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Thromboembolic complications (TEC) in patients with acute leukemias and lymphomas – single center experience

Powikłania zakrzepowo-zatorowe u pacjentów z ostrymi białaczkami i chłoniakami – doświadczenia własne

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Summary

Introduction. Thromboembolic complications (TEC) are common abnormalities in cancer patients and they refere expecially to solid tumours. The pathogenesis of thromboembolic disease in neoplasias is complex and multifactorial. In patients with hematological malignancies may occur some of thromboembolic complications such as: venous thromboembolism (VTE), pulmonary embolism (PE) and disseminated intravascular coagulation (DIC).

Material and methods. The aim of our study was to analyse the incidence of thromboembolic complications in patients with acute leukemias and lymphomas as well as association between risk factors and development of TEC and effect of TEC on overall survival (OS). The study population included 70 patients with acute leukemias and 65 patients with lymphomas treated in Department of Hematology Medical University Wroclaw, Poland.

Results. In group of patients with acute leukemias we found thromboembolism complications in 9 patients (12.8%), in group of patients with lymphomas we observed TEC in 8 patients (12.3%). Patients with acute leukemias and VTE were significantly older than patients without thrombotic complications. Moreover, patients associated thrombotic events in acute leukemias with high risk of disease.

Conclusions. This analysis confirm high incidence of TEC in patients with hematologic malignacies.

Key words: acute leukemia, non Hodgkin lymphoma, Hodgkin lymphoma, thromboembolic complications

Streszczenie

Wstęp. Powikłania zakrzepowo-zatorowe stanowią częste zaburzenia u pacjentów z chorobami nowotworowymi zwłaszcza w przebiegu guzów litych. Ich etiologia ma charakter złożony i wieloczynnikowy. Do najczęściej występujących powikłań zakrzepowo-zatorowych w przebiegu chorób rozrostowych układu krwiotwórczego należą: żylna choroba zakrzepowo-zatorowa, zatorowość płucna oraz zespół rozsianego wykrzepiania wewnątrznaczyniowego.

Materiał i metody. Celem pracy była ocena częstości występowania powikłań zakrzepowo-zatorowych w populacji pacjentów z ostrymi białaczkami i chłoniakami, korelacja incydentów zakrzepowo-zatorowych ze współistniejącymi czynnikami ryzyka zakrzepicy, a także wpływ powikłań zakrzepowo-zatorowych na całkowite przeżycie. Analizą objęliśmy 70 pacjentów z ostrymi białaczkami oraz 65 pacjentów z chłoniakami leczonymi w Klinice Hematologii, Nowotworów Krwi i Transplantacji Szpiku AM we Wrocławiu.

Wyniki. W grupie pacjentów z ostrymi białaczkami powikłania zakrzepowo-zatorowe stwierdzone zostały u 9 pacjentów (12,8%), w grupie chorych z chłoniakami u 8 pacjentów (12,3%). Pacjenci z ostrymi białaczkami i towarzyszącymi incydentami zakrzepowo-zatorowymi byli istotnie statystycznie starsi aniżeli chorzy bez powikłań zakrzepowo-zatorowych. Incydenty zakrzepowo-zatorowe częściej występowały w populacji pacjentów z ostrymi białaczkami wysokiego ryzyka.

Wnioski. Przeprowadzone badania potwierdziły zwiększoną częstość występowania powikłań zakrzepowo-zatorowych u pacjentów z nowotworami hematologicznymi.

Słowa kluczowe: ostre białaczki, chłoniak nieziarniczy, chłoniak Hodgkina, powikłania zakrzepowo-zatorowe

INTRODUCTION

Thromboembolic complications are common events in cancer patients. TEC occur in solid tumors as well as in hematologic malignancies and may cause substantial mortality and reduced survival (1, 2). The association between cancer and venous thrombosis

was described in 19 century by Trousseau (3). The pathogenesis of venous thromboembolism in cancer is complex and includes many multiple interactions between tumors, components of hemostasis system and cells proliferation. VTE is a result of mechanisms such as: inflammation, necrosis and paraprotein production (4). Also, the expression of tissue factor (TF) on cancer cells, an important activator of coagulation, may cause increased risk of VTE (5). The clinical presentation of TEC in patients with acute leukemias (AL) includes: disseminated intravascular coagulation, pulmonary embolism and major bleedings. The frequency of TEC in patients with acute leukemias depends on cytostatic treatment and type of leukemia (6). Recent studies suggest that incidence of VTE in patients with hematologic malignancies is similar to the events which occur in patients with solid tumors and amounts to about 3.87-5.79% (6, 7). In children with acute lymphoblastic leukemia VTE is diagnosed in 2-10.6% cases (6, 9).

AIM OF THE STUDY

The aims of our retrospective study was to analyse the frequency of TEC in patients with acute leukemias and lymphomas and to determine risk factors associated with developmet of VTE.

