Editorial Commentary

More options for older patients with acute myeloid leukemia: venetoclax in combination with low dose cytarabine

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Provenance: This is an invited article commissioned by the Academic Editor Dr. Xueya Zhang (Department of Hematology, The Second Affiliated Hospital of Fujian Medical University, Fuzhou, China).

Comment on: Wei AH, Strickland SA Jr, Hou JZ, *et al*. Venetoclax combined with low-dose cytarabine for previously untreated patients with acute myeloid leukemia: results from a phase Ib/II study. J Clin Oncol 2019;37:1277-84.

Submitted Sep 16, 2019. Accepted for publication Sep 27, 2019.
doi: 10.21037/cco.2019.09.03
View this article at: http://dx.doi.org/10.21037/cco.2019.09.03

Acute myeloid leukemia (AML) is hematopoietic malignancy occurring in any age group, but with a peak in the older population. The median age at the time of diagnosis is 68 years, and the incidence is 12.2 cases in 100,000 in patients older than 65 years compared to 1.3 in patients younger than 65 years (1). Nonetheless, historical therapeutic studies in AML routinely restricted their enrollment to younger and fit patients, thereby excluding many newly diagnosed AML patients only based on age. The rationale behind this approach has been "the misconception" that disease remission and cure in AML can only be accomplished with intensive regimens such the cytarabine-daunorubicin-based "7+3" in which tolerability is unfortunately a major concern with increased age. The modest activity of less intensive regimens such as low dose cytarabine (LDAC) or single agent hypomethylating agents (HMAs) (i.e., decitabine or azacitidine), along with higher incidences of adverse-risk cytogenetic and molecular findings, prior antecedent hematological disorders (secondary AML), and prior exposure to cytotoxic therapies (therapy-related AML) have had a concurrent role in determining the dismal prognosis of older patients with AML with no substantial progress in their outcomes for the last several decades (2,3).

Nowadays, cancer treatment has been shifted from delivering non-specific conventional cytotoxic therapies toward targeting the underlying molecular aberrations on individual basis, the so-called "precision medicine". In contrast to chemotherapies, newer targeted and molecular therapies are in general better tolerated even in older individuals. Therefore, integrating such novel drugs in the treatment of older population with malignancies, including AML, has become an attractive area for investigation.

B-cell leukemia/lymphoma-2 (BCL-2) family members are essential regulators of intrinsic apoptosis pathways and determine cell fate through either prompting pro-apoptotic or anti-apoptotic activity (4,5). Venetoclax is a selective potent BCL-2 inhibitor that has shown promising activity in variety of hematological malignancies (6-8). Venetoclax restores the process of apoptosis and triggers mitochondrial outer membrane permeabilization and leads into activating caspases. BCL-2 is overexpressed in leukemic stem cells and contributes to treatment resistance in AML cells (9,10). As a single agent, venetoclax only produced modest response in relapsed and refractory (r/r) AML (8). Resistance to single agent venetoclax is multifactorial including upregulation of other antiapoptotic members of the BCL-2 family proteins such as myeloid cell leukemia-1 (MCL-1). Preclinical studies have demonstrated that drugs such as HMAs, anthracycline and cytarabine can induce downregulation of MCL-1 (10-12), and thus, providing a good rationale for combining these drugs with venetoclax. In AML, higher response rates have been reported in patients treated with venetoclax in combination with HMAs compared to

historical data with single agent (8,13,14).

In the *Journal of Clinical Oncology*, Wei *et al.* reported on the results of a phase Ib/II study in which venetoclax was combined with standard LDAC in elderly and unfit patients with newly diagnosed AML (15). The study enrolled a total of 82 patients with a median age of 74 (range, 63–90) years. The maximum tolerated dose of venetoclax was 600 mg daily in the phase I part. The regimen was well-tolerated with only 6% of early mortality. Notably, the anti-leukemic activity of venetoclax and LDAC was very encouraging in this challenging patient population with an overall response rate [complete remission (CR) and CR with incomplete blood count recovery (CRi)] of 54%, a median time to response of 1.4 (range, 0.8 to 14.5) months and a median overall survival (OS) of 10 months. These response rates compared favorably to previously reported results with single agent LDAC (16,17), despite that approximately half of the patients enrolled in this trial had secondary AML, 29% had prior HMA, and overall a high frequency of adverse-risk cytogenetics (32%). All patients who achieved CR in this study were alive at one year compared to 5% in non-responders and 49% in patients who achieved CRi, indicating a strong impact on survival duration of the initial treatment response. As expected, bone marrow suppression and febrile neutropenia were the main toxicities associated with this regimen, while no clinical tumor lysis syndrome was observed.

