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ORIGINAL ARTICLE

Late relapse of Hodgkin's lymphoma – is it different in clinical characteristics and outcome?

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Summary

Purpose: *The purpose of this study was to evaluate the clinical characteristics, prognostic factors, therapy and outcomes of patients with very late relapse (>5 years) of Hodgkin's lymphoma (HL).*

Methods: *We retrospectively reviewed the database of all relapsed patients with HL treated between 1999 and 2009 and compared the clinical characteristics and survival of patients who relapsed before and after 5 years of follow up.*

Results: *Among the group of 102 patients with relapsed HL 16 (15.68%) patients had very late relapse of disease. Median time to very late relapse was 86 months (range 61-199). On relapse most of these patients (11; 68.5%) were in advanced clinical stage. Eleven (68.75%) patients with very late relapse were treated with high dose chemotherapy and autologous stem cell transplantation (ASCT). Second complete response was achieved in 13 (81.25%) patients. At a median follow up of 4.5 years after therapy, 13 (81.25%) patients are still alive (10 without disease and 3 with disease), while 3 patients died (2 from HL, and 1 from brain tumor). There was no significant difference between patients with very late relapse and patients who relapse earlier in terms of initial clinical parameters. Median overall survival of patients with very late relapse was significantly longer than in patients with earlier relapse (p=0.001), but survival calculated from the time of relapse was not significantly different between these two groups of patients (p=0.83).*

Conclusion: *An open question that remains is whether high dose therapy and ASCT is necessary in most patients with very late relapse of disease. Individualization of therapy in patients with very late relapse of HL is mandatory, tailored on risk factors and comorbidities.*

Key words: *Hodgkin, lymphoma, prognosis, therapy, very late relapse*

Introduction

HL is one of the most curable forms of cancer, especially if it is diagnosed and treated early. Depending on the stage and risk factor profile, up to 90% of patients with HL achieve complete remission (CR) after the initial standard treatment including radiotherapy, chemotherapy or their combinations [1]. Recent studies have indicated that even patients with advanced HL have 5-year survival rates of approximately 90% [2,3]. Still, approximately one-third of the patients will not have a response to frontline treatment or will subsequently relapse [4].

The relapse of HL usually occur within the first 5 years after the completion of therapy, with a trend of decrement after 3 years and only a minority of patients relapses after 5 years. According

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to literature data only 3-8% HL patients relapse after 5 years [5,6]. Standard treatment of relapse is high dose chemotherapy followed by conditioning regimen and ASCT [7]. A minority of patients with late relapse can be treated by using some of the conventional treatment regimens for newly diagnosed HL patients, depending on previous treatment and disease extent [7,8]. Since modern treatment approach in HL is based on treatment tailored to the presence of certain risk factors, many studies were carried out with this goal [9,10]. Recent trials, besides the clinical parameters, examined molecular parameters as potential risk factors, as well as early response assessed by PET scan [11,12]. However, as very late relapse is rare, there are only scanty data regarding prognostic parameters which correlate with risk of very late relapse. So far, only a few small studies identified some clinical parameters as predictors for very late relapse [13,14].

The aim of this study was to evaluate clinical characteristics, treatment and outcome of patients with very late relapse of HL and to correlate them with patients who relapsed earlier.

