Received: November 30, 2025
Accepted: April 29, 2026

Acad Med J 2026;6(2):131-138
UDC:616.155.392.8:{602.9:611.018.5:[616-089.843
Case report

CHALLENGING POST-TRANSPLANT COURSE AND MULTIORGAN COMPLICATIONS IN FLT3-POSITIVE ACUTE MYELOID LEUKEMIA

Mojsovska Tara [1,2], Ridova Anastasovska Nevenka [1,2], Gjeorgjieva Janev Olivera [1,2], Purde Merve [1], Stojanoski Martin [1], Chadievski Lazar [1,2], Stojanoski Zlate [1,2], Krstevska Balkanov Svetlana [1,2], Panovska Stavridis Irina [1,2], Pavkovikj Marica [1,2], Genadieva Stavrikj Sonja [1,2], Pivkova Veljanovska Aleksandra [1,2]

[1]University Clinic for Hematology - Skopje, Republic of N. Macedonia
[2]Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Republic of N. Macedonia
e-mail: tara-bt@hotmail.com

Abstract

Introduction: FLT3-mutated acute myeloid leukemia (AML) represents a biologically aggressive subtype associated with high relapse rates and poor overall survival. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains the most effective curative therapy, yet it carries substantial risk of transplant-related morbidity and mortality.

Case report: We report the case of a 42-year-old woman diagnosed with FLT3-ITD positive AML who underwent several chemotherapy regimens and achieved complete molecular remission prior to a matched unrelated donor allo-HSCT (9/10, MM in HLA-A). Following myeloablative conditioning (BuCy-ATG), engraftment occurred by day +19. The post-transplant course was complicated by cytomegalovirus (CMV) reactivation (day +28), acute graft-versus-host disease (aGvHD) with severe cutaneous and gastrointestinal involvement (day +31), and transplant-associated thrombotic microangiopathy (TA-TMA) accompanied by hemolysis, thrombocytopenia, and hyperbilirubinemia (day +40). Subsequent neurologic deterioration revealed posterior reversible encephalopathy syndrome (PRES) related to calcineurin-inhibitor toxicity. Despite combined therapy including corticosteroids, plasmapheresis, rituximab, and antiviral treatment, multiorgan dysfunction developed, culminating in fatal cardiorespiratory failure on day +99 post-transplant.

Conclusions: This case underscores the extreme clinical complexity of post-transplant management in FLT3+ AML. The sequential onset of immune-mediated, endothelial, infectious, and neurologic complications highlights the necessity for vigilant monitoring, early diagnostic work-up, and coordinated multidisciplinary care. Proactive risk stratification and individualized prophylactic approaches remain essential to improve survival after allo-HSCT in high-risk AML.

Keywords: allo-HSCT, FLT3+ AML, aGvHD, CMV reactivation, PRES, thrombotic microangiopathy

Introduction

Acute myeloid leukemia (AML) is an aggressive hematologic malignancy, and the presence of FLT3 mutations is associated with a poor prognosis. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains a curative strategy for many patients with high-

risk AML, particularly those with FLT3 mutations[1]. However, allo-HSCT is associated with significant complications including graft-versus-host disease (GvHD), infections, and endothelial injuries such as thrombotic microangiopathy and posterior reversible encephalopathy syndrome (PRES)[2]. This report details the complex clinical course of a FLT3+ AML patient following allo-HSCT, highlighting the cascade of multisystemic complications leading to death.

Case report

A 42-year-old woman was presented with enlarged submandibular lymph nodes along with difficulty swallowing. Laboratory testing revealed leukocytosis-WBC: 21.1×10⁹/L and bicytopenia (anemia-Hb: 67 g/L and thrombocytopenia-PLT: 77×10⁹/L) and her general practitioner referred her to the University Clinic for Hematology for further evaluation in May 2024. Written informed consent was obtained from the patient for clinical and academic purposes.

Past medical history of the patient included hypertension treated with bisoprolol 2.5 mg half a tablet daily and perindopril-indapamide 4 mg/1.25 mg daily. She was nulliparous and had a history of infertility treatment.

