

HOW WE TREATED ACUTE PROMYELOCYTIC LEUKEMIA: WHERE WE ARE NOW?

Krstevska Balkanov Svetlana¹, Trajkova Sanja¹, Pivkova Veljanovska Aleksandra¹,
Cvetanovski Milche¹, Ridova Nevenka¹, Panovska Stavridis Irina¹, Pendovska Marija²,
Spasovski Dejan³

¹University Clinic for Hematology, Faculty of Medicine, Ss. Cyril and Methodius University,
Skopje, Republic of North Macedonia

²Goce Delchev University in Shtip, Faculty of Medical Sciences, Republic of North
Macedonia

³University Clinic for Rheumatology, Faculty of Medicine, Ss. Cyril and Methodius
University, Skopje, Republic of North Macedonia
e-mail: svetlanakrstevskaa@yahoo.com

Abstract

Acute promyelocytic leukemia (APL) is a unique subtype of acute myeloid leukemia (AML), accounting for about 15% of AML cases. APL is a distinct clinical entity characterized by a marked tendency towards coagulopathy, hemorrhage and early death, as well as by a block in differentiation where leukemic cells are halted at the promyelocytic stage. A characteristic balanced chromosomal translocation between chromosomes 15 and 17 t(15;17)(q24;q21) is seen in 95% of cases - the translocation results in the formation of PML-RAR α fusion protein. The introduction of retinoic acid (RA) and arsenic trioxide (ATO) has been responsible for initially remarkable cure rates. Our retrospective-prospective study was performed at our Clinic, from January 2004 until December 2022. Fifty-six patients were included with demographic characteristic (male - 27, female - 29), at the age of 15 to 77 years (median range 45) with APL, according to FAB and WHO regimens for diagnosis with confirmed molecular diagnosis. Risk stratification was done according to Sanz risk score, WBC, PL and clinical presentation of the disease. The overall survival has shown that 30 patients (53.6%) are alive and 26 (46.4%) died. With reference to treatments, 5 patients (8.9%) died before starting chemo-treatment. Early death was observed in 16 patients (61.5%), and in 10 patients (38.5%) death occurred after 30 days of diagnosis. The main reason of mortality was also analyzed. To prevent ED prior to treatment, suspected APL patients should be immediately hospitalized, treated as medical emergency.

Keywords: acute promyelocytic leukemia, PML - RAR α fusion protein, early death, all trans retinoic acid

Introduction

Acute promyelocytic leukemia (APL) is a different subtype of acute leukemia (AL) that is cytogenetically characterized by a balanced reciprocal translocation between chromosomes 15 and 17, also with distinctive blast morphology, unique coagulopathy and different biological characteristics such as hemorrhage and early death^[1]. APL is a rare disease, it has become a well-recognized entity, characterized as the M3 subtype of AML within the French-American-British (FAB) classification system, that accounts for < 10% of all AML cases, with estimated incidence of 0.1/100,000^[2,3]. The disease is characterized by a unique balanced reciprocal translocation t(15;17) which fuses the promyelocyte (PML) gene

on chromosome 15 to the retinoic acid receptor alpha (RAR α) gene on chromosome 17. Variant chromosomal translocation t(11;17), t(5;17) can be detected in no more than 2% of APL patients^[4,5].

In the past, APL was considered as one of the most rapidly lethal forms of AML, but recently has come to be the most curable subtype of AL. Nevertheless, APL is still a medical emergency because it requires prompt treatment at the first suspicion of the diagnosis. Treatment is initiated even before cytogenetic or molecular confirmation, because of the high-level early mortality with APL, which is mostly due to hemorrhage and disseminated intravascular coagulation (DIC) with primary hyperfibrinolysis^[6]. Biologic features of APL account for its unique phenotype providing potential targets for tailored treatment.

Flow cytometric immunophenotypic analysis can facilitate prompt diagnosis of APL. It is well documented that CD2+, CD34+, and CD56+ phenotypes are associated with lower overall survival (OS) rate, shorter remission, decreased incidence of remission, and increased incidence of early death, respectively, however they are also considered as additional diagnostic information^[7,8].

In aspect of the treatment development, historically APL was treated with standard AML-directed chemotherapeutic induction regimens (CT). Treatment from the 70's demonstrated that APL leukemic cells were relatively sensitive to chemotherapy (CT: daunorubicin) that yielded a complete remission (CR) rate of 55% in patients with APL. From then on, CT composed of an anthracycline (daunorubicin, idarubicin, or others) and cytosine arabinoside (Ara-C) was the frontline treatment of APL, and the CR rates could reach 75% to 80% in newly diagnosed patients^[9]. However, the frequently observed aggravation of bleeding syndrome by CT, leading to high early death rate, necessitated intensive platelet and fibrinogen support. The new tailored treatment started in the mid-1980's when differentiating agent all-trans retinoic acid (ATRA) was discovered, but shortly after the introduction of ATRA the need arose for addressing retinoic acid resistance. Resistance to ATRA was partially alleviated by the advent of arsenic trioxide (ATO), but treatment resistance still remains an issue to this day. APL is now considered curable disease, and therefore the success of ATRA and ATO in APL treatment furnishes the first model of molecular target-based induction of differentiation and apoptosis. The recent results of each drug provide high CR rates (90%-94%) and high 5-year DFS rates (90%) using ATRA/ATO/CT in low-risk APL. With the introduction of these agents, the natural history of APL has changed, as they induce differentiation and maturation of leukemic promyelocytes to neutrophils^[10-19].

The primary issue with APL is still early death (ED), due to coagulopathy and secondary fibrinolysis, which is defined as early death due to any cause within 30 days after diagnosis. Most of those deaths are caused by bleeding in CNS and infections, which result in sepsis development, while not so often in ATRA syndrome and acute renal failure. The white blood cells (WBCs) count before treatment is a confirmed risk stratification marker for early death, and it is the only known independent risk factor that predicts prognosis for this disease. Patients were stratified according to Sanz risk score into three groups (low, intermediate, and high risk) depending on their initial white blood cell (WBC) and platelet (PL) counts^[20-22].

Conversions of 13-cis-retinoic acid and 9-cis-retinoic acid to ATRA is very rapid and time dependent and it is important to administer fast two major doses of this agent. The antiproliferative effect of ATRA appears only 24 hours after application and induces differentiation and maturation of promyelocytes. Prior to ATRA therapy, ED related to hemorrhage occurred in up to 26 to 60%. Other researchers report ED rates of 5-10%, the percentage that varies compared to different centers. Also, the Swedish Adult Acute Leukemia Registry reported ED of 29%. The ED does not appear to have changed significantly despite routine use of ATRA^[23-25].

In the process of treatment of APL with ATRA or ATO, the differentiation syndrome (DS) represents a life-threatening complication in patients being treated with these agents; up to 50% of patients with this treatment will develop DS. Clinically, DS is characterized by weight gain, fever not attributable to infection, respiratory distress, cardiac involvement, hypotension, acute renal failure, fluid retention as pleural and pericardial effusion. DS pathogenesis is not completely understood, but it is believed that an excessive inflammatory response is the main phenomenon involved, which results in increased production of chemokines like interleukin 1 (IL)-1, IL-Beta, IL-6, IL-8, TNF alfa and expression of adhesion molecules on APL cells. Due to the high morbidity and mortality associated with DS, its recognition, especially in high-risk patients, and the prompt initiation of the treatment is most important. Recommended management of DS is immediate administration of corticosteroids and disruption of the ATRA/ATO therapy. Once the syndrome has resolved, the steroids can be discontinued^[26-29].

