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# Breast Cancer

# High-dose thiotepa, melphalan and carboplatin (TMCb) followed by autologous stem cell transplantation in patients with advanced breast cancer: a retrospective evaluation

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**Summary:**

**This study was conducted to evaluate the efficacy of high-dose thiotepa, melphalan and carboplatin (TMCb) regimen in 27 patients undergoing autologous stem cell transplantation (ASCT) for metastatic breast cancer. A total of 27 patients with stage IV breast cancer underwent ASCT following thiotepa (500 mg/m$^2$), melphalan (100 mg/m$^2$) and carboplatin (1200–1350 mg/m$^2$). Of 27 patients, 17 had refractory relapse, eight had responding relapse, and two had no evidence of disease (NED) at the time of transplant. In all, 11 patients had only bone disease, nine had bone plus visceral disease, three had only visceral disease, and two had locoregional recurrent disease. The median time from diagnosis to transplant was 1081 days (range 180–2341). Staging for evaluation of response was performed 4–6 months after transplantation. Five patients were not evaluable (NE) for response because of NED at transplant ($n = 2$) or early death due to transplant-related complications ($n = 3$) (two of viral pneumonia and one of regimen-related toxicity) occurring at a median of 4 days (range 11–46) post-transplant. One of the two patients who was NED at the time of transplant is still NED on day 760 post-transplant. Seven of 15 refractory (47%) and 5/7 (71%) responsive patients with evaluable disease achieved a complete response of all measurable disease or all soft-tissue disease with at least improvement in bone lesions. Of 27 patients (37%),[10] are alive and progression-free, a median of 582 days (range 410–1380) after treatment, 6/17 (35%) with refractory disease and 4/10 (40%) with responsive disease. The probability of progression-free survival (PFS) for all patients was 0.50. The probabilities of PFS at 2 years for patients with refractory ($n = 17$) and responsive ($n = 10$) disease were 0.42 and 0.60, respectively. PFS at 2 years for the 14 patients who were NED or achieved CR/PR* following-HDC was 0.67. PFS at 2 years for patients who did not achieve CR/PR* following-DHC was 0.33. These preliminary data suggest that high-dose TMCb followed by autologous stem cell transplantation is an effective regimen for patients with advanced breast cancer and may be comparable to some previously used regimens.**

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## Introduction

Thiotepa and melphalan are active drugs in the treatment of hematologic malignancies.[1,2] Melphalan and thiotepa are also among the most active single agents in the treatment of breast and ovarian cancer.[3–5] The busulfan, melphalan and thiotepa (Bu/Mel/TT) regimen has shown high activity in the treatment of patients with metastatic breast cancer.[6–8] Bensinger *et al* reported estimated probabilities of EFS at 1.5 years for patients with metastatic responsive and refractory disease as 0.53 and 0.24, respectively, with this regimen.[8] Similarly, carboplatin as a single agent has significant activity against ovarian, testicular and lung cancer.[9] Carboplatin as a part of ifosfamide, carboplatin and etoposide (ICE) and cyclophosphamide, thiotepa, carboplatin (STAMP-V) HDC regimens has been used for the treatment of various solid tumors with autologous PBSCT.[10–13] In considering the current literature for use of carboplatin in the setting of autologous transplantation for solid tumors, we decided to combine carboplatin with thiotepa and melphalan. Therefore, we developed a regimen of thiotepa, melphalan and carboplatin (TMCb) in a phase-I trial.[14] These drugs have marrow ablation as their dose-limiting toxicity, allowing significant dose escalation with the infusion of autologous hematopoietic stem cells.[14] The maximum-tolerated dose (MTD) of carboplatin that could be added to fixed doses of thiotepa 500 mg/m$^2$ and melphalan 100 mg/m$^2$ was 1350 mg/m$^2$ associated with a

demonstrable activity in patients with breast cancer.[14] Upon seeing intractable diarrhea at this dose level in the clinical setting, we decided to use a cumulative carboplatin dose of 1200 mg/m$^2$ (one step down) in this regimen. Therefore, here we retrospectively evaluated the efficacy of this regimen in 27 patients with advanced breast cancer in order to verify these initial observations and extend them to a larger group of patients with solid tumors.