MATERIAL AND METHODS

135 patients with hematologic malignancies (67 females and 68 males) hospitalized in Department of Hematology Medical University Wroclaw, Poland in years 2009-2011 were evaluated. 70 patients (52%) had acute leukemia, 37 patients (28%) had non Hodgkin lymphoma and 19 patients (20%) had Hodgkin lymphoma (HL). The clinical data of patients was summarized in tables 1 and 2.

TEC were confirmed by duplex ultrasound, CT scan, echocardiografie and some laboratory parameters such as D-dimers level, fibrinogen level, antithrombin III level and platelets count.

Statistical analysis was performed with the use of "Statistica 6,0" program (Stat Soft, Poland). Means (x) and standard deviation (sd) were given. The distribution of the variables was checked with W-Shapiro-Wilk test. A nonparametric U-Mann-Whithney test and ANOVA Kruskal-Wallis test were used because variables had non-parametric distribution. Values of $p < 0.05$ were accepted as statistically significant. Survival curves of patients were prepared using the Kaplan-Meier method. Differences between the survival curves were evaluated by the Wilcoxon and Cox-Mantel tests.

RESULTS

TEC were confirmed in 9 patients (12.8%) with acute leukemias and in 8 patients (12.3%) with lymphomas. VTE was reported in 12 patients (8.88%), 3 patients (2.22%) had pulmonary embolism and 2 patients (1.48%) had symptoms of disseminated intravascular coagulation associated with promyelocytic leukemia (PML). Patients with AL older than 60 years had higher risk of TEC than younger patients ($p < 0.05$). We observed that TEC occured more often in patients with higher cytogenetic risk ($p < 0.05$). Besides, non Hodgkin lymphoma diagnosis was associated significantly with an increased risk of TEC compared with Hodgkin lymphoma cases ($p < 0.05$). We investigated the association between the frequency of TEC and OS in AL and lymphomas patients. Median follow up was 48 months. No negative impact on OS was found.

The results are shown in tables 3 and 4 and on figure 1.

Table 1. Clinical data of patients with acute leukemias.

Parameter	AML	ALL
Number of patients	57	13
Age (years)	52 (19-88)	51 (18-74)
Sex	24 F/33 M	4 F/9 M
Subtypes of AML acc. FAB and subtypes of ALL acc.EGIL	M0-6 M1-12 M2-14 M3-2 M4-17 M5a-3, M5b-3	ALL B common – 11 ALL pre B – 1 ALL T – 1
Cytogenetic risk	HR – 37 MR – 1 SR – 19	HR – 9 SR – 4
Median of fibrinogen level (g/l)	475.96 (210-950)	518.46 (230-880)
Median of D-dimers level (ng/ml)	3906.23 (242-43 350)	3141.66 (490-10 000)
Median of platelets count (x109/l)	78.17 (7-433)	64.15 (12-179)
Response to treatment	CR – 31 PR – 5 NR – 20	CR – 6 PR – 1 NR – 6

AML – acute myelogeneus leukemia, ALL – acute lymphoblastic leukemia, HR – high risk, MR – median risk, SR – standard risk, CR – complete response, PR – partial response, NR – no response.

Table 2. Clinical data of patients with lymphomas.

Parameter	nHL	HL
Number of patients	37	28
Age (years)	56 (23-79)	33 (17-62)
Sex	20 F/17 M	19 M/9 M
Subtypes of lymphomas	DLBCL-21 (Diffuse Large B-cell Lymphoma) MCL-3 (Mantle Cell Lymphoma) BL-2 (Burkitt Lymphoma) FL-2 (Follicular Lymphoma) Other – 9	NS-19 (Nodular Sclerosis) MC-4 (Mixed Cellularity) LR-4 (Lymphocyte Rich) LD-1 (Lymphocyte Depletion)
Stage acc. Ann Arbor	I and II-13 III and IV-24	I and II-16 III and IV-12
Risk IPI for nHL EORTC/IPS for HL	Low – 6 Intermediate/low – 12 Intermediate/high – 9 High – 10	EORTC (I and II) Without risk factors – 12 Risk factors – 6 IPS (III and IV) 0-1 = 4 2-3 = 4 > 4 = 2
Bulky disease	4	6
Response to treatment	CR – 20 PR – 10 NR – 7	CR – 24 PR – 2 NR – 2