The findings from the peripheral blood smear were: Neutrophils: 16%, Lymphocytes: 40%, Monocytes: 5%, Blasts: 35%, Myelocytes: 4%, Erythroblasts: 2 per 100 WBCs. Initial diagnostic evaluation included flow cytometry and bone marrow examination via sternal puncture. Flow cytometry demonstrated that approximately 80% of CD45-positive cells corresponded to a blast population expressing myeloid-associated antigens, including CD13, CD33, CD117, CD34, HLA-DR, and CD56, consistent with acute myeloid leukemia (AML). Sternal puncture revealed a hypercellular bone marrow with marked blast infiltration, confirming the diagnosis morphologically. Molecular analysis of the AML panel identified a FMS-like tyrosine kinase 3 internal tandem duplication mutation (FLT3-ITD) located in exon 12. This molecular marker is of high clinical significance, as it is associated with increased leukemic proliferation, higher relapse risk, and poor overall survival. Classified as an intermediate-risk marker by the 2022 ELN criteria, it often requires intensive treatment and proceeding with allogeneic hematopoietic stem cell transplantation (allo-HSCT) in first complete remission[3].

Induction therapy was initiated according to the DA (7+3) regimen combined with a FLT3 inhibitor-sorafenib. Following disease evaluation, remission was not achieved-flow cytometry showed 27% CD45+ blasts and low-level FLT3 expression. Due to inadequate response, salvage therapy with FLAG-Ida plus sorafenib was initiated in June 2024. Reevaluation confirmed hematological and molecular remission. An additional cycle of Flag-Ida + sorafenib was administered in July 2024, followed by two consolidation cycles with high-dose ARA-C + sorafenib (first in September 2024 and second in October 2024). A reevaluation conducted in November 2024 confirmed complete remission of the disease. During follow-up assessments in January 2025 and April 2025, complete remission of the disease was confirmed. Following the achievement of complete hematological and molecular remission, the next step in the treatment strategy was allogeneic hematopoietic stem cell transplantation (allo-HSCT). However, the patient was haploidentical to the potential donor - her brother (6/12) in loci HLA-A, -B, -C, -DRB1, -DQA1 and -DQB1. Therefore, the Macedonian Bone Marrow Donor Registry was searched, and no donor with a complete allele match was found. The global bone marrow donor registry WMDA (World Marrow Donor Association) was also searched, and no donor with a complete allele match (10/10) was found; there were only potential donors with one or more mismatches (7/8).

In January 2025, the patient underwent allogeneic hematopoietic stem cell transplantation (allo-HSCT) from a mismatched unrelated donor (9/10 in HLA-A locus)

following myeloablative conditioning chemotherapy according to the BuCy-ATG regimen. Baseline clinical status and transplant characteristics are presented in Table 1.

Table 1. Baseline Clinical Status and Transplant Characteristics

Variable	Result
Performance status (ECOG)	1
HCT-CI	1 (low risk)
Donor type	Matched Unrelated Donor (7/8)
Sex/Age	D:F/40 R:F/43
Conditioning regimen	BuCy-ATG
GvHD prophylaxis	CyA + Methotrexate
$CD34^+$ cell dose infused	7.0×10^6/kg
Stem cell source	Peripheral blood
Blood type	D:A+ / R:B+
MRD	2%
Molecular marker	FLT3: negative
CMV serostatus	IgM: neg., IgG: pos.
Toxoplasma gondii serostatus	IgM: neg., IgG: neg.
EBV serostatus	IgM: neg., IgG: pos.
HBV	HbsAg: neg., Anti HBs: 1.9, Anti HBc: neg.
HCV	Anti HCV: negative
HIV	Negative

The donor was a 40-year-old female unrelated individual from Turkey with blood group A Rh positive (+). Donor-recipient compatibility revealed a 9/10 human leukocyte antigen (HLA) match, with mismatch in HLA-A. The donor was CMV and EBV IgG positive and CMV and EBV IgM negative.

After appropriate premedication, the patient underwent allogeneic unrelated hematopoietic stem cell transplantation using the cryopreserved cells with a total CD34+ count of 7.0 x 10^6/kg.

She received antibacterial, antifungal, and antiviral prophylactic therapy to prevent infectious complications and therapy for the prevention of VOD. Graft-versus-host disease (GvHD) prophylaxis consisted of a calcineurin inhibitor (cyclosporine A) in combination with methotrexate, according to institutional protocol. Supportive therapy required significant transfusion support, including 121 doses of platelet concentrates, 8 doses of filtered platelet products, 8 units of packed red blood cells, and 6 units of fresh frozen plasma (220 mL each). Prior to transplantation, the patient was cytomegalovirus (CMV) IgG positive and IgM negative, indicating previous exposure.