## Patients and methods

### *Patients and treatment regimen*

From January 1998 to September 2001, 27 patients with advanced breast cancer were treated. All patients were $<60$ years of age, had a Karnofsky score of $>70\%$, a left ventricular ejection fraction $\geqslant 50\%$, a creatinine clearance $\geqslant 50$ ml/min, a bilirubin $<2$ mg/dl, and a Dlco $\geqslant 60\%$. Oral and written informed consent was obtained from all patients or their guardians. Patient characteristics are given in Table 1.

A cumulative thiotepa dose of 500 mg/m$^2$ was administered on days $-9$ and $-8$. This was given in two equally divided doses of 250 mg/m$^2$/day i.v. Thiotepa was given in 1000 cm$^3$ normal saline as a 2-h infusion. All patients received a cumulative dose of melphalan 100 mg/m$^2$ administered in two doses of 50 mg/m$^2$/day i.v. infused in 500 cm$^2$ normal saline over 60 min on days $-7$ and $-6$. A cumulative carboplatin dose of 900–1350 mg/m$^2$ was administered on days $-5$, $-4$, and $-3$. This was given in three equally divided doses of 300–450 mg/m$^2$/day i.v. Carboplatin was given in 1000 ml D5W with 50 g mannitol (%5 solution) as a 2-h infusion.[14] Renal function was monitored during the last 3 days of carboplatin infusion. If there was a significant change in renal function (clearance droping below 60 ml/min) carboplatin was discontinued. On the basis of a dose finding study, four patients received a cumulative carboplatin dose of 900 mg/m$^2$, three received 1150 mg/m$^2$ and one received 1350 mg/m$^2$.[14] Of 27 patients, 19 received a cumulative carboplatin dose of 1200 mg/m$^2$. The treatment schedule is given in Table 2.

**Table 1** Patient characteristics ($n=27$)

| | *No. of patients (%)* |
|---|---|
| Median age years (range) | 41 (36–57) |
| History of adjuvant chemotherapy | 27/27 (all patients received doxorubicin-based regimens) |
| Median no. of adjuvant cycles | 6 (3–11) |
| History of prior chemotherapy for metastatic disease (excluding mobilization regimen) | 25/27 (92.5) |
| Median no. of total cycles given for metastatic disease | 4 (3–15) |
| Median no. of regimens for metastatic disease | 1 (1–6) |
| Median time from diagnosis to transplant | 1081 days (180–2341) |
| Marrow involvement by histology | 9/27 (33) |
| *Disease status at transplant* | |
| Refractory relapse | 17/27 (63) |
| Responding relapse | 8/27 (29.5) |
| NED | 2/27 (7.5) |
| *Disease site at transplant* | |
| Bone only disease | 11 (8/11 HR+) |
| Bone + visceral | 9 (4/9 HR+) |
| Visceral only | 3 (1/3 HR+) |
| Loco-regional disease | 2 (1/2 HR+) |
| NED | 2 (2 HR+) |
| *Receptor status* | |
| ER+/PR+ | 7 |
| ER+/PR- | 6 |
| ER-/PR+ | 3 |
| ER-/PR- | 7 |
| Unknown | 4 |

Abbreviation: HR = hormone receptor.

