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Patient management strategies and transplantation techniques in European stem cell transplantation centers offering breast cancer patients high-dose chemotherapy with peripheral blood stem cell support: a joint report from the EORTC and EBMT

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ABSTRACT

Background and Objectives. **It is increasingly being realized that there are very considerable variations in individual hospitals' strategies for managing a particular group of patients, even if using similar therapeutic regimens. Such variations make it impossible to generalize estimations of treatment costs from one setting to others. The objective of this study is to examine the extent of variation in the current approaches in Europe to peripheral blood stem cell transplantation (PBSCT) in breast carcinoma.**

Design and Methods. **A questionnaire was developed and sent to the EBMT member institutions. The questionnaire comprised 85 questions covering the technical and clinical issues involved and the strategies followed for the management of the patients. This paper reports the results of the survey primarily by means of descriptive, univariate frequency distributions. The results of a more analytical approach, aiming at explaining patterns in the variations observed are also presented.**

Results. **A completed questionnaire was returned by 162 centers; 60% university hospitals, 14% cancer centers and the rest general hospitals. Considerable variations are observed between the centers with respect to all aspects of patient management and technical procedures investigated. In many respects, general hospitals follow different routines from university hospitals and dedicated cancer centers.**

Interpretation and Conclusions**. Variability to the extent observed indicates an important scope for optimization of the procedures and a large potential for reduction of costs and perhaps for improvement of outcomes. Economic evaluations, for instance comparing PBSCT with autologous BMT as support for high dose chemotherapy, cannot be generalized from one setting to another without careful examination of the procedures and strategies followed in each setting. European hospitals treating breast cancer patients with high dose chemotherapy supported by transplantation of peripheral blood stem cells use very different technical procedures for mobilization, harvest and re-implantation of stem cells. In addition, there are also wide variations in the way they manage the patients, e.g. with regard to the criteria for discharge from hospital after re-implantation.**

Key words: peripheral blood stem cell transplantation, breast cancer, patient management strategies, resource utilization, costs

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Since its introduction into clinical practice in the late 1980s, peripheral blood stem cell transplantation (PBSCT) has quickly become the dominant, if not virtually the only, source of hematopoietic support in anti-cancer high-dose chemotherapy (HDC) programs. Data collected by the EBMT (*European Group for Blood and Marrow Transplantation*) Solid Tumors Working Party show that the diffusion of PBSCT as source of hematopoietic support in solid tumors very closely follows the S-shaped curve often postulated for the diffusion of technological innovations.[1] After a rather slow start since its first introduction in 1987-88, the penetration of PBSCT started to increase dramatically. By 1992, 20% of HDC therapies performed (for all tumor types combined) were supported by PBSCT, reaching a level of 90-95% in 1996.[2] Breast cancer patients constitute more than half (57% in 1998) of all the adult solid tumor patients treated with HDC and stem cell support in Europe, and almost all of these treatments of breast cancer patients are supported with PBSCT.[2]

PBSCT was originally conceived as having several advantages, which would make it a favorable substitute for autologous bone marrow transplantation (ABMT). Among these advantages are that peripheral stem cells can be harvested without general anesthesia, and that the technique may be used in patients who have inadequate bone marrow for harvesting, e.g. because of previous irradiation of the pelvis. Additionally, it was thought that the possible contamination by tumor cells would probably be less

in leukapheresis products obtained from the peripheral blood than in harvested bone marrow cells.

The principal argument for PBSCT, however, is thought to be the rapidity of hematopoietic recovery after it compared to following ABMT.[3,4] The reasoning is that, as the progenitor cells harvested by PBSCT apheresis are more mature than their counterparts in the bone marrow, they will develop into differentiated and functional blood cells more quickly. As the number of progenitor cells is also much higher than in the bone marrow, the use of PBSCT will therefore lead to accelerated hematopoietic recovery. The period of neutropenia and thrombocytopenia may be reduced to less than 2 weeks, wheras in ABMT patients full hematopoietic recovery is usually first obtained after 20-30 days. In addition, the more rapid hematopoietic recovery should also reduce the mortality risk associated with auto-grafting and allow HDC in patients for whom the risk of ABMT is considered to be too high. *Inter alia*, this would mean that the age limits set for treating patients in HDC programs with stem cell support may be increased.

Not surprisingly, PBSCT as an alternative to ABMT has attracted considerable interest from economists interested in the economics of health care and in assessing the relative costs and benefits of competing treatment options. According to studies published so far,[5-10] which have primarily dealt with leukemia and lymphoma patients, PBSCT compared with ABMT represents one of the infrequent instances of a so-called *dominant solution* observed in economic evaluations of health care interventions. A dominant solution refers to the situation where one treatment is simultaneously more effective and less costly than another treatment option for the same patients, while the usual case is that treatment benefits are obtained only at the expense of a certain increase in costs. The economic evaluations published so far agree that compared to ABMT as support for HDC, PBSCT is a dominant solution with lower risks, lower costs and better clinical outcomes.

However, the results of any cost assessment are entirely dependent on the practice followed by the center(s) at which the determination of costs is carried out, and one should not uncritically generalize the cost figures from one setting to others. The total cost of an intervention such as PBSCT is determined as the sum of a series of sub-elements, each of these being the product of the quantity used of a particular type of resource and its appropriate unit price. For HDC with PBSCT support, some of the resources concerned may be the cytotoxics and/or colony-stimulating factors (CSFs) used for mobilization of stem cells, personnel surveying the apheresis procedure, days of hospital stay (part of the time in a protected facility) for the patients during the hypoplastic period, and many others.

Unit prices of resources obviously vary from one country to another, but they may also vary considerably between locations within individual countries. Less obviously, there may be important differences in the clinical practice followed by centers treating the same population of patients with the same type of intervention, if this is understood in a rather broad sense, such as HDC with PBSCT support. When examined in closer detail, such broadly defined types of intervention may turn out to be quite heterogeneous, and it becomes clear that the costs of treatment in one particular setting cannot just be assumed to be generalizable to other settings.

The objective of the present study is to document the current standard protocols used by transplant centers across Europe for treating breast cancer patients in HDC programs with PBSCT support and to examine the extent of diversity in the practices followed. Breast carcinoma was chosen because it is the solid tumor most frequently treated with HDC, thereby providing the greatest likelihood that the centers have actually established a sort of standard treatment protocol.

