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Prognostic value of thymidine kinase activity in patients with chronic lymphocytic leukemia*

Prognostyczne znaczenie aktywności kinazy tymidynowej u chorych na przewlekłą białaczkę limfocytową*

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Thymidine kinase (TK) activity is a marker of biological activity that allows the indolent and aggressive forms of chronic lymphocytic leukemia (CLL) to be distinguished. The aims of the study were to determine the relationship between TK activity and clinical status and prognosis, as well as to compare its activity with that of other prognostic and predictive factors. TK activity was measured in patient sera at the time of diagnosis using the DiviTum method, with the mean value being 439 Du/L. A correlation was found between TK activity and risk of disease progression (p=0.045). The optimal discriminative value of TK activity in the prediction of CLL progression was found to be 600 Du/L. TK activity significantly differed between the patients who achieved complete remission and those who only partially responded to therapy. In 93% of patients without any response to treatment and 18 out of 20 patients with progressive disease, TK activity over 600 Du/L was noted. In addition, all of the 10 patients with 17p13 deletion displayed TK activity of over 600 Du/L (p=0.0004). High TK activity also correlated with elevated levels of LDH (p=0.001) and β_2-microglobulin (p=0.03) in the study group. The results of the study indicated the importance of TK activity as a prognostic factor in patients with CLL.

Keywords: **17p13 deletion • β_2-microglobulin • chronic lymphocytic leukemia • prognostic factors • thymidine kinase**

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Abbreviations: **β_2M** – β_2-microglobulin, **BrdU** – 5-bromodeoxyuridine, **BrdUTP** – 5-bromo-2′-deoxyuridine 5′-triphosphate, **CLL** – chronic lymphocytic leukemia, **CLL-IPI** – International Prognostic Index for CLL, **CR** – complete response, **Hb** – hemoglobin, **IWCLL** – International Workshop on Chronic Lymphocytic Leukemia, **CC** – cyclophosphamide, cladribine, **LDH** – lactate dehydrogenase, **LDT** – lymphocyte doubling time, **NR** – no response, **PFS** – progression-free survival, **PR** – partial response, **RCC** – rituximab, cyclophosphamide, cladribine, **ROC** – receiver operating characteristic, **TK** – thymidine kinase, **WBC** – white cell blood count.

Introduction

Chronic lymphocytic leukemia (CLL) is the most frequently diagnosed type of leukemia in Europe and North America with four new cases per year seen among 100,000 people [11,26]. Two clinical classifications were developed independently by Rai et al. and Binet et al. in the 1970s, and they still have significant prognostic value in clinical practice [3,22]. However, these classifications are not relevant prognostic factors in patients with an early stage of the disease and do not predict the response to treatment. In recent years, a number of newer agents have been implemented, which are used to select patients with poorer prognosis and stage A disease according to Binet [23,24,27]. These include humoral factors comprising the activity of thymidine kinase (TK) and concentrations of β2-microglobulin in serum, the expression of CD38 on leukemic cells, as well as genetic markers, together with deletion 17p13 (del(17p)), *TP53* mutation and the mutation status of IgV_H [25]. Recently, an International Prognostic Index for CLL (CLL-IPI) has been proposed, identifying four risk groups with significantly different five-year survival. The CLL-IPI takes into account the genetic risk factors (mutation status of IgV_H, *TP53* mutation and/or del(17p)), clinical stage, age, and β_2-microglobulin (β_2M) concentration, allowing the clinician to make a more accurate prognosis and plan an individualized treatment approach [12].

Although serum markers such as TK are not specific for CLL, they accurately reflect the activity and course of the disease. Thymidine kinase is involved in the synthesis of DNA strands and shows a significant correlation with cell proliferative activities in CLL. The results of several previous studies have highlighted the prognostic significance of TK activity in patients with lymphoproliferative disorders [5,9,28]. In CLL, this correlates not only with the Rai clinical staging system but also with the biology of the disease, which allows for differentiation between its indolent and aggressive form [7,8,12,29,30]. It has also been shown that the activity of serum TK may be an independent predictive factor of disease duration without progression, and may complement the definition of indolent CLL in its early stage. A major problem in the wide use of TK as a prognostic factor for patients with CLL is the lack of a simple assay. The serum TK level is so low that the best method of measurement is to assess its activity [14].