Methods

We retrospectively reviewed the database of relapsed patients with HL treated at the Clinic of Hematology, Clinical Center of Serbia, Military Medical Academy and Department of Hematology, Clinical-Hospital Center "Bezanijska kosa" between 1999 and 2009. Diagnosis of disease and relapse were established by referent hematopathologists according to REAL and WHO classification [15,16]. The patients were staged according to the Ann Arbor staging system [17]. All included patients fulfilled the following criteria: relapse occurred after achieving first complete remission, relapse was histologically proven and clinical and laboratory data on presentation and follow-up records were accessible. The following data were collected from medical records: gender, the International Prognostic Score (IPS), clinical stage, presence B symptoms, "bulky" disease, presence of extranodal disease, dates of initial diagnosis and relapse, response to treatment and overall survival (OS). All patients were initially treated according to the institutional standards of care at the time of diagnosis by ABVD, MOPP, LOPP/ABVD and baseline or dose-escalated BEACOPP protocol, followed by additional radiotherapy (RT) in some patients, on the sites of initial tumor involvement. The patients with relapse within 5 years who responded to the salvage chemotherapy (DHAP or MINE) received BEAM followed by ASCT. The patients with very late relapse were treated or retreated with some of the anthracycline-based regimens for initial treatment, if it was possible to avoid cumulative anthracycline toxicity. Otherwise, they were treated the same way as the patients with relapse within 5 years. Response to treatment has been evaluated according to standardized guidelines for response assessment [18]. Patients were followed from their diagnosis every 3 months during the first 2 years, every 6 months between 2 and 5 years, and annually thereafter. In all patients who relapsed, biopsy was taken to prove the HL histology of relapse.

Statistics

The statistical analyses were performed using SPSS version 15 software (SPSS Inc, Chicago Ill, USA). Chi-square test was used to evaluate the differences in clinical characteristics, therapy response and survival in the groups of patients relapsed before and after 5 years. OS was calculated as the time from diagnosis to the date of death or last contact. OS and survival from the point of disease relapse was analyzed using the Kaplan-Meier method and log-rank test was used to correlate the difference of the survival data. P values were two-sided, and values of 0.05 or less were considered as indicating statistical significance.

Results

In our group of 102 patients with relapsed HL, very late relapse occurred in 16 (15.68%) patients. Median time to very late relapse was 86 months (range 61-199). The median follow up from very late relapse was 46 months (range 13-128).

Clinical characteristics of patients at the moment of relapse (patients with very late relapse and patients who relapsed earlier) are summarized in Table 1. Median age of patients with very late relapse when the initial diagnosis was established was 34 years with higher percentage of males. Advanced clinical stage had 11 (68.5%) patients and 4 (25.0%) had "bulky" disease (≥10cm). Supradiaphragmatic localization disease presentation was present in 7 cases (43.75%), infradiaphragmatic in 3 (18.75%) and localization on both sides of diaphragm in 6 cases (37.5%). Extranodal disease was noticed in 5 patients (31.25%), with bone marrow infiltration detected in 3 patients, lung infiltration in 2 patients, liver infiltration in 2 patients and skin lesions in 1 patient. Relapse occurred more often on the same localization as initially, in 10 (62.5%) patients. Three patients (21.43%) relapsed within the region of irradiated field and 3 relapsed at sites of bulky disease. In the group with very late relapse, the same histological subtype of classical HL, as at initial diagnosis, was confirmed in 13 patients. One patient with initially mixed cellularity subtype, in relapse experienced transfor-

Table 1. Clinical characteristics of Hodgkin's lymphoma patients with very late relapse and with relapse within 5 years after the end of therapy

Characteristics	*Patients with very late relapse (>5 years) n (%)*	*Patients who relapsed within 5 years n (%)*
Age, years		
Median	34	29
Range	25-70 (IQR 12)	19-71 (IQR 13)
Gender (M/F), years (range)	56 (7-132) (IQR 71.8)	73 (36-138) (IQR 36.8)
B symptoms, Yes	7 (43.75)	51 (59.30)
SE>50 cm/1h	10/6 (62.5)	52/86 (60.4)
IPS		
L	4 (25.0)	30 (34.88)
IM	8 (50.0)	36 (41.86)
H	4 (25.0)	20 (23.25)
Clinical stage		2 (2.3)
I	0 (0.0)	
II	5 (31.3)	40 (46.51)
III	6 (37.5)	27 (31.39)
IV	5 (31.3)	17 (19.76)
Bulky disease ≥ 10 cm	4 (25.0)	22 (24.41)
EN localization, Yes	5 (31.3)	19 (22.09)