Design and Methods

A questionnaire containing 85 questions was set up and sent to all centers in the EBMT Solid Tumors Working Party's Registry known or presumed to treat breast cancer patients. The questionnaire had the following subsections: description of the transplantation center and its extent of experience with stem cell transplantations; techniques used for mobilization of stem cells; how the optimal time for harvesting of stem cells is determined and how the yield of stem cells is evaluated; whether purging of $CD34^+$ cells is performed; techniques used for processing and cryopreservation of stem cells; regimens of high dose chemotherapy used for conditioning before re-infusion of stem cells; supportive therapy given; and hospitalization and discharge policy.

This paper reports the results of the survey by means of descriptive, univariate frequency distributions. Most of the distributions are summarized by their median values and range, but in many cases modal values are also reported in order to indicate the most typical practice. For some variables, the interquartile range (from the 25th to the 75th percentile) is reported in addition to the full range, because it was considered that certain responses most likely refer to outliers and single extreme cases and could not conceivably represent standard practice of the centers. For instance, a few centers responded that the average PBSCT patient receive 40 or more platelet transfusions, while the interquartile range is 2-4.

The paper also reports the results of a more analytical approach, in which the centers' standard practices have been related to various possible explanatory variables to see whether systematic differences in practice could be explained by differences in the determining factors. The possible explanatory variables and the reasoning behind their selection are the following: 1) the type of institution (specialized cancer hospital, university hospital, general district hospital), as the physicians working in the various types can be expected to have different levels of expertise and may, therefore, manage the patients differently; 2) the centers' cumulative experience with performing stem cell transplantations, as accumulating experience may engender modifications in patient management over time; 3) the budget mechanism of the hospitals, i.e. whether they are allotted a predetermined budget at the beginning of the year, which they must adminis-

ter without any possibility of receiving additional allocations during the year or whether they can spend freely during the year and have their expenses reimbursed retrospectively. It is assumed that such differences in the way budgets are set may have an impact on the amount of resources typically used.

In order to enable the analysis of the possible relations between differences in standard protocols and the hypothetical explanatory factors, certain variables examined (such as the age limit set for patients or the centers' cumulated experience in terms of total number of PBSCT performed) must be reclassified into two or three categories. In most cases, this reclassification of variables, such as subdividing a continuous variable into two or three categories, involves an arbitrary choice of cut-off point between the categories, as there are no theoretical arguments for selecting one cut-off point rather than any other. For continuous variables, such as the average number of days the patients are hospitalized, the 25th and 75th percentiles of the observed distribution have in general been used to subdivide the variables into three categories, low, middle, and high.

The results are presented unmodified, with each center given the same weight as all the others, no matter what its size or accumulated experience with the procedure. Another possibility would have been to weigh the answers, for instance by the number of patients treated per year (as done by e.g. Peters *et al*.[11] in their study of pediatric centers). This would have provided a more representative picture of the current practice in terms of the number of patients subjected to the various protocols. However, the principal objective of the present study is to document current standard protocols and investigate the extent of diversity in these. Such a documentation may help to create incentives to establish more uniform practices based on scientific evidence of effectiveness. It is also of considerable importance to realize that a high degree of variability in patient management will invalidate generalizations of the results of cost studies to settings other than those in which they have been carried out.

Results

One hundred and sixty-two centers completed and returned the questionnaire, which was sent out in the autumn of 1998, but the exact response rate obtained is uncertain, because the appropriate denominator is not known precisely. The questionnaire was sent to 235 EBMT members that were registered as having a HDC program in breast cancer, and 162 completed questionnaires correspond to a response rate of 69%. However, several centers returned the questionnaire uncompleted, explaining that they primarily treat non-solid tumors or are mainly pediatric centers and had only treated a few breast cancer patients. Being registered as having a HDC program in breast cancer is evidently not equivalent to carrying out this treatment regularly.

The 162 centers participating in the study come from 20 different European countries, most from Italy (31 centers), Germany (28), Spain (22), France (18) and Belgium (12). Sixty percent of the centers are university hospitals, 14% are specialized cancer centers, while one quarter are general district hospitals. This relatively high proportion of general hospitals in the sample is a reflection of the fact that PBSCT requires less specialized facilities than allogeneic BMT and therefore can diffuse more widely. The proportion of general district hospitals among the responders is a good deal higher, above 40%, in countries such as Belgium, Austria and Italy, while it is much smaller in other countries, notably France (6%). Eighty-five percent are public hospitals, while the rest are private. Four-fifths of the latter are institutions not aiming to maximize the income of the owners (non-profit), while one fifth (corresponding to only 3% of all the centers) are profit maximizers.

The dominating financing mechanism for the hospitals is that they receive a predetermined annual budget, which they have to administer in such a way as to be able to cover expenses occurring throughout the whole year. Only 4% of the institutions have a financing system based singularly on retrospective reimbursement of expenses, while another 17% have more complicated systems, combining a predetermined budget with a certain amount of retrospective reimbursement of expenses. In the explorative, causal analyses, all centers with an element of retrospective reimbursement of expenses have been grouped together, totaling 21% of all the centers.

General district hospitals implemented their PBSCT programs somewhat later than cancer centers and university hospitals. Indeed, 57% and 44% of the cancer centers and university hospitals, respectively, initiated their program prior to or in 1991, versus only 15% of the general hospitals. Almost a third of the general hospitals started their program in 1996 or later as opposed to 9% and 14% of the cancer centers and university hospitals, respectively. As would be expected, there is a clear negative association between the year of initiating the HDC with PBSCT support program and the cumulated number of PBSCTs performed per center, and, by implication, also between category of center and cumulated experience. Cancer centers and general hospitals occupy the extreme positions in terms of experience with university hospitals in between.

Table 1 summarizes the data concerning the centers' facilities and experience. Altogether, the centers have carried out around 11,600 PBSCTs in solid tumors, with a median value of 37.5% and an extremely wide range. This reflects not only the different points in time of starting the HDC-program but also a very wide spread in the number of procedures performed per year. The median number of procedures has grown from 32 in 1996 to 37 in 1997, while the spread has almost doubled. The interquartile range stretches from 20 to 58, and 10% of the centers performed more than 90 SCTs in1997. More than half the general hospitals have carried out 20 or fewer PBSCTs in 1997, while around a third of the cancer centers and university hospitals performed more than 60 procedures.