Evaluation of enzyme level with the ELISA or *dot blot* methods is rarely applied in clinical practice [1]. Non-radioactive measurement methods, which were developed in the 1990s, used a derivative of thymidine, azidothymidine, as a substrate, instead of a radioactively labeled base residue (TK Liaison probe). An alternative, non-radioactive, method (DiviTum) uses as a substrate 5-bromodeoxyuridine (BrdU), whose phosphorylation to monophosphate and then triphosphate (BrdUTP) is catalyzed by TK. BrdUTP is attached to a poly(A) oligonucleotide and then converted to a poly(A)/BrdU oligomer by reverse transcriptase, with the oligomer acting as a target for the antibody used in the probe. Both methods (TK Liaison and DiviTUM) are commercially available and have similar sensitivity [20], but neither has been widely used in patients with CLL.

The present study uses the DiviTUM method to assess the prognostic significance of TK in diagnosing CLL. The use of a DiviTum probe in determining TK activity was developed to avoid radioisotope determination. Yeast enzymes are used to induce phosphorylation in BrdU, a substrate for the studied enzyme. The DiviTum method is characterized by a higher sensitivity than the TK-REA assay and enables more precise determination of the metabolic activity of the enzyme at higher activity.

Materials and methods

Patient characteristics

The study group comprised 67 previously untreated CLL patients, 31 (53.7%) women and 36 (46.3%) men aged 28-87 years. The median age was 71 years. Patient characteristics are summarized in Tables 1 and 2. Diagnostic criteria for CLL comply with the criteria proposed by Hallek et al. [6]. The diagnosis was based on the complete blood count and lymphocyte immunophenotyping test. Next, the Rai and Binet clinical stage as well as routine parameters in CLL, including LDH activity and β_2M concentration, were determined. Therapy was administered in 27 (40.2%) patients, including nine patients (33.3%) treated according to the cyclophosphamide, cladribine (CC) regimen, seven (25.9%) according to the CC combined with rituximab (RCC) regimen, and seven were given chlorambucil in monotherapy. One patient received rituximab with methylprednisolone and one rituximab with bendamustine. All investigations were carried

out in accordance with the principles of the Declaration of Helsinki.

Evaluation of treatment efficacy

Evaluation of response to anti-leukemic therapy was based on the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria [6]: Physical examination, imaging (X-rays, ultrasound, computed tomography) examinations and assessment of the complete blood count as well as bone marrow were performed. Progression-free survival (PFS) was measured from the date of therapy initiation until disease progression or death.

Evaluation of chromosomal aberrations by the fluorescence in situ hybridization (FISH) test

Peripheral blood was taken prior to treatment. Chromosomal aberrations were analyzed by the FISH method according to generally accepted principles [15]. A standard panel of probes for the detection of 13q14 (D13S319), 11q22 (*ATM*), 17p13 (*TP53*) deletions, and trisomy 12 (Cytocell, UK) was used.

Evaluation of thymidine kinase activity

Peripheral blood was taken prior to treatment. The TK activity in the serum was determined in the Genloxa laboratory in Puck, using the DiviTum manual kit (Biovica International AB, Uppsala, Sweden) in accordance with manufacturer's instructions (www.Biovica.com) [2]. The activity was expressed in DiviTum/L (Du/L) units.

Statistical analysis

The Statistica for Windows program, version 9.0 (StatSoft, Inc., Tulsa, USA) was used for the statistical analysis. Differences were considered significant for values of $p < 0.05$ in all assays. To verify the differences between the groups, the analysis of variance and Kruskal-Wallis test were carried out. Logistic regression analysis based on univariate and multivariate models was applied to assess the relationship between the two-state dependent variable and a group of independent variables. Receiver operating characteristic (ROC) curve analysis was combined with the determination of a continuous variable cut-off point at which the optimal discrimination properties were achieved, and this was used to dichotomize and construct the dependent variable for logistic regression analysis. A multivariate model was built stepwise, including variables significantly changing the adjustment of univariate models. The analysis of survival along with the construction of Kaplan-Meier curves was combined with the uni – and multivariate Cox regression models. The nonparametric Mann-Whitney test was used to compare independent grouped variables. Pearson's chi-square test was used to analyze qualitative variables (categorical). The arithmetic mean (X), standard deviation (SD), median, 25th and 75th percentiles, and the range of values (minimum – maximum) were determined.

Results

Laboratory and clinical characteristics of patients qualified for the study are shown in Tables 1 and 2. The study group included 31 (46.3%) women and 36 (53.7%) men, aged 28-87 years. At diagnosis, Rai stage 0 or 1 chronic lymphocytic leukemia was detected in half of the patients (49.25%), and Binet stage A CLL was found in 41 patients (61.2%). The median value of leukocytosis was 48.6 x 10^9/L. The median values of hemoglobin concentration and platelet count were within the normal range: 12.3g/dL and 145x10^9/L, respectively (Table 2).

