High-dose Chemotherapy with Autologous Stem Cell Rescue in Stage IIIB Inflammatory Breast Cancer

KIRAN YALAMANCHILI[1], JUDY LALMUANPUII[1], FAISAL WAHEED[1], SASSAN FARJAMI[1], RAM KANCHERLA[1,2], ZEESHAN QURESHI[1], ALBERT HOANG[3], YUSUF KHALED[1], DIANA LAKE[4], CARMELLO PUCCIO[1], HOO G. CHUN[1], KAREN SEITER[1] and TAUSEEF AHMED[1]

[1]*Division of Oncology and Hematology, New York Medical College and Zalmen A. Arlin Cancer Institute, Westchester Medical Center, Valhalla, NY;*
[2]*Hudson Valley Hematology/Oncology, Poughkeepsie, NY;*
[3]*George Washington University School of Medicine, Washington, DC;*
[4]*Memorial Sloan Kettering Cancer Center, New York, NY, U.S.A.*

Abstract. *Background: Despite the advances in breast cancer care, inflammatory breast cancer (IBC) has a poor prognosis. The purpose of this study was to determine the efficacy of high-dose chemotherapy (HDCT) with thiotepa, mitoxantrone and carboplatin (TMJ regimen) in women with TNM stage IIIB IBC. Patients and Methods: Between 1991 and 1998, twenty-eight patients with stage IIIB IBC underwent an autologous stem cell transplant after undergoing chemotherapy, surgery and/or radiation. Stem cells were collected from the bone marrow and periphery after mobilization with growth factors. Patients received thiotepa 250 mg/m^2 once daily i.v. for 3 days, mitoxantrone 40 mg/m^2 for 1 day and carboplatin 333 mg/m^2 once daily i.v. for 3 days as the conditioning regimen for the HDCT. Radiation therapy and tamoxifen was offered to patients post HDCT if appropriate. Progression-free survival and overall survival was assessed over a 15-year period. Results: At the time of last follow-up in May, 2007, sixteen patients had relapsed. The median overall survival was 49.5 months. The median progression free survival was 40 months. There were no transplant-related deaths. Mucositis and infections were the major side-effects. These results show that HDCT with the TMJ regimen is safe and effective in patients with stage IIIB IBC.*

IBC is an aggressive form of breast cancer that accounts for approximately 3-4% of all breast cancer cases (1). Conventional therapy consists of surgery, chemotherapy, local irradiation and hormonal therapy. Progression-free survival (PFS) and overall survival (OS) remain unsatisfactory, with approximately 30% of patients alive at 5 years (1). The median survival of patients with IBC is about 2.9 years (1). With improved techniques in dose-intensive chemotherapy and supportive care, there have been reports of 3-year event-free survival (EFS) for patients with IBC undergoing HDCT ranging from 42-64% (2-8). We have previously published our results with the TMJ regimen in patients with breast cancer at high risk of relapse and with metastatic breast cancer (9). We present herein our results using the same regimen in patients with stage IIIB IBC.

Correspondence to: Dr. Tauseef Ahmed, 19 Bradhurst Ave, Suite 2100, Hawthorne, NY 10532, U.S.A. Tel: +1 9144938374, Fax: +1 9143471832, e-mail: hdtrans@gmail.com

Key Words: Inflammatory breast cancer, chemotherapy, autologous stem cell transplant, thiotepa, mitoxantrone, carboplatin.

Patients and Methods

Patient selection. Patients with a clinical diagnosis of stage IIIB IBC that had been rendered free of clinically evident disease by using chemotherapy either alone or in combination with surgery or radiation were eligible for this study. The criteria for exclusion were age ≤18 and ≥60 years, performance status (ECOG) >2, prior malignancies (with the exception of cured stage I cervical cancer, non-melanoma skin cancer), infection with human immunodeficiency virus, abnormal left ventricular ejection fraction (<40%), chronic respiratory disease (carbon monoxide diffusing capacity <40% of predicted), abnormal liver tests (serum bilirubin >2 mg/dl or serum alanine aminotransferase levels more than three times the upper limit of normal) and a serum creatinine level more than 1.5 mg/dl. Written informed consent was obtained from the patients for the study, which was approved by the Institutional Review Board of New York Medical College.

