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High Dose Chemotherapy and Peripheral Blood Stem Cell Transplantation for High Risk Primary Breast Cancer: A Single Center Experience in Thailand

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SUMMARY Twenty patients with high risk primary breast cancer underwent a high dose chemotherapy program at Ramathibodi Hospital, Bangkok. Eligible patients included 21 women who had a histological diagnosis of breast cancer with more than 10 axillary lymph nodes involved. The patients first underwent modified radical mastectomy, followed by conventional doxorubicin containing adjuvant chemotherapy, before entering the treatment program. Peripheral blood stem cells were mobilized with cyclophosphamide and G-CSF and were harvested by leukapheresis. High dose chemotherapy consisted of cyclophosphamide 5,625 mg/m^2, cisplatinum 165 mg/m^2 and carmustine (BCNU) 600 mg/m^2 were subsequently given, followed by infusion of the harvested peripheral blood stem cells. The median duration of cytopenia after transplantation was 8 days (range 7-12). The median expense for the transplantation, in addition to the cost of mastectomy and conventional chemotherapy, was 224,396 Baht (~ US $5,350). Three out of the first four patients developed interstitial pneumonitis within three months after transplantation. There was one fatal case which was the only regimen related mortality. BCNU was then reduced to 450 mg/m^2 and lung complications were markedly reduced afterwards. The median follow up time was 37 months with a median disease free survival of 38 months and overall survival of four years at 84%.

Breast cancer has been one of the top five cancers and leading causes of death of women in Thailand and all over the world for several decades. The pathophysiology, natural course of disease, and effects of various modalities of breast cancer treatment have been the focuses of world leading oncology study groups until the present. Evidence based knowledge gathered during the last two decades has pointed out that breast cancer indeed is a systemic disease, with a high chance of metastasis or micrometastasis at the time of diagnosis. Tumor removal surgery, therefore, is theoretically inadequate especially in the patients who have aggressive form of the disease. Adjuvant treatments such as chemotherapy and radiation therapy are warranted in these patients.[1,2]

Aggressive characteristics of breast cancer have been defined by several parameters. Tumor size, number of axillary lymph nodes involved and biological properties of the tumor are considered important prognostic factors of the disease.[3] Of these parameters, the number of axillary lymph nodes involved is found to be closely associated with the capacity of the disease to spread systemically, and therefore, the most important indicator of aggressiveness. An example of this association can be seen in the long term chance of relapse, which was approximately 10-20% in stage 3 patients who had 1-2 lymph nodes involved, compared to more than 60% in patients in the same stage who had more than 10 nodes involved.[4]

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Several investigators have studied the impact of adjuvant chemotherapy after tumor removal surgery on the outcome of treatment in different groups of patients, classified by the number of axillary lymph nodes involved. They have found that the chance of disease relapse has been decreased by approximately 25% in the patients who received adjuvant chemotherapy compared to those who did not.[1] The impact of chemotherapy is, therefore, to be calculated upon several other existing prognostic factors of each patient such as number of axillary lymph node involvement, tumor size and hormonal receptor status. If the contribution to the chance of relapse of multiple axillary lymph node involvement is taken into account, we can see that the chance of relapse in this group of patients still approaches 50%, even after conventional adjuvant chemotherapy.

Evidence from several *in vivo* and *in vitro* studies suggested that breast cancer is a chemosensitive tumor with a characteristic pattern of responsiveness. The pattern of response to chemotherapy was found to be dose responsive, *i.e.* the higher the dose, the more response it will get. The pattern of the dose response curve of the tumor was S shaped. The maximum dose of chemotherapy which can be given by conventional method is at the middle of the curve. Based on this dose response curve, we can assume that more response could be achieved if more chemotherapy could be given.[5] However, dose related toxicity and bone marrow suppression precluded the increase of the dose of the chemotherapy.

At present, there are several strategies to overcome dose related toxicity causing bone marrow suppression. The use of growth factors such as G-CSF or GM-CSF permits the dose to be increased twice to three times. The use of autologous stem cell support in the way of autologous stem cell transplantation allows the dose to be increased even higher in the range of 3 to 7 times of the conventional dose. These strategies theoretically should improve the outcome of treatment when combined with conventional treatment, and therefore remained the focus of breast cancer treatment research in the western countries over the last decade.[6] The results of these treatment strategies, however, are still inconclusive and more clinical studies in this field are still warranted.

