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LETTER TO THE EDITOR

Response to: 'Are there still reasons to believe that high-dose chemotherapy plays a role in breast cancer management?'

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I am the senior author of the article that was published in *Journal of Clinical Oncology*, reporting a meta-analysis using individual data from randomized trials of high-dose chemotherapy (HDC) with autologous stem cell support (ASCT) in high-risk primary breast cancer (BC) patients. This was a joint effort of EBMT, STWP and MDACC. Here is my response to the letter of Drs Castagna and Martino.

Of 6210 patients who participated in the 15 trials, HDC achieved a significant 13% reduction in the risk of recurrence ($P<0.001$), but this did not translate into a significant OS benefit ($P=0.13$).[1] Therefore, this conclusion of the meta-analysis may raise the question in the scientific community whether HDC with ASCT in high-risk primary BC should continue to be explored or abandoned owing to a lack of definite OS benefit.

Drs Castagna and Martino (CM) raise four points about our article.

(1) OS has been traditionally used as the major end point of the effectiveness of a new treatment modality. In recent years, this concept has been challenged. Instead, relapse-free survival (RFS) is often considered the best way of evaluating a treatment, including adjuvant therapy and this is not influenced by old and newer treatments given after relapse.

I agree with CM that RFS is a well-accepted parameter for evaluating the efficacy of various treatment modalities in the conventional setting. When it comes to HDC and ASCT almost all conventional oncologists focus on OS. They would like to see a clearcut benefit on OS. I would say that this is very peculiar and difficult to understand for supporters and users of HDC. I think the main reason for this approach is the limited use of HDC and ASCT methods and techniques by conventional oncologists, because HDC and ASCT require a special education at the centers that have experience and staff in this field. Most of the medical oncology trainees do not have exposure to and experience in this field.

(2) Early studies of HDC showed unacceptably high mortality, and these distort the meta-analysis. In fact, outcome analysis, which excludes treatment-related mortality, suggests an advantage of HDC, in terms of OS.

CM suggests that excluding deaths due to toxicity would show that the advantage of HDC is clinically relevant. We think that this kind of analysis is dangerous and at best questionable because it is impossible to know how these patients would have fared had they not died due to toxicity. However, despite these reservations we reported the results of this analysis in our article: of 89 total deaths attributed to toxicity, 72 (6%) occured among the 1207 deaths in the HDC arms and 17 (1.4%) occured among the 1261 deaths in the control arms. To evaluate survival separately from treatment-related mortality, we conducted an additional analysis that excluded patients whose deaths were attributed to toxicity. The hazard ratio (HR) was 0.90 (95% CI, 0.83–0.99; $P=0.011$). This compares with a HR of 0.94 (95% CI, 0.87–1.02; $P=0.13$) when considering all deaths. Whether this difference achieves clinical relevance is open to question.

(3) Not all patients in those trials, which were included in this meta-analysis, had biomarker information, such as HER2 and hormone receptor (HmR) status, and the meta-analysis was not able to address biomarker-based subgroups of patients who would benefit from HDC. In fact, in this analysis, OS data in the HER2-negative patients appear quite encouraging. The positive effect of HDC was even more marked in the triple-negative disease.

Some previous meta-analyses suggested that intensive dosing of chemotherapy is more effective in HmR-negative tumors than HmR-positive tumors. In the beginning of this meta-analysis, our expectations were in line with these data. Namely, we expected that HDC would show a greater benefit in HmR-negative tumors. As substantially more patients had available HmR status than HER2 status, we were able to address this issue with greater confidence. It turned out not to be so.

When it comes to HER2 status, the issue is complicated by the fact that only 5 of the 15 trials had some patients with HER2 status available. Nevertheless, a detailed analysis of this question has been provided on the MDACC website (www.Mdanderson.org). As we indicated in our article, the observation about patients with HER2-negative tumors was driven by the NKI and WSG trials. These two trials had the second and ninth highest (of 15) differences in SPID. I think our conclusion still seems appropriate: the overall study results do not provide compelling evidence that HDC are effective in triple-negative BC.

(4) The heterogeneity of the trials in terms of chemotherapy regimens used may affect the results of the meta-analysis.

I do not have any objection to this statement by CM. For sure, different high-dose regimens and different conventional regimens that were used in the some of these trials included in this meta-analysis may have some effect on the results. This is always a concern in these kind of meta-analysis. It is obvious that study parameters can not be made near match in these previously done 15 trials.

In summary, the meta-analysis that was performed by our team documented a disease-free survival benefit for HDC and ASCT but not an OS benefit in patients with high-risk primary BC. This meta-analysis did not show any clearcut evidence of benefit for HmR-negative and/or HER2-negative tumors.

T Demirer
Deparment of Hematology, Ankara University Medical School, Ankara, Turkey
E-mail: demirer@medicine.ankara.edu.tr

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