Factors affecting treatment outcome of acute promyelocytic leukemia in Egyptian patients

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Abstract

Aim: Acute promyelocytic leukemia (APL) is a peculiar subtype of acute myeloid leukemia clinically and morphologically. To date, only a few studies reported the treatment outcome of APL in developing countries. Thus, we investigated the challenges and factors affecting APL treatment in Egypt. Material and Method: This study included 27 APL patients treated at Kasr Al Ainy Center of Clinical Oncology and Nuclear Medicine (NEMROCK) – Cairo University hospital, Egypt from 2010 till 2014. Results: The mean age at presentation was 35 years, and intermediate and high-risk Sanz scores constituted 44% and 30% of patients, respectively. Complete remission (CR) was achieved by 17 patients (63%), 1 patient had a refractory disease (3.7%), and the response could not be evaluated in 5 patients. No deaths were encountered before treatment, and early mortality rate was 14.8% (n=4). All patients in CR received consolidation therapy, and molecular remission was achieved by 14 patients (82.4%). By December 2015, relapse occurred in 5 patients (29.4%). The median disease-free survival (DFS) was 27.1 months, the mean overall survival (OS) was 84.4 months, and the median OS was not reached. Factors affecting survival included: body mass index (DFS: p-0.012, OS: p-0.009), type of induction regimen (OS: p-0.007), treatment interruption (OS: p-0.035), number of consolidation cycles (OS: p-0.001), duration of maintenance therapy (DFS: p-0.018) and response to salvage therapy (OS: p-0.046). Discussion: Our findings elucidate the challenges met by developing countries owing to limited resources and financial constraints.

Keywords

Acute Myeloid Leukemia (AML); Acute Promyelocytic Leukemia (APL); Survival; Mortality Rate; Relapse.

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Introduction

Acute myeloid leukemia (AML) is one of the challenging hematological malignancies worldwide. In adults, it is the commonest type of leukemia with the highest 5-year relative survival reported in acute promyelocytic leukemia (APL) patients compared to all other subtypes [1]. The outcome of APL patients has improved over the years and patients who achieved complete remission (CR) for at least 3 years have a very low incidence of late relapses [2]. Several clinical situations represent a daunting challenge in the management of AML patients, posing a high risk of increased morbidity and mortality. In APL patients, hemorrhagic complications remain the most frequent cause of mortality. Thus, prompt diagnosis and recognition of any coagulation defect is imperative at presentation [3].

This retrospective study sheds light on challenges and treatment outcome of APL patients at a single cancer center in Egypt, during the period from January 2010 to December 2014.

Material and Method

The current study was designed to evaluate treatment outcome of APL patients treated at Kasr Al Ainy Center of Clinical Oncology and Nuclear Medicine (NEMROCK) – Cairo University Hospital, Egypt. During the period from January 2010 to December 2014, 27 APL cases were treated at our center, and they represent our study cohort. The study was approved by the ethical committee and institutional review board.

Patients' medical records were reviewed for baseline clinical characteristics at presentation. Patients diagnosed with APL were identified by the presence of t(15;17), and risk stratified according to Sanz score [4]. All-trans-retinoic-acid (ATRA) was initiated immediately at presentation based on clinical and/or morphological suspicion. A dose of 45mg/m^2 in 2 divided doses was received till morphological remission or for a maximum of 30 days. When the diagnosis of APL was confirmed, anthracyclines were added to ATRA for 3 days: idarubicin 12 mg/m^2/day, doxorubicin 25mg/m^2/day or mitoxantrone 10mg/m^2/day in case of unavailability of idarubicin. Cytarabine was added in the context of "7+3 protocol" in 5 patients, while ATRA single agent was reserved for old patients with a poor general condition.

After complete recovery of blood counts and clearance of blast cells, bone marrow examination was done for response assessment. Patients who were refractory to treatment received a second induction course using the same or alternative anthracycline, with cytarabine 100 mg/m^2/day continuous infusion for 7 days in initially high-risk patients. Patients in remission received 1-3 consolidation cycles of ATRA 45 mg/m^2 for 15 days in combination with an anthracycline for 3 days. Molecular status was assessed using reverse transcriptase polymerase chain reaction (RT-PCR) for PML-RARA transcripts. Patients who achieved complete molecular remission (CR) were scheduled for risk-adapted maintenance therapy. Low-risk patients were not offered maintenance treatment, intermediate risk patients were offered maintenance for 6 months, while high-risk patients were offered treatment for 2 years. Maintenance therapy consisted of 6-mercaptopurine 60mg/m^2/day, oral methotrexate 20mg/m^2 weekly and ATRA 45mg/m^2 for 15 days every 3 months.