Bone marrow and peripheral blood stem cell mobilization. Bone marrow was collected from the posterior iliac crest under general anesthesia. In addition peripheral blood stem cells (PBSC) were collected following mobilization with either growth factors (GCSF or GMCSF) alone or in combination with administration of cyclophosphamide 2 g/m^2/once daily for 2 days (total dose of 4 g/m^2)

and etoposide 150 mg/m^2 once daily for 3 days (total dose 450 mg/m^2) intravenously. A minimum of 2.0×10^6 CD 34+ cells/kg of patient body weight were collected and cryopreserved.

High-dose chemotherapy and transplantation. Patients received thiotepa 250 mg/m^2 once daily on days 1, 2 and 3 (total dose 750 mg/m^2), mitoxantrone 40 mg/m^2 on day 1 and carboplatin 333 mg/m^2 once daily on days 1, 2 and 3 (total dose 1g/m^2) intravenously. PBSCs were reinfused along with bone-marrow cells four days after chemotherapy. Standard supportive care was provided to patients during the posttransplant phase.

Posttransplant treatment. Patients were offered external beam irradiation to the chest wall or the affected breast if it was not part of the original treatment. Patients with estrogen or progesterone receptor positive tumors were offered tamoxifen for a five-year period. Follow-up examinations were scheduled quarterly for the first two years and twice yearly thereafter.

Statistical methods. Data management was performed by commercially available database and spreadsheet programs. Survival curves were calculated with Kaplan-Meier's product limit using software from SAS, Raleigh, USA. OS was defined as time from diagnosis until death from any cause, with living patients censored at date of last contact. PFS was defined as the time from diagnosis to first recurrence of any breast cancer.

Results

Patient characteristics. Twenty-eight patients with stage IIIB IBC were enrolled in this study. Patient characteristics are summarized in Table I. One patient was Her2/neu-positive, 1 was negative. The other 26 patients' Her2/neu status was unknown. Following the initial staging, 24 patients received neoadjuvant chemotherapy at the discretion of the treating physician. Regimens consisted of CAF (cyclophosphamide, adriamycin, 5-fluorouracil) in 15; adriamycin in 3; adriamycin and paclitaxel in 2; TAC (docetaxel, adriamycin and cyclophosphamide) in 1; adriamycin and cyclophosphamide in 2, and CAF/TAC/methotrexate in 1 patient. HDCT was followed by PBSC infusion in 15 patients and PBSC and bone marrow stem cell infusion in 13. After recovery from transplant, radiation to the ipsilateral chest wall was initiated; if it was not part of the original treatment (24 patients received it after transplant). Patients with hormone receptor-positive tumors were placed on tamoxifen 20 mg/day for 5 years (16/28 patients).

Toxicity. The regimen was well tolerated. The median days to recovery of absolute neutrophil count $>0.5\times10^9$/l and platelets $>20\times10^9$/l were 11 (range 8-38) and 11 (range 7-104) respectively. There were no treatment-related deaths. Sixteen patients (57%) developed grade 3-4 mucositis, 7 patients (25%) had grade 3-4 infection and 5 patients (17%) had mild hyperbilirubinemia (serum bilirubin ≥2 mg/dl). One patient was diagnosed with myelodysplastic syndrome 2 years after therapy, which lead to her death.

Table I. *Patient characteristics*.

Characteristic	Number of patients
Median age (range)	45 years (29-58 years)
Menopausal status	
Premenopausal	22
Post menopausal	6
Tumor histology	
Infiltrating ductal carcinoma	27
Invasive lobular carcinoma	1
Hormone receptor status	
ER+/PR+	17
ER–/PR–	10
Unknown	1
Race	
Caucasian	25
Asian	3
Median number of previous chemo regimens (range)	1 (1-3)
Previous anthracycline use	28
Previous taxane use	8
Type of surgery	
MRM before transplant	24
Biopsy only	1
Simple mastectomy before transplant	1
MRM after transplant	1
Bilateral mastectomy after transplant	1

ER: Estrogen receptor, PR: progesterone receptor, MRM: modified radical mastectomy.

Survival. The mean duration of follow-up calculated from those alive at the time of the last follow-up was 140.7 months. At the time of the last follow-up, 12 patients were alive with no progression of disease and 16 patients had died. Fifteen patients died due to progression of disease. Two patients had local relapse, while 14 had systemic (visceral/bone) relapse. The median OS and PFS were 49.5 months and 40 months respectively. The Kaplan-Meier curves of the PFS and OS are shown in Figures 1 and 2.

