ORIGINAL ARTICLE

Treatment of patients with acute promyelocytic leukemia using AIDA regiments: 20-year single-center experience

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Summary

Introduction: The introduction of all-trans retinoic acid (ATRA) has transformed acute promylocitic leucaemia (APL) from a highly fatal to a curable disease. However, significant frequency of early death (ED) and relapse represent challenges in everyday practice. The aims of this study are to report our 20 years long experience using AIDA-based protocols and to assess the predictive value of clinical and laboratory parameters for ED/relapse development.

Material and methods: This retrospective study included patients treated at the Clinic for Hematology, UKCS in the period 2004-2024. RS was defined as death within the first 30 days of hospitalization.

Results: 158 patients were included. ED and relapse occurred in 38/158 (24%) and 15/119 (12.6%) patients. ED rate stayed stable through time (2004-2008 period 20.6%, 2009–2013 21.9%, 2014–2018 23.1%, 2019–2024 27%) with bleeding as the most frequent cause (42%), followed by DS (24%) and infection (16%). Final predictors for ED development were ISTH DIC score (p=0.008, OR 2.38, 95% *CI* 1.25-4.53), aPTT (p=0.009, OR 0.79, 95% *CI* 0.66-0.94), ECOG PS (p<0.001, OR 2.96, 95% *CI* 1.63-5.39). Predictors for relapse were: ECOG PS ≥ 3 (21.7% vs 78.3%, p=0.019) and bcr3 PML-RARA transcript (29.6% vs 70.4%, p=0.046).

Conclusion: Our experience showed a very high rate of ED, with haemorrhage, DS and infection as a main reason. Preventive strategies should include comprehensive medical education, regarding prompt recognition, appropriate early transfusion support therapy, and the rapid initiation of ATRA. Patients with high ECOG PS and ISTH DIC score probably need different coagulation monitoring and reinvented therapy.

Keywords: acute promyelocytic leukemia, early death, relapse

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INTRODUCTION

Acute promyelocytic leukemia (APL) is a distinct subtype of acute myeloid leukemia (AML), representing 10–15% of newly diagnosed AML cases (1–4). APL is cytogenetically characterized by the presence of a balanced translocation involving the retinoic acid receptor alpha (*RARA*) gene on chromosome 17 and promyelocytic leukemia (*PML*) gene on chromosome 15, resulting in the formation of the *PML: RARA* fusion gene, the driver gene for APL development (2-4). The clinical presentation of APL is aggressive, frequently marked by disseminated intravascular coagulation (DIC), severe bleeding and hemorrhagic death, which framed APL as the most lethal AML (2–4). However, following the introduction of all-trans retinoic acid (ATRA) and subsequently arsenic trioxide (ATO) APL has become acute leukemia with the best therapeutic responses (2–5). Different study groups reported early death (ED) rate between 5 -10% and relapse rate (RR) up to 12% resulting in complete remission (CR) rate as > 90%, 10-year survival of > 80% (2–5). However, highly selected patients in clinical studies probably do not represent the real-world population. Different APL registries, database as well as single center experiences reported significantly higher ED rate, ranging between 20-30% (5–11). On the other hand, RR is stable in all reports with a sharp decrease after the introduction of chemotherapy free, ATO + ATRA regiments (2–11). Therefore, reducing ED rate is a top priority in the treatment of APL. Several predictive factors for ED, such as age, socioeconomic status (SES), marital status, poor performance status (PS), high white blood cell (WBC) and peripheral blast counts, elevated serum lactate dehydrogenase (LDH), low fibrinogen level, low platelet count, prolonged prothrombin time (PT), high International Society on Thrombosis and Hemostasis (ISTH) DIC score were identified as predictive (2–11). Additionally, a few predictive models were constructed (2–11). However, there is not a generally recommended preemptive approach for reducing ED (8, 9).

The aim of our single-center retrospective study is to report our 20-year experience using AIDA based, PETHEMA protocols in the treatment of patients with APL. Moreover, we tried to assess the potential predictive value of some clinical and laboratory parameters for ED and relapse development.