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 14 (SPSS Inc., Chicago, IL) for Windows. Data was presented as numbers and percentages or mean ± standard deviation. OS was calculated from the date of the first presentation to the date of death. DFS was calculated from the date of bone marrow-documented CR to the date of relapse. The Kaplan-Meier method was used for survival analysis, and the significance of the difference in survival was determined using the log-rank test.

Results

Patients' characteristics

Twenty-seven patients diagnosed as APL were identified in our study, and their baseline characteristics are shown in table 1. A slight female predominance was noted (male: female 1:1.25), and the majority of patients (74.1%) aged between 20 and 60 years. More than half of patients presented with ECOG performance status 1 and bleeding tendency was the most common presenting symptom. All patients suffered from anemia and thrombocytopenia, while only 1 patient presented with hyperleukocytosis (defined as TLC >100X10^3/mL). Intermediate and high-risk Sanz scores constituted 44% and 30% of our patients' cohort, respectively.

Table 1. Baseline characteristics of 27 APL patients.

Variable	Number	Percentage
Gender		
Male	12	44.4%
Female	15	55.6%
Age		
Range	17-67	
Mean	35	
<20 years	3	11.1%
20-60 years	20	74.1%
>60 years	4	14.8%
Performance status (ECOG)		
1	15	55.6%
2	7	25.8%
3	5	18.6%
Body mass index		
Range	15.1-38.6	
Mean	26	
Underweight (<18.5)	2	7.4%
Normal (18.5 - ≤25)	7	25.8%
Overweight (>25 – 30)	2	7.4%
Obese (>30)	6	22.2%
Unknown	10	37.2%
Clinical manifestations		
Anemic symptoms	17	63%
Bleeding tendency	23	85%
Recurrent infections	12	44.4%
Hemoglobin level (g/dL)		
Range	3.7-9	
Mean	6.5	
Total leukocyte count (/mL)		
Range	0.6-358 X10^3	
Mean	33 X10^3	
Platelet count (/mL)		
Range	7-59 X10^3	
Mean	24.4 X10^3	
Sanz score		
Low risk	2	7%
Intermediate risk	12	44%
High risk	8	30%
Unknown	5	19%

APL: acute promyelocytic leukemia; ECOG: the Eastern Cooperative Oncology Group

Treatment results

All 27 APL patients started receiving ATRA upon their presentation, based on clinical and/or laboratory suspicion. The majority of patients (63%) received either doxorubicin or mitoxantrone in combination with ATRA, while 14.8% of patients received single-agent ATRA (table 2). Only 3 patients (11.1%) necessitated treatment interruption due to development of either differentiation syndrome or febrile neutropenia. First complete remission (CR1) was achieved by 15 patients (55.6%), 3 patients (11.1%) were refractory to treatment, while treatment-related mortality was encountered in 4 cases (14.8%). The response was inevaluable in 5 patients due to loss of follow up.

The refractory cases were scheduled for a second induction cycle in addition to ATRA. Two patients received 7+3 protocol and achieved CR, while one patient had persistent refractory disease after receiving doxorubicin. Overall, CR was achieved by 17 patients (63%), and 1 patient had persistent refractory disease (3.7%). No deaths were encountered before starting treatment, and 4 patients died within 30 days from induction therapy (14.8%).

All patients in CR received 1-3 consolidation cycles. Fourteen patients (82.4%) achieved molecular remission and received maintenance treatment, while 3 patients lost to follow up and didn't receive any further treatment. By December 2015, relapse occurred in 5 patients (29.4%), while 12 patients (70.6%) were still alive in remission. Out of 5 relapsed patients, 1 patient died of intracranial hemorrhage before starting active treatment. Salvage therapy was given in 4 patients; 3 of them achieved the second remission, and 1 died of uncontrolled infection.

Table 2. Results of first induction therapy in 27 APL patients.

Variable	Number	Percentage
Induction regimen (+ATRA)		
7+3 protocol	5	18.5%
Doxorubicin	9	33.3%
Idarubicin	1	3.7%
Mitoxantrone	8	29.7%
ATRA single agent	4	14.8%
Treatment interruption		
Yes	3	11.1%
No	24	88.9%
Response		
CR1	15	55.6%
Refractory	3	11.1%
Death	4	14.8%
Unknown	5	18.5%

APL: acute promyelocytic leukemia; ATRA: all-trans-retinoid acid; CR1: first complete remission.