In Thailand, we have initiated a program of high dose chemotherapy for breast cancer as a feasibility study in Ramathibodi Hospital since 1995. This program is a collaborative study between several departments in the hospital and the National Cancer Institute. The preliminary results will be discussed in this paper.

MATERIALS AND METHODS

Patients

Patients who were pathologically diagnosed with infiltrating ductal or infiltrating lobular carcinoma were included in the study. Patients who had inflammatory breast cancer were excluded. Patients would be included if pathological examination showed that there were metastatic tumors in more than ten of the resected axillary lymph nodes. The patients must have normal cardiac, pulmonary, liver and renal functions and their metastatic work up showed no metastatic lesion.

Surgery and adjuvant chemotherapy

The patients underwent tumor removal surgery, which in our center is routinely performed as modified radical mastectomy. After the surgery, the patients would be followed up and given chemotherapy by medical oncologists. Chemotherapy regimen given included doxorubicin: either 5-FU, doxorubicin, cyclophosphamide (FAC) or doxorubicin and taxol (AT). Chemotherapy was given for at least four cycles.

Peripheral blood stem cell mobilization

After conventional adjuvant chemotherapy was finished, the patients underwent repeated metastatic work up examination and cardiac and pulmonary function evaluation. If the results were normal, the patients would enter the high dose chemotherapy protocol. For stem cell mobilization, the patients were given cyclophosphamide 2 g/m^2 intravenously over 24 hours followed by G-CSF 7.5 μg/kg daily. G-CSF was given until the end of leukapheresis. Complete blood counts were done on a daily basis beginning on the eighth day after cyclophosphamide to monitor the recovery of WBC counts. Once WBC counts returned to more than 5,000 cells/mm^3, leukapheresis would be started. Leukapheresis was performed daily until the targeted number of CD34 positive cells (more than 2 x 10^6 cells/kg) was collected. The stem cells collected were cryopreserved at -80°C using DMSO as cyropreservant.

High dose chemotherapy

High dose chemotherapy was started shortly after the com-

pletion of stem cell collection. Chemotherapy regimen used were cyclophosphamide 5,675 mg/m^2 given over 3 days, cisplatinum 165 mg/m^2 given over 3 days, and BCNU 600 mg/m^2 single dose. Anti-emetics, parenteral nutrition, antibiotics and transfusion support were given as indicated until marrow recovery occurred.

Statistical analysis

The patients' statistic parameters were calculated using descriptive statistical methods. Disease free survival and overall survival of the patients were calculated by Kaplan-Meier method. Disease relapses, either local or distant, were used as endpoints in disease free survival.

RESULTS

Twenty-one patients entered the study protocol after finishing conventional adjuvant chemotherapy following tumor removal surgery. Nineteen patients received FAC and 2 patients received AT as their adjuvant chemotherapy. Metastatic work up after adjuvant chemotherapy showed that all of the patients were still without metastatic disease. The demographic and disease characteristics of the patients are shown in Table 1.

All patients received mobilizing regimen according to the protocol. Twenty patients had their stem cells collected to adequate amounts within 5 leukapheresis cycles. However, one patient was a poor mobilizer and her total CD34 counts were still below 1 x 10^6 cells/kg after the fifth cycle. This patient was subsequently taken out of the study. Thereafter, only twenty patients were therefore given high dose chemotherapy.

Chemotherapy was tolerated in most patients with acceptable severity of emesis. White blood cell counts began to descend shortly after chemotherapy was finished. Cryopreserved stem cells were given to the patients without immediate complications. During bone marrow suppression period, all of the patients had fever requiring broad spectrum antibiotics. All of them also received prophylactic platelet transfusions. Duration of bone marrow suppression, number of days on non-prophylactic antibiotics and number of prophylactic platelet transfusions are shown in Table 2.