The relapse rate of APL, which with modern therapy occurs in less than 5-10%, regardless of their risk stratification, typically occurs within the first three years of the first complete remission and rarely later. The probability of relapse is significantly higher in high-risk subset of patients undergoing treatment for APL.

It is not known that low/intermediate risk group patients achieve excellent outcomes chemotherapy free ATRA/ATO based induction and consolidation protocol. Only high-risk patients who are successfully induced with ATRA/ATO with anthracycline can be consolidated with ATRA/ATO with the omission of chemotherapy. But still, it is unclear if there remains any benefit of cytarabine exposure in high-risk patients, unless their CNS is positive for disease at diagnosis^[30-33].

The aims of this study were to recognize the clinical features and possible risk factors for early mortality in APL patients and to determine the overall survival and analyze the causes of mortality of APL patients treated at the Center at the University Clinic for Hematology in Skopje.

Material and methods

This retrospective-prospective study was performed at the University Clinic for Hematology in Skopje, in the period from January 2004 until December 2022, and included 56 APL patients. Diagnostic criteria of APL were based on the French-American-British classification system (FAB) and the World Health Organization Classification of Tumors-Pathology and Genetic of Tumors of Hematopoietic and Lymphoid Tissues^[2,4].

Cytogenetic and flow cytometry were done whenever possible. Molecular diagnosis was confirmed by reverse transcription-polymerase chain reaction (RT-PCR) analysis in all patients and it was performed from bone marrow and peripheral blood. Risk stratification was done according to Sanz risk score, which classifies patients into three groups depending on their initial white blood cell (WBC) and platelet counts^[25]:

- High risk: when the presenting WBC count $>10 \times 10^9/L$ and irrespective of platelets counts,
- Intermediate risk: when the presenting WBC count $\leq 10 \times 10^9/L$ and platelets $\leq 40 \times 10^9/L$, and
- Low risk: when patients have WBC $\leq 10 \times 10^9/L$, but their platelet count is $>40 \times 10^9/L$.
- Also, the risk stratification was done according to the level of white blood cells (WBCs) at the time of diagnosis:^[29]
- High risk: WBCs $>10 \times 10^9/L$; Platelets $<30 \times 10^9/L$
- Low risk: WBCs $\leq 10 \times 10^9/L$; Platelets $>30 \times 10^9/L$

All patients were observed during the clinical presentation of the disease at diagnosis.

The first group of patients were treated with AIDA protocol (Idarubicin 12 mg/m²/day given as an intravenous bolus on days 2, 4, 6 and 8 and ATRA, 45 mg/m² oral doses, divided into two daily doses which was maintained until complete remission). Cytarabine 100 mg/m² was added in the high-risk category patients in the second group according to WBC, platelets and clinical presentation of bleeding. Adjustment of the dosage was provided in the older-aged patients with significant comorbidities. The third group of patients was added in the high-risk category patients and were treated with Daunorubicin 50 mg/m² /day given as an intravenous bolus on days 1,2, 3, Cytarabine 100 mg/m² for 7 consecutive days and ATRA. The fourth group of patients were treated with ATRA and ATO 0.15 mg/kg daily 5 days for 4 weeks every 8 weeks. In the group with high risk, 3 patients were treated with FLT3 inhibitors, Sorafenib in an oral form. The last group of two patients received only ATRA for two days. Supported treatment with platelet transfusions, fresh frozen plasma and cryoprecipitate was applied in all patients.

Our study was approved by the Ethics Committee at the University Clinic for Hematology. Written informed consent was obtained from all patients before starting the study. All historical data were taken from patients' record database at the University Clinic for Hematology.

Statistical analysis

Statistical analysis was performed using the SPSS software, version 22. The Kaplan-Mayer survival curves were plotted for the three risk categories.

Results

A total of 56 patients were involved in the study between January 2004 and December 2022.

Patients' characteristics were: 29 females (51.8%) and 27 males (48.2%), with median age of 45 years, ranging from 15-77 years. Patients were divided in two groups: under the age of 55 (43 patients, 76.8%) and above the age of 55 (13 patients, 23.2%). Over two third were young adults. (In our Center) In the period from 2010 to 2022 593 patients were diagnosed with acute myeloblastic leukemia (AML). APL was observed in 44 (7.4%) patients, which correlated with other centers.

Of the total number of APL patients, at the end of study period, the overall survival has shown that 30 patients (53.6%) are alive and 26 (46.4%) died (Figure 1).

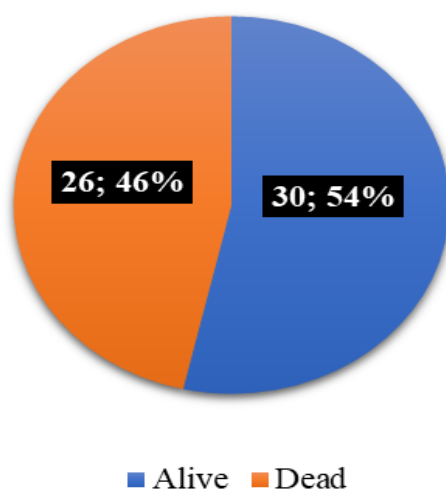


Fig. 1. Outcome of treated patients with APL

During treatments in all 56 patients, five patients (8.9%) passed away before starting the management plan and chemotherapy treatment. They were treated only for coagulopathy with platelet transfusions and cryoprecipitate and fresh frozen plasma (FFP). Therefore, 51 patients (91.1%) received different initial induction therapy (Figure 2).

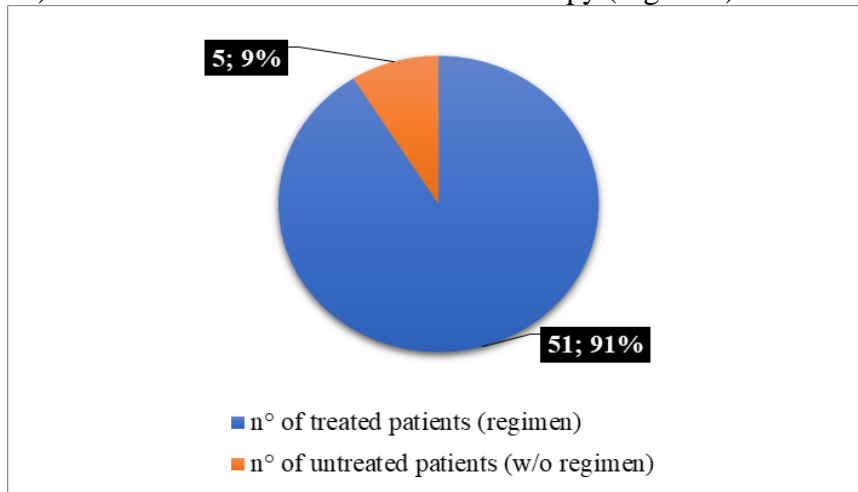


Fig. 2. Diagnosed patients with APL in the period 2004 - 2022

AIDA protocol was applied in 28 patients i.e. (54.9%), the second group of 13 patients (25.5%) was treated with AIDA protocol and Cytarabine, the third group of 5 patients (9.8%) was treated with Daunorubicin, Cytarabine and ATRA, 2 patients (3.9%) were treated with ATRA and ATO, 2 patients (3.9%) were treated with ATRA, only 1 patient (2.0%) was treated initially with AIDA and Cytarabine and she received CR, but during relapse she was treated with ATRA plus ATO (Figure 3).

