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- Antineoplastic Agents, Combined/therapeutic use
- Bone Marrow Transplantation*
- Breast Neoplasms/therapy*
- Combined Modality Therapy
- Comparative Study
- Dose-Response Relationship, Drug
- Female
- Hematopoietic Stem Cell Transplantation*
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- Ovarian Neoplasms/therapy*
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High-dose chemotherapy for the treatment of breast and ovarian cancer

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Breast cancer is currently the primary indication for high-dose chemotherapy with autologous hematopoietic progenitor cell support. Recent advances include the first randomized trial comparing high-dose chemotherapy with conventional-dose chemotherapy in patients with metastatic disease, new and improved methods for detection of tumor cells in the autologous graft, new high-dose chemotherapy regimens, new trials exploring multicycle high-dose chemotherapy, and the development of prognostic factors that may predict the outcome of patients who receive this treatment. In patients with ovarian cancer, a recently activated intergroup randomized study of high-dose chemotherapy compared with conventional dose chemotherapy should help clarify the role of high-dose chemotherapy for the treatment of this disease.

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Abbreviation

AHPCS autologous hematopoietic progenitor cell support

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Breast cancer is currently the most common indication for high-dose chemotherapy with autologous hematopoietic progenitor cell support (AHPCS). The results of recently published and forthcoming studies will likely increase the number of patients treated with this modality. The rationale and historical results of high-dose chemotherapy with AHPCS, both in the adjuvant and metastatic breast cancer setting, have been recently reviewed [1,2]. In this review, we focus on recently published high-dose therapy studies of patients with breast and ovarian cancer.

High-dose chemotherapy for the treatment of breast cancer

In 1995, Bezwoda *et al.* [3••] reported the results of a randomized trial in patients with metastatic breast cancer. Ninety patients without prior chemotherapy in the metastatic setting were enrolled. Patients were treated with either two cycles of high-dose cyclophosphamide, mitoxantrone, and etoposide followed by AHPCS or six cycles of standard-dose cyclophosphamide, mitoxantrone, and vincristine. Fifty-one percent of the patients in the high-dose arm achieved a complete response in contrast to only 5% in the conventional-dose arm. Both the median duration of response (34 versus 80 weeks) and survival (45 versus 90 weeks) were significantly longer for patients enrolled in the high-dose arm.

The University of Colorado in collaboration with the Cleveland Clinic and the University of Arizona Cancer Center have completed a pilot high-dose study in patients with stage II and III breast cancer involving four to nine axillary lymph nodes [4]. Fifty-four patients were treated with four cycles of adriamycin and cyclophosphamide followed by high-dose cyclophosphamide, cisplatin, and carmustine with AHPCS. With a median follow up of 16 months, 47 patients (87%) are alive and disease free. All patients received radiation therapy to the chest wall and axilla after undergoing transplantation. To confirm these promising preliminary results, a randomized intergroup trial has been initiated in this patient population. Patients will be treated with either the treatment regimen described previously or an intensive sequential chemotherapy regimen, including three cycles of adriamycin, cyclophosphamide, and paclitaxel, each, supported by granulocyte colony-stimulating factor [5].

Patients with inflammatory breast cancer have a poor prognosis with conventional chemotherapy. Ayash *et al.* [6] recently presented their results with the use of induc-

tion chemotherapy, followed by high-dose chemotherapy, surgery, and radiotherapy in 27 patients with stage IIIB breast cancer. At the time of this report, and with a median follow-up of 22 months, four patients had relapsed, all of whom had gross residual disease after high-dose chemotherapy.

Detection of minimal residual disease in the autologous graft

Significant progress has been made in the detection of breast cancer cells, both in the bone marrow and peripheral blood specimens. Studies at the University of Colorado using a combination of four monoclonal antibodies in an immunocytochemistry assay have shown breast cancer cell contamination in 35% of the bone marrow aspirates, and 10% of the peripheral blood samples prior to transplantation [7•]. Vredenburgh *et al.* [8] used the same assay to study patients with breast cancer and more than 10 axillary lymph nodes involved with cancer. They found that 36% of the bone marrow specimens contained tumor cells, and that the presence or absence of these cells was correlated with disease-free survival. Using a polymerase chain reaction for cytokeratin K19, Fields *et al.* [9•] studied bone marrow aspirates from 83 patients with high-risk or metastatic breast cancer. The presence or absence of bone marrow micrometastases correlated with clinical outcome in patients with stage IV disease but not stage II–III disease.