Among the examined patients, 35 individuals (52.2%) did not require treatment for the entire period of observation. Chemotherapy was necessary in 32 (47.7%) patients.

Table 1. Patient characteristics (clinical data)

Characteristic Number of patients	N (%) X±SD 67 (100)
Demographic data	
Age [years], mean ±SD (min-max)	71.1±10.4 (28 – 87)
Male, N (%)	36 (53.7)
Clinical data, N (%)	
Lymphadenopathy	31 (46.3)
Splenomegaly	17 (25.4)
Autoimmune hemolytic anemia	7 (10.4)
Immune thrombocytopenia	2 (3.0)
Infections	8 (11.9)
Richter's syndrome	3 (4.5)
Rai clinical staging:	
0	13 (19.4)
1	23 (34.3)
2	7 (10.4)
3	9 (13.4)
4	15 (22.4)
Binet clinical staging:	
A	41(61.2)
B	11(16.4)
C	15(22.4)

Table 2. Patient characteristics (laboratory data)

Characteristic N(%) 67(100)	
Leukocytosis [WBC x 10^9/L], median (quartile distribution)	48.6 (22.8-130.0)
< 30 x 10^9/L, n (%)	27 (41)
> 30 x 10^9/L, n (%)	40 (59)
Hb [g/dl], median (quartile distribution)	12.3(10,5-14.2)
<11 g/dL, N(%)	22 (32.8)
>11 g/dL, N(%)	45 (67.2%)
Blood platelets [cells x 10^9/L], median (quartile distribution)	145 (99-200)
< 100 x 10^9/L, n(%)	17 (25.3)
> 100 x 10^9/L, n(%)	50 (74.7)
β_2M [mg/dL], median (quartile distribution)	3.87 (2.8-4.9)
< 3.5, N (%)	38 (57.7)
> 3.5, N (%)	29 (43.3)
LDH [U/L], median (quartile distribution)	222(165-283)
< 210	27 (41%)
> 210	40 (59%)
LDT [months], median (quartile distribution)	7(3-24)
N <12	17 (65.3)
N >12	9 (35.7)
17p13 deletion N (%)	10 (15.2)
11q22 deletion N (%)	6 (9.1)
13q14 deletion N (%)	36 (54.5)
Trisomy 12 N (%)	4 (6.1)

β2M – β2-microglobulin; Hb – hemoglobin; LDH – lactate dehydrogenase; LDT – lymphocyte doubling time; WBC – white cell blood count

Table 3. Comparison of relationship between thymidine kinase level and response to treatment

Comparison – Dunn's test*	Difference in rank sums	Statistical analysis
CR vs PR	-12.68	*P* < 0.05
CR vs NR	-14.88	*P* < 0.05
PR vs NR	-2.200	P>0.05

* with modification for multiple comparisons

CR – complete response; PR – partial response; NR – no response

First-line treatment resulted in a complete remission (CR) in eight patients, partial remission (PR) in 10, and stable disease (SD) in four. Ten patients did not respond to the applied therapy. Progression of the disease in the treated group occurred in 19 out of 32 patients.

Serum TK activity was measured in the peripheral blood of all patients. The median TK activity was 439 Du/L. The ROC curve analysis showed that the TK activity obtained an optimal discriminative ability to predict disease progression at the value > 600 Du/L. This value was determined as the optimal cut-off point in subsequent analysis.

The relationship between TK activity and response to treatment was shown by the defined multi-state variable taking into account the patients who achieved CR, PR, SD and NR (no remission) (p = 0.0018) (Fig. 1). The TK activity was compared in particular categories of the variable defining the treatment outcome (Table 3). Significant differences in the baseline TK level were noted between the patients who achieved CR and those who did not (p = 0.0018). In all patients who achieved PR following treatment, the TK activity was above the usual cut-off value (600 Du/L). TK activity above 600 Du/L was found in 92.8% of the patients with no response to treatment. The progression-free survival (PFS) analysis revealed significant differences in patients in whom the TK level was ≥600 Du/l at diagnosis, as compared to PFS in those with the TK level <600 Du/l (p = 0.045) (Fig. 2).

A significant correlation between serum TK activity and severity of disease was detected at diagnosis, according to Rai (p = 0.0001) and Binet (p = 0.006) staging (Fig. 3). However, no significant correlation was found between TK activity and age of patients.