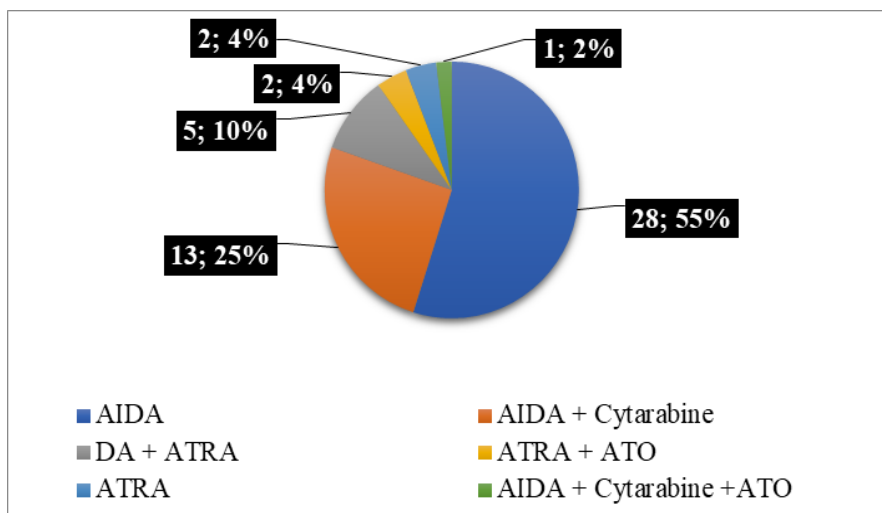


Fig. 3. First line treatment of APL patients in the period 2004 - 2022

Complete remission (CR) after treatment was observed in 37 patients (66.1%), 2 patients (3.6%) had refractory disease (RD) while 17 patients (30.4%) died during diagnosis, induction and consolidation treatment without achieving any response (Figure 4).

Of the patients who achieved CR, 7 patients (18.9%) developed relapse of the disease later, 5 of them (13.5%) died and 2 (5.4%) are still in second remission (Figure 5)..

In the CR group of patients, 18 patients (48.6%) were treated initially with AIDA and 2 patients (5.4%) with ATRA and ATO, 9 patients (24.3%) were treated with AIDA and Cytarabine and 5 of them (13.5%) with Daunorubicin, Cytarabine and ATRA. From these high-risk group, 3 patients (8.1%) had FLT3 mutation and were also treated with FLT3 inhibitors.

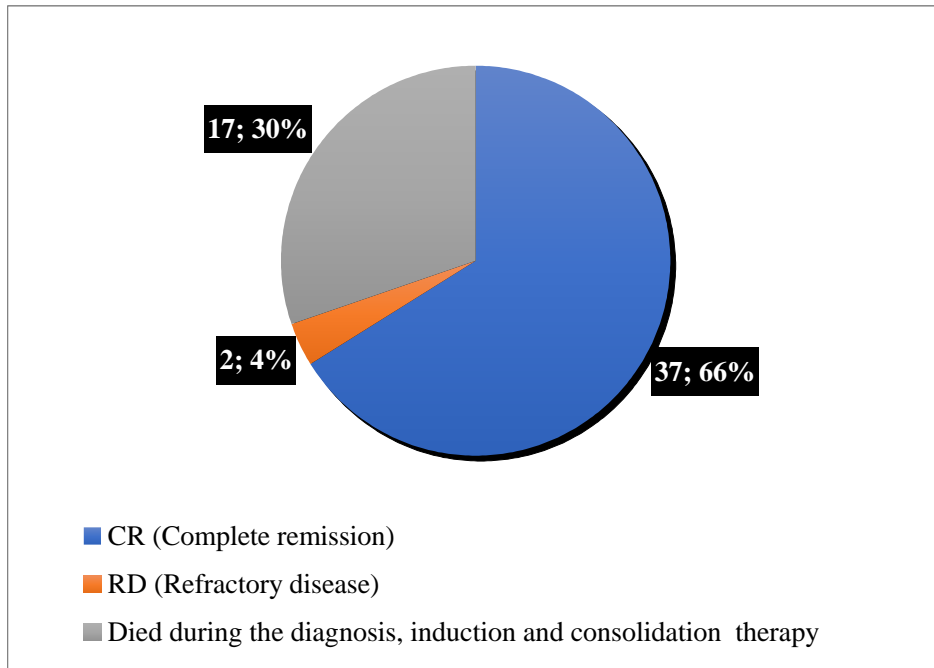


Fig. 4. Outcome of patients treated with different regimens

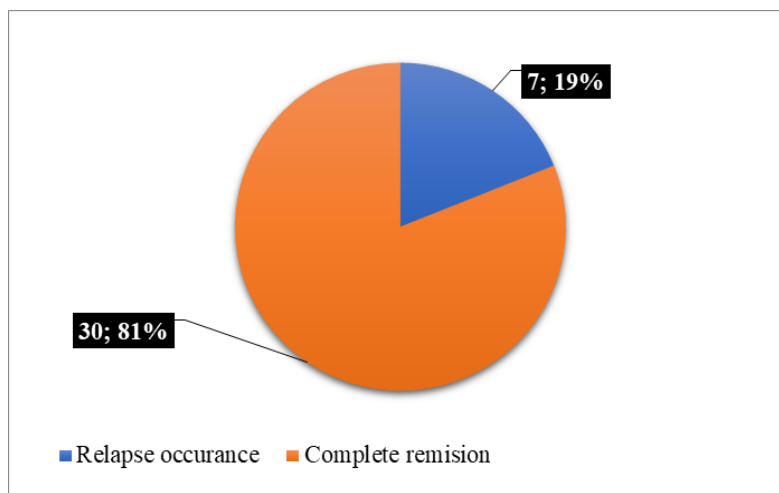


Fig. 5. Relapse occurrence in patients with CR

Death occurred in 26 patients, among them early death (ED) was observed in 16 patients (61.5%), and in 10 patients (38.5%) death occurred after 30 days of diagnosis.

The main reasons for mortality in the group of early death were also analyzed. They included bleeding in CNS (8 patients, 50%), infections (5 patients, 31.3%), ATRA syndrome (1 patient, 6.3%), 1 patient (6.3%) with respiratory failure and 1 patient (6.3%) with acute renal failure (Figure 6).

Regarding the time of death, in the ED group 5 patients (31.3%) died prior to treatment and 11 patients during the induction period (68.7%). Regarding the time of death

after 30 days, 5 patients passed away from relapse of the disease, 4 of them with bleeding in CNS and 1 from infection.

