Prognostic factors in adult Non-Hodgkin's lymphoma patients

Edyta Jabłońska

Purpose. *Over the past 30 years the incidence of the Non-Hodgkin's lymphoma (NHL) in Europe and in the United States has increased dramatically. The Polish NHL patients have yet significantly poorer survival as compared with the NHL patients in the E.U. countries.*
The aim of this study was to define prognostic factors determining the prognosis of NHL patients. This could help to select a group of patients who require more intensive treatment.
Patients and methods. I reviewed and reclassified 174 cases of NHL patients treated in the Oncology Clinic of the Jagiellonian University in Krakow in 1971-1999. I estimated some social-economic features of the patients as well as the diagnostic and clinical features of the disease.
Results. Univariate analysis showed that there were two groups of factors influencing survival: lack of the abdominal computer tomography examination and certain clinical features of the disease. Therefore I decided to search for prognostic factors among the patients who were properly diagnosed, e.g. who underwent the abdominal computer tomography examination. Multivariate analysis in the group of patients with indolent NHL showed that there were two factors decreasing the overall survival (OS): diffused localisation of the disease and the elevated level of LDH. For disease-free survival (DFS) there was one independent prognostic factor, e.g. the value of International Prognostic Index (IPI). In patients with aggressive NHL the value of IPI significantly influenced the OS and the DFS. In this group I discovered also that anemia decreases the OS. In patients with high-aggressive NHL the independent prognostic for the OS was clinical stage IV and for the DFS the elevated level of LDH. Retrospective analysis revealed that the achievement of the CR substantially improves the OS. Common features that make difficult to achieve the CR in all lymphoma group were: bulky disease with the tumour size over 10 cm, low performance status (>1 according the WHO) and anemia.
Conclusion. In summary, my analysis indicates that the improvement of the outcome among the Polish NHL patients is associated with the improvement of the diagnosis. In addition, the high-risk NHL patients according the IPI should be considered as candidates for more intensive treatment. In the high-risk group of indolent NHL patients, chemotherapy combined with immunotherapy is recommended. In the high-risk group of aggressive NHL patients earlier qualification for myeloablative chemotherapy with subsequent PBSCT should be suggested.

Czynniki rokownicze u chorych dorosłych na chłoniaki nieziarnicze

Cel. W ciągu ostatnich trzydziestu lat w całej Europie i Ameryce Północnej obserwuje się wyraźny wzrost zachorowalności na chłoniaki nieziarnicze. W populacji polskiej zwracają uwagę znamiennie gorsze 5-letnie przeżycia w porównaniu z krajami Unii Europejskiej. Wzrost ryzyka zachorowania na chłoniaki nieziarnicze wiąże się prawdopodobnie ze zwiększeniem ekspozycji na czynniki rakotwórcze, zakażeniami wirusami (HIV, HTLV-1, Epstein-Barr), poprawą diagnostyki i zmianami w klasyfikacji. Obecnie utworzona nowa klasyfikacja REAL zakłada, że chłoniaki nieziarnicze stanowią heterogenną grupę nowotworów, z których każdy jest odrębną jednostką chorobową, definiowaną przez określone cechy kliniczne, histopatologiczne, immunologiczne i genetyczne. W praktyce jednak najbardziej użyteczny z klinicznego punktu widzenia pozostaje nadal podział na trzy grupy: o niskiej, wysokiej i najwyższej złośliwości. Podział ten uwzględnia „sformułowanie robocze", które stało się podstawą przeklasyfikowania wszystkich postaci morfologicznych analizowanych chłoniaków.
Materiał i metody. Weryfikacji histopatologicznej poddano 174 chorych leczonych w Klinice Onkologii CMUJ w latach 1971–1999. Założeniem niniejszej analizy była próba ustalenia przed rozpoczęciem leczeniem niezależnych czynników pogarszających rokowanie, a tym samym możliwość wyselekcjonowania grupy chorych wymagających bardziej intensywnego lecze-

Oncology Clinic of the Jagiellonian University Medical College,
Cracow, Poland
Ph.D. thesis

nia. Każdego chorego oceniono pod względem cech społeczno-ekonomicznych, prześledzono przeprowadzone badania diagnostyczne oraz uwzględniono charakterystykę kliniczną choroby.

W y n i k i . Analiza jednocechowa wykazała, że istotne dla przeżyć są dwie odrębne grupy czynników, tj. brak badania tomografii komputerowej jamy brzusznej oraz niektóre cechy kliniczne choroby. Stąd też postanowiono dodatkowo przeprowadzić poszukiwanie niezależnych czynników rokowniczych dla chorych prawidłowo zdiagnozowanych, tj. tych, u których wykonano badanie KT jamy brzusznej, zakładając, że u takich chorych prawidłowo oceniono zasięg choroby. Cechy, które okazały się istotne w analizie jednocechowej, wprowadzono następnie do modelu wielocechowego Coxa w poszukiwaniu niezależnych czynników rokowniczych. Analiza wielocechowa w grupie chorych o niskiej złośliwości wykazała, że cechami istotnie pogarszającymi przeżycia całkowite były: obecność lokalizacji rozlanej i podwyższony poziom LDH. Dla przeżyć bezobjawowych natomiast istotne znaczenie rokownicze ma wartość międzynarodowego wskaźnika rokowniczego ponad 1. W grupie chorych z chłoniakami o wysokiej złośliwości istotnie pogarszająca przeżycie całkowite i bezobjawowe okazała się wartość międzynarodowego wskaźnika rokowniczego ponad 1. Wykazano ponadto, że istotne znaczenie rokownicze dla przeżyć całkowitych w tej grupie chorych ma niedokrwistość. W grupie chorych z chłoniakami o najwyższej złośliwości niezależnym czynnikiem rokowniczym dla przeżyć całkowitych był IV stopień zaawansowania klinicznego choroby, a dla przeżyć bezobjawowych podwyższony poziom dehydrogenazy mleczanowej. W retrospektywnej ocenie wyników i odpowiedzi na leczenie okazało się, że uzyskanie najlepszej odpowiedzi na leczenie, tj. uzyskanie całkowitej remisj, poprawia istotnie przeżycia chorych. Wspólną cechą utrudniającą uzyskanie całkowitej remisji jest masywność zmiany z wymiarem ponad 10 cm oraz obniżony stan ogólnej sprawności (według WHO≥2).

