

**BCL-2 Inhibitor and Conventional Chemotherapy Combinations for Acute Myeloid Leukemia: Shifting From the Unfit to the Fit Patient With AML** Gert Ossenkoppele, MD, PhD<sup>1</sup> and Paresh Vyas, PhD, MD

Anthracycline and cytarabine-based intensive combination chemotherapy has been the backbone therapy for patients with acute myeloid leukemia (AML) for nearly 50 years. The classic 7+3 combination, piloted in the 1970s and reported as a randomized study in 1981,<sup>1</sup> is the basis of most induction regimens. Since then, many studies have tested different doses and schedules of daunorubicin and cytarabine,<sup>2-11</sup> and they have added or substituted drugs that interfere with DNA replication (eg, etoposide, thioguanine, fludarabine, clofarabine, cladribine).<sup>8,12-15</sup> Unfortunately, such approaches have thus far not resulted in breakthrough results leading to drug approval by the regulatory authorities. However, things are beginning to change. Targeted therapies have been shown to benefit specific genetic/ biologic AML subgroups when added to intensive anthracycline-cytarabine chemotherapy regimens. There is now a consensus that gemtuzumab ozogamicin, a humanized murine anti-CD33 antibody linked to a cytotoxic antibiotic derivative calicheamicin, improves survival in good-risk-prognosis disease and, probably, intermediate-prognosis-risk AML.<sup>16-19</sup> Similarly, midostaurin, a multikinase inhibitor (including FMS-related tyrosine kinase 3, FLT3), improves survival in patients with FLT3-mutant AML when added to induction and consolidation anthracycline-cytarabine combinations.<sup>20</sup> Finally, the liposomal formulations of daunorubicin and cytarabine,<sup>21</sup> which gain cell entry via lipid scavenger receptors, have been shown to improve survival in secondary and treatment-related AML. Targeted agents have also been proven to be of benefit in the relapsed/refractory setting.<sup>22</sup> In the article that accompanies this editorial, Chua et al<sup>23</sup> report the results of the CAVEAT study, a phase Ib dose-escalation trial of the oral BCL-2 inhibitor venetoclax in combination with chemotherapy in newly diagnosed patients with AML over the age of 65 years, or 60 years of age with monosomal karyotype, fit for intensive chemotherapy. The important backstory to this study is the impressive results of the addition of venetoclax to either hypomethylating agents (HMA), or low-dose cytarabine (LDAC) in older unfit patients with AML. In phase II studies, venetoclax added to either HMA<sup>24</sup> or LDAC<sup>25</sup> improved complete remission (CR) plus complete remission with incomplete count recovery (CRi; CR 1 CRi) rates to 67% and 54%, respectively, from 24.6% and 27.8% for HMA<sup>26,27</sup> and a CR rate of 18% with LDAC.<sup>28</sup> This prompted the Food and Drug Administration to approve venetoclax-HMA and venetoclax-LDAC for newly diagnosed patients with AML unfit for intensive chemotherapy. The phase III study of venetoclax plus LDAC versus LDAC plus placebo (VIALE-C study) has now been reported.<sup>29</sup> It confirms the high CR 1 CRi rate (48%) of venetoclax plus LDAC. However, although the median overall survival (OS) was improved with venetoclax-LDAC, the increase was not statistically significant. The phase III data of the venetoclax-azacitidine versus azacitidine plus placebo (VIALE-A study) have just been reported online in abstract form,<sup>30</sup> again confirming the high CR 1 CRi rate of 66% for patients receiving venetoclaxHMA, but showing a highly statistical, and clinically significant, survival extension to 14.5 months from 9.6 months in the control arm. Given this, it is likely that venetoclax-based combinations will be the new standard of care for newly diagnosed patients with AML unfit for intensive chemotherapy. Given this background, investigating the potential benefit of adding venetoclax to intensive AML therapy in fit patients is very timely. A natural starting point was to study older patients fit for intensive chemotherapy because the outcome of treatment resulting from differences in the genetics and biology of AML in older patients is inferior compared with that of younger patients. The CAVEAT study reports data on 51 newly diagnosed patients with AML, either de novo (28 patients) or