For breast cancer patients, HDC with PBSCT support is used more in the adjuvant setting than in patients with metastatic disease, and for both types of patients, the average number treated increased from 1996 to 1997. Fifteen percent of the centers

Table 1. The centers' facilities and their extent of experience with SCT.

Facilities and experience	*Median*	*Range*
No. of SCTs/center/year*	37	2-452
Isolation rooms and their use		
No. of isolation rooms/center	6	1-18
No. of SCTs/room/year*	6	1-27
Personnel		
No. of SCTs/physician/year*	15	3-120
No. of SCTs/nurse/year*	5	1-29

*Notes: SCT = stem cell transplantation, all kinds; *Year is 1997.*

Table 2. Drug regimens used for mobilization of stem cells before apheresis.

Drug regimens	*% of centers*
G-CSF alone	20
Anthracycline based plus G-CSF	25
Cyclophosphamide +/- other non-anthracyclines plus G-CSF	20
Taxol based plus G-CSF	4
Unspecified chemotherapy (eg "according to trial protocol") plus G-CSF	32

consider it a routine treatment, while 80% use it mainly or only on patients enrolled in clinical trials. The most common maximum age limit is 60 years (56%), while a third have a limit of 65 years and 4% use a limit of 70 years. The lowest age limit reported is 50 years, while the highest is 72. Where the use of the treatment is exclusively limited to patients enrolled in clinical trials, the age limit set is generally near the lower end of the range.

Almost all the centers (94%) declare that they are in favor of the institution of an accreditation system. A third of those favoring accreditation think that such a system should be instituted at the national level only, while 56% think that it should be at the European level. The rest favor a combined system established both at national and European levels. The questionnaire did not contain any further questions about the desirable characteristics of such a system.

Mobilization of stem cells and apheresis

Table 2 shows the types of drug regimens used for mobilization of stem cells before apheresis. Twenty percent of the centers use colony-stimulating factors (CSF) alone. Only granulocyte-CSFs (G-CSF) were mentioned in the replies, so this is clearly the type of CSF predominantly used in standard protocols, while granulocyte-macrophage-CSFs are probably used from time to time.[14] Thirteen percent of the centers variously use G-CSF alone and chemotherapy followed by G-CSF, while the rest only use the latter option. The variety of combination chemotherapy regimens used is vast. Even disregarding variations in the specific dosages used and the exact duration of period of treatment, 17 different mobilization regimens consisting of chemotherapy followed by G-CSF are used. Moreover, a third of the centers gave only unspecified answers such as *according to the trial protocol*. Most commonly used regimens are anthracycline-containing ones (30%) and cyclophosphamide alone or combined with other non-anthracycline drugs (24%). Taxol-based regimens (which may also contain anthracyclines) are used by 5%.

Most centers monitor the patients' level of $CD34^+$ and carry out WBC counts to determine the optimum time for harvesting stem cells. Only 6% of the centers have set a fixed number of aphereses in their protocols, while the rest continue apheresis until a threshold level of $CD34^+$ cells has been reached. Three quarters of the centers reach the target level of $CD34^+$ cells with an average of two aphereses or fewer per patient. Twelve percent use only one apheresis per patient, while 11% need three or more. Almost two thirds of the centers normally intend to carry out apheresis as an outpatient procedure, but for most of them a certain proportion of the patients (up to half) must nevertheless be treated as inpatients.

Implantation of a central venous catheter before the harvesting of stem cells begins is very frequent. This is apparently done mostly as a matter of routine and without really taking the condition of the patients' veins into consideration. Thirty-nine percent of the centers implant a central venous catheter in all patients, and the median proportion of patients for whom this procedure is performed is 90%.

The proportion of patients given platelet transfusions during the apheresis phase varies between 0 and 100 percent, with a median value of 10% and a 75th percentile equal to 30%. Nevertheless, 14% of the centers give platelet transfusions to all or almost all their patients. Most centers (52%) use a threshold value for platelet transfusions of 20×10^9/L, while 25% have set the limit at a lower number of platelets. Seventeen percent have set a higher limit, up to 50×10^9/L, and start giving transfusions as soon as the patient's platelet count becomes lower than this value. There is no statistically significant association between the proportion of patients given platelet transfusions and the threshold value set for giving these transfusions.

Most commonly, the apheresis machine is operated by a nurse (46%), but in a third of the centers a physician performs this task. This is the case in half of the general hospitals, while only in 15% of the cancer centers and in a third of the university hospitals, but this tendency does not reach statistical significance at the conventional level ($p = 0.08$). Sixty-four percent of the centers perform large volume apheresis at least occasionally, but this is not to say that this is the procedure usually performed. Eighty-seven percent of the centers answered "no" to performing stem cell expansion procedures, and almost all the centers currently using or experimenting with such techniques were university hospitals.

Evaluation of the yield of progenitor cells

The most commonly used method for the evaluation of the yield of progenitor cells is CD34+ flow cytometry combined with CFU-GM assay (60% of the centers) followed by CD34+ flow cytometry alone (37%). Almost two thirds (64%) indicate their threshold value of CD34+ cells as 2×10^6/kg, few (7%) use a value as low as 1×10^6/kg, and the rest use higher values, primarily within the range from 3 to 5×10^6/kg. These differences may of course also reflect different HDC regimens with different intensities.

With respect to types of laboratory tests used for assessing the apheresis product, 80% of the centers test only for CD34+, while the rest add various other parameters to this, such as CD38 and Thy1. Two thirds consider that their threshold value for CD34+ corresponds to the minimum required for clinical feasibility of the procedure. The rest generally apply a threshold value, which is higher than that which they consider the minimally required number. It also appears that there are divergent opinions about what the minimally required number of progenitor cells actually is.

Only 6% of the centers indicate that they tend to give up the stem cell transplantation and try other possibilities, such as using standard chemotherapy, if the usual mobilization procedures have not succeeded in reaching the critical number of CD34+ cells. Most of the others tend to try another mobilization, in many cases after harvesting bone marrow as a back-up procedure. Seventeen percent of the centers indicate that they would, in most cases, switch to autologous bone marrow transplantation as the method for hematopoietic rescue.