MATERIAL AND METHODS

Patients and APL diagnostic procedures

Our study included 158 consecutive APL patients who were diagnosed and treated at the Clinic of Hematology, University Clinical Center of Serbia, from 2004 to 2024. The diagnosis was made using morphology, cytogenetics, molecular genetics and immunophenotyping of bone marrow (BM). The morphological diagnosis was made according to the contemporary World Health Organization (WHO) classifications of myeloid neoplasms and acute leukemia (12, 13). Cytogenetic analysis was performed by using conventional G-band karyotyping (14, 15). In all patient's detection *PML::RARA* rearrangements were performed by using reverse transcriptase polymerase chain reaction (RT-PCR) (15). Immunophenotyping was performed at diagnosis by direct multicolor immunofluorescence with a wide panel of monoclonal antibodies (CD2, CD3, cCD3, CD7, CD11a, CD11b, CD11c, CD13, CD15, CD16, CD19, CD33, CD34, CD38, CD45, CD56, CD64, CD114, CD117, HLA-DR, MPO) applied to the whole bone marrow specimen (16). Positivity was defined as expression in ≥ 20% of cells.

Clinical and treatment data

All patients were treated with AIDA regimens, including induction cycle of ATRA plus idarubicin, followed by three ATRA plus polychemotherapy consolidation cycles (17-19). In the period from September 2004 to August 2010 we used PETHEMA APL 99, from September 2010 to May 2013 PETHEMA APL 2005, and since June 2013 we have been using PETHEMA APL 2012 protocol (17-19). Differentiation syndrome (DS) prophylaxis applies in patients with initial WBC > $5x10^9$/L with dexamethasone from day 1 to day 15 (17-21). DS was diagnosed if ≥2 of the following signs were present: dyspnea, unexplained fever, weight gain ≥ 5 kg, unexplained hypotension, acute renal failure, and chest radiograph demonstrating pulmonary infiltrates or pleuro-pericardial effusion (17-21). Patients with confirmed DS were treated with therapeutic dexamethasone dose and in some cases ATRA was withheld until the patient's condition stabilized (17-21). Death from any causes that occurred during the initial 30 days after hospital admission were defined as ED (22-23). Bleeding events were graded according to the modified WHO grading system (24-25). Bleeding associated with moderate or severe hemodynamic instability, requiring red blood cell transfusion or central nervous system (CNS) bleeding, were classified as severe. Transfusions of platelet concentrates were used to obtain platelet count > 30-50 $\times10^9$/L, while cryoprecipitate was used to obtain fibrinogen level > 1-1.5 g/L. Fresh frozen plasma was transfused in case of INR > 1.5. These supportive measures were applied until the correction of coagulopathy, previously defined as normalization of fibrinogen and PT and bleeding cessation (17-19, 21). All patients were followed up from the diagnosis to death or the final check-up.

The retrieval of information and publication of these results were approved by the Institutional Review Board of the University Clinical Center of Serbia (protocol number 1435/10, 11-102-102, date: September 08, 2011). Patient consent was waived due to retrospective nature of study.

Data collection

We collected the following data: age, gender, bleeding at presentation, Eastern Cooperative Oncology Group performance status (ECOG PS), complete blood count, fibrinogen, PT, activated partial thromboplastin time (aPTT), D-dimer, immunophenotype, cytogenetics and molecular genetics, presence of DS during hospitalization. The Sanz risk score was used to classify patients to low (WBC ≤10x10^9/L, platelet count ≥ 40x10^9/L) intermediate (WBC ≤10x10^9/L, platelet count ≤ 40x10^9/L), and high-risk group (WBC > 10x10^9/L). The DIC diagnosis was made according to the recommendations of the International Society on Thrombosis and Hemostasis (ISTH). Patients with ISTH DIC score ≥ 5 were considered to have overt DIC (17, 18).

