Peripheral Blood Stem Cells: Transplantation and Beyond

ALBERT K.W. LIE, L. BIK TO

Division of Haematology, Hanson Centre for Cancer Research, Institute of Medical and Veterinary Science, Adelaide, Australia

Key Words. Stem cells · Peripheral blood progenitor cells · Transplantation · Chemotherapy · Hemopoietic growth factors · Apheresis

ABSTRACT

Peripheral blood stem cells are rapidly becoming a major source of hemopoietic stem cells for transplantation in patients with various hematological and oncological conditions. Clinical results of peripheral blood stem cell transplantation (PBSCT) have shown benefits of earlier hemopoietic recovery, lower morbidity, and greater cost-effectiveness compared with conventional bone marrow transplant. Moreover, the relative ease of obtaining large amounts of stem cells has made multicycle transplantation a viable option in the treatment of malignancies, allowing further escalation of chemotherapy dose intensity. The extension of PBSCT into the use of allogeneic and cord blood cells so far has been met with encouraging results, and the latter holds promise to increasing donor availability to patients requiring transplantation. Developments in cytokine research and ex vivo manipulation of hemopoietic stem cells are enabling new approaches to anticancer treatment involving tumor purging, immunomodulation, ex vivo expansion of stem cells and gene therapy. PBSCT may also become a therapeutic option in certain nonmalignant diseases. This review will discuss the current clinical practice and future developments in PBSCT.

The Oncologist 1997;2:40-49

INTRODUCTION

Hemopoietic progenitor cells circulate in low number during steady-state hemopoiesis but do not seem to serve any particularly useful purpose outside the bone marrow milieu. However, it was demonstrated that such circulating progenitor cells could be administered to rescue irradiated mice with marrow failure [1]. Even then, it was only natural to use bone marrow as a source of stem cells in the clinical setting because there are more progenitor cells, and presumably stem cells, in 200 ml of marrow than in the 5 liters of circulating blood in a human [2, 3]. Not surprisingly, early attempts at peripheral blood stem cell transplant (PBSCT) using steady-state peripheral blood in humans had met with discouraging results due to the lower number of progenitor cells infused [4, 5].

The important breakthrough was the discovery that the number of circulating progenitor cells dramatically increased under various conditions, especially during the recovery from cytopenic phase following chemotherapy [6-9]. This process of mobilization of progenitor cells into circulation made PBSCT more feasible. However, doubts remained as to the self-renewing quality of such cells [10]. Laboratory and clinical data have since provided evidence that primitive progenitor cells were indeed harvested from peripheral blood, and durable hematopoietic reconstitution after PBSCT has been reported. [11-13].

In recent years, there has been an increase in PBSCT performed for malignant conditions, both hematological and solid tumors. The number of PBSCTs has rapidly surpassed the number of bone marrow transplants (BMTs) performed in the autologous setting and PBSCT is also increasingly applied in the allogeneic setting [14]. The main interest in PBSCT is in its increased safety.

Early hemopoietic reconstitution with enhanced granulocyte and platelet recovery reduces the risks of infection and hemorrhage. This is reflected in shortened hospital stay, less use of antibiotics, and lower transfusion requirements, especially with platelet concentrates in PBSCT as compared with BMT [15-17]. A wider margin of safety also allows exploration of higher doses of chemotherapy, especially in solid tumors, which in the past was partly limited by hematological toxicity. Accumulating data also suggest
an earlier reconstitution of the immune system with PBSCT which may translate into lower risk of late post-transplant infection [18-20].

As with autologous PBSCT, early data on the use of allogeneic sources of blood stem cells, including cord blood, for transplantation are providing encouraging results. Together with technology to process the collected cells ex vivo, PBSCT is offering new therapeutic options for malignant as well as nonmalignant diseases. The current clinical practice and future developments of PBSCT are reviewed in this article.

**PBSC Mobilization**

The higher number of progenitor cells in mobilized compared with steady-state peripheral blood enables sufficient cell harvest with fewer apheresis sessions. Furthermore, the benefits of enhanced hemopoietic recovery in PBSCT are only seen using mobilized but not steady-state collection [21, 22]. Clinically, mobilization regimes consist of chemotherapy or hemopoietic growth factors (HGFs) or both.