Significantly higher TK activity was observed in patients with lymphadenopathy than in patients without this disorder (p = 0.013) (Fig. 4). No significant correlation was observed between TK activity and presence of splenomegaly (p = 0.05) (Fig. 4). Patients with autoimmune hemolytic anemia (AIHA) showed significantly higher TK activity than those without (p=0.005).

The patients with del(17p) were found to have a significantly higher TK level than the group of patients without del(17p) (p=0.0004) (Fig. 5). In all patients with del(17p), the enzyme activity exceeded 600 Du/L. No significant difference in TK activity was observed between the patients with del(11q), those with del(13q) and those with trisomy 12. The TK activity in patients with β_2M> 2.2 was significantly higher than in patients with β_2M <2.2 (p = 0.03) (Fig. 5).

Discussion

Our findings indicate that high serum TK activity correlates with a poorer response to treatment. In a study of the TK activity in 188 patients with progressive or advanced CLL treated with fludarabine, Di Raimondo et al. [4] found significantly greater TK activity in 92% of patients, and similarly to our study, correlated with tumor mass parameters (lymphocytosis, bone marrow cellularity). In addition, the authors noted that TK activity may be a parameter predicting the response to treatment, which is consistent with our observations. It has been demonstrated that 83% of patients with serum TK activity <10 U/L obtained partial or complete remission after the treatment with fludarabine, whereas only 45%

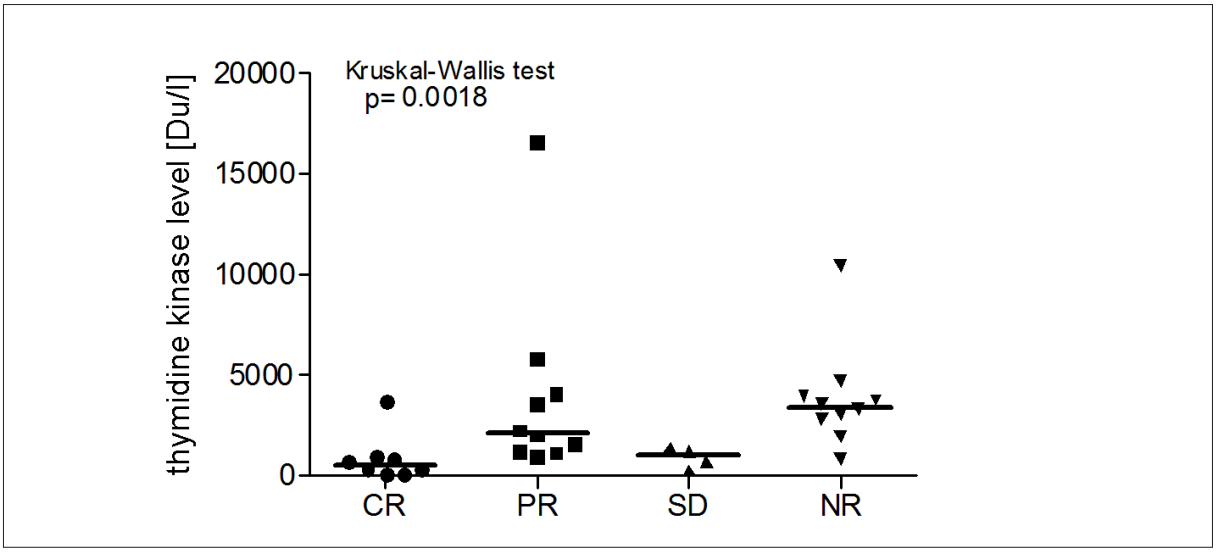


Fig. 1. Evaluation of relationship between thymidine kinase level and response to treatment Abbreviations: CR – complete response; PR – partial response; SD – stable disease; NR – no response