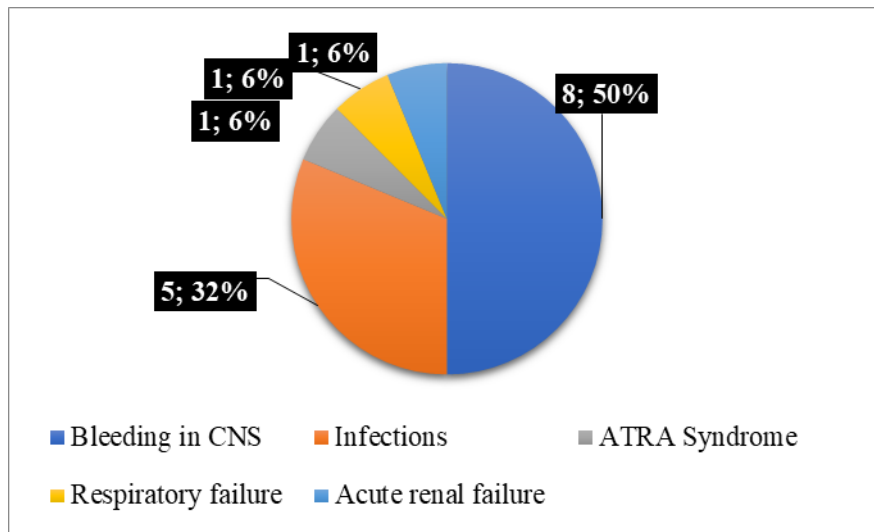


Fig. 6. Causes of early death (<30 days)

Two patients died as a result of refractory disease and 2 patients died during consolidation phase with infection. One patient died from different disease; he had new infection with *Leishmania donovani*. He developed sepsis which was not in correlation with basic disease APL (Figure 7).

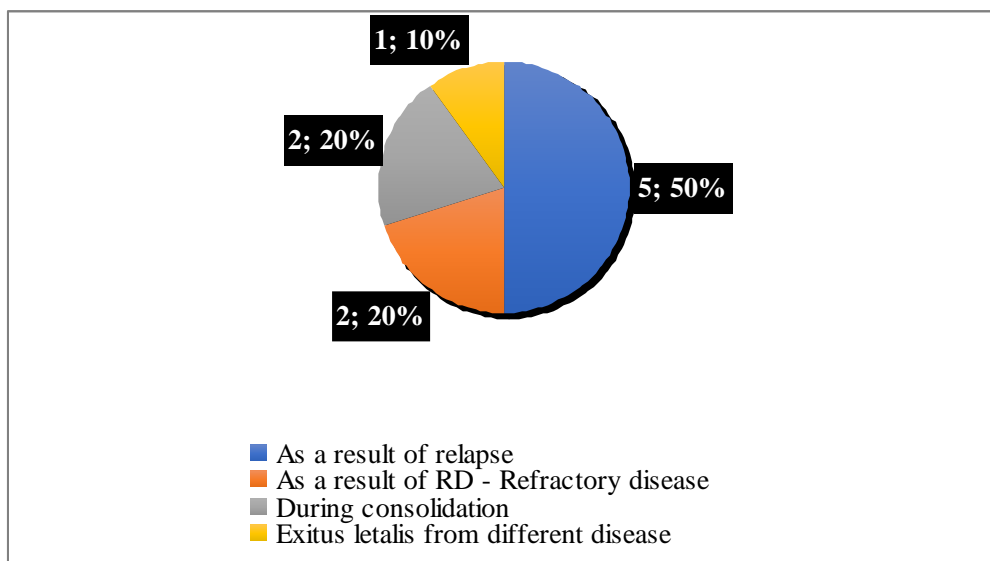


Fig. 7. Causes of death in patients (> 30 days)

Sixteen patients died earlier than 30 days; the factors found to be significantly associated with early death were Sanz risk score, level of WBC, level of platelets, clinical presentation of coagulopathy like massive bleeding and onset of infections (Figures 8a, 8b, 8c, 8d). The more risk score, the higher the rate of early death; 5 (31.1%) patients were with intermediate Sanz score, 9 patients (56.3%) with high risk, and 2 patients (12.5%) were with low risk. The ED rate was higher in high-risk group for WBC>10 x 10⁹/L: 9 patients (56.3%) compared to 7 patients with low risk (43.8%). In regards to platelet count, high risk was

observed in 11 patients (68.8%) and low risk in 5 patients (31.3%). All patients had bleeding and it was the major cause of death.