**Myelosuppressive Chemotherapy Alone**

During recovery from the cytopenic phase after myelosuppressive chemotherapy, there is a 50-fold or more increase of granulocyte-macrophage colony-forming units (CFU-GM) in peripheral blood [12, 23, 24]. This phenomenon was the first employed clinically to collect mobilized PBSCs. Various chemotherapeutic agents have been used either singly or in combination to achieve an adequate harvest. Cyclophosphamide is the most common drug used as a single agent. The yield of stem cells has been shown to be dose-dependent on the chemotherapeutic regime [25-27].

Myelosuppressive chemotherapy mobilization has the additional effect of tumor bulk reduction before the PBSCT proper. The main drawbacks are neutropenic infection, severe thrombocytopenia, and organ-specific toxicity such as hemorrhagic cystitis [25, 26, 28]. The timing for haematological recovery, hence the apheresis schedule, is also much less predictable than mobilization regimes including HGF. With the introduction of various HGFs for clinical use, chemotherapy alone is rapidly falling out of favor as the method of choice.

**Myelosuppressive Chemotherapy Plus HGFs**

The use of HGFs, most commonly G-CSF or GM-CSF, following myelosuppressive chemotherapy has several advantages. The duration of cytopenia is shortened, reducing the associated risks and hospital stay [15, 29]. Scheduling of apheresis is also more predictable. Furthermore, both G-CSF and GM-CSF enhance PBSC yield following chemotherapy mobilization [16, 30, 31]. This suggests that adequate mobilization may be attained at a lower dose of chemotherapy with a further reduction of toxicity. Alternatively, fewer apheresis sessions will be required or a larger number of stem cells can be collected for repeated cycles of treatment.

The dose of G-CSF used in combination with chemotherapy is between 3 and 6 mg/kg/d. Schwartzberg reported the largest series of 382 patients where the addition of G-CSF doubled the mononuclear cell yield with a four- to sixfold rise in CD34+ cell yield compared with chemotherapy alone [29]. GM-CSF is usually administered at 5 mg/kg/d or 250 mg/m²/d following chemotherapy. Higher doses are rarely used because of associated side effects. Interleukin 3 (IL-3) [32] and the hybrid molecule of GM-CSF and IL-3, PIXY321 [33, 34], have also been used in conjunction with chemotherapy to enhance mobilization.

Most of the combination regimes commence HGF the day following chemotherapy. It is noteworthy that in a recent study where G-CSF was started from day 5 after chemotherapy, an adequate yield of CD34+ cells was obtained [35]. In another study, GM-CSF was started on either day 1 or 5 postchemotherapy with sufficient progenitor cell yield in either situation [36]. This highlights the optimal dosages and scheduling of combined chemotherapy, and HGF mobilization regimes are yet to be defined.

**HGF Alone**

Using HGF alone in mobilization has the obvious advantage of avoiding the cytotoxic side effects for the patient as well as on the collected PBSCs. It would also be a suitable method for harvesting PBSCs from normal healthy donors in the appropriate setting. The time of rise in PBSCs is very predictable, in particular with G-CSF. In general, side effects are few and easily controlled.

G-CSF is the HGF most commonly used alone for mobilization. There is a dose-dependent response with G-CSF mobilization up to 10-16 µg/kg/d, beyond which further enhancement is not seen. Circulating CFU-GM increase 40 to 80 times above the steady-state level after four to five days [16, 37]. Bone pain, myalgia, headache and a rise in serum alkaline phosphatase level are common side effects. Symptoms are usually mild, readily controlled with analgesics, and subside with termination of G-CSF administration. There is some concern about the possible long-term adverse effect of G-CSF on normal PBSC donors, such as its potential for inducing leukemia. A study on three normal donors who received short courses of G-CSF for mobilization with five years of follow-up did not reveal any hematological or cytogenetic abnormality [38]. Considering that bone marrow...
harvest in itself is not free from risk, HGF mobilization in normal donors is a reasonable and acceptable option.