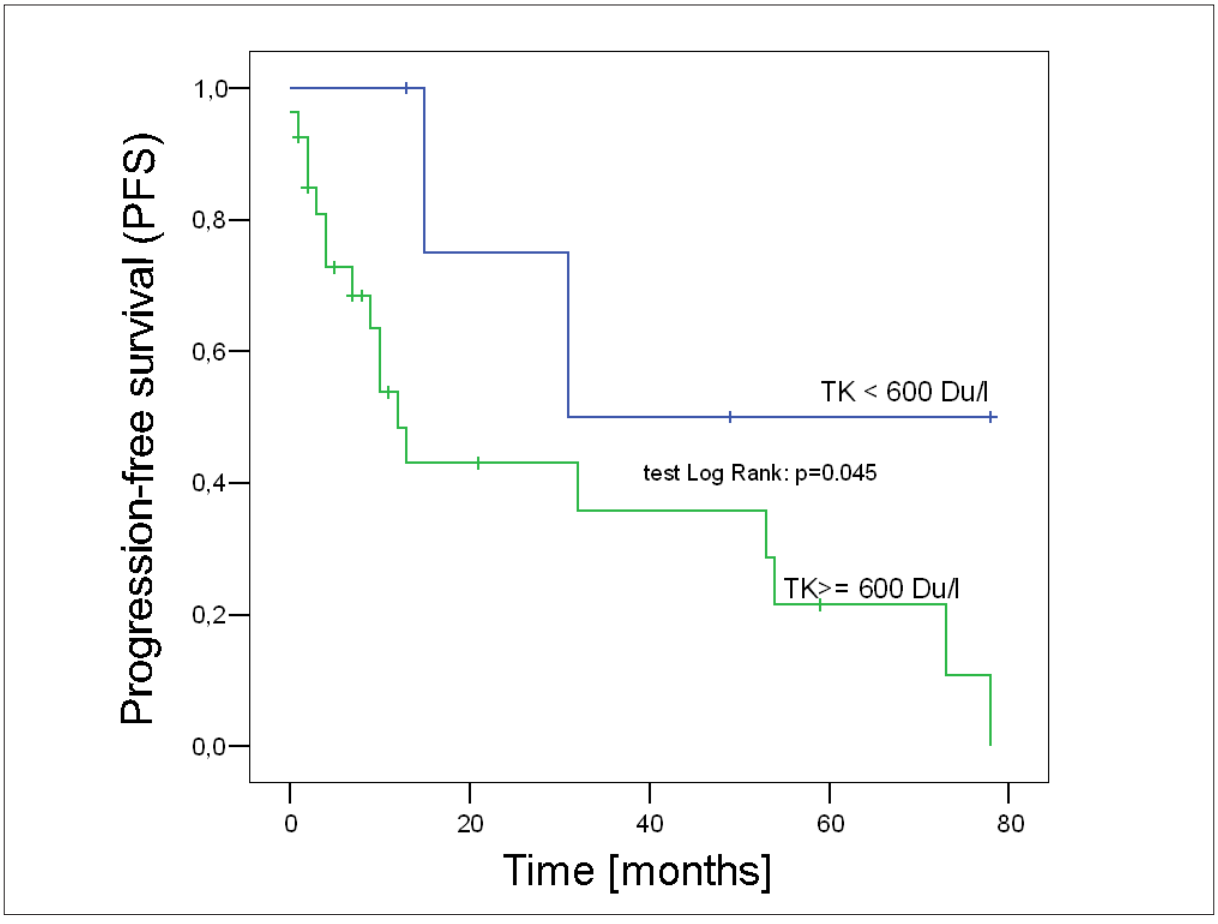
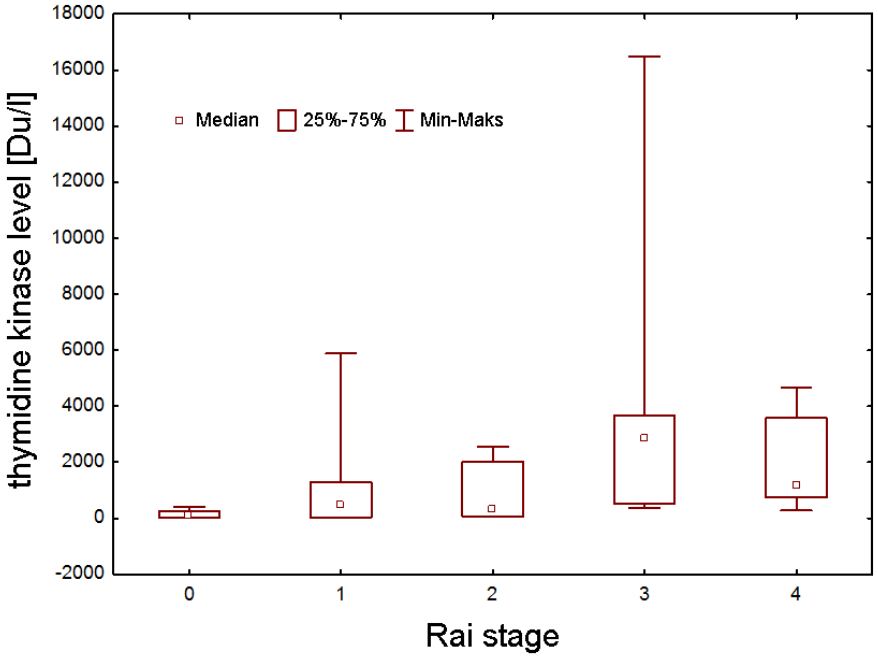


Fig. 2. Progression-free survival (PFS) in patients with TK (thymidine kinase) level <600 Du/L vs ≥600 Du/L

of patients with TK levels >10 U/L have been found to have a satisfactory response to treatment [4].

