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CHALLENGING PRESERVATION OF THE RENAL FUNCTION IN A CASE OF AN ACUTE ERYTHROID LEUKEMIA (FAB M6) KNOWN WITH MODERATE-TO-SEVERE CHRONIC KIDNEY DISEASE

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ABSTRACT

Acute erythroid leukemia (AEL) is a subtype of Acute Myeloid Leukemia (AML), comprising less than 5% of AML cases, characterized by erythroblastic proliferation. It's a rare and aggressive form of acute leukemia whose biology remains poorly described, and there are many controversies around diagnosis influencing prognostic and therapeutic challenges. The average survival time for this type of Leukemia is 3 months. We present a unique case of a patient already known to have Chronic Kidney Disease stage G4, diagnosed with Acute Erythroid Leukemia (Fab M6), confirmed by Flow-Cytometry (infiltration of 93% erythroblasts in the Bone Marrow), who underwent specific chemotherapy (Azacitidine and Venetoclax) for 4 months. Due to severe pancytopenia and the presence of leukemic hiatus, it was challenging to avoid hemodialysis/hemofiltration, overcome metabolic acidosis and hyperuricemia, preserve serum creatinine levels at acceptable levels, and maintain hydroelectrolytic balance. All drug dosages (chemotherapy and supportive treatment) were adapted to the patient's renal function.

Keywords: acute erythroid leukemia, chronic kidney disease, chemotherapy

Introduction

Acute erythroid leukemia (AEL) is a rare and aggressive subtype of acute myeloid leukemia (AML) characterized by abnormal proliferation of immature erythroid precursors in the bone marrow (1-3). It represents a distinct entity within the spectrum of AML and comprises less than 5% of AML cases. AEL is also known as erythroleukemia or Di Guglielmo syndrome (4). AEL is characterized by the presence of a significant proportion (≥50%) of erythroid precursors, including proerythroblasts, basophilic erythroblasts, and polychromatophilic erythroblasts, in the bone marrow and peripheral blood. These cells often display dysplastic features and exhibit a block in erythroid maturation. The pathogenesis of AEL remains poorly understood, and it is often associated with complex cytogenetic abnormalities and gene mutations (1). Risk factors for developing AEL include exposure to cytotoxic agents, radiation, previous myelodysplastic syndrome (MDS), and certain genetic syndromes. Diagnosing AEL can be challenging due to its overlapping features with other subtypes of AML and myelodysplastic/myeloproliferative neoplasms. Flow cytometry, cytogenetic analysis, and molecular profiling are important tools in establishing an accurate diagnosis and determining prognostic factors.

The prognosis of AEL is generally poor, with a median survival of around 3 to 6 months (5). The aggressive nature of the disease, high relapse rates, and resistance to chemotherapy contribute to the unfavorable outcomes. AEL is often associated with a higher risk of extramedullary involvement and organ infiltration compared to other AML subtypes. The optimal treatment approach for AEL is not well-defined due to its rarity and limited clinical data (6-9). Intensive chemotherapy regimens, similar to those used for other AML subtypes, are typically employed. However, the response to treatment and overall outcomes are often inferior in AEL compared to other AML subtypes. Allogeneic stem cell transplantation may be considered for eligible patients, especially those with a suitable donor and good performance status. In recent years, efforts have been made to better understand the molecular characteristics of AEL and identify potential targeted therapies. However, further research is needed to unravel the underlying biology of AEL and develop novel treatment strategies to improve outcomes for patients with this aggressive subtype of acute myeloid leukemia. Venetoclax is a targeted therapy that has shown promising results in the treatment of various hematological malignancies, including acute myeloid leukemia (AML). While its effectiveness has been well-documented in certain subtypes of AML, its efficacy in rare forms of leukemia, such as Acute Erythroid Leukemia (AEL), remains an area of ongoing research.

