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Source / Izvornik: **Annals of Hematology, 2016, 95, 1129 - 1136**

Journal article, Published version
Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

https://doi.org/10.1007/s00277-016-2676-0

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:105:978993

Original article

HIGH-DOSE IFOSFAMIDE AND MITOXANTRONE (HDIM) IN PATIENTS WITH RELAPSED OR REFRACTORY HODGKIN'S LYMPHOMA

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Running head: HDIM in relapsed/refractory Hodgkin’s lymphoma

ABSTRACT

Relapsed /refractory Hodgkin's lymphoma (HL) is treated with salvage chemotherapy and autologous stem-cell transplantation (ASCT). Optimal chemotherapy is unknown. We retrospectively analyzed outcomes of 58 patients treated with two cycles of high-dose ifosfamide and mitoxantrone (HDIM). HDIM consisted of ifosfamide 5 g/m^2/day and MESNA 5 g/m2/day in continuous 24-hour infusion (days 1,2), MESNA 2.5 g/m^2 over 12 hours (day 3), and mitoxantrone 20 mg/m^2 (day 1) administered every two weeks. Stem cells were collected after the first cycle. Responding patients proceeded to ASCT. Toxicity was acceptable. Stem-cell mobilization was successful in 96% of patients. Overall response rate was 74% (89% in relapsing and 45% in refractory patients) with 31% complete remissions. After a median follow-up of 54 months, 5-year event-free survival was 56% (69% for relapsing, 35% for refractory patients), and 5-year overall survival was 67% (73% for relapsing, 55% for refractory patients). Significant adverse prognostic factors were refractoriness to previous therapy and HDIM failure. No differences in outcomes were noted between patients with early and late relapses nor between complete and partial responders. HDIM is a well tolerated and effective regimen for relapsed and refractory HL with excellent stem-cell mobilizing properties. Patients failing HDIM may still benefit from other salvage options.

KEY WORDS

Hodgkin’s lymphoma; Antineoplastic combined chemotherapy protocols; Ifosfamide; Mitoxantrone; Autologous stem cell transplatation

INTRODUCTION

Patients with relapsing or refractory Hodgkin's lymphoma (HL) are treated with salvage chemotherapy to induce remission and collect stem cells for autologous stem-cell transplantation (ASCT) [1, 2]. Responding patients are subsequently autografted. ASCT is not effective in chemoresistant patients. Therefore, inducing a response is of paramount importance. Different salvage chemotherapy regimens are usually used in this setting; miniBEAM (carmustine, etoposide, cytarabine, melfalan), DexaBEAM (dexamethasone + miniBEAM), DHAP (dexamethasone, cytarabine, cisplatin), ICE (ifosfamide, carboplatin, etoposide), GDP (gemcitabine, dexamethasone, cisplatin) and IGEV (ifosfamide, gemcitabine, etoposide, vinorelbine) [3-9]. Reported response rates and survival of these regimens are comparable. Patients who are refractory to front-line treatment (operationally defined as response lasting less than 3 months) have a significantly inferior prognosis. In some studies, patients relapsing less than 12 months from the end of front-line treatment (early relapses) fare worse than those relapsing later than 12 months since the end of treatment [6, 7].
Salvage regimens consisting of high-dose ifosfamide and mitoxantrone were described in the nineties [10,11]. We performed a phase II trial of a similar regimen with an intensified dose of ifosfamide (HDIM) for stem-cell mobilization in patients with lymphoid malignancies and were favorably impressed by its antitumor activity [12]. HDIM has since been used as our standard salvage chemotherapy regimen in patients with relapsed or refractory HL eligible for ASCT. Here we report a retrospective analysis of our experience in 58 patients treated between 2003 and 2015.

