The Randomized Trials of Dose-Intensive Therapy for Breast Cancer: What Do They Mean for Patient Care and Where Do We Go From Here?

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ABSTRACT
At the May 1999 meeting of the American Society of Clinical Oncology (ASCO), results of some of the randomized trials conducted in the 1990s assessing the value of high-dose (dose-intensive) therapy for breast cancer were presented. The number of women treated with such therapy has grown almost exponentially since the early 1990s so that breast cancer is now the most common malignancy treated with stem cell transplant. At the same time the cost of such treatment (from $60,000 upwards to $150,000) has caused it to become the most controversial issue in all of medical oncology during this past decade. Does such therapy truly provide a benefit to women with breast cancer, and is it therefore a therapy that should be routinely offered to suitable patients? This article will attempt to put this issue in some perspective with emphasis on the recently reported randomized studies of this treatment for both early-stage and metastatic disease. In addition, some comments will be made regarding where research regarding this topic will likely be focused in the next few years. The Oncologist 1999;4:450-458

INTRODUCTION
At the May 1999 meeting of the American Society of Clinical Oncology (ASCO), results of some of the randomized trials conducted in the 1990s assessing the value of high-dose (dose-intensive) therapy for breast cancer were presented. The number of women treated with such therapy has grown almost exponentially since the early 1990s so that breast cancer is now the most common malignancy treated with stem cell transplant. At the same time the cost of such treatment (from $60,000 upwards to $150,000) has caused it to become the most controversial issue in all of medical oncology during this past decade. Does such therapy truly provide a benefit to women with breast cancer, and is it therefore a therapy that should be routinely available and covered by third-party payers? This article will attempt to put this issue in some perspective with emphasis on the randomized studies of this form of treatment for both early-stage and metastatic disease. In addition, some comments will be made regarding where research regarding this topic will likely be focused in the next few years.

BACKGROUND
Breast cancer occurs in 175,000 women yearly in the USA, and approximately 43,500 die from the disease [1]. It is the most common female cancer in North America, Europe, and Australasia. It is the most common cancer in women, but more women (68,000) die of lung cancer than breast cancer each year in the USA [1]. Despite this fact, because the female: male incidence of this disease is at least 100:1 and because it occurs in an organ with so much psychosexual overlay, its prominence in oncology is greatly magnified. As an illustration of this point, there are numerous lay organizations (both national and local) devoted to this disease, and many are politically active and powerful. While more women die of lung cancer than breast cancer, there is not a single disease-oriented lay organization devoted to lung cancer in women.

The natural history of breast cancer has perhaps the greatest heterogeneity of all human malignancies. Although apparent initially only as a small breast lump, a woman may have disease that causes her demise only a year or two after diagnosis. Conversely, another woman’s cancer recurs with...
metastases literally two decades after she undergoes primary curative treatment. This is the only human cancer where late (i.e., >10 years after diagnosis) recurrences after primary treatment occur with any frequency. As many as 10% of the women whose cancer ever recurs will have the relapse >10 years from the original treatment. Moreover, survival with metastases can occasionally range up to a decade or more after the stage IV disease becomes apparent.

There are presently several dozen factors that influence the prognosis of this disease. Many are accepted, while others have been proposed as being important but are not yet confirmed as having a meaningful role in the prognosis. For example, the most important and accepted prognostic factors are: nodal status, tumor size, hormone receptor status, and histologic grade, particularly nodal status. Some accepted additional but less important factors that play a role in outcome are vascular invasion, presence of the HER-2/neu oncogene, and young age (<35). There is a direct correlation between the number of axillary nodes involved and the risk of harboring subclinical metastases that will become evident at some future time. Although this correlation is roughly linear with the number of involved nodes, there have been a number of studies that have divided the nodal segments into 1-3, 4-9, and >10 (and even >13) for convenience of analysis [2-4]. Of course, the more axillary nodes involved, the higher the risk for recurrence after primary treatment.