Statistical Analyses

Statistical analysis was performed using IBM SPSS statistical software (SPSS for Windows, release 25.0, SPSS, Chicago, IL, USA). We used absolute or relative frequencies to present categorical variables, which were compared using either Chi-square test or the Fisher's exact test. The Kolmogorov-Smirnov test and histogram were used to assess the normality of data distribution. Continuous variables with normal distribution are shown as mean and standard deviation (mean ± SD), while variables not complying with normal distribution are presented as median and range. T-test or Mann-Whitney U test were used for comparisons between groups for continuous variables. The significance level was set at 0.05. Univariate and multivariate logistic regression analyses were used to calculate and validate the risk factors for ED development. Variables with a $p < 0.05$ in the univariate model were included in the multivariate logistic regression analysis.

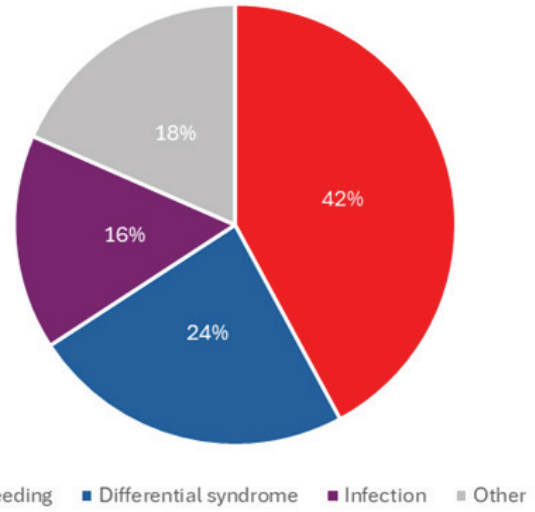


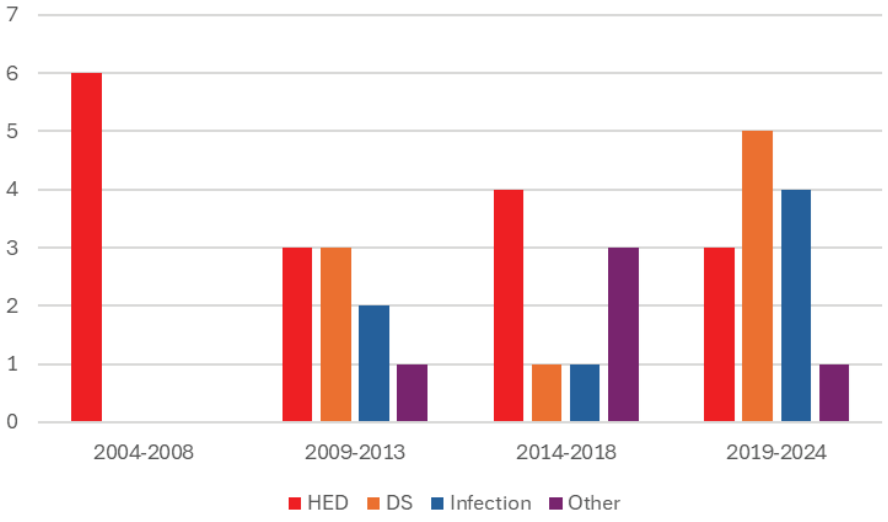
Figure 1. Causes of ED among our group of patients

Results

Among 158 patients of median age 45.3 years (range 18-78), 81 (53.8%) were females. At presentation, mild hemorrhagic syndrome was noted in 126 (85.7%) patients, severe hemorrhage in 9 (9.1%) patients, while bleeding was absent in 12 (10.9%) patients. Diagnosis of DS was made in 44/158 (27.8%) subjects. Early death occurred in 38/158 (24%). Bleeding was the most frequent cause of ED, followed by DS and infection **(Figure 1)**.

CR after induction cycle was achieved in 119/120 (99.2%) of patients. Consolidation death rate was 5/120 (4.2%). All patients died due to infections. RR was 15/119 (12.6%). Median overall survival was not reached.

To analyze trends in early death (ED) rates over time, the 20-year period was divided into four 5-year intervals. In the first period 2004 – 2008 ED rate was 6/29 (20.6%), in the second (2009 – 2013) ED rate was 9/41 (21.9%), in the third (2014 – 2018) it was 9/39 (23.1%) and in the last one (2019 – 2024) 15/39 (27). The distribution of early deceased patients by cause of death is shown in **Figure 2**.