Other studies have shown that TK activity has independent prognostic value in patients with CLL, and particularly in patients with less advanced disease (Binet A) [7]. Hallek et al. [8] suggest that in these patients, TK activity in serum can be a particularly valuable prognostic marker. In the Binet A-stage patients at high risk and with TK activity> 7.1 U/L, the mean PFS time was found to be

A



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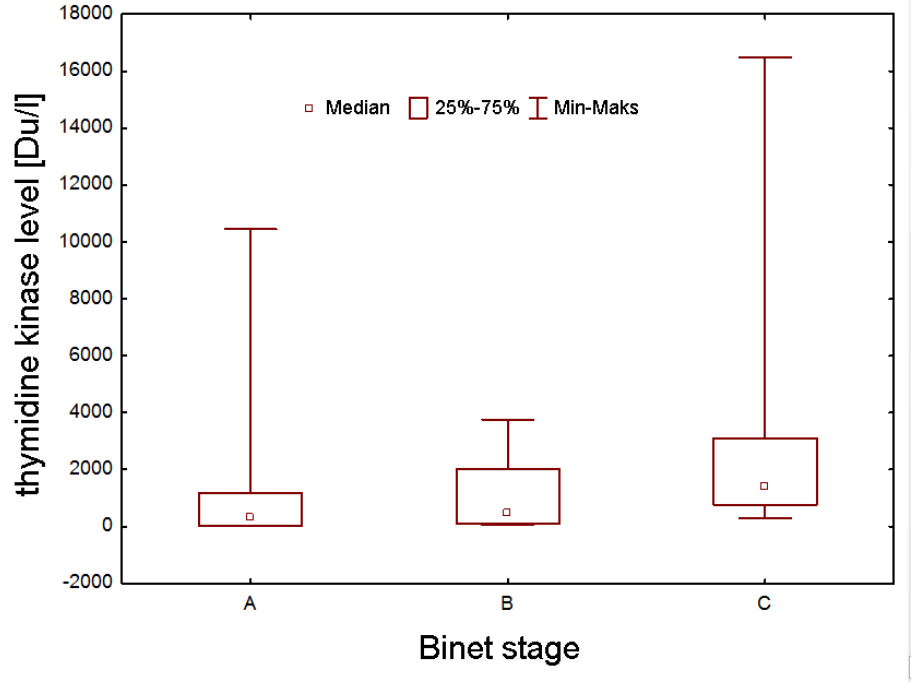
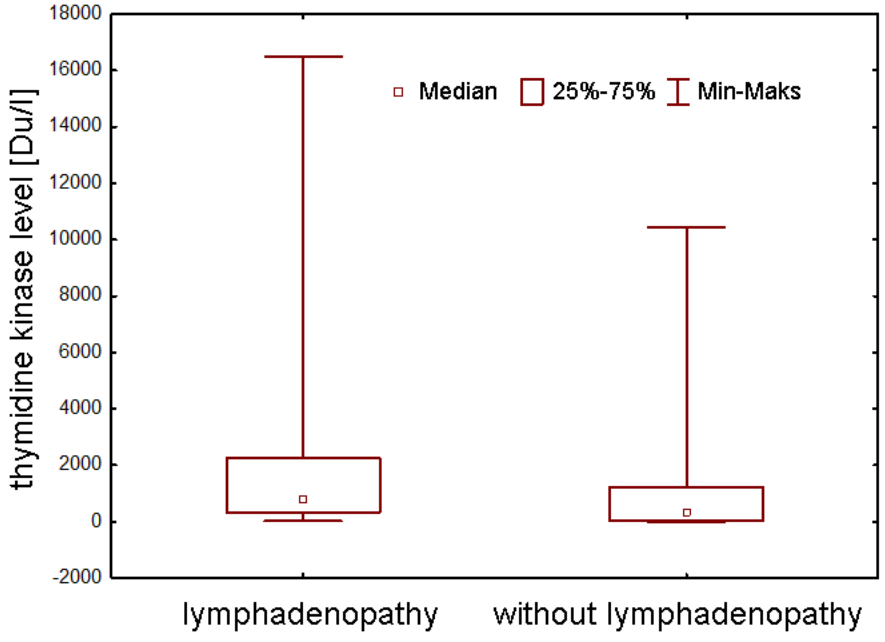


Fig. 3. Relationship between thymidine kinase (TK) level, Rai stage (A) (p=0.0001) and Binet stage (B) of the disease (p=0.006)

about eight months, while the PFS time was 49 months for Binet A patients at low risk, with an enzyme level <7.1 U/L [8]. Other studies have demonstrated that only three parameters can be used as independent prognostic factors for PFS, including TK above 7.1 U/L, the presence of lymphadenopathy and lymphocytosis above $75x10^9$/l [13].