GM-CSF used alone also increases circulating CFU-GM by a median of 18-fold in an earlier study [39]. A more recent report by Peters et al. [40] comparing the use of GM-CSF and G-CSF in mobilization suggested a lower overall efficacy with GM-CSF. IL-3 itself has little mobilizing activity [41], and PIXY321 gives a three- to sixfold increase in CFU-GM and CD34+ cells [42].

Stem cell factor (SCF) caused a 10- to 1,000-fold increase in CD34+ cells, CFU-GM and BFU-E in baboons [43]. Results in humans so far indicate that together with G-CSF, SCF enhances mobilization and, depending on the dose scheduling, the yield of CFU-GM was reported to be 70% to 250% higher than with G-CSF alone [44, 45].

In a murine study, Brasel reported an 83-fold increase of circulating CFU-GM with Flt3 ligand only, a 2,193-fold increase when given with G-CSF, but minimal synergism with GM-CSF [46]. Other agents which have been studied in human or animal studies include erythropoietin [47], macrophage inflammatory protein-1α [48], IL-1 [49] and IL-8 [50], but none of these are in current clinical use. A comparison of the results of the described mobilization regimes is provided in Table 1.

### Table 1. Comparison of mobilization regimes

<table>
<thead>
<tr>
<th>Regime used</th>
<th>Mobilization achieved with regime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myelosuppressive chemotherapy alone</td>
<td>50-fold or more increase in CFU-GM</td>
</tr>
<tr>
<td>Myelosuppressive chemotherapy plus G-CSF</td>
<td>Doubled mononuclear cell yield, four- to sixfold rise in CD34+ cells compared with chemotherapy alone</td>
</tr>
<tr>
<td>G-CSF alone</td>
<td>40-to 80-fold increase in circulating CFU-GM above the steady-state level</td>
</tr>
<tr>
<td>IL-3 alone</td>
<td>Has little mobilizing activity</td>
</tr>
<tr>
<td>PIXY321</td>
<td>Three- to sixfold increase in CFU-GM and CD34+ cells</td>
</tr>
<tr>
<td>SCF alone</td>
<td>10- to 1,000-fold increase in CD34+ cells, CFU-GM, and BFU-E</td>
</tr>
<tr>
<td>SCF plus G-CSF</td>
<td>70%-250% higher yield of CFU-GM than with G-CSF alone</td>
</tr>
<tr>
<td>Flt3 alone</td>
<td>83-fold increase in circulating CFU-GM</td>
</tr>
<tr>
<td>Flt3 plus G-CSF</td>
<td>2,193-fold increase in circulating CFU-GM</td>
</tr>
<tr>
<td>Flt3 plus GM-CSF</td>
<td>Minimal synergism</td>
</tr>
</tbody>
</table>

### PBSC Collection

PBSC collection is usually performed with a continuous-flow apheresis machine with acid-citrate-dextrose as anticoagulant. Heparin may be added, particularly when patients have high leucocyte counts. Problems common to all apheresis procedures, such as difficult vascular access, citrate toxicity and hypotension may arise. Hence, expertise in apheresis procedure is essential. In particular, thrombocytopenia may be a problem with repeated apheresis, especially when performed in the recovery phase of myelosuppression. Returning the platelet fraction of the harvest helps to alleviate this problem. Large-volume apheresis has been designed to maximize PBSC collection, achieving adequate yield in a single procedure, but patient tolerance and citrate toxicity may be a problem [51].

### Timing of Collection and Monitoring of Cell Yield

With chemotherapy mobilization, collection usually begins when leucocyte count rises above $1 \times 10^9/l$, especially when it is associated with a rapid rise in platelet count [52]. With combined chemotherapy and HGF regimes, most groups start when leucocyte count is between $2 - 5 \times 10^9/l$ [53] and others suggest commencing at a level above $10 \times 10^9/l$ [54]. Mobilization with G-CSF alone is usually harvested on days 5 to 7, and prolonging the schedule is of little advantage as the progenitor cell level falls despite continuation of G-CSF [16, 55].

Total mononuclear cell yield is one of the parameters used to monitor cell yield. An arbitrary level of $3 \times 10^8/kg$ body weight (BW) has been used as the target end point [56]. Currently, CD34+ cell enumeration by immunofluorescence flow cytometry is more commonly performed to determine when to commence apheresis and to monitor cell yield. A minimum level of $20 - 40 \times 10^6$ is often used as the trigger level for starting apheresis. CFU-GM is the most commonly performed assay to assess the proliferative capacity of the yield. However, it cannot be used clinically to adjust the apheresis schedule because of the 14-day culture period needed to obtain a result.