Survival and mortality outcomes

Of our cohort of 27 APL patients, 17 patients achieved complete remission, and their median disease-free survival (DFS) was 27.1 months. The mean overall survival (OS) of our 27 APL cases was 84.4 months (95% CI: 51.4 – 117.4), and the median OS was not reached. Several factors were proven to significantly affect survival in our patients, including body mass index (BMI), type of first induction regimen, its interruption, number of consolidation cycles received, duration of maintenance therapy and response to salvage therapy. On the other hand, age, gender, performance status, and hyperleukocytosis lacked significant impact on survival outcomes.

BMI has been shown to influence both disease-free and overall survival significantly. Normal BMI patients had the highest survival outcomes while underweight patients had the lowest outcomes when compared to other BMI groups (p-value 0.009) (figure 1 and 2). Patients who received single-agent ATRA as first induction had a poor median OS of 5.6 months when compared to those who received ATRA in combination with chemotherapy (median OS was not reached) (p-value 0.007) (figure 3). Moreover, interruption of induction therapy significantly altered the survival of our patients, as illustrated in figure 4. Patients who necessitated treatment interruption had a lower median OS of 9.2 months, as opposed to those who completed their full course of treatment (median OS was not reached) (p-value 0.035).

As regards post-remission treatment, patients who received only 1 consolidation cycle had the lowest overall survival outcome (p 0.001) when compared to those who completed 3 cycles. On the other hand, patients who received ≥ 12 months of maintenance therapy had significantly longer DFS than those received < 12 months (figure 5). Also, patients who were refractory to salvage therapy had an OS of 23.8 months, as opposed to patients who achieved CR2 (median OS was not reached) (p-value 0.046).

A total of 7 patients (26%) died by December 2015 in our study. Treatment-related deaths accounted for 71% of all deaths; 57% of deaths occurred during induction treatment (4 patients: 1 died of intracranial hemorrhage, and 3 died of febrile neu-

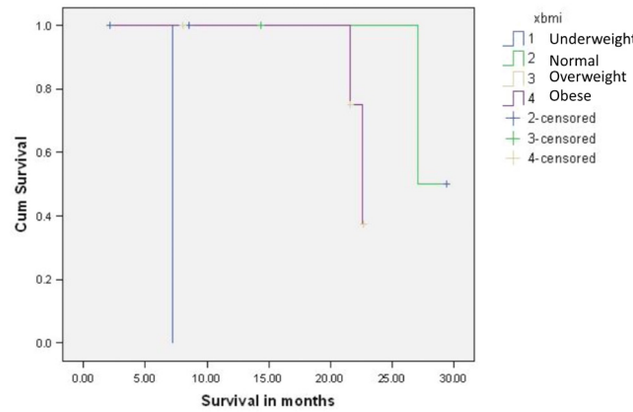

Figure 1. Impact of BMI on DFS of 17 APL patients in remission.

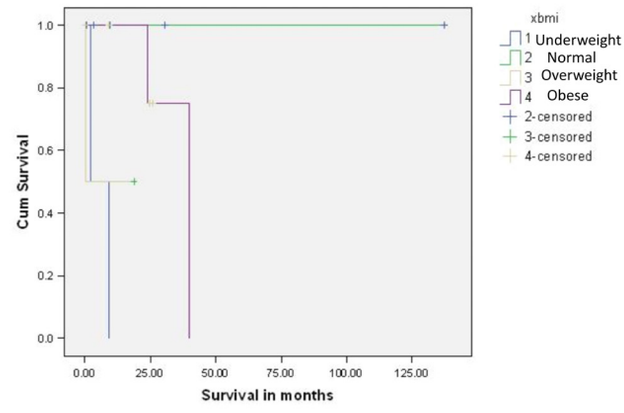

Figure 2. Impact of BMI on overall survival in 27 APL patients.

tropenia), while 14% occurred during salvage therapy. On the other hand, disease-related mortality accounted for 29% of deaths due to either relapse or refractory disease.