### *Autologous stem cell harvest and cryopreservation*

In all, 27 patients received peripheral blood stem cells (PBSC) collected following the administration of chemotherapy followed by recombinant human granulocyte colony-stimulating factor (rhG-CSF-Neupogen, Amgen-Roche, Thousand Oaks, CA, USA). A total of 11 patients received chemotherapy consisting of cyclophosphamide (CY) 4 g/m$^2$/day $\times$ 1 on day 1 and paclitaxel 250 mg/m$^2$/day $\times$ 1 on day 2 followed by rhG-CSF 8-16 $\mu$g/kg/day (subcutaneously b.i.d.) starting the day after completion of paclitaxel until the last day of apheresis.[15,16] In all, 11 patients received chemotherapy consisting of CY 4 g/m$^2$/day $\times$ 1 on day 1 and epirubicin 120 mg/m$^2$/day $\times$ 1 on day 2 followed by rhG-CSF 8–16 $\mu$g/kg/day (subcutaneously b.i.d.) starting the day after completion of paclitaxel, until the last day of apheresis. The remaining five patients received CY + etoposide 200 mg/m$^2$/day $\times$ 3 on days 1–3 followed by rhG-CSF.[17] CY was given in 500 ml D5W over 1 h. Hydration was started 1 h prior to CY and continues for 24 h. All patients received MESNA to prevent hemorrhagic cystitis due to CY. MESNA dose was 4 g/m$^2$ as equally divided doses given prior to infusion of CY and 4 and 8 h afterwards. Patients received antibiotic prophylaxis with ciprofloxacin 750 mg orally twice per day when the WBC count was less than $0.5 \times 10^9$/l. Apheresis was started when WBC counts reached $\geqslant 2 \times 10^9$/l (following a nadir). The techniques of PBSC harvesting, cryopreservation, thawing and transfusion have been described elsewhere.[18] Day 0 designates the day of PBSC infusion. All patients in this study received post-transplant growth factor (rhG-CSF) at a dose of 5 $\mu$g/kg/day until successful engraftment. Engraftment was defined as the first of two consecutive days on which the patient's neutrophil count was greater than $0.5 \times 10^9$/l following the nadir and the first of seven consecutive days on which the patient's unsupported platelet count was greater than $20 \times 10^9$/l.

### *Regimen-related toxicity grading*

Regimen-related toxicity (RRT) was graded using a previously described system, to assess morbidity.[19] Toxicities affecting renal, hepatic, cardiac, pulmonary, gastrointestinal, bladder, the central nervous system and mucous membranes were evaluated. RRTs were graded prospectively from days 0 to 28. Grade 3 toxicity was considered life threatening and grade 4 toxicity was a fatal consequence of the treatment regimen.

**Table 2** Transplant treatment schedule for TMCb regimen

| *Day* | *−9* | *−8* | *−7* | *−6* | *−5* | *−4* | *−3* | *−2* | *−1* | *0* |
|---|---|---|---|---|---|---|---|---|---|---|
| Thiotepa (250 mg/m$^2$/day × 2) | X | X | | | | | | | | |
| *Melphalan* (50 mg/m$^2$/day × 2) | | | X | X | | | | | | |
| Carboplatin (400 mg/m$^2$/day × 3) | | | | | X | X | X | | | |
| Rest | | | | | | | | X | X | |
| PBSC infusion | | | | | | | | | | X |

*Evaluation of response*

Patients were considered to have refractory disease if they did not achieve a partial remission (PR), or progressed following initial chemotherapy for stage IV disease. Patients who achieved a 50% reduction in the spread of all measurable metastatic disease (PR) or complete response (CR) following initial chemotherapy for metastatic disease or who were rendered disease-free following surgery or radiation therapy without receiving chemotherapy were classified as having responsive disease. Bone-only disease was categorized as responsive if sclerosis of prior lesions was demonstrated with no new lesions and normalization of a tumor marker following initial chemotherapy. Patients who entered HDC without measurable disease were classified as having no evidence of disease (NED). *De novo* patients were defined as those who presented with stage IV disease at the time of initial diagnosis. Local/regional disease included ipsilateral or contralateral nodal, chest wall or breast recurrences. Visceral disease was defined as liver, lung or abdominal metastases.

Baseline evaluation was carried out within 10 weeks of HDC using imaging studies (CT or MRI scans of brain, chest, abdomen and pelvis and radionuclide bone scans or skeletal MRIs), tumor markers (CA 15-3, CEA or CA 125) and bilateral bone marrow biopsies. Patients had tumor markers repeated within 6 weeks of HDC and those with measurable visceral or soft-tissue disease were restaged by CT or MRI scanning of previous sites of disease. All patients were restaged at 60–80 days, at 6 months and yearly after HDC.