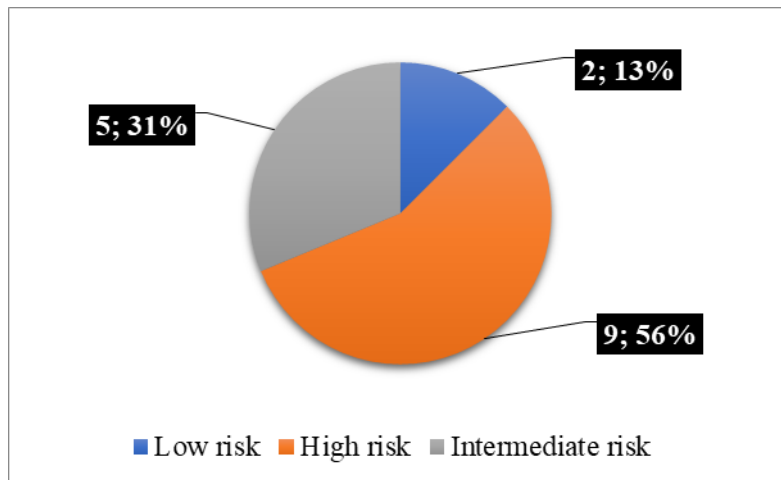


Fig. 8a. Rate of early death by Sanz Score

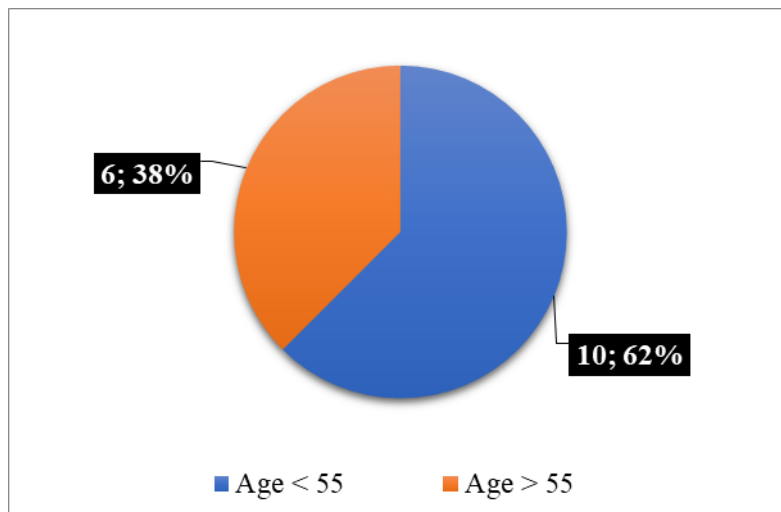


Fig. 8b. Rate of early death by age

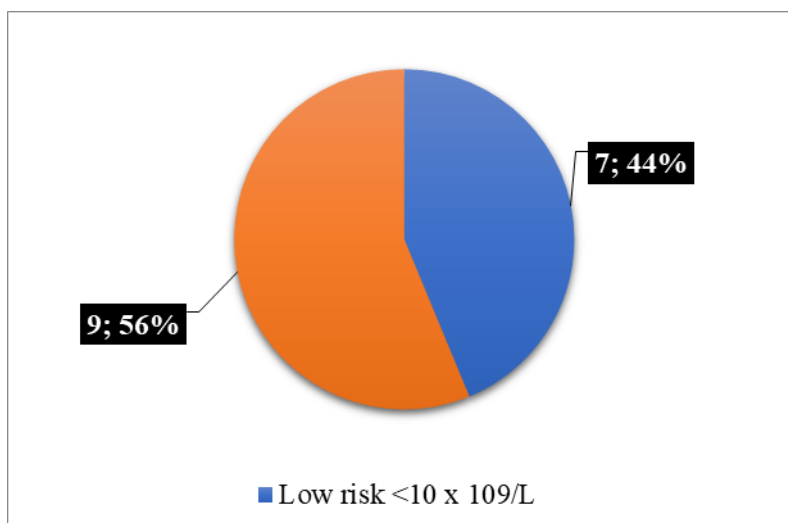


Fig. 8c. Rate of early death by level of WBCs

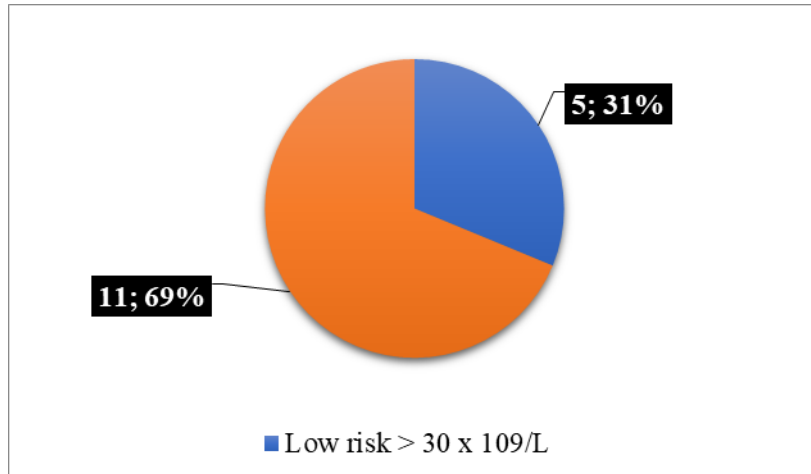


Fig. 8d. Rate of early death by level of platelets

The overall survival in APL patients in the 19-year period showed that 52% of APL patients survived, while death was noted in 47.8% of patients. 45% of patients survived more than 4000 days (death outcome was noted in the first 30 days, 25% survived only 12 days). The average survival time in the 19-year observation period was 1479 days with the most common cause of death being the nature of the disease itself (Figure 9).

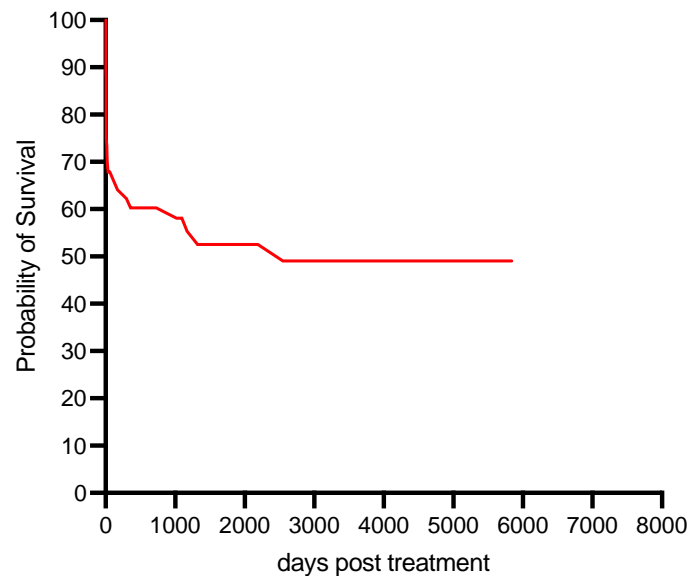


Fig. 9. OS in APL patients in the period 2004 - 2022

Of the total number of treated patients, there were 61% < 55 years and 29% > 55 years with an average survival time of 200 days (in both groups the mortality rate was higher in the first days of diagnosis, and was 34.2% in both groups). The median survival time in patients <55 years was 2535 days, and the median survival time in patients >55 years was 826 days. There was a statistically significant difference ($p= 0.0051$ Hazard ratio 0.3422 95% CI of ratio 0.1249 to 0.9376) (Figure 10).

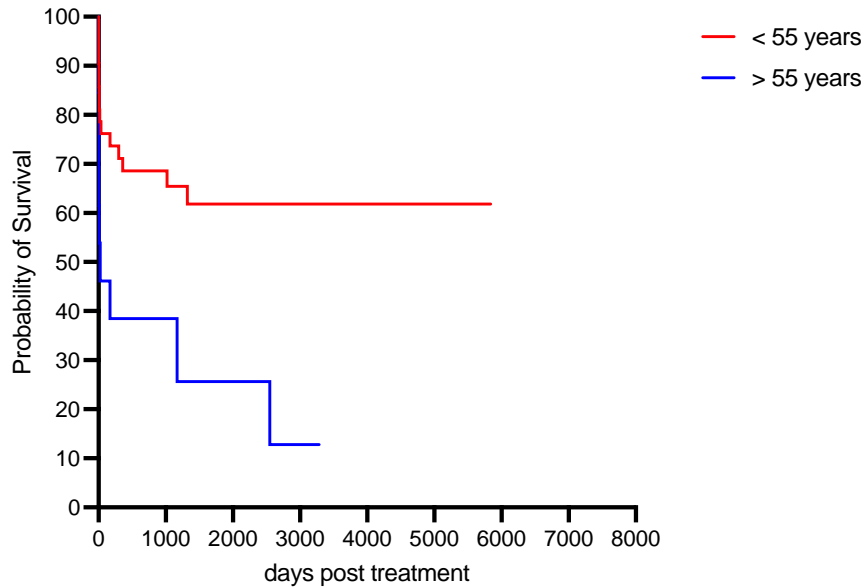


Fig. 10. Plot of overall survival time in APL patients by age (over and under 55 years)

31% of patients with PLT <30x 10⁹/l survived more than 1000 days compared to 62% of patients with PLT >30x 10⁹/l. Mortality was highest in the first 30 days, 35% of both groups died after the start of treatment. Patients with PLT <30x10⁹/l had a median survival time of 558 days, while PLT >30x10⁹/l had a median survival time of 2133 days. (p=0.1535; Hazard ratio 0.5588; 95% CI of ratio 0.2133 to 1.464) (Figure 11).