Abbreviations: HED – hemorrhagic early death, DS - Differential syndrome

Figure 2. Distribution of ED causes overtime

Early death predictors

The clinical and laboratory features and comparison of all APL patients are shown in **Table 1**. Patients who experienced ED were significantly older (50.4 vs. 43.7 years, $p = 0.023$), had a higher ECOG performance status (ECOG PS ≥ 3 in 81.6% vs. 35.8%, $p < 0.001$), and more frequently presented with severe bleeding (16.2% vs. 2.7%, $p = 0.001$). They also had higher WBC counts (16.2×10^9/L vs. 2.6×10^9/L, $p = 0.001$), a higher incidence of high Sanz risk score (57.9% vs. 26.7%, $p < 0.001$), elevated D-dimer levels (31.0 vs. 18.8, $p = 0.002$), prolonged PT (57.8% vs. 7.0%, $p < 0.001$), shorter aPTT (25.4 s vs. 26.9 s, $p = 0.016$), and higher ISTH DIC scores (6 vs. 5, $p < 0.001$). Additionally, variant disease type was more common in this group (18.4% vs. 5.0%, $p = 0.016$), as was the development of differentiation syndrome (DS: 52.9% vs. 22.8%, $p = 0.001$).

Due to the multicollinearity between Sanz risk score and WBC as well as platelet count, two last variables were omitted from the model. Moreover, due to multicollinearity between ISTH DIC and platelet count, PT and D-dimer, only ISTH DIC score were included in the model. Given the number of identified predictors relative to the limited number of outcomes, we opted to perform logistic regression in two steps. In the first step, the predictors are divided into two groups. In the second step, variables that were significant in the initial two models were included in the final model.

Multivariant model 1 included patient and disease characteristics **(Table 2)**. Significant predictors for ED were: ECOG PS ($p < 0.001$, *OR* 2.73, 95% *CI*: 1.69-4.40), DS development ($p = 0.008$, *OR* 3.65, 1.40-9.47) and variant disease type ($p = 0.028$, *OR* 5.14, 1.20-22.07).

Table 2. Multivariate model 1

Step 1	B	p	0R	95% *CI*
Age	0.028	0.080	10.28	0.99-1.06
ECOG	1.003	< 0.001	2.73	1.69-4.40
DS	1.294	0.008	3.65	1.40-9.47
Variant disease type	1.637	0.028	5.14	1.20-22.07

Abbreviations: ECOG PS - Eastern Cooperative Oncology Group Performance Status, DS - Differential syndrome.

Multivariant model 2 included laboratory parameters **(Table 3)**. Significant predictors of ED were bleeding on admission ($p = 0.048$, *OR* 5.34, 1.01-28.18), ISTH DIC score ($p = 0.001$, *OR* 2.58, 1.45-4.60) and aPTT ($p = 0.033$, *OR* 0.86, 0.74-0.99)

Table 1. Comparison of clinical and laboratory data between alive and early deceased patients