### Target and Thresholds

As the rate of hemopoietic reconstitution in PBSCT is correlated with the amount of progenitor cells infused, the target cell yield should be set at a point which ensures rapid and sustained engraftment [57-59]. A target set too low may result in slow engraftment and will thus compromise the desired benefits in safety and cost. Too high a target, on the other hand, would mean unnecessary patient discomfort with apheresis and extra cost in cell collection and storage. The target cell yield should, of course, be adjusted if multiple PBSCTs are contemplated.

There is a highly significant correlation between CFU-GM and CD34+ cells, and either assay may be used clinically. Earlier reports suggested a minimum threshold dose of $30 - 50 \times 10^6$ CFU-GM/kg BW [57]. More recent data, however, indicate that $15 - 20 \times 10^6$ CFU-GM/kg BW or $1 - 2 \times 10^6$ CD34+ cells/kg BW are acceptable minimum thresholds to enable
rapid hematopoietic recovery [58, 60]. In general, increasing the cell dose above the minimum threshold is associated with progressive improvement of recovery rate. However, above an upper threshold of $50 \times 10^6$ CFU-GM/kg BW or $5 - 8 \times 10^6$ CD34+ cells/kg BW, further enhancement of recovery does not seem to occur [61]. Indeed, an obligatory cytopenic phase of 7-10 days seems to be inevitable, even with large amounts of PBSC infusion or with post-PBSCT G-CSF administration [58, 59].

**Factors Affecting Cell Yield**

The PBSC yield is dependent upon the mobilization regimen administered. Higher dose of chemotherapy [25-27], addition of HGF to chemotherapy [16, 27, 30-34], and use of the appropriate combination of HGFs [32, 44, 45] enhance progenitor yield. With myelosuppressive chemotherapy mobilization, the severity of myelosuppression, reflected by platelet nadir and number of days with neutrophil count <0.5 x 10^9/l, as well as the rate of leucocyte recovery, are positive features of higher yield [26, 31, 52].

Patient factors affecting yield include extent of bone marrow involvement by disease and amount of chemotherapy received prior to mobilization [53]. The latter factor should be taken into consideration to determine the timing of PBSC collection in the design of treatment plans for various diseases. A study by Dreger et al. [62] illustrated the adverse effects on cell yield and engraftment due to prior chemotherapy insult on stem cells.

**Tumor Control**

The rapid hematological recovery with PBSCT allows higher doses of chemotherapy to be administered safely. Together with the relative ease of collecting large numbers of PBSCs, it is possible to further increase dose intensity by repeated high-dose therapy with PBSC support. The rationale for this strategy is to increase tumor kill according to Gompertzian kinetics and thereby improve tumor control and possibly cure rate.

Evidence in support is seen in a study by Bezwoda et al. [63]. Previously untreated patients with metastatic breast cancer were randomized to having either 6 to 8 courses of combination chemotherapy or double high-dose therapy with PBSC rescue. The latter group had significantly better response (53% versus 95%) and complete remission rates (4% versus 51%), as well as longer median duration of response (34 weeks versus 80 weeks) and of survival (45 weeks versus 90 weeks). Another study in myeloma patients with grade III disease by Durie-Salmon classification demonstrated significantly improved median survival in the group having high-dose therapy plus PBSC rescue than in the group receiving conventional combination chemotherapy [64].

The role of PBSCT for malignancies of earlier stages is yet to be defined. Basser et al. [65] reported the use of multiple cycles of PBSCT as adjuvant therapy for high-risk stage II and III breast cancer and demonstrated it to be feasible and safe. Long-term clinical outcomes comparing PBSCT with conventional chemotherapy will be awaited with great interest.

**Tumor Contamination**

Detection of tumor contamination in stem cell harvest is most often by immunological methods or molecular markers with sensitivity levels between $10^{-5}$ and $10^{-4}$. All these tests rely on the studied characteristics being present in tumor cells only. However, whether all cells expressing the markers are tumorogenic at all levels is a question which remains to be answered. The clonogenic assay reported by Ross et al. [66] to detect viable breast cancer cells perhaps sheds some light on this issue. Positive detection by the assay correlated with the immunocytochemical method.

