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Venetoclax and other BH3 mimetics in Acute Myeloid Leukemia – current practice and future perspective

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On 21st of May, Michael R. Savona from Vanderbilt University Medical Center, Nashville, US, and Andrew Wei from Monash University, Clayton, AU, published a commentary in Journal of Clinical Oncology.[1] The article highlights the clinical impact of venetoclax in potential therapy combinations, discusses possible mechanisms of resistance and ways to overcome them, as well as the future of ventoclax and other BH3 mimetics in acute myeloid leukemia (AML).

Current standard treatment for patients with AML is cytotoxic chemotherapy, which lacks specificity, destroying both cancer and normal cells leading to a range of side effects. Moreover, older patients have poor response to chemotherapy, while having increased risk of treatment-related complications. Therefore, a selective therapy targeting cancer cells and leaving the surrounding normal tissue undamaged is urgently needed.

Venetoclax, a highly specific, second generation B-cell lymphoma 2 Homology 3 (BH3) mimetic targeting pro-survival protein B-cell lymphoma 2 (BCL-2) was developed to address this need. Although single agent clinical phase I data[2] showed only a modest response of 19% in relapse/refractory AML (R/R AML), combination with DNA methyltransferase inhibitors[3,4] (DNMTi) or low dose cytarabine[5] (LDAC), achieved a high rate of clinical response (67% and 54% accordingly) and was well tolerated (Table 1). Based on this evidence, in November 2018, the FDA approved venetoclax combination therapy for the use in older/unfit patients with AML.

Table 1. Clinical characteristics and outcome of venetoclax with DNMTi (Azacitidine/ Decitabine) or LDAC in older patients with AML.[4,5]*

Parameter		**Venetoclax + DNMTi**	**Venetoclax + LDAC**
Characteristics	Venetoclax RP2D	400mg days 1–28	600mg days 1–28
	No.	145	82
	Median age (range), years	74 (65–86)	74 (63–90)

	Secondary AML, No. (%)	36 (25)	40 (49)
	Prior DNMTi therapy, No (%)	–	24 (29)
	Poor risk CG, No (%)	71 (49)	26 (32)
Treatment	30-day mortality (%)	3	6
	Median time to response (months)	1.2	1.4
	Median cycles, No. (range)	5 (1–25)	5 (1–30)
CR/ CRi (%)	Total	67	54
	No prior DNMTi	–	62
OS (months)	Total	17.5	10.1
	No prior DNMTi	–	13.5

*OS, overall survival; CR, complete remission; CRi, complete remission with incomplete hematologic recovery

The authors stress the importance of understanding potential mechanisms underlying resistance to BH3 (BCL-2, BCL-X_L and MCL1) mimetics, in order to fully utilise the benefits of venetoclax combination therapy. Some evidence suggests that *BCL-2* mutations similar to those seen in chronic lymphatic leukemia[6] and an altered metabolic control of apoptosome leading to overexpression of *MCL1*[7,8] could be associated with resistance. Therefore, BH3 profiling of patients[9] and mutation screening might guide identification of those who are most likely to benefit, and could potentially be useful in monitoring cancer evolution in response to the therapy.

Additionally, the efficacy of venetoclax in a fitter population of patients with AML is currently being investigated. Early data in *NPM1* or *IDH* mutant AML subgroups indicates high efficacy with CR and incomplete hematopoietic count recovery rates around 90% and 70% respectively.[4,6] However, long-term studies are needed to confirm these results and to explore the

potential benefits of combination with other targeted therapies including FLT3 or IDH inhibitors.

The success of venetoclax has stimulated interest in other BH3 mimetics. Preclinical studies using MCL1 inhibitors (S63845,[10] VU661013,[11] AMG-176,[12] and AZD599128[13]) showed enhanced sensitivity of malignant cells to simultaneous inhibition of MCL1 and BCL-2, indicating their importance in survival of leukemic cells. However most importantly, this combination approach seems to have the potential to overcome resistance, and has been shown to be effective in chemotherapy R/R AML and tumours resistant to BCL-2 inhibition[10,11,]. This therapy may also solve problems arising from genomic diversity and clonal plasticity, which currently complicate long-term disease control with conventional cytotoxic therapies.

Several new drugs targeting MCL1 are in clinical development for hematologic cancers, including AML, as a single agent and in combination with venetoclax (NCT02979366, NCT02675452, NCT03218683, and NCT03672695). Moreover, efficacy and safety of venetoclax combinations with compounds indirectly targeting MCL1, such as XPO1, CDK9, MDM2, and MEK are also being studied[14-16]. Time will show which of these approaches will be able to balance high efficacy with good tolerability.

Currently, elderly patients are the only subgroup of AML population with proven benefit of venetoclax. However in the next few years, we should have a clearer picture whether younger patients with more aggressive disease will respond equally as well to venetoclax combinations. In the future, novel BH3 mimetic combinations could replace the more toxic chemotherapy in the clinic, and potentially overcome chemotherapy resistance in R/R AML.

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