Discussion

APL is a peculiar subtype of AML that usually presents with abrupt onset, with a high early mortality rate because of hemorrhage and coagulopathy. Once the diagnosis is suspected, it should be managed as a medical emergency, and treatment must be started immediately with ATRA therapy **[5].** A risk-adapted strategy was designed by the cooperative group Programa Español de Tratamientos en Hematología (PETHEMA) based on the combination of ATRA and anthracyclines (PETHEMA LPA99 and LPA2005 trials) and demonstrated high anti-leukemic efficacy in APL patients **[6].**

This study included 27 APL patients, constituting 23% of AML patients treated at our center during the period 2010-2014. A close proportion of APL among AML diagnoses has been reported in Mexico (20%). Whereas a higher proportion has been documented in Brazil (28%), and Latin America (37.5%) **[7].** Ages of our patients ranged from 17 to 67 years, with a mean of 35 years. A male: female ratio of 1:1.25 was demonstrated showing a slight female predominance. The bleeding tendency was the most frequent clinical manifestation at presentation (85% of cases), and the majority of our patients were of intermediate risk Sanz score (44%), while 30% were high risk. Comparable epidemiological features of Egyptian patients were demonstrated in a retrospective study held at National Cancer Institute, Cairo. The median age was 29 years (range: 3-72), and there was a slight male predominance (53%). Bleeding was the presenting symptom in 79% of cases, whereas intermediate and high-risk Sanz scores constituted 49% and 34% of patients, respectively **[8].**

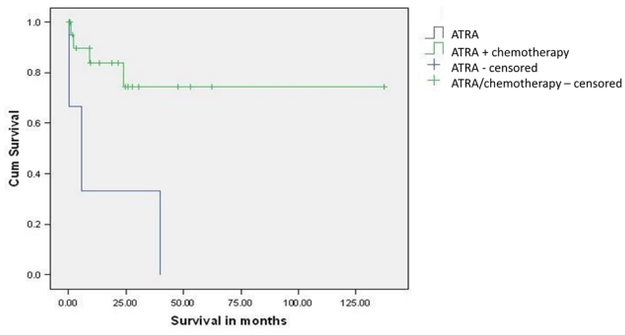

Figure 3. Overall survival of 27 APL patients according to type of 1st induction regimen.

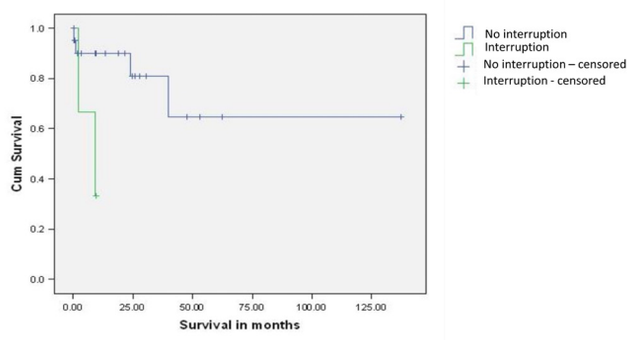

Figure 4. Impact of induction treatment interruption on overall survival of 27 APL patients.

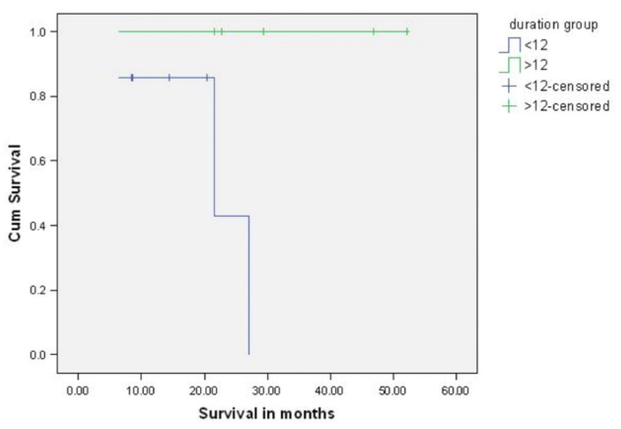

Figure 5. DFS of 14 APL patients who received maintenance therapy according to its duration.

When BMI was used for patient stratification, normal BMI was the most common group followed by obesity (25.8% and 22.2%, respectively). Our study revealed a strong correlation between BMI and both DFS and OS, as normal BMI patients had the highest survival outcomes compared to other BMI groups (DFS p=0.012, OS p=0.009). This finding is in concordance with a study conducted on 446 APL patients to investigate the role of obesity as an adverse prognostic factor. It was shown that obese APL patients had significantly shorter OS and DFS than non-obese patients **[9].**

Several treatment variables were proven to affect the survival of our patients adversely. Although the use of ATRA single agent was restricted to 4 elderly patients with debilitating co-morbidities, it was associated with a significant reduction of OS (5.6 months vs. OS not reached in combination regimen) (p=0.007). However, the small number of cases receiving ATRA cannot reliably account for significance. The poor outcome could also be partly attributed to the old age and poor performance status of those patients.

