Haematologica
Journal of Hematology
volume 84 – number 10 – October 1999

Haematologica 1999; 84:865-867 editorial

Towards the integration of hematopoietic stem cells into therapy of breast cancer?

Breast cancer (BC) is the most common malignancy among women in the Western world and is the leading cause of cancer death among European women.[1] For locally advanced and metastatic disease the indication for high dose chemotherapy (HDC) with hematopoietic stem cell (HSC) support is still controversial mainly because of the lack of large randomized trials.[2,3] Nevertheless, the wide utilization of HDC with HSC support for BC as documented by registries of the EBMT and IBMTR[4-6] is based on the encouraging results of phase II and III studies showing an increase in disease-free and overall survival, and suggesting that this approach may be curative in a small subset of patients with stage IV disease.[6-8] Interestingly, there is strong evidence that the efficacy of HDC with HSC support for BC is mainly dependent on the possibility of treating women with chemosensitive neoplasms who have shown a response to conventional chemotherapy regimens.[6] In this scenario one may hypothesize that the ideal first-line regimen for patients with locally advanced or metastatic (stage IIIB and stage IV) BC should have potent anticancer effect measured by the highest rate of induction of tumor regression, as well as potent ability to mobilize hematopoietic stem cells into peripheral blood measured by the highest yield of $CD34^+$ cells in a single leukapheresis collection.

It is well documented that anticancer chemotherapy with a combination of an anthracycline, e.g. doxorubicin or epirubicin, and a taxane, e.g. docetaxel or paclitaxel, meets the first requirement. Although tumor cell resistance to taxanes and to anthracyclines shares the same pleiotropic mechanisms, in the clinical setting the combination of either drug of these classes results in unprecedented response rates in chemotherapy-naive women with BC.[9] Furthermore, approximately 20-40% of patients failing to respond to first-line anthracycline treatment do benefit from second-line therapy with a taxane.[10] In most treated patients, iatrogenic toxicity to the hematopoietic system is usually treatable with commercially available hematopoietic growth factors. Because of these pieces of evidence, the association of a taxane with an anthracycline has now become the first treatment option for selected patients with advanced BC and its efficacy in an adjuvant setting is also being explored in a series of controlled clinical trials.[11,12]

The therapeutic index of HDC requiring the support of autologous HSC transplantation is mainly dependent on the number of transplanted $CD34^+$ cells. In the autologous transplantation setting, the dose of reinfused HSC measured by the $CD34^+$ cell assay[13] is an accurate predictor of the kinetics of reconstitution of marrow function following the inevitable drug-induced pancytopenia.[14] A dose greater than 5×10^6 $CD34^+$ cells per kg of body weight is recommended because this dose is associated with significantly more rapid and complete reconstitution of marrow functions than lower doses. This effect implies the reduction or abrogation of transfusion requirements, extra-hematopoietic toxicity, supportive care, duration of hospital stay, and overall treatment costs.[15,16] In addition, optimal hematopoietic reconstitution after transplantation allows early curative surgery and the delivery of boost radiation therapy for locally advanced BC and further chemotherapy for metastatic BC. In view of cell therapy, the availability of large numbers of HSC facilitates the application of *ex-vivo* manipulation and purification aimed at removing undesired tumor cells.[17]

In the present issue of Haematologica, Zibera *et al.*[18] report on the possibility of harvesting large amounts of progenitor cells following epirubicin/paclitaxel (EP) combination plus G-CSF in 25 patients with stage IV BC. The authors document that the tempo for circulating progenitor cell collection is highly predictable (day 10 to day 12 following combination chemotherapy) and in most of patients a single leukapheresis is sufficient for optimal $CD34^+$ cell yield. The authors accomplished this result by carrying out leukapheresis in patients with >30 $CD34^+$ cell per mL. Based on data recently published in Haematologica,[19] it is expected that even better results could be achieved by adopting modern technology of leukapheresis that allows harvesting of the target dose of 5×10^6 $CD34^+$ cells per kg by a single leukapheresis also in patients with lower blood $CD34^+$ cell counts.[19] In the study by Zibera *et al*., mobilization and harvesting was performed in patients showing response to three cycles of chemotherapy with EP. In this regards, it is relevant that the EP regimen does not hamper either the mobilization capacity of patients after three cycles of therapy or the quality of the HSC, the latter measured by the LTC-IC count in the leukapheresis products. Consequently, oncologists have the opportunity to give three courses of anticancer therapy, evaluate the tumor response, and decide whether or not to harvest HSC for a subsequent HDC approach.