Once a woman has developed stage IV disease, the median survival varies from 26 to 43 months [5-7] or approximately three years. There are many treatments that will improve the survival and overall quality of life of women with stage IV disease (e.g., hormones, antihormones, and chemotherapeutic agents), but very few women survive this cancer once metastases have appeared. In a report [8] of 1,581 women with stage IV disease who were treated with combination chemotherapy at M.D. Anderson Cancer Center, only 3% were alive and disease-free >5 years (with 2% >10 years) later. Perhaps some of these few women were indeed cured of the metastases. Hormonal treatments often add months to years of high-quality life for women with stage IV disease. Chemotherapy can also improve survival, but once chemotherapy is started, the median survival is only some two years and the degree of response to systemic therapy has only modest influence on this figure [9, 10].

Another point to keep in mind about breast cancer is the fact that the benefits of a particular treatment may be sufficiently marginal, (especially for certain categories of patients) that very large numbers of patients are necessary to show a true and reliable effect. For example, it has only been the large overview of adjuvant therapy of breast cancer performed at Oxford University that has reliably demonstrated a benefit for giving chemotherapy to postmenopausal women with stage II breast cancer [11]. This compilation of trials has involved some 120,000 women with early-stage breast cancer treated all over the world on randomized studies.

These facts above must be borne in mind whenever one assesses the value of any particular therapy of this cancer, whether for primary or stage IV disease. If one selects the patients with sufficient care, one can demonstrate almost any therapy does or does not have value. This point is why randomized trials are so important when one is testing the value of a new therapy in breast cancer. All patients entered undergo the careful selection process prior to being enrolled in the study, and thus selection biases are obviated. Moreover, the patients are stratified for known prognostic factors prior to randomization, which furthers the objectivity of the treatment assessment.

The concept of dose intensification in breast cancer was developed at the Dana-Farber Cancer Institute by Dr. Emil Frei, who was the first to demonstrate that the cell kill effected by multiple alkylating agents had a steep dose-response correlation [12]. He and his colleagues theorized that greater cancer cell kill could be achieved if the doses of alkylating agents could be escalated above lethal levels. Because most of the toxicity of these agents was to the marrow, one could administer these lethal doses if one could protect marrow stem cells. Thus was born the concept of dose-intensification and autologous progenitor (stem) cell transplant. During the 1980s such treatment was tried mainly in women with stage IV disease and produced a rare long-term survivor but at a considerable (23%) risk of treatment-related mortality [13].

In 1991 the two white cell growth factors, filgrastim (G-CSF) and sargramostim (GM-CSF), were released for marketing. These two drugs changed the whole process of stem cell transplant, because now transplants could be accomplished with greater safety due to the effect of these two drugs in stimulating marrow recovery. Both community hospitals and academic centers established transplant centers for women with this common disease. Expansion of availability of this form of treatment skyrocketed in the early 1990s [14].

Although it was hoped that significant numbers of women with metastatic breast cancer could achieve improved survival with dose-intensive chemotherapy (DIC), it has become clear that only a small minority (approximately 15%) of women were not relapsing within several years after undergoing such treatment. It was theorized that the greatest effect of this form of treatment would be in women with stage II disease who were at a high risk for recurrence. Peters and colleagues [15] initiated a phase II study of this form of treatment for women with stage II breast cancer involving 10 or more axillary nodes because of the known high risk of such women for harboring...
subclinical disease. This figure of 10 nodes was arbitrarily designated as the number necessary before transplant would be considered. Some cut-off number was necessary, and this number was both round and reasonable but nevertheless arbitrary. This study [15] showed that the outcome after transplant was superior to historical control groups of women treated with an adjuvant CMF or CAF regimen after primary surgery. However, one must realize that the women treated in these past studies did not undergo the careful and thorough process of searching for obvious metastatic disease as did the women who underwent transplant [15]. This selection process included computerized tomography scans of the head, chest, abdomen, and pelvis, bilateral marrow biopsies, and assessments of cardiopulmonary function for tolerating transplant that the women treated in the past did not receive. Such selection bias could have influenced the results of this phase II study [16, 17] more than the transplant treatment. Others also reported their results of phase II studies [18-20] and showed a similar better outcome for transplant therapy. Despite the known selection bias in these studies, many women with high-risk early disease underwent transplant therapy outside of any randomized trials because of these reported favorable results.

