Cellular Therapy and Transplantation (CTT), Vol. 3, No. 10

Please cite this article as follows: Van Hoef MEHM. Tutorial: Treatment and hematopoietic cell transplantation for breast cancer: the past, the present, is there a future? Cell Ther Transplant. 2011;10:e.000090.01. doi:10.3205/ctt-2011-en-000090.01

Submitted: 9 December 2010, accepted: 31 January 2011, published: 23 February 2011

Tutorial: Treatment and hematopoietic cell transplantation for breast cancer: the past, the present, is there a future?

Marlies E.H.M. Van Hoef, MD, PhD

Transplant Creations, www.transplantcreations.com, Amsterdam, The Netherlands

Correspondence: Marlies E.H.M. Van Hoef, MD, PhD, Transplant Creations, P.O. Box 51342, 1007 EH Amsterdam, The Netherlands; Phone: 0031-6-12433616, E-mail: mvanhoef@transplantcreations.com

Abstract

At the end of the past century chemotherapy for breast cancer was characterized by dose intensification. Several authors reported on dose-dense (more frequent) and dose-intense (high-dose) treatment. In addition, studies of high-dose chemotherapy and autologous stem transplantation for stage II to IV breast cancer were started. The first results of allogeneic hematopoietic cell transplantation for breast cancer revealed a positive immune effect and encouraged a handful of small case studies in the last decade of the last century.

This article summarizes the results of several studies using high-dose chemotherapy and autologous stem cell transplantation, as well as the results of studies using allogeneic transplantation for breast cancer.

Keywords: breast cancer, semi-high-dose, autologous, reduced intensity, conditioning, allogeneic, dose-dense treatment, chemotherapy

Introduction

One of ten women in the Western world will develop breast cancer during their lifetime. About 25% are premenopausal. Ten to fifteen percent of these women present initially with stage III and fewer with stage IV disease. The majority of stage III breast cancer cases relapse over time. Ten percent of patients developing metastatic disease survive at ten years with standard treatment. It was for this reason that dose intensification was practiced in the past century and herein we discuss the results observed, the current practice and answer the question whether there is hope for the future.

Dose-dense chemotherapy

In the past century dose intensification by dose-dense induction in stage III and IV breast cancer showed an increase in response rates that were reflected in the significant improvement of disease-free survival in one study in stage III disease [1]; the other studies confirmed higher response rates but showed no impact on disease-free and overall survival [2-4]. Dose density sets the stage for further therapy.

High-dose chemotherapy, stage II and III disease

Peters et al. compared adjuvant AMF chemotherapy (adriamycin, methotrexate, 5-fluoro-uracil) plus intermediate dose chemotherapy and granulocyte colony stimulating factor with upfront and delayed high-dose conditioning (cyclophosphamide, cisplatin, carmustine)

plus autologous transplants in 785 women with ten or more positive lymph nodes [5]. Seventy-five percent were younger than fifty years of age. The estrogen receptor (ER) or progesterone receptor (PR) was positive in 70% of patients. A 7% treatment related mortality rate was reported following high-dose conditioning autologous transplants and 0% following the intermediate dose preparative regimen. No difference in disease-free survival was found. It is noteworthy that at 11 years follow-up almost all recipients of intermediate dose chemotherapy had relapsed whereas only 75% of recipients of high-dose conditioning autologous transplants had. Women younger than fifty years tolerated high-dose chemotherapy better, and intermediate dose chemotherapy was better for older women.

In earlier years Peters et al. reported extensively about high-dose chemotherapy and autologous transplants for breast cancer in an outpatient setting, and the cost-efficiency of such a setting compared to the conventional in-patient setting [6].

Rodenhuis et al. reported the results of a study comparing dose-intensive adjuvant versus high-dose chemotherapy (cyclophosphamide, thiotepa, carboplatin) and autologous transplants after three cycles of intensified chemotherapy (5-fluorouracil, epirubicin, cyclophosphamide) in 885 women with four or more positive lymph nodes, aged 55 years or younger [7]; in the standard arm five cycles of FEC were given. The majority of women had receptor positive breast cancer. Patients with receptor positive breast cancer received five years of tamoxifen. At three years follow-up significant disease free survival was reported in the high-dose cohort (0.037). There was no significant overall survival advantage although 4% more patients survived at 3 years follow-up in the high-dose cohort.

