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Case Report

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High-Risk Myelodysplastic Syndrome and Acute Myeloid Leukemia: Challenges of Complex Karyotype and TP53

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Abstract

This case report elucidates the clinical trajectory of a 60-year-old male with a history of mild cytopenias, subsequently diagnosed with myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) characterized by a complex karyotype and a TP53 mutation. The initial diagnostic evaluation included a bone marrow biopsy revealing 34% myeloid blasts with aberrant immunophenotyping and complex cytogenetic abnormalities, including losses and gains of chromosomal regions. Genetic analysis confirmed a high Variant Allele Frequency of 80% for the TP53 mutation. The patient's management strategy commenced with a combination of Inqovi (decitabine and cedazuridine) and Venetoclax, supported by prophylactic measures to mitigate tumor lysis syndrome and vigilant infection control. While offering a glimmer of hope for improving outcomes in this high-risk cohort, this treatment approach underscores the inherent challenges posed by the aggressive nature of the disease and the TP53 mutation's contribution to therapeutic resistance. The case highlights the critical need for personalized treatment regimens and rigorous follow-up to optimize patient care and advance our understanding of this complex malignancy.

Keywords: FLT3-ITD, FLT3-TKD, Next-generation sequencing (NGS), MDS/AML, acute myeloid leukemia (AML)

Introduction

Myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML) are clonal hematopoietic stem cell disorders characterized by ineffective hematopoiesis, dysplasia in one or more myeloid cell lines, and an elevated risk of progression to AML. These malignancies predominantly affect older adults and are associated with significant morbidity and mortality (1). MDS manifests with hematologic abnormalities such as anemia, neutropenia, and thrombocytopenia, and is classified based on the number of dysplastic lineages, bone marrow blast percentage, and cytogenetic abnormalities (4). AML is marked by the rapid proliferation of abnormal white blood cells, with a diagnosis confirmed when the bone marrow contains 20% or more blasts (1). The coexistence of MDS and AML, often termed MDS/AML, is particularly notable in patients with complex cytogenetic abnormalities and TP53 mutations. Complex karyotypes, defined by the presence of three or more chromosomal abnormalities, are frequently observed in MDS/AML cases and include deletions, duplications, and translocations that disrupt normal gene function and promote disease progression (4).TP53 mutations are a critical factor in these malignancies. The TP53 gene, located on chromosome 17p, encodes the p53 protein, a key tumor suppressor involved in DNA repair, cell

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cycle regulation, and apoptosis (2). TP53 mutations occur in approximately 5-10% of de novo MDS and AML cases but can be as high as 20-40% in therapy-related cases or those with complex karyotypes (4). These mutations result in a dysfunctional p53 protein, leading to genomic instability and resistance to standard therapies. Multiple TP53 mutations are particularly concerning, as they are associated with chemotherapy resistance, higher relapse rates, and shorter overall survival (3). The poor prognosis associated with MDS/AML with TP53 mutations and complex karyotypes underscores the need for novel therapeutic approaches. Current treatments include hypomethylating agents, such as decitabine and azacitidine, often in combination with targeted therapies like Venetoclax, which have shown some promise in improving outcomes for high-risk patients (1). This case report describes a 60-year-old male patient with high-grade myeloid neoplasm, likely MDS/AML, characterized by a complex karyotype and TP53 mutation. It highlights the challenges in managing this aggressive disease and emphasizes the importance of personalized treatment strategies and ongoing monitoring to enhance patient outcomes.

Case Presentation

A 60-year-old male presented with symptoms of mild cytopenia, neutropenia, and thrombocytopenia. His primary care physician, suspecting autoimmune neutropenia, referred him to a hematologist for further evaluation. Despite initiating treatment with prednisone, there was no improvement in his condition. After 3 months, a bone marrow biopsy was performed, revealing 34% abnormal myeloid blasts. The blasts exhibited aberrant co-expression of CD9, CD11b, CD56, and CD123, accompanied by increased monocytes. The differential diagnosis included acute myeloid leukemia (AML), chronic myelomonocytic leukemia (CMML), myelodysplastic syndrome (MDS) with increased blasts or a combination of MDS and AML. The biopsy results were negative for FLT3-ITD and FLT3-TKD mutations. Additionally, fluorescence in situ hybridization (FISH) analysis demonstrated loss of 5q, monosomy 7, an additional intact KMT2A signal, loss of an intact ETV6 signal, diminished TP53 signal, and loss of D20S108, indicating a complex karyotype with multiple chromosomal abnormalities. A follow-up bone marrow biopsy after 10 days, confirmed the diagnosis of AML with multilineage dysplasia and 23% blasts. Next-generation sequencing (NGS) further identified a TP53 mutation with a Variant Allele Frequency (VAF) of 80%. This finding corroborated the high-grade myeloid neoplasm diagnosis, likely indicating a myelodysplastic syndrome/acute myeloid leukemia (MDS/AML) with a complex karyotype and significant TP53 mutation. The initial treatment plan, which commenced 15 days later, included a regimen of Inqovi (decitabine and cedazuridine) administered on days 1-5, combined with Venetoclax 50 mg daily from days 1-14. To mitigate tumor lysis syndrome (TLS), Allopurinol 300 mg daily was prescribed. Hematologic management involved regular blood transfusions to maintain hemoglobin levels above 7 g/dL and platelet counts above 10K/mcL, with all blood products irradiated and leukoreduced. For infection prophylaxis, the patient was not exhibiting signs of active infection, but prophylactic antimicrobials including Acyclovir, Ciprofloxacin, and Posaconazole were provided, along with education on monitoring for febrile neutropenia. The management of comorbid conditions included continuing gabapentin for neuropathy, transitioning from simvastatin to rosuvastatin to address drug-drug interactions in hyperlipidemia, ongoing treatment with tamsulosin for benign prostatic hyperplasia (BPH), and maintaining venlafaxine for anxiety. The patient was scheduled for a follow-up clinic visit on August 20, 2024, for a repeat bone marrow biopsy. Patient counseling focused on a detailed discussion of his diagnosis, treatment plan, and the potential risks and benefits, including the option of allogeneic bone marrow transplantation. Emphasis was placed on the risks associated with myeloablative conditioning, engraftment, and graft-versus-host disease (GVHD).