Concurrent with the evolution in transplant for women with high-risk early disease, there was a large increase in the use of such therapy for women with metastatic disease [14]. However, it became apparent [14] that such therapy was rarely of benefit to women who had not demonstrated some sensitivity to induction chemotherapy given in conventional doses prior to undergoing the dose-intensive therapy.

Throughout the 1990s a clash occurred between patients and the third-party payers for this therapy. A heated debate raged over whether this therapy was “standard” or “investigational.” If it were the latter, many insurance contracts specifically excluded coverage for such therapy. Such exclusions inevitably resulted in lawsuits [21], some of which produced large and successful claims against the insurers. This debate raged because there were mostly only phase II trials (with most involving only a few dozen patients) to provide data on which to frame the argument. To address political concerns in this battle, the legislatures of 10 states passed laws making mandatory some form of insurance coverage for transplant therapy for breast cancer, and the various health plans for Federal Government employees were also directed by Congress to provide coverage.

Against this background we now have a number of clinical trials that have recently been reported that compare transplant therapy for breast cancer to some lesser therapy not requiring transplant support, including some presented at the May 1999 meeting of the ASCO. The results of these trials will be discussed below.

THE SOUTH AFRICAN METASTATIC DISEASE TRIAL

This study compared DIC versus conventional-dose chemotherapy (CDC) as first-line chemotherapeutic treatment of stage IV disease [22, 23]. The patients receiving DIC were treated with a combination of cyclophosphamide, mitoxantrone, and etoposide given for two (tandem) cycles. The patient group receiving the CDC regimen was treated with a combination of cyclophosphamide, mitoxantrone, and vincristine given in intermittent cycles.

Ninety patients were registered on this trial, 45 of whom received transplant therapy. Of these 45 patients, nine received a single cycle of dose-intensive therapy and transplant, while the remainder were treated with tandem cycles. The response rate was 95% in the transplant group, but only 53% in the other group. The median durations of response and overall survival were significantly longer for the patients who received the DIC. This group had a median survival time of 90 weeks versus only 45 weeks in the other group. With five years of follow-up, nine (20%) of the original 45 patients treated with transplant were reported to be alive and disease progression-free [23].

The authors concluded these results indicate that DIC “is capable of achieving a high proportion of long-term complete responders” [23]. However, one must keep in mind that the CDC regimen employed was not one used in the USA and consisted of one agent (vincristine) that has little activity in breast cancer and another (mitoxantrone) that is inferior in activity to doxorubicin or epirubicin. Furthermore, the median survival of the CDC group in this study was only 10 months, a result approximately half the median survival achieved in the USA with such regimens as CAF or its variations [24].

THE EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) TRIAL IN METASTATIC DISEASE

This study assessed the value of transplant therapy in the overall management of breast cancer in comparison to continued use of chemotherapy given in a conventional regimen [25]. A total of 553 women were enrolled in this trial and received induction chemotherapy with four to six cycles of CAF. Those patients who achieved either a partial or complete response were then randomized to receive DIC and transplant or maintenance therapy with CMF. Of the women who achieved at least a partial regression, 199 were randomized to receive either more chemotherapy in conventional doses or undergo transplant. Ninety-seven other responding patients were not randomized for a variety of reasons. The DIC regimen employed in this study was STAMP (Solid Tumor Autologous Marrow Transplant Program) Regimen V, consisting of cyclophosphamide, thiopeta, and carboplatin. Currently, this transplant regimen is the one most widely used [14].
As presented at ASCO the median follow-up time is now 37 months, and the three-year survival for all patients (calculated from the date of randomization) is 32% in the transplant group and 38% in the maintenance CMF group. There is no significant difference between the two treatments for time-to-progression or overall survival, regardless of whether the patient achieved a complete or only a partial response to the induction chemotherapy. Fourteen patients were randomized to receive CMF but declined this therapy. Ten of these women subsequently had a transplant and all have relapsed; eight have died of their cancer already.