Table 3. Frequency of use of the 23 HDC regimens used in the adjuvant setting and 26 HDC regimens used in metastatic disease, according to the proportion of centers using them.

Drug regimen	*Adjuvant setting*	*Metastatic disease*
Cyclophosphamide/thiotepa/carboplatin	33%	34%
According to trial protocol	15%	14%
Thiotepa/melphalan	12%	7%
Ifosfamide/carboplatin/etoposide	6%	9%
Others	34%	36%

Table 4. Supportive therapy to prevent febrile neutropenia and infections.

Intervention	*Proportion of centers using it*
Routine use of G-CSF, alone	22%
Primary antibiotic prophylaxis, alone	12%
G-CSF and primary antibiotic prophylaxis	59%
Neither G-CSF nor primary antibiotic prophylaxis	8%

Purging or purifying of CD34+ cells

Sixty-two percent of the centers perform purging of the CD34+ cells resulting from the apheresis, at least for some of their patients. Among the centers that do carry out purging, only 7% do so regularly, while 9% do it occasionally, but without revealing what determines the lack of regularity. A third of these centers purge, in cases in which they consider the risk of contamination to be particularly elevated, while the rest do so only if required to by the protocol of the trial in which the patient is enrolled. The most commonly used purging method is an immunomagnetic procedure, which is used by almost three quarters of the centers actually purging. In a third of these, this technique is combined with a biotin-avidin monoclonal antibody system, which is used alone by another fifth of the centers.

In more than half the centers (56%), processing and cryopreservation of the stem cells harvested is carried out within the department itself, while in a third it is taken care of by the blood-bank of the hospital. Other possibilities used, although only by very few hospitals, are regional or national blood transfusion centers and the hospital's own department of experimental hematology.

Conditioning of patients for re-infusion of progenitor cells

The variety of high dose chemotherapy regimens used for conditioning patients before re-infusion of progenitor cells is impressive, even when not taking into account variations in the actual dosages given of each of the drugs in the combinations used, and ignoring the variety that may be masked by the quite frequent answer *according to trial protocol* (around 14% of the responses overall). Altogether, 23 different regimens are used in the adjuvant setting, while 26 are used for metastatic disease. The picture may be slightly simplified by grouping the relevant regimens into alkylator regimens and taxol-containing regimens, but there still remain 17 to 20 different regimens in the respective settings. Table 3 shows the most frequently used regimens, but the pick-up category *others* is the most frequent in both treatment settings. In the adjuvant setting as well as for patients with metastatic disease, the CTCb or STAMP V regimen (cyclophosphamide, thiotepa, carboplatin) is used by around one third of the centers. Next follows the response *determined by the trial protocol*, after which the third most common reply in the adjuvant setting is thiotepa plus melphalan (12%), while for metastatic disease it is the ICE (ifosfamide, carboplatin, etoposide) regimen with 9%.

Supportive therapy

In order to support the hematopoietic recovery of the patients after re-infusion of progenitor cells, 80 % of the centers administer CSFs as primary prophylaxis as a matter of routine, cf. Table 4. The rest do not do so routinely, but this is not to say that they will not use such growth factors if indicated for the individual patient. In almost all cases of routine use, the dose is stated to be 5 μg/kg, but 6% use 10 μg/kg. As to the duration of CSF administration, the most frequent reply (48% of the answers) is that CSF is given

from 1 to 2 weeks, while 13% give it for up to 1 week and 37% *until hematopoietic recovery*. The period of hypoplasia is usually claimed to be 2 weeks at the maximum (cfr. ref. #3,4), so only 2% of the centers would be giving CSF for more than 2 weeks, while 85% will be administering it for a period of 1-2 weeks. However, hematopoietic recovery may be defined rather differently by the various centers, and the duration of CSF therapy would be expected to vary accordingly. Thus, some of the responses state the applied criteria for hematopoietic recovery, and these vary widely, e.g. from ANC > 0.5×10^9/L to WBC > 3×10^9/L.

Seventy percent of the centers give their HDC breast cancer patients primary antibiotic prophylaxis, most frequently using ciprofloxacin. Fifty-nine percent of all centers give both antibiotic prophylaxis and CSF, 22% give CSF alone, 12% give only antibiotics and 8% give neither. Despite these protective measures, there is a high incidence of febrile neutropenia (FNE) among breast cancer patients in HDC programs with PBSCT support. The median value, which is at the same time the modal response, is that the incidence is 80%. If the 25th percentile of the distribution, corresponding to an incidence of FNE of 50%, is used as the separation point between low and high incidence, it turns out that there is no relation between the level of incidence and using CSF routinely or not, just as the incidence is not significantly related to the duration of the use of CSF. Nor is the incidence of FNE related to the use of antibiotic prophylaxis, and it is just as high in centers using both CSF and antibiotics as in centers using neither. With respect to the usual duration of these episodes of febrile neutropenia, there is a rather wide range from 1 to 15 days, but the interquartile range is quite narrow, from 3 to 5 days.

The incidence of bacterial infections among breast cancer patients in HDC programs ranges over the whole scale from 0 to 100%, and the interquartile range is also very wide, 65 percentage points. There is no statistically significant relation between this incidence and the centers' policy with respect to giving primary anti-bacterial prophylaxis or CSFs as a routine. The type of bacterial infection most frequently reported (24%) is *Staphylococcus epidermidis*, but 17% of the centers declare that they do not have good local data.

The incidence of fungal infections is much lower, and even though the range is quite wide (0 to 60%), the interquartile range is only 10 percentage points (and the 75th percentile is 10%). The most commonly mentioned type of fungi is Candida species (45%), but a third of the centers do not have good local data. With respect to viral infections, the incidence is even lower and the range more narrow, with a 75th percentile of 5%. The most common type of viral infections is Herpes zoster (29% of the centers), but more than a third of the centers are not capable of providing data on this.

The centers were also asked about their policy with regard to giving blood products to the patients in breast cancer HDC programs. As appears from Table 5, the distribution of threshold values for giving platelet transfusions is bimodal, with almost half the centers (43%) using a value of 10×10^9/L and another 43% using 20×10^9/L. For hemoglobin, the variation is much smaller, and two thirds of the centers use a threshold value of 8 g/dL. Only a fifth of the centers have a threshold value for hematocrit, and 90% of these have set this value between 25 and 30%.