Engraftment was achieved by day +19 post-allo-HSCT. Thus, on day +20, the patient was discharged for home treatment with normal results from hemogram and biochemical parameters.

CMV reactivation was detected on day +28 post-transplant by polymerase chain reaction (PCR), with a viral load of 155 IU/mL, consistent with early viremia, and was managed with valganciclovir.

On day +31, she developed cutaneous and gastrointestinal aGvHD, presenting as body redness, most prominent on the décolletage and face, along with severe diarrhea, initially with 17 liquid stools. Therapy with intravenous and topical corticosteroids was initiated, and the dose of CyA was increased.

Additionally, *C. difficile* was isolated. A gastroenterologist was consulted, and oral vancomycin was prescribed. Gradual improvement in symptoms was observed.

On day +39, elevated levels of total bilirubin were noted. A gastroenterologist was consulted, and based on their recommendation, a MRI of the upper abdomen with MRCP was performed, showing normal findings.

By day +40, the patient developed thrombocytopenia, along with further elevation of bilirubin levels, an increase in reticulocyte count; elevated LDH levels were also documented and the appearance of macroscopic hematuria. Coombs test was performed and returned negative. A peripheral blood smear was performed, revealing schistocytes.

Due to suspicion of secondary thrombotic thrombocytopenic purpura (TTP), i.e., transplant-associated thrombotic microangiopathy (TA-TMA), treatment was initiated with rituximab, alongside high-dose corticosteroids.

When bilirubin levels exceeded 425, the patient became lethargic and somnolent. As a result, seven plasmapheresis procedures were performed. A decrease in bilirubin levels to 200 was recorded. The patient remained jaundiced, with persistently high bilirubin levels and thrombocytopenia.

The patient experienced neurological symptoms starting on day +42, including headache, blurred vision, followed by the onset of epileptic seizures (some generalized, others resembling absence seizures). PRES was diagnosed via brain MRI and linked to elevated cyclosporinaemia and immunosuppressive therapy with CyA was discontinued. An infectious disease specialist was consulted. A lumbar puncture was performed, and multiple cerebrospinal fluid (CSF) analyses (cytological, biochemical, microbiological, PCR for CMV) were conducted - all results were negative.

A neurologist was also consulted, and antiepileptic therapy with levetiracetam was initiated. Neurological improvement was observed over 3 days; however, epileptic seizures reappeared in the form of repetitive clonic movements. A second neurological consultation was conducted, the antiepileptic dose was increased, and a follow-up brain MRI with contrast showed partial regression of the previously described lesions.

In the period of two months after the performed allo-MUD HSCT, complete chimerism was detected (presence of at least 95% donor DNA in the recipient's bone marrow).

On day +99, ocular involvement emerged, with macerated and necrotic skin on the eyelid margins, with areas of madarosis, hyperemia, hemorrhagic-crusted lesion in the medial canthus of the right eye, diffuse subconjunctival suffusions across the entire ocular surface, generalized desquamation of the conjunctival and corneal epithelium, fluorescein sodium (FlNa+) uptake on 100% of the corneal surface, seromucous discharge, and pseudo-membranes on the tarsal conjunctiva. Local antibiotic and immunomodulatory therapy were administered. The patient was referred to a medical board, and it was decided to continue treatment with ruxolitinib (Figure 1).