W n i o s k i . Na podstawie przeprowadzonej analizy stwierdzono, że poprawa przeżyć chorych z chłoniakami nieziarniczymi wiąże się z poprawą diagnostyki, jak i rozważeniem indywidualnie bardziej intensywnego leczenia u chorych z grup podwyższonego ryzyka zgonu i nawrotu choroby, obarczonych przede wszystkim wartością międzynarodowego wskaźnika rokowniczego ponad 1. U takich chorych z chłoniakami o niskiej złośliwości należałoby rozważyć wcześniejszą kwalifikację do chemio-immunoterapii, a u chorych z chłoniakami o wysokiej złośliwości do chemioterapii mieloablacyjnej z autologicznym przeszczepieniem komórek macierzystych.

Introduction

In Poland 1747 were observed newly diagnosed cases of non-Hodgkin's lymphoma (1.6% of all malignant neoplasms), and 1148 deaths (1.4% of all deaths) in 1996 [1]. In 1990 in non-Hodgkin's lymphomas made up about 3% of all malignant neoplasms and 3.5% of all deaths the European Union [2]. These data suggest that the proportion of non-Hodgkin's lymphomas to all malignant neoplasms is lower in Poland than in Western countries. Since 1960 almost everywhere in Europe, especially in Scandinavian countries and the European Union the incidence of non-Hodgkin's lymphoma has been rising by 15-40% every 5 years [3]. In Poland mortality due to NHL in men has been rising since mid 60s. The risk of death in Poland increased in men by 1.5-fold and in women by 1.6-fold from 1965 to 1995. Both in women and men born in the 60s the risk of death due to NHL was 10 times higher than in those born at the end of the 20th century [3]. In Krakow the risk of NHL increased between 1983 and 1992 in men by 23% whereas in women it remained unchanged [4, 5]. In contrast to Hodgkin's disease the therapeutic outcome is much lower and mortality due to NHL has not decreased. In Europe an average relative 5-year survival of patients with Hodgkin`s disease was 72% in 1985-1989, but in those with NHL it was c. 45%.The relative survival in the Polish population of patients with Hodgkin's disease does not differ significantly from that in Europe. In case of NHL the relative 5-year survival in Polish patients was only 32% i.e. by 14% lower than the European average, the difference being significant [6]. These facts i.e. the rising risk of NHL in the Polish population and significantly worse 5-year survival as compared with the European Union prompted me to undertake a search for factors significantly affecting prognosis in patients with these malignancies. In consequence this should facilitate adequate treatment and improve survival of Polish patients with NHL. The identification of the prognostic factors significantly affecting the prognosis in the Polish population is the main objective of the present study. Three main types of NHL are analysed: low grade, intermediate grade and high grade lymphomas.

Material and methods

Between 1971 and 1999 were admitted to 174 patients with NHL in whom the diagnosis was confirmed by histopathology the Department of Oncology Jagiellonian University Medical College. In all patients we revised the morphological diagnosis of NHL. For the purposes of the present analysis NHL was divided into three main groups: low grade, intermediate grade and high-grade lymphomas. Using clinical documentation of the patients their age, sex, residence, marital status, occupation and smoking status were established.

The following diagnostic procedure were also taken into account:

a) lactate dehydrogenase level (according to the Laboratory of Diagnostics of the Jagiellonian University Medical College 150–460 U/L),

b) imaging studies: ultrasound of the abdomen, computerised tomography of the abdomen, bilateral limb lymphography and liver scintigraphy,

c) microscopy studies of the bone marrow (biopsy and myelogram).

The following clinical characteristics were analysed: presence of generalised symptoms (B) or their absence (A) [7–9], performance status according to the WHO (scale from 0 to 4), bulk of the lesion i.e. dimension of the largest palpable mass of the lymphoma in centimetres (physically or by imaging), bone marrow and spleen involvement, location (nodal, extranodal, diffuse), clinical stage (according to the Ann Arbor system, 1971) and the International Prognostic Index (IPI). For all patients the International Prognostic Index was calculated based upon the presence or absence of the following high risk factors [16–19]:

a) age over 60,
b) stage according to the Ann Arbor system > II
c) more than one extranodal site,
d) limited performance (according to the WHO ≥2),
e) serum lactate dehydrogenase > normal level.

Depending on the number of high-risk factors the patients were divided into four groups at risk. For each group overall and disease free 5-year survival was calculated. Additionally the age-adjusted international prognostic index was calculated based upon the presence or absence of the following high--risk factors:

a) stage according to the Ann Arbor system > II,
b) serum lactate dehydrogenase > normal level,
c) limited performance (according to the WHO ≥2).

The calculations were done separately for the patients aged 60 and younger and for the patients over 60. This dichotomy was used because survival of patients over 60 years of age is usually worse than in younger patients [20-26]. For each risk group overall and symptom free 5-year survival was established.

Treatment modalities taken into account were chemotherapy, radiotherapy, surgical and combined treatment. A group of untreated patients was identified. The methods of combined treatment were characterised. The effect of splenectomy on the outcome was established. I also identified the number and proportion of patients who received chemotherapy containing anthracyclines or not, as well as required and decreased chemotherapy dose.

Statistical analysis

Prognostic factors were analysed using standard procedures. All potential prognostic factors were either by nature qualitative (e.g. sex) or were categorised according to the generally accepted cut-off points (e.g. norm in case of LDH). Overall and symptom free survival curves were estimated according to Kaplan-Meier, including truncated data points [27]. Survival was compared using log-rank tests [28]. Tables summarise 5-year survival and p values. In certain categories of features survival did not exceed 5 years, but a certain number of patients is still under observation. The last observed survival is marked in parentheses, which means that 5-year survival cannot be higher than that. The most important results were plotted to obtain survival curves. In all statistical tests used in the study a difference was deemed significant when the value of the associated test probability (p value) was lower than the level of significance $\alpha = 0.05$. Base upon the results of log-rank test a set of initial significant prognostic factors was identified. Complete data were obtained using multidimensional Cox models. A preliminary set of explanatory variables in these models were factors with variability found in univariate analysis (i.e. log-rank test). Then a step-wise regression procedure in the descending mode was used removing from the model step by step those variables which in a given estimating process had the highest (and higher than 0.05) p value. The process of variable removal was completed when all relative risks were statistically significant. This model permits identification of independent prognostic factors, their mutual standardisation and comparison of power [29]. Tables summarise the relative risk with the 95% confiden-

ce interval and p value associated with this risk. In some univariate analyses because of a small number of nontruncated observations (that is terminated by relapse or death) it was not possible to estimate survival or Cox models. These data are marked with a dot in the table. In analyses of relationships between qualitative and categorised variables (e.g. the presence of anaemia and severity) chi square test of independence was used [30].