New high-dose chemotherapy regimens

Numerous groups have shown that 10% to 27% of the patients with metastatic breast cancer can be rendered disease-free long-term with the use of high-dose chemotherapy followed by AHPCS. However, the fact that the majority of patients relapse after high-dose chemotherapy underscores the need for more effective high-dose chemotherapy regimens.

Fields *et al.* [10] attempted to increase the dose intensity of high-dose chemotherapy. They performed a phase I study of ifosfamide, carboplatin, and etoposide in patients with poor-prognosis malignancies (99 of 154 had breast cancer). The maximally tolerated dose for this combination was ifosfamide at 20,100 mg/M^2, carboplatin at 1800 mg/M^2, and etoposide at 3000 mg/M^2, all given in divided doses for 6 days. The dose limiting toxicities for the combination were central nervous system and acute renal failure. In a subsequent analysis of this study, the authors suggested that patients with anthracycline-responsive breast cancer treated at the higher dose levels had a higher response rate than those treated at the lower dose cohorts [11]. At least two groups have explored the possibility of using busulfan-cyclophosphamide, a commonly used regimen for hematologic malignancies, in patients with breast cancer [12,13]. No long-term responders were seen in one of these series [12].

One way to improve the current results obtained in patients with metastatic breast cancer is by the incorporation of drugs with novel mechanisms of action. In a recently published phase I study, the feasibility to incorporate paclitaxel in a high-dose chemotherapy regimen was demonstrated [14•]. The rationale for this study was based on the promising antitumor activity of paclitaxel in breast cancer, the lack of life threatening extrahematologic toxicity of conventional dose paclitaxel, the preclinical evidence for a dose-response effect with paclitaxel, and the *in vitro* synergism exhibited when paclitaxel and cisplatin are combined [15–18]. The maximum tolerated dose for this regimen is 775 mg/M^2 of paclitaxel infused for 24 hours, cyclophosphamide at 5625 mg/M^2 in three daily doses, and cisplatin at 165 mg/M2 intravenously given by continuous infusion for 72 hours followed by AHPCS. We are currently conducting a follow up study testing the incorporation of carmustine into this high-dose paclitaxel-based regimen [19]. Another strategy is to incorporate agents with very high single-agent activity against breast cancer into high-dose chemotherapy regimens. With this in mind, Somlo *et al.* [20•] conducted a phase I study of etoposide (60 mg/kg) and cyclophosphamide (100 mg/kg) with escalated doses of adriamycin given as a continuous infusion for 96 hours. The maximum tolerated dose for adriamycin in this combination was determined to be 165 mg/M^2, and no toxic fatalities occurred.

Multicycle high-dose chemotherapy

Based on initial studies by Dunphy *et al.* [21] and Ayash *et al.* [22], several investigators have explored the possibility of giving more than one high-dose chemotherapy cycle using AHPCS. Bitran *et al.* [23] administered high-dose thiotepa and cyclophosphamide to 27 patients, followed within 180 days by single-agent melphalan. Two patients died after the first cycle of high-dose chemotherapy, and two did not respond, making them ineligible for the second cycle. Eighteen of 22 eligible patients received the second cycle of high-dose chemotherapy. Two patients did not receive the second cycle because of persistent thrombocytopenia, one because of progressive disease and another one because of inadequate cardiac function. With a median follow-up of 24 months, the actuarial freedom from relapse was 56%.

Rodenhuis *et al.* [24] have recently demonstrated that it is feasible to administer multiple cycles of high-dose cyclophosphamide, thiotepa, and carboplatin with AHPCS. They treated 48 patients with metastatic breast cancer or germ cell tumors with two or three cycles of cyclophosphamide, thiotepa, and carboplatin followed by AHPCS. Their main finding was that 80% of the second courses were given on time and without the need for dose reduction; only one toxic death was reported. Ghalie *et al.* [25] treated 39 patients with an additional cycle of high-dose busulfan and etoposide following their standard

high-dose cyclophosphamide, thiotepa, and carboplatin. They reported a 2-year event-free survival for complete responders of 25%, which is comparable to previous experience with single-cycle high-dose chemotherapy.