Despite advances in HDC with autologous HSC transplantation for hematologic malignancies and solid tumors, relapse of the underlying disease remains a major obstacle which has yet to be overcome. Future developments of anticancer therapy may rely on the exploitation of HSC beyond their use as hematopoietic support. Recent advances in tumor vaccine development, specifically, the molecular identification of novel tumor antigens and the understanding of cellular signals delivered by cytokines and co-stimulatory molecules required for efficient T-cell activation, now make it possible to consider combining active specific immunotherapy with HSC transplantation as a strategy for elimination of residual tumor following intensive primary chemotherapy. A powerful means of inducing both cellular and humoral immunity is the expression of antigen-encoding DNA sequences in host antigen presenting cells (APC). Dendritic cells are among the most potent APC described and it is now possible to prepare large numbers of DCs from human circulating $CD34^+$ hematopoietic progenitors.[20] This has led to an explosion in DC research as well as the potential to treat patients with therapeutic doses of autologous DCs. Various BC-associated antigens, including HER-2/neu, CEA, MAGE-1, p53, and MUC-1 appear to be ideal targets for immunotherapy and are currently under investigation in humans.[21,22] Primitive hematopoietic progenitors are also attractive targets for gene therapy because of their potential to self-renew and generate a large population of progeny cells with new genetic material. The potential use of gene-modified HSC has already branched out into several directions, as it has been applied in cancer therapy. First, the introduction of HSC modified with a drug resistance gene is being investigated as a means to select those cells that express the introduced drug resistance gene and to protect the infused bone marrow cells from destruction by repeated chemotherapy treatments.[23] An additional strategy may be the use of this drug-resistance selection to increase the frequency of gene-modified cells that also contain a therapeutic transgene with antitumor activity.[24] Finally, HSC have been proposed as targets for the introduction of chimeric receptor gene(s) with reactivity to tumor-associated antigens, which would potentially offer the patient receiving a gene-modified HSC transplant a long-term antitumor immune response that is biased to recognize autologous tumor.[25,26]

In conclusion, we welcome the study by Zibera *et al*. as a well documented guideline for treating BC with the potent taxane-anthracycline regimen while also taking advantage of the availability of copious HSC mobilized into peripheral blood, these cells being potentially useful tools for further innovative therapies.

Salvatore Siena

Divisione di Oncologia Medica Falck,
Ospedale Niguarda Ca' Granda,
piazza Ospedale Maggiore 3, 20162 Milan, Italy.
E-mail: salsiena@tin.it