Results – impact on survival

Low grade lymphomas

In analysis of overall survival in all patients with low grade NHL the following variables significantly affecting overall survival in univariate analysis were used in the preliminary model: age over 60, no CT scan of the abdomen, diffuse location, anaemia, elevated LDH, stage IV disease and IPI over 1, assuming that the index may be the most significant prognostic factor. None of the above mentioned characteristics was a significant prognostic factor affecting overall survival. In analysis of symptom free survival in patients with low grade NHL the preliminary model included the following variables which appeared significant in univariate analysis: presence of B symptoms, diffuse location, bulk over 10 cm, anaemia, elevated LDH and IPI over 1. Using step-wise regression in the multivariate model no independent characteristic was found to significantly affect symptom free survival. A separate multivariate analysis of overall survival was carried out for patients who underwent abdominal computerised tomography introducing in the initial stage the factors which were significant in univariate analysis: age over 60, stage IV disease, anaemia, elevated LDH, involvement of the bone marrow, diffuse location and IPI over 1. In the final model one significant prognostic factor was identified for this group of patients i.e. elevated LDH. The results are summarised in the Table I.

Tab. I. The effect of prognostic factors on overall 5-year survival in patients with low grade non Hodgkin's lymphomas who underwent computerised tomography of the abdomen

Characteristic	Relative risk of death	p	Confidence interval
LDL level			
Normal	1.00		
> normal	6.47	0.0002	2.41 – 17.35

Multivariate analysis of symptom free survival in this group of patients included the following factors which appeared significant in univariate analysis: presence of generalised B symptoms, diffuse location, bulk over 10 cm, anaemia, elevated LDH and IPI over 1. The final analysis revealed one prognostic factor significant for symptom free survival i.e. international prognostic index IPI over 1 (see Tab. II).

Tab. II. The effect of prognostic factors on symptom free 5-year survival in patients with low grade non-Hodgkin's lymphomas who underwent computerised tomography of the abdomen

Characteristic	Relative risk of relapse	p	Confidence interval
IPI			
IPI≤	1.00		
IPI>1	2.42	0.0131	1.20 – 4.90

Intermediate grade lymphomas

Analysis of overall survival in all patients with intermediate grade non-Hodgkin's lymphomas included in the initial model the following variables which appeared significant in univariate analysis: age over 60, no CT scan of the abdomen, anaemia, stage IV disease, performance status according to the WHO ≥2, elevated serum LDH and IPI over 1 assuming that similar to low-grade lymphomas IPI may be the most significant prognostic factor. In the final step the proportional hazard model revealed three independent prognostic factors: no CT scan of the abdomen, anaemia and IPI over 1.

Tab. III. The effect of prognostic factors on overall 5-year survival in patients with intermediate grade non-Hodgkin's lymphomas (all patients)

Characteristic	Relative risk of death	p	Confidence interval
CT of the abdomen			
Yes	8.43	0.0003	2.66 – 26.74
No	1.00		
Anaemia			
Yes	3.31	0.0214	1.19 – 9.18
No	1.00		
IPI			
IPI1≤1	1.00		
IPI>1	6.45	0.0010	2.13 –19.49

When analysing symptom free survival of patients with intermediate-grade NHL the following variables which appeared significant in univariate analysis were taken into account: no CT scan of the abdomen, stage IV disease, anaemia, elevated LDH and IPI >1. In the final step multivariate analysis of 5-year symptom free survival revealed two independent prognostic factors i.e. no CT scan of the abdomen and IPI >1 (see Table IV).

Tab. IV. The effect of prognostic factors of symptom free 5-year survival in patients with high-grade non Hodgkin's lymphomas (all patients)

Characteristic	Relative risk of relapse	p	Confidence interval
CT of the abdomen			
Yes	3.36	0.0161	1.25 – 9.04
No	1.00		
IPI			
0.1	1.00		
>1	4.81	0.0015	1.83 – 12.68

An additional multivariate analysis of survival was carried out in patients who underwent abdominal CT scanning. Analysis of overall survival included in the initial stage factors which were significant in univariate analysis: age over 60, performance status according to the WHO ≥2, stage IV disease, anaemia, elevated LDH and IPI >1.

The final model revealed two independent prognostic factors in this group of patients i.e. anaemia and IPI >1 (see Table V).

Tab. V. The effect of prognostic factors on overall 5-year survival in patients with high grade non Hodgkin's lymphomas who underwent abdominal computerised tomography

Characteristic	Relative risk of death	p	Confidence interval
Anaemia			
Yes	4,19	0,01339	1,35 – 13,04
No	1,00		
IPI			
0, 1	1,00		
> 1	4,72	0,00965	1,46 – 15,32

Analysis of symptom free survival in this group of patients included the following features significantly affecting survival in univariate analysis: stage IV disease, anaemia, elevated LDH and IPI >1. In the final version analysis of symptom free survival revealed one independent prognostic factor i.e. IPI >1 (see Table VI).

Tab. VI. The effect of prognostic factors on symptom free 5-year survival in patients with high grade non Hodgkin's lymphomas who underwent abdominal computerised tomography

Characteristic	Relative risk of relapse	p	Confidence interval
IPI			
0.1	1.00		
>1	6.07	0.0056	1.69-21.75

High grade lymphomas

Analysis of high grade lymphomas was carried out separately because this group included lymphoblastic and Burkitt's lymphomas. These variants are characterised by rapid growth, and their detection is an indication for immediate treatment without completing the diagnostic procedure. The results of analysis in this group of patients, because of its small size were regarded as approximate. In the final version multivariate analysis of overall 5-year survival revealed one independent prognostic factor: stage IV disease. Analysing the effect of prognostic factors on symptom free survival of patients with high grade non Hodgkin's lymphomas only elevated LDH was taken into consideration as the only statistically significant variable in univariate analysis. For this reason it was not possible to establish a multivariate model.