During induction therapy, adverse events frequently impose considerable clinical challenges that necessitate treatment interruption. In this study, 2 patients developed differentiation syndrome and 1 patient suffered from severe febrile neutropenia during induction therapy. The interruption of treatment significantly hampered OS in those patients when compared to those who completed their treatment course (9.2 months vs. OS not reached, respectively) (p=0.035). This observation emphasizes the importance of timely delivery of treatment and optimal supportive care in APL patients.

After two induction cycles, the overall CR rate in our study was 63% which is markedly lower than that reported in PETHEMA LPA99 and APL2000 trials (92.9% and 97.2%, respectively). Moreover, our early mortality rate was higher than that reported in those trials (14.8% vs. 6.8% in PETHEMA LPA99 vs. 2.8% in APL2000 trials) **[10].** However, it is noteworthy that mortality rates from several institute-based or population-based studies have been shown to be considerably higher than in clinical trials. The highly selected patients within a clinical trial setting do not reflect the population characteristics accurately. In addition, clinical trials do not fully account for patients who die early of hemorrhagic complications. This is why population studies are more likely to represent the real-world incidence of early mortality rates **[11].**

Several studies concluded that early mortality rates in APL patients remain to be a daunting challenge, particularly in developing countries. An earlier study in Egyptian patients reported lower induction mortality (4.8% vs. 14.8% in our study); however, another 7.5% of patients died early before treatment, which was not encountered in our study **[8].** Another study in the United Arab Emirates revealed an early mortality rate of 11.9%, a slightly lower figure than that reported in our patients **[12].** Early APL deaths seem to be a distressing problem in some developed countries as well. A Canadian population-based study and a SEER analysis of patients treated in the United States reported higher early mortality rates than that observed in our institute (21.8% vs. 17.3% vs. 14.8%, respectively) **[11, 13].**

Other treatment variables that were shown to affect survival in our patients include the number of consolidation cycles and duration of maintenance treatment. All patients in remission received 1-3 consolidation cycles, where patients who completed 3 cycles exhibited the longest OS (p=0.001). All patients in molecular remission following consolidation treatment proceeded to receive maintenance therapy, the duration of which impacted DFS. Half of our patients received maintenance for less than 12 months, which resulted in a significantly shorter DFS than those who received treatment for ≥12 months (p=0.018). However, no difference was noted in OS. Of note, all patients who received maintenance treatment for less than 12 months were of the intermediate risk group, except for 1 high-risk patient who was still on maintenance therapy by the end of the study.

In contrast with our results, the AIDA 0493 trial demonstrated that maintenance treatment did not provide any survival advantages for patients achieving molecular remission. Bearing in mind that the relative benefit of maintenance therapy depends on prior induction and consolidation treatment, the intensive regimens used in that trial might have abolished the possible benefit of maintenance treatment **[14].** On the other hand, a meta-analysis of 10 randomized trials including 2,072 APL patients concluded that any maintenance treatment compared with observation prolongs DFS but not OS **[15].**

Out of 17 patients in remission in our study, 5 patients (29.4%) eventually relapsed. Two of them had lost follow up after consolidation cycles and did not receive maintenance treatment, and the remaining three patients had received maintenance for less than 12 months. One of the relapsed patients died of intracranial hemorrhage before commencing salvage therapy, while the remaining 4 patients received ATRA in combination with either adriamycin in 3 patients, or "7+3 protocol" in 1 patient. A second complete remission was achieved in 3 cases (75%) and 1 patient (25%) died of uncontrolled infection. Both PETHEMA LPA99 and APL2000 trials reported lower relapse incidence and higher deaths in remission than that experienced by our patients. The cumulative incidence of relapse at 3 years was 7.4% and 12% respectively, while 29.4% of our patients eventually relapsed within 3 years. Death in remission occurred in 1.3% and 2.9% of patients in both trials respectively, whereas none of our patients died in remission **[10].**

In conclusion, we realize the several limitations of a retrospective study design and a small number of patients. However, it is obvious that treatment outcome of APL in Egyptian patients is in dire need of improvement. The inconsistent supply of chemotherapeutics and supportive care facilities, as well as financial constraints, are some of the greatest challenges faced by healthcare policies in a developing country like Egypt.

