EDITORIALS

Window of Opportunity

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In the development of any new treatment strategy, there is a time when the evidence is sufficiently promising to justify comparative trials but insufficient to conclude that the therapy is superior to more conventional treatments. We are at that point in the use of very-high-dose chemotherapy with autologous bone marrow transplantation in the treatment of breast cancer.

The first report on the use of autologous bone marrow transplantation to treat breast cancer appeared almost 15 years ago (*1*). Subsequent trials have employed increasingly higher drug doses using unusual drug combinations designed, in part, to prove that ablated bone marrow could be reconstituted from a patient's own frozen marrow and, in part, to identify those drugs thought most likely to induce a steep dose response without nonmyelosuppressive dose-limiting toxicity. None of the commonly used marrow ablative regimens were based on regimens known to be effective when used at conventional doses. The early phase I trials were performed in patients who had failed at least one prior chemotherapy regimen, and the fact that these patients frequently responded, sometimes with a complete response, provided the impetus for subsequent studies. These more recent studies have employed high-dose regimens with autologous bone marrow transplantation in patients with previously untreated metastatic breast cancer, in patients with locally advanced or inflammatory breast cancer, and in patients with early breast cancer and more than 10 histologically involved axillary lymph nodes. In these studies, the overall response rate has been equal to or higher than that usually obtained with conventional chemotherapy (*2*). The impressive complete response rate in most of the studies has generated great enthusiasm in much of the oncologic community for employing high-dose therapies either in phase III studies or as a standard alternative to more conventional chemotherapy.

Despite the impressive complete response rates, however, the duration of response to and survival following high-dose chemotherapy and autologous bone marrow transplantation has been disappointingly short. Many investigators have suggested that the optimal setting for the use of this treatment is in patients whose tumors are known to be sensitive to chemotherapy as evidenced by a response to conventional-dose chemotherapy prior to the administration of very-high-dose chemotherapy. It is reasoned that the tumor burden will be low at that point, and the possibility of eradicating all remaining tumor by the high drug doses will be increased. The fact that chemotherapy has a much greater impact on patient survival when it is used as an adjuvant to surgery and radiotherapy in patients with early breast cancer than when it is given to patients with metastatic disease lends this strategy considerable credence. There are now five trials (Table 1), including the one published in this issue of the Journal (*3*), which have employed this strategy and have reported the duration of response and/or survival in addition to response rate.

All of these studies were uncontrolled, and our interpretation of these results will depend in large part on which group of patients we select as appropriate controls. Because of the intensity of the high-dose regimens, even the patients in the phase I studies were generally young with a good performance status and a limited amount of disease. As a result, the response rates obtained from the phase I trials cannot be compared with the response rates obtained from more conventional phase I/II studies performed in patients with end-stage disease. For similar reasons, it is difficult to choose appropriate historical controls for the more recent studies, as well. In three of these studies (*4-6*), the estimations of time to treatment failure and survival are based entirely on those patients who had responded to conventional chemotherapy, i.e., patients who had no disease progression for 3-6 months prior to the transplant. In contrast, the time to treatment failure and survival estimates from most trials of conventional therapy include all patients, responders and nonresponders.

Interpretation of these studies is further confounded by the fact that the number of patients in some of these studies is small, and the median follow-up for each study is still short. Both of these factors may heavily influence time to treatment failure and survival estimates. For example, in 1981 we published the early results of a trial performed at the Dana-Farber Cancer Institute in which drug doses had been modestly increased by today's standards (*8*). At the time of that first analysis, 66 patients had

Table 1. Trials using high-dose chemotherapy and autologous bone marrow transplantation in patients who have responded to induction therapy with conventional-dose regimens*

Study (reference)	Complete response rate, %	Median TTF†	Survival, mo	PFS,‡ %, at 24-30 mo
Royal Marsden Hospital (*4*)	NA	7	12	~7
M.D. Anderson Cancer Center (*5*)	58	13	26	25
Duke University Medical Center (*6*)	25	8§	NA	NA
University of Chicago (*7*)	48	10	NA	20
Johns Hopkins Oncology Center (*3*)	37	13	22	10

*NA = not applicable.
†TTF = time to treatment failure.
‡PFS = progression-free survival.
§Time measure from transplant. Other values determined from beginning of induction therapy.