		All (n = 158)	ED patients (n = 38)	Alive (n = 120)	P
Female, n (%)		85 (53.8)	22 (57.9)	63 (52.5)	0.561
Age, mean±sd		45.3±15.9	50.4±14.0	43.7±16.2	**0.023**
ECOG PS, n (%)	0	15 (9.5)	0 (0.0)	15 (12.5)	**< 0.001**
	1	66 (41.8)	7 (18.4)	59 (49.2)	
	2	37 (23.4)	11 (28.9)	26 (21.7)	
	3	31 (19.6)	14 (36.8)	17 (14.2)	
	4	9 (5.7)	6 (15.8)	3 (2.5)	
	5	0 (0.0)	0 (0.0)	0 (0.0)	
Bleeding on presentation, n (%)	Without	12 (8.2)	0 (0.0)	12 (10.9)	**0.001**
	Moderate	126 (85.7)	31 (83.8)	95 (86.4)	
	Severe	9 (9.1)	6 (16.2)	3 (2.7)	
Hb (g/L), mean±sd		96.9±21.2	92.0±19.6	98.4±21.6	0.106
WBC (x109/L), median (range)		3.6 (0.4-208.8)	16.2 (0.4-208.8)	2.6 (0.4-91)	**0.001**
Plt (x109/L), median (range)		27.0 (0-279)	26 (0-64)	30 (2-279)	0.066
Sanz high risk, n (%)		54 (34,2)	22 (57.9)	32 (26.7)	**< 0.001**
Fibrinogen (g/L), median (range)		2.7 (0.4-8.8)	2.27 (0.9-8.8)	2.8 (0.4-6.2)	0.210
PT (%), mean±sd		67,0±17.0	57.8±16.5	69.9±18.8	**< 0.001**
aPTT (s), mean±sd		26.5±4.0	25.4±2.8	26.9±4.2	**0.016**
D dimer (μg/L), median (range)		24.0 (0.70 – 2345.0)	31.0 (2.1-233.0)	18.8 (0.7-2345.0)	**0.002**
ISTH DIC, median (range)		6 (1-8)	6 (5-7)	5 (1-8)	**< 0.001**
Variant disease type, n (%)		13 (8.3)	7 (18.4)	6 (5.0)	**0.016**
Additional cytogenetic abnormalities, n (%)		24 (15.8)	7 (19.4)	17 (14.7)	0.388
PML RARA, n (%)	Bcr 1	54 (60.7)	7 (63.6)	47 (60.3)	1.000
	Bcr 2	3 (3.4)	0	3 (3.8)	
	Bcr 3	32 (36.0)	4 (36.4)	28 (35.9)	
ATRA, n (%)		44 (29.7)	18 (52.9)	26 (22.8)	**0.001**

Abbreviations: ECOG PS -Eastern Cooperative Oncology Group Performance Status, Hb – hemoglobin, WBC – with blood cells, Plt – platelets, aPTT - activated partial thromboplastin time, ISTH DIC score - International Society on Thrombosis and Hemostasis disseminated intravascular coagulation score.

Table 3. Multivariate model 2

Variables	B	p	0R	95% *CI*
Sanz risk	0.180	0.628	1,20	0.58-2,47
ISTH DIC score	0.949	0.001	2.58	1.45-4.60
Bleeding	1.675	0.048	5,34	1.01-28.18
aPTT	-0.157	0.033	0,86	0.74-0.99

Abbreviations: aPTT - activated partial thromboplastin time

Our final model included: ECOG PS, DS development, variant disease type, bleeding on admission, ISTH DIC score and aPTT. Final predictors for ED development were ISTH DIC score (p = 0.008, *OR* 2.38, 1.25-4.53), aPTT (p = 0.009, *OR* 0.79, 0.66-0.94), ECOG PS (p < 0.001, *OR* 2.96, 1.63-5.39). Data are presented in **Table 4**.

Table 4. Final model

Variables	B	p	0R	95% *CI*
ISTH DIC score	0.867	0.008	2.38	1.25-4.53
Bleeding	1.142	0.293	3.13	0.37-26.39
aPTT	-0.241	0.009	0.79	0.66-0.94
ECOG PS	1.086	< 0.001	2.96	1.63-5.39
Variant disease type	0.991	0.198	2.69	0.60-12.16
DS	0.955	0.069	2.60	0.93-7.28

Abbreviations: ISTH DIC score - International Society on Thrombosis and Hemostasis disseminated intravascular coagulation score, aPTT - activated thromboplastin time, ECOG PS - Eastern Cooperative Oncology Group Performance Status, DS - Differential syndrome

Predictors of relapse

In the examined group of parameters, statistically significant difference showed ECOG PS ≥ 3 1(0/46, 21.7% vs 36/46, 78.3%, p = 0.019) and bcr3 PML RARA transcript (8/27, 29.6% vs 19/27, 70.4%, p = 0.046). All other parameters were not statistically significant different (female gender 8/62, 12.9% vs 54/62, 84.1%, p = 0.948); age (51.33 vs 60.69), p = 0.322; variant disease type (1/6, 16.7% vs 5/6, 83.3%, p = 0.569); additional cytogenetic abnormalities (4/16, 25% vs 12/16, 75%, p = 0.213), Hb level (101.86 vs 96.76, p = 0.357); WBC (4.85 vs 2.4, p = 0.235); platelet count (28.50 vs 29/00, p = 0.810), Sanz risk score (high risk 6/32. 18,8% vs 9/86, 10,5% p=0.231), fibrinogen (2.24 vs 2.92, p = 0.094), PT (66.79% vs 69.09%, p = 0.787), aPTT (27.84 vs 26.48, p = 0.331), D dimer (132.65 vs 223.6, p = 0.944), ISTH DIC score > 4 (2/27, 7.4% vs 12785, 14.1/, p = 0.512), Differential syndrome development (9/88, 10.2% vs 79/88, 89.2%, p = 0.299).

