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ALLOGENEIC TRANSPLANTS OF rhG-CSF-MOBILIZED PERIPHERAL BLOOD STEM CELLS (PBSC) FROM NORMAL DONORS

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**Gruppo Italiano Trapianto di Midollo Osseo, e di cellule staminali ematopoietiche, nell'adulto e nel bambino. Commissione di Studio per l'impiego di cellule staminali periferiche da donatore sano e relativo trattamento con fattori di crescita*

ABSTRACT

There is a growing interest in the use of peripheral blood stem cells (PBSC) for allogeneic transplantation. This is due in part to the idea that, as with autologous transplantation, increasing the number of allogeneic hemopoietic progenitors infused may lead to reduced complications. However, introducing the PBSC technique into allogeneic transplants implies theoretical as well as ethical problems involving both patient and donor. We are still uncertain whether the PBSC technique will result in an increase of GVHD or (better) of GVL. G-CSF, necessary for effective PBSC mobilization, is safe but its use in normal subjects should be regarded with caution. For this reason, a Study Committee promoted by the GITMO (Gruppo Italiano Trapianto di Midollo Osseo) evaluated the key aspects of allogeneic PBSC collection and transplantation. The present paper summarizes the scientific data and suggests some guidelines for the introduction of allogeneic PBSC transplantation into clinical practice. The procedure should be considered experimental and the Committee strongly recommends the use of allogeneic PBSC in experienced centers, initially in patients with advanced disease. The donor should be given a complete explanation of the advantages and risks of G-CSF therapy, leukapheresis and general anesthesia. A careful monitoring of both patient and donor should also be included to watch for short-term and long-term side effects.

Key words: PBSC, allogeneic transplantation, G-CSF, donor

The use of peripheral blood stem cells (PBSC) in the setting of autologous transplantation has become increasingly popular,[1] in some cases superseding that of bone marrow cells. On the contrary, in the allogeneic setting PBSC have been used only occasionally in the past,[2-4] but growing interest is documented by a number of publications on this topic as well as by several reports of transplants currently being performed.[5-7] (Dipersio J, unpublished; Bacigalupo A, personal communication; Rizzoli V, personal communication).

The introduction of the PBSC technique into allogeneic transplants implies theoretical as well as ethical problems, including those involving the donor. For this reason, in October 1993 the GITMO promoted a Study Committee to evaluate the aspects linked to collection and transplantation of allogeneic PBSC. This was also intended to provide hematologists in our country with data useful for addressing clinical and laboratory work in this field. The present paper represents a summary of the scientific data collected by the Committee and offers indications for the introduction of allogeneic PBSC transplantation into the clinical practice.

Background

Allogeneic marrow transplant recipients may not always receive an adequate number of hemopoietic progenitors. This is due to indi-

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vidual variations; in a recent paper[8] the median number of infused CFU-GM was 2.4×10^4/kg but the range was wide. There was no significant difference in the speed of engraftment in patients receiving more or less than 2.4×10^4 CFU-GM/kg, but the quality of engraftment differed: patients receiving suboptimal numbers of CFU-GM had significantly lower platelet counts on day +80, +100 and +150, more CMV infections, and a significantly greater transplant related mortality.

Therefore, increasing the number of allogeneic hemopoietic progenitors infused may lead to reduced complications. The only way to increase the number of progenitors is to use mobilized PBSC.

After adequate priming, PBSC can restore hematopoiesis very rapidly in the autologous setting. Concerning the long-term repopulating capacity of PBSC, laboratory,[9] animal[10] and human clinical data[11-15] confirm the hypothesis that PBSC contain uncommitted stem cells capable of self-renewal that would ensure long-term engraftment. Howewer, PBSC differ from bone marrow cells in many aspects, not only in number and quality of precursor cells, but also in accessory and stromal cell content. Whether this can influence the nature of the transplant, and how, is presently unknown.

Advantages

The advantages of transplant with allogeneic PBSC are expected to be a more rapid engraftment with possibly lower incidence and severity of infectious complications, a shorter stay in hospital and a lesser need for transfusional support. But an influence on the disease itself may also be hypothesized on the basis of the high number of $CD3^+$ve and $CD56^+$ve cells infused. Being able to avoid giving general anesthesia to the donors is envisaged as an important step, both for physical and psychological reasons. Should the results prove at least comparable to those of bone marrow, within the unrelated donor transplant program this would reasonably imply a sharp increment of donor accrual, as well as a better consensus toward a *second donation* in case of graft failure. In fact, although experience with unrelated bone marrow donors shows short-term sequelae from bone marrow harvesting in 5% of donors, the whole procedure is well tolerated overall with few serious problems.[16]

When considering the possible advantages of PBSC one should keep in mind at least three possible problems: one related to the collection procedure itself, in particular the venous access; another related to the use of mobilizing drugs and, last but not least, the risk of severe GVHD, possibly the result of infusing a higher (5-10 times) number of lymphoid cells.