Discussion

Stage IIIB IBC has not been cured in most patients with the present day treatment strategies. Over a follow-up time of 16.8 years, median OS of 3.8 years and event-free survival (EFS) of 2.3 years was reported in 46 patients by Low *et al*. with the combined modality treatment (10). It is reasonable to assume that 15-27% of patients have durable remissions and are likely to be cured with this therapeutic approach. Thus, although combined modality therapy may be curative, most patients with IBC experience systemic relapse and die of their disease, usually within 4-5 years of diagnosis.

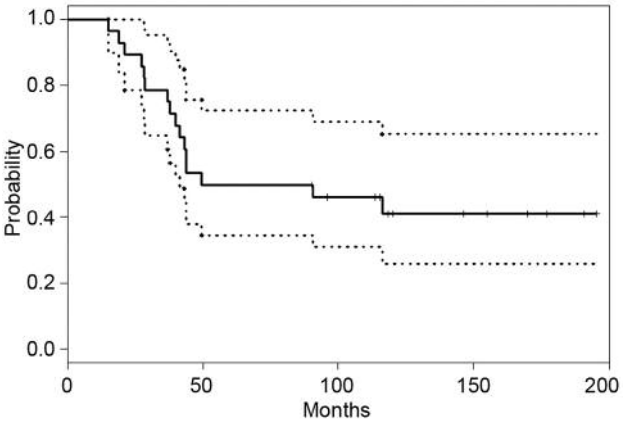

Figure 1. *Survival probability from date of diagnosis.*

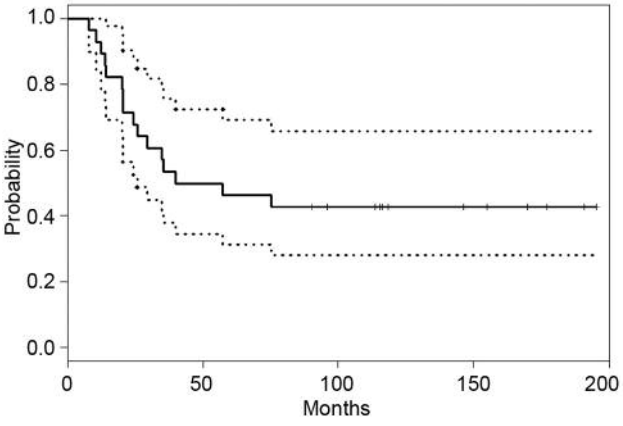

Figure 2. *Progression-free probability from date of diagnosis.*

Antman *et al*. analyzed the International Bone Marrow Transplant Registry and reported a 42% EFS at 3 years for 224 patients with IBC receiving HDCT (5). However, there were no details regarding the sequence of therapy in these patients. Somlo *et al*. reported OS and EFS of 72% and 50% respectively from diagnosis for 22 patients with IBC receiving HDCT consisting of etoposide, cyclophosphamide and either doxorubicin or cisplatin, with a mean follow-up of 46 months (6). Cagnoni *et al*. treated 30 patients with high dose cyclophosphamide, cisplatin and carmustine and stem cell support after surgery; with a median follow-up of 23.5 months from diagnosis, 70% of the patients were alive (3). Adkins *et al*. reported their experience with various HDCT regimens in 47 patients (4). Estimated Kaplan-Meier (KM) 4-year DFS and OS were 51.3% and 51.7% respectively. In another HDCT trial by Ayash *et al*. with cyclophosphamide, thiotepa and carboplatin on 42 patients, the estimated KM 2.5-year DFS and OS were 64% and 89% respectively (2). Schwartzberg *et al*. used cyclophosphamide, thiotepa and carboplatin regimen in 56 patients. (7). At a mean follow-up of 3 years, estimated KM OS and DFS were 72% and 53% respectively.

We undertook this trial of TMJ for IBC to determine whether improved survival could be obtained using this regimen along with surgery and radiation. Overall, our treatment regimen was well tolerated when compared to prior regimens that included carmustine or cisplatin. The follow-up in our study is the longest to date for patients with IBC who underwent HDCT. Limitations of our study include the small number of patients included and the biases associated with selecting a patient for HDCT.

With the use of anthracycline, taxane and trastuzumab-based chemotherapy, tumor response in excess of 80% can be obtained at the present time (11, 12) but the long-term survival benefit is not yet known. Taxanes were not available when we started our study. Selected patients later received them at the discretion of the referring physician but the number is too small to permit adequate analysis.