PATIENTS AND METHODS

Patients

Patients were eligible for inclusion in this analysis if they had relapsed or refractory HL, were at time of salvage treatment start eligible for ASCT and were scheduled to receive two cycles of HDIM. We identified 58 patients by retrospective chart review. Their characteristics are presented in Table 1. Twenty-one were refractory to prior treatment (duration of response to the last treatment less than 3 months), 19 were in early (duration of response to the last treatment 3-12 months) and 18 in late relapse (duration of response to the last treatment more than 12 months).

None was known to be HIV positive. All patients were staged prior to treatment. Staging included careful palpation of peripheral nodes, CT scanning of the thorax, abdomen and pelvis and a bone marrow biopsy. PET was not used in all patients.

TABLE 1 Patients' characteristics

Age at relapse (years)	range	15-49
	median	30
Gender (*N*)	M	34
	F	24
HL type (*N*) NLP / NS / MC / NOS	NS / MC	44 / 7
	NLP / NOS	2 / 5
Front-line therapy (*N*) /	ABVD / BEACOPP	48 / 1b+1e
	EBVP / COPP/ABV(D) / other	1 / 5 / 2
Previous radiotherapy (*N*)		29
Previous treatment lines (*N)*	range	1-3
	median	1
Stage at relapse (*N*)	II / III	19 / 14
	IV / unknown	24 / 1
Response to prior treatment (N)	refractory	21
	early relapse / late relapse	19 / 18

N= number; NLP = nodular lymphocyte predominant; NS = nodular sclerosis; MC = mixed cellularity; NOS = not otherwise specified classical HL; ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; BEACOPP = bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; b = baseline; e = escalated; EBVP = epirubicin, bleomycin, vinblastin, prednisone; COPP/ABV(D) = hybrid or alternating COPP (cyclophosphamide, vincristine, procarbazine, prednisone) and ABVD

Treatment

HDIM consisted of ifosfamide 5 g/m^2/day in continuous 24-hour infusion for 2 days, MESNA 5 g/m^2/day in continuous 24-hour infusion for 2 days and 2.5 g/m^2 over 12 hours on day 3 and mitoxantrone 20 mg/m^2 on day 1. G-CSF 10 ug/kg/day sc was started on day 6. At recovery, stem cells were collected by leukapheresis. A second cycle of HDIM was started on day 15 or after stem cell collection and hematologic recovery and was followed by G-CSF 5 ug/kg/day until leukocyte recovery. Patients with bone marrow infiltration were mobilized after the second HDIM cycle, provided the repeated bone marrow biopsy was negative. Treatment was given in an in-patient setting. Patients were discharged after the end of chemotherapy and, if no complications

occurred, readmitted for stem cell collection, chemotherapy or ASCT. All received routine supportive care, including blood product transfusions and antiemetic prophylaxis with serotonin antagonists.
Patients with chemosensitive disease were autografted after conditioning with BEAM. Areas not in complete remission (CR) prior to ASCT were irradiated with 30-36 Gy after recovery from transplantation. Twenty patients received posttransplant radiotherapy.

Response assessment and follow-up

Restaging by CT scanning was performed after two cycles of HDIM. Response was determined according to the older, pre-PET, version of standard criteria [13]. CT or PET-CT was repeated after ASCT (or posttransplant radiotherapy). Patients who achieved remission were followed clinically, every three months for the first 3 years, every 6 months during the 4^{th} and 5^{th} year and yearly thereafter. Imaging methods were repeated only if clinically indicated.
Overall (OS) and event-free survival (EFS) were calculated from the date of HDIM start until the last follow-up, death or event, respectively. Events were defined as introduction of unplanned antitumor therapy due to lack of efficacy of HDIM, relapse, disease progression or death.

Toxicity

Toxicity was analyzed by chart review and graded using the National Cancer Institute Common Toxicity Criteria for Adverse Events v3.0.

Data Analysis

OS and EFS were estimated using the method of Kaplan & Meier. Fisher's exact test was used for 2x2 table analyses and log-rank test for survival comparisons. The assumed level of significance was 0.05.

