Mobilization of hematopoietic progenitor cells with a combination of docetaxel, adriamycin, 5-fluorouracil and filgrastim in breast cancer patients

A series of 26 breast cancer patients were mobilized with G-CSF after a course of TAF (taxotere-adriamycin-5-fluorouracil). The median number of CD34+ cells collected in the first large-volume leukapheresis was 5.4x10⁶/kg. The scheduled positive/negative CD34+ selection could be performed in 25 cases. This combination of three of the most active drugs for breast cancer allows optimal cellular yields for graft engineering.

An optimal mobilization regimen should ideally be composed of active drugs against the primary tumor.[1] Docetaxel-based combinations are highly active against breast cancer, but their mobilization potential has been scarcely evaluated. Twenty-six patients with stage II-IV breast cancer were mobilized during the recovery from the last of a series of cycles of docetaxel 80 mg/m² plus adriamycin 75 mg/m² plus 5-fluorouracil 2,400 mg/m². Filgrastim, 12 μg/kg/day subcutanously, was administered beginning on the 8th to 10th day. Large-volume aphereses (4-6 blood volumes) were used. Simultaneous positive/negative CD34+ cell selection with Isolex 300i (Nexell inc, Brussels, Belgium) was intended, providing the collection was sufficient. Descriptive data are given as median with extreme values.

There were three episodes of febrile neutropenia, one non-severe documented infection and no grade II-IV non-hematologic toxicity during mobilization. The collections could be initiated by day 13 (9-17). The total days of G-CSF administration were 6 (5-9). The median peak blood CD34+ count was 65×10⁶/L cells. The collection results are outlined in Table 1. The first apheresis yielded more than 2 ×10⁶/kg CD34+ cells in all but one of the patients (this remaining patient yielded 1.8×10⁶/kg). There was a significant correlation between the peripheral blood CD34+ count and the number of CD34+ cells obtained in the apheresis ($r = 0.71$; $p < 0.0005$). Table 2 shows the study of CD34+ cell subsets in the collected apheresis products of ten patients. A single cellular selection could be performed in 25 of 26 cases, with a median yield of 48% (30-83) and purity of 95% (78-99). The median CD34+ dose in the selected fraction was 5 x 10⁶/kg (1.1-12.4). The number of days to reach 0.5×10⁹/L granulocytes was 9 (extreme values: 8-12) and to the last platelet transfusion 9 (extreme values: 7-19). One year after transplantation all assessable patients had a stable graft. Tumor contamination of the graft has been correlated with poorer clinical outcome after transplantation.[2-4] When selection of CD34+ cells is intended, the mobilization should ideally allow the collection of huge amounts of cells in one or two aphereses. A rich mobilization, as was obtained with the TAF protocol, together with high efficiency large volume cellular collections make immunomagnetic selection feasible in most breast cancer patients. Moreover, the use - for mobilization - of chemotherapy regimens with high antitumoral activity may lead to an interesting effect of *in vivo* purging.[5] Docetaxel is a very active agent against breast cancer. Some preliminary data on its mobilization capacity are promising.[6,7] We found it capable of highly successful mobilizations in combination with two drugs also considered among the most active ones for breast cancer.

When used to stimulate granulocyte recovery, delayed filgrastim administration is an effective alternative.[8] The optimal timing for collection in mobilizations with filgrastim (without chemotherapy) is the fifth to sixth day of administration. We found an optimal mobilization response with late administration of filgrastim, leading to a median of only 6 days of granulocyte-colony-stimulating factor. This approach allows unnecessary cytokine treatment to be avoided. Similar results have been obtained by other authors.[9] There might be no need for mobilization schemata different from the therapeutic chemotherapy when a combination of highly active drugs may satisfactorily play both roles.[10]

Table 1. Collection results.

