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ANALYSIS OF PROGNOSTIC FACTORS IN HODGKIN'S LYMPHOMA WITH REGARD TO RESPONSE TO TREATMENT

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Summary. *Hodgkin lymphoma (HL) is an uncommon malignancy involving lymph nodes and lymphatic system. Due to the progress of the treatment, HL becomes a potentially curable disease. International Prognostic Index (IPI) was defined as the number of adverse prognostic factors presented at diagnosis. This report aims to assess the predictive power of the IPI for HL patients. On the basis of the retrospective study of patients with HL, we analyzed the prognostic significance of several factors with regard to response to treatment. We reviewed the medical records of 26 patients with HL, who were diagnosed and treated in our Clinic between 2004 and 2008. The median age of patients was 40 years, out of which 61.7% were males. Most patients had nodular sclerosis (57.7%) and mixed cellular (38.5%) histology. Clinical stage at diagnosis (AAS) was: I - II 46.1%, III - IV 53.9%. Presentation of IPI score was: low 26.9%, low intermediate 30.8%, high intermediate 34.6% and high 7.7%. B-symptoms were recorded in 64.5% of patients. Most of the patients received standard multi-agent chemotherapy with the well-established ABVD regime which provides the best balance of effectiveness and minimization of toxicity. Complete remission (CR) was achieved in 69% of patients after the first-line therapy. Significantly associated with the decrease of probability of achieving CR was the increased IPI score itself (p=0.02) and two of the five factors analyzed: extranodal disease >1 site (p=0.003) and poor performance status >1 (p=0.04). The International Prognostic Index shows good prognostic power in HL.*

Key words: *Hodgkin lymphoma, IPI, prognosis, treatment*

Introduction

Hodgkin lymphoma is a unique neoplasm of B-lymphocytes. Hodgkin lymphoma is characterised histologically by a minority of malignant Hodgkin and Reed-Sternberg cells surrounded by benign cells, and clinically by a relatively good prognosis (1). Recent data provide new understandings of the pathogenesis and options for staging and therapy of the disease. The past few decades have seen significant progress in the management of HL; it is now curable in high percent of patients (2).

The international prognostic project has developed a concept of international prognostic score, based on five adverse prognostic factors for newly diagnosed Hodgkin's lymphoma patients. The International Prognostic Index offers a predictive model for patients with Hodgkin's disease manifestations at presentation (3, 4).

Our intention was to evaluate our recently treated patients with HL, in which ABVD is the chemotherapy regimen of choice as induction treatment, regardless of whether it is used in combination with other chemotherapy regimen or with radiotherapy. We have analyzed their clinical and biochemical parameters and the impact that various parameters have on their prognosis. In the process, we analyzed the parameters identified as prognostically relevant in the IPI study. The aim of the study was to explore the feasibility of the International Prognostic Score in Hodgkin's lymphoma.

Patients and Methods

We performed a retrospective review of 26 patients at Clinic of haematology of the Clinical Center Niš with previously untreated histologically proven locally extended or advanced Hodgkin's lymphoma, treated during the period between January 2004 and June 2008.

Age, clinical stage, performance status according to Karnofsky's scale, serum lactic dehydrogenase level and the number of extranodal sites of the disease were used for determination of the International Prognostic Index, as shown in Table 1. The index divides patients into 4 risk groups: low, low intermediate, high intermediate and high. All cases were staged according to Ann Arbour Staging System and pathologically classified according to the Revised European-American Lymphoma (REAL) classification. Complete remission (CR) was defined as the resolution of clinical and radiological evidence of disease for minimum of 4 weeks. Other degrees of response were considered to represent the failure of treatment. Extranodal organ was defined as presentation in other sites with or without local lymph node involvement. Patients were treated with conventional chemotherapy regimens, with or with out radio-

therapy. Chi-square and Fisher exact test were used for testing proportions independence. All p values of 0.05 or less were considered statistically significant.