Responses after HDC and PBSC infusion for patients with measurable disease were defined as CR if there was disappearance of all tumor for more than 30 days, and PR if there was a reduction of 50% or more in the size of measurable disease for at least 30 days. Responses of less than PR or progressive disease were considered no response (NR). Patients with measurable disease and bone metastases or bone-only disease were defined as PR* if there was a CR of measurable disease in nonbone areas and sclerosis of prior lytic bone lesions but continuing activity by bone scan in areas of prior uptake without the development of new bone lesions.[20]

*Statistics*

Survival was calculated from the time of PBSC infusion until death or date of last contact. Progression-free survival (PFS) was calculated by censoring at the date of relapse and progression, respectively. Patients who died with evidence of recurrent or persistent disease were categorized as dying from relapse or progressive disease, irrespective of the immediate cause. Student's *t*-test was used to analyze the difference between two independent means. Actuarial probabilities of survival and PFS were computed according to the method of Kaplan and Meier.[21]

## Results

*Treatment compliance*

All 27 patients received all of the prescribed doses of drugs. High-dose chemotherapy and autologous PBSC infusion was performed at the bone marrow transplant units of Ankara Numune Education and Research Hospital ($n=16$) and Ankara University Medical School ($n=11$). Median hospital stay was 16 days (range 12–26).

*PBSC mobilization*

A total of 27 patients received chemotherapy followed by rhG-CSF for PBSC mobilization and a median of $5.55\times10^6$ CD34+cells/kg (range 2.20–14.57) was collected with a median of two (range 1–5) aphereses. In 11 patients receiving Cy+paclitaxel followed by rhG-CSF for PBSC mobilization, a median of $6.5\times10^6$ CD34+cells/kg (range 2.59–14.57) was collected with a median of 2 (range 1–4) aphereses. In 11 patients receiving Cy + epirubicin followed by rhG-CSF for PBSC mobilization, a median of $4.75\times10^6$ CD34+cells/kg (range 2.20–12.21) was collected with a median of 2 (range 1–5) aphereses. In five patients receiving Cy+etoposide followed by rhG-CSF for PBSC mobilization, a median of $5.24\times10^6$ CD34+cells/kg (range 2.92–10.40) was collected with a median of two (range 1–3) aphereses. Patients began the preparative regimen a median of 36 days (range 31–49) following administration of chemotherapy for PBSC mobilization.

*Engraftment*

All patients received unmanipulated PBSCs collected with submyeloablative mobilization chemotherapy followed by rhG-CSF. Of 27 patients, 26 were evaluable for engraftment. Median days of ANC $0.5\times10^9$/l and platelet of $20\times10^9$/l were 10 (range 8–17) and 11 (9–16) after stem cell infusion, respectively. Median numbers of RBC and platelet transfusion requirements were 2 units (range 0–5) and 6 (4–12), respectively.

*Transplant-related deaths and RRTs (Table 3)*

Grade III–IV RRTs occurred in two of 27 (7%) patients, causing regimen-related mortality in one (3.5%) patient.

One patient who had grade IV RRT died of congestive heart failure associated with a decreased ejection fraction and acute arrythmia on day 22. One of 27 (3.5%) patient experienced grade III gastrointestinal toxicity associated with diarrhea. Two patients died of viral interstitial pneumonia, one due to influenza and one probably due to CMV, on post-transplant days 9 and 21, respectively. Thus, a total of three patients (11%) died from complications of HDC during the first 100 days after transplant. There were two episodes of nonfatal bacteremia secondary to *Staphylococcus epidermidis* ($n=1$) and *E. coli* ($n=1$) at 100 days.

