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Title: Mini-HCVD plus inotuzumab plus or minus blinatumomab: hype or hope?

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Condensed Abstract: The propensity score matched analysis by Jabbour and colleagues of the innovative regimen of mini-HCVD plus inotuzumab plus or minus blinatumomab in acute lymphoblastic leukemia leaves us with several unanswered questions. Without a randomized trial to answer these questions, it is unclear if such an approach should be adopted as standard of care.

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We commend Dr. Jabbour and colleagues on their innovation of the mini-HCVD plus inotuzumab plus or minus blinatumomab propensity score matched analysis.[1] In the absence of randomized controlled trials

(RCTs) 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 acute lymphoblastic leukemia (ALL)? The historical control (implemented 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 1990's and 2000's have likely improved overall survival at MD Anderson (MDACC) over the years.[2,3] To illustrate this, it would be interesting to know what off-protocol standard of care treatment regimen is currently employed by the group for elderly ALL, how these outcomes have changed over time, and why their more contemporary regimen was not chosen for the basis of this propensity-score analysis. Utilizing a more contemporary control could have better matched the supportive care advancements and knowledge gained over the past two decades that a propensity score cannot adjust for. A retrospective review of patients receiving age-adjusted HCVAD at MDACC between 2011-2018 reported a median EFS of 24.7 months and median OS of 31.3 months which also compares quite favorably against the median EFS and OS of the historical control in this publication (15 months and 17 months respectively).[4] Phase II, single-arm, single-institutional studies cross-compared to decades-old historical controls tell us little 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 demonstrates the addition of blinatumomab to standard BFM therapy in adult patients (up to the age of 76) with minimal residual disease (MRD) positivity resulted in 80% of patients achieving MRD negativity and achieving favorable long-term survival outcomes.[5] Ideally, a comparison of blinatumomab + chemotherapy (e.g., HCVD, BFM induction) to blinatumomab + inotuzumab + chemotherapy should be conducted to truly determine the relative impact of each high-cost, high-risk, novel therapeutic addition. Furthermore, because the majority of ALL patients will attain a morphologic remission with relatively low-intensity therapy (90% CR/CRi/CRp in HCVAD arm without inotuzumab), perhaps an MRD-adapted approach would allow for utilization 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 seen with inotuzumab, resulting in several protocol amendments, only 9 patients were treated on the final, recommended treatment protocol of inotuzumab (0.9 mg/m2 cycle 1, 0.6 mg/m2 cycles 2-4) with short follow up. The survival curves of the various dosing cohorts

were highly variable (supplemental figures 1-2 of the analysis). Furthermore, only 8 patients in this trial received blinatumomab. The sample of patients receiving the recommended regimen is too small to assess the efficacy and safety of the final protocol recommended. Thus, it is premature to alter practice based on such small, non-randomized comparisons. Finally, the toxicity of mini-HCVD plus inotuzumab plus or minus blinatumomab is not compared to the historical cohort. How can we adequately judge the morbidity of this new combination without such comparative data?

In the clinical trial setting where drug is provided for free from the pharmaceutical company, inotuzumab plus mini-HCVD plus blinatumomab is possible. However, such a regimen would cost greater than $1.2 million for a treatment course; $180,000 for 8 doses of inotuzumab and $840,000 for 8 courses of blinatumomab (does not include costs for hospitalization or 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 appropriate randomized comparator, and many unanswered clinical questions about efficacy and safety of the final protocol (n=9), it is premature to conclude that this regimen is "a superior frontline approach for older patients with Ph-negative ALL." In this era of high-cost anti-cancer medications, we must practice oncologic stewardship and design appropriate trials to answer these questions before adopting this into practice or moving this costly approach into younger patients.

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