Zander et al. reported on 307 patients with 10+ lymph nodes randomized to four cycles of induction chemotherapy (epirubicin and cyclophosphamide) whereafter either three additional chemotherapy cycles (cyclophosphamide, methotrexate or 5-fluorouracil) or high-dose chemotherapy (cyclophosphamide, thiotepa and mitoxantrone) and autologous transplant were administered [8]. At a median follow-up of 6.1 years 166 events had been reported. Five years disease-free survival was 49% in the high-dose chemotherapy cohort and 42% in the standard dose cohort. The difference was non-significant. Overall survival was respectively 64% and 62%.

Nitz et al. reported on 403 patients with at least nine positive lymph nodes, randomly assigned to either two cycles of dose-dense standard treatment (cyclophosphamide and epirubicin) followed by two courses of high-dose conditioning (epirubicin, cyclophosphamide and thiotepa) and autologous stem cell transplant or four identical cycles of dose-dense standard treatment followed by three cycles of accelerated cyclophosphamide, methotrexate, and fluorouracil [9]. Four-year event-free survival was 60% in high-dose chemotherapy and 44% in the control group (p=.00069). Overall survival was 75% versus 70% (p=.02) respectively. There were no treatment-related deaths.

High-dose chemotherapy, stage IV disease

Vredenburgh et al. published twice in 2006. He compared standard chemotherapy (AFM) with standard chemotherapy plus high-dose chemotherapy and autologous transplants up-front versus delayed in patients with bone metastatic disease [10,11]. Radiotherapy was part of the therapeutic plan. One study included 425 chemotherapy-naïve women with metastatic (387) or inflammatory (39) breast cancer [10]. Patients were receptor negative or had experienced treatment failure of at least one round of hormonal therapy if the tumor was ER or PR receptor positive. The other study included 85 chemotherapy naïve breast cancer patients who were confirmed metastatic with only bony metastases [11]. Patient with receptor positive breast cancer had failed at least one hormonal treatment. He showed that upfront transplants induced better disease free survival than observation and transplantation in the second instance. The significance at ten-year follow-up reached 10% despite a 9.7% treatment related mortality. Radiotherapy might have contributed to the high treatment related mortality. Patients transplanted in complete remission did better than patients with less than complete response to first-line chemotherapy.

Kroger et al. reported on 187 women who were randomly assigned to one or two cycles of high-dose chemotherapy (stamp V, cyclophosphamide, thiotepa, carboplatin) and autologous stem cell rescue after no more than six cycles of first line therapy [12]. Fourty-nine percent and 43% respectively were ER positive and 50% and 40% were PR positive. A 3% treatment-related mortality was observed with first and second high-dose transplants, but the second high-dose cycle could not be administered in the majority of patients. Patients who had achieved complete response after first line therapy did remarkably better than patients who had obtained a partial response. There was no disease-free or overall survival advantage observed following high-dose chemotherapy and autologous transplants in either cohort.

Farquhar et al. reported a meta-analysis representing 483 women from six studies of high-dose chemotherapy and autologous transplants. In all studies conventional chemotherapy had been compared with first line chemotherapy and high-dose conditioning autologous transplants. The authors found statistically significant improvements of disease free survival at one and five

years in the high-dose arm but this was not reflected in a significant improvement in the overall survival at either one, three, or five-year follow-ups [13]. One of these reports was that by Stadtmauer et al. (b). The authors randomized patients who had metastatic breast cancer and who achieved complete (58) or partial response (252) after four to six cycles of standard chemotherapy to either high-dose chemotherapy and autologous stem cell rescue (110) or up to 24 cycles of standard dose cyclophosphamide, methotrexate, and fluorouracil (89) [14]. Prior treatment had consisted of adjuvant chemotherapy or hormonal therapy or hormonal therapy for metastatic disease. ER was positive in about 50% of patients. Time to progression was 9.6 and 9.0 months respectively. Overall survival at three years was not significantly different with a rate of 32% and 38% respectively.

Schulman et al. performed an economic analysis of 180 women enrolled in a study of conventional chemotherapy (up to 24 cycles CMF) versus high-dose chemotherapy (cyclophosphamide, carboplatin, thiotepa) plus autologous stem cell transplant for metastatic breast cancer, who responded to first line treatment (CMF or CAF) [15]. Mean follow-up was 758 days in the conventional group and 690 days in the transplant group. Patients in the transplant group were hospitalized for more days (p=.0041) and incurred higher costs than patients receiving conventional treatment with a mean difference of $ 55,886. Clinical results showed no improvement in survival. Thus high-dose chemotherapy plus stem cell transplant resulted in substantial additional morbidity and costs; the authors concluded that there was no place for such treatment outside clinical trial setting.