### *Response and survival (Table 4)*

Of 27 patients, two were NED pre-HDC and three died before day 100 from treatment-related complications, leaving 22 patients evaluable for response. Of 22 patients (54%),[12] achieved a CR/PR* (seven with refractory and five with responsive disease) of whom seven are alive and progression-free a median of 613 days (range 570–1380) after HDC. One of the two patients who was NED at the time of transplant is still NED on day 760 post-transplant. Two of seven patients who achieved PR after transplant are alive with stable disease on days 410 and 453 post-transplant. Of 27 patients (37%), 10 are alive and progression-free a median of 582 days (range 410–1380) after treatment, 6/17 (35%) with refractory disease and 4/10 (40%) with responsive disease. The probability of progression-free survival for all patients was 0.50. The probabilities of progression-free survival (PFS) at 2 years for patients with refractory ($n=17$) and responsive ($n=10$) disease were 0.42 and 0.60, respectively. PFS at 2 years for the 14 patients who were NED or achieved CR/PR* following HDC was 0.67. PFS at 2 years for patients who did not achieve CR/PR* following HDC was 0.33.

### *Outcome for refractory patients*

Among 17 patients with refractory disease, two died before day 100 from treatment-related complications. Thus, 15 were evaluable for response. Seven of 15 (47%) achieved a

**Table 3** Regimen-related toxicities

| *Category* | *Toxicity grade* | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *0* | | *1* | | *2* | | *3* | | *4** | |
| | *No.* | *(%)* | *No.* | *(%)* | *No.* | *(%)* | *No.* | *(%)* | *No.* | *(%)* |
| Pulmonary | 27 | (100) | 0 | (0) | 0 | (0) | 0 | (0) | 0 | (0) |
| Cardiovascular | 20 | (74) | 4 | (15) | 2 | (7) | 0 | (0) | 1 | (3.5) |
| Skin | 27 | (100) | 0 | (0) | 0 | (0) | 0 | (0) | 0 | (0) |
| Liver | 25 | (93) | 2 | (7.5) | 0 | (0) | 0 | (0) | 0 | (0) |
| Mucositis | 7 | (26) | 5 | (18.5) | 15 | (56) | 0 | (0) | 0 | (0) |
| Renal | 17 | (63) | 8 | (30) | 2 | (7) | 0 | (0) | 0 | (0) |
| Diarrhea | 1 | (3.5) | 9 | (33) | 16 | (59) | 1 | (3.5) | 0 | (0) |
| Neurologic | 27 | (100) | 0 | (0) | 0 | (0) | 0 | (0) | 0 | (0) |
| Bladder | 27 | (100) | 0 | (0) | 0 | (0) | 0 | (0) | 0 | (0) |

*Fatal toxicity.

**Table 4** Response and outcome ($n=27$)

| *Disease status* | | *Response* | | | *Progression-free* | | |
|---|---|---|---|---|---|---|---|
| | | *NED* | *ED* | *CR/PR** | *PR* | *NR* | *Survivors* |
| *Bone only disease* | 11 | | | | | | |
| Refractory | 7 | — | 1 | 2 | 2 | 2 | 2 |
| Responding | 4 | — | — | 2 | 2 | — | 2 |
| *Bone + visceral disease* | 9 | | | | | | |
| Refractory | 6 | — | — | 3 | 2 | 1 | 2 |
| Responding | 3 | — | 1 | 2 | — | — | 1 |
| *Visceral only disease* | 3 | | | | | | |
| Refractory | 2 | — | 1 | 1 | — | — | 1 |
| Responding | 1 | — | — | 1 | — | — | — |
| *Loco-regional disease* | 2 | | | | | | |
| Refractory | 2 | — | — | 1 | 1 | — | 1 |
| *NED* | 2 | 2 | — | — | — | — | 1 |
| *Total* | 27 | 2 | 3 | 12/22 (54%) | 7/22 (32%) | 3 | 10/27 (37%) |
| Refractory | 17 | — | 2 | 7/15 (47%) | 5/15 (33%) | 3 | 6/17 (35%) |
| Responding | 10 | 2 | 1 | 5/7 (71%) | 2/7 (29%) | — | 4/10 (40%) |

Abbreviations: NED = no evidence of disease, ED = early death, CR = complete remission, PR* = complete response in the setting of bone disease, PR = partial remission, NR = no response.