Ethics

This is a non-interventional retrospective study of patient data performed with the approval of the Ethical Committee of the Medical School, University of Zagreb in accordance with pertinent

Croatian, EU and international rules and regulations and the Declaration of Helsinki. Prior to treatment all patients gave informed consent for intensive chemotherapy and autologous stem cell transplantation.

RESULTS

Toxicity

There was no treatment-related mortality. The 2nd cycle was not administered in 2 patients, one due to progressive disease and the other due to toxicity. Median time to the start of 2nd cycle was 16 days. As expected, hematological toxicity was universal. All patients developed severe granulocytopenia, 26% needed platelet or red blood cell transfusions; 73% had fever or proven infections (Table 2). Three patients had neurological side-effects: one delirium, one seizures and one syncope. One patient developed acute renal failure and received miniBEAM as the 2nd cycle of therapy. Fourteen patients had nausea or vomiting, mostly while not receiving maximal prophylactic treatment; two had mucositis, three troublesome hiccups, one deep venous thrombosis and one an algic syndrome. Thirty did not have any significant non-hematological and non–infectious side-effects. All patients successfully recovered and none had to abstain from ASCT due to toxicity.

TABLE 2 Severe side-effects of HDIM

Side-effect	**No. of patients**	
	Grade 4	
Granulocytopenia	58	
Anemia	14	
Trombocytopenia	8	
	Grade 3	**Grade 4**
Infections	38	3
Nausea & vomiting	1	0
Mucositis	2	0
Delirium	1	0
Syncope	1	0
Acute renal failure	1	0
Deep venous thrombosis	1	0

As can be ascertained by routine clinical follow-up, no unusual symptomatic long-term toxicity was noted in survivors. A single patient developed secondary cancer (melanoma), and none had

clinically manifest cardiac failure.

Stem-cell collection

In two patients, stem cell collection was not performed due to HL progression. Stem-cell collection was successful (> $2x10^6$ CD34+ cells per kg body weight collected) in 54 patients (96%). The remaining two failed to mobilize after HDIM, but responded to plerixafor and were successfully autografted.
Hematologic recovery after ASCT was not delayed in comparison to patients that had been treated with miniBEAM or DHAP at our center.

Response to treatment and prognosis

After two cycles of HDIM, 18 patients achieved CR, 24 partial remission (PR), 11 had stable disease (SD) and 4 progressive disease (PD), for a response rate of 74%. Data from restaging were not available for one patient. The response rate in primary refractory disease was significantly lower than in early and late relapse (45% vs. 89% vs. 89% respectively, $p<0.001$). In non-responders, different treatment regimens were tried (e.g. miniBEAM) in order to obtain a response and continue with auto- or allografting. Patients relapsing after ASCT were treated with DHAP, escalated BEACOPP or gemcitabine + steroids. A single patient received brentuximab-vedotin; 9 underwent allo-SCT.
After a median follow-up of survivors of 54 months (range 2-120 months), 16 patients (28%) have died and 26 (45%) had an event. Actuarial 5-year EFS of the whole group was 56%±7% (95% confidence interval) and OS 67%±7%. EFS was significantly worse in refractory in comparison to early or late relapsing patients, (5-year EFS 35%±10% vs. 67%±11%, vs. 71%±11%, respectively; p=0.012) (Fig. 1). The difference in OS was not statistically significant (5-year OS 55%±11% vs. 74%±12% vs. 72%±12%, respectively; p=0.131) (Fig. 1). EFS and OS in early and late relapsing patients were similar. Beyond 5 years of follow-up a single patient relapsed, none died.

