Re: Randomized Trial of High-Dose Chemotherapy and Blood Cell Autografts for High-Risk Primary Breast Carcinoma

In the February 2 issue of the Journal, Hortobagyi et al. *(1)* reported on a randomized trial of high-dose chemotherapy (HDCT) and stem-cell support versus conventional chemotherapy in high-risk patients with breast cancer, who showed no clinically or statistically significant difference in relapse-free or overall survival. This trial was based on

previous phase II studies *(2)* that showed a substantial advantage for patients treated with HDCT in comparison with historical control subjects. The authors enrolled only 78 patients because they expected a overly optimistic 3-year difference of 30% between the two groups. The present study and other recent reports *(3)* clearly show that improvements, if any, of HDCT on the outcome of high-risk patients with breast cancer are likely to be slight. For this reason, all the clinicians working in this field, including the authors of the paper, agree that the results of large randomized trials (which have now completed their accrual) must be awaited to finally understand the role of the HDCT approach in the treatment of breast cancer. This attitude is even more necessary in view of the reported serious irregularities in the only randomized study showing a statistically significant survival advantage for this type of approach as adjuvant therapy for high-risk patients *(4)*.

In addition, we believe that major medical journals should consider the policy of not publishing small, albeit randomized, studies that at this point, are likely to add little clinical information to this issue.

It has been reported that HDCT with stem-cell transplantation is more effective in patients with advanced breast cancer who respond to conventional treatment *(5)*. Furthermore, lymph node status and the degree of tumor remission after primary chemotherapy in patients with operable breast cancer represent the most important prognostic factors for relapse-free survival *(6)*.

Similar to stage IV disease, the benefits of HDCT intensification in patients with stage II or III disease may well be modest in those who respond poorly to primary chemotherapy. Zambelli et al. *(7)* have recently reported discouraging results with HDCT in high-risk ($\geq$10 lymph nodes involved at surgery) patients with breast cancer whose tumors respond poorly to neoadjuvant anthracycline-containing regimens.

In the study by Hortobagyi et al. *(1)*, randomization included 30 patients with axillary lymph node involvement after four cycles of preoperative chemotherapy, but the authors did not specify whether tumor response was a criterion for accrual. Moreover, the authors do not appear to consider additional prognostic factors, including c-erbB-2 status and proliferative capacity. Given the small number of patients studied, these drawbacks might have hampered the evaluation of clinical results.

Finally, in the study by Hortobagyi et al., patients in the HDCT arm were given two cycles of high-dose, nonmyeloablative chemotherapy with stem-cell rescue. In contrast, the uncontrolled studies of HDCT that showed a survival advantage in patients with breast cancer *(2)* relied on single, more intensive, and possibly more active regimens.

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EDITOR'S NOTE

Like other journals, we give particularly high priority to definitive clinical studies, whether positive or negative. Small studies often have wide confidence intervals associated with treatment effects and are more subject to random error than are large studies. Therefore, small studies can fail to detect small treatment benefits. On the other hand, they are also more subject to falsely positive results. However, when the procedure itself (i.e., bone marrow transplantation) carries a high risk of morbidity and finite risk of mortality, the potential magnitude of benefits should be accordingly large. In such cases, even small studies can supply important information in guiding clinical practice.

Additionally, no study exists in a vacuum. In the last year, there have been several studies on high-dose chemotherapy, bone marrow transplantation, and high-risk primary breast cancer—one positive *(1)* [that has been discredited *(2)*] and four negative *(3–6)*. The results of the negative studies can be used in aggregate to help determine if a benefit of sufficient magnitude exists to fully counterbalance the substantial toxicity incurred by high-dose chemotherapy and bone marrow or stem-cell "rescue." The jury is still out on the ultimate role of high-dose chemotherapy in operable breast cancer. However, the results of randomized trials such as those conducted by Hortobagyi et al. do suggest that the substantial number of published uncontrolled studies gave an overly optimistic impression of the therapy's strategic worth.

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RESPONSE

The letter by Pedrazzoli et al. endorses the conclusions of our randomized, high-dose chemotherapy trial for high-risk primary breast cancer. It also underlines our plea that definitive conclusions about the efficacy of high-dose chemotherapy be reserved until the mature results of large randomized trials become available.

Furthermore, Pedrazzoli et al. propose that high-dose chemotherapy might be more effective for patients with breast cancer who respond to conventional treatment. This type of analysis is erroneous and misleading. Patients with advanced breast cancer who respond to conventional therapy have a better prognosis than those who do not *(1).* This is true whether they receive high-dose chemotherapy or not *(1,2).* However, in the absence of compelling evidence that high-dose chemotherapy improves outcomes in the overall group of patients with advanced disease, it is inappropriate to conclude that response to conventional therapy selects patients who will benefit from high-dose chemotherapy.

Patients who still demonstrate multiple, positive axillary lymph nodes after preoperative chemotherapy have an unfavorable prognosis *(3).* In our study, eligible patients who received preoperative chemotherapy had responded to preoperative therapy, but they still had four or more positive axillary lymph nodes. When this study was designed, only patients at very high risk of recurrence were acceptable candidates for high-dose chemotherapy, which in the late 1980s was associated with a substantial (5%–8%) treatment-related mortality rate.

The results of our study showed no differences in outcome for the overall randomly assigned groups and for the subsets whom we planned to analyze prospectively. Many additional subset analyses could be undertaken retrospectively. However, considering the small sample size and the retrospective and unplanned nature of additional analyses (such as a search for prognostic factors), any results would be tentative at best. We thought that the presentation of the overall results, based on the planned analyses, would best serve our readers.

We discussed the nonmyeloablative character of the high-dose CEP (cisplatin, etoposide, and cyclophosphamide) therapy on page 231 of our paper. Although Pedrazzoli et al. suggest that other high-dose regimens might have greater antitumor efficacy, the evidence in support of this statement is lacking. The report of the North American Bone Marrow Transplant Registry found no statistically significant differences among the various preparatory regimens in use today *(4).* Furthermore, the second reference used by Pedrazzoli et al. to suggest the superiority of other "single, more intensive, and possibly more active regimens" failed to show any difference between conventional dose and high-dose chemotherapy *(5).*

We again conclude that, on the basis of our small randomized trial, we were able to rule out a large (>30%) difference in progression-free and overall survival rates in patients with high-risk breast cancer. Definitive conclusions about the therapeutic worth of high-dose chemotherapy for primary and/or metastatic breast cancer await the mature results of ongoing, large, randomized clinical trials.

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