Patient selection for high-dose chemotherapy in stage II and IV breast cancer
Schrama, J.G.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Chapter 5.

Prolonged survival associated with early lymphocyte recovery after autologous hematopoietic stem cell transplantation for patients with metastatic breast cancer

Correspondence

JG Schrama, S Rodenhuis, GC de Gast

Department of Medical Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands

Published in: Bone Marrow Transplantation 2003;31:141-142
Prolonged survival associated with early lymphocyte recovery after autologous hematopoietic stem cell transplantation for patients with metastatic breast cancer

Correspondence

Recently, Porrata et al. [1] reported in this journal a retrospective analysis of the absolute lymphocyte count (ALC) in patients with metastatic breast cancer treated with high-dose chemotherapy followed by autologous stem cell transplantation (ASCT). They found that ALC counts of ≥ 500 cells/μl on day 15 post ASCT predicted a significant better overall (OS) and disease free survival (DFS). A total of 29 patients with metastatic breast cancer were included in two different studies, both using STAMP V as high-dose treatment regimen (cyclophosphamide 1.5 g/m²/day; carboplatin 200 mg/m²/day and thiotepa 125 mg/m²/day on 4 consecutive days). The ALC threshold for immunologic engraftment was determined at 500 cells/μl on day 15 of transplantation based on experience with hematologic malignancies. After a median follow-up of 2.25 years for living patients (minimum follow-up 2 years or until death) they reported a significantly better median OS and DFS in the 20 patients with ALC ≥ 500 cells/μl than in the 9 patients with ALC < 500 cells/μl on day 15 post-ASCT (not reached vs 14 months p< 0.0011; 24 vs 7 months p<0.0015, respectively).

Recently, we published a phase II study of multiple courses of chemotherapy with ASCT in patients with stage IV breast cancer [2]. Our high-dose regimen consists of the same agents as STAMP V, but was administered at different doses over multiple courses. As our patient group was quite similar to the patient group described by Porrata et al.[1], we analyzed the lymphocyte count at day 15 after ASCT in our patient group. We also analyzed ALC before the start of chemotherapy, because one could argue that the patients with a lower ALC at day 15 post ASCT already had lower values at the start of therapy because of bone marrow infiltration. These patients could have a worse prognosis owing to tumor invasion in the bone marrow.

A total of 41 patients with advanced hormone refractory breast cancer were included in the study. The treatment started with two FE120C courses (5-fluorouracil 500 mg/m², epirubicin 120 mg/m² and cyclophosphamide 500 mg/m²) followed by ASCT harvesting. The high-dose treatment consisted of three subsequent courses of “tiny” CTC (cyclophosphamide 4000 mg/m², thiotepa 320 mg/m² and carboplatin 1060 mg/m² (target AUC 13.3 mg/ml/min) divided over 4 consecutive days). The second and third course were planned for day 28 after the previous transplantation. Thirty three of these 41 patients (seven patients were unresponsive to FE120C and one patient had an estrogen-receptor positive tumor) received high-dose chemotherapy of whom 23 patients received 3 courses, seven patients received two courses and three patients only one course. In all, 29 patients (49%) achieved a complete response, nine a partial response (22%) and three patients stable disease. There was one therapy-related death. After a median follow-up of 43 months (range 25-61), the OS and PFS
for the patient group treated with high-dose chemotherapy were 29 and 28%, respectively with a median duration of 28 and 11 months, respectively. The ALC on day 15 after the last HD-CT course with ASCT was < 500 cells/µl in 18 patients, and of these patients 11 had died, three were alive with disease and four showed no evidence of disease. In the patient group with an ALC ≥ 500 cells/µl, 10 patients had died and five had no evidence of disease. Survival curves were constructed by the Kaplan-Meier method and compared by the log-rank test. We found no significant difference in time to progression or death between the patient group with an ALC < 500 and ≥ 500 cells/µl at day 15 (Figure 1). There was also no significant association between survival and ALC before start of induction therapy, the high-dose chemotherapy and at day 29 post-ASCT.

Disappointingly, our data do not show a survival benefit for patients with an ALC ≥ 500 cells/µl. Like the study of Porrata et al., our study was small and might lack the power to identify differences.

It is important to study the recovery of cellular immunity after ASCT, as it is possible that anti-tumor immunity plays a role in controlling minimal residual disease. Recently, we published results of a study with the same chemotherapeutic regimen completed with reinfusion of autologous lymphocytes [3]. In this study, three patients were monitored for immune recovery without reinfusion of lymphocytes. In 11 patients, the stem cells were harvested after FEM2C+G-CSF and lymphocytes were harvested after FEM2C+GM-CSF+interleukin-2. The patients received stem cells and G-CSF after the first HD-CT; stem cells, G-CSF, and lymphocytes after the second and stem cells; GM-CSF, and lymphocytes after the third HD-CT. The study showed that lymphocyte reinfusion had a significant effect on the recovery of CD8+ T-cells, but recovery of CD4+ T-cells also required GM-CSF for a good and rapid recovery. Whether the rapid recovery of these cells has influence on the time to progression should be further investigated.
Chapter 5

Figure 1. Time to progression or death by lymphocyte count at day 15 post-transplantation

References