All of the patients recovered from bone marrow suppression period. Their neutrophils rose to more than 1,000/mm^3 within a median of 9 days. They were out of platelet transfusion dependency within the first two weeks. There was no immediate regimen related mortality. One patient developed interstitial pneumonitis two months after high dose chemotherapy. The pneumonitis was refractory to steroids and became progressive, the patient died four months after the symptoms had developed. Another two of the first four patients also developed similar but non-fatal pulmonary complications, where the dose of BCNU was reduced by 25%. After the dose reduction, the rest of the patients did not have major complications.

All of the patients were followed up to a median follow up time of 37 months. Five out of 20 patients developed relapse of their disease. Four of the relapses occurred as bone metastasis. The median disease free survival of the entire group was 38 months (Fig. 1). Two of the patients died from metastatic disease, bringing the 4-

Table 1 Characteristics of the patients

Age (years)*	42 (29-52)
Tumor size (cm)*	4 (2-10)
Number of axillary lymph nodes involved*	13 (10-38)
Adjuvant chemotherapy	
CAF	19
AT	2
Number of days to stem cell transplant from mastectomy*	217 (111-328)

*median (minimum-maximum)

Table 2 Bone marrow suppression from high dose chemotherapy

CD34 positive cells infused (x 10^6/kg)*	5.45 (1.53-11.82)
Number of days with a WBC < 500/mm^3*	7 (4-9)
Number of days on non-prophylactic antibiotics*	8 (5-13)
Number of prophylactic platelet transfusions*	2 (0-4)

*median (minimum-maximum)

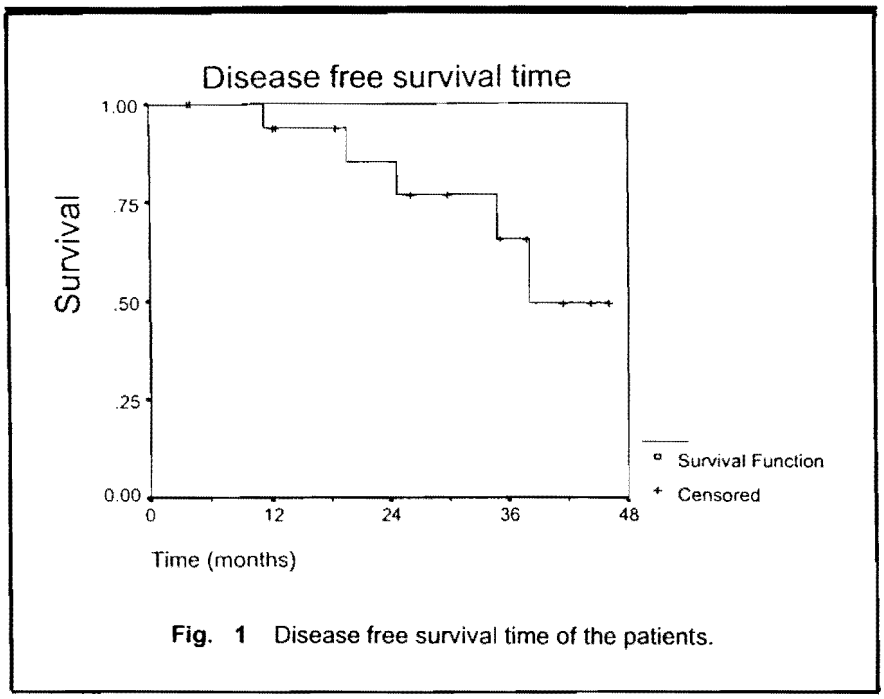

Fig. 1 Disease free survival time of the patients.