Ablative allogeneic transplants and cell therapy for stage IV disease

In 1996 Eibl et al. reported on a pregnant women with grade III, ER-, PR- inflammatory breast cancer [16]. Her pregnancy was terminated. After three neoadjuvant and two adjuvant cycles (cyclophosphamide and epidoxorubicin) her liver and bone metastases became progressive. The option of a high-dose autologous or ablative allogeneic transplant was considered and ablative allogeneic transplant was selected; high dose conditioning was done with thiotepa, carboplatin and cyclophosphamide. At day 28 post-transplant, graft versus host disease (GVHD) became manifest and her metastatic disease had disappeared; this was attributed to a graft versus tumor effect. At day 72 post-transplant she had a liver relapse and at day 110 she died due to progressive liver metastases. At autopsy no bone disease was found.

In the same year Ben Josef et al. reported on a 36 year old woman referred for a left breast mass [17]. She had 17+ lymph nodes. She received seven cycles of CAF neoadjuvant chemotherapy and a left quadrantectomy and radiotherapy on the axilla and breast. Twenty-three months after treatment she relapsed on the left chest wall and acute myeloid leukemia M2 was detected. The leukemia was treated with chemotherapy and an ablative allogeneic bone marrow transplant with donor lymphocyte infusion. Twelve months post- transplant she remained in complete remission of leukemia and the chest wall abnormality had disappeared.

In 1998 Or et al. of the same group reported on six cases who received high-dose autologous transplants and IL2-activated allogeneic cell therapy [18]. It was well tolerated with little toxicity. Disease-free survival was observed in one of the six patients at the time of the report, 34 months after her treatment. Five of the six had progressive disease after seven to thirteen months and died as result of their disease.

Ueno et al. reported a case series of ten patients with liver and bone metastases [19] in 1998. Their median age was 42 years and there were six relapsed and four primary cases. They received FAC induction and then cyclosphosphamide, thiotepa and BCNU and allogeneic cell transplants. All patients engrafted. Graft versus host disease was seen in three of ten patients. There was a 50% response rate with one complete response and no treatment-related mortality. At a median follow-up of 510 days one patient was progression free and she initially had stable disease, and the overall survival rate was 70%. In two patients a graft versus tumor effect was seen concurrently with graft versus host disease and this was observed at withdrawal of cyclosporin; thus the response observed was mainly a post transplant immune modulation effect.

In 2008 Ueno et al. reported about 66 breast cancer patients from the international center for bone marrow transplant registry who received either ablative (n=39) or non-myeloablative (n=27) allogeneic transplants (RIC) for stage IV breast cancer [20]. More patients in the RIC group had a poor pre-transplant performance status (63% vs. 26%, p=.002). In ablative transplants more acute and chronic graft versus host disease at one year (p=.003) was seen and treatment-related mortality at 100 days was 29% versus 7% in non-myeloablative transplants (p=.03). Progression- free survival at one year was 23% with myeloablative conditioning and 8% with RIC (p=.09). Acute graft versus host disease was associated with longer progression-free survival and associated with a graft versus tumor effect.

Non-myeloablative reduced intensity conditioning allogeneic transplants, stage IV

Transplant Creations was founded in 2000 to work on the improvement of clinical research and disease outcome. High-dose autologous transplants for breast can-

cer had just received negative press and an allogeneic immune response in breast cancer had been observed. Non-myeloablative reduced intensity conditioning allogeneic transplants, a venture of the turn of the century, offered opportunities for cure. The goal was to establish a collaboration between disciplines to better use existent treatment modalities and thereto a study plan was designed consisting of dose dense induction, an autologous transplant strategy and a non-myeloablative reduced intensity conditioning allogeneic transplant [21-23]. Subsequently a handful of case studies were reported.

Pedrazzoli et al. reported in 2001 on two stage IV breast cancer patients who received a non-myeloablative reduced intensity conditioning allogeneic transplant using fludarabine and cyclophosphamide [24]. Cyclosporin and short term methotrexate was used as graft versus host prophylaxis. Both engrafted and there was no treatment-related mortality, both cases obtained partial remission, and both died within one year of the transplant due to progressive disease.