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been entered. The complete response rate was 27%, and the median time to treatment failure was 21.6 months. Progression-free survival at 2 years was about 45%. Eventually, 128 patients were entered into the study, and all patients have now been followed for 8-15 years. The final complete response rate is 15%. The median time to treatment failure has fallen to 16.2 months and the 2-year progression-free survival to about 25%. The median survival is 24 months, and the actuarial 10-year survival exceeds 10%. As with the high-dose chemotherapy plus autologous bone marrow transplantation trials, we cannot determine how the results from this uncontrolled trial are related to the therapy used ("super CMF," i.e., cyclophosphamide, methotrexate, fluorouracil). However, these outcomes from a fairly conventional program by today's standards compare favorably with those reported from the use of high-dose chemotherapy plus autologous bone marrow transplantation, and our experience demonstrates how the results of therapy may become less promising with larger accrual and longer follow-up.

The rationale for high-dose chemotherapy (*9*) and the available data from phase II studies are more than adequate to justify randomized, phase III studies in which high-dose chemotherapy plus autologous bone marrow transplantation is compared with more conventional-dose chemotherapy, and such studies are now being initiated under the sponsorship of the National Cancer Institute. We must be prepared for the possibility that these randomized trials will show a substantial advantage, no advantage, or even a disadvantage from the higher doses of drug, especially if there is any mortality associated with the treatment. One of these trials, a Cancer and Leukemia Group B study, has already begun to enroll patients with operable breast cancer and 10 or more histologically positive nodes. After four courses of CAF (cyclophosphamide, doxorubicin, fluorouracil), these patients are randomly assigned to receive either very-high-dose CPB (cyclophosphamide, cisplatin, carmustine) plus autologous bone marrow transplantation or high-dose CPB without autologous bone marrow transplantation. An intergroup study designed for patients with previously untreated metastatic disease has been proposed by the Southwest Oncology Group and the Eastern Cooperative Oncology Group. After the induction of a response with CAF, patients in this trial will be randomly assigned to receive one of three regimens: CMF (cyclophosphamide, methotrexate, fluorouracil) at conventional doses, CEP (cyclophosphamide, etoposide, cisplatin) at high doses requiring growth factor support but no autologous bone marrow transplantation, or very-high-dose CTCb (cyclophosphamide, thiotepa, carboplatin) with autologous bone marrow transplantation.

All of this would be relatively noncontroversial were it not for the considerable cost and toxicity associated with high-dose chemotherapy and autologous bone marrow transplantation. While costs and toxicity should not be our primary concern when evaluating a new therapy (we would never have embarked on studies of such worthwhile treatments as coronary artery bypass grafts if that were so), these phase I/II studies of autologous bone marrow transplantation have been exceedingly difficult to perform because of very limited funding. In the past, most patient-care costs during the evaluation phase of new therapies have been covered (wittingly or unwittingly) by insurance carriers. However, because of the very high cost of autologous bone marrow transplantation and increasing competition for a shrinking health-care dollar, insurance companies have usually disallowed the cost of autologous bone marrow transplantation. In response, patients (often with the support or encouragement of their transplant physician) have sued for coverage and, in most instances, have been successful. However, this may be a Pyrrhic victory with lamentable long-term consequences. The struggle over payment has resulted in considerable acrimony between clinical investigators and insurance company executives. Some insurance companies are tightening the language in their contracts to further restrict patient access to investigational treatment unless it is covered by a specific clause, usually with an additional premium. Of even greater concern, the legal battles have created a precedent for the intrusion of the courts into yet another arena where the physician has traditionally had full responsibility for making recommendations to his or her patient regarding the most appropriate treatment.

It may not be quite as difficult to conduct the phase III trials of high-dose chemotherapy and autologous bone marrow transplantation for patients with breast cancer, since the national Blue Cross/Blue Shield Association has recently created a special fund to help support the National Cancer Institute-sponsored randomized trials. Possibly other insurance companies will follow suit, establishing a different type of precedent, one in which third-party payors support and collaborate in clinical investigation. However, to pay for the cost of clinical research without increasing the overall health-care budget, it may be necessary to search for other areas to save money. Physicians might contribute to these savings by avoiding the use of expensive drugs in settings where the data supporting this use are weak or nonexistent. A specific example in the treatment of breast cancer is the use of etoposide and platinum in patients who are refractory to cyclophosphamide and doxorubicin.