Table 5. Indications for transfusions of blood products.

Threshold value	*Percentage of centers*
Packed red blood cells	
Hemoglobin < 5 g/dL	1
Hemoglobin < 7 g/dL	10
Hemoglobin < 8 g/dL	68
Hemoglobin < 9 g/dL	13
Hemoglobin < 10 g/dL	8
Platelet concentrates	
Plateletes < 10×10^9/L	44
Plateletes < 15×10^9/L	13
Plateletes < 20×10^9/L	43
Plateletes < 50×10^9/L	1

The number of platelet transfusions given to the average breast cancer HDC patient varies from 2 to 40. The high numbers, around 35 to 40 transfusions, mentioned by several centers, are not impossible or unreasonable, but should probably be considered as rare exceptions rather than standard treatments. This is corroborated by the fact that the modal value for platelet transfusions is two (30% of the centers), and that the interquartile range is quite narrow, from two to six. The number of platelet transfusions is neither related to the strictness of the threshold value for giving transfusion nor to any of the other potential explanatory factors examined. However, the proportion of centers giving many platelet transfusions is significantly smaller ($p = 0.03$) among the centers using single donor blood products (13%) than among centers that never use these (50%) or those that use single donor blood products for only some of their patients (33%).

In an attempt to render the centers' responses to the question about the number of units of platelet transfusions more comparable, the questionnaire also included questions about the definitions of one unit of platelet and red blood cells transfusion, respectively, used by the center. In response to this, 19 different definitions of a unit of platelet transfusions were provided and 15 different definitions of a unit of red blood cell transfusion. Although the differences between many of the definitions may be minor, e.g. 200-400 mL RBC versus 350 ml RBC, some of the definitions used do vary importantly (eg 1×10^{11} platelets versus 6×10^{11} platelets), and it is clear that considerable care must be taken when comparisons are made.

The number of red blood cell transfusions given to the average patient is also variable, but much less so than for platelets. The modal value is again 2 transfusions (25% of the centers), and the interquartile range goes from 2 to 4, while the maximum value is 10 transfusions.

Fifty-nine percent of the centers use single donor blood products for all their patients, while 3% claim never to use this type of product. The extent of use of single donor blood products is related neither to the type of the institution nor to its experience nor to the kind of financing mechanism employed, but it is very clearly related to the threshold values set for transfusions. Thus, of the centers that give single donor blood products to all patients, 54% have a threshold value of 20×10^9/L for platelets, while 32% have set the value at 10×10^9/L. Among the centers that reserve single donor blood products for only some of their patients, the corresponding proportions are 26% and 57%, respectively ($p = 0.018$).

Eighty-one percent of the centers irradiate all blood products, and this policy is not dependent on any of the explanatory factors examined. While 89% and 72% of the centers that use single donor blood products for all or some of their patients respectively irradiate all blood products, this is only done by half of the centers that never use single donor blood products ($p = 0.005$, Fisher's exact test). Leukocyte filters are used by 89% of the centers.

Protective facilities and hospital discharge policy

About one third of the centers (35%) have no particularly protected facilities for their HDC patients, but admit them into private rooms. Sixteen percent have high efficiency particulate air filtration (HEPA) rooms, 10% have laminar air flow (LAF), 14% private rooms with HEPA, and 11% LAF plus HEPA. Other combination possibilities, which 13% of the centers have, include *positive pressure rooms* and *reverse isolation air flow rooms*. There is no statistically significant relation between the extent of the protective facilities and the type of hospital, although the use of private rooms only is more frequent in general hospitals. Eighty-four percent of all the hospitals routinely admit all patients into protected rooms during the hypoplastic period, 13% do so only under certain conditions (not specified), while 3% do so only if the patient has severe complications, or if it is expected that she will have an absolute neutrophil count (ANC) of less than 0.5×10^9/L for at least 1 week. This policy does not seem to be related to the kinds of protected facilities available. However, there is a tendency ($p = 0.10$) that a larger proportion (26%) of centers with particularly protected facilities to keep patients in isolation for more than 20 days, compared to centers with only private rooms (15%).

Table 6 summarizes the centers' policies with regard to keeping the patients in protected facilities and length of stay in the hospital after re-infusion. The average number of days the patients are kept in protected facilities varies from 1 to 28, with a modal value of 10 days and an interquartile range stretching from 10 to 20 days. The number of days is not related to any of the potential explanatory factors examined, nor is it statistically related to the centers' policy with regard to routine admission into protected facilities. However, centers with a policy of routine admission into protection also tend to keep the patients in the protected facility for a longer period. For example, half the centers that only admit the patients under particular circumstances keep them in protection for 10 days or less versus only 29% of the centers admitting all patients.

Table 6. Distribution of the centers according to the number of days the average patient is kept in protected facility and the total number of days in hospital after HDC and PBSCT. Percentage of centers.

Number of days for average patient	*Protected facility*	*Total stay in hospital*
Depending on recovery	10	NA
7 or less	6	4
8 – 11 days	29	14
12 – 16	33	61
17 – 21	18	18
More than 3 weeks	4	4
Total	100	100

The average number of days that breast cancer patients are kept in the hospital after re-infusion varies from 3 to 40, both extremes only representing one observation. The modal value is 14 days (20% of the centers), and the interquartile range is from 12 to 16 days. Five percent of the centers keep the patients for 3 weeks or more, while 11% discharge them after a little more than a week, 7-10 days.

Concerning their criteria for discharging the patients from hospital, the centers responded by providing more than 40 different sets of criteria, all combining the same relatively few factors but using different threshold values and combinations of these. The factors comprise resolution of fever, state of hematopoietic recovery (determined by counts of WBC, platelets and – sometimes – hemoglobin), nutritional and ambulatory status, absence of serious mucositis or other serious adverse events. It may seem that such differences are small and can be ignored, but in fact they may have a decisive impact on the actual length of hospital stays, which is the most important cost factor in the majority of analyses of the costs of treatment. Four centers gave responses such as *clinical decision, clinical recovery*, while the rest used more formal and supposedly more objective criteria, although not always well defined. One quarter of the centers gave the response *full hematopoietic recovery, no fever*, which was stated in the questionnaire as an example of the possible responses. It is, however, quite obvious that full hematopoietic recovery is far from being an unambiguous concept and that it may be defined quite differently by different centers. Thus, the discharge criteria stated in the responses comprise threshold values for leukocytes ranging from 0.5 to 3×10^9/L, and for platelets from *platelets stable* or *platelets increasing* over 10×10^9/L to 50×10^9/L.