Discussion

From the clinical point of view it is still most useful to divide non-Hodgkin's lymphomas into low grade, intermediate grade and high grade (aggressive) lymphomas [11, 12, 31]. This division best reflects "working formulation" and it served as the basis of revised classifications of all morphological forms of non-Hodgkin's lymphomas treated in the Department of Oncology Jagiellonian University Medical College between 1972 and 1999. Available data indicate that it is not a selected material and clinically resembling to the material of the Centre of Oncology Ward in Krakow [32] (see Table VII).

Tab. VII. Clinical characteristics of patients with non-Hodgkin's lymphomas treated in the Centre of Oncology in Krakow (COOK) between 1978 and 1986 and in the Department of Oncology Jagiellonian University Medical College (KO) between 1972 and 1999

Characteristic	Low grade		High grade	
	COOK (n=156)	KO (n=87)	COOK (n=97)	KO (n=87)
Sex				
Men	99 (63.5%)	54 (58.6%)	53 (54.6%)	49 (56.3%)
Women	57 (36.5%)	33 (37.9%)	44 (45.4%)	38 (43.7%)
Staging				
I	30 (19.2%)	12 (13.8%)	12 (12.4%)	10 (11.9%)
II	22 (14.5%)	16 (18.3%)	25 (25.8%)	32 (36.7%)
III	32 (20.5%)	29 (33.3%)	22 (22.6%)	18 (20.6%)
IV	72 (46.2%)	30 (34.5%)	38 (39.2%)	24 (28.6%)
Symptoms				
A	112 (71.8%)	57 (65.5%)	63 (64.9%)	57 (65.5%)
B	44 (28.2%	30 (34.5%)	34 (35.1%)	30 (34.5%)

There were no statistically significant differences in the clinical characteristics between the Centre of Oncology and the Department of Oncology. For this reason it is highly probable that the analysed material is representative for the patients treated in specialised institutions in Krakow. The therapeutic outcome reflecting 5-year survival achieved in both institutions is summarised in Table VIII. Additionally it was compared with survival of patients in other institutions [17].

Tab. VIII. Five-year survival in patients with non Hodgkin's lymphomas obtained in the Centre of Oncology in Krakow (COOK) and the Department of Oncology Jagiellonian University Medical College (KO)

Centre	5-year survival	
	Low grade	High grade
COOK (1978-1986) [33]	39.1% (35.2 – 43.0)	22.7% (14.4 – 31.0)
KO (1971-99)	47.8% (37.3 – 58.3)	31.8% (21.3 – 42.3)
Other institutions [34]	68.2% (59.2 – 77.2)	52.0% (49.8 – 54.2)

The data in this table suggest that the therapeutic outcome in both centres in Krakow is not significantly different. However, it is significantly worse than in other countries. In order to improve these results it seems justified to find out significant adverse prognostic factors that would permit identification of patients requiring more aggressive treatment. This will enable us to tailor therapy to the individual patients identifying a subgroup of patients who would benefit from intensive treatment and avoiding too aggressive treatment in patients without adverse prognostic factors. Initial univariate analysis revealed that the following characteristics had a statistically significant effect on overall survival in patients with low grade NHL: age over 60, no abdominal CT scan, diffuse location, bone marrow involvement, stage IV disease, anaemia, elevated LDH and IPI over 1. For symptom free survival the significant features were as follows: presence of B symptoms, diffuse location, bulk over 10 cm, anaemia, elevated LDH and IPI over 1. In patients with intermediate grade NHL log rank test revealed that overall survival was affected by age over 60, no abdominal CT scan, stage IV disease, performance status according to the WHO ≥2, anaemia, elevated LDH and IPI over 1. The characteristics affecting symptom free survival in this group of patients were no abdominal CT scan, stage IV disease, anaemia, elevated LDH and IPI over 1. Finally in patients with high grade NHL univariate analysis revealed that overall survival was influenced significantly by stage of the disease (I+II+III versus IV), and whereas symptom free survival was affected by LDH level.

Failure to perform abdominal computerised tomography has a significant adverse effect on the prognosis both in patients with low grade (overall survival) and in patients with high grade NHL (overall and symptom free survival). Computerised tomography of the abdomen is a stage-of-the-art technique most useful in evaluating the lymph nodes below the diaphragm and abdominal organs [35]. For this reason no CT scan of the abdomen is equivalent to imprecise staging of NHL. This in turn results in the fact that the patients frequently do not receive treatment, which is adequate to the disease extent. Figures 1 and 2 display survival curves in patients with NHL depending on whether CT scan of the abdomen was obtained or not.

These figures show that the lack of CT data is a significant factor adversely affecting overall survival. For this reason it was decided to regard as most significant those prognostic factors which were significant in fully diagnosed patients i.e. with CT scan of the abdomen. In patients with low grade NHL elevated LDH was an independent prognostic factor significantly aggravating overall survival, and in patients with IPI over 1 symptom free survival was significantly decreased. In other words, in patients with low grade NHL the presence of more than one characteristic referred to as the international prognostic index precipitates relapse. The International Prognostic Index (IPI) was primarily established and its usefulness for survival was confirmed in patients with high grade lymphomas [10, 16, 19, 36, 37]. Based upon this index we identify four groups at risk corresponding to the number of risk factors. It has been demonstrated
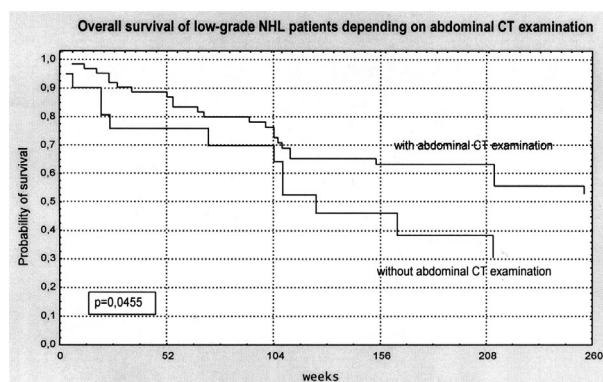
Fig. 1. Overall survival in patients with low grade non-Hodgkin's lymphomas depending on whether abdominal CT examination was obtained or not
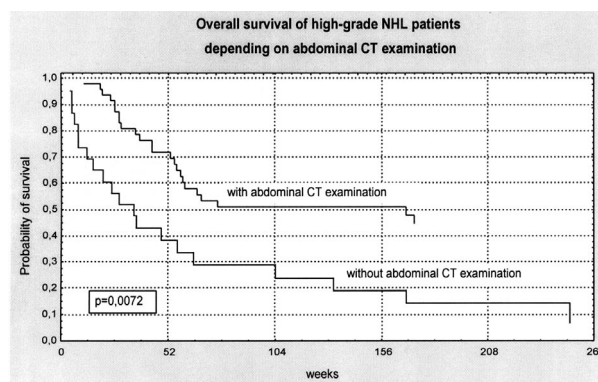

