncol 1996; 14:1262-8.
9. Zinzani PL, Bendandi M, Tura S. FMP regimen (fludarabine, mitoxantrone, prednisone) as therapy in recurrent low-grade non-Hodgkin's lymphoma. Eur J Haematol 1995; 55:262-6.
10. Pigaditou A, Rohatiner AJS, Whelan JS, et al. Fludarabine in low-grade lymphoma. Semin Oncol 1993; 20:24-7.
11. Hochster HS, Kyungmann Kim, Green MD, et al. Activity of fludarabine in previously treated non-Hodgkin's low-grade lymphoma: results of an Eastern Cooperative Oncology Group Study. J Clin Oncol 1992; 10:28-32.
12. Saven A, Lee T, Kosty M, Piro L. Cladribine and mitoxantrone dose escalation in indolent non-Hodgkin's lymphoma. J Clin Oncol 1996; 14:2139-44.
13. Hoffman M, Tallman MS, Hakimian D, et al. 2-Chlorodeoxyadenosine is an active salvage therapy in advanced indolent non-Hodgkin's lymphoma. J Clin Oncol 1994; 12:788-92.
14. Kay AC, Saven A, Carrera CJ, et al. 2-Chlorodeoxyadenosine treatment of low-grade lymphomas. J Clin

Oncol 1992; 10:371-7.
15. McLaughlin P, Grillo-López AJ, Link BK, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. J Clin Oncol 1998; 16:2825-33.
16. Harris NL, Jaffe ES, Stein H, et al. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. Blood 1994; 84:1361-92.
17. López R, Martino R, Sureda A, et al. Autologous stem cell transplantation in advanced follicular lymphoma. A single center experience. Haematologica 1999; 84: 350-5.
18. Gribben JG, Neuberg D, Freedman AS, et al. Detection by polymerase chain reaction of residual cells with the bcl-2 translocation is associated with increased risk of relapse after autologous bone marrow transplantation for B-cell lymphoma. Blood 1993; 81:3449-57.
19. López-Guillermo A, Cabanillas F, McLaughlin P, et al. The clinical significance of molecular response in indolent follicular lymphomas. Blood 1998; 91:2955-60.
20. Martínez C, Sureda A, Martino R, et al. Efficient peripheral blood stem cell mobilization with low-dose G-CSF (50 µg/m^2) after salvage chemotherapy for lymphoma. Bone Marrow Transplant 1997; 20:855-8.
21. Santamaría A, Martino R, Martínez C. Factors predicting an adequate mobilization of peripheral blood stem cell following IAPVP-16 + G-CSF in patients with lymphoid malignancies [abstract]. Blood 1998; 92 (Suppl.1):306b.
22. Freedman AS, Gribben JG, Nadler LM. High dose therapy and autologous stem cell transplantation in follicular non-Hodgkin's lymphoma. Leuk Lymphoma 1998; 28:219-30.
23. Muñoz L, Martino R, Subirà M, et al. Intensified prophylaxis of febrile neutropenia with ofloxacin plus rifampicin during short-duration neutropenia in patients with lymphoma. Leuk Lymphoma (in press).