Sixteen percent of the centers responded that they have an outpatient HDC program, but these hospitals do not report shorter average hospitals stays than the others. Forty-one percent of all centers believe that it will eventually become possible to carry out all the procedures in connection with a PBSCT on an outpatient basis. The short descriptions given of the outpatient programs currently in place or under

development indicate that only selected patients will be affected by this, depending on an evaluation of the suitability of their accommodation and of their personal compliance and reliability. After the high dose chemotherapy treatment and re-infusion of stem cells the patients may be followed on an outpatient basis, depending on the results of regular (for instance biweekly) whole blood counts to evaluate the need for blood transfusions. Patients will usually be readmitted if the blood cell counts are not satisfactory or if fever develops.

Discussion

This survey demonstrates that there are wide differences in the methods of managing patients and in the particular techniques applied in the various transplant centers. This is in line with the results of a recent paper by Peters *et al.*[11] that made a similar survey of about 60 European transplant centers treating pediatric patients. Such variability in patient management and treatment patterns has been an issue of much concern in recent years, primarily because it most likely reflects a considerable uncertainty about the most appropriate ways of managing the particular patients in question. Such uncertainties may be expected to lead to poorer outcomes and perhaps also higher costs of treatment than necessary. It is evident that, even if differences in the unit prices of resources are ignored, the costs of treating breast cancer patients in HDC programs with PBSCT support will vary greatly between centers because of differences in the types and amounts of resources used. Whether the outcomes of the treatments differ to the same extent, and what the relation is between costs and outcomes (higher costs would normally be expected to result in better outcomes) cannot be determined on the basis of the data collected in this survey.

We have tentatively explored possible systematic relations between variations in patient management and some hypothetical explanatory factors. Contrary to what was expected, the financing mechanism of the hospitals does not seem to have any systematic relation with the choice of management strategies and the resulting use of resources, e. g. in terms of the average number of days the breast cancer patients are kept in hospital after high-dose chemotherapy and re-infusion of stem cells. It should be noted, though, that only 4% of the hospitals responded that they are financed exclusively by retrospective reimbursement of expenses, the form of financing mechanism expected to lead to the largest overall use of resources. The other 17% of the centers included in this category in the analyses all responded that their financing system was some combination of a fixed predetermined budget and reimbursement of expenses. This probably means that reimbursement is subject to certain conditions, and this may restrain the impact on the incentives to spend that otherwise might be expected to result from the possibility of having expenses reimbursed.

Another possibility of subdividing the centers according to the financing mechanism is to examine whether they are financed via some type of diagnosis-related group (DRG) system, in which the hospitals receive a certain fixed sum per patient with a particular diagnosis, a sum that has to cover everything for the patient concerned. The yearly budget of the hospital for each type of diagnosis recognized by the system is then determined in advance by the expected number of patients presenting with this diagnosis, and the total budget is determined as the sum of these diagnosis-related budgets, plus some additions to cover unforeseen changes. Hospitals operating within a DRG system receive a given amount of money per patient with a particular DRG diagnosis, no matter what the patient's actual state of health and need for treatments is, and may be expected to have an incentive to reduce the resource utilization for the average patient in order to be able to afford treating patients with a greater need for care. Thirty-two percent of the centers in the survey are financed by some sort of DRG mechanism, while the rest have budget mechanisms without any direct link with the patient mix of the hospital. However, the analyses have not revealed any systematic relations between the budget system used and the centers' choice of patient management strategy or use of resources.

The two other hypothetical explanatory factors examined, type of institution and experience measured as cumulated number of PBSCTs in solid tumors performed, seem to matter, however. The categories of the variable experience were determined by the quartiles of the variable cumulated number of PBSCTs. Thus, Q1 is 18 and Q3 = 86, so low experience corresponds to from 1 to 18 transplants performed, medium experience from 19 to 86, and high experience 87 or more transplants.

The facts that district general hospitals typically started their HDC programs several years later than most of the cancer centers and the university hospitals and generally treat far fewer patients per year mean that these two explanatory factors may easily be confounded making it difficult to estimate whether they have a separate impact. However, when statistically controlling for differences in one of the factors, the systematic differences in patient management observed for the other factor analyzed tend to persist. In some of the analyses, the differences become statistically not significant at the conventional level (p = 0.05), but this is due to the reduced number of observations within each category of the factors statistically controlled for, and the clear differences remain. What to conclude from the differences observed is another matter, though, but it is generally possible to make some common sense of them.

The age limit is significantly related to the experience of the center, with 58% of the most experienced centers having an age limit higher than 60 years versus 32% of the least experienced (p = 0.005). It is not surprising that growing experience with and increasing skills in carrying out the transplantation procedure should lead to a widening of the criteria for receiving the treatment, in this case maximum age.

The support for an accreditation system is less pronounced among the general district hospitals, although this tendency is not statistically significant at the conventional level of significance (p = 0.11). It is likely that one of the criteria for obtaining accreditation would be a minimum threshold of number of

SCTs performed per year, in line with the EBMT recommendations[13] that each transplant center should perform at least 20 procedures per year. Twenty-five percent of the centers in our sample had performed 20 or fewer SCTs in 1997, while the median number of procedures performed was 36 (double the amount found by Peters *et al*.[11] in their investigation of centers performing PBSCT on pediatric patients). As the general district hospitals generally perform a fairly low number of transplants per year, their lower degree of support for the institution of an accreditation might be engendered by an expectation of having too few patients to obtain accreditation.

University hospitals apparently perform more apheresis procedures per patient than the other types of hospitals, as only two thirds of the university hospitals had an average of two aphereses or fewer per patient, while the proportions were 78% and 88% for cancer centers and general hospitals, respectively. This might be due to selection of patients, if the patients expected to be more difficult to treat are typically referred to the university hospitals from the other institutions, particularly the general hospitals. This is of course only a possible explanation, which needs further analysis to be corroborated or discarded.