Fig. 2. Overall survival in patients with high grade NHL depending on whether abdominal CT examination was obtained or not

that patient survival both overall and symptom free decreases with the increasing number of risk factors. For patients up to 60 years of age and for patients over 60 years an additional simplified model was defined the so-called age-adjusted prognostic index. This model is used in experimental clinical trials in younger patients i.e. up to 60 years of age [19]. So far it has not been clear whether in low-grade lymphomas the same features which are included in the international prognostic index are significant. According to some investigators such features as extranodal sites, age over 60, stage IV disease and elevated LDH are associated with adverse prognosis in patients with low grade NHL [17, 38, 39]. Other investigators made an attempt to establish a predictive model based upon the presence of the following features: bulk over 5 cm, number of extranodal sites >1, male sex and extent of bone marrow involvement over 20%. These features were independent prognostic factors of relapse and their presence had an adverse effect on survival [40]. In recent reports a significant factor adversely affecting overall survival was age over 60, B symptoms and at least three nodal sites each larger than 3 cm [41]. The present study has demonstrated that also for patients with low grade NHL in whom CT scan of the abdomen was obtained it is important to establish before treatment. It appeared the only independent prognostic factor affecting symptom free survival. As Table II shows IPI score >1 is associated with a two-fold increase of risk for relapse. According to recent reports the IPI also significantly affects overall survival, especially in patients with more than three risk factors [18, 38, 42]. In patients with intermediate grade lymphomas in whom CT of the abdomen was performed multivariate analysis revealed that the presence of such characteristics as anaemia and IPI score >1 significantly decreases overall survival. As for symptom free survival only IPI score >1 is the most significant prognostic factor. The Table IX summarises the effect of the IPI on survival in patients with low- and high-grade non-Hodgkin's lymphomas.

As the table shows IPI score >1 has a significant effect on survival in patients with complete diagnosis. In patients with high grade non-Hodgkin's lymphomas it significantly increases the risk of death and relapse. In pa-

Tab. IX. The effect of the IPI on overall and disease-free survival in patients with low- and high-grade non-Hodgkin's lymphomas in whom CT scan of the abdomen was obtained

Grade	IPI	overall survival relative risk of death	p value	disease-free survival relative risk of relapse	p value p
Low	0.1	1.00	0.4232	1.00	0.0131
	>1	2.07		2.42	
High	0.1	1.00	0.01339	1.00	0.0056
	>1	4.72		6.07	

tients with low-grade lymphomas IPI score >1 is associated with a significantly increased risk of relapse, but it does not significantly affect overall survival.

The present study shows that the IPI calculated prior to treatment helps us to estimate the percent of complete remission and survival indicating a significant deterioration of therapeutic outcome with the increasing IPI. Thus, to the best of our knowledge the information about IP appears to be most important when deciding about treatment for patients with low- and intermediate-grade non-Hodgkin's lymphomas [17, 18, 38, 41, 43, 44].

In patients with high-grade lymphomas stage IV disease was the only, independent prognostic factor influencing overall survival. Symptom free survival in this subgroup deteriorated significantly with increasing LDH. Because of a small size of the group it was not possible to search for the prognostic factors in patients who underwent CT of the abdomen.

From the viewpoint of cure it is most important to achieve symptom free survival. Complete remission is a fundamental indicator of symptom free survival [45]. The present study shows that complete remission is a statistically significant characteristic affecting patient survival. However, complete remission is a characteristic, which cannot be predicted before treatment. For this reason, multivariate models to analyse the prognostic factors, which are important before the onset of treatment did not include this characteristic. However, chi-square test of independence revealed a relationship between complete remission and other characteristics.

The clinical characteristics, which negatively affected complete remission in patients with low- and intermediate grade lymphomas were as follows: bulk over 10 cm, anaemia and limited performance according to the WHO ≥2. Thus, improvement of therapeutic outcome depends on improved diagnostic process in its broad sense. Another important step is appropriate treatment administered to patients with IPI >1, both in low- and intermediate grade lymphomas. Patients with low-grade lymphomas can be managed in different ways. In asymptomatic patients at first diagnosis it seems most appropriate to take a wait-and-see approach [40, 46, 47, 48]. Treatment in these patients is usually initiated when they develop subjective and secondary symptoms of progression [49]. This approach is based on the assumption that the chances of cure are very small. The natural course of the disease is slow (for this reason they are referred to as indolent lymphomas), with frequent relapses manifest as clinical progression [50]. That is why treatment is administered not to cure but to stabilise the disease process using minimal toxic modalities. This is reflected in the present findings in patients with low-grade lymphomas in whom symptom free survival is even poorer than in patients with intermediate grade lymphomas. However, it seems that in patients with low-grade non-Hodgkin's lymphomas and IPI score >1 treatment should be more aggressive. In patients with increased risk of death and relapse in whom it is possible to estimate a probability of remission and survival initiation of intensive treatment should be considered. Chemotherapy drugs should include alkylating agents (cyclophosphamide, chlorambucil), steroids and purine analogues (Fludarabine, Cladribine) as first choice drugs [51]. Especially purine analogues are promising, because they affect inactive lymphocytes in the cellular cycle, which are predominant in patients with low-grade lymphomas. Interferon alpha-2 has also been found to prolong the duration of remission after chemotherapy [10, 52]. The combination of chemotherapy and immunotherapy (Rituximab, Campath) with radioimmunotherapy seems also effective [53-56]. In younger patients high-dose chemotherapy with subsequent stem cell transplantation should also be considered [57-59]. This highly toxic approach prolongs the duration of remission in 70% of patients [58-59]. The effect of these monoclonal antibodies on long-term survival has yet to be evaluated. Such treatments cannot be offered to all patients. They should be considered in those patients in whom IPI score exceeds 1. At present the CHOP + Mabthera regimen can be effective (cyclophosphamide 750 mg/m^2 on day 1 + doxorubicin 50 mg/m^2 on day 1 + vincristine 1.4 mg/m^2 on day 1, prednisone 100 mg/m^2 orally on days 1 to 5 every 3 weeks combined with Mabthera 375 mg/m^2 every 2-4 weeks) [53, 56].