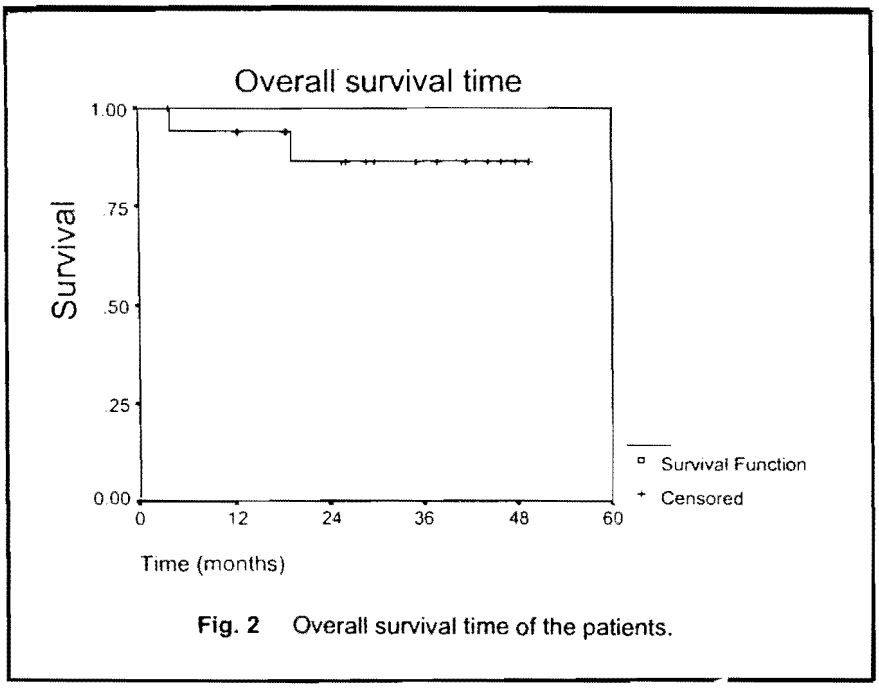

Fig. 2 Overall survival time of the patients.

year survival rate to 85%. The median overall survival time of the patients can not be re-calculated yet (Fig. 2).

Treatment costs of the high dose chemotherapy section, from mobilization regimen to the time that the patients were discharged from the hospital ranged from 138,384 Baht (~ US$ 3,300) to 382,170 Baht (~ US $9,100). The median cost of the procedure was 224,396 Baht (US $5,350).

DISCUSSION

The use of high dose chemotherapy for breast cancer has started in the late 1980's, with its indications in both patients with high risk primary disease and with metastatic diseases. Data from the Cancer and Leukemia Group B Thai (CALGB), which used cyclophosphamide, cisplatin and BCNU as high dose regimen, have reported a high mortality in the early phase due to pulmonary complications believed to result from high dose BCNU and cyclophosphamide.[7,8] However, the long term results with the novel therapeutic method were quite impressive. Disease related mortality rate and relapse rate were significantly lower when compared to the historical control group. Three years relapse free survival was 70% compared to 30-40%.[7] After the first few reports, stem cell transplantation for breast cancer became a widespread practice in North America. The number of patients receiving autologous stem cell transplantation for breast cancer exceeded the number of patients transplanted for other indications.[9]

Bone marrow transplantation is a procedure with relatively high complications requiring experienced hands. This is because of the complexity of the treatment, and also proved true for breast cancer patients undergoing transplantation. The duration of bone marrow suppression after transplantation was a major cause of morbidity. Transplantation specific complications, such as veno-occlusive disease and interstitial lung disease were also leading morbidity causes.

During the last decade, the shift of the stem cells source used for transplantation from bone mar-

row stem cells to peripheral blood derived stem cells has significantly improved transplantation outcome. The most important contributing factor is the shortening of the bone marrow suppression period following transplantation, which was decreased from 20-30 days to 10-14 days. By using the peripheral blood stem cells, morbidity and mortality rate of transplantation has greatly decreased.[10] It is generally accepted that the mortality rate of autologous transplantation should be less than 10%. Therefore, the results of high dose chemotherapy with stem cell transplantation for breast cancer today is much better than in the earlier days.

Though high dose chemotherapy for high risk primary breast cancer has been practiced all over the world, its impact on the natural course of the disease has not yet been concluded.[6] In the 1999 Annual Meeting of the American Society of Clinical Oncology, the issue of autologous stem cell transplantation for breast cancer was the main topic. Most of the studies presented in the meeting compared high dose chemotherapy with autologous stem cell transplantation to other kinds of high dose chemotherapy supported with growth factors, which showed no significant improvement of outcomes in the transplantation groups.[11,12] The impact of high dose chemotherapy in the high risk primary setting following tumor removal surgery and adjuvant chemotherapy should be clarified in the next two or three years when the NCI Intergroup study is completed, since this is the only study that compares high dose chemotherapy with autologous stem cell transplantation to conventional adjuvant therapy only.