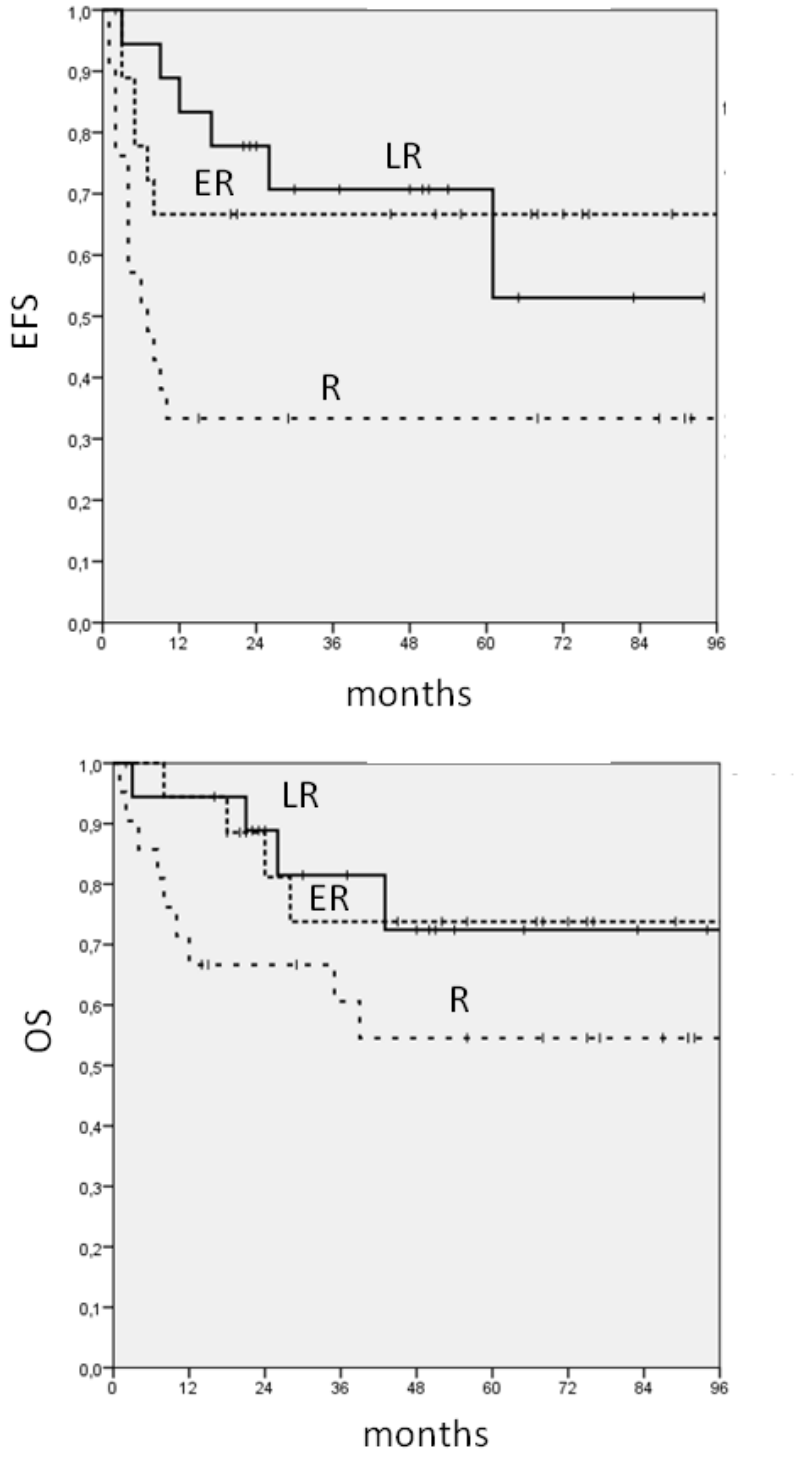

FIG 1 Event-free survival (EFS) and overall survival (OS) of patients with late relapses (LR), early relapses (ER) and refractory (R) Hodgkin's lymphoma treated with HDIM

We analyzed the impact of additional possible prognostic factors on EFS and OS. Gender, HL type, front-line regimen, previous radiotherapy, B symptoms, stage and anemia did not influence outcomes. Response to HDIM was very important (Fig. 2). Patients achieving CR had a 5-year EFS of 78%±10%, PR 68%±10%, SD 18%±12 and PD 0% (CR and PR vs. SD and PD, $p<0.001$). Median EFS was not reached in responding patients and was 6 and 2 months in the latter two groups, respectively. Patients achieving CR had a 5-year OS of 76%±11%, PR 81%±9%, SD 49%±17% and PD 25%±22% (CR and PR vs. SD and PD, $p=0.044$). Median OS was not reached in responding patients and was 39 and 2 months in the latter two groups, respectively.