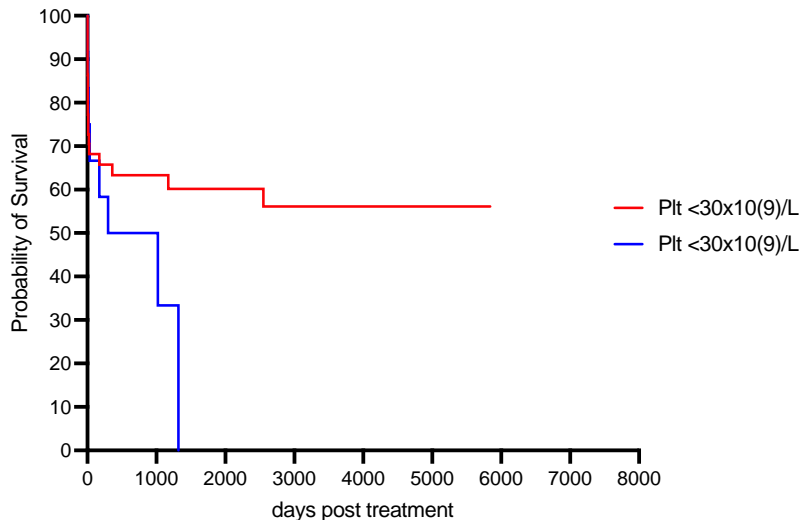


Fig. 11. Plot of overall survival in APL patients in relation to platelet values

62% of patients with high Sanz risk survived more than 1000 days, 41% with intermediate risk survived more than 4000 days, 61% with low risk survived more than 4000 days. On average, patients with low Sanz score risk survived 3180 days, with intermediate 1589 days, with high risk 720 days. Statistical significance was p=0.0178 (Figure 12).

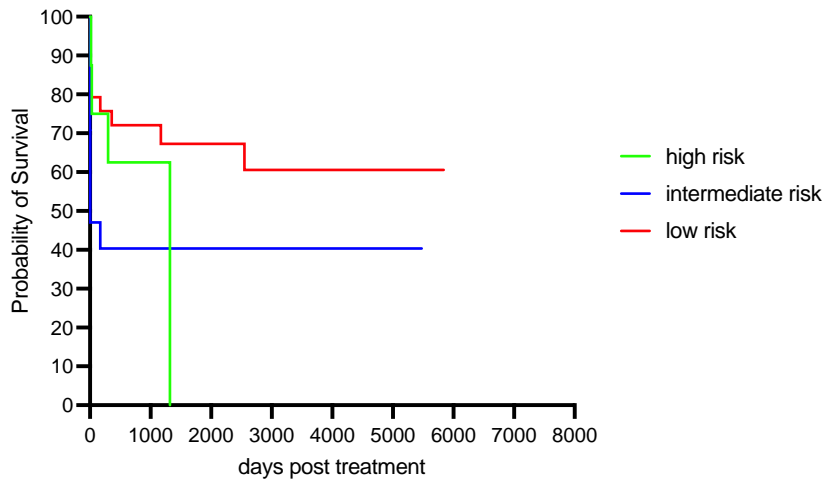


Fig. 12. Overall survival in APL patients according to Sanz risk score

55% of patients with $WBC < 10 \times 10^9/l$ survived more than 4000 days, and only 36% of patients with $WBC > 10 \times 10^9/l$. In both groups, the death rate was higher in the first days, 47% in the first group and 20% in the second group. These clinical findings have confirmed the value of elevated WBC as an independent prognostic risk factor for early mortality ($P=0.0068$; 95% CI of ratio 0.1863 to 1.101; Hazard Ratio (logrank) 0.4530) (Figure 13).

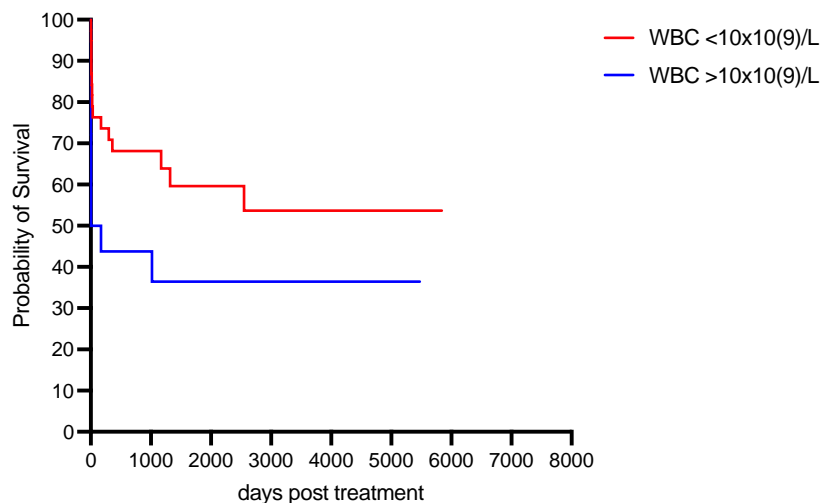


Fig. 13. Plot of overall survival in APL patients in relation to white blood cell values

Discussion

An impressive improvement has been acknowledged in the outcomes of treatments of APL patients, but however the challenges are still existing in the registry-based studies in the real world. In large population-based analyses, and among patients treated in single institutions, the rate of mortality is even higher and can range from 9.6% to 61.5%. Our observations correlate with the literature data, the mortality rate is 47.8% of all APL patients. As noted above, most ED is attributable to bleeding and represents the biggest obstacle to cure APL. The rates of ED remain substantial to this day, especially for patients treated outside of a clinical trial, so any knowledge gained into the determinations of hemorrhagic episodes during induction for APL can potentially result in significant improvements of long-term survival for this disease^[34-36].

Our study indicate that early mortality is currently an underestimated phenomenon. There is an ongoing need to decrease the early death rate (within the first 30 days from diagnosis), which is still the primary cause of treatment failure rather than the resistant disease that is so common for all other subtypes of AML^[37]. Large clinical trials have reported an early death rate of 3-10%^[30,38,39]. This study has shown that Sanz score, high number of white blood cells, low number of platelets, initial clinical presentation of bleeding, DIC, infections, delayed treatment at time of diagnosis are predictors for early death. An explanation for this challenge of early death is the rarity of APL coupled with the fact that the majority of APL patients in some countries are treated outside clinical trials and in smaller centers.

We report ED (61.5%) in our patients, which is high; it could be probably due to a delayed supportive treatment, late visit to a doctor and appropriate medical experience care. In some case we delayed administration of ATRA, because we did not confirm molecular analysis.

Some studies have identified prognostic factors that are capable of predicting early deaths.

Regarding the causes of death, in our study the main cause was hemorrhage in CNS, and the second cause were infections. These findings correlate with other studies which showed hemorrhage as the main cause of death^[40-42].

Some small center reports the infections as main cause of death, where late presentation to the hospital, delayed treatment, absence of isolation rooms in a hospital, lack of accurate microbial cultures, inability of patients to afford expensive drugs like antifungals are given as potential explanations for the high percentage of infections. Limitation of our study is the fact that not all patients with APL have completed induction chemotherapy protocol. During induction, there were 8 patients with early death and two patients during induction and consolidation who died later. Since there was a lack of more aggressive supportive measures and addition of ATO to the induction regimen, the patients with high risk of early death were not treated appropriately. The OS was generally decreased, but was longer in patients that had low Sanz score than in patients who had high Sanz score. High levels of WBC and low levels of PL were shown to be main risk factors for death outcome.