In 2002 Bregni et al. reported six breast cancer patients who received non-myeloablative conditioning with thiotepa, fludarabine, and cyclophosphamide [25]. Graft versus host disease prophylaxis consisted of cyclosporin and methotrexate. All engrafted and two received a donor lymphocyte infusion (DLI). Two achieved partial response, one after cyclosporin withdrawal and one after the DLI. Responses were accompanied by the occurrence of acute graft versus host disease and extensive chronic graft versus host disease. The patient who received a DLI died as result of the procedure; other patients died due to progressive disease. The median survival was 450 days.

Ueno et al. reported in 2003 on eight breast cancer patients who received reduced intensity conditioning with fludarabine and melphalan [26]. Graft versus host prophylaxis consisted of tacrolimus and methotrexate. All engrafted and two received DLI. They observed acute graft versus host disease in two cases and chronic graft versus host disease in six cases. There was no treatment-related mortality and two patients obtained partial remission and two patients a minor response. At a median of 10,3 months and 23 months follow-up four patients were alive.

Bishop et al. reported in 2004 on 16 recipients of a T-deplete, T-replete procedure [27]. Patients who had progressed after treatment with anthracyclines, taxanes, hormonal agents and trastuzumab received reduced intensity conditioning allogeneic transplants. The conditioning regimen consisted of cyclophosphamide and fludarabine. Graft versus host prophylaxis consisted of cyclosporin. Stem cell grafts were depleted of T-lymphocyte cells and donor lymphocyte infusions at 1, 5, and 10 x 10e6 CD3+ cells/kg were administered on days +42, +70, and +98 post-transplant. Primary engraftment occurred in 15 patients, and 12 received DLI. Complete donor chimerism was observed in all 15 patients by six months post-transplant after the scheduled DLI. Acute GVHD occurred in 10 patients, and 9 had complete resolution of GVHD after treatment with steroids. Four of 13 assessable patients developed chronic GVHD, which was extensive in two cases. Two patients had partial response, three had minor response, six had stable disease and six had progressive disease. At a follow-up of 23.4 months, median survival was 10.3 months. One patient died early post-transplant from multiple organ failure and one six months post-transplant from hemorrhage during thoracentesis to drain a malignant pleural effusion.

In 2004 Carella reported on 17 heavily pretreated patients who received tandem transplants with high dose chemotherapy and autologous transplants and non-myeloablative reduced intensity conditioning allogeneic transplants and DLI [28]. Thirteen allogeneic transplant recipients primarily engrafted and 4 had primary engraftment failure and secondarily engrafted with DLI. In total 11 patients received DLI. Acute and chronic graft versus host disease occurred in 25% and 39% of patients. Five patients had extensive chronic graft versus host disease. No 100 days treatment-related mortality occurred and overall response was 24%. At a median follow-up of 1320 days, 29% were alive.

Blaise et al. reported in 2004 and 2006 on 18 cases [29]. Whether they gave a DLI is not reported neither is there any notice whether graft versus host disease had been observed. Treatment related mortality did not occur, the response was 18% and at 2 years overall survival was 22%.

De Souza et al. reported on 18 patients who received a reduced intensity conditioning allogeneic transplant [30]. Twelve had stable disease and six were in partial response after standard dose chemotherapy. The preparative regimen consisted of melphalan and fludarabine. Tacrolimus and methotrexate were given as graft versus host prophylaxis. All patients engrafted. Acute GVHD occurred in 50% and chronic GVHD in 78%. Treatment-related mortality was observed in 11%. Median progression free survival was at 202 days and median survival 643 days. The authors observed prolonged disease control in 17% of patients: two were in complete remission 1555 and 2525 days after stem cell transplantation, and one with progressive bone metastatic disease was 1118 days after stem cell transplantation.

The future

The question arises whether there is a future for transplantation for breast cancer. In the late nineties transplantation for breast cancer received negative press as

the procedure was used at random and at a too advanced stage. The benefits of autologous transplants were observed when transplants were conducted in stage II and III premenopausal women [5-9] and good risk stage IV disease who achieved complete remission prior to transplant [10-12]. Beyond these stages there is no place for autologous nor for allogeneic transplantation [30]. Transplantation is a costly procedure and should only be used if significance can be obtained and cure is the goal of the treatment.