References

1. Moller-Jensen O, Esteve J, Moller H, Renard H. Cancer in the European Community and its member states. Eur J Cancer 1990; 26:1167-256.
2. Hortobagyi GN. Treatment of breast cancer. N Engl J Med 1998; 339:974-84.
3. Crown J. High dose chemotherapy of metastatic breast cancer: the end of the beginning. Br J Cancer 1997; 75:467-9.
4. Anonymous. Chaos surrounds high-dose chemotherapy for breast cancer. Lancet 1999; 353:1633.
5. Gratwhol A, Passweg J, Baldomero H, Hermans J. Blood and marrow transplantation activity in Europe 1997. Bone Marrow Transplant 1999; 24:231-45.
6. Antman KH, Rowlings PA, Vaughan WP, et al. High-dose chemotherapy with autologous hematopoietic stem-cell support for breast cancer in north America. J Clin Oncol 1997; 15:1870-9.
7. Bezwoda WR, Seymour L, Dansey RD. High-dose chemotherapy with hematopoietic rescue as primary treatment for metastatic breast cancer: a randomized trial. J Clin Oncol 1995; 13: 2483-9.
8. Adkins D, Brown R, Trinkaus K, et al. Outcomes of high-dose chemotherapy and autologous stem cell transplantation in stage IIIB inflammatory breast cancer, J Clin Oncol 1999; 17: 2006-14.
9. Gianni L, Munzone E, Capri G, et al. Paclitaxel by 3-hour infusion in combination with bolus doxorubicin in women with untreated metastatic breast cancer: high antitumor efficacy and cardiac effects in a dose-finding and sequence-finding study. J Clin Oncol 1995; 13:2688-99.
10. Gianni L, Munzone E, Capri G, et al. Paclitaxel in metastatic breast cancer: a trial of two doses by 3-hour infusion in patients with disease recurrence after prior therapy with anthracyclines. J Natl Cancer Inst 1995; 87:1169-75.
11. Goldspiel BR. Clinical overview of the taxanes. Pharmacotherapy 1997; 17:110S-125S.
12. Esteva FJ, Hortobagyi GN. Integration of systemic chemotherapy in the management of primary breast cancer. The Oncologist 1998; 3:300-13.
13. Siena S, Bregni M, Brando B et al. Flow cytometry for clinical estimation of circulating hematopoietic progenitors for autologous transplantation in cancer patients. Blood 1991; 77:400-9.
14. Bensinger W, Appelbaum F, Rowley S, et al. Factors that influence collection and engraftment of autologous peripheral-blood stem cells. J Clin Oncol 1995; 13:2547-55.
15. Schmitz N, Linch DC, Dreger P, et al. Randomized trial of filgrastim-mobilized peripheral blood progenitor cell transplantation versus autologous bone-marrow transplantation in lymphoma patients. Lancet 1996; 347:353-7.
16. Schulman KA, Birch R, Zhen B, Pania N, Weaver CH. Effect of $CD34^+$ cell dose on resource utilization in patients after high dose chemotherapy with peripheral blood stem cell support. J Clin Oncol 1999; 17: 1227-33.
17. Spyridinidis A, Schmid M, Bernhardt W, et al. Purging of mammary carcinoma cells during ex vivo culture of CD34+ hematopoietic progenitor cells with recombinant immunotoxins. Blood 1998; 91:1820-7.
18. Zibera C, Pedrazzoli P, Ponchio L, et al. Efficacy of epirubicin/paclitaxel combination in mobilizing large amounts of hematopoietic progenitor cells in patients with metastatic breast cancer showing optimal response to the same chemotherapy regimen. Haematologica 1999; 84:924-9.

19. Granzow K, Schiavo R, Timofeeva I, Moroni G, Santoro A, Siena S. New technology and changing parameters of leukapheresis for blood cell transplantation. Haematologica 1999; 84:752-3.
20. Siena S, Di Nicola M, Bregni M, et al. Massive ex vivo generation of functional dendritic cells from mobilized CD34+ blood progenitors for anticancer therapy. Exp Hematol 1995; 23:1463-71.
21. Hadden JW. The immunology and immunotherapy of breast cancer: an update. Int J Immunopharmacol 1999; 21:79-101.
22. Di Nicola M, Siena S, Bregni M. Gene transfer into human dendritic antigen-presenting cells by vaccinia virus and adenovirus vectors. Cancer Gene Ther 1998; 5:350-6.
23. Hesdorffer C, Ayello J, Ward M, et al. Phase I trial of retroviral-mediated transfer of the human MDR1 gene as marrow chemoprotection in patients undergoing high-dose chemotherapy and autologous stem-cell transplantation. J Clin Oncol 1998;16:165-72.
24. Koc ON, Davis BM, Reese JS, Friebert SE, Gerson S. Transfer of drug resistance genes into hematopoietic progenitors. In: Lattime EC, Gerson SL, eds. Gene therapy of cancer. London: Academic Press, 1999, p. 177-200.
25. Wilke LG, Reynolds CM, McDonagh KT, et al. Engineering immune effector cells to target the Her2/neu breast cancer antigen. SSO Annual Cancer Symposium 1997; 51:P4.
26. Hwu P, Shafer GE, Treisman J, et al. Lysis of ovarian cancer cells by human lymphocytes redirected with a chimeric gene composed of an antibody variable region of the Fc receptor γ chain. J Exp Med 1993; 178:361-6.