Thirty-seven percent of the general hospitals purge as opposed to 73% of the university hospitals, with the cancer centers in between with 59% ($p = 0.001$). When the question of purging or not is related to the centers' cumulated experience with carrying out PBSC transplantations, another statistically significant relation is found, in that 70% of the centers with the most experience purge, as opposed to 42% of the centers with least experience ($p = 0.018$). Examining these relations more fully, we find that the significant positive relation between the extent of experience and carrying out purging only holds for general hospitals, of which two thirds of the most experienced versus 13% of the least experienced purge ($p = 0.03$, Fisher's exact test). Cancer centers show the same tendency between experience and purging, but this is not statistically significant at the conventional 5%-level. No matter the extent of their experience, around 70% of the university hospitals purge.

The value of purging is still a strongly contested issue, and more than 80% of the centers performing this procedure respond that they only purge if required by the protocol of a clinical trial, or if the risk of contamination for the individual patient is considered to be particularly high. As the university hospitals participate much more in clinical trials (on every level, local, national and multinational) than general hospitals, this is a likely explanation of the difference in the proportion of centers in the various categories confirming that they purge.

That university hospitals have been found to use a much wider spectrum of cytotoxic regimens for mobilization of stem cells and conditioning of the patients before re-infusion of stem cells may not surprise, given the current uncertainty about the most appropriate regimen. Likewise, it is in accordance with their role as research institutions and providers of new knowledge that some university hospitals and almost none of the others are experimenting with stem cell expansion procedures.

The period over which CSFs are routinely administered is not related to the type of institution or their cumulated experience with PBSCT-supported HDC, while the fact of giving CSF or not clearly is. Thus, 95% of the general hospitals give CSF routinely, while only three out of four cancer centers and university hospitals do this. The use of CSF is also significantly related to the cumulated experience of the centers, with the least experienced centers using it most frequently.

It is clearly important to analyze the impact of either factor, when the other is controlled for. If this is done, for instance by analyzing the association between use or not of CSF and category of center, controlling for the three different levels of cumulated experience, the relationship is no longer statistically significant, mainly as a result of the reduced number of centers included in each sub-analysis. The tendencies are still clear, as most obviously observed in the group of centers with most experience, in which 89% of the general hospitals use CSF routinely versus 62% and 69% of the cancer centers and university hospitals, respectively.

The practice of giving primary antibiotic prophylaxis is significantly more frequent in general hospitals than in the other types of centers, and it is also significantly more frequent in less experienced than in more experienced centers. When the association between use of antibiotics and category of hospital is analyzed controlling for level of experience, the associations are no longer statistically significant (because of the reduction in the number of observations in each sub-category), but the tendencies are still quite clear. Thus, in the group of hospitals with most experience, 89% of the general hospitals give primary antibiotic prophylaxis, while this is done by 46% and 52% of the cancer centers and university hospitals respectively.

Giving CSF as hematologic support and primary antibiotics prophylaxis, and especially both combined, is much more frequent in general hospitals than in cancer centers and university hospitals. The same pattern as for the use of CSFs is seen. Eighty-one percent of the general hospitals do both, versus 39% of the cancer centers and 53% of the university hospitals. Conversely, 13% of the cancer centers and 10% of the university hospitals give neither, versus none of the general hospitals. This relation is highly statistically significant ($p = 0.006$), but once again the relation is no longer significant when controlling for experience.

Despite the variations in protective measures taken, the incidence of FNE is high and uniform across center types; moreover, it does not seem to be lower in centers using CSF and primary antibiotic prophylaxis routinely than in centers using neither.

The length of stay in protected facilities during the hypoplastic period varies widely between centers, but without any distinct relationship with the type of institution or the use of protective measures. Neither is the average number of days clearly related to the threshold value of $CD34^+$ cells, even though one might be tempted to believe this on the basis of the results reported by Faucher *et al*.,[12] who found that the number of $CD34^+$ cells re-infused was the only predictive factor for hematopoietic recovery.[15] However, a tendency pointing in this direction may be dis-

cerned, as the proportion of centers that keep patients in protection for shorter periods is higher among centers with a threshold value for $CD34^+$ cells above 3×10^6/kg.

The interquartile range for the average duration of the entire stay in hospital after high dose chemotherapy and re-infusion of stem cells is not very wide, from 12 to 16 days. However, the amount of variation observed must nevertheless be considered important from an economic viewpoint, as half the centers will be outside this range. The difference in costs between an average stay of 1 week and 3 weeks will be considerable. The average number of hospital days is not statistically related to any of the potential explanatory factors examined, such as the category of hospital or their cumulated experience. Nor is it related to the routine use of CSF to support hematopoietic recovery. However, a statistically significant relation ($p = 0.03$) between the number of hospital days and the use or not of primary antibiotic prophylaxis is found. The most important contribution to the χ^2 value comes from the fact that a larger proportion than expected (in the statistical sense) of the hospitals not using primary antibiotic prophylaxis keep their patients hospitalized for a period longer than 16 days (the cut-off value determined by the 75th percentile).

Presumably, the average number of hospital days must be decisively determined by the stringency of the discharge criteria practised by the individual hospitals. However, after careful examination of the criteria stated in the responses we have refrained from trying to categorize them into a few groups according to increasing stringency. This is because the various elements in the criteria seem to be given widely diverging importance, and because there are too many ambiguities involved to make such an analysis permissible.

With regard to the existence or not of an outpatient program, the responses did not vary significantly with the hypothesized explanatory factors, but a few, not statistically significant, tendencies may nevertheless be mentioned. Thirty percent of cancer centers compared with 15% of university hospitals and 10% of general hospitals have an outpatient program ($p = 0.095$). It also turns out that centers that are financed on a per case basis (using a DRG system or something akin to this) are more likely to have an outpatient program than centers using other financing mechanisms (24% vs 13%, $p = 0.10$).

Before an accreditation system can be established, whether on a national or a European level, a high degree of consensus must be reached about the required facilities, the recommended HDC regimens, supportive therapies and procedures in general. Judging from the evidence presented in the present study, such a consensus may be difficult to obtain, because each and every center seems to have found its own ways of proceeding. Without prospective, comparative studies of the alternatives available at each step of the procedure, it will be difficult to provide systematic evidence on which to base the necessary choices. Obviously, many of the participating centers are involved in currently running trials, which may be hoped to provide more definitive answers to some of the questions, but it may be a long time before the information gathered will be considered sufficient.