CR/PR* and five (33%) are alive progression-free. Of five patients who achieved PR, one is alive and progression-free at day 410. Sites of disease involvement for the six survivors (40%) with refractory disease included bone-only ($n=2$), bone + visceral disease ($n=2$), visceral disease only ($n=1$), and loco-regional disease ($n=1$). The probability of PFS for the 17 patients with refractory disease at 2 years were 0.42.

### *Outcome for responsive patients*

In all, 10 patients were defined as having responsive disease. Seven of these had measurable disease, of whom five achieved a CR/PR* and two PR. Overall, four of 10 patients (40%) (two in CR/PR*, one in PR and one NED) are alive and progression-free on post-transplant days 453, 760, 1020 and 1380. Sites of disease involvement in the three of four survivors with responsive disease included bone-only ($n=2$) and bone + visceral disease ($n=1$). The probability of PFS for the 10 patients with responsive disease at 2 years was 0.60.

## Discussion

Hyrniuk and Bush have demonstrated a consistent correlation between dose of chemotherapy administered and frequency of response in metastatic breast cancer.[22,23] Alkylating agents appear more effective than other classes of drugs and have been shown to give single-agent response rates from 20 to 54% in metastatic breast cancer.[23] Response rates of 75% have been achieved in high-dose single-alkylating agent therapy in failed or refractory breast cancer.[3,5] The major obstacle to curing patients with advanced breast cancer and other malignancies with HDC and autologous PBSCT is relapse.[24–27] Strategies to reduce relapse rates include increasing the intensity of the preparative regimen and administering the HDC earlier in the course of the disease when disease burden is small and tumor resistance is less likely to have developed.

Several groups have reported their experience with HDC followed by hematopoietic stem cell rescue for treatment of patients with metastatic breast cancer.[11,26,28–33] and commonly used HDC regimens for the treatment of breast cancer have resulted in CR rates of 0–50% in the initial phase I and II trials. Bensinger *et al* reported high response rates in patients with metastatic breast cancer receiving Bu/Mel/TT regimen.[34] In that study, CR/PR* and PR rates were 34 and 23% in patients with evaluable disease, respectively, after transplant. Of 12 patients evaluable for response who achieved a CR/PR*, eight (four with refractory and four with responsive disease) remain in remission a median of 581 days after HDC.[34] Antman and Gale reviewed 27 trials involving 172 patients with advanced breast cancer who had received prior chemotherapy for metastatic disease and who underwent autologous marrow transplantation. The overall response rate was 58% with the highest response rates being in trials involving multiple alkylating agents (76%) or previously untreated patients (81%).[35] In a review of 15 studies involving patients undergoing HDC with marrow support in responding stage IV breast cancer, Antman *et al* reported CR rates that averaged 25% (range 7–60%) with the duration of CR ranging from 1 to 42 months.[11]

In the current study, a regimen of high-dose TMCb followed by PBSC infusion in patients with metastatic breast cancer was associated with 7% grade III–IV RRTs and 3.5% regimen-related mortality. Death occurred by 100 days following transplantation in 2/17 patients with refractory disease and 1/10 with responsive disease. The major nonhematologic morbidity was gastrointestinal with 56 and 59% of patients developing grade-II mucositis and gastroenteritis, respectively, with grade-III gastroenteritis occurring in one patient (3.5%). In a similar study, Schiffman *et al* reported a 14% grade III–IV RRTs, 6% regimen-related mortality and 10% transplant-related mortality with a BU-Mel-TT regimen.[7] Although numbers of patients in the current study are small, response rates were high with CR/PR* and PR rates of 54 and 32%, respectively, in patients with evaluable disease. Of the 12 patients evaluable for response who achieved a CR/PR*, seven (five with refractory and two with responsive disease) remain in remission after HDC. The probability of PFS for all patients was 0.50. The probabilities of PFS at 2 years for patients with refractory ($n=17$) and responsive ($n=10$) disease were 0.42 and 0.60, respectively. When HDC was administered to patients with stage IV breast cancer who were responding to initial induction therapy, other studies have reported CR rates of 30–60% with 10–25% of patients remaining in CR for more than 2 years.[31,32] In the present study, 4/10 patients (40%) with responsive disease are surviving without progression on post-transplant days 453, 760, 1020 and 1380.