Clinical studies in lymphoma and acute lymphoblastic leukemia indicate detectable residual tumor cells in harvested stem cells are associated with a higher risk of relapse [67, 68]. Gene marking studies in acute myeloid leukemia, neuroblastoma, and chronic myeloid leukemia also demonstrated the significance of tumor contamination, confirming that infused cells do contribute to relapse after autologous bone marrow transplant [69-71].

PBSCT is not spared from this problem. Studies in breast cancer, lung cancer, acute myeloblastic leukemia, lymphoma, and myeloma indicated presence of tumor cells in mobilized PBSC [66, 72-75]. Nevertheless, it is of interest to note that the degree of tumor contamination seems to be lower in PBSC than in bone-marrow harvest [76, 77]. Moreover, the timing of tumor cell mobilization may be different from that of stem cell mobilization [72, 78], in which case appropriate scheduling of apheresis may help to reduce contamination.

Ultimately, it would be ideal to be able to clear the harvest of all tumor cells. Various purging techniques, based on either negative or positive selection, take advantage of intrinsic differences between normal stem cells and tumor cells. It remains to be seen whether these differences are entirely reliable for making the separation, bearing in mind that tumor cells are known to be phenotypically heterogeneous.

**Cost-Effectiveness**

As mentioned earlier, PBSCT is associated with less use of antibiotics, a lower transfusion requirement, and a shorter hospital stay. One would naturally expect PBSCT to be more cost-effective than autologous BMT. Indeed, this is confirmed in a retrospective cost-effectiveness analysis.
study where PBSCT was 21% less costly (US $29,000 versus US $36,800) than autologous BMT [79]. In our center, PBSCT costs 35% less.

More interesting is to consider PBSCT as a first-line treatment. Hénon et al. [64] studied Durie-Salmon grade III myeloma patients receiving high-dose therapy plus PBSC rescue (group I, n = 12), conventional combination chemotherapy (group II, n = 10), or conventional chemotherapy (group III, n = 15). The total global cost was higher in group I than in group II (US $56,700 versus US $46,555), but because of significantly better median survival in group I, the absolute cost-effectiveness (corrected for survival) was lower for every week of life gained in group I than in group II (US $350/week versus US $1,862/week). When corrected for quality-of-life assessment, costs for group I were only US $74/week extra compared with group II in qualitative cost-effectiveness. Group III patients had a lower quality-of-life index but not survival than group I. Absolute cost-effectiveness and qualitative cost-effectiveness were US $125/week less and US $966/week less, respectively, in group III than in group I.

Clearly, the cost-effectiveness issue is complex and intertwined with survival and quality of life. There is a great need for more similar studies to assess the overall impact of new forms of therapy on patients and the health system.

**Future Developments**

**Allogeneic PBSCT**

Allogeneic PBSCT was initially attempted in cases of graft failure requiring second infusion of stem cells and for donors unsuitable for general anesthesia [80, 81]. Recently, allogeneic PBSCTs are being performed in greater number, and results of studies are appearing in the literature. G-CSF at a dose of 5-10 µg/kg/d for 4 to 5 days is most often employed [82-86]. A minimum threshold dose of 3 × 10^6 CD34+ cells/kg BW is in general associated with rapid engraftment. This target can often be reached with a single apheresis, which helps to improve acceptability by donors. Nevertheless, an occasional donor may fail mobilization, in which case marrow harvest is necessary.

From the European Group for Blood and Marrow Transplantation data on 59 patients, median times to neutrophil count >0.5 × 10^9/l and platelet count >20 × 10^9/l were 15 and 16 days, respectively [87]. A study by Schmitz et al. [83] suggested that the inclusion of methotrexate in graft-versus-host disease (GVHD) prophylaxis delayed engraftment compared with using cyclosporine alone.

