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General AML

ISAL 2019 | Novel therapeutic combinations containing venetoclax for the treatment of acute myeloid leukemia

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On February 25, 2019, Andrew Wei from the Alfred Hospital and Monash University, Melbourne, Australia, presented at the Acute Leukemias XVII Biology and Treatment Strategies biennial symposium, in Munich, Germany on the topic of novel treatment combinations for acute myeloid leukemia (AML), particularly focusing on venetoclax.[1]

Treatment options for elderly patients with AML are limited, with few new drug approvals over the last decade. Since this patient population has poor survival outcomes and are often ineligible for intensive chemotherapy, there is an unmet need for novel therapies in this setting.

BCL-2 and MCL1 are anti-apoptotic proteins, making them targets for inhibitory agents. Inhibiting these proteins leads to cell apoptosis and negates the need for upstream inhibitors such as p53, which are commonly mutated or silenced in tumor cells. On November 21, 2018, venetoclax, a BCL-2 inhibitor was approved by the U.S. Food & Drug Administration (FDA), as was glasdegib, a selective hedgehog pathway inhibitor.

Since venetoclax only inhibits BCL-2, it has limited activity in AML. In a phase II study by Konopleva *et al.*, 2016, an overall response rate of 19% and median overall survival (OS) of 4.7 months was achieved with venetoclax alone.[2] Therefore, it is plausible that combining venetoclax with chemotherapy, may increase response rates.

In a phase I/II study (NCT02287233) by Wei *et al.*, 2018, venetoclax was combined with low-dose cytarabine (LDAC) in patients with treatment naïve AML who were considered unfit for intensive chemotherapy. In this study, LDAC was administered subcutaneously at a dose of 20 mg/m^2 daily on days 1–10, with venetoclax in a dose-escalation stage starting at 50 mg or 100 mg and increasing to 600 mg and then at 600 mg onwards.[3]

There are currently no results available from randomized trials comparing venetoclax + LDAC to LDAC alone. However, there are trials conducted with the same LDAC regimen, which may provide evidence of the efficacy of this regimen. **Table 1** shows the venetoclax + LDAC study compared to a study by Kantarjian *et al.*, 2012, investigating LDAC alone, and Cortes *et al.*, 2018, comparing LDAC to LDAC + glasdegib.[4,5]

	LDAC + Venetoclax[3]	**LDAC[4]**	**LDAC[5]**	**LDAC + glasdegib[5]**
N	82	243	38	78

Median age	74 (63–90)	73 (64–91)	75 (58–83)	77 (63–92)
ECOG >1	29%	24%	52%	53%
Prior HMA	29%	-	18%	17%
CR/CRi	54%	11%	5.2%	24%

Table 1: Complete remission (CR), complete remission with incomplete blood count recovery (CRi), hypomethylating agent (HMA)

In a recent study by Wei *et al.,* 2019, in the Journal of Clinical Oncology, the survival outcomes of LDAC with venetoclax were found to be promising, with an average 13.5-month median overall survival (OS) in patients without prior HMA. There was a 62% CR/CRi rate in patients without prior HMA, compared to 33% in patients with prior HMA exposure.[6] In the Kantarjian *et al.,* 2012, study of LDAC alone, a median OS of 5 months was achieved.[4]

The survival was especially prominent in patients who achieved a CR, with 100% (100–100) of patients alive at 12 months, compared to 73% (62–90) who achieved CR/CRi and 5% (0–19) who did not respond. This was at a median follow-up of 20 months. There was also a short time to first response of 1.4 months (median). Patients who were long-term survivors have also ceased therapy.

In patients who did not respond, it is important to understand the mechanism of resistance in order to find viable alternative options. When analyzing cytogenetics (Wei *et al.,* 2017)[7]:

- Intermediate cytogenetic risk:
  - Resistant disease: 22%
  - *FLT3*^{MUT}*:* 63% (5/8)
- Adverse/unknown cytogenetic risk
  - Resistant disease: 58%
  - *TP53*^{MUT}: 43% (6/14)
- OS by molecular subgroups showed:
  - *TP53*-aneuploidy and *FLT3*^{MUT} with chromatin-spliceosome had the poorest OS with no long-term survivors
  - Patient with NPM1 mutations, with or without *FLT3*^{MUT}*,* had the longest OS rate and all achieved a CR/CRi
- In relapsed patients, at least three patients had acquired the *FLT3*^{MUT} at relapse suggesting it may play a role in resistance mechanisms