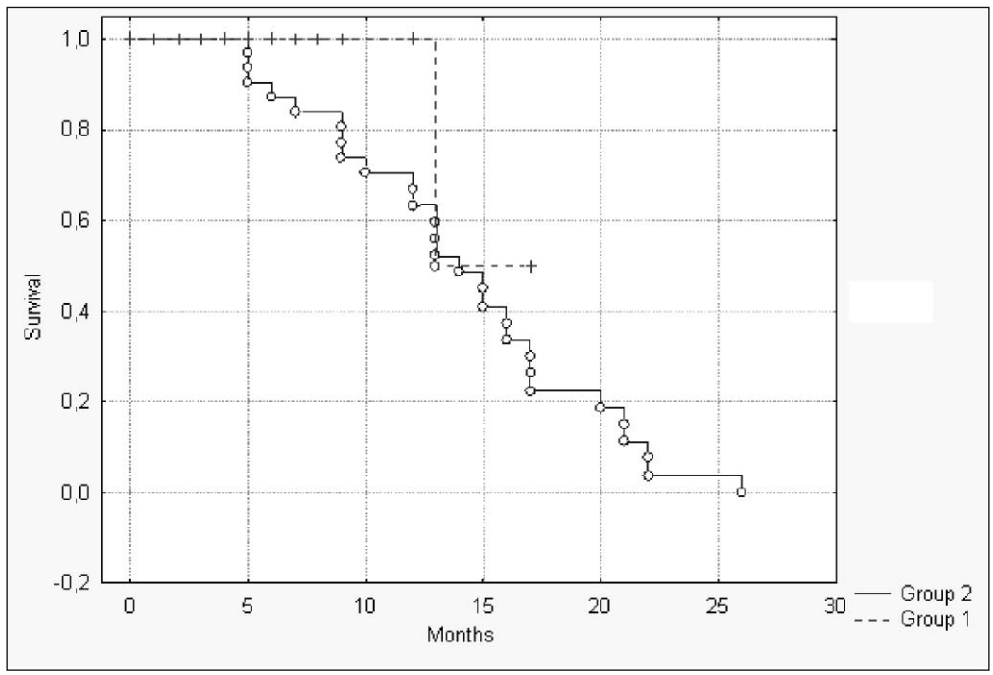

Fig. 1. The survival in patients with acute leukemia and lymphomas with thrombotic events.
Group 1 – without TEC
Group 2 – with TEC
Conflict of interest statement: Nothing to disclose.

DISSCUSION

Thromboembolic events are common complication in cancer patients. The incidence of TEC in patients with hematologic malignancies is similar to thromboembolic events in patients with solid tumors such as pancreatic, ovarian and breast cancer (7-9). Cytostatic treatment and antiangiogenic therapy in patients with hematologic malignancies may cause an increased risk of TEC. Tumor cells may activate hemostasis due to producing procoagulant and fibrynolytic molecules, releasing proinflammatory cytokines and interactions between tumor cells and host vascular cells (10). Many studies investigated the incidence of TEC in patients with solid tumors and hematologic malignancies. Sal-

lah et al. showed that in 1041 patients with solid tumors VTE occured in 7.6% (1). The similar result was published by Mohren et al. In 7.7% of 1038 patients with high-grade malignant lymphoma VTE was confirmed (11). Data of TEC in acute leukemia patients remains scarce. A recently published study has reported VTE in 3.4% of 379 patients with acute leukemias (9). Ziegler et al. found VTE in 2.1% of 719 patients with AL (6). In both studies high frequency of VTE was connected with PML. Mohren et al. in retrospective study of 455 patients with AL observed that 12.1% patients had VTE. In 5.9% cases VTE was related to central venous catheter. Also, the authors found that in patients older than 60 years VTE occured more often comparing to younger patients (11).

In our retrospective analysis we observed TEC in 12.8% patients with acute leukemias and in 12.3% patients with lymphomas. Our results in AL patients were similar in comparison to study of Mohren et al. However, the frequency of TEC in malignant lymphoma patients was higher than in the previous studies. We found that increased risk of VTE is higher in patients older than 60 years. Our observation was in contrast with results of Mohren et al. who suggest that in patients younger than 60 years overall VTE rate is higher (12). In younger patients VTE was associated with central venous catheter. In older patients with cancers additional risk factors of VTE include: immobility, history of previous thromboses and chronic comorbid medical conditions. In study of Ku GH et al. there was no difference in the VTE rate in older vs younger patients with AL (13). An interesting finding of our report may be the association between VTE and high cytogenetic risk in AL patients. However, further research is needed to confirm this observation. The relationship between VTE rate and cytogenetic risk in AL patients was not evaluated. Similar to study of Mohren et al. we showed a higher rate of VTE in patients with malignant lymphoma in stage III and IV according to the Ann Arbor classification in comparison to patients in stage I and II (11). Advanced stage of cancer and intensive chemotherapy may predict TEC in solid tumors as well as hematologic malignancies.

In conclusion, this analysis confirm high incidence of TEC in patients with hematologic malignacies. Prospective studies are necessary to characterize the risk factors of TEC in patients with AL and lymphomas and to determine efective thromboprophylaxis in preventing of TEC in high risk group of patients.

Table 3. Correlation between thrombotic events and some clinical parameters in acute leukemias group.

Parameter	P value
Age < 60 years vs > 60 years	P < 0.05
Sex F vs M	NS
Cytogenetic risk HR and MR vs NR	P < 0.05
Response to treatment CR and PR vs NR	NS
AML vs ALL	NS

NS – not significant

Table 4. Correlation between thrombotic events and some clinical parameters in lymphomas group.

Parameter	P value
Age < 60 years vs > 60 years	NS
Sex F vs M	NS
Stage of disease I and II vs III and IV	P < 0.05
Response to treatment CR and PR vs NR	NS
nHL vs HL	NS

NS – not significant

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