Conclusion

Mutation-targeted therapy has transformed the treatment of APL, and most deaths now occur not from failure to induce or maintain complete remission, but rather from early death-related mortality which depends on the basic disease. To prevent ED prior to treatment, patients with suspected APL should be immediately hospitalized and prioritized as medical emergency, especially high-risk patients. That is the most important approach to patients with APL, even if the diagnosis is not sure, especially in cases when we do not confirm the molecular PML-RAR α fusion. Almost all cases of fatal hemorrhage occur in the first month of APL therapy, with over half occurring within the first week of treatment.

In this kind of situation, aggressive prophylactic transfusion is necessary to maintain high platelet more than 30000-50000/ μ L and cryoprecipitate or fresh frozen plasma to maintain the fibrinogen concentration above 100-150 mg/dl. This approach could reduce bleeding complications which is the main reason for ED. Induction treatment should be started as soon as possible, treatment with ATRA should be started immediately even a diagnosis of APL is still only suspected for APL. Furthermore, there is minimal to no harm if ATRA is given for misdiagnosed APL, but a great potential benefit if diagnosis is confirmed.

These elements should be considered at our Center in order to improve the overall survival and consequently to decrease the early death rates, which is the greatest challenge for the future treatment of APL. High-risk patients with APL and those with relapsed disease

will be another challenge in the story of the evolution of APL treatment. However, further progress is needed, most urgently in reduction of induction mortality and ED.

Conflict of interest statement. None declared.

References

1. Mantha S, Taliman MS, Soff GA. What's new in the pathogenesis of the coagulopathy in acute promyelocytic leukemia? *Curr Opin Hematol* 2016; 23(2): 121-126. Do: 10.1097/MOH.0000000000000221.
2. Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DA, Gralnick HR, et al. Proposals for the classification of the acute leukemias. French-American-British (FAB) co-operative group. *Br J Haematol* 1976; 33(4): 451-458. doi: 10.1111/j.1365-2141.1976.tb03563.x.
3. Sanz MA, Montesinos P, Rayón C, Holowiecka A, De la Serna J, Milone G, et al. Risk-adapted treatment of acute promyelocytic leukemia based on all-trans retinoic acid and anthracycline with addition of cytarabine in consolidation therapy for high-risk patients: further improvements in treatment outcome. *Blood* 2010; 115(25): 5137-5146. doi: 10.1182/blood-2010-01-266007.
4. Vardiman JW, Thiele J, Arber DA, Brunning RD, Borowitz MJ, Porwit A, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. *Blood* 2009; 114(5): 937-951. doi: 10.1182/blood-2009-03-209262.
5. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, et al. The 2016 revision to the world health organization classification of myeloid neoplasms and acute leukemia. *Blood* (2016) 127(20): 2391-2405. doi: 10.1182/blood-2016-03-643544.
6. Yanada M, Matsushita T, Asou N, Kishimoto Y, Tsuzuki M, Maeda Y, et al. Severe hemorrhagic complications during remission induction therapy for acute promyelocytic leukemia: incidence, risk factors, and influence on outcome. *European Journal of Haematology* 2007; 78(3): 213-219. doi: 10.1111/j.1600-0609.2006.00803.x.
7. Ahmad EI, Akl H, Hashem ME, Elgohary TAM. The biological characteristics of adult CD34+ acute promyelocytic leukemia. *Medical Oncology* 2012; 29(2): 1119-1126. doi: 10.1007/s12032-011-9895-y.
8. Albano F, Mestice A, Pannunzio A, Lanza F, Martino B, Pastore D, et al. The biological characteristics of CD34+ CD2+ adult acute promyelocytic leukemia and the CD34- CD2- hypergranular (M3) and microgranular (M3v) phenotypes. *Haematologica* 2006; 91(3): 311-316. PMID: 16531253.
9. Bernard J, Weil M, Boiron M, Jacquillat C, Flandrin G, Marie-François G. Acute promyelocytic leukemia: results of treatment by daunorubicin. *Blood* 1973; 41(4): 489-496. PMID: 4510926.
10. De Thé, H., Le Bras, M., Lallemand-Breitenbach, V., 2012. The cell biology of disease: acute promyelocytic leukemia, arsenic, and PML bodies. *J Cell Biol.* 198, 11–21. Available at: <https://doi.org/10.1083/jcb.201112044>.
11. Wang ZY, Chen Z. Acute promyelocytic leukemia: from highly fatal to highly curable. *Blood* 2008; 111(5): 2505-2515. doi: 10.1182/blood-2007-07-102798.
12. Asou N, Adachi K, Tamura J, Kanamaru A, Kageyama S, Hiraoka A, et al. Analysis of prognostic factors in newly diagnosed patients with acute promyelocytic leukemia: the APL92 study of the Japan Adult Leukemia Study Group (JALSG). *Cancer Chemother Pharmacol* 2001; 48(Suppl 1): S65-S71. <https://doi.org/10.1007/s002800100308>.

13. Choudhry A, DeLoughery TG. Bleeding and thrombosis in acute promyelocytic leukemia. *Am J Hematol* 2012; 87(6): 596-603. doi: 10.1002/ajh.23158.
14. Daver N, Kantarjian H, Marcucci G, Pierce S, Brandt M, Dinardo C, et al. Clinical characteristics and outcomes in patients with acute promyelocytic leukaemia and hyperleucocytosis. *Br J Haematol* 2015; 168(5): 646-653. doi: 10.1111/bjh.13189.
15. Karim F, Shaikh U, Adil SN, Khurshid M. Clinical characteristics, outcome and early induction deaths in patients with acute promyelocytic leukaemia: a five-year experience at a tertiary care centre. *Singapore Med J* 2014; 55(8): 443-447. doi: 10.11622/smedj.2014105.
16. Zhu H, Hu J, Chen L, Zhou W, Li X, Wang L, et al. "The 12-year follow-up of survival, chronic adverse effects and retention of arsenic in patients with acute promyelocytic leukemia. *Blood* 2016; 128(11):1525-8. doi: 10.1182/blood-2016-02-699439.
17. Abaza Y, Kantarjian H, Garcia-Manero G, Estey E, Borthakur G, Jabbour E, et al. "Long term outcome of acute promyelocytic leukemia treated with all-trans-retinoic acid, arsenic trioxide and gemtuzumab". *Blood* 2017; 129(10): 1275-1283. doi: 10.1182/blood-2016-09-736686.
18. Platzebecker U, Avvisati G, Cicconi L, Thiede C, Paoloni F, Vigneti M, et al. Improved outcomes with retinoic acid and arsenic trioxide compared with retinoic acid and chemotherapy in non-High-Risk acute promyelocytic leukemia: Final results of the randomized Italian-German APL0406 trial. *J Clin Oncol* 2017; 35(6): 605-612. doi: 10.1200/JCO.2016.67.1982.
19. Iland HJ, Collins M, Bradstock K, Supple SG, Catalano A, Hertzberg M, et al. Use of arsenic trioxide in remission induction and consolidation therapy for acute promyelocytic leukemia in the Australasian leukemia and lymphoma group (ALLG) APLM4 study: A non-randomised phase 2 trial. *Lancet Haematol* 2015; 2(9): e357-e366. doi: 10.1016/S2352-3026(15)00115-5.
20. Watts JM, Tallman MS. Acute promyelocytic leukemia: what is the new standard of care? *Blood Rev* 2014; 28(5), 205-212. doi: 10.1016/j.blre.2014.07.001.
21. McClellan JS, Kohrt HE, Coutre S, Gotlib JR, Majeti R, Alizadeh AA, et al. "Treatment advances have not improved the early death rate in acute promyelocytic leukemia. *Haematologica* (2023)samo vo 2012 go naogjam, neznam od kade 2023 2012; 97(1):133-136. doi: 10.3324/haematol.2011.046490.
22. Chang H, Kuo MC, Shih LY, Dunn P, Wang PN, Wu JH, et al. Clinical bleeding events and laboratory coagulation profiles in acute promyelocytic leukemia. *Eur J Haematol* 2012; 88(4): 321-328. doi: 10.1111/j.1600-0609.2011.01747.x.
23. Siddikuzzaman, Guruvayoorappan C, Berlin Grace VM. All trans retinoic acid and cancer. *Immunopharmacology and immunotoxicology* 2011; 33(2): 241-249. doi: 10.3109/08923973.2010.521507.
24. Di Bona E, Avvisati G, Castaman G, Luce Vegna M, De Sanctis V, Rodeghiero F, et al. Early haemorrhagic morbidity and mortality during remission induction with or without all-trans retinoic acid in acute promyelocytic leukaemia. *Br J Haematol* 2000; 108(4): 689-695. doi: 10.1046/j.1365-2141.2000.01936.x.
25. Sanz MA, Lo Coco F, Martin G, Avvisati G, Rayon C, Barbui T, et al. Definition of relapse risk and role of nonanthracycline drugs for consolidation in patients with acute promyelocytic leukemia: a joint study of the PETHEMA and GIMEMA cooperative groups. *Blood* 2000; 96, 1247-1253. <https://doi.org/10.1182/blood.V96.4.1247>.
26. Rego EM, Kim HT, Ruiz-Arguelles GJ, Undurraga MS, Uriarte Mdel R, Jacomo, RH, et al. Improving acute promyelocytic leukemia (APL) outcome in developing

