Commentary
Volume 13:3,2023

Journal of Blood & Lymph

ISSN: 2165-7831 Open Access

Commentary on *TP53* Mutated Myeloid Malignancies and Their Treatment Strategy

Yasuhito Nannya*

Department of Hematopoietic Disease Control, Institute of Medical Science, The University of Tokyo, Japan

About the Study

TP53-mutated myeloid neoplasms are currently recognized as a distinct entity based on the findings that *TP53*-mutated myeloid neoplasms have highly distinctive clinical and genetic features: Cases with mutations in this gene tend to have genomic instability, as represented by the complex karyotype almost inevitably involving -5/del(5q), a lower number of other driver mutations, and a dismal clinical outcome that is resistant to most treatments, including hematopoietic stem cell transplantation.

However, it has been shown that these characteristic features of *TP53*-mutated myeloid tumors apply only to cases with biallelic *TP53* alterations, which include compound heterozygosity and mutation of one allele plus loss of heterozygosity of the other allele. To complicate matters, this allele-status-based classification of *TP53*-mutated tumors is particularly well suited to low-risk MDS, whereas these differences are less obvious in high-risk MDS and almost unobserved in AML. In AML, it is the magnitude of the variant allele frequency (usually >10% threshold) that confers prognostic significance rather than the allele status.

Undoubtedly, the most significant problem with this tumor is the lack of effective treatment. Intensive treatment of AML achieves CR in only 20%-40% of patients, with median overall survival of less than 8 months. Several studies, including ours, have demonstrated a specific response of In addition, sabatolimab, a TIM-3 antibody, and immune checkpoint inhibitors are also in development. Currently, the strategy of consolidating the deep remission achieved by these novel therapies with allogeneic transplantation seems a realistic approach.-mutated tumors to hypomethylating agents (azacitidine or decitabine), but the response rate for hypomethylating agent monotherapy remains at 20% to 30% and these responses are usually not durable and do not result in a significant improvement in survival. We also found that post-transplant relapse was almost inevitable when *TP53*-mutant clones with complex karyotypes remained immediately prior to transplantation.

Therefore, we investigated the feasibility of a treatment strategy using demethylating agents as induction therapy to achieve shrinkage of *TP53*-mutated clones and allow patients to undergo stem cell transplantation while in molecular response. The results of this trial, when examined prospectively, showed that only a very limited number of patients could achieve allogeneic transplantation in a state of molecular remission, due to the fact that a period of molecular response was achieved only in a small fraction of cases, and even in those cases where it was achieved, the duration of response was too short.

The conclusion is that it is imperative to develop treatments that can achieve a more profound response. Here, we provide a brief introduction to novel treatment modalities that have been developed to achieve these goals.

Venetoclax, a *BCL2* inhibitor, is often used in combination with demethylating agents. This combination was more effective than the demethylating agent alone in patients with *TP53* wild-type, but did not improve the outcome of *TP53*-mutated cases.

Eprenetapopt (APR-246) exerts its function by restoring the DNA binding capacity of mutant p53 by repairing conformational changes. A recent report of a phase III trial comparing APR-246+azacitidine with azacitidine alone in MDS cases showed a higher CR rate in the former compared to the latter (33 *vs*. 22%), although the difference did not reach statistical significance.

CD47 is a membrane receptor that allows cancer cells to escape phagocytosis by macrophages and is expressed in >50% of *TP53*-mutated AML/MDS. Thus, anti-CD47 antibody (Magrolimab) promotes anti-cancer mechanisms. Indeed, in combination with azacitidine, magrolimab achieved CR+CRi ratio of 42% of *TP53*-mutated cases with OS of 10.8 months. In another study, this combination achieved molecular response of *TP53* mutant clone (variant allele frequency <7%) in 54% of cases at cycle 3 and 75% at cycle 5. The combination of azacitidine+ magrolimab is currently being evaluated in a Phase III trial (ENHANCE-2 trial).

Pevenodistat, an inhibitor of the NEDD8 activating enzyme, is another option that has been evaluated in combination with azacitidine for *TP53*-mutated tumors. In a phase I/II study, the addition of pevenodistat to azacitidine showed no benefit in terms of overall response (25% *vs*. 28%).

In addition, sabatolimab, a TIM-3 antibody, and immune checkpoint inhibitors are also in development. Currently, the strategy of consolidating the deep remission achieved by these novel therapies with allogeneic transplantation seems a realistic approach.

***Address for Correspondence:** Dr. Yasuhito Nannya, Department of Hematopoietic Disease Control, Institute of Medical Science, The University of Tokyo, Japan, E-mail: yasuhito.nannya@gmail.com*

Received: 12-Sep-2023, Manuscript No. JBL-23-113471; **Editor assigned**: 18-Sep-2023, PreQC No. JBL-23- 113471 (PQ); **Reviewed:** 02-Oct-2023, QC No. JBL-23-113471; **Revised:** 09-Oct-2023, Manuscript No. JBL-23- 113471 (R); **Published:** 16-Oct-2023, DOI: 10.37421/2165-7831.2023.13.306

How to cite this article: Nannya, Yasuhito. " Commentary on *TP53* Mutated Myeloid Malignancies and Their Treatment Strategy " *J Blood Lymph* 13(2023):306.