In patients with intermediate grade lymphomas treatment is initiated to achieve complete remission. Only this approach is associated with cure and even long-term survival in about 35% of patients. The most frequent cause of failure in this subgroup is the dynamics of the disease leading sometimes to refractoriness as well as expansiveness at critical sites (mediastinum, central nervous system, and abdomen). For this reason chances of cure increase with aggressiveness of chemotherapy. Recent studies have demonstrated that the duration of remission and LDH at relapse significantly affect long-term survival. In patients with the disease relapsing within a period shorter than 12 months as well as in patients who did not respond to initial conventional chemotherapy one should consider intensified chemotherapy with subsequent peripheral blood stem cell transplantation [36, 60, 61, 62, 63]. To the best of our knowledge the most appropriate criterion of eligibility to this treatment is increased risk according to the international prognostic index. In these patients myeloablation with autologous stem cell transplantation should be considered as first choice treatment [57, 58, 59, 64]. An increasing number of reports indicates that other immunological and genetic characteristics of cells may have a significant influence on therapeutic outcomes in patients with the same level of risk [65]. Novel treatments include the use of nonsense oligonucleotides and idiotypic vaccination [49]. Overexpression of bcl2 plays a major role in malignant transformation leading to the development of certain lymphomas and may decrease the efficacy of treatment through inhibition of apoptosis [66]. If a nonsense oligonucleotide fragment were bound with mRNA fragment blocking the production of bcl2 protein on the transcriptional level we could reverse drug refractoriness or even bring back normal apoptosis in cancer cells. Preliminary results of studies using intravenous nonsense oligonucleotide bcl2 are promising, confirming low toxicity and good clinical efficacy [67]. In some lymphomas gene rearrangement sometimes results in overexpression of the receptor, which is an immunoglobulin molecule. A lymphoma-specific variable immunoglobulin portion is referred to as an idiotype. Such immunoglobulin administered to asymptomatic patients or those with residual disease could induce an immune response and antiimmunoglobulin production. The results of available studies indicate that in patients with the immune response symptom free survival is markedly improved [68]. Preliminary results of using new modalities are promising, thus increasing the possibilities of treating non-Hodgkin's lymphomas in future.

Summing up, in each lymphoma apart from identifying its morphological type it is important to submit a patient to a complete diagnostic process and to obtain the information on the clinical characteristics that have an adverse effect on prognosis. The identification of these characteristics before the onset of treatment would allow us to adjust the intensity of treatment to the disease aggressiveness, which increases with the presence of adverse prognostic factors [34, 69, 70, 71]. At present the best prognostic indicator both in low- and intermediate grade lymphomas is the international prognostic index, which is calculated based upon age (≤60 years vs. >60), stage according to the Ann Arbor system (≤II vs. > II), number of extranodal sites (≤1 vs. >1), performance status (according to the WHO <2 vs. ≥2) and serum lactate

dehydrogenase (normal vs. > normal). In patients with low-grade lymphomas and IPI >1 it seems wise to consider a more intensive treatment e.g. CHOP + Mabthera regimen as first choice therapy [53, 55, 56]. Patients with intermediate grade lymphomas should also be considered as candidates for high-dose chemotherapy combined with peripheral blood stem cell transplantation [59, 64, 71].

Conclusion

1. Improved prognosis in patients with non-Hodgkin's lymphomas depends on exact staging of the disease, and especially obtaining a CT scan of the abdomen.
2. The international prognostic index is an important prognostic factor both in low- and high grade lymphomas.
3. The presence of IPI score > 1 is associated with the need for intensified treatment.
4. The achievement of complete remission significantly affects overall survival in patients with low- and high--grade lymphomas.
5. Tumour bulk (> 10 cm in diameter), limited performance (according to the WHO ≥2) and anaemia decrease the chances of remission in all types of non--Hodgkin's lymphomas.

Edyta Jabłońska M.D.
Oncology Clinic
of the Jagiellonian University Medical College,
Kopernika 19, 31-501 Kraków