**THE FRENCH RANDOMIZED STUDY IN METASTATIC BREAST CANCER**

Similar to the ECOG study, this trial compared the outcome of women with metastatic breast cancer who had demonstrated a response to induction chemotherapy, but the regimen used was a combination of cyclophosphamide, mitoxantrone, and melphalan [26]. The women were then randomized to be treated with either a consolidation cycle of DIC/transplant using high doses of the same drug combination or continued treatment with the conventional-dose regimen. Sixty-one women were randomized on this study. At randomization 21% of the women had achieved a complete remission of their evaluable tumor, and the remainder had achieved a partial remission. The rate of relapse at three years was approximately 80% in the conventional-dose group versus 51% in the DIC group, but at five years the relapse rates were identical at 91% each. The study authors [26] believed this delay in relapse at three years after transplant could perhaps be advantageous to the patient because there would be a longer interval where no therapy had to be administered.

**THE DUTCH RANDOMIZED TRIAL FOR HIGH-RISK PRIMARY BREAST CANCER**

This was a single institution study involving only women age <60 who had extensive axillary lymph node metastases that were confirmed by “a tumor-positive infraclavicular lymph-node biopsy” [27]. There was no effort to count the number of nodes involved in the axilla. Ninety-seven women were entered and received three cycles of a chemotherapy regimen given in conventional doses consisting of cyclophosphamide, epirubicin, and 5-fluorouracil (CEF). All women who did not have evidence of disease progression were then randomized to receive a fourth cycle of the conventional-dose regimen or transplant. The DIC regimen consisted of cyclophosphamide, thiotepa, and carboplatin (i.e., STAMP V). Results with a median follow-up of 49 months showed no significant difference in survival whether the patients received the fourth cycle of chemotherapy in conventional doses or the consolidation cycle of transplant therapy. The authors [27] concluded that the high-dose chemotherapy “did not even yield minimum evidence of a survival advantage over optimum conventional therapy and was associated with severe toxic effects.”

**THE M.D. ANDERSON RANDOMIZED TRIAL IN HIGH-RISK PRIMARY BREAST CANCER**

This trial involved women with primary breast cancer involving 10 or more lymph nodes after primary surgery or four or more lymph nodes after four cycles of neoadjuvant chemotherapy for locally advanced disease [28]. Seventy-eight women were registered and randomized. All patients received eight cycles of the CAF regimen, and they were then randomized to receive no further therapy or two (tandem) cycles of DIC using cyclophosphamide, etoposide, and cisplatin followed by transplant. The four-year disease-free survival rates were 55% and 48%, respectively, for the conventional therapy and the DIC groups (p = 0.45), and the corresponding overall survival figures were 68% and 60%, respectively (p = 0.27). The numerical results actually favored the non-transplant treatment but without statistical significance.

**THE SCANDINAVIAN BREAST GROUP RANDOMIZED TRIAL IN HIGH-RISK PRIMARY BREAST CANCER**

This study involved women age <60 calculated to have a >70% chance of relapse by five years after primary surgery [29]. Women who had >8 involved nodes or other adverse risk factors were eligible. A total of 525 women were randomized to receive either a “customized” (i.e., the doses were adjusted to achieve certain desired levels of myelosuppression) standard-dose regimen of CEF for a total of nine cycles or three cycles of the same regimen followed by a single cycle of high-dose transplant therapy. With a median follow-up of approximately two years, there has been no advantage demonstrated in either relapse-free or overall survival for the transplanted patients over the CEF regimen given for nine cycles. The number of women who relapsed after treatment was 92 in the transplant group and 66 in the CEF group. At the time of presentation, the number of deaths in the transplant group was 54, while in the CEF group it was 47. Once again the raw numbers favored the non-transplant therapy, but there was no statistically significant difference. There were eight deaths in the CEF-treatment group due to secondary acute leukemia or myelodysplastic syndrome (but none in the transplant group), which attests to the aggressive nature of the CEF regimen used.