While our study shows that combination chemotherapy with thiotepa, mitoxantrone and carboplatin followed by autologous stem cell rescue is safe in patients with stage IIIB IBC, it should be noted that randomized control trials have not shown an improvement in OS with HDCT. Since IBC comprises only 1-4% of all breast cancer cases, randomized trials comparing conventional chemotherapy to HDCT would be difficult to perform without the collaboration of large cooperative groups. New approaches incorporating taxanes and trastuzumab into HDCT regimens may further improve results in this fatal disease.

References

1 Hance K, Anderson W, Devesa S, Young H and Levine P: Trends in inflammatory breast carcinoma incidence and survival: the surveillance, epidemiology, and end results program at the National Cancer Institute. J Natl Cancer Inst *97*: 966-975, 2005.

2 Ayash L, Elias A, Ibrahim J, Schwartz G, Wheeler C, Reich E, Lynch C, Warren D, Shapiro C, Richardson P, Hurd D, Schnipper L, Frei Er and Antman K: High-dose multimodality therapy with autologous stem-cell support for stage IIIB breast carcinoma. J Clin Oncol *16*: 1000-1007, 1998.

3 Cagnoni P, Nieto Y, Shpall E, Bearman S, Barón A, Ross M, Matthes S, Dunbar S and Jones R: High-dose chemotherapy with autologous hematopoietic progenitor-cell support as part of combined modality therapy in patients with inflammatory breast cancer. J Clin Oncol *16*: 1661-1668, 1998.

4. Adkins D, Brown R, Trinkaus K, Maziarz R, Luedke S, Freytes C, Needles B, Wienski D, Fracasso P, Pluard T, Moriconi W, Ryan T, Hoelzer K, Safdar S, Rearden T, Rodriguez G, Khoury H, Vij R and DiPersio J: Outcomes of high-dose chemotherapy and autologous stem-cell transplantation in stage IIIB inflammatory breast cancer. J Clin Oncol *17*: 2006-2014, 1999.

5 Antman K, Rowlings P, Vaughan W, Pelz C, Fay J, Fields K, Freytes C, Gale R, Hillner B, Holland H, Kennedy M, Klein J, Lazarus H, McCarthy PJ, Saez R, Spitzer G, Stadtmauer E, Williams S, Wolff S, Sobocinski K, Armitage J and Horowitz M: High-dose chemotherapy with autologous hematopoietic stem-cell support for breast cancer in North America. J Clin Oncol *15*: 1870-9, 1997.

6 Somlo G, Doroshow J, Forman S, Odom-Maryon T, Lee J, Chow W, Hamasaki V, Leong L, Morgan RJ, Margolin K, Raschko J, Shibata S, Tetef M, Yen Y, Simpson J and Molina A: High-dose chemotherapy and stem-cell rescue in the treatment of high-risk breast cancer: prognostic indicators of progression-free and overall survival. J Clin Oncol *15*: 2882-2893, 1997.

7 Schwartzberg L, Weaver C, Lewkow L, McAneny B, Zhen B, Birch R, West W, Tauer K and Buckner C: High-dose chemotherapy with peripheral blood stem cell support for stage IIIB inflammatory carcinoma of the breast. Bone Marrow Transplant *24*: 981-987, 1999.

8 Cristofanilli M, Buzdar A and Hortobágyi G: Update on the management of inflammatory breast cancer. Oncologist *8*: 141-148, 2003.

9 Razis E, Samonis G, Cook P, Beer M, Mittelman A, Lake D, Feldman E, Puccio C and Ahmed T: TMJ: a well-tolerated high-dose regimen for the adjuvant chemotherapy of high risk breast cancer. J Med *25*: 241-250, 1994.

10 Low J, Berman A, Steinberg S, Danforth D, Lippman M and Swain S: Long-term follow-up for locally advanced and inflammatory breast cancer patients treated with multimodality therapy. J Clin Oncol *22*: 4067-4074, 2004.

11 Limentani S, Brufsky A, Erban J, Jahanzeb M and Lewis D: Phase II study of neoadjuvant docetaxel, vinorelbine, and trastuzumab followed by surgery and adjuvant doxorubicin plus cyclophosphamide in women with human epidermal growth factor receptor 2-overexpressing locally advanced breast cancer. J Clin Oncol *25*: 1232-1238, 2007.

12 Cristofanilli M, Gonzalez-Angulo A, Buzdar A, Kau S, Frye D and Hortobagyi G: Paclitaxel improves the prognosis in estrogen receptor negative inflammatory breast cancer: the M.D. Anderson Cancer Center experience. Clin Breast Cancer *4*: 415-419, 2004.

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