M: male, F: female, IPS: international prognostic score, L: low, IM: intermediate, H: high, EN: extranodal, SE: Erythrocyte sedimentation

Table 2. Initial clinical characteristics of the patients with relapse within 5 years and with very late relapse of Hodgkin's lymphoma

Parameters	*Patients with relapse (<5 years) n (%)*	*Patients with very late relapse (>5 years) n (%)*	*p value**
Gender			
M	52 (60.5)	10(62.5%)	0.743
F	34 (39.5)	6(37.5%)	
B symptoms			0.885
No	23 (26.7)	4 (25.0)	
Yes	63 (73.3)	12 (75.0)	
SE /1h			0.378
≤50	24 (31.6)	3 (18.8)	
>50	52 (68.4)	13 (81.3)	
IPS (L/IM/H)			0.765
L	34 (39.5)	5 (31.3)	
IM	30 (34.9)	7 (43.8)	
H	22 (25.6)	4 (25.0)	
Clinical stage			0.534
I	2 (2.3)	0 (0.0)	
II	43 (50)	4 (25.0)	
III	26 (30.2)	7 (43.8)	
IV	15 (17.4)	5 (31.3)	
Bulky disease			0.448
No	62 (72.1)	10 (62.5)	
Yes	24 (27.9)	6 (37.5)	
Extranodal localization			0.305
No	69 (80.2)	11 (68.8)	
Yes	17 (19.8)	5 (31.3)	

*x^2 For abbreviations see footnote of Table 1

mation of disease to lymphocyte depletion, while in 2 patients with nodular sclerosing subtype, the disease had transformed into mixed cellularity subtype.

None of the analyzed demographic or clinical characteristics on initial disease presentation was found to be present in significantly higher percentage in patients with very late relapse com-

Table 3. Treatment of patients with very late relapse (initially and at relapse)

No of patients	*First line therapy*	*Therapy at relapse*	*Response*	*Second relapse*	*Cause of death*
1	ABVD + I.F. RT	DHAP/ASCT	SD		
2	ABVD	BEACOPP/ASCT	CR		
3	MOPP	ABVD	CR	x	
4	ABVD	BEACOPP/ASCT	CR		
5	ABVD	ABVD4+COPP4	CR		
6	ABVD	COPP/ABV+RT	CR		
7	ABVD+I.F. RT	DHAP/ASCT	CR		
8	ABVD	ABVD	CR	x	Hodgkin's disease
9	BEACOPP (basic)	DHAP/ASCT	PD		Hodgkin's disease
10	ABVD	ABVD	CR		
11	ABVD +I.F. RT	DHAPx2 BEACOPPex2/ASCT	PR		
12	$BEACOPP_b$	ESHAP/ASCT	CR		Brain tumor
13	ABVD + infrad. RT	$BEACOPP_b$/ASCT	CR		
14	LOPP/ABVD+ RT (rev. Y)	BEACOPPex2 DHAPx4/ASCT	CR		
15	ABVD	DHAP/ASCT	CR		
16	ABVD	DHAP/ASCT	CR		

CR: complete remission, PR: partial remission, SD: stable disease, PD: progressive disease, b: basic, I.F: involved field

pared to patients who relapsed within 5 years (Table 2).

Most of patients with very late relapse (75.0%) were initially treated with the ABVD protocol (Table 3) At the relapse, 5 patients were treated with conventional therapy for newly diagnosed disease and 11 patients were treated with salvage protocol followed with BEAM conditioning regimen and ASCT (Table 3). Combination of chemotherapy and RT was applied in only one patient. Second CR was achieved in 13 (81.25%) patients. One patient (6.3%) achieved partial response, one patient stable disease (6.3%), while progression of disease was noticed in one patient. In one patient, retreatment with initial chemotherapy (ABVD regimen) was administered. This patient achieved a second CR followed with second relapse occurring at the same localization as in first relapse, with lethal outcome 8 months later. One patient, who had been treated with MOPP regimen initially, in very late relapse was treated with ABVD regimen with achievement of CR, and experienced a second relapse 13 months after the end therapy. One patient progressed after ASCT and one patient experienced relapse 10 months after ASCT. In patients who achieved PR after ASCT, treatment with brentuximab-vedotin has been administered without effect on further tumor reduction. The overlook of initial and treatment in relapse of both patients with very late relapse and relapse within 5 years is given in Table 3.