Table 1. International prognostic index (IPI)

A point is assigned in case of presence of each of the following negative prognostic factors:	
• *Age over sixty years*	
• *LDH > 1× normal values*	
• *ECOG performance status 2-4*	
• *Clinical stage III and IV*	
• *Extranodal disease > one localization*	
Degree of risk depending of IPI score:	
• *Low*	*0 or 1*
• *Low-intermediate*	*2*
• *High-intermediate*	*3*
• *High*	*4 or 5*

Results

Clinical characteristics of examined patients are presented in Table 2. Their age ranged between 21 and 73 years, with median age of 40 years. B symptoms were present in 64.5% patients.

In all patients, a uniform scheme of chemotherapy was applied: ABVD or BAECOPP regimens were used as first line treatments. After that appropriate radiotherapy was usually performed. Among the total of 26 patients with HL observed and/or treated at our Clinic, we identified 17 patients in which ABVD was at least one of the treatment options used with the intention of remission induction. Patients who were treated with standard ABVD received 4 to 8 cycles, every 28 days.

Two categories of response to the first–line therapy were noted: CR and resistance to first-line treatment (which included partial remission, no change, or progressive disease). CR was achieved in 18 patients (69%) after the first line therapy. Eight (31%) patients did not achieve CR after the first-line treatment, and second–line therapy was administrated.

The real prognostic significance of traditionally used IPI parameters is presented in Table 3. Two of the five factors analyzed showed their independent statistical significance, and predictive strength. Analysis of probability of inducing CR showed that poor performance status >1(p=0.04), extranodal disease >1 site (p=0.003) and increased IPI (p=0.02) were significantly associated with decreased probability of achieving CR. The probability of inducing CR was associated with low and low intermediate International Prognostic Index.

Table 2. Clinical characteristics of examined patients

Characteristics of patients	Number	%
Age(years)		
<60	23	(88.5)
≥60	3	(11.5)
Sex		
Male	16	(61.5)
Female	10	(38.5)
Histopathology		
Nodular sclerosis	15	(57.7)
Mixed cellularity	10	(38.5)
Lymphocyte depletion	1	(3.8)
Performance Status (ECOG)		
0-1	17	(65.4)
≥2	9	(34.6)
Extranodal disease		
0-1	18	(69.3)
≥2	8	(30.7)
LDH		
Normal	11	(42.3)
High	15	(57.7)
Clinical stage (according Ann Arbour)		
I	3	(11.5)
II	9	(34.6)
III	13	(50.0)
IV	1	(3.9)
IPI		
Low	7	(26.9)
Low-intermediate	8	(30.8)
High-intermediate	9	(34.6)
High	2	(7.7)

Discussion

Factors identified by IPI score are well known and traditionally used clinical and laboratory parameters. They have major impact on tumour control and prediction of outcomes in HL patients, but require further validation. An appropriate therapy scheme, chosen in compliance with prognostic factors, is a very important condition for cure. These prognostic factors offer the best available tool for identification of low and high risk patients and demand combined-modality of treatment which reduces toxicity or increases efficiency (5).

The combination of doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) emerged as the standard therapy because of its low toxicity profile and equivalent efficiency when compared to other regimens. Patients with limited stage Hodgkin's lymphoma should receive treatment that includes 2-4 cycles of chemotherapy followed by involved-field radiation therapy or ABVD chemotherapy alone (6, 7). Patients with an advanced stage Hodgkin's lymphoma should be treated more aggressively using 6-8 cycles of chemotherapy followed by consolidative radiotherapy whose effec-

Table 3. Effects of various variables on achieving complete remission

	CR (69.2%)		No CR (30.8%)		
	Number	%	Number	%	p-value
Age(years)					
<60	17	73.9	6	26.1	
≥60	1	33.3	2	66.7	0.44
LDH					
Normal	8	72.7	3	27.3	
High	9	60.0	6	40.0	0.38
PS (ECOG)					
0-1	14	82.4	3	17.6	
≥2	4	44.4	5	55.6	0.04
Clinical stage					
I – II	9	75.0	3	25.0	
III – IV	8	57.1	6	42.9	0.12
Extranodal					
0-1	16	88.9	2	11.1	
≥2	2	25.0	6	75.0	0.003
IPI					
Low/Low-intermediate	12	80.0	3	20.0	
High/High-intermediate	4	36.4	7	63.6	0.02

tiveness is still not proven (8). Risk adapted treatment has two aims: to maximize chance of cure and to minimize late toxicity, such as infertility, premature menopause, cardiac disease and risk of second neoplasm. Predicting the outcome is important in order to avoid overtreating some patients and to identify others in whom standard treatment is likely to fail.

