Is There a Role for Dose-Intensive Chemotherapy With Stem Cell Rescue in Breast Cancer?

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During the 1990s, perhaps no other therapy for women with breast cancer was more controversial than high-dose chemotherapy with autologous bone marrow and/or peripheral stem cell support. With encouraging results from late phase I and early phase II trials in the early to mid-1990s, high-dose chemotherapy was promoted by its many enthusiastic proponents as a potentially great leap forward for women with high-risk, node-positive or metastatic disease.

In the absence of controlled randomized phase III clinical trial data, as noted by Williams in this excellent review, breast cancer became the leading indication for autologous stem cell transplant in North America in the 1990s. Most of these stem cell transplants occurred outside of a clinical trial, which led to many heated and publicized battles between insurers and women for access to these therapies. Indeed, the battle became so heated, and positions so ingrained, that one investigator resorted to outright research fraud to make the case for high-dose therapy.[1]

At the plenary session of the American Society of Clinical Oncology in 1999, investigators presented several abstracts detailing preliminary results from phase III randomized studies of high-dose therapy vs the more "standard" chemotherapy regimens for both high-risk node-positive breast cancer and metastatic breast cancer. After these studies demonstrated little or no apparent benefit for high-dose chemotherapy over the standard regimens, interest in high-dose therapy, both inside and outside the context of clinical trials, waned. After 3 years of reflection, is there currently a role for high-dose chemotherapy in the management of breast cancer?

Rational Basis, Disappointing Results

Williams correctly notes that high-dose therapy has a reasonable experimental and perhaps reasonable clinical rationale. Alkylating agents demonstrated a steep dose-response curve in experimental systems,[2] and an early phase II clinical trial demonstrated high overall and complete response rates in metastatic breast cancer.[3]

The data from randomized clinical trials presented to date, however, have been mixed. As noted, one randomized trial in metastatic disease was fraudulent.[1] One trial enrolled women with metastatic disease and a complete response to initial standard-dose induction therapy to immediate or delayed high-dose therapy at progression.[4] Immediate consolidation with high-dose therapy produced a better disease-free survival than delayed consolidation but a poorer over-all survival. Another study randomized women with metastatic breast cancer and a response to induction therapy to high-dose or standard chemotherapy.[5] This trial demonstrated no difference in disease-free or overall survival between the arms.

Randomized trials of high-dose chemotherapy as adjuvant therapy for high-risk node-positive breast cancer have fared no better. To date, although there have been encouraging signs of a trend toward improved disease-free survival in one study,[6] no trial randomizing women to high-dose vs standard-dose regimens has demonstrated a significant disease-free or overall survival benefit.

Looking Ahead

Williams correctly points out that more long-term follow-up is needed before definitive results can be determined, perhaps through a meta-analysis of completed trials. However, it is likely that the benefit, if any, from high-dose chemotherapy in these studies will be small. In addition, newer agents for the treatment of both metastatic and early-stage disease, such as the aromatase inhibitors, taxanes, and trastuzumab (Herceptin), are gaining widespread clinical acceptance. High-dose
chemotherapy would likely have to prove superior to these newer, less toxic agents to gain acceptance in the therapeutic armamentarium.

Williams suggests that the failure of high-dose chemotherapy to improve the outcome of women with breast cancer may be due to residual minimal disease and/or autograft contamination by tumor. These are reasonable hypotheses that deserve clinical investigation. Proof-of-principle trials exploring, for example, high-dose chemotherapy in combination with immunomodulatory strategies[7] such as tumor antigen vaccination or dendritic cell vaccination, are also reasonable and will likely teach us much about the host immune response to minimal residual breast cancer. Whether such studies can be translated into large clinical trials with the potential for altering clinical care remains an open question.

Conclusions
In summary, Williams has provided an excellent brief review of the current state of high-dose chemotherapy for breast cancer. As we await updated analyses of multiple randomized clinical trials, it is clear that high-dose chemotherapy remains an experimental therapy that should be performed only in the context of well-designed clinical trials. While the era of dose intensity (higher dosing) may be closing, randomized trials testing the concept of dose density (more frequent dosing) will soon be presented at national clinical meetings. If such trials prove promising, physicians involved in the treatment of breast cancer may be asking not "how much," but rather, "how fast."

References:


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