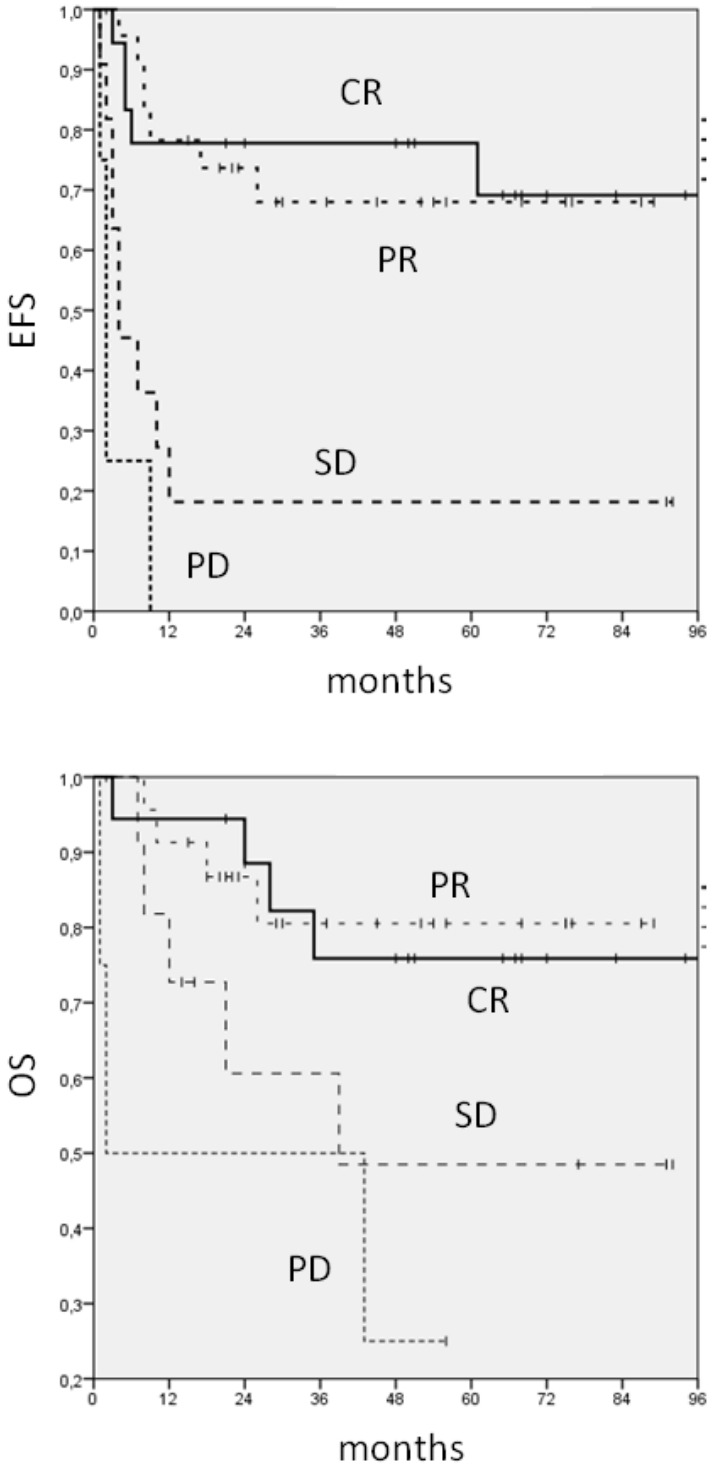

FIG 2 Event-free survival (EFS) and overall survival (OS) of patients according to response to HDIM