In our study, morbidity was originally high due to regimen related pulmonary toxicity as reported in the CALGB study. The reason for this was the high dose of BCNU and chest wall radiation therapy following the high dose regimen.[8] The use of other conditioning regimen such as cyclophosphamide, carboplatin and thiotepa was associated with less pulmonary toxicity.[13] In Thailand, we do not have an access to thiotepa, therefore, we chose to reduce the dose of BCNU by 25%. After the BCNU dose reduction, we rarely encountered pulmonary complications. Whether the dose reduction would lead to a compromised therapeutical outcome is undetermined as yet.

Our reported median disease free survial in was 38 months. This is less than originally reported by the investigators in the United States. The majority of the relapses occurred as distant relapses, mostly in the bone. Since the study was not designed as a phase 3 study, we cannot identify the impact of treatment on disease outcome or the long term results. However, at least the feasibility and toxicity of such treatment in Thai patients could be pointed out.

REFERENCES

1. Early Breast Cancer Trialists' Collaborative Group. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. Lancet 1992; 339: 1-15.
2. Bonadonna G, Valagussa P, Moliterni A, Zambetti M, Brambilla C. Adjuvant cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer: The results of 20 years of follow-up. N Engl J Med 1995; 332: 901-6.
3. Valagussa P, Bonadonna G, Veronesi V. Patterns of relapse and survival following radical mastectomy. Cancer 1978; 41: 1170-8.
4. Nemoto T, Vana J, Bedwani RN, Baker HW, McGregor FH, Murphy GP. Management and survival of female breast cancer: Results of a national survey by the American College of Surgeons. Cancer 1980; 45: 2917-24.
5. Antman K, Gale RP. Advanced breast cancer: High-dose chemotherapy and bone marrow autotransplants. Ann Int Med 1988; 108: 570-4.
6. Eddy DM. High-dose chemotherapy with autologous bone marrow transplantation for the treatment of metastatic breast cancer. J Clin Oncol 1992; 10: 657-70.
7. Peters WP, Ross M, Vredenburgh JJ, Meisenberg B, Marks LB, Winer E, *et al.* High-dose chemotherapy and autologous bone marrow support as consolidation after standard-dose adjuvant therapy for high-risk primary breast cancer. J Clin Oncol 1993; 11: 1132-43.
8. Todd NW, Peters WP, Ost AH, Roggli VL, Piantadosi CA. Pulmonary drug toxicity in patients with primary breast cancer treated with high-dose combination chemotherapy and autologous bone marrow transplantation. Am Rev Resp Dis 1993; 147: 1264-70.
9. Passweg JR, Rowlings PA, Armitage JO, Gale RP, Pelz CJ, Sobocinski KA, *et al.* Report from the International Bone Marrow Transplant Registry and Autologous Blood and Marrow Transplant Registry-North America. Clin Transpl 1995; 117-27.
10. Fisher DC, Vredenburgh JJ, Petros WP, Hussein A, Berry DA, Elkordy M, *et al.* Reduced mortality following bone marrow transplantation for breast cancer with the addition of peripheral blood progenitor cells is due to a marked reduction in veno-occlusive disease of the liver. Bone-Marrow-Transplant 1998; 21: 117-22.
11. Peters W, O'Rosner G, Vredenburgh J, *et al.* A prospective randomized comparison of two doses of combination alkylating agents as consolidation after CAF in high-risk primary breast cancer involving ten or more axillary lymph nodes: Preliminary results of the CALGB9082/SWOG9114/NCIC MA-13. In: 35th Annual ASCO Meeting; 1999; Atlanta, GA, 1999.
12. The Scandinavian Breast Cancer Study Group 9401. Results from a randomized adjuvant breast cancer study with high dose chemotherapy with CTCb supported by autologous bone marrow stem cells versus dose escalated and tailored FEC therapy. In: 35th Annual ASCO Meeting; 1999; Atlanta, GA, 1999.
13. Antman K, Ayash L, Elias A, Wheeler C, Hunt M, Eder JP, *et al.* A phase II

study of high-dose cyclophosphamide, thiotepa, and carboplatin with autologous marrow support in women with measurable advanced breast cancer responding to standard-dose therapy. J Clin Oncol 1992; 10: 102-10.