In stage I to III breast cancer bone marrow assessment by immunohistochemistry has been shown to be strongly predictive for risk of relapse, independent of the lymph node status [31]. The quantitative polymerase chain reaction has been reported to be even more sensitive [32]. Thus application of methods to define the disease status at microscopic level in the bone marrow are warranted.

This century almost no autologous transplants for breast cancer have been conducted and if at all, they were in combination with reduced intensity conditioning allogeneic transplants [21-23,28].

There is though just a handful of reports on the application of non-myeloablative reduced intensity conditioning allogeneic transplants for advanced breast cancer, and the treatment modality has not yet been practiced in earlier stage disease [24-30]. These reports show that risks are limited if the treatment is administered in experienced hands.

There is a future for transplantation for stage II-III breast cancer, and may be good risk stage IV disease but only when the disease status is assessed by evaluation of micrometastatic disease in stage II and III and clinical complete remission has been obtained prior to autologous transplantation in stage IV. It will be critical to follow the procedure that has in the past shown to induce cure in leukemia, namely to induce response by standard or dose dense therapy, to double consolidate response with semi-high-dose conditioning autologous transplants and to eradicate minimal residual disease by reduced intensity conditioning allogeneic transplantation [23]. The results by Peters et al. also suggest that double consolidation is mandatory for optimization of disease outcome, as risk of relapse remained after single intermediate dose chemotherapy [5]. Institutions are invited to license the method, participate in studies and contribute to the program [23].

References

1. Citron ML, Berry DA, Cirrincioe C, Hudis C, Winer EP, Gradishar WJ, et al. Randomized trial of dose dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B trial 9741. J Clin Oncol 2003;21:1431-1439.

2. Van Hoef MEHM, I Baumann, C Lange, M Ranson, T Luft, EA de Wynter, et al. Dose-escalating induction chemotherapy supported by lenograstim preceding high-dose consolidation chemotherapy for advanced breast cancer: Selection of the optimal regimen to induce maximal tumor response and investigation of the optimal time to collect peripheral blood progenitor cells for bone marrow rescue. Ann Oncol 1994;5:217- 224.

3. Venturini M, Del Mastro L, Aitini E, Baldini E, Caroti C, Contu A, et al. Dose dense adjuvant chemotherapy in early breast cancer patients: results form a randomized trial. J Natl Cancer Institute 2005;97:1724-1733. doi: 10.1093/jnci/dji398.

4. Baldini E, Gardin G, Giannessi PG, Evangelista G, Roncella M, Prochillo T, et al. Accelerated versus standard cyclophosphamide, epirubicin and 5-fluorouracil or cyclophosphamide, methotrexate and 5-fluorouracil: a randomized phase III trial in locally advanced breast cancer. Ann Oncol 2003;14:227-232. doi: 10.1093/annonc/mdg069.

5. Peters WP, Rosner GL, Vredenburgh JJ, Shpall EJ, Crump M, Richardson PG, et al. Prospective randomized comparison of high-dose chemotherapy with stem cell support versus intermediate dose chemotherapy after surgery and adjuvant chemotherapy in women with high-risk primary breast cancer: a report of CALGB 9082, SWOG 9114, NCIC MA-13. J Clin Oncol 2005;23:2191-2200.doi: 10.1200/JCO.2005.10.202.

6. Peters WP, Ross M, Vredenburgh JJ, Hussein A, Rubin P, Dukelow K, et al. The use of intensive clinic support to permit out patient autologous bone marrow transplant for breast cancer. Semin Oncol. 1994;21(4 suppl 7):25-31.

7. Rodenhuis S, Bontenbal M, Beex LVAM, Wagstaff J, Richel DJ, Nooij MA, et al. High dose chemotherapy with hematopoietic stem cell rescue for high-risk breast cancer. N Eng J med 2003;349:7-16.

8. Zander AR, Schmoor C, Kroger N, Kruger N, Moba V, Frickenhofen N, et al. Randomized trial of high-dose adjuvant chemotherapy with autologous hematopoietc stem-cell support versus standard dose chemotherapy in breast cancer patients with ten or more positive lymph nodes: overall survival after 6 years follow-up. Ann Oncol 2008;19(8):1082-9. doi: 10.1093/annonc/mdn023.