At the moment of closing this study 3 patients (18.8%) died. One patient died in second CR due to brain tumor, 3 years after the confirmation of second CR, while 2 patients died of HL.

The survival analysis revealed that OS of the patients with very late relapse was significantly longer than in the group of patients who relapsed within 5 years after the end of therapy (log rank 10.922, 95% CI 71.497-126.503, p=0.001) (Figure 1A). However, when survival was calculated from the moment of relapse there was no significant difference between these two groups of patients (log rank 1.771, 95% CI 45.617-72.783, p=0.183) (Figure 1B). In the group of patients with very late relapse 3 (18.8%) patients died, and this death rate was significantly lower than in the group of patients who relapsed within 5 years (p=0.032).

Discussion

In previous studies 5 years was selected as border for defining 'very late relapse' because the actuarial rate of relapse appears to plateau at 5 years [5,19]. According to literature data only 3.5-8% of patients relapsed after 5 years [5,6]. Somewhat higher rate of very late relapses was registered in our study.

As very late relapse is rare, there are not consistent prognostic parameters which correlate with risk of very late relapse. An increased risk of very late relapse had been found to be related to male gender, presence of B symptoms, mediastinal involvement, age >30 years at diagnosis, type of initial therapy and advanced stage [13,14]. In our study, we didn't find difference in initial clin-