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the University Clinical Center (protocol number 1435/10, 11-102-102, date 08.09.2011.). Informed consent was obtained from all subjects involved in the study after September 8th, 2011. Due to the retrospective nature of the study, the inform consents were waived before this date.

DISCUSSION

The introduction of ATRA and ATO have transformed APL from a highly fatal to a highly curable disease (2-11). However, significant frequency of ED and occurrence of relapse remain a challenge in everyday clinical practice.

In our group of patients, the ED rate was 24%, which is significantly higher in comparison to reports from clinical studies, but in line with data from registries, national or single center experience publications (2-11). ED rate has often been significantly underestimated in clinical studies due to exclusion of patients with high ECOG PS, comorbidities and even more patients who died even before the treatment (8, 9).

Over decades, the frequency of ED in APL has been decreasing (7, 27). With the widespread introduction of ATRA into clinical practice after 1995, the ED rate was significantly reduced for the first time. A subsequent decline was observed after 2006, coinciding with advancements in the medical environment, including the implementation of aggressive rescue measures, improved supportive care, and better management of complications. However, after these two periods the ED rate has remained stable (7, 27). In our group of patients treated since 2004, a decrease in ED rate has not been observed. However, we observed a significant change in the rate of specific causes. HED remained a significant reason for ED, but the rate was reduced after the 2004-2008 period. This reduction is probably related to better transfusion support in our center. Moreover, since predictive value of conventional coagulation tests is not consistent, we recently investigated the utility of rotational thromboelastometry (ROTEM) in APL patients. According to our previous publication, ROTEM parameters could be surrogates for HED and beneficial in identifying at least those patients with excessive fibrinolysis who need different transfusion support (7, 28).

The frequency of deaths due to DS remained high in our cohort despite corticosteroid prophylaxis. However, the optimal prophylaxis scheme remains controversial (29). Additionally, patients with DS insensitive to steroids typically have a poor prognosis, highlighting the necessity for improved management strategies in this area. Early DS recognition as well as corticosteroid therapy initiation in full doses are essential (19, 29). Wu at al. suggested that inclusion of ruxolitinib for managing DS in APL resulted in a reduction of early death rate (19).

Unfortunately, during the last period we saw a significant increase in ED caused by infections. Currently, our infection-related mortality rate matches that reported by PETHEMA, likely due to improved diagnostic capabilities and better differentiation from pulmonary bleeding and DS. It is well documented that geographical distribution (high vs mild and low-income countries) make a significant impact on ED rate. Multidrug availability, considering antibiotics and antimycotics will significant-

ly reduce our infection-related ED rate (30-33). However, the availability of non-chemotherapy is more significant. Therapy based on ATRA and ATO combination is not myeloablative which results in a significant decrease of infection rate (6, 33, 34). New data from Harmony registry confirms the superiority of ATRA-ATO over ATRA-chemotherapy in patients with APL (6).