9. Nitz UA, Mohrmann S, Fischer J, Lindemann W, Berdel WE, Jackisch C, et al. Comparison of rapidly cycled tandem high-dose chemotherapy plus peripheral blood stem cell support versus dose-dense conventional chemotherapy for adjuvant treatment of high-risk breast cancer: results of a mulicentre phase III trial. Lancet. 2005;366(9501):1935-1944.

10. Vredenburgh JJ, Coniglio D, Broadwater G, Jones RB, Ross M, Shpall EJ, et al. Consolidation with high-dose combination alkylating agents with bone marrow transplantation significantly improves disease-free survival in home-intensive metastatic breast cancer in complete remission compared with intensive standard dose chemotherapy alone. Biology of Blood and Marrow Transplant. 2006;12:195-203. doi: 10.1016/j.bbmt.2005.10.009.

11. Vredenburgh JJ, Madon B, Coniglio D, Rod M, Broadwater G, Niedzwecker D, et al. A randomized phase III comparative trial of immediate consolidation with high-dose chemotherapy and autologous peripheral blood progenitor cell support compared to observation with delayed consolidation in women with metastatic breast cancer and only bone metastases following intensive induction chemotherapy. Bone Marrow Transplant. 2006; 37(11):1009-15.

12. Kroger N, Frick M, Gluz O, Mohrman S, Metzner B, Jackisch C, et al. Randomized trial of single compared with tandem high-dose chemotherapy followed by autologous stem cell transplantation in patients with chemotherapy sensitive metastatic breast cancer. J Clin Oncol. 2006;24:3919-3926. doi: 10.1200/JCO.2005.04.0352.

13. Farquhar C, Majoribanks J, Basser R, Hetrick S, Lethaby A. High dose chemotherapy and autologous bone marrow or stem cell transplantation versus conventional chemotherapy for women with metastatic breast cancer. The Cochrane database of systematic reviews 2005, issue 3, Art. No: CD003142.pub2.

14. Stadtmauer EA, O'Neill A, Goldstein LJ, Crilley PA, Mangan KF, Ingle JN et al. Conventional dose chemotherapy compared with high-dose chemotherapy plus autologous hematopoietic stem-cell transplantation for metastatic breast cancer. N Engl J Med 2000;342(15): 1069-1076.

15. Schulman KA, Stadtmauer EA, Reed SD, Glick HA, Goldstein LJ, Pines JM, et al. Economic analysis of conventional-dose chemotherapy compared with high-dose chemotherapy plus autologous hematopoietic stem-cell transplantation for metastatic breast cancer. Bone Marrow Transplant. 2003;31:205-210.

16. Eibl B, Schwaighofer H. Nachbaur D, Marth C, Gachter A, Knupp R, et al.Evidence for graft versus tumor effect in a patient treated with marrow ablative chemotherapy and allogeneic bone marrow transplantation for breast cancer. Blood. 1996;88:11501-1508.

17. Ben-Yosef R, Or R, Nagler A, Slavin S. Graft versus tumor and graft versus leukemia effect in patient with concurrent breast cancer and acute myelocytic leukemia. Lancet. 1996;348(9036):1242-1243.

18. Or R, Ackerstein A, Nagler A, Kapelushnik J, Narpastek E, Samuel S, et al. Allogeneic cell-mediated immune therapy for breast cancer after autologous stem cell transplantation: a clinical pilot study. Cytokines Cell Mol Ther. 1998;4:1-6.

19. Ueno NT, Rondon G, Mirza NQ, Geisler DK, Anderline P, Giralt SA, et al. Allogeneic peripheral blood progenitor cell transplantation for poor risk patients with metastatic breast cancer. J Clin Oncol. 1998;16:986-993.

20. Ueno NT, Rizzo JD, Demirer T, Cheng YC, Hegenbart U, Zang MJ, et al. Allogeneic hematopoietic cell transplantation for metastatic breast cancer. Bone Marrow Transplant. 2008; 41(6):537-45.

21. Van Hoef MEHM. Development of non-myeloablative transplant strategy (NMTx) for breast cancer. Blood. 2001;98(suppl 1):415b(abst 5451).

22. Van Hoef MEHM. Non-myeloablative transplant development program inviting participation by laying the basis for collaborative clinical research between oncologists, hematologists and transplanters. Blood. 2001;98(suppl 1):415b(abst5452).