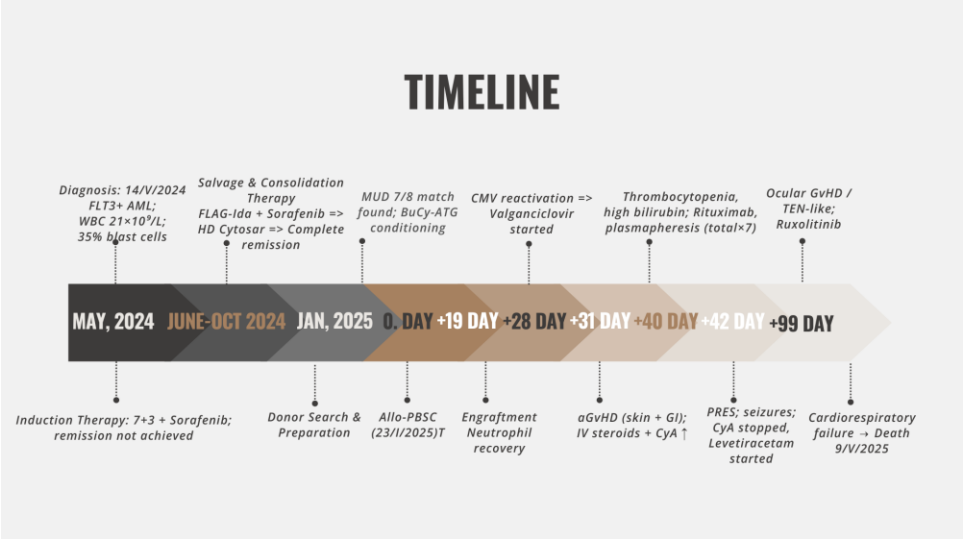

Fig. 1. Chronology of clinical events and complications

In the final stages, the patient's condition further deteriorated. Despite the intensive supportive treatment, she died from cardiorespiratory failure on May 2025 (99 days after allo-HSCT).

Discussion

This case illustrates the cumulative burden of early post-transplant complications after allogeneic hematopoietic stem cell transplantation (allo-HSCT) in acute myeloid leukemia (AML). Before transplantation, the patient already had several clinically relevant risk factors that should be emphasized: FLT3 internal tandem duplication (FLT3-ITD) AML, failure to achieve remission after first induction, the need for salvage therapy, prior exposure to multiple intensive chemotherapy cycles, and subsequent transplantation after myeloablative conditioning with busulfan, cyclophosphamide, and antithymocyte globulin (BuCy-ATG). In addition, the graft source was peripheral blood stem cells, the donor was unrelated, 9/10 (MM in HLA-A), the recipient was cytomegalovirus (CMV) seropositive, and there was ABO incompatibility (donor A+, recipient B+), all of which may increase post-transplant complexity. According to current classifications, FLT3-ITD is generally considered an intermediate-risk molecular abnormality, but it remains associated with substantial relapse risk and often influences the decision to pursue transplantation in first complete remission[1,16]. In this patient, transplantation was therefore justified not by a single variable alone, but by the combination of molecular risk, initial chemoresistance, and the overall therapeutic course.

More broadly, early complications after allo-HSCT arise from the interaction of conditioning-related tissue injury, endothelial damage, delayed immune reconstitution, and pharmacologic immunosuppression. Even when donor matching is optimal, early morbidity is driven by a limited number of major syndromes: acute graft-versus-host disease (aGvHD), opportunistic infection or viral reactivation, endothelial complications such as transplant-associated thrombotic microangiopathy (TA-TMA), drug-related neurotoxicity including posterior reversible encephalopathy syndrome (PRES), and later ocular or multisystem manifestations of alloreactivity[1]. Contemporary reviews and the 2024 EBMT Handbook emphasize that these complications frequently overlap rather than occur in isolation, and that one event, such as aGvHD or infection, may amplify the risk of the next through intensified immunosuppression and progressive endothelial injury[2,17].

A first major complication in this patient was acute graft-versus-host disease, with cutaneous and gastrointestinal involvement beginning on day +31 after transplantation, treated with intravenous and topical corticosteroids and escalation of cyclosporine exposure. The HLA

mismatch, unrelated donor transplantation, peripheral blood stem cell grafts, and myeloablative conditioning are all recognized contributors to aGvHD risk. In addition, gastrointestinal microbial disruption and concurrent *Clostridioides difficile* infection may worsen intestinal inflammation and complicate both diagnosis and treatment response[3-5]. From a mechanistic standpoint, conditioning-induced mucosal injury promotes cytokine release and antigen presentation, thereby facilitating donor T-cell activation and tissue damage. Prognostically, severe early aGvHD remains one of the main causes of non-relapse mortality after allo-HSCT[3,4,18].