CR = complete remission, PR = partial remission, SD = stable disease, PD = progressive disease

Prognostic indices

The difference in EFS or OS between three prognostic groups defined by the original Josting's score (anemia, response duration < 1 year, stage III & IV) was not significant (Table 3) [14]. EFS differed significantly between the favourable and unfavorable group but not between either of them and the intermediate group as defined by the modified Josting's score (anemia, response duration < 1 y, stage IV) [6]. The difference in OS between these three groups was not significant. The index described by Moskowitz and coworkers (B symptoms, response duration < 1 y, stage IV) was the only one able to divide patients into three groups with significantly different EFS and identify a favorable group with 100% OS [7].

TABLE 3 Prognostic scores

Prognostic score	***N*. of risk factors**	**% of patients**	**5-y EFS (%)**	***p value***
Josting's (response < 1 year, anemia, stage III&IV) [14]	0	11	86	0 vs. 1 *0,198*
	1	35	53	0 vs. 2-3 *0,092*
	2-3	55	52	1 vs. 2-3 *0,442*
Modified Josting's (response<1 year, anemia, stage IV) [6]	0	15	88	0 vs. 1 *0,146*
	1	47	56	0 vs. 2-3 *0,027*
	2-3	38	43	1 vs. 2-3 *0,131*
Moskowitz et al (response < 1 year, stage IV, B) [7]	0	17	100	0 vs. 1-2 *0,026*
	1-2	66	56	0 vs. 3 *0,002*
	3	17	33	1-2 vs. 3 *0,015*

5-y EFS = 5-year event-free survival

DISCUSSION

This is a retrospective study based on chart-review. In comparison to prospective, controlled trials, this type of analysis could lead to underestimation of some types of toxicity and overestimation of efficacy. Lack of regular follow-up imaging might result in delayed identification of relapses. This should be kept in mind when comparing our results with those of

prospective controlled studies.

The toxicity of HDIM was acceptable, with a specter different from other salvage regimens [3-9]. Hematologic and infectious toxicity was very frequent but short. Renal side-effects seem to be less severe than with DHAP (due to avoidance of cisplatinum) and duration of pancytopenia shorter than with miniBEAM or DexaBEAM. Neurological side-effects occurring in three patients were probably related to high-dose ifosfamide. All of them had refractory stage IV HL and severe systemic symptoms. HDIM is very emetogenic, intensive antiemetic prophylaxis is needed. The toxicity of the regimen is not cumulative; most patients tolerated the second cycle better than the first.

HDIM had excellent mobilization potential. Only two patients who were not progressing on treatment failed to collect sufficient stem cells after HDIM but responded to plerixafor. These results are probably better than those achieved with miniBEAM or DexaBEAM and similar to those of ICE, GDP, IGEV and DHAP.

Within the limitations imposed by the retrospective nature of the study, the antitumor activity of HDIM seems superior to miniBEAM and DexaBEAM and comparable to that of the newer regimens (Table 4). A possible exception is IGEV, with a response of 81% and a CR rate of 54% [9]. However, EFS after IGEV is similar to that obtained using the other newer regimens, suggesting that the observed difference could be a consequence of evaluation at different time-points (response evaluation of IGEV is performed after 4 and of the other regimens after 2 cycles) and not of different antitumor activity. To our knowledge, no phase III trials comparing different chemotherapies (e.g. DHAP with ICE or similar) for pretransplant salvage therapy in HL have been performed. Therefore, as with large B-cell lymphoma, all of these regimens can still be regarded as standard and probably equivalent. The choice between them will depend on need to avoid some types of toxicity (i.e. renal for DHAP and neurological for HDIM) and local expertise. Irrespective of this, outcome of relapsing or refractory patients receiving very aggressive front-line therapy such as eBEACOPP will be inferior to that reported.