References

1. Zatoński WA, Tyczyński JE. *Nowotwory złośliwe w Polsce w 1996 roku.* Warszawa: Centrum Onkologii-Instytut im. Marii Skłodowskiej-Curie; 1999.
2. Coleman, MP, Esteve, J, Damiecki P, et all. *Trends on Cancer Incidence and Mortality.* Lyon: IARC Scientific Publications 1993; 121.
3. Zatoński WA, Tyczyński JE. *Epidemiologia nowotworów złośliwych w Polsce w piętnastoleciu 1980–1994.* Warszawa: Centrum Onkologii-Instytut im. M. Skłodowskiej-Curie, 1997.
4. Pawlęga J. Poland, Cracow city. In: *Cancer Incidence in Five Continents* (eds. Parkin DM, Muir CS, Whelan SL, et all.) VI. IARC Scientific Publication 1992; 120; 678–681.
5. Pawlęga J. Poland, Cracow city. In: *Cancer Incidence in Five Continents* (eds. Parkin DM, Whelan SL, Ferlay J, et all) VII, IARC Scientific Publication 1997; 143: 598–601.
6. Carli PM, Coebergh JWW, Verdecchia A and the EUROCARE Working Group.: Variation in survival of adult patients with haematological malignancies in Europe since 1978. *Eur J Cancer* 1998; 34: 2253–2263.
7. Finke J. Non-Hodgkin`s lymphome (NHL). In: *Das rote Buch Hematologie und internistische Onkologie* (reds. Berger DP, Engelhardt R, Mertelsmann R) Landsberg/Lech. Ecomed; 1997, 247–291.
8. Issacson PG. Gastric MALT lymphoma: from concept to cure. *Ann Oncol* 1999; 10: 619–621.
9. McVie JG, Hossfeld DK. Chłoniaki złośliwe. In: *Podręcznik onkologii klinicznej* UICC (eds. Hossfeld DK, Sherman CD, Love RR, et all). Warszawa – Kraków: Wydawnictwo Naukowe PWN; 1994, 396–409.
10. Canellos GP, Lister TA, Sklar JL. *The lymphomas.* Philadelphia: W.B. Saunders Company, 1998.
11. De Vita Jr VT, Hellman S, Rosenberg SA. *Cancer. Principles and Practice of Oncology.* 5th Edition, Philadelphia, New York: Lippincott – Raven Publishers; 1997, 2131–2183.
12. Walewski J. Chemioterapia chłoniaków nieziarniczych. In: *Chemioterapia onkologiczna dorosłych i dzieci* (ed. Grzegorz Madej). Warszawa: PZWL; 1999, 238–263.
13. Casadevall N. Update in the role of epoetin alfa in haematological malignancies and myelodysplastic syndromes. *Semin Oncol* 1998; 25: Suppl. 7: 12–18.
14. Jędrzejczak, WW. Problem niedokrwistości u chorych na nowotwory: zasady postępowania. *Nowotwory* 1996; 46: 691–697.
15. Moullet I, Salles G, Ketterer N, et all. Frequency and significance of anemia in Non-Hodgkin`s lymphoma patients. *Ann Oncol* 1998; 9: 1109–1115.
16. Blay JY, Gomez F, Bachelot T, et all. The international Prognostic Index correlates to survival in intermediate-high grade lymphoma (NHL) in relapse: Analysis of the Parma trial. *Proc Am Soc Clin Oncol* 1996; 15: 151.
17. Lopez-Guillermo A, Monserrat E, Bosch F, et all. Applicability of the International Index for aggressive lymphomas to patients with low-grade lymphoma. *J Clin Oncol* 1994; 12: 7;1343–1348.
18. Schneider T, Deak B, Molnar BZs, et all. Role of international prognostic index (IPI) in low-grade lymphoma. *Ann Oncol* 1999; 10: supp. 3, 468.
19. Shipp MA, et al. A predictive model for aggressive Non-Hodgkin`s lymphoma. *N Eng J Med* 1993; 329: 987–993.
20. Coffier B. Non-Hodgkin`s lymphoma in the elderly: therapeutics strategies and results in clinical trials. *Ann Oncol* 1998; 9: 26.
21. Gomez H, Hidalgo M, Casanova L, et all. Risk factors for treatment-related death in elderly patients with aggressive Non-Hodgkin`s lymphoma: Results of a multivariate analysis. *J Clin Oncol* 1998; 16: 2065–2069.
22. Kovner F, Merimsky O, Soyfer V, et all. Prognostic importance of advanced age in aggressive Non-Hodgkin`s malignant lymphomas. *Oncology* 1996; 53: 435–440.
23. Monnerat C, Bauer J, Kettere N, et all. Age is the main prognostic factor of dose-intensity for intermediate and high grade Non-Hodgkin`s lymphoma. *Ann Oncol* 1999; 10: supp. 3, 397.
24. Pivot V, Boulat O, Gressin R, et all. Overall survival prognostic factors analysis for aggressive Non-Hodgkin`s lymphoma in the elderly. *Ann Oncol* 1999; 10: supp. 3, 408.
25. Salminen E. Age-related survival in Non-Hodgkin`s lymphoma. *Oncology* 1998; 55: 7–9.
26. Van der Maazen RWM, Noordjik EM, Thomas J, et all. Combined modality treatment is the treatment of choice for stage I/IE intermediate and high grade Non-Hodgkin`s lymphomas. *Radiother Oncol* 1998; 44: 1–7.
27. Kaplan GL, Meier P. Non-parametric estimation from incomplete observations. *J Amer Statist Assoc* 1958; 53: 457–481.
28. Klein JP, Moeschberger ML. *Survival analysis.* Berlin: Springer 1997.
29. Mould RF. *Introductory medical statistics.* III Edition, Inst. of Physics Publishing, Bristol-Philadelphia: IOP Publishing; 1998.
30. Kleinbaum DG. *Survival analysis – A self learning test.* Berlin: Springer; 1996.
31. Harris NL, Jaffe ES, Stein HI, et all. A Revised European-American Classification of Lymphoid Neoplasms: A proposal from the International Lymphoma Study Group. *Blood* 1994; 84: 1361–1392.
32. Rolski J. Ocena wybranych klinicznych czynników rokowniczych u chorych na chłoniaki nieziarnicze. *Pol Merk Lek* 1997; 2: 324–326.
33. Cortelazzo S, Rossi A, Bellavita P, et all. Clinical outcome after autologous transplantation in Non-Hodgkin`s lymphoma patients with high international prognostic index (IPI). *Ann Oncol* 1999; 10: 4:427–432.
34. Navarro JT, Ribera JM, Oriol A, et all. International prognostic index is the best prognostic factor for survival in patients with AIDS-related Non-Hodgkin`s lymphoma treated with CHOP. A multivariate study of 46 patients. *Haematologica* 1998; 83: 508–513.
35. Rodriguez M, Rehn SM, Nyman RS, et all. CT in malignancy grading and prognostic prediction of Non-Hodgkin`s lymphoma. *Acta Radiol* 1998; 40: 191–197.
36. Blay JY, Gomez F, Sebban C, et all. The International prognostic index correlates to survival in patients with aggressive lymphoma in relapse: analysis of the Parma trial. Parma Group. *Blood* 1998; 92: 3562–3568.
37. Nicolaides C, Fountzilas G, Zoumbos N, et all. Diffuse large cell lymphomas: identification of prognostic factors and validation of the International Non-Hodgkin`s lymphoma Prognostic Index. A Hellenic Co-operative Oncology Group Study. *Oncology* 1998; 55: 405–414.
38. Decaudin D, Lepage E, Brousse N, et all. Low-grade stage II-IV follicular lymphoma: Multivariate analysis of Prognostic factors in 484 patients – a study of the Groupe d`Etude des Lymphomes de l`Adulte. *J Clin Oncol* 1999; 17: 2499–2505.

39. Tuset E, Ribera JM, Granada I, et all. Analysis of clinico-pathologic characteristics and prognostic factors of 117 low-grade Non-Hodgkin`s lymphoma from a single centre. *Ann Oncol* 1999; 10: supp. 3, 450.

40. Freedman AS, Nadler LM. Non – Hodgkin's lymphomas. *Cancer Medicine*. 4th Edition, 1997; 2: 2757–2795.

41. Wahidi GFEl, Awadi MMAl, Saker HA, et all. Prognostic factors in low grade Non-Hodgkin`s lymphoma. (A multivariate analysis). *Eur J Cancer* 1997; 33: suppl. 8, 269.