Matthews et al. [18] compared the activity of serum TK with other parameters associated with a worse prognosis, including the absence of gene mutation for IgV_H, adverse chromosomal aberrations, increased expression of zeta chain-associated protein of 70 kDa kinase (ZAP-70) and CD38 expression [18]. It was found that TK activity was significantly higher in patients without IgV_H mutations

A



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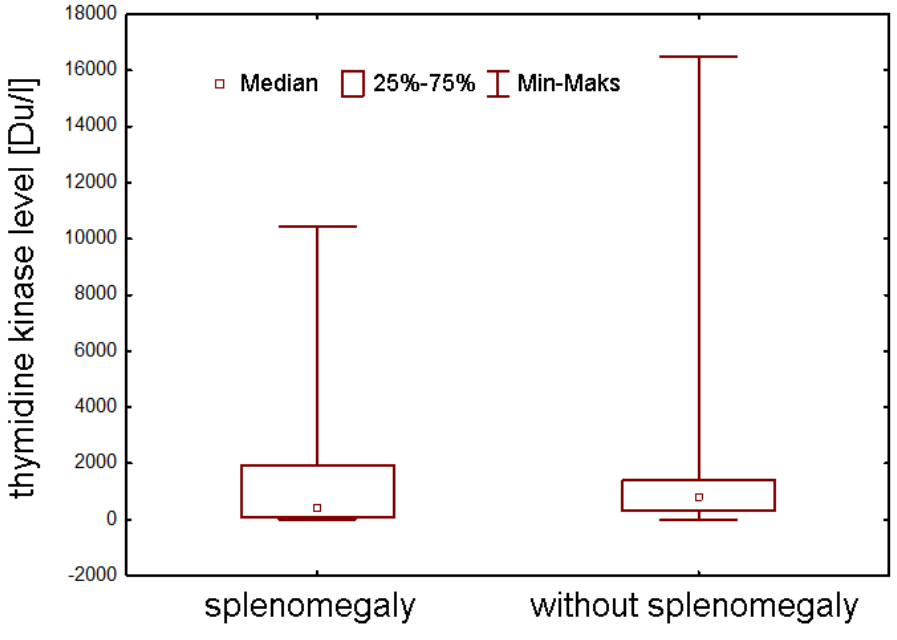
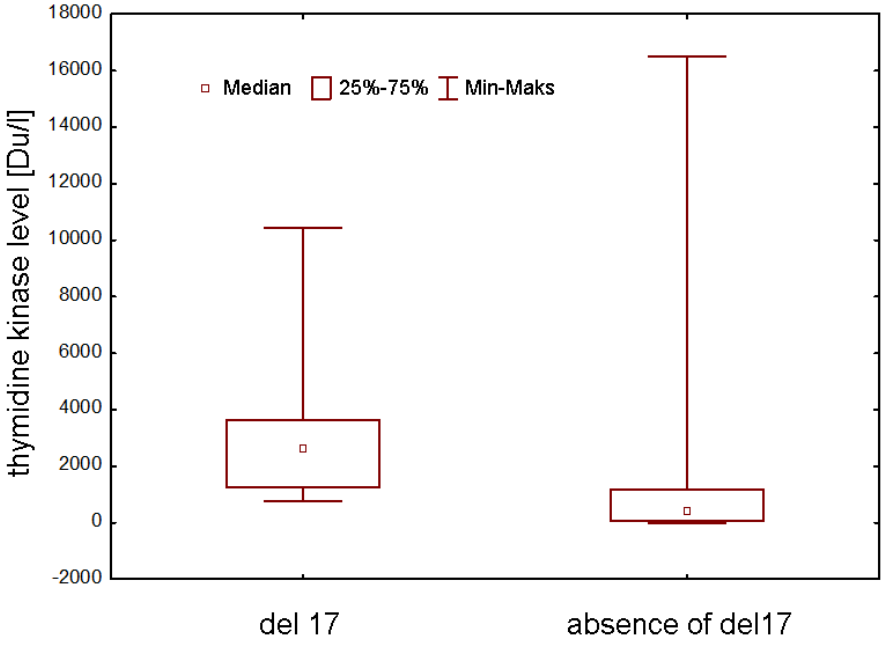