Case report

We present the case of a 76-years-old patient diagnosed with Acute Erythroid Leukemia M6 FAB, also suffering of Chronic Kidney Disease stage IV, Tubulointerstitial nephritis, Non-obstructive bilateral nephrolithiasis, High Blood Pressure stage II – risk very high, Type II Diabetes under treatment with Oral Diabetes Medications, prostate hypertrophy and Mixed Dyslipidemia. The patient presents to the hematology clinic in a severe condition, acusing nausea, vomiting, marked asthenia, and fatigue. Following the performed analyses, the patient is found to have bicytopenia (leukopenia-530/mmc with severe neutropenia-130/mmc; moderate normochromic, normocytic anemia-9.4g/dL), thrombocytosis-778.000/mmc, and acute exacerbation of chronic renal failure in the polyuric phase (Creatinine: 6.69 mg/dL; eGFR: 8), along with hyperkalemia-5mmol/L. An urgent arterial blood gas analysis (ABG) reveals metabolic acidosis, leading to the decision to transfer the patient to the Intensive Care Unit (ICU) for monitoring and reequilibration. After reequilibration, a bone marrow immunophenotyping (Flow-Cytometry) is performed, confirming the diagnosis of Acute Erythroid Leukemia M6 with the presence of 93% precursor cells of the erythroid lineage. A nephrologist consultation is requested, who recommends hemodialysis/hemofiltration; however, the patient refuses. Considering the severity of the disease, decompensation of renal function, and the results of the analyses, it is decided to administer the first cycle of Azacitidine, with a reduced dose of 100mg per day for 5 days. During hospitalization, broad-spectrum antibiotic therapy was administered prophylactically, adequate hydration with forced diuresis was maintained, and red blood cell transfusions were performed. After 28 days, renal function improves (creatinine: 2mg/dL), and it is decided to administer the second cycle of Azacitidine and to add Venetoclax at a reduced dose of 100mg/day for 28 days. After administering the second cycle of Azacitidine and the first cycle of Venetoclax, a slight increase in leukocytes and granulocytes is observed (Leucocytes: 2000/mmc; Neutrophiles: 1000/mmc), while the platelet count decreases significantly (Platelets: 500/000/mmc). However, the creatinine levels fluctuate, necessitating multiple hospitalizations for adequate hydration and administration of diuretics. At the end of the second cycle of Venetoclax administration, renal function deteriorates, develops oliguria, necessitating a temporary halt in Venetoclax treatment and a decision is made to insert a urinary catheter.Two additional cycles of Azacitidine were continued. At the end of the fourth cycle of Azacitidine, the patient's general condition worsens, presenting with a febrile syndrome, chills, hypertensive crisis, sinus tachycardia, and oxygen desaturation of up to 76% in ambient air. The patient is transferred to the Intensive Care

Unit with a diagnosis of Acute Pulmonary Edema, intubated, and placed in an induced coma. During the last hospitalization, due to the presence of pancytopenia and sepsis, broad-spectrum antibiotic therapy, granulocyte growth factors, multiple red blood cell and platelet transfusions were administered. Hemofiltration was attempted but without success. Unfortunately, the patient's condition deteriorated, leading to a fatal outcome.

Treatment Challenges

The patient's lack of cooperation and the presence of important comorbidities hindered the continuation of Venetoclax treatment. However, it is important to highlight that even after just one month of treatment with a reduced dose of Venetoclax, significant improvements were observed in the patient's hematological profile. .

Positive Outcome

Notably, the patient's hemoleukogram values reached normal levels after the initiation of Venetoclax treatment. This suggests that Venetoclax holds promise as an effective therapeutic option for AEL, even in cases where patient compliance and comorbidities present significant challenges.

Discussion

The efficacy of Venetoclax in treating rare forms of leukemia, such as AEL, underscores the importance of targeted therapies in personalized medicine. Despite the limitations in our case, the positive response observed in the patient's hematological profile demonstrates the potential of Venetoclax to improve outcomes in AEL patients.

Conclusions

Although the discontinuation of Venetoclax treatment in our case prevented us from fully exploring its long-term effectiveness, the initial response observed in the patient's hemoleukogram highlights the potential of Venetoclax as a valuable treatment option for AEL and other rare forms of leukemia. Further research and clinical trials are warranted to elucidate the optimal use of Venetoclax in these challenging cases and to identify strategies to overcome patient non-compliance and comorbidity-related obstacles

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