Vahdat *et al.* [26] from the Memorial Sloan-Kettering Cancer Center (New York, NY) have explored the possibility of giving multiple cycles of intermediate-dose chemotherapy supported by AHPCS. Breast cancer patients received two courses of cyclophosphamide followed by two cycles of thiotepa. Following each cyclophosphamide cycle, peripheral blood progenitor cells were collected and used to support the two thiotepa cycles. All cycles were supported with granulocyte colony-stimulating factor. Forty-two patients were enrolled; 10% did not receive the second cycle of thiotepa. Forty two percent of the patients with measurable disease achieved a complete response, and 21% of the 42 patients are progression free at a median follow-up of 28 months.

Prognostic factors after high-dose chemotherapy

Despite the increasing number of patients being treated with high-dose therapy, the subset of patients who are more likely to benefit other than those that have chemotherapy-responsive disease at the time of transplantation remains unclear. Dunphy *et al.* [27] studied the factors predicting for long-term survival in patients with metastatic breast cancer that were treated with two cycles of high-dose etoposide, cyclophosphamide, and cisplatin with AHPCS. All the patients in this study had stable or responsive disease after conventional-dose chemotherapy, and either estrogen receptor-negative or hormone-refractory disease. In the multivariate analysis, three factors were independently associated with poor prognosis: liver metastases, soft tissue metastases, and those who received prior adjuvant chemotherapy. Investigators from the City of Hope Medical Center (Duarte, CA) presented their analysis of prognostic factors for patients treated in the adjuvant and metastatic settings. For patients with stage II–III breast cancer they found that low tumor grade, moderatly and well differentiated primary tumors, and stage II and IIIA (as opposed to IIIB) were associated with a significantly longer progression-free survival [28]. In terms of overall survival, stage IIIB, positive margins after surgery, and high-dose chemotherapy without doxorubicin were associated with poor prognosis. In patients with metastatic disease, univariate analysis showed that complete remission at the time of high-dose chemotherapy, absence of liver metastases, and fewer sites of metastatic disease predicted for longer progression-free survival [29]. A disease-free interval of more than 1 year in addition to the above mentioned factors, predicted for longer overall survival. Ayash *et al.* [30] presented their study of prognostic factors in 62 patients with metastatic breast cancer that were followed for a median of 50 months. The progression-free survival for this group is 22%. In multivariate analysis, the presence of a single metastatic site and complete response at the time of transplantation were associated with longer progression-free survival. Importantly, patients that received high-dose chemotherapy after achieving a complete response had a 5-year progression-free survival of 31%. Bitran *et al.* [31•] studied 25 patients with breast cancer treated with high-dose chemotherapy in the adjuvant setting for overexpression of her2/neu. All four patients with overexpression relapsed, whereas none of 21 patients with no or borderline overexpression relapsed.

High-dose chemotherapy for the treatment of ovarian cancer

Most studies of high-dose chemotherapy for the treatment of ovarian cancer have included heterogenous groups of patients, with a large proportion of women with refractory disease. Most of these trials demonstrated higher response rates than those obtained with conventional chemotherapy, but the long-term benefit of this approach is still unclear. Recently, Stiff *et al.* [32•] analyzed the results of high-dose chemotherapy in 100 patients with ovarian cancer. They identified tumor bulk and platinum sensitivity as the best predictors of progression-free survival. Lower age, in addition to these two factors, predicted for better overall survival. Interestingly, patients defined as having platinum-resistant, low-volume disease had a median overall survival after high-dose chemotherapy of more than two years, suggesting in the view of the authors, that these patients might benefit from high-dose chemotherapy with a nonplatinum containing regimen.

Under the sponsorship of the Southwest Oncology Group and the Gynecologic Oncology Group, a randomized trial comparing high-dose chemotherapy with conventional-dose chemotherapy has been recently activated (Stiff, Personal communication). It is imperative that eligible patients be enrolled in this study, which will help clarify the role of high-dose therapy in the management of ovarian cancer.

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