In this study, we proved that two independent clinical pre-treatment factors and increased IPI score are negatively correlated with response to the first-line treatment. Our observations are consistent with results of some other authors, but the outcomes from different studies are still controversial.

Since its publication, IPI score is used to predict the result of the first-line therapy. It has been shown that IPI performs reasonably well in data sets which divide patients into two groups: lower risk (IPI<2) and higher risk (IPI>2). For example, in Italian study (5), patients (N=516) with an IPI above 2 had a 36% failure rate, whereas patients with an IPI of 2 or less had a failure rate of about 20%. The IPI, like other prognostic models, is not able to select either a very low risk group lower than 10% failure rate or very high risk group over than 50% failure rate. The conclusion of most of the studies is that prognostic models only discriminate between relatively low risk and relatively high risk patients. It may be clinically important for advanced HL to recognize patients who may be overtreated and to identify others in whom experimental approaches may be indicated. Over the past decades the outcome of the patients with all stages of Hodgkin's lymphoma has improved (8, 9, 10).

In the last several years, scientists have been searching for new, more specific and sensitive prognostic markers in HL. For example, immunohistochemical parameters which include the expression of PCNA (marker of cell proliferation) and protein products of the p53 and bcl-2 genes on Reed-Sternberg cells and their mononuclear variants, can be correlated with the prognosis. A number of other laboratory parameters, such as serum beta-2-microglobulin level, interleukin-2, CD-8 antigen or urinary excretion of pseudouridine, have also been considered as valuable for the prognosis in HL (11).

Conclusions

In this study, we proved that two independent clinical pre-treatment factors and increased IPI score are negatively correlated with response to the first-line treatment. Our observations are consistent with results of some other authors, but the outcomes from different studies are still controversial.

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ANALIZA PROGNOSTIČKIH FAKTORA KOD HOČKINOVOG LIMFOMA U ZAVISNOSTI OD ODGOVORA NA TERAPIJU

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Kratak sadržaj: *Hočkinov limfom (HL) je neobičan malignitet koji zahvata limfne žlezde i limfni sistem. Zbog napretka u lečenju, HL je postao potencijalno izlečiva bolest. Internacionalni prognostički indeks (IPI) definiše se kao broj nepovoljnih prognostičkih faktora koji se prezentuju pri dijagnozi. Cilj ovoga rada je da proceni predskazujuću moć IPI skora kod pacijenata sa HL. Na osnovu retrospektivne studije pacijenata obolelih od HL, analizirana je prognostička signifikantnost više faktora prema odgovoru na terapiju. Razmatrane su medicinske istorije 26 pacijenata koji su dijagnostikovani i lečeni na našoj Klinici u periodu od 2004. do 2008. godine. Prosečna starost pacijenata bila je 40 godina a 61,7% od njih bili su muškarci. Većina pacijenata je od histoloških tipova imala nodularnu sklerozu (57,7%) ili mešovitu celularnost (38,5%). Klinički stadijum pri dijagnozi (AAS) bio je: I-II 46,1%, III-IV 53,9%. Prezentacija IPI skora je bila: nizak 26,9%, srednje nizak 30,8%, srednje visok 34,6% i visok 7,7%. B simptomi su bili prisutni kod 64,5% pacijenata. Većina pacijenata je dobijala standardnu polihemioterapiju po dobro utvrđenom ABVD protokolu koji obezbeđuje najbolji balans efikasnosti i minimalne toksičnosti. Kompletna remisija (KR) je bila postignuta u 69% pacijenata posle prve terapijske linije. Opadajuća mogućnost postizanja KR je bila signifikantno udružena sa višim IPI skorom (p=0,02) i sa dva od pet analiziranih faktora: ekstranodalna bolest >1 mesta (p=0,003) i loš performans status >1 (p=0,04). Internacionalni prognostički indeks pokazao je dobru prognostičku moć kod HL.*

Ključne reči: *Hočkinov limfom, IPI, prognoza, tretman*