Ethical Responsibilities

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of interest

All authors declare there are no conflict of interests.

Source of fund

None.

References

1. Dores GM, Devesa SS, Curtis RE, Linet MS, Morton LM. Acute leukemia incidence and patient survival among children and adults in the United States, 2001-2007. Blood. 2012; 119(1): 34-43. Doi: 10.1182/blood-2011-04-347872.
2. Wang ZY, Chen Z. Acute promyelocytic leukemia: from highly fatal to highly curable. Blood. 2008; 111(5): 2505-15. Doi: 10.1182/blood-2007-07-102798.
3. Breen KA, Grimwade D, Hunt BJ. The pathogenesis and management of the coagulopathy of acute promyelocytic leukaemia. British journal of haematology. 2012; 156(1): 24-36. Doi: 10.1111/j.1365-2141.2011.08922.x.
4. 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 monochemotherapy: long-term outcome of the LPA 99 multicenter study by the PETHEMA Group. Blood. 2008; 112(8): 3130-4. Doi: 10.1182/blood-2008-05-159632.
5. Yoo ES. Recent advances in the diagnosis and management of childhood acute promyelocytic leukemia. Korean journal of pediatrics. 2011; 54(3): 95-105. Doi: 10.3345/kjp.2011.54.3.95.
6. 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): 5137–46. Doi: 10.1182/blood-2010-01-266007.
7. Testi AM, D'Angiò M, Locatelli F, Pession A, Coco FL. Acute promyelocytic leukemia (APL): Comparison between children and adults. Mediterranean journal of hematology and infectious diseases. 2014; 6(1): e2014032. Doi: 10.4084/MJHID.2014.032.
8. Khorshid O, Diaa A, El Moaty MA, El Fatah RA, El Dessouki I, El Hamid MA, et al. Clinical features and treatment outcome of acute promyelocytic leukemia patients treated at cairo national cancer institute in Egypt. Mediterranean journal of hematology and infectious diseases. 2011; 3(1): e2011060. Doi: 10.4084/MJHID.2011.060.
9. Castillo JJ, Mulkey F, Geyer S, Kolitz JE, Blum W, Powell BL, et al. Relationship between obesity and clinical outcome in adults with acute myeloid leukemia: A pooled analysis from four CALGB (alliance) clinical trials. American journal of hematology. 2016; 91(2): 199-204. Doi: 10.1002/ajh.24230.
10. Ades L, Sanz MA, Chevret S, Montesinos P, Chevallier P, Raffoux E, et al. Treatment of newly diagnosed acute promyelocytic leukemia (APL): a comparison of French-Belgian-Swiss and PETHEMA results. Blood. 2008; 111(3): 1078-84. Doi: 10.1182/blood-2007-07-099978.
11. 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): 1248-54. Doi: 10.1182/blood-2011-04-346437.
12. Hassan IB, Al Zaabi MR, Alam A, Hashim MJ, Tallman MS, Kristensen J. Characteristics features and factors influencing early death in Acute promyelocytic leukemia; Experience from United Arab Emirates (UAE). International Journal of Hematology. 2017; 106(1): 90-8. Doi: 10.1007/s12185-017-2211-7.
13. Paulson K, Serebrin A, Lambert P, Bergeron J, Everett J, Kew A, et al. Acute promyelocytic leukaemia is characterized by stable incidence and improved survival that is restricted to patients managed in leukaemia referral centres: a pan-Canadian epidemiological study. British journal of haematology. 2014; 166(5): 660-6. Doi: 10.1111/bjh.12931.
14. Avvisati G, Lo-Coco F, Paoloni FP, Petti MC, Diverio D, Vignetti M, et al. AIDA 0493 protocol for newly diagnosed acute promyelocytic leukemia: very long-term results and role of maintenance. Blood. 2011; 117(18): 4716-25. Doi: 10.1182/blood-2010-08-302950.
15. Muchtar E, Vidal L, Ram R, Gafter-Gvili A, Shpilberg O, Raanani P. The role of maintenance therapy in acute promyelocytic leukemia in the first complete remission. Cochrane Database Syst Rev. 2013; 3: CD009594. Doi: 10.1111/ajco.12003.

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