Fig. 4. Relationship between thymidine kinase (TK) level and lymphadenopathy (A) (p=0.01) or splenomegaly >12 cm (B) (p>0.05)

and, as in our study, with del(17p); however, in contrast to our study, they also reported a correlation between TK activity and trisomy 12 and del (11q). Konoplev et al. pointed out that, like CD38 and ZAP 70, TK activity may be an intermediate exponent of the presence or absence of IgV_H mutations [14]. The correlation between TK activity in plasma and the presence of IgV_H mutation has also been observed by other researchers. By determining the activity of LDH, IgV_H mutation and CD38 expression, it was found that only increased TK activity is an independent factor associated with mutation absence [18,30].

No differences were found between TK activity and patient age in the present study. Szantho et al. [29] compared the

A



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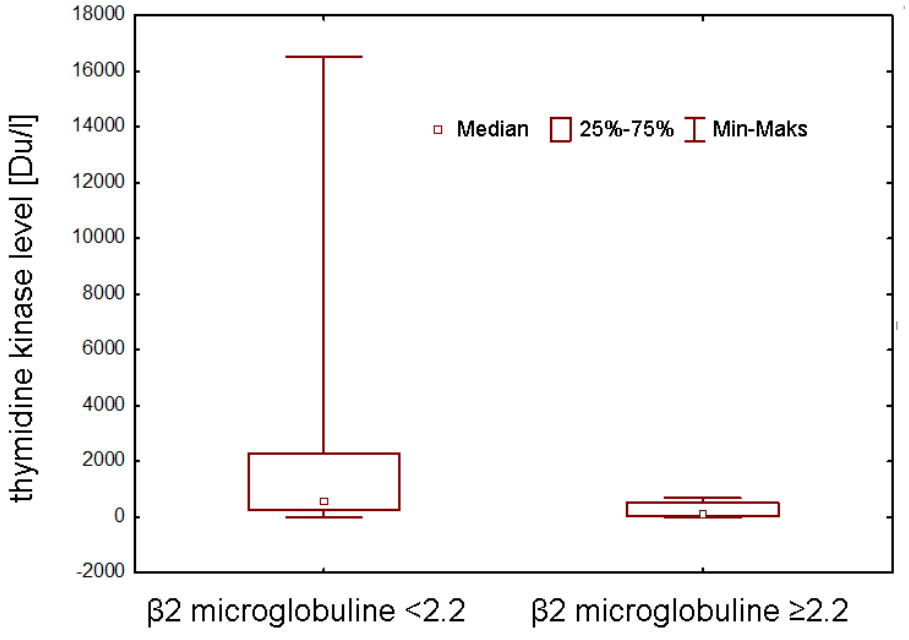

Fig. 5. Relationship between thymidine kinase (TK) level and occurrence of 17p13 deletion (A) (p=0.0004) and β2 microglobulin concentration (B) (p=0.0003)

results of TK activity in different age groups of patients with CLL and in healthy volunteers and proposed that the range of enzyme activity should be changed depending on patient age. In both healthy volunteers and patients with leukemia, the enzyme activity was higher among younger people as compared to the group of elderly patients.

Attention should be drawn to the prognostic model proposed recently by Pflug et al. [21], in which TK activity was used as one of the prognostic parameters. The researchers prospectively analyzed 23 prognostic markers in 1,948 patients from three randomized studies conducted by the German CLL Study Group. The multivariate Cox regression model was used to assess the impact of TK and seven other independent prognostic factors on overall survival: age, sex, general condition according to the Eastern Cooperative Oncology Group (ECOG), del(17p), del(11q), the state of *IgVH* mutation, β_2M concentration

and TK activity in serum. Letestu et al. [16] demonstrated that a relatively simple evaluation of the TK level may be one of the key parameters classifying Binet stage A patients into high-risk or low-risk groups. Those authors suggest that early treatment may be possible in some of the patients from the stage A low-risk group, who are at a greater risk of progression. This model allows us to reduce the number of ambulatory visits for patients at low risk and, on the other hand, to monitor more frequently patients at high risk of progression [21].

To conclude, our findings confirm the value of serum TK as a prognostic factor. The method used in the study is relatively simple and is available for the majority of hematological centers.

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