**THE CANCER & LEUKEMIA GROUP B (CALGB) INTERGROUP STUDY 9082**

This study involved women with at least 10 involved axillary nodes and no inflammatory features at the time of
primary surgery [30]. After undergoing extensive screening for any evidence of detectable metastases, the patients received four cycles of CAF followed by high-dose combination chemotherapy using cyclophosphamide, cisplatin, and carmustine (the STAMP I regimen) at doses requiring transplant support or at lower (but still intensive) doses requiring only filgrastim support.

A total of 874 patients were treated with the initial CAF, and 783 were randomized to receive a fifth cycle of treatment using the STAMP I regimen in either transplant doses or lower doses without transplant support. At a median follow-up of three years, the failure-free survival is nearly identical at 69 months for the two treatment groups (p = 0.7). Overall survival is also not different between the two groups. The chance of a patient being alive and disease free at three years is 68% for the DIC group and 64% for the “standard” treatment group. There were 31 treatment-related deaths in this study with two occurring from the CAF treatment and 29 occurring from the high-dose therapy. The overall treatment-related mortality rate was 7.4% for the transplant group with some deaths occurring as long as 2.5 years after the transplant procedure. The relapse percentages to date are 22% for the DIC regimen and 32% for the non-DIC treatment (p = 0.11).

The early results of this randomized trial indicate at the present time there is no difference in the chance of a woman being alive and disease free at three years whether she received transplant-supported therapy or the nontransplant treatment. The percentage of women relapsing with metastatic disease slightly favors (but not significantly) the transplanted patients. These results are preliminary and perhaps will change with further follow-up.

THE SOUTH AFRICAN HIGH-RISK PRIMARY BREAST CANCER STUDY

This study also compared high-dose chemotherapy to a regimen in conventional doses, but similar to the South African study in metastatic disease, no induction therapy was administered to the transplant group [31]. All the transplanted patients went directly to two (tandem) cycles of dose-intensive therapy. The women entered had >9 involved axillary lymph nodes or >7 involved nodes plus a tumor >5 cm that was also negative for estrogen receptors. The DIC regimen consisted of cyclophosphamide, mitoxantrone, and etoposide; the conventional-dose regimen was CAF or CEF.

The study was initiated in 1990 and completed in 1995 with a total of 154 women entered. After more than five years of follow-up, the DIC group has experienced significantly fewer cancer relapses and lower mortality. The relapse rate in the DIC group was 25%, whereas it was a striking 66% in the other group. Mortality has been 17% in the DIC group and 35% in the other group. Both of these comparisons are statistically significant.

THE CALGB AND AUTOLOGOUS TRANSPLANT REGISTRY RETROSPECTIVE STUDY

Although this study was retrospective and not randomized as were all the others discussed above, it is included here because of the large patient sample involved in the comparison. The overall survival of women with metastatic breast cancer registered on four CALGB trials involving CDC was compared to the survival of women treated with transplant therapy and enrolled in the Autologous Blood and Marrow Transplant Registry in Milwaukee, WI [32].

The initial data set included 1,621 patients treated on CALGB studies between 1980 and 1992 with various doxorubicin-based combination chemotherapy regimens and 1,188 registry patients transplanted from 1989 to 1995. Half of the registry patients received cyclophosphamide and thiotepa plus/minus other drugs; the remainder received other DIC regimens. To minimize selection biases the analysis focused on women with chemotherapy-sensitive disease (i.e., they had achieved at least a partial remission in response to the chemotherapy) and who were <61 years of age. To minimize time-to-treatment biases and adjust for potential confounding prognostic factor differences, a Cox regression technique was utilized for statistical analysis. The women in the transplant group had a markedly better performance status and were younger in average age, reflecting some of the selection factors that determine who undergoes a transplant.