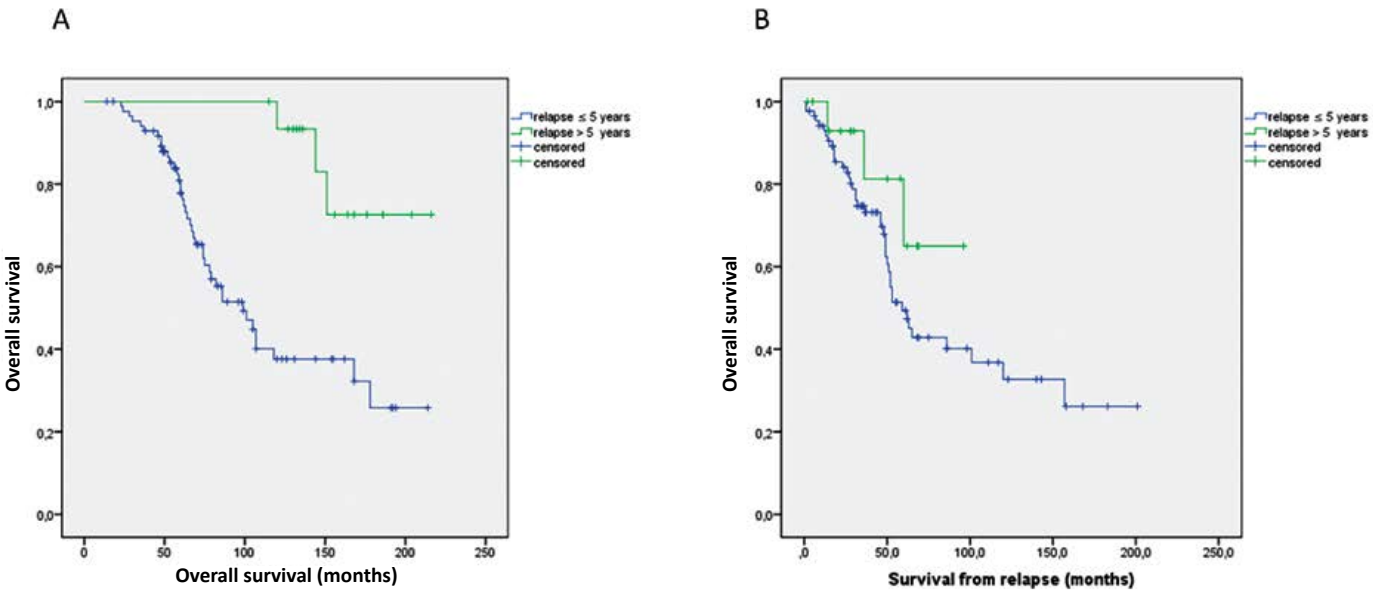

Figure 1. A) Kaplan-Meier survival of patients with relapse within 5 years and patients with very late relapse (> 5 years) (p=0.001). **B)** Kaplan-Meier survival of the patients with relapse within 5 years and with very late relapse measured from the point of relapse of disease (p=0.83).

ical features, including well established prognostic factors, between patients with very late relapse and patients who relapsed earlier.

Since relapse can appear in the same initial localization or on different places, it remains unclear whether the very late relapse is completely new and clonally unrelated secondary neoplasia or true relapse arising from the primary tumor (reactivation of HL) [6]. It is well known that Hodgkin and Reed–Sternberg cells have defective cell cycle and apoptosis regulation, which enables them to escape therapy and result in clonally related recurrences [20]. On the other hand, both genetic and environmental factors may increase a risk for a second clonally unrelated HL in patients with "recurrent" disease. Analysis of immunoglobulin heavy chain (IgH) gene fragment lengths showed that late relapses can be clonally unrelated neoplasms [20] or recurrences of the primary tumor [21]. Consequently, this can raise the dilemma about optimal therapeutic approach in this group of patients - is it necessary to apply the aggressive strategies in all patients with late relapse ? - since clonally unrelated relapsed HL may be candidates for less intensive therapeutic approaches (conventional chemotherapy or RT) [20]. ESMO recommendations as a treatment of choice in most patients suggest high-dose chemotherapy followed by ASCT [7]. In selected patients with long disease free intervals and other favorable features, the selection of second-line therapy should be individualized. Some patients with localized late relapse can be treated successfully with standard-dose chemotherapy and involved field radiation [22]. Nevertheless, it is believed that the identification of biologic predictors of outcome after very late relapse would be of great help in making treatment decisions, with primary goal to identify those patients who are curable with less intensive treatment in order to avoid unnecessary treatment toxicity [22]. The patients in our study with very late relapse were treated both with conventional first line therapy and high dose chemotherapy followed by ASCT. However, due to the small group of analysed patients the possibility for reliable analysis is limited.

By now, there are only few data about the outcome of patients with very late relapse. Results of previous studies showed that prognosis of patients with very late relapse of HL is favorable [5,13]. Moreover, very late relapse didn't compromise OS although most patients in these studies were treated with conventional therapy [5,13]. In line with previous reports our patients with very late relapse also had favorable OS, but in contrast more than two-thirds (68.75%) of them were treated with high dose chemotherapy and ASCT.

We believe that our study has contributed to the elucidation of the prognosis and outcome of patients with very late relapse of HL followed for a long period of time. Given that very late relapses of HL are rare and that the literature data on the prognosis and treatment of these patients are

limited, each contribution in this area is valuable. On the other hand, the limitation of our study is the small number of patients, especially given the diversity of treatment (initially and in relapse). Therefore, reliable conclusions regarding therapeutic strategies in very late relapse of patients with HL can't be drawn. Additional clinical trials are needed to define the best approach in patients with very late relapse, tailored on risk factors and comorbidities.

Conflicts of interest

The authors have no conflicts of interest.