Designing a risk-stratified trial for elderly patients with AML

- Elderly patients with AML, over the age of 60, stratified based on non-adverse *versus* adverse/unknown karyotype in the front-line setting
- In the non-adverse group:
  - Initial LDC and venetoclax with midostaurin
  - Initial LDC and venetoclax
- In the adverse/unknown group:
  - Initial LDC and venetoclax with pracinostat
  - Initial LDC and venetoclax
- Rationale for including pracinostat in the adverse/unknown group:
  - Panobinostat, a histone deacetylase (HDAC) inhibitor, exhibited *TP53* independent activity. Studies showed primary AML cells, including p53 mutant cells, were found to be sensitive to the combination of panobinostat with a BCL-2 inhibitor with a clearance of bone marrow disease on day 8
  - In panobinostat treated cells, several BH3-only proteins were upregulated, including NOXA, which directly targets MCL1
  - This led to the hypothesis that HDAC inhibitors increase BH3-only protein burden and overcome the adverse risk when combined with venetoclax
  - Panobinostat was unavailable for clinical trials, so pracinostat, another HDAC inhibitor, was used instead

Combining a BCL-2 inhibitor with an MCL1 inhibitor is another route to explore. There are four MCL1 inhibitors currently in clinical development. Targeting both BCL-2 and MCL1 with respective inhibitors has been shown to be effective in treatment naïve AML as well as relapsed/refractory AML by Moujallad *et al.,* 2018, in preclinical models.[8] This is interesting as the primary AML cells utilized would likely have had diverse molecular abnormalities, yet showed a promising overall response, showing these abnormalities may not affect the effectiveness of the combination.

The BCL-2 and MCL1 combination has been shown to be effective in multiple settings; including primary AML, diverse genotype primary AML, chemoresistant AML samples and, venetoclax/LDAC resistant samples. Since effectiveness is shown in venetoclax/LDAC resistant samples, this indicates resistance is to the cytotoxic component of treatment meaning that the combination of venetoclax with a novel agent such as an MCL1 inhibitor can restore the potential for sensitivity.

Colony assays on normal CD34 cells show combining BCL-2 and MCL1 is well-tolerated. In preclinical toxicity experiments in humanized MCL knock-in mice models, monocytes and B-cells are suppressed when an MCL1 inhibitor is used, but no gross organ toxicity was been reported. Trials are underway investigating the BCL-2 and MCL1 combinations.

Conclusion

There are many potential applications for venetoclax in AML treatment, including combination therapy with targeted drugs such as IDH, FLT3, MCL1 inhibitors, or drugs which are more active against p53 mutant AML. Understanding the resistance mechanisms involved may assist in developing the optimal combinations, and the dual-targeting of BCL-2 and MCL1 is showing strong results so far. There may also be a role for these drugs in the maintenance setting. The treatment of elderly patients with AML is becoming more feasible and effective with these novel agents.

References

1. Wei A. *et al.* Venetoclax and novel combinations. 2019 Feb 25. ACUTE LEUKEMIAS XVII Biology and Treatment Strategies Meeting, Munich, DE.
2. Konopleva M. *et al.* Efficacy and Biological Correlates of Response in a Phase II Study of Venetoclax Monotherapy in Patients with Acute Myelogenous Leukemia. Cancer Discovery. 2016 Aug 12. DOI: 10.1158/2159-8290.CD-16-0313
3. Wei A. *et al.* Venetoclax with Low-Dose Cytarabine Induces Rapid, Deep, and Durable Responses in Previously Untreated Older Adults with AML Ineligible for Intensive Chemotherapy. Abstract #284. ASH 60th Annual Meeting and Exposition, San Diego, CA.
4. Kantarjian H.M. *et al.* Multicenter, Randomized, Open-Label, Phase III Trial of Decitabine Versus Patient Choice, With Physician Advice, of Either Supportive Care or Low-Dose Cytarabine for the Treatment of Older Patients With Newly Diagnosed Acute Myeloid Leukemia. J Clin Onc. 2012 Jun 11. DOI: 10.1200/JCO.2011.38.9429
5. Cortes J.E. *et al.* Glasdegib in combination with cytarabine and daunorubicin in patients with AML or high-risk MDS: Phase 2 study results. Am J Hemat. 2018 Aug 03. DOI: 10.1002/ajh.25238
6. Wei A. et al. 2019. Journal of Clinical Oncology, currently in print.
7. Wei A. *et al.* Phase 1/2 Study of Venetoclax with Low-Dose Cytarabine in Treatment-Naive, Elderly Patients with Acute Myeloid Leukemia Unfit for Intensive Chemotherapy: 1-Year Outcomes. Blood. 2017 Dec 17. Abstract #890. ASH 59th Annual Meeting and Exposition, Atlanta, GA.
8. Moujallad D. *et al.* Combining BH3-mimetics to target both BCL-2 and MCL1 has potent activity in pre-clinical models of acute myeloid leukemia. Leukemia. 2018 Sep 10. DOI: 10.1038/s41375-018-0261-3