- countries through networking, results of the International Consortium on APL. *Blood* 2013; 121(11): 1935-1943. doi: 10.1182/blood-2012-08-449918.
27. Rego EM, De Santis GC. Differentiation syndrome in promyelocytic leukemia: clinical presentation, pathogenesis and treatment. *Mediterr J Hematol Infect Dis* 2011; 3(1): e2011048. doi: 10.4084/MJHID.2011.048.
 28. Rogers JE, Yang D. Differentiation syndrome in patients with acute promyelocytic leukemia. *J Oncol Pharm Pract* 2012; 18(1): 109-114. doi: 10.1177/1078155211399163.
 29. Sanz MA, Fenaux P, Tallman MS, Estey EH, Löwenberg B, Naoe T, et al. Management of acute promyelocytic leukemia: updated recommendations from an expert panel of the European LeukemiaNet. *Blood* 2019; 133(15): 1630-1643. doi: 10.1182/blood-2019-01-894980.
 30. Lo-Coco F, Avvisati G, Vignetti M, Thiede C, Orlando S, Iacobelli S, et al. Retinoic acid and arsenic trioxide for acute promyelocytic leukemia. *N Engl J Med* 2013; 369(2): 111-121. doi: 10.1056/nejmoa1300874.
 31. Douer D, Zickl L, Schiffer C, Appelbaum F, Feusner J, Shepard L, et al. Late relapses following all-trans retinoic acid for acute promyelocytic leukemia are uncommon, respond well to salvage therapy and occur independently of prognostic factors at diagnosis: Long-term follow up of north American intergroup study I0129. *Blood* 2011; 118(21): 83. doi: 10.1182/blood.V118.21.83.83.
 32. Crespo-Solis E, Contreras-Cisneros, J, Demichelis-Gomez R, Rosas-Lopez A, Vera-Zertuche JM, Aguayo A, et al. Survival and treatment response in adults with acute promyelocytic leukemia treated with a modified International Consortium on Acute Promyelocytic Leukemia protocol. *Rev Bras Hematol Hemoter* 2016; 38(4): 285-290. doi: 10.1016/j.bjhh.2016.08.002.
 33. Iyer SG, Elias L, Stanchina M, Watts J. The treatment of acute promyelocytic leukemia in 2023: Paradigm, advances and future directions. *Front in Oncol* 2023; 12: 1062524. doi: 10.3389/fonc.2022.1062524.
 34. Park JH, Qiao B, Panageas KS, Schymura MJ, Jurcic JG, Rosenblat TL, et al. Early death rate in acute promyelocytic leukemia remains high despite all-trans retinoic acid. *Blood* 2011; 118(5): 1248-1254. doi: 10.1182/blood-2011-04-346437.
 35. Paulson K, Serebrin A, Lambert P, Bergeron B, Everett J, Kew A, et al. Acute promyelocytic leukemia is characterized by stable incidence and improved survival that is restricted to patients managed in leukemia referral centers: a pan-Canadian epidemiological study. *Br J Haematol* 2014; 166: 660-666. doi: 10.1111/bjh.12931.
 36. Thomas, X. Acute Promyelocytic Leukemia: A History over 60 Years-From the Most Malignant to the most Curable Form of Acute Leukemia. *Oncology and Therapy* 2019; 7: 33-65. <https://doi.org/10.1007/s40487-018-0091-5>.
 37. Rahmé R, Thomas X, Recher C, Vey N, Delaunay J, Deconinck E, et al. Early death in acute promyelocytic leukemia (APL) in French centers: a multicenter study in 399 patients. *Leukemia* 2014; 28: 2422-2424. <https://doi.org/10.1038/leu.2014.240>.
 38. Iland HJ, Bradstock K, Supple SG, Catalano A, Collins M, Hertzberg M, et al. Australasian Leukemia and Lymphoma Group. All-trans-retinoic acid, idarubicin, and IV arsenic trioxide as initial therapy in acute promyelocytic leukemia (APML4). *Blood* 2012; 120(8): 1570-1580. doi: 10.1182/blood-2012-02-410746.
 39. Sanz MA, Montesinos P. Risk-adapted treatment for low and intermediate-risk acute promyelocytic leukemia. *Clin Lymph Myeloma Leuk* 2010; 10(suppl 3): S130-S134. doi: 10.3816/CLML.2010.s.025.
 40. Serefhanoglu S, Buyukasik Y, Goker H, Sayinalp N, Haznedaroglu IC, Aksu S, et al. Clinical features and outcomes of 49 Turkish patients with acute promyelocytic

- leukemia who received ATRA and anthracyclines (PETHEMA protocol) therapy. *Leuk Res* 2010; 34(12): e317-e319. doi: 10.1016/j.leukres.2010.07.027.
41. Jillella AP, Kota VK. The global problem of early deaths in acute promyelocytic leukemia: a strategy to decrease induction mortality in the most curable leukemia. *Blood Rev* 2018; 32(2): 89-95. doi: 10.1016/j.blre.2017.09.001.
 42. Sanz MA, Montesinos P, Vellenga E, Rayón C, de la Serna J, Parody R, et al. Risk-adapted treatment of acute promyelocytic leukemia with all-trans retinoic acid and anthracycline mono-chemotherapy: long-term outcome of the LPA 99 multicenter study by the PETHEMA Group. *Blood* 2008; 112(8): 3130-3134. <https://doi.org/10.1182/blood-2008-05-159632>.