	Median	Min	Max	Mean*	SD*	95%CI*
Peak PB CD34 count (×10⁶/L)	65	33	344			
CD34 cells collected the peak day (×10⁶/kg)	5.4	1.8	21.6			
CD34 cells per processed blood volume (×10⁶/kg)	1	0.3	3.8			
CD34 cells per day of leukapheresis (×10⁶/kg)	5.8	1.5	17.9			
Total CD34 cells collected (×10⁶/kg)	12.4	3	35.8	14.7	8.4	11.2-18.1
Number of leukaphereses°	2	2	3			

**Provided only for normally-distributed variables; °a single leukapheresis was not intended; PB: peripheral blood. SD: standard deviation. CI: confidence interval for the mean.*

Table 2. Phenotype of CD34+ cells collected.

	Median absolute number collected in 1 apheresis (×10⁶/Kg)	Median percentage over total CD34+ cells
CD34+	5.2 (2.6-14.2)	100%
CD34+ CD90+	3 (0.3-11.3)	74.5% (11.8-99.9)
CD34+ AC133+	3.6 (2.4-10.4)	83.8% (20.1-99.9)
CD34+ CD38-	0.4 (0.001-4.3)	3.4% (0.01-35)
CD34+ HLADR+	4.9 (2.1-13.6)	95.3% (80-100)
CD34+ CD38- HLADR+	0.4 (0.001-4.3)	3.4% (0.01-35.4)
CD34+ CD33-	2.1 (0.001-11.7)	49.3% (0.1-98.4)
CD34+ CD33- CD42a-	0.9 (0.001-12.1)	22.1% (0.1-86)

Javier Pérez-Calvo, Óscar Fernández-Hidalgo, Maria Luisa Subirá, Salvador Martín-Algarra, Esteban Salgado, Antonio Brugarolas

Cell Therapy Area and Department of Oncology, Clínica Universitaria de Navarra, Pamplona, Spain

Key words: mobilization, docetaxel, stem cell transplantation, breast cancer, positive selection.

Correspondence: J. Pérez-Calvo, M.D., Departamento de Oncología, Clínica Universitaria de Navarra, Pío XII 36, 31008 Pamplona, Spain. Phone: international +34.948.296696 - Fax: international +34.948.255500 - E-mail: jpcalvo@unav.es

References

1. Siena S. Towards the integration of hematopoietic stem cells into therapy of breast cancer? Haematologica 1999; 84:865-7.
2. Ross AA. Minimal residual disease in solid tumors malignancies: a review. J Hematother 1998; 7:9-18.

3. García-Conde J, Badía B, Benet I, et al. Prognostic significance of contaminating tumor cells in BM and apheresis in breast cancer treated with autologous peripheral blood transplantation (Auto-PBT). Proc Am Soc Clin Oncol 1999; 18:Abstract 352.
4. Pecora AL, Preti RA, Lazarus HM, et al. Breast cancer cell contamination of blood stem cell products in patients with metastatic breast cancer: predictors and clinical outcomes. Blood 1999; 94 (Suppl 1): 665a. Abstract 2952.
5. Gluck S, Ross AA, Layton TJ, et al. Decrease in tumor cell contamination and progenitor cell yield in leukapheresis products after consecutive cycles of chemotherapy for breast cancer treatment. Biol Blood Marrow Transplant 1997; 3:316-23.
6. Ojeifo JO, Wu AG, Miao Y, Herscowtiz HB, Meehan KR. Docetaxel-induced mobilization of hematopoietic stem cells in a murine model: kinetics, dose titration, and toxicity. Exp Hematol 2000; 28: 451-9.
7. Weaver CH, Schwartzberg LS, Zhen B, et al. Mobilization of peripheral blood stem cells with docetaxel and cyclophosphamide (CY) in patients with metastatic breast cancer: a randomized trial of 3 vs 4 g/m^2 of CY. Bone Marrow Transplant 1999; 23:421-5.
8. Bence-Bruckler I, Bredeson C, Atkins H, et al. A randomized trial of granulocyte colony-stimulating factor (Neupogen) starting day 1 vs day 7 post-autologous stem cell transplantation. Bone Marrow Transplant 1998; 22:965-9.
9. Benet I, Prosper F, Marugan I, et al. Mobilization of peripheral blood progenitor cells (PBPC) in patients undergoing chemotherapy followed by autologous peripheral blood stem cell transplant (SCT) for high risk breast cancer (HRBC). Bone Marrow Transplant 1999; 23:1101-7.
10. 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.