Allogeneic PBSC harvest has a larger number of T cells than bone marrow (1-5 × 10^9/kg versus <0.5 × 10^9/kg). The initial concern was a greater risk of GVHD from the larger T cell yield. Nevertheless, several reports so far indicated that the incidence of severe GVHD was not increased and that the severity of GVHD did not correlate with the number of T cells infused [81, 82, 87, 88]. On the other hand, T cell depletion by CD34+ selection has been attempted to reduce the risk of GVHD.

As mentioned before, data suggested an earlier immune reconstitution with PBSCT compared with BMT [18-20, 89]. Whether this will be translated into clinical benefits of reduced post-transplant infection and, perhaps, improved graft-versus-leukemia effect and survival remains to be studied.

**Cord-Blood Transplant (CBT)**

High levels of stem and progenitor cells with high renewable and proliferative capacities are present in cord blood. This normal physiological state of cord blood provides a unique opportunity to collect PBSCs, which otherwise would be wasted, in quantity sufficient for transplantation.

The first CBT was reported in 1989 by Gluckman et al. in a child with Fanconí’s anemia using HLA-identical sibling cord blood [90]. Initial reports of HLA-matched and -mismatched sibling CBTs showed a lower incidence of GVHD, which seems to hold true for unrelated CBTs as well [91-93]. Incidence of primary graft failure was also low despite mismatch. Most CBTs have been performed in the pediatric population, but data on adults receiving unrelated CBTs are appearing, supporting the feasibility of this procedure in adults [94]. The full potential of CBT is yet to be explored, and interested readers are referred to an article by Broxmeyer [95].

**Ex Vivo Manipulation of PBSC**

Efforts to process blood or marrow cells in vitro with the aim of achieving therapeutic goals have been an ongoing quest. PBSC mobilization has provided a means of obtaining stem cells in large quantities with relative ease, compensating for the cell loss during these ex vivo manipulations. Areas of oncological interest are tumor purging, immunomodulation, expansion of hematopoietic cells, and gene therapy.

Attempts to kill or remove tumor cells include the use of chemicals, immunotoxins, and immunomagnetic separation, which rely on the expression of certain tumor markers [96-98]. The shortcomings of these methods are nonspecific toxicity to normal stem cells and possible nonexpression of the targeted marker by a subpopulation of tumor cells. CD34+ selection by the immunomagnetic method offers a nontoxic way of purging tumor cells that do not express the CD34 antigen. In a study by Schiller et al. [99] in advanced multiple myeloma, CD34+ selection gave a 2.7-4.5 log tumor depletion on PBSC harvest while maintaining the median time to both neutrophil and platelet recovery (>0.5 × 10^9/l and >20 × 10^9/l, respectively) at 12 days.
CD34+ selection has also been applied to allogeneic PBSCT in an attempt to reduce GVHD [100-102]. A two- to four-log depletion of T cells can be achieved. Early results from Bensinger et al. [101] and Link et al. [102] confirmed rapid engraftment and no primary graft failure. However, incidence of GVHD remained significant. Immunosuppression may also be possible to potentiate antitumor activity by utilizing the larger quantities of T and NK cells in a PBSC harvest [100].

The availability of various HGFs has made it possible to expand progenitor cells ex vivo [103]. With new cytokines being identified, the optimal combination of agents has yet to be defined. The practicality and safety of such an approach on cryopreserved PBSCs have been demonstrated clinically by Alcorn et al. [104]. Ex vivo expansion will be useful in situations of small initial harvest, multiple cycles of PBSCT and possibly abrogation of the obligatory cytopenic phase.

Gene therapy offers novel approaches to cancer therapy. One approach in a murine model was to insert the multiple drug-resistant gene (MDR-1) into hemopoietic cells to reduce chemotherapeutic toxicity and allow administration of higher doses of chemotherapy [105]. Tumor cell eradication may also be enhanced by genetic modification of chemosensitivity and immunomodulation [106, 107].

PBSCT and Non-Malignant Diseases

Enriched CD34+ cells are a suitable source of stem cells for carrying out gene therapy in certain nonmalignant conditions. Diseases of single-gene defects in hemopoietic cells, such as adenosine deaminase deficiency, chronic granulomatous disease, and Gaucher disease would be possible candidates.