TP53 Mutation in MDS and AML

The presence of a complex karyotype in MDS and AML is a well-established indicator of poor prognosis. Complex karyotypes, defined by the presence of three or more chromosomal abnormalities, disrupt normal gene function and contribute to disease progression (2, 3). In this case, the patient's karyotype revealed significant abnormalities, including losses of 5q and monosomy 7, which are commonly associated with high-risk MDS/AML and indicate a more aggressive disease course.TP53 mutations are particularly problematic in the context of MDS and AML. The TP53 gene, located on chromosome 17p, encodes the p53 protein, a crucial tumor suppressor involved in DNA repair, cell cycle regulation, and apoptosis (4). Mutations in TP53 can lead to the production of a dysfunctional p53 protein, which undermines these vital processes and contributes to genomic instability. The high VAF of 80% observed in this patient suggests a significant burden of TP53-mutant cells, which is associated with resistance to conventional therapies and a poorer overall prognosis (2, 3). The frequency of TP53 mutations in MDS and AML varies with disease type and patient history. TP53 mutations are present in approximately 5-10% of de novo MDS and AML cases but are found in up to 40% of patients with therapy-related or complex karyotype cases (2, 4). This elevated mutation rate in complex cases reflects the cumulative genetic damage and selective pressures that drive disease progression. Additionally, TP53 mutations often co-occur with other genetic alterations, further complicating the disease and therapeutic management (4).

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Current therapies for TP53-mutated MDS and AML:

The treatment of MDS and AML with TP53 mutations presents considerable challenges. For MDS, hypomethylating agents (HMAs) such as decitabine and azacitidine are standard treatments, with response rates ranging from 17% to 77% and median overall survival (OS) between 8.2 to 12.4 months (5, 6). However, patients with high VAF TP53 mutations experience poorer outcomes, with OS often reduced to 4.1 to 7.7 months. Achieving a reduction in VAF to below 5% has been associated with better outcomes, especially for those who proceed to stem cell transplantation (5, 6).In AML, treatment options include low-intensity therapies like HMAs or low-dose cytarabine, which show response rates of 14% to 62% and median OS of 2.1 to 8.1 months. Intensive chemotherapy regimens offer higher response rates but come with increased toxicity (7, 8). Venetoclax, a BCL2 inhibitor, has shown promise in combination with HMAs, achieving a complete remission rate of approximately 41% and an OS of 6.5 months (9, 10). However, the effectiveness of Venetoclax is often limited by altered mitochondrial responses in TP53-mutant cells. When combined with decitabine, Venetoclax shows a complete remission rate of 57% but with a median OS of 5.2 months and a high 60-day mortality rate (11).

Research Directions and Future Directions

The ongoing research focuses on understanding the mechanisms by which TP53 mutations contribute to disease progression and resistance to therapy. Novel treatments targeting apoptotic pathways and other aspects of cellular metabolism are under investigation to address the limitations of current therapies (9, 10). Additionally, there is a need for personalized treatment strategies that take into account the specific genetic and molecular profile of each patient, including the presence and burden of TP53 mutations. Emerging therapies, such as targeted inhibitors and combination regimens tailored to the genetic profile of the disease, hold promise for improving outcomes in this challenging patient population. The development of novel agents and therapeutic combinations that can effectively target TP53-mutant cells while minimizing toxicity is crucial for advancing treatment strategies and enhancing patient survival.

Discussion

Myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML) are complex hematological malignancies with significant clinical challenges, particularly when associated with complex karyotypes and TP53 mutations. This case report illustrates the difficulties in managing a 60-year-old male patient with MDS and AML, characterized by an 80% Variant Allele Frequency (VAF) of TP53 mutation and a complex karyotype. This discussion delves into the implications of these genetic abnormalities, the current treatment landscape, and the ongoing research efforts aimed at improving patient outcomes.

Conclusion

This case highlights the complexities and challenges of diagnosing and managing high-risk MDS/AML with TP53 mutations and complex karyotypes. A personalized treatment approach, including novel chemotherapy regimens and comprehensive supportive care, is critical for improving patient outcomes. Continuous monitoring and adjustments to the treatment plan based on the patient's response are essential for optimal care.

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Table 1: Current and Future Therapies for TP53-Mutant MDS/AML

Therapy	Description	Efficacy	References
Hypomethylating Agents (HMAs)	Decitabine, Azacitidine	Response rates 17%-77%, Median OS 4.1 to 12.4 months	(5, 6)
Low-Intensity Therapies	Low-dose cytarabine	Response rates 14%-62%, Median OS 2.1 to 8.1 months	(7, 8)
Intensive Chemotherapy	High-dose regimens	Higher response rates but increased toxicity	(7, 8)
Venetoclax + HMA	Combination of venetoclax with decitabine or azacitidine	Complete remission rate ~41%, OS 6.5 months	(9, 10)
Venetoclax + Decitabine	Combination of Venetoclax with decitabine	Complete remission rate 57%, Median OS 5.2 months, high 60-day mortality	(11)

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