In this setting of cost constraint, can we justify the use of high-dose chemotherapy with autologous bone marrow transplantation outside the context of a clinical trial? I think not, but the appropriate application of this technology may be very difficult at this point because we have raised the public's expectations far beyond what is supported by the published data. We have no evidence as yet that any patient will be cured by this therapy who would not have been cured by more conventional treatment. But when we suggest to patients that we are treating with "intent to cure" and when we publicly justify the toxicity and costs of the therapy by statements such as "...if this therapy were to cure even 2% of patients," we often mislead our patients who, in their desperation, fail to hear the conditional nature of these phrases. When we say that a particular therapy is a patient's "only chance for cure," no jury (even an institutional review board) in our society, which places a high value on action, is likely to look critically at the evidence and deny a patient treatment. To many people, lay and medical alike, such a denial is equivalent to passing a sentence of death. Although there is no agreement among transplanters about whether this technology should ever be used for the treatment of breast cancer outside the context of a clinical trial or, if so, what settings might be appropriate, there seems to be considerable agreement that the regimens developed thus far will not cure a patient with

metastatic breast cancer who is refractory to all forms of conventional chemotherapy.

High-dose chemotherapy regimens are in evolution, and there are many unanswered questions about high-dose chemotherapy which deserve support. Several key, but unproven, assumptions have been made in designing these programs. These include the supposition that alkylating agents (e.g., cyclophosphamide and thiotepa) used in combinations are synergistic or that drugs with limited activity at conventional doses in the treatment of breast cancer (e.g., etoposide and platinum) will be very active when used at high doses. These hypotheses deserve careful evaluation. New phase I/II studies are likely to demonstrate ways to reduce both the toxicity and cost of these therapies. In fact, both the mortality from treatment and the number of hospital days required to recover from autologous bone marrow transplantation have dramatically decreased during the past 2 years. Unfortunately, no provisions have yet been made to routinely cover patient-care costs associated with these studies, and it seems inappropriate to suspend all such investigations for the next 5-10 years while we await the results from the three or four randomized trials designed to evaluate the regimens developed thus far. A broad agreement is urgently needed between clinical investigators and third-party payors to cover all or a substantial portion of the costs of legitimate research approved by peer review groups outside the investigator's own institution, such as the National Cancer Institute and the American Cancer Society.

At this time, there are really several open windows of opportunity. If very-high-dose chemotherapy is as effective as some investigators believe it is, we have the opportunity to demonstrate this conclusively to the doubters and to identify an avenue for further research which is likely to lead to cures, even if the current regimens prove to be only a small step along the way. If very-high-dose chemotherapy is really no better or slightly worse than conventional therapy, we have an opportunity to avoid treating millions of women with a toxic regimen for many years before finding out that it really has no advantage over conventional treatments (as with the Halsted radical mastectomy), to close what may be a blind alley, and to invest our limited research dollars in more promising investigations. And finally, we have an opportunity to establish a more rational way of distributing limited health-care dollars and to insure the continual investigation of new therapies in an orderly fashion. Windows of opportunity are usually open for a very short time. It is vitally important that we seize these opportunities now.

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Cell Cycling, cdc2, and Cancer

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Recent results concerning the cell division cycle of the yeast *Schizosaccharomyces pombe* (*1*) highlight the potential contribution of yeast genetics to our understanding of the mechanisms that control tumor cell growth. The current intense interest in the role of the cell division control (cdc2) protein in regulating the mammalian cell division cycle has its origins in the identification of the cdc loci in yeast (*2*). The implications of the complex cdc2 protein-dependent pathways on tumor cell behavior are now beginning to emerge.

The cdc2 gene product in both yeast and mammalian cells is a protein kinase that interacts with a family of cellular proteins called cyclins. Interaction of the cdc2 protein with mitotic cyclins produces a complex termed maturation-promoting factor (MPF) that coordinates the extraordinarily diverse activities required during the M phase, including catalysis of chromosome condensation (*3*), homogenization of the endoplasmic reticulum (*4*), reorganization of microtubules to allow chromosome separation during mitosis (*5*), and reorganization of microfilaments to promote cell division (*6*).

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