42. Zahner J. Prognostic factors and survival in low-grade Non-Hodgkin`s lymphoma – Analysis of 329 cases. *Ann Oncol* 1999; 10: supp. 3, 446.

43. Dumontet C, Sebban C, Bosly A, et all. Factors predictive of early death in patients receiving ACVB for aggressive Non-Hodgkin`s lymphoma. *Ann Oncol* 1999; 10: supp. 3, 194.

44. Foussard C, Desablens B, Sensebe L, et all. Is the international prognostic index for aggressive lymphomas useful for low-grade lymphoma patients? Applicability to stage III-IV patients. The Goelams Group. *Ann Oncol* 1997; 8: suppl. 1, 49–52.

45. Cheson BD, Horning SJ, Coiffier B, et all. Report of an international workshop to standardise response criteria for Non- Hodgkin`s lymphomas. *J Clin Oncol* 1999; 17: 1244–1253.

46. Armitage JO. Treatment of Non-Hodgkin`s lymphoma. *N Eng J Med* 1993; 328: 1023–1030.

47. Dranitsaris G. Treatment of Non-Hodgkin`s lymphoma. *Anticancer Drugs* 1998; 9: 879–888.

48. Vose JM. Current approaches to the management of Non-Hodgkin`s lymphoma. *Sem Oncol* 1998; 25: 483–491.

49. Connors JM, Klasa R. Treatment of follicular lymphoma. *Curr Opin Oncol* 1998; 10: 392–395.

50. Federico M, Vitolo U, Zinzani P, et all. The prognosis of follicular lymphoma: A predictive model based on a retrospective analysis of 987 cases of the Italian Lymphoma Intergroup.: *ASCO – 1999 Annual Meeting Summaries*, Thirty Fifth Annual Meeting, Atlanta, Georgia, 1999; 30–37.

51. Press O. Non Hodgkin` s lymphoma. *ASCO – 1999 Annual Meeting Summaries*. Thirty Fifth Annual Meeting, Atlanta, Georgia, 1999; 79–82.

52. Hagenbeek, A, Carde P, Meerwaldt JH, et all. Maitenance of remission with Human Recombinant Interferon Alfa-2a in patients with stages III and IV low-grade malignant Non-Hodgkin`s lymphoma. *J Clin Oncol* 1998; 16: 41–47.

53. Czuczman M. The role of Mabthera in the treatment of indolent lymphoma. In: *Mabthera: a new perspective in the treatment of NHL*, Amsterdam, abstract book 1998.

54. Kaminsky MS, Vose JM, Kroll SM, et all. Predictive value of international prognostic index for chemotherapy relapsed/refractory indolent Non-Hodgkin`s lymphoma. Patients treated with Iodine-131 Anti-B1 antibody. *Ann Oncol* 1999; 10: supp. 3, 448.

55. Lundin J, Österborg A, Brittinger G, et all. CAMPATH-1H Monoclonal antibody in therapy for previously treated Non-Hodgkin`s lymphomas: A phase II multicenter study. *J Clin Oncol* 1998; 16: 3257–3263.

56. Maloney DG. Antibody therapy has arrived. Now where does it fit? *Ann Oncol* 1999; 10: 619–621.

57. Bierman P, Vose J, Anderson J, et all. High-dose therapy with autologous hematopoietic rescue for follicular low-grade non-Hodgkin` s lymphoma. *J Clin Oncol* 1997; 15: 445– 450.

58. Philip T. Role of high-dose chemotherapy and autologous bone marrow transplantation in the treatment of lymphoma. *Eur J Cancer* 1997; 33: suppl. 8, 221.

59. Fanin, R., Silvestri, F., Geromin, A. i wsp.:Autologous stem cell transplantation for aggressive Non-Hodgkin`s lymphomas in first complete or partial remission: a retrospective analysis of the outcome of 52 patients according to the age-adjusted International prognostic index. *Bone Marr Transplant* 1998; 21: 263–271.

60. Gugliemi C, Gomez F, Philip T, et all. Time to relapse has prognostic value in patients with aggressive lymphoma enrolled onto the Parma Trial. *J Clin Oncol* 1998; 16: 3264–3269.

61. Martelli M, De Sanctis V, Avvisati G, et all. Current guidelines for the management of aggressive Non-Hodgkin`s lymphoma. *Drugs* 1997; 53: 957–972.

62. Horning SJ, Fisher RI, Gascoyne RD. Large-cell lymphoma: Let's CHOP down barriers to progress. *1999 Educational Book. American Society of Clinical Oncology*. Thirty Fifth Annual Meeting, Atlanta, Georgia 1999.

63. Shipp MA, Abeloff MD, Antman KH i wsp. International Consensus Conference on High-Dose therapy with hematopoietic stem cell transplantation in aggressive Non-Hodgkin`s lymphomas: Rapport of the Jury. *J Clin Oncol* 1999; 17: 423–429.

64. Shipp MA. Can we improve upon the international Index?, *Ann Oncol* 1997; 8: suppl. 1, 43–47.

65. Gascoyne RD, Adomat SA, Krajewski S, et all. Prognostic significance of Bcl-2 protein expression and Bcl-2 gene rearrangement in diffuse aggressive Non-Hodgkin`s lymphoma. *Blood* 1997; 90: 244–251.

66. Webb A, Cunningham D, Cotter F, et all. BCL-2 antisense therapy in patients with Non-Hodgkin`s lymphoma. *Lancet* 1997; 349: 1137–1141.

67. Stevenson FK, Rice J, King CA, et all. Current and future role of vaccines in lymphoma. *Ann Oncol* 1999; 10: supp. 3, 095.

68. Aviles A, Díaz- Maqueo JC, Talavera A, et all. Bone marrow protection with amifostine on the treatment of high-risk malignant lymphoma. *Eur J Cancer* 1997; 33: 1323–1325.

69. Moore DFJr, Cabanillas F. Overview of prognostic factors in Non-Hodgkin`s lymphoma. *Oncology* 1998; 12: suppl. 8, 17–24.

70. Zucca E, Bertoni F, Roggero E, et all. Management of rare forms of lymphoma. *Curr Opin Oncol* 1998; 10: 377–384.

71. Oinonen R, Franssila K, Teerenhovi L, et all. Mantle cell lymphoma: clinical features, treatment and prognosis. *Eur J Cancer* 1998; 34: 329–336.