TABLE 4 Results of different regimens used for salvage treatment of HL

Regimen	**Disease state**	**RR / CR**	**EFS**	**OS**
DexaBEAM [4]	relapsed	81% / 27%	45% at 36 mo.	NR
MiniBEAM [3]	all	68% / 32%	36% at 18 mo.	86% at 18 mo.
ICE [7]	all	88% / 26%	58% at 43 mo.	73% at 43 mo.
	relapsed	NR	65% at 43 mo.	NR
	refractory	NR	52% at 43 mo.	NR
DHAP [5,6]	relapsed	70% / 24%	71% at 36 mo.	87% at 36 mo.
	refractory	65% / 12%	41% at 30 mo.	48% at 30 mo.
GDP [8]	all	62% / 9%	76% at 18 mo.	90% at 18 mo.
IGEV [9]	all	81% / 54%	53% at 36 mo.	70% at 36 mo.
	relapsed	85% / 67%	NR	NR
	refractory	61% / 33%	NR	NR
HDIM	all	74% / 32%	56% at 60 mo.	67% at 60 mo.
	relapsed	89% / 41%	69% at 60 mo.	73% at 60 mo.
	refractory	45% / 15%	35% at 60 mo.	55% at 60 mo.

RR = response rate; CR = complete remission rate; EFS = event-free survival; OS = overall survival; mo = months;

The response to front-line therapy is the most important pretreatment prognostic factor. In all studies, including ours, refractory patients fared worse than relapsed. We did not find a difference in outcomes between late and early relapsing patients. This is in accordance with some [8, 9, 15], but in contrast to other studies [6, 7, 16]. The reason for this is not clear. Multiple studies have identified short response duration, extranodal disease, B symptoms and anemia as negative prognostic factors. While the influence of any of these alone might not be very important, their combination seems to have additive effects. Patients with none have excellent, while those with three or more factors have a very poor prognosis. The index described by Moskowitz and coworkers was in our series superior to the modified Josting's index [6,7]. The original Josting's score, with disease stages III and IV considered unfavorable, was not of prognostic significance

[12]. A similar finding was reported previously in studies using dose-dense therapy with ICE and DHAP [6,7]. This suggests that short dose-dense treatment improves outcomes of nodal more than extranodal relapsed and refractory HL.

As in all other studies that analyzed it, response to salvage treatment was the most important prognostic factor. The outcome of patients with refractory disease who responded to HDIM was rather good, and more than half were cured with autografting (and radiotherapy in selected cases). Our experience indicates that patients with stable disease after salvage chemotherapy should not go on to ASCT. Only 2 of them did not relapse, both have received posttransplant radiotherapy. Recent studies suggest that PET-CT response evaluation prior to ASCT has an even better prognostic value and should be used to determine whether patients should proceed to transplant and/or receive posttransplant brentuximab consolidation [17,18].

Median OS in patients with SD after HDIM was longer than 3 years. This indicates that, even before the availability of brentuximab-vedotin, non cross-resistant chemotherapy treatment options existed for relapsed and refractory HL, and only patients progressing during treatment had a dismal prognosis. Some of those responding to subsequent lines of treatment can be cured with ASCT and radiotherapy. This is in accordance with the guidelines of the French Lymphoma Study Association [2] and results of Gerrie and coworkers [19], and in contrast to those of Villa and coworkers [20]. The outcome of this high-risk patient population can possibly additionally be improved with the use of double-transplants or combinations of brentuximab with chemotherapy [21,22].

In conclusion, HDIM is an effective treatment for relapsed and refractory HL with acceptable toxicity and excellent mobilizing potential. It should be added to the armamentarium of salvage regimens for this type of lymphoma.

ACKNOWLEDGEMENTS

Presented in part at the 8th International Symposium on Hodgkin's Lymphoma, Cologne, Germany 2010.

FUNDING

Supported in part by the Croatian Ministry of Science and Education [grant number 108-1081872-1908].

DISCLOSURE

The authors have declared no conflicts of interest.

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