Drawbacks of serum transferrin receptor as a diagnostic tool

In this issue Mockenhaupt *et al.*[1] report on interesting studies performed in Nigeria to evaluate the usefulness of serum transferrin receptor as a diagnostic tool for iron deficiency. The soluble transferrin receptor is a tool for both the quantitative determination of marrow erythropoietic activity and the diagnosis of iron deficiency. Previous papers in this journal have described various clinical applications of such a diagnostic tool.[2-9] More recently, two studies have evaluated the diagnostic efficiency of the soluble transferrin receptor assay in the diagnosis of iron depletion in patients with anemia of chronic disorders, providing partially conflicting results.[8,9] In conclusion: a) the soluble transferrin receptor level is influenced by the erythroid marrow activity (and therefore by congenital and acquired erythroid disorders); b) this assay might not assess the iron status of patients with anemia of chronic diseases accurately; c) the available kits are expensive. Based on these considerations, it is unlikely that serum transferrin receptor may be largely employed as a diagnostic or screening tool in Africa.

References

1. Mockenhaupt FP, May J, Stark K, Fallisi AG, Meyer CC, Bienzle U. Serum transferrin receptor levels are increased in aymptomatic and mild Plasmodium falciparum-infection. Haematologica 1999; 84:866-70.
2. Beguin Y. The soluble transferrin receptor: biological aspects and clinical usefulness as quantitative measure of erythropoiesis. Haematologica 1992; 77:1-10.
3. Vannucchi AM, Bosi A, Linari S, et al. High doses of recombinant human erythropoietin fail to accelerate platelet reconstitution in allogeneic bone marrow transplantation. Results of a pilot study. Haematologica 1997; 82:53-6.
4. Remacha AF, Bellido M, Garcia-Die F, Marco N, Ubeda J, Gimferrer E. Serum erythropoietin and erythroid activity in vitamin B12 deficiency. Haematologica 1997; 82:67-8.
5. Gimferrer F, Ubeda J, Remacha AF. Serum transferrin receptor levels are "physiologically" high in heterozygous β-thalassemia. Haematologica 1997; 82:728-9.
6. Manteiga R, Remacha AF, Sarda MP, Ubeda J. Serum transferrin receptor in polycythemia. Haematologica 1998; 83:958-9.
7. Beguin Y, Baron F, Fillet G. Influence of marrow erythropoietic activity on serum erythropoietin levels after autologous hematopoietic stem cell transplantation. Haematologica 1998; 83:1076-81.
8. Junca J, Fernandez-Aviles F, Oriol A, et al. The usefulness of the serum transferrin receptor in detecting iron deficiency in the anemia of chronic disorders. Haematologica 1998; 83:676-80.
9. Remacha AF, Sarda MP, Parellada M, Ubeda J, Manteiga R. The role of serum transferrin receptor in the diagnosis of iron deficiency. Haematologica 1998; 83:963-6.

Towards identification of subsets of patients with multiple myeloma who benefit from high-dose chemotherapy

Haematologica has recently published a review article on treatment of multiple myeloma,[1] an analysis of optimization of peripheral blood progenitor cell autologous transplantation in this condition[2] and the GITMO experience in this field.[3] Previous papers dealt with treatment of multiple myeloma.[4-9]

In this issue, Boccadoro *et al*.[10] report on a study comparing high-dose vs conventional chemotherapy. Their findings strongly suggest the superiority of high-dose chemotherapy for multiple myeloma patients below 55, at least in terms of complete remission and event-free survival. Although this observation needs to be confirmed by other independent studies, it represents a step forward towards identification of subsets of patients who would be best candidates for high-dose chemotherapy.

References

1. San Miguel JF, Blade Creixenti J, Garcia-Sanz R. Treatment of multiple myeloma. Haematologica 1999; 84:36-58.
2. Harousseau JL Optimizing peripheral blood progeni-