EDITORIAL

Successful venetoclax and Actinomycin D-based treatment for relapsed acute myeloid leukemia post allogeneic hematopoietic cell transplantation

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Allogeneic hematopoietic cell transplantation (allo-HCT) is a potentially curative procedure for a subset of patients with acute myeloid leukemia (AML) which otherwise have a high risk of relapse if treated with intensive chemotherapy alone. Major advances in the field of allo-HCT in regards to donor selection, conditioning regimens with reduced intensity, graft-versus-host disease prophylaxis, and supportive care expanded the applicability of allo-HCT while reducing the non-relapse mortality. However, AML relapse post allo-HCT remains a hard nut to crack that poses an enormous challenge. Despite increasing survival rates of young patients relapsing post allo-HCT in recent years [1], attaining a prolonged remission and long-term survival is still difficult to reach, and new therapeutic approaches in this setting are a pressing necessity.

The choice of treatment for relapsed AML post allo-HCT is largely depending on the patient's age, performance status, remission duration post allo-HCT, genetic and molecular characteristics. Generally, the 2-year overall survival (OS) of AML patients relapsing post allo-HCT rarely exceeds 20% regardless of salvage treatment used [2]. The main concept of treatment is first aiming at reducing the leukemic burden and achieving remission if possible using chemotherapy or hypomethylating agents, with or without additional targeted agents, and more importantly, enhancing the graft-versus-leukemia effect that is best achieved by cellular therapy either with donor lymphocyte infusion (DLI) or a second allo-HCT.

Zucenka et al. in their published article retrospectively analyzed the clinical outcomes of a new combination regimen for AML patients relapsing post allo-HCT, involving venetoclax, a BCL2 inhibitor in addition to low dose cytarabine and Actinomycin-D [3]. They compared their results to higher intensity chemotherapy including high dose cytarabine in combination with fludarabine and idarubicin (FLAG-Ida). They treated a total of 20 patients with the new regimen called ACTIVE, and 29 patients with FLAG-Ida. The baseline patients' characteristics were balanced between the two groups, except that patients treated in the ACTIVE group more likely received reduced-intensity conditioning (RIC) before relapse in 85% of the patients compared to 55% in the FLAG-Ida group ($p = 0.035$), this difference probably translated into a significantly higher proportion of patients (80%) in the ACTIVE group relapsing within 12 months of allo-HCT versus 41% in the FLAG-Ida group. Interestingly, the ACTIVE regimen that was followed by maintenance venetoclax, low dose cytarabine, and DLI demonstrated an impressive overall response rate (ORR) of 75%, and a complete remission or complete remission with

incomplete platelet recovery (CR/CRp) rate of 70%, and an undetectable measurable residual disease (MRD) that was achieved in 54% of responders. These response rates compare favorably with the FLAG-Ida regimen where ORR, CR/CRp, and MRD rates were significantly lower at 66% ($p = 0.54$), 34% ($p = 0.02$) and 10% ($p = 0.03$) respectively. An improvement in OS was also observed with a median OS of 13.1 months in the ACTIVE group, significantly longer than 5.1 months in the FLAG-Ida group ($p = 0.03$). The ACTIVE regimen was well tolerated with no associated treatment-related deaths, whereas the FLAG-Ida regimen was associated with a higher incidence of infections (31%) and graft-versus-host disease (45%) as well as treatment-related mortality (34%).

Recently, the addition of venetoclax to lower intensity chemotherapy, such as 5-azacitidine or low dose cytarabine has become a new standard of care in the treatment of elderly and/or unfit patients with newly diagnosed AML based on two pivotal trials, VIALE-A and VIALE-C with a reported composite CR rate of 66 and 48% respectively [4, 5]. This combination was also used in the relapsed and/or refractory (R/R) setting with a modest ORR of 21% and 6-month OS of 24% [6]. Data regarding venetoclax-based therapies in relapsed AML post allo-HCT are scarce and include a limited number of patients. Few retrospective studies have reported an ORR of 38–46% [7, 8]. More recently, a prospective clinical trial combining FLAG-Ida regimen with venetoclax in the R/R setting reported a composite CR rate of 57% among patients with prior allo-HCT, with a 75% rate of second allo-HCT among responders [9]. Despite these encouraging results, this intensive regimen is usually limited to younger and relatively fit patients.

In order to further improve on venetoclax-based combinations, especially in the most difficult-to-treat patients, multiple investigational drugs have been used to overcome resistance to BCL-2 inhibition. One of the most recognized pathways of resistance to venetoclax is the upregulation of MCL-1, an anti-apoptotic protein. Preclinical data suggested a synergistic anti-leukemic effect of selective MCL-1 inhibitor with venetoclax that is currently being tested in clinical trials, in addition to other targeted agents that cause MCL-1 degradation, such as MDM2 inhibitor [10, 11].

Interestingly, Zucenka et al. [3] evaluated the addition of Actinomycin-D to the venetoclax-based combination as a new therapeutic strategy to overcome venetoclax resistance in the post allo-HCT setting. Actinomycin D is an old inexpensive drug that showed promising results in *NPM1*-mutant AML and might be synergistic with venetoclax targeting MCL-1 as per the authors' hypothesis. A recent study showed that Actinomycin D targets mitochondria, yielding reactive oxygen species which enforce PML nuclear body-biogenesis and restore senescence. Dual targeting of mitochondria with Actinomycin-D and venetoclax sharply potentiates their anti-AML activities in vivo [12].

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It is certain that venetoclax- based combinations have revolutionized the treatment of adult patients with AML. Current and future studies are ongoing to optimize treatment, especially in many subgroups of patients with suboptimal outcomes, including those relapsing post allo-HCT. One interesting approach is avoiding relapse using prophylactic post-transplant maintenance [13]. When relapse happens, the ACTIVE regimen with the addition of Actinomycin-D to venetoclax and low dose cytarabine looks promising, feasible, and safe, allowing deeper remissions and easier transition to cellular therapy [3]. Larger prospective studies investigating multiple novel agents in combination with venetoclax are eagerly awaited.

Iman Abou Dalle¹ and Ali Bazarbachi¹✉

¹Department of Internal Medicine, American University of Beirut medical center, Beirut, Lebanon. ✉email: bazarbac@aub.edu.lb

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IAD and AB wrote the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to A.B.

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