One of the strategies to reduce ED rate is to identify high risk patients. Factors that were previously identified as ED predictors such as age, WBC, low platelet count, Sanz score, prolonged PT, variant disease type were also identified as predictive in our univariate analyses but lost significance in the final model. After final multivariate analyses our model included ISTH DIC score, aPTT and ECOG PS. Patients with APL have: 2.38-time higher risk for ED with every point of ISTH DIC score rising; 0.786-time lower risk of ED with every second of aPTT prolongation and 2.964 higher risk of ED with every ECOG PS grade rising. Predictive value of disease-unrelated parameters such as ECOG PS probably can be explained by higher disease burden and represent sicker patients in which ED is more likely. Our data suggest that DIC is the major cause of bleeding and death in APL patients and that the degree of DIC may correlate with the risk of ED. Interestingly, a majority of studies with a focus on bleeding and HED did not assess predictive values of DIC scores (8). Patients with high risk probably need different therapy strategies. In the first step coagulation parameters monitoring should be intensified with a new global coagulation test adding to identified patients who may benefit from intensive transfusion support [8]. Although HED rate stays high with ATRA+ATO regiments, this approach will reduce ED rate associated with infections (5, 34, 35).

CONCLUSION

In conclusion, our 20-year long experience showed a very high rate of ED, with hemorrhage, DS and infection as main causes. Preventive strategies should include comprehensive medical education, especially in emergency departments, regarding prompt recognition, appropriate early transfusion support therapy, and the rapid initiation of ATRA (30-33). Using the ATO regiment can contribute to the further reduction of ED. However, patients with high ECOG PS and high ISTH DIC score probably need different coagulation and DS monitoring and reinvented therapy.

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Ethical approval: The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the University Clinical Center (protocol number 1435/10, 11-102-102, date: September 08, 2011). Informed consent was obtained from all subjects involved in the study after September 08, 2011. Due to the retrospective nature of the study, the inform consents were waived before this date.

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LEČENJE PACIJENATA SA AKUTNOM PROMIJELOCITNOM LEUKEMIJOM PRIMENOM AIDA PROTOKOLA: DVADESETOGODIŠNJE ISKUSTVO JEDNOG CENTRA

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Sažetak

Uvod: Uvođenje all-trans retinoične kiseline (ATRA) transformisalo je akutnu promijelocitnu leukemiju (APL) iz visoko smrtonosne u izlečivu bolest. Međutim, značajna učestalost rane smrti (RS) i relapsa i dalje predstavlja izazov u svakodnevnoj praksi. Ciljevi ovog rada su prikazati 20-godišnje iskustvo u lečenju bolesnika AIDA zasnovanim protokolima i proceniti prediktivnu vrednost kliničkih i laboratorijskih parametara za razvoj RS i relapsa bolesti.

Materijal i metode: U ovu retrospektivnu studiju su uključeni pacijenti lečeni u Klinici za hematologiju, UKCS u period 2004-2024. RS je definisana kao smrt u prvih 30 dana hospitalizacije.

Rezultati: U studiju je uključeno 58 pacijenata. RS i relaps su se javili kod 38/158 (24%) odnosno 15/119 (12,6%) pacijenata. Stopa RS je ostala stabilna tokom vremena (2004-2008 period 20,6%, 2009-2013 21,9%, 2014-2018 23,1%, 2019-2024 27%) sa krvarenjem (42%), diferencijacionim sindromom (DS, 24%) i infekcijama (16%) kao najčešćim uzročnicima. Konačni prediktori za razvoj RS bili su: ISTH DIC skor (p=0,008, *OR* 2,380, 95% *CI* 1,25-4,53), aPTT (p=0,009, *OR* 0,79, 95% *CI* 0,66-0,94), ECOG PS ($p < 0.001$, *OR* 2.96, 95% *CI* 1.63-5.39). Kao faktori povezani sa relapsom identifikovani su: ECOG PS ≥3 (21,7% naspram 78,3%, p=0,019) i bcr3 PML-RARA transkript (29,6% naspram 70,4%, p=0,046).

Zaključak: Veoma visoku stopa RS perzistira u našoj grupi, sa krvarenjem, DS i infekcijom kao glavnim uzrocima. Preventivne strategije bi podrazumevale sveobuhvatnu medicinsku edukaciju, sa ciljem brzog prepoznavanja, adekvatne terapije transfuzijama derivata i komponenata krvi, i brzom započinjanju terapije ATRA-om. Pacijentima sa visokim ECOG PS i ISTH DIC potrebno je intenzivnije praćenje koagulacionih paremetara i intenzivnija suportivna terapija.

Ključne reči: akutna promijelocitna leukemija, rana smrt, relaps

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