References

1. Gobbi PG, Ferreri AM, Ponzoni M, Levis A. Hodgkin lymphoma. Oncology Hematol 2013; 85:216-237.
2. Engert A, Haverkamp H, Kobe C et al. Reduced-intensity chemotherapy and PET-guided radiotherapy in patients with advanced stage Hodgkin's lymphoma (HD15 trial): a randomised, open-label, phase 3 non-inferiority trial. Lancet 2012;379:1791-1799.
3. Moccia AA, Donaldson J, Chanabhai M et al. International Prognostic Score in advanced-stage Hodgkin's lymphoma: altered utility in the modern era. J Clin Oncol 2012;30:3383-3388.
4. Brice P. Managing relapsed and refractory Hodgkin lymphoma. Br J Haematol 2008;141:3-13.
5. Proventio M, Salas C, Millan I et al. Late relapses in Hodgkin lymphoma: a clinical and immunohistochemistry study. Leukemia Lymphoma 2010;51:1686-1691.
6. Gaudio F, Giordano A, Pavone V et al. Outcome of Very Late Relapse in Patients with Hodgkin's Lymphomas. Hindawi Publishing Corporation, Advances in Hematology Volume 2011, Article ID 707542. doi:10.1155/2011/707542.
7. Eichenauer DA, Engert A, André M et al on behalf of the ESMO Guidelines Working Group. Hodgkin's lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014;25 (Suppl 3):70-75.
8. Yuen AR, Rosenberg SA, Hoppe RT et al. Comparison between conventional salvage therapy and high-dose therapy with autografting for recurrent or refractory Hodgkin's disease. Blood 1997;89:814-822.
9. Hasenclever D, Diehl V, Armitage JO et al. A prognostic score for advanced Hodgkin's disease. N Engl J Med 1998;339:1506-1514.
10. Specht L. Tumour burden as the main indicator of prognosis in Hodgkin's disease. Eur J Cancer 1992;28A:1982-1985.
11. Steidl C, Lee T, Shah SP et al. Tumor-associated macrophages and survival in classic Hodgkin's lymphoma. N Engl J Med 2010;362:875-885.
12. Gallamini A, Patti C, Viviani S et al. Early chemotherapy intensification with BEACOPP in advanced-stage Hodgkin lymphoma patients with a interim-PET positive after two ABVD courses. Br J Haematol 2011 Mar;152:551-560.
13. Garcia-Carbonero R, Paz-Ares L, Arcediano AJ. Favorable prognosis after late relapse of Hodgkin's disease. Cancer 1998;3:560-565.
14. Bodies S, Henry-Amar M, Bosq et al. Late relapse in early stage Hodgkin's disease after 25 years. Indian J Cancer 1990;27:17-19.
15. Jaffe ES, Harris NL, Stein H (Eds): World Health Organization Classification of Tumours; Pathology and genetics of tumours of haemopoietic and lymphoid tissues. Lyon, France: IARC Press, 2001.
16. Stein H. Hodgkin lymphoma in WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. In: Swerdlow SH, Campo E, Harris, NL et al (Eds): International Agency for Research on Cancer Lyon, France 2008;322-334.
17. Lister TA, Crowther D, Sutcliffe SB et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Costwolds meeting. J Clin Oncol 1989;7:1630-1636.
18. Cheson BD, Horning SJ, Coiffier B et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. J Clin Oncol 1999;17:1244-1253.
19. Montanari F, Diefenbach C. Relapsed Hodgkin Lymphoma: Management Strategies. Curr Hematol Malig Rep 2014;9:284-293.
20. Obermann EC, Mueller N, Rufle A et al. Clonal Relationship of Classical Hodgkin Lymphoma and its Recurrences. Clin Cancer Res 2011;17:5268-5272.
21. Geurts-Giele WRR, Wolvers-Tettero ILM, Dinjens W. Successive B-Cell Lymphomas Mostly Reflect Recurrences Rather Than Unrelated Primary Lymphomas. Am J Clin Pathol 2013;140:114-126.
22. Hope RT, Advani RH, Ai WZ et al. Hodgkin Lymphoma;NCCN Guidelines Version 3, 2016.