The subsequent development of TA-TMA in this case is also biologically coherent. The patient developed thrombocytopenia, hemolysis with schistocytes, elevated lactate dehydrogenase, hyperbilirubinemia, and macroscopic hematuria, after which rituximab, high-dose corticosteroids, and repeated plasmapheresis were administered. Current understanding views TA-TMA as an endothelial injury syndrome that is often triggered by a combination of conditioning toxicity, calcineurin inhibitors, infection, active GvHD, and systemic inflammation[6,7,19]. In this patient, several of these drivers coexisted. Recent consensus literature stresses that TA-TMA is underrecognized and associated with poor outcomes once organ dysfunction becomes clinically evident[6,7]. While plasma exchange and rituximab have historically been used, outcomes remain guarded in severe disease[8].

Neurological deterioration in this patient was consistent with posterior reversible encephalopathy syndrome (PRES), manifested by headache, blurred vision, and epileptic seizures. PRES after transplantation is most often linked to calcineurin inhibitor exposure, hypertension, and endothelial dysfunction[9,10]. Although considered reversible, delayed recognition may lead to permanent neurological damage or death[11].

Another key issue was CMV reactivation, which occurred in a recipient who was already CMV IgG positive before transplantation. CMV-seropositive recipients remain at higher risk of post-transplant reactivation, and that risk is further amplified by unrelated donor transplantation and immunosuppression[12,13,20]. CMV may also exacerbate GvHD and contribute to overall morbidity and mortality[13].

The ocular findings later in the course further suggest severe alloimmune tissue injury, most likely ocular graft-versus-host disease. Ocular GvHD can affect up to 60% of patients and may lead to significant morbidity if not promptly managed[14,15].

Taken together, this case demonstrates that the prognosis after allo-HSCT is determined by the interaction of pre-transplant disease biology and post-transplant complications.

Despite the multidisciplinary approach, the patient's condition deteriorated, and she succumbed to cardiorespiratory failure. This case underscores the high morbidity associated with allo-HSCT in FLT3+ AML patients and highlights the necessity for timely recognition and aggressive management of complications.

Conclusion

Allogeneic HSCT remains the cornerstone of curative therapy for FLT3+ AML. However, post-transplant complications including aGvHD, TA-TMA, PRES, and opportunistic infections significantly affect outcomes. This case exemplifies the need for early detection, aggressive supportive care, and multidisciplinary intervention to mitigate transplant-related mortality. Personalized risk stratification and prophylactic strategies should be a focus of future studies.

Conflict of interest statement. None declared.