Disadvantages

In normal donors, any mobilization technique should strictly avoid the use of cytotoxic agents. The administration of hemopoietic growth factors, namely G-CSF, is more debatable. G-CSF combines the best mobilizing capacity with a safe clinical profile, at least in the short term. With doses up to 32 μg/kg/day, serious side effects have not been recorded.[17] However, at present we are unaware of the ability of G-CSF and other cytokines to produce unwanted effects in the long term.

Experience with G-CSF in normal donors indicates that with doses from 2.5 μg/kg up to 16 μg/kg/day for 5 consecutive days an adequate number of PBCS is easily collected with acceptable side effects,[15, 18-21] which include bone pain, malaise, headache and a propensity for thrombosis. The apheresis product has been successfully employed in syngeneic[15] as well as in allogeneic transplant,[2,3,5,6,] (and Dipersio J, unpublished; Buckner D, unpublished) with or without concomitant infusion of bone marrow cells and without any apparent increase in GVHD incidence or severity. In three cases PBSC were also used in transplants from matched unrelated donors.[5] In these latter patients the PBSC were given after a bone marrow graft failure, but the results were not evaluable due to relapse or second failure in two of them.

Selected $CD34^+$ve PBSC have also been employed. The purification step was undertaken in order to reduce the theoretical risk of GVHD by depleting the T-cell population (Di-

persio J, unpublished). However, this reduces the speed of engraftment. After G-CSF priming, the $CD3^+$ve cell content was considered to be 7 times greater than that of a standard bone marrow collection, and that of $CD56^+$ve cells 20 times higher.

Despite incouraging initial results, employing a drug that acts on the maturation and proliferation of the myeloid cell line should be considered with caution. This subject has been a matter of debate within the GITMO Committee. One opinion is that the use of G-CSF in healthy donors should initially be limited to selected situations, namely to subjects with contraindications for or refusal of general anesthesia, or in cases of a second donation after graft rejection, or when it is believed that the HLA barrier will be overcome by a high number of progenitors, as in the program of mismatched related donor transplants carried out in Perugia.[6] This opinion also favors the use of G-CSF in cases of donor leukocyte infusion as treatment for relapses after allogeneic bone marrow transplantation.

A second opinion within the group is less restrictive and would apply PBSC technology whenever a donor prefers this to bone marrow collection, provided he has been told of the theoretical risk of G-CSF through a written informed consent form previously approved by an official ethical committee.

Transplants performed

In Italy several teams have started carried out allogeneic PBSC: the Perugia team[6] has now performed more than 20 graft procedures from haploidentical, related, MLC reactive donors. An additional ten transplants have been completed in Genoa (Bacigalupo A, personal communication), Palermo[7] and Parma (Rizzoli V, personal communication) from HLA-matched siblings, and others are currently being performed. Short-term results seem encouraging, with no increased risk of acute GVHD and good engraftment. Other allogeneic PBSC transplants have been reported in the literature from matched siblings[5] (and Dipersio J, unpublished, Buckner D, unpublished). All were advanced leukemia patients. The procedure should still be considered experimental and we certainly need more patients and a careful evaluation of results.

Recommendations

1. It is the opinion of this group, and that of many other hematologists in Europe and in the U.S., that administration of G-CSF and collection of PBSC from normal donors is ethically acceptable in donors above the age of 18.
2. The donor should be informed of the potential short-term and long-term risks of G-CSF therapy, of the risks of leukapheresis and of the risks of general anesthesia, and he should be given the possibility of choosing.
3. We do not believe it is ethically acceptable to place a venous catheter in the donor; if venous access does not allow leukapheresis, standard bone marrow donation is probably better.
4. Mobilization with G-CSF 5 μg/kg/day up to a maximum of 10 μg/kg/day should be performed for 5 consecutive days; the donor's total WBC should not rise above 50×10^9/L because of the danger of thrombosis.
5. Two leukaphereses, or at most three, should be performed on days +6, +7 (and +8). Thrombocytopenia has been reported after 3 leukaphereses (unpublished); the cells should be infused without further manipulation to the recipient on day +6 and +7. The optimal dose of $CD34^+$ve cells is uncertain but would appear to be above 5×10^6/kg of recipient body weight.
6. The recipient should receive standard conditioning (busulfan-cyclophosphamide or cyclophosphamide-TBI) and cyclosporin-A+methotrexate (MTX) for GVHD prophylaxis.
7. Donor and recipient should be followed carefully for short-term and long-term side effects.

Conclusions

Allotransplants with PBSC are not likely to overcome the many different problems of allo-

geneic marrow transplantation. This Committee strongly recommends the use of allogeneic PBSC in experienced centers, in well-defined clinical settings, possibly in patients with advanced disease, at least for the time being until the results of a large randomized european trial comparing blood and marrow are available for analysis.

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