secondary (23 patients), with a median age of 71 years (range, 63-80 years). They were treated in five venetoclax dose-escalation cohorts (50- 600 mg; venetoclax given over 14 days, day 26 to 17) with induction (infusional cytarabine 100 mg/m<sup>2</sup> days 1-5 and idarubicin 12 mg/m<sup>2</sup> intravenously days 2-3), four cycles of consolidation (cytarabine, days 1-2, and idarubicin, day 1), and as maintenance (up to seven 28-day cycles). Of the 51 patients, 10 were favorable risk, 16 were intermediate risk, and 25 were adverse risk per ELN (European LeukemiaNet) 2017 criteria.<sup>3</sup> The authors show that the combination is safe. There were no dose-limiting toxicities up to 400 mg. At 600 mg, two of 11 patients had a dose-limiting toxicity (DLT), one patient with myelofibrosis and one patient with antecedent myelodysplasia who had received prior HMA. Patients with myelofibrosis and prior HMA were then excluded by a protocol amendment, and an additional seven patients did not have a DLT at 600 mg of venetoclax. The main toxicity was myelosuppression. Median time to recovery of neutrophil ( $0.5 \times 10^9 /L$ ) and platelet ( $50 \times 10^9 /L$ ) counts after induction was 26 days (range, 19-36 days) and 25 days (range, 20 days-not reached by day 42), respectively. The 30-day all-cause mortality was 6% (three of 51 patients). Myelosuppression was even more marked with consolidation, with the platelet lineage being most sensitive (median time to recovery, 39-47 days). Myelosuppression during consolidation was dose dependent, such that none of the 17 patients who received 400 or 600 mg venetoclax completed all four cycles of consolidation. However, even at lower venetoclax doses, only six of 19 patients completed four consolidation cycles. Consequently, only 14 of 51 patients (27%) received maintenance therapy, of whom six completed all six cycles. Grade 3/4 thrombocytopenia was seen in seven of 14 patients. The overall CR 1 CRi rate was 72% but was 97% in the 28 patients with de novo AML and only 43% in secondary AML (21 patients). Better CR 1 CRi rates were seen in intermediate (85%) versus adverse (43%) risk groups; patients younger and older than 75 years of age did equally well. There was a dose-response relationship in terms of initial response, with patients receiving doses  $\geq 200$  mg of venetoclax doing better than those receiving doses below 200 mg. Given the short follow-up and small study size, the impact on OS is too premature to draw conclusions other than to note that patients with de novo, intermediate-risk AML who achieved a CR did better. There were interesting correlations between genetic mutational state and response. Patients with NPM1, IDH2 (but not IDH1), and SRSF2 mutations fared best, and patients with these mutations also showed the greatest decline in blast counts in the venetoclax-only prephase, suggesting that these mutations impart sensitivity to BCL2 inhibition. IDH2- and NPM1-mutant AML were associated with deep reductions in molecular minimal residual disease (MRD) burden. In contrast, patients with FLT3, RAS, PTPN11, and TP53 mutations were least sensitive to venetoclax alone. Concordantly, higher OS was seen in patients with mutations imparting venetoclax sensitivity compared with those with lower sensitivity, and at relapse, FLT3-ITD-, TP53-, and PH6-mutant clones were detected. Although this study did not test venetoclax with the more standard 7 1 3 combination, it represents an important landmark in the field. It is a logical starting point to test the concept in older patients, given the positive results of venetoclax combined low-dose chemotherapy in older patients. It was also important to test for safety with lower cumulative doses compared with 7 1 3. A study of venetoclax combined with 7 1 3 is underway in younger patients with AML (ClinicalTrials.gov identifier: NCT03709758), and others are due to start. For these and other studies, it clearly shows that myelosuppression may well dictate tolerability, and the ideal dose and schedule in induction as well as consolidation will need careful examination. There is strong suggestion that venetoclax combined with intensive chemotherapy may be best for NPM1, IDH2, and SRSF AML, as is the case when venetoclax is combined with HMA and LDAC.<sup>24,25,29</sup> Thus, for these groups, it would be worth testing the possibility of consolidation with less aggressive and outpatient-based cycles of venetoclax-HMA or

venetoclaxLDAC, rather venetoclax combined with intensive chemotherapy. In this regard, testing for MRD may help provide an early warning system to identify patients who are not responding adequately and need therapy intensification. For these patients, the traditional separation between intensive chemotherapy and low-dose chemotherapy, reserved for the unfit patient, may blur. Therefore, after a long time of having a relatively simple one-size-fits-all 7 1 3 approach followed by consolidation (with or without allogeneic stem cell transplantation [alloSCT]), we are rightly now well into the age of more genetically directed therapy, where understanding genetic landscape at diagnosis may dictate quite differing treatment options. Other therapeutic options for targeted agents can also be studied by international collaboration, including use in maintenance after achievement of CR, bridging to alloSCT, and MRD conversion. Further down the line, as we increasingly monitor genetic clonal evolution, constructing trials to deal with this issue will become the next challenge.