Berry *et al*[36] compared the outcomes of women with metastatic breast cancer treated with standard chemotherapy on Cancer and Leukemia Group B (CALGB) trials ($n=1509$) to those of women who received autotransplantation with data submitted to the ABMTR ($n=1188$). The analysis was limited to women under 65 years of age with chemosensitive disease (635 standard and 441 HDC patients). HDC recipients tended to be younger with a better performance status, and to have hormone receptor-positive disease with less visceral involvement. After controlling for these prognostic factors, no survival differences were observed after 2 years. The curves only began to separate after 3 years of follow-up. The actuarial 5-year OS was superior for women receiving HDC, 23 *vs* 15% ($P=0.03$).[36] Although conclusions are limited in that these data are not derived from randomized studies, the data do represent the largest sample size yet reported, do have the statistical power to detect benefits in the range of 10% absolute, and they do reflect multi-institutional experience. However, after almost two decades of clinical research in this field and thousands of women with breast cancer receiving HDC, the appropriatness of this approach remains unsettled. Most of the randomized trials reported in the last few years,[37–41] although demonstrating the noninferiority of HDC (excluding Stadtmauer *et al*), have failed to show a survival benefit, though the follow-up was generally short and the number of patients was, in some series, too small to reach the expected survival benefit. In

addition, because of heterogeneity of the intensity and duration of the standard dose chemotherapy in the control arm, the outcomes of these studies have been quite variable. Therefore, studies reported to date do not support the use of this therapy outside of clinical trials. Two large randomized trials in the metastatic setting from North America did not show a survival benefit on behalf of HDC.[38,41] Stadtmauer's trial clearly shows no hint of benefit for HDC compared with a nonstandard, but conventional dose maintenance chemotherapy.[38] The trial has limited power and can only exclude major survival advantages in excess of 15–20% absolute, but it does not have the power to exclude the differences observed, for example, in the Berry study.[36] Moreover, many have questioned whether maintenance chemotherapy represents standard of care, or whether women, when faced with a decision to get one cycle of HDC *vs* 18 months of further treatment, would choose the HDC as being less invasive of their quality of life. In addition, the conversion rate from partial to complete response with HDC was only 5%, much lower than the typical findings in phase II trials of 15–60%.[11,27] This may be due to the different selection biases between patients typically enrolled in phase II studies of transplant. Although the Canadian NCIC trial which was conducted by Crump *et al* showed a PFS benefit for HDC arm there was no overall survival benefit.[41] In that study, follow-up is too short to draw any firm conclusion. One may conclude that Crump's study has to be watched closely regarding long-term outcomes.

Based on many phase-II and III studies conducted in patients with advanced breast cancer, certain prognostic factors have been associated with long-term DFS following HDC for patients with responsive metastatic breast cancer.[8,9,11,24–27,29,31,37–41]. Patients who achieve CR with initial therapy for stage IV disease and have a single metastatic site of disease had improved PFS following HDC with STAMP-V.[20] Most of these trials showed that the presence of liver or lung metastases or a history of receiving doxorubicin as adjuvant therapy were adverse risk factors, with no patient surviving progression-free with any one of these factors.[8,9,11,24–27,37–42] It is clear that these documented adverse risk factors have to be considered in the design of future trials, especially of randomized ones, and patients have to be stratified appropriately, according to these adverse risk factors. In this way, transplanters will be able to define characteristics of advanced breast cancer patients who will benefit most from HDC.

Although the number of patients treated with TMCb regimen in the current study was relatively small, outcomes for patients with refractory or responsive disease are at least comparable and may be superior to those after other treatment regimens. This can only be verified by further trials with large numbers of patients, comparing outcomes with commonly used HDC regimens.

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