PBSCT also holds promise for the treatment of paroxysmal nocturnal hemoglobinuria (PNH), multiple sclerosis, and other autoimmune diseases. In PNH, hemopoietic cells show impaired surface expression of phosphatidylinositol-linked proteins such as decay-accelerating factor (DAF) and membrane inhibitor of reactive lysis (CD59). Prince et al. [108] reported relative enrichment of DAF+ CD59+ cells in the CD34+ CD38- fraction of G-CSF- or GM-CSF-mobilized blood, suggesting a possible source of unaffected stem cells for autologous transplantation.

Multiple sclerosis is a disease which can lead to severe, intractable neurological disabilities. Therapy has included severe immunosuppression by total nodal irradiation, anti-lymophile globulin, and high-dose cyclophosphamide with some success. It has been suggested that complete lymphoid and myeloid ablation with subsequent recapitulation of immune ontogeny by marrow rescue may correct the autoimmune process [109]. Anecdotal reports also exist in the literature where autoimmune diseases such as psoriasis, ulcerative colitis, and rheumatoid arthritis went into long-term remission after BMT for coincidental hematological diseases [110, 111]. Indeed, for aplastic anemia, which has an autoimmune basis in etiology, high-dose immunosuppression with or without stem cell rescue is an established therapeutic approach.

CONCLUSION

PBSCT is a relatively safe and cost-effective form of treatment which enables further chemotherapy dose escalation in anticancer therapy. Mobilization is now most commonly using chemotherapy plus G-CSF or GM-CSF or, alternatively, with G-CSF alone. A minimum threshold of 15-20 × 10^6 CFU-GM/kg BW or 1-2 × 10^6 CD34+ cells/kg BW enables rapid hemopoietic reconstitution in autologous PBSCT. A higher threshold of 3 × 10^6 CD34+ cells/kg BW is recommended in the allogeneic setting. The timing of PBSCT collection should be taken into consideration in the overall treatment strategy to avoid excessive exposure to marrow toxic agents. Various tumor purging techniques are being studied to overcome the problem of tumor contamination in the harvest.

Together with developments in cytokine research, ex vivo processing, and gene therapy, PBSCT using autologous or allogeneic stem cells is offering new dimensions to the treatment of both malignant and nonmalignant diseases. Efforts to determine the mechanism of mobilization and to define the functional and proliferative capacities of different subpopulations of harvested cells may help to improve yield and engraftment kinetics. Standardization of stem cell measurement ensures the quality of infused product and enables proper comparison among studies. Finally, carefully designed clinical trials to compare PBSCT and present standard therapy are necessary to define the therapeutic role of PBSCT.

ACKNOWLEDGMENT

This article is adapted from a presentation given at the International Society of Hematology meeting held in Singapore, August 1996.

REFERENCES


7 Richman CM, Weiner RS, Yankee RA. Increase in circulating haemopoietic stem cells (CFU-C) into the peripheral blood of man by endotoxin. Exp Hematol 1977;5:186-190.


17 To LB, Roberts MM, Haylock DN et al. Comparison of haematological recovery times and supportive care requirements of autologous recovery phase peripheral blood stem cell transplants, autologous bone marrow transplants and allogeneic bone marrow transplants. Bone Marrow Transplant 1992;9:277-284.


46 Brasel K, McKenna HJ, Charrier K et al. Synergistic effects in vivo of flt3 ligand with GM-CSF or G-CSF in mobilization of colony forming cells in mice. Blood 1995;86(suppl 1):499a.


51 Hillyer CD. Large volume leukapheresis to maximize peripheral blood stem cell collection. J Hematother 1993;2:529-532.


71 Deisseroth AB, Zü Z, Claxton D et al. Genetic marking shows that Ph+ cells present in autologous transplants of chronic myelogenous leukemia (CML) contribute to relapse after autologous bone marrow in CML. Blood 1994;83:3068-3076.


89 Ottinger HD, Scheulen B, Beelen DW et al. Immune reconstitution after allogeneic peripheral blood progenitor cell transplantation. Bone Marrow Transplant 1996;17(suppl 2):S70.


104 Alcorn MJ, Holyoake TL, Richmond L et al. CD34-positive cells isolated from cryopreserved peripheral-blood progenitor cells can be expanded ex vivo and used for transplantation with little or no toxicity. J Clin Oncol 1996;14:1839-1847.