References

1. Döhner H, Wei AH, Appelbaum FR, Craddock C, DiNardo CD, Dombret H, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. *Blood*. 2022;140(12):1345-1377. doi:10.1182/blood.2022016867.
2. Daver N, Venugopal S, Ravandi F. FLT3 mutated acute myeloid leukemia: 2021 treatment algorithm. Blood Cancer J. 2021 May 27;11(5):104. doi: 10.1038/s41408-021-00495-3. PMID: 34045454; PMCID: PMC8159924.
3. Zeiser R, Blazar BR. Acute Graft-versus-Host Disease-Biologic Process, Prevention, and Therapy. *N Engl J Med* 2017; 377(22): 2167-2179. doi: 10.1056/NEJMra1609337.
4. Michonneau D, Devillier R, Keränen M, Rubio MT, Nicklasson M, Labussière-Wallet H. et al. Treatment Patterns and Clinical Outcomes of Patients with Moderate to Severe Acute Graft-Versus-Host Disease: A Multicenter Chart Review Study. Hematol Rep. 2024 May 6;16(2):283-294. doi: 10.3390/hematolrep16020028. PMID: 38804281; PMCID: PMC11130792.
5. Weber S, Scheich S, Magh A, Wolf S., C. Enßle J., Brinnberg U. et al. Impact of *Clostridioides difficile* infection on the outcome of patients receiving a hematopoietic stem cell transplantation. International Journal of Infectious Diseases, 2020; 99, 428-436. DOI: 10.1016/j.ijid.2020.08.030
6. Schmidt V, Prell T, Treschl A, Klink A, Hochhaus A, Sayer HG. Clinical Management of Posterior Reversible Encephalopathy Syndrome after Allogeneic Hematopoietic Stem Cell Transplantation: A Case Series and Review of the Literature. Acta Haematol. 2016;135(1):1-10. doi: 10.1159/000430489. Epub 2015 Jul 4. PMID: 26159650.
7. Fugate JE, Rabinstein AA. Posterior reversible encephalopathy syndrome: clinical and radiological manifestations, pathophysiology, and outstanding questions. *Lancet Neurol* 2015; 14(9): 914-925. doi: 10.1016/S1474-4422(15)00111-8.
8. Hinchey J, Chaves C, Appignani B, Breen J, Pao L, Wang A, *et al*. A reversible posterior leukoencephalopathy syndrome. *N Engl J Med* 1996; 334(8): 494-500. doi: 10.1056/NEJM199602223340803.
9. Jodele S, Davies SM, Lane A, Khoury J, Dandoy C, Goebel J, *et al.* Diagnostic and risk criteria for HSCT-associated thrombotic microangiopathy: a study in children and young adults. *Blood* 2014; 124(4): 645-653. doi: 10.1182/blood-2014-03-564997.
10. Ho VT, Cutler C, Carter S, Martin P, Adams R, Horowitz M, *et al*. Blood and marrow transplant clinical trials network toxicity committee consensus summary: thrombotic microangiopathy after hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* 2005; 11(8): 571-575. doi: 10.1016/j.bbmt.2005.06.001.
11. Au WY, Ma ES, Lee TL, Ha SY, Fung AT, Lie AK, Kwong YL. Successful treatment of thrombotic microangiopathy after haematopoietic stem cell transplantation with rituximab. Br J Haematol. 2007 Jun;137(5):475-8. doi: 10.1111/j.1365-2141.2007.06588.x. Epub 2007 Apr 13. PMID: 17433026.
12. Boeckh M, Ljungman P. How we treat cytomegalovirus in hematopoietic cell transplant recipients. *Blood* 2009; 113(23): 5711-5719. doi: 10.1182/blood-2008-10-143560.
13. Girmenia, C., Lazzarotto, T., Martino, M., Bonifazi, F., Baldanti, F., Clerici, P., Citterio, F., De Carlis, L., Barosi, G. and Grossi, P.A. (2025), Management of Cytomegalovirus Infection in Allogeneic Hematopoietic Stem Cell and in Solid Organ Transplantation: Updated Recommendations by the GITMO, SITO, SIMIT, and AMCLI Italian Societies. Clinical Transplantation., 39: e70255. https://doi.org/10.1111/ctr.70255

14. Ogawa Y, Okamoto S, Wakui M, Watanabe R, Yamada M, Yoshino M, *et al*. Dry eye after haematopoietic stem cell transplantation. *Br J Ophthalmol* 1999; 83(10): 1125-1130. doi: 10.1136/bjo.83.10.1125.
15. Shikari H, Antin JH, Dana R. Ocular graft-versus-host disease: a review. *Surv Ophthalmol* 2013; 58(3): 233-251. doi: 10.1016/j.survophthal.2012.08.004.
16. Kantarjian HM, DiNardo CD, Kadia TM, Naval GD, Altman J.K, Stein ME. et al. Acute myeloid leukemia management and research in 2025. CA Cancer J Clin. 2025;75(1):46-67. doi:10.3322/caac.21873
17. Zamperlini G, Martins AF, Silva B da CA e, Cardoso MF, Rodrigues AM, Silva TCPM da, et al. Non-infectious complications after hematopoietic cell transplantation. J Bone Marrow Transplant Cell. DOI:https://doi.org/10.46765/2675-374X.2025v6n1e283.
18. Kasikis S, Etra A, Levine JE. Current and Emerging Targeted Therapies for Acute Graft-Versus-Host Disease. BioDrugs. 2021 Jan;35(1):19-33. doi: 10.1007/s40259-020-00454-7. PMID: 33201499; PMCID: PMC7855093.
19. Young JA, Pallas CR, Knovich MA. Transplant-associated thrombotic microangiopathy: theoretical considerations and a practical approach to an unrefined diagnosis. Bone Marrow Transplant. 2021 Aug;56(8):1805-1817. doi: 10.1038/s41409-021-01283-0. Epub 2021 Apr 19. PMID: 33875812; PMCID: PMC8338557.
20. El Chaer F, Hourigan CS, Zeidan AM. How I treat AML incorporating the updated classifications and guidelines. *Blood* 2023; 141(23): 2813-2823. doi: 10.1182/blood.2022017808.