Mini-HCVD Plus Inotuzumab Plus or Minus Blinatumomab: Hype or Hope?

We commend Jabbour et al for their innovation of the mini–hyperfractionated cyclophosphamide, vincristine, and dexamethasone (mini-HCVD) plus inotuzumab plus or minus blinatumomab propensity score matched analysis.[1] In the absence of randomized controlled trials in this setting, this retrospective propensity score matched comparison allows for a less biased estimate of treatment effects. However, such an analysis leaves us with several unanswered questions.

First, is historical HCVD the best comparator in elderly patients with acute lymphoblastic leukemia? The historical control (implemented in 1992 through 2010) in this propensity score analysis had a 3-year overall survival rate of 34% after matching; however, advances in supportive care and updated treatment regimens since the 1990s and 2000s likely have improved overall survival at The University of Texas MD Anderson Cancer Center over the years.[2,3] To illustrate this, it would be interesting to know what off-protocol standard-of-care treatment regimen currently is used by the authors for elderly patients with acute lymphoblastic leukemia, how these outcomes have changed over time, and why their more contemporary regimen was not chosen for the basis of this propensity score analysis. Using a more contemporary control could have better matched the advances in supportive care and knowledge gained over the past 20 years that a propensity score cannot adjust for. A retrospective review of patients receiving age-adjusted hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD) at The University of Texas MD Anderson Cancer Center between 2011 and 2018 reported a median event-free survival of 24.7 months and a median overall survival of 31.3 months, which also compares quite favorably against the median event-free survival and overall survival of the historical control in this publication (15 months and 17 months, respectively).[4] Phase 2, single-arm, single-institutional studies cross-compared with decades-old historical controls provide us with little data for external validity; multi-institutional randomized trials in this setting are feasible and should be performed.

Second, we wonder about the relative impact of blinatumomab compared with inotuzumab when added to HCVD. Recent data have demonstrated that the addition of blinatumomab to standard Berlin-Frankfurt-Münster (BFM) chemotherapy in adult patients (up to the age of 76 years) with minimal residual disease (MRD) positivity resulted in approximately 80% of patients achieving MRD negativity and achieving favorable long-term survival outcomes.[5] Ideally, a comparison of blinatumomab plus chemotherapy (eg, HCVD with BFM induction) with blinatumomab, inotuzumab, and chemotherapy should be conducted to truly determine the relative impact of each high-cost, high-risk, novel therapeutic addition. Furthermore, because the majority of patients with ALL will attain a morphologic remission with relatively low-intensity therapy (90% complete response [CR]/complete response with incomplete count recovery [CRi]/complete response with incomplete platelet recovery [CRp] rate in the hyper-CVAD arm without inotuzumab), perhaps an MRD-adapted approach would allow for the use of novel therapies in select patients while sparing those who achieve good responses the need to receive potentially toxic and high-cost therapies.

Third, given the considerable toxicity noted with inotuzumab, resulting in several protocol amendments, only 9 patients were treated on the final recommended treatment protocol of inotuzumab (at a dose of 0.9 mg/m^2 in cycle 1 and 0.6 mg/m^2 in cycles 2-4) with short follow-up. The survival curves of the various dosing cohorts were highly variable, as shown in Supporting Figures 1 and 2 of the study by Jabbour et al.[1] Furthermore, only 8 patients in this trial received blinatumomab. The sample of patients receiving the recommended regimen was too small to assess the efficacy and safety of the final recommended protocol. Thus, it is premature to alter practice based on such small, nonrandomized comparisons. Finally, the toxicity of mini-HCVD plus inotuzumab plus or minus blinatumomab was not compared with the historical cohort. How can we adequately judge the morbidity of this new combination without such comparative data?

In the clinical trial setting in which the drug is provided for free from the pharmaceutical company, treatment with inotuzumab plus mini-HCVD plus blinatumomab is possible. However, such a regimen would cost >$1.2 million for a treatment course: $180,000 for 8 doses of inotuzumab and $840,000 for 8 courses

of blinatumomab (which does not include costs for hospitalization or the supportive care requirements associated with the mini-HCVD backbone or costs to administer 8 cycles of a 28-day continuous infusion).[6] Given the small sample, lack of an appropriate randomized comparator, and many unanswered clinical questions regarding the efficacy and safety of the final protocol (9 patients), it is premature to conclude that this regimen is "a superior frontline approach for older patients with Ph [Philadelphia chromosome)-negative ALL." In this era of high-cost anticancer medications, we must practice oncologic stewardship and design appropriate trials to answer these questions before adopting this costly approach into practice or moving the approach into younger patients.

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Bernard L. Marini, PharmD, BCOP
Anthony J. Perissinotti, PharmD, BCOP
Lydia L. Benitez, PharmD, BCOP
Department of Pharmacy Services and Clinical Sciences, Michigan Medicine, University of Michigan College of Pharmacy, Ann Arbor, Michigan

Dale L. Bixby, MD, PhD
Patrick W. Burke, MD
Kristen M. Pettit, MD

Division of Hematology and Oncology, Department of Internal Medicine, Michigan Medicine, Ann Arbor, Michigan

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Reply to Mini-HCVD Plus Inotuzumab Plus or Minus Blinatumomab: Hype or Hope?

Marini et al have raised questions related to our recent article regarding the combination of mini–hyperfractionated cyclophosphamide, vincristine, and dexamethasone (mini-HCVD) plus inotuzumab plus or minus blinatumomab in older patients with newly diagnosed Philadelphia chromosome–negative acute lymphoblastic leukemia (ALL).[1]

To the best of our knowledge, there is no standard of care for older patients with ALL. In academic and community settings, survival was shown to be poor, even in the modern era. Medicare and the Surveillance, Epidemiology, and End Results (SEER) program reported a median survival of 5 to 10 months.[2,3] We and others have reported poor survival and high rates of death in complete remission. In our study,[1] the prematched cohort of patients treated with hyperfractionated cyclo phosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD) had an early death rate of 8%. The German Multicenter Study Group for Adult ALL reported higher rates of early death, with a mortality rate of 13% in patients aged >55 years using a dose-reduced chemotherapy approach.[4] Therefore, despite optimized supportive care, chemotherapy is poorly tolerated in these patients and thus there is a need for novel regimens in these patient populations. As shown before and after matching, the safety profile is favorable with a very low early mortality rate, a fact that may translate into a better overall outcome.

Furthermore, this regimen was shown to be highly effective, with a negative minimal residual disease status of 80% and 95%, respectively, at complete remission and overall, a milestone with a positive impact on long-term outcome.[5] With longer follow-up, we expect these results to be sustained. The sequential addition of blinatumomab hopefully will improve efficacy by deepening the responses and preventing disease recurrence and will improve safety by allowing the administration of lower doses of weekly inotuzumab and thus reduce the rate of veno-occlusive disease (VOD).