Several recent studies[16-18] are concerned with determining the costs of performing peripheral blood stem cell transplantations in various settings and with examining the factors that may explain variations in costs and perhaps even identifying ways to reduce costs (especially ref. #18). It has not been the ambition of the present study to actually estimate the differences in costs implied by the observed variations in patient management strategies, although this could be achieved by using a single set of unit prices derived from a particular setting. In this way, one would be able to focus on the size of cost differences due only to variations in resource use, without confounding them with differences caused by differences in unit prices.

One of the papers mentioned above, the one by Glaspy,[17] is of particular interest in relation to the data reported in the present study. Glaspy explores issues concerning definition and measurement of the quality of the PBSCT grafts, and the possible impact of this quality on resource utilization or costs and on outcome of treatment as well. Quality is defined in terms of the optimal number of $CD34^+$ cells per kilogram bodyweight. Most centers define 1×10^6 $CD34^+$ cells/kg as the minimum number required to ensure engraftment, while many centers, according to Glaspy, define the *optimal* number to be $4\text{-}5\times10^6$ $CD34^+$ cells/kg. Eighty-six percent of the centers participating in the present study use a threshold value less than or equal to 3×10^6 $CD34^+$ cells/kg.

Of the potential benefits of optimal mobilization of $CD34^+$ cells, Glaspy[17] mentions three that are expected to be associated with reductions in resource utilization: 1) a decrease in the number of aphereses required to obtain an optimal number of $CD34^+$ cells; 2) a decreased need for repeat mobilization and for backup of bone marrow harvest; and 3) more rapid and consistent hematopoietic recovery. He reviews several studies that show that infusing a minimum of $4\text{-}5\times10^6$ $CD34^+$ cells/kg leads to reduced use of supportive care during the engraftment phase, including shorter admissions in hospital, a smaller number of transfusions and reduced use of medications such as antibiotics and hematopoietic growth factors.

Considering only the cost side of the equation, the potential cost savings during the engraftment phase should be balanced against the additional costs during the mobilization phase of increasing the number of $CD34^+$ cells harvested per apheresis. The currently most feasible strategy for increasing the harvest is to use chemotherapy with cytokines or cytokine combinations for mobilization, but there are as yet no estimates of the cost increases that these medications may imply. The reported cost savings from using a threshold of $4\text{-}5\times10^6$ $CD34^+$ cells/kg for re-infusion vary between US $ 6,500 and $ 46,000 and are due primarily to shorter stays in hospital and a reduction in the number of platelet transfusions.

It is also claimed by Glaspy[17] that enhanced harvest and re-infusion of $CD34^+$ cells may have clinical benefits in the form of improved survival and a positive impact on quality of life. The mechanisms envisioned behind these expected effects are: 1) a higher number

of CD34+ cells per apheresis will enhance the feasibility of various purging procedures that result in the loss of substantial numbers of normal hematopoietic stem cells; and 2) re-infusion of larger numbers of CD34+ cells may improve the possibility of giving tandem high-dose chemotherapy treatments that may, it is to be hoped, lead to improved survival outcomes. These potential clinical benefits are of considerable interest, but they still need to be demonstrated.

Before going on with attempts at optimizing the procedures involved, many would demand more convincing evidence that high-dose chemotherapy with stem cell support does actually meet the expectations of leading to significant improvements in terms of more final outcomes, such as survival, or, preferably, quality-adjusted survival. Recently presented results of randomized clinical trials[19-22] demonstrate that the evidence for the superiority of high dose compared to standard chemotherapy continues to be conflicting and highly contentious. However, if Glaspy[17] is right, the issues are more complex but also very promising, as attempts to optimize the quality of the PBSCT graft may be expected to lead to better clinical outcomes, while at the same time reducing the costs of supportive care during the engraftment phase.

Conclusions

This survey of the patient management strategies followed and techniques used by European transplant centers for high-dose chemotherapy programs with PBSCT support in breast cancer patients documents that each center has found its own particular solution to the various technical and management problems involved in such a program.

To mobilize stem cells, 20% use G-CSF alone, the rest combine chemotherapy and G-CSF using more than 20 different drug combinations. Likewise, around 25 different high-dose chemotherapy combination regimens are used in the conditioning phase before re-infusion of stem cells. Five percent of the centers regularly purge CD34+ cells, while 47% do so if required by the protocol of the trial in which the patient is included or if the risk of contamination is considered to be particularly high. Eighty-two percent of the centers routinely admit the patients into specially protected facilities during hypoplasia, with the average stay in protection varying between 1 and 28 days. Average total number of days in hospital after re-infusion of stem cells ranges from 3 to 40 days, although with a clustering between 12 and 16 days. Almost all the centers have established objective criteria for discharge from hospital. These criteria combine the same few factors (e.g. absence of fever, blood counts, ability to eat), but with important differences in the details, leading to 40 different sets of criteria.

Presumably, variability in patient management to the extent observed in this study is not optimal, as it more than anything reflects a lack of convincing evidence for or against any particular choice of HDC regimen or patient management procedure. Before any recommendations on how to optimize the procedures involved in delivering high-dose chemotherapy with stem cell support can be made, there is a need for studies providing the necessary evidence. However, there are still very conflicting results from studies investigating the superiority of high-dose chemotherapy versus standard chemotherapy in breast cancer. Achieving a clear resolution of this issue should probably take priority.

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NN conceived the idea of providing an overview of the practice of this therapy in Europe by a questionnaire survey, worked out a draft questionnaire, entered the data in a data base upon receipt of the completed questionnaires, carried out the data analysis, and drafted the paper submitted. GR contributed to the design of the final questionnaire, provided substantial help in the analysis and interpretation of the data, did a critical revision of the paper draft and has approved the version of the paper hereby submitted.

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Potential implications for clinical practice

- As it highlights the significant extent of variability in current practice, this study is expected to contribute to ongoing efforts of working out guidelines for clinical practice in this therapeutic field. Admittedly, however, first priority should be given to determine conclusively whether the potential benefits of high-dose chemotherapy in breast cancer can be realized in practice. The evidence for this has so far not been convincing.

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