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# Management strategies for the hard-to-mobilize patient

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GCSF+SCF有助於提升癌症化療期間CD34幹細胞

**Summary:**

**Delayed hematopoietic engraftment, particularly of platelets, is seen in 5–35% of patients undergoing high-dose chemotherapy with autologous stem cell transplantation. Studies indicate that delayed engraftment is related to low CD34$^+$ cell dose, and that risk factors for poor mobilization of CD34$^+$ cells relate primarily to the type and extent of prior therapy. Data indicating an appropriate strategy to ensure that 'hard-to-mobilize' patients will achieve adequate CD34$^+$ cell numbers are limited. It is clear, however, that marrow harvesting (performed frequently by a number of centers), is of limited value. Remobilization, best accomplished with a regimen of high-dose chemotherapy and cytokines, is of benefit in selected patients, but has substantial costs and morbidity. Instead of *ad hoc* treatment of patients who have a poor first mobilization, high-risk groups should be identified prospectively, and strategies should be developed to ensure adequate mobilization in *all* high-risk patients. The first randomized trial utilizing this approach has recently been reported. In this trial, stem cell mobilization with granulocyte colony-stimulating factor (G-CSF) alone was compared to mobilization with G-CSF combined with stem cell factor (SCF) in heavily pretreated patients with Hodgkin's and non-Hodgkin's lymphoma. The combination of G-CSF and SCF led to collection of a higher total CD34$^+$ cell dose compared to G-CSF alone. Further, more patients in the combination group were able to mobilize an optimal CD34$^+$ cell dose (ie $5 \times 10^6$/kg). Additional trials are needed to determine long-term outcomes and the economic impact of achieving optimal stem cell mobilization in these patients, who would otherwise not be candidates for high-dose chemotherapy.**

**Keywords:** stem cell mobilization; high-dose chemotherapy; stem cell transplantation

Autologous peripheral blood progenitor cell (PBPC) transplantation has become commonplace for a variety of malignant disorders including lymphoma, leukemia, and various solid tumors.[1] PBPC transplantation has replaced autologous bone marrow transplantation largely because of the more rapid hematopoietic recovery, with attendant decreases in hospital stay and costs. With adequate PBPC doses, neutrophil recovery will usually occur 9–10 days post-transplant, and platelet recovery will occur 10–11 days post-transplant. While neutrophil recovery is prompt in almost all patients regardless of disease or prior therapy, 5–35% of patients will experience delays in platelet engraftment after PBPC transplantation.[2–5]

Many studies have indicated that a high CD34$^+$ stem cell dose is correlated with prompt engraftment of platelets.[1–7] Several retrospective series document a minimum safe cell dose of 1 x $10^6$ CD34$^+$/kg, with further improvement in median time to platelet engraftment at doses $>1 \times 10^6$/kg.[5–9] Below this dose, there is up to an 80% incidence of delayed platelet engraftment and a significant risk of severe hemorrhage. The most significant correlation of CD34$^+$ cell dose to engraftment is the number of patients who do not engraft by day 28 post-transplant. It appears that the opti-mal CD34$^+$ cell dose for prompt platelet engraftment (ie engraftment in >85% of patients by day 14 post-transplant) is $5 \times 10^6$ CD34$^+$/kg.[5–9]

Taken together, three groups of patients can be described based on the ability to mobilize CD34$^+$ cells for PBPC transplantation:

(1) The non-mobilizable patient: a patient who, after repeated aphereses, does not reach the minimum cell dose of $1 \times 10^6$ CD34$^+$/kg.
(2) The hard-to-mobilize patient: a patient who, after repeated aphereses, does not reach the optimal cell dose of $5 \times 10^6$ CD34$^+$/kg.
(3) The easy-to-mobilize patient: a patient who mobilizes $>5 \times 10^6$ CD34$^+$/kg in three to five aphereses.

The risk factors associated with the inability to rapidly collect $5 \times 10^6$ CD34$^+$/kg have been studied by various groups. In general, the amount of myelosuppressive therapy (chemotherapy and radiation therapy) a patient receives prior to transplant is the most important factor associated with the number of CD34$^+$ cells collected.[2,3,9,10] Certain chemotherapeutic agents, such as melphalan, nitrosoureas, procarbazine, nitrogen mustard, and platinum compounds appear to be more toxic than other widely used agents. Univariate analyses have identified the following risk factors: type of malignancy (breast cancer, non-Hodgkin's lymphoma as compared to leukemia