Earlier this year, DiNardo *et al.* reported a phase Ib/expansion study combining venetoclax with either decitabine or azacitidine in elderly and unfit patients with newly diagnosed AML and demonstrated a CR/CRi of 67% for all patients and 73% for patients treated with venetoclax at the dose of 400 mg (13). In contrast to the study of Wei *et al.*, DiNardo *et al.* excluded patients with prior HMA therapy. Notably, failure of prior HMA is associated with low response to standard induction therapies in AML (18,19). Thus, once the analysis was restricted to HMA-naïve patients, Wei *et al.* reported a CR/CRi rate of 62% with venetoclax and LDAC combination (15), thereby approaching the response rate observed with venetoclax and HMA regimen (13). Prior treatment with HMA was also associated with inferior OS even in patients treated with venetoclax and LDAC (4.1 *vs.* 13.5 months) as compared to HMA-naïve patients. Thus, secondary AML with prior exposure to HMA continue to represent an area of unmet need even with venetoclax-based therapy and require further optimization of the regimen or alternative innovative therapy.

Yet, leukemia genetic is another key predictor for response to venetoclax and LDAC combination, and poor-risk cytogenetics had an adverse influence when compared to intermediate-risk group (CR/CRi, 42% *vs.* 63%). Likewise, high-risk molecular markers such as *FLT3-ITD* and *TP53* mutations also impacted response unfavorably. In contrast, and in concordance to what previously observed in respect to the sensitivity of *IDH*-mutated AML to venetoclax (8), the combination of venetoclax with LDAC was particularly effective in *IDH*-mutated AML patients with a CR/CRi rate of 72% and a median OS of 19 months. A very encouraging response rate was also observed in patients carrying the *NPM1* mutation (CR/CRi, 89%), a molecular marker that also predicts a relatively high response to intensive cytarabine-anthracycline-based induction therapy for fit, older AML patients, and is therefore a frequently advocated approach for this molecular subgroup (20).

Notwithstanding the encouraging initial response rate with venetoclax and LDAC in AML, the durability of remission remains unsatisfactory. Furthermore, responses in patients with high-risk genetics and clinical features were suboptimal. Thus, additional studies and new therapeutic approaches must be considered in this challenging patient population. The proven safety of venetoclax and LDAC allows us to consider this regimen as an ideal backbone to combine with other emerging novel molecular targeted therapies. Additionally, this regimen could also have the potential to represent a safe induction therapy to bridge older adults with AML to a curative intensification approaches such as allogeneic hematopoietic cell transplantation, since it would allow patients to avoid the co-morbidities inherent to high-intensity and more-toxic chemotherapy-based induction regimens prior to transplant. However, data with regard to post-transplant outcomes for older AML patients receiving venetoclax-based induction therapy are lacking at this time.

Finally, while venetoclax with LDAC or HMA represent substantial steps forward in managing untreated AML in elderly patients, given the safety profile and relatively high efficacy, it would not be unreasonable to test these combinations in younger and fit AML patients. Current standard intensive regimens continue to convey non-trivial risks for treatment-related morbidity and mortality, even in younger patients with AML, and the intensity of such regimens create obstacles toward safely combine with other promising agents.

In conclusion, "low" intensity venetoclax-based regimens may represent a safer backbone in AML patients across

all ages and warrant to be compared directly to current standard of care in fit AML patients. If venetoclax-based induction proven to be at least comparable to the intensive induction regimen "7+3" in terms of response including achievement of "minimal residual disease" negative status, it is very likely that the safety profile would favor the venetoclax-based regimens at least in some subset of newly diagnosed AML.

Acknowledgments

None.

Footnote

Conflicts of Interest: Ibrahim Aldoss has served on an Advisory Board with Abbvie. Guido Marcucci is on the Speaker Bureau for Abbvie.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Aldoss I, Marcucci G. More options for older patients with acute myeloid leukemia: venetoclax in combination with low dose cytarabine. Chin Clin Oncol 2019;8(Suppl 1):S25. doi: 10.21037/cco.2019.09.03