Reason for CPXcitement in AML

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In this issue of Blood, Lancet et al report their findings that CPX-351, a liposomal formulation of cytarabine and daunorubicin in a 5:1 molar ratio, produces superior response rates compared with 7+3 in older patients with acute myeloid leukemia (AML).1

The management of AML poses many therapeutic challenges. 7+3, defined as 7 days of cytarabine and 3 days of an anthracycline, was initially established as a standard induction regimen for newly diagnosed AML patients in the early 1980s after several large cooperative group trials by the Cancer and Leukemia Group B demonstrated its efficacy.2 However, a critical dilemma that continues to frustrate those who treat AML is how best to manage older AML patients (>55 years) and those with secondary AML. These subgroups of patients respond poorly to induction chemotherapy, frequently develop toxicities and complications from chemotherapy, and are rarely cured with standard therapeutic regimens.

Fortunately, Lancet et al provide optimism for older patients presenting with AML. Using a randomized phase 2 comparison, with up-front stratification according to critical poor-risk features, the investigators show that CPX-351 produced higher overall complete remission (complete remission [CR] + complete remission with incomplete blood count recovery [CRi]) rates compared with 7+3. Of note is that CPX-351 appeared to produce more CRi than CR compared with 7+3. It is unclear what the significance of this relative increase in CRi denotes; will these patients have comparable outcomes to their CR counterparts? One potential explanation for the increased CRi is the longer maintenance of a steady-state amount of daunorubicin delivered liposomally. This CRi may in fact relate to an increased therapeutic effect of CPX-351. Nonetheless, it appears that CPX-351 is less toxic than 7+3 (at least when analyzing treatment-related mortality) and may be an appropriate initial strategy in older AML patients with an adequate performance status to withstand intensive therapy.

Of keen interest were the promising results seen in patients with secondary AML. Secondary AML (treatment-related AML or AML from a preexisting hematologic disorder) has a dismal outcome with 7+3. Lancet et al demonstrate not only superior CR rates, but also prolonged overall survival (OS) and a signal of improved event-free survival (EFS) in secondary AML patients treated with CPX-351 as shown in the figure, although this subanalysis will need to be confirmed in a larger phase 3 trial. This may significantly advance our therapeutic armamentarium for AML, as secondary AML is a feature that can be gleaned on history alone, as opposed to waiting for other poor-risk features such as cytogenetics/genetic markers. Providing these patients with a therapeutic alternative to 7+3 would be a considerable achievement.

Results of CPX-351 vs 7+3. (A) EFS of secondary AML patients. (B) OS of secondary AML patients. See the complete Figure 1 in the article by Lancet et al that begins on page 3239.
Questions still remain, however, about the applicability of these results. (1) Is the 60-mg/m² daunorubicin dose in the control arm adequate for comparison? Although there have not been randomized clinical trials comparing daunorubicin 60 mg/m² to daunorubicin 90 mg/m², it appears that higher doses of daunorubicin (90 mg/m²) are more effective than lower doses (45 mg/m²) in patients with favorable and intermediate cytogenetics and those ≤65 years of age.3,4 However, higher doses of daunorubicin may have led to even further increases in toxicity in the control arm in this older group of patients (60-75 years). (2) Although the response rates were higher with CPX-351, why did this not translate to an OS benefit? One of the main reasons for the dearth of therapies approved for AML is the difficulty of showing a significant OS benefit for experimental approaches, in part because of variable approaches to the treatment of minimal residual disease (ie, consolidation, maintenance, and stem cell transplant strategies). In addition, the cross-over design further adds to the complexity of the OS analysis in this study. Improving OS is the holy grail of clinical cancer research and AML in particular; however, there are challenges when considering OS as an end point in therapeutic trials. Although allogeneic stem cell transplantation is a goal for most patients with unfavorable risk disease, there are a panoply of conditioning regimens (myeloablative, reduced intensity, and nonmyeloablative) at each institution that may impact overall outcome. Additionally, there is a lack of consistent consolidation/maintenance therapeutic approaches, and the ultimate choice of regimen (and how many cycles) may also impact overall outcome. How do we circumvent these biases to determine whether an experimental therapy is effective in AML patients? One approach would be to design phase 3 trials with identical postremission therapeutic strategies in each arm, clearly delineating which patients are to undergo stem cell transplantation, what type of consolidation therapy is to be administered, how many cycles, and at what doses. Another approach may be to determine alternative end points that may appear to be surrogates of OS. Lancet et al’s secondary end point of EFS represents a promising evaluation that may mitigate some of the biases seen with clinical studies in AML.

Will CPX-351 become the new “standard” regimen for older adults presenting with AML? Time will tell, and we eagerly await the phase 3 comparison of CPX-351 vs 7+3 in older patients. To date, there has been considerable variability in response rates and duration for diverse novel agents including tipifarnib,5,6 clofarabine,7 and gemtuzumab8 in older AML patients. We can remain optimistic with Lancet et al’s findings and other investigational approaches demonstrating potential benefit in elderly AML,9 and secondary AML.9,10 We hope that these confirmatory trials will ultimately improve outcomes and provide us with additional therapeutic options for our patients. Moreover, this study represents a superb template to explore the combination of CPX-351 with mechanistically distinct modalities such as inhibitors of DNA damage response pathways, cyclin-dependent kinase inhibitors, tyrosine kinase inhibitors, and immunotherapeutic strategies, so that the salutary effects of CPX-351 could be extended to other stages of AML where effective therapy is lacking. From Lancet et al’s work, there is reason for excitement for the future of AML therapies.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

REFERENCES