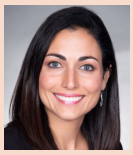
Targeting p53 in MDS: Highlights From SOHO 2021



Alexis C. Geppner, MLS, CTTS, PA-C, of The University of Texas MD Anderson Cancer Center, evaluates data from the session on p53 in myelodysplastic syndrome presented by David A. Sallman, MD, of H. Lee Moffitt Cancer Center and Research Institute, at the 2021 SOHO Annual Meeting.

P53 is a tumor suppressor gene encoded by the *TP53* gene which, in response to stress, regulates transcription of target genes. The loss of functional tumor suppressor genes leads to overactivation of ONCA genes. Dr. David Sallman of Moffitt Cancer Center speaks about the impact *TP53* mutation has on the prognosis of myelodysplastic syndrome (MDS), outcomes of hypomethylating agent (HMA)-based therapy vs. stem cell transplantation, and novel therapies targeting *TP53*.

TP53 mutations are often associated with aberrations of chromosome 5 (in addition to chromosomes 7 and 17) with 72% harboring a complex chromosomal karyotype (Kulasekararaj et al., 2013). Given the adverse prognosis, rapid identification of these patients is extremely important. Patients harboring these mutations are notoriously difficult to treat and have very short-term remissions, with a median overall survival (OS) of 6 to 12 months (Cluzeau et al., 2021a). *TP53* mutations are also associated with resistance to cytarabine-based chemotherapy (Takahashi et al., 2016).

In patients with MDS with excess blasts, there is ~90% certainty that a p53 mutation exists. *TP53* mutations with a very high allelic frequency (VAF) over 40% can predict inferior survival, and VAF expansion is the driver of poor outcomes. Hypomethylating-agent (HMA)-based therapy such as 5-azacitadine (AZA) and decitabine (DAC) have become standard of care in high-risk MDS patients; however, remissions are not durable.

5-AZACITADINE + VENETOCLAX

Venetoclax (Venclexta) is a selective small-molecule BCL2 inhibitor that induces apoptosis in malignant cells dependent on BCL2 for survival. AZA induces a synergistic effect through the downregulation of MCL1 and the induction of expression of pro-death proteins, boosting a dependance of leukemia cells to BCL2 (Jin et al., 2020). The combination AZA + venetoclax is under investigation in MDS.

Preliminary results of 73 patients from a phase Ib multicenter clinical trial showed promising results, with an overall response rate (ORR) of 79%, including 39.7% of patients with complete response (CR). Additionally, a randomized phase III clinical trial is ongoing (NCT04401748).

Key Points

- In patients with aberrations of chromosome 5, rapid identification of p53 mutations is imperative.
- *TP53* mutations with a VAF ≥ 40% can predict inferior survival.
- HMA-based therapy remains the standard of care; however, remissions are not durable. Further research into novel therapies is needed.
- Venetoclax, eprenetapopt, and magrolimab offer promising options.

J Adv Pract Oncol 2022;13(suppl 1):15–16
https://doi.org/10.6004/jadpro.2022.13.1.12

5-AZACITADINE + EPRENETAPOPT

Eprenetapopt (APR-246) is a novel small molecule prodrug converted to methylene quinuclidinone (MQ) that binds mutant p53, activates normal p53 activity, and selectively induces apoptosis in *TP53*-mutant cancer cells (Cluzeau et al., 2021a).

A phase I/IIb study of APR-246 plus AZA showed an ORR of 73%, with 50% of those patients achieving a CR (Cluzeau et al., 2021b). Median overall survival was 7 months but improved if p53 was cleared.

A pivotal phase III MDS randomized trial of frontline AZA ± APR-246 in p53-mutant MDS yielded high rates of CR and molecular response. The CR rate was 53% higher in the APR arm but was not statistically significant (Sallman et al., 2021).

5-AZACITADINE + MAGROLIMAB

CD47 is a dominant macrophage checkpoint that acts as a "don't eat me" signal and is increased on cancer cells. Magrolimab is an IgG4 monoclonal antibody targeting CD47 to activate cellular phagocytosis. AZA induces a phagocytic "eat me" signal and works in synergy with CD47 to block eight of the "don't eat me" signals leading to enhanced phagocytosis (Cluzeau et al., 2021b).

In an ongoing phase Ib study, AZA + magrolimab led to higher response rates (ORR 91%, CR 42%) and low immune-related adverse events (Garcia-Manero et al., 2021). Patients with magrolimab combination therapy typically had cytopenias. However, most patients were cytopenic at baseline. ●

The Advanced Practitioner Perspective

Patients with myelodysplastic syndrome harboring a p53 mutation have minimal options with short-term remissions and low overall survival. Current research and clinical trials focus on the urgent need for targeted therapies in this patient population. As advanced practitioners, we need to be aware of the ever-changing landscape of therapy for our patients. It is imperative to continue to understand the rationale for therapy and the direct impact on the patient in addition to focusing on the patient's blood counts, need for frequent transfusions, and high risk for opportunistic infection.

As we know, p53-mutated diseases have a poor prognosis and the internet does not shield our patients from this knowledge. Educating patients early on and throughout their treatment will assist in their understanding, help to build rapport and trust, and allow for honest and important conversations on goals of care.

Disclosure

Ms. Geppner has served as a consultant and advisor for AbbVie.

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