Among the four CALGB studies there were no significant differences in outcomes between the treatment regimens or the individual trials. Among the registry patients survival did not differ across DIC regimens. The final study sample included 1,217 women; 657 from the serial CALGB studies and 560 from the registry. A multivariate model including disease-free interval after primary treatment, performance status, number of metastases, and hormone-receptor status showed no significant difference in survival between the registry patients treated with transplant and the CALGB patients treated with conventional-dose CAF regimens (p = 0.19). The median survival in both groups was approximately 1.8 years, a figure consistent with the approximate two-year median survival achievable once chemotherapy is initiated for metastatic disease. Subset analyses of those women who were age <51, had a good performance status, bone-only metastases, or visceral metastases again showed no differences in outcome between the two patient groups.

THE ECOG HIGH-RISK BREAST CANCER STUDY

This study also involved women with 10 or more positive axillary lymph nodes. They were randomized to receive the
CAF regimen alone or CAF plus a single cycle of consolidation DIC and transplant. A total of 540 women were entered on this study, and it reached its accrual goal in May 1998. The ECOG investigators have elected not to present the results of this study yet, presumably because they want to have further follow-up before doing so.

**THE INTERGROUP TRIAL IN PATIENTS WITH FOUR TO NINE INVOLVED AXILLARY NODES**

This study is still ongoing and accruing patients. It compares transplant therapy to treatment with a dose-dense regimen consisting of repeated cycles of doxorubicin, then paclitaxel, then cyclophosphamide (i.e., the Memorial Sloan-Kettering Cancer Center combination [33] termed a “dose-dense” regimen). Accrual of approximately 1,000 patients is planned, and as of June 1999 approximately 500 had been entered.

**PRELIMINARY CONCLUSIONS**

The conclusions regarding all these trials must be considered preliminary because, with the exception of two, they are as yet published only in abstract form and one is not published in any form. In addition, for several of them the follow-up is somewhat limited, but the overall message for each is unlikely to change. At this time the preponderance of scientific evidence is that transplant therapy for metastatic breast cancer has failed to have a significant effect on overall survival. It is indeed true that the South African trial [22, 23] shows a statistically significant superior survival for the transplanted group. However, the patients receiving the nontransplant therapy were treated with a regimen not used in the USA and one not likely to have meaningful antitumor activity. Thus, the superior outcome of the transplanted patients may reflect more the inferior survival of the other group rather than a benefit from a more efficacious therapy. At this time there are no plans to initiate further randomized trials supported by the National Cancer Institute in metastatic disease.

The overall results in high-risk early disease also do not demonstrate a strong effect of transplant therapy, at least in comparison to a therapy that is intensive but not to a degree requiring transplant support. The Scandinavian trial used a regimen in the control group that did not require transplant, but it was so intensive it has already engendered some cases of acute leukemia and preleukemia. In similar fashion the control treatment in the CALGB Intergroup Trial also was intensive and differed from the transplant regimen only that it was not sufficiently high enough to require transplant but did require filgrastim support for myelosuppression. Another point is that the relapse rate for the CALGB trial is lower in the transplant group while the overall survival is the same, probably because of the 7.4% mortality rate in the transplanted patients. Thus, it is possible that once the effect of early mortality is diluted over time, the benefit of a lower relapse rate will translate to a superior and significant overall survival for the transplanted patients. Moreover, we have not yet seen the results of the large, closed ECOG trial and a large trial ongoing in the Netherlands [34], and they will have an additional influence on the debate when they are made public. At this time transplant therapy for high-risk disease has not proven either effective or ineffective. What can be said is that the promise of a sensational advantage in outcome in favor of transplant therapy engendered by the phase II trials [15, 18-20] has not been fulfilled. Once again we have seen the hazards of using historical-control data as the basis for comparing new and “promising” treatments with previous ones, a lesson that has been repeated many times in the past 30 years in the field of oncology. The effect of patient selection (especially for a cancer with such a large degree of heterogeneity) must always be a consideration in the apparent benefit of new therapies, and a treatment should only become accepted and widely available when tested in randomized phase III trials with adequate statistical power to answer the scientific questions. Selection bias was a large factor in the phase II trial results, as is made evident, for example, by the randomized CALGB Intergroup Trial [30]. The disease-free survival of both groups is at present just under 70%, a figure commensurate with the results reported by Peters et al. [15] in the phase II transplant trial that was the basis for proceeding with the phase III trial. With our present state of knowledge, transplant for breast cancer should continue to be a subject confined to innovative randomized clinical trials testing a valid hypothesis, which are disease and stage-directed, have a high probability of answering the scientific question under test, and are subject to external peer review.