23. Van Hoef MEHM. Clinical development of non-myeloablative transplants: application as integrated treatment strategy. Hematol Journal. 2002;3(suppl 1):161 (abst 534).

24. Pedrazzoli P, Da Prada GA, Giorgiani G, Schiavo R, Zambelli A, Giraldi E, et al. Allogeneic blood stem cell transplantation after a reduced intensity, preparative regimen: a pilot study in patients with refractory malignancies. Cancer. 2002;94(9):2409-2415.

25. Bregni M, Dodero A, Peccatori J, Bernardi M, Sassi I, Vena C, et al. Non-myeloablative conditioning followed by hematopoietic cell allografting and donor lymphocyte infusions for patients with metastatic renal and breast cancer. Blood. 2002;99(1): 4234-4236.

26. Ueno NT, Chung Cheng Y, Rondon G, Tannir NM, Gajewsli JL, Courike DR, et al. Rapid induction of complete donor chimerism by the use of reduced intensity conditioning regimen composed of fludarabine and melphalan in allogeneic stem cell transplantation for metastatic solid tumors. Blood. 2003;102:3829-3837.

27. Bishop MR. Allogeneic lymphocytes induce tumor regression of advanced metastatic breast cancer. J Clin Oncol. 2004;22(19):3886-3892. doi: 10.1200/JCO.2004.01.127.

28. Carella AM, Beltrami G, Corsetti MT, Nati S, Musto P, Scalzulli P, et al. Reduced intensity conditioning for allograft after cytoreductive autograft in metastatic breast cancer. Lancet. 2005;366:318-320.

29. Blaise D, Furst S, Facer C, Bay JO, Goncalves A, Viet F, Mohty M, et al. Allogeneic hematopoietic stem cell transplantation for metastatic breast cancer. Bone Marrow Transplant. 2006;37(suppl 1): S14 abst 148.

30. De Souza JA, Davis ML, Rondon JA, Cheng YC, Jones RB, Champlin RE, et al. Prolonged disease control by non-myeloablative allogeneic transplantation for metastatic breast cancer. Bone Marrow Transplant. 2009;44(2):81-7.

31. Braun S, Pantel K, Muller P, Janni W, Hepp F, Kentenich LR, et al. Cytokeratin positive cells in the bone marrow and survival of patients with stage I, II or III breast cancer. N Engl J med 2000;342;525-533.

32. Slade MJ, Smith BM, Sinnett HD, Cross NC, Coombes RC. Quantitative polymerase chain reaction for the detection of micrometastases in patients with breast cancer. J Clin Oncol. 1999;17(3):870-9.

Please cite this article as follows: Van Hoef MEHM. Tutorial: Treatment and hematopoietic cell transplantation for breast cancer: the past, the present, is there a future? Cell Ther Transpl. 2011;10:e.000090.01. doi:10.3205/ctt-2011-en-000090.01

Ссылка: Cell Ther Transplant. 2011;10:e.000090.01. doi:10.3205/ctt-2011-en-000090.01

Учебное руководство: лечение и гематопоэтическая трансплантация клетки при раке молочной железы: прошлое, настоящее, есть ли будущее?

Марлис Е.Г.М. Ван Гуф

Резюме

В конце прошлого века для лечения рака молочной железы были широко внедрены в практику программы интенсивной химиотерапии. Ряд авторов сообщили о схемах лечения с применением более плотного по частоте введения или более высоких доз химиопрепаратов. Кроме того, были начаты клинические исследования по сочетанию высокодозной химиотерапии и трансплантации аутологичных стволовых клеток больным раком молочной железы II-IV стадий. Первые результаты аллогенной трансплантации гемопоэтических клеток при раке молочной железы в последнем десятилетии 1900-х годов свидетельствовали о положительном иммунном эффекте такого подхода и способствовали началу подобных клинических исследований на небольших группах больных.

В данной работе обсуждаются результаты нескольких исследований эффективности высокодозной химиотерапии и трансплантации аутологичных стволовых клеток, а также аллогенной трансплантации при раке молочной железы.

Ключевые слова: рак молочной железы, средневысокие дозы, аутологичный, сниженная интенсивность, кондиционирование, аллогенный, уплотнение режима введения препаратов, химиотерапия

Ссылка: Cell Ther Transplant. 2011;10:e.000090.01. doi:10.3205/ctt-2011-en-000090.01