A scientific point possibly to test further is the use of transplant as the only therapy for high-risk disease, similar to the South African trial [31]. The fact that the results of this trial showed a benefit for transplant may be due to the sole use of transplant therapy and elimination of the induction therapy given in conventional doses. The induction therapy may cause preferential selection of drug-resistant cancer cells that will survive no matter the doses of drugs to which they are exposed. Such a study may be developed in the near future. In the meantime participation in the current nontransplant trials being conducted by the cooperative groups for early-stage disease (Table 1) is to be highly encouraged, both for medical oncologists and their patients. Patients can be assured that transplant therapy is not so clearly effective it must be employed no matter the obstacles.
Noteworthy is the fact that some of these cooperative group trials incorporate a taxane (either paclitaxel or docetaxel) into the chemotherapy regimen. These two drugs are among the most active for treatment of any stage of breast cancer [35]. A study completed in 1997 by the CALGB tested the value of paclitaxel added to a cyclophosphamide-doxorubicin combination for 3,170 patients with node-positive primary disease [36]. Four cycles of paclitaxel given sequentially after four cycles of the combination regimen produced a significant improvement in both overall and disease-free survival. This study [36] has been used as the basis for obtaining marketing approval from the FDA for paclitaxel treatment of patients with node-positive breast cancer. None of the transplant studies discussed above used either taxane, so there is no information available concerning how the outcome might be affected by use of these agents in either a dose-intensive regimen or in conventional doses in comparison to transplant therapy.

For women with stage IV disease, the options include combination regimens involving doxorubicin (Adriamycin), a taxane (either Taxol or Taxotere), and/or cyclophosphamide (Cytoxan) as initial chemotherapy. Both taxanes have now been established as highly effective agents in combination with doxorubicin as part of the initial chemotherapy of metastatic disease. Paclitaxel plus doxorubicin [37] produced a response rate and overall time-to-treatment-failure superior to either

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Abbreviations: CALGB = Cancer and Leukemia Group B; ECOG = Eastern Cooperative Oncology Group; NCCTG = North Central Cancer Treatment Group; NSABP = National Surgical Adjuvant Breast Project; SWOG = Southwest Oncology Group.

*Information for this table was kindly provided by Dr. Jeffrey S. Abrams of the Cancer Therapy Evaluation Program, National Cancer Institute, Bethesda, MD.
agent used alone. Docetaxel plus doxorubicin also is highly active [38]. Trastuzumab added to initial chemotherapy provides a further benefit over chemotherapy alone for those women with tumor positive for the HER-2/neu oncogene [39]. When such treatment is no longer effective, available second-line agents include the taxanes and trastuzumab (if not used initially) and vinorelbine (Navelbine). There is no evidence that meaningful survival differences exist among the various options. For women with primary breast cancer and a high risk for harboring subclinical metastases who cannot be entered into one of the cooperative group trials (Table 1), one could use the combination of cyclophosphamide and doxorubicin given in four cycles, followed by four cycles of paclitaxel [36]. All women with hormone receptor-positive breast cancer should also receive tamoxifen as part of the therapy given after initial surgery, and the current recommendation is to give it for five years. For premenopausal women goserelin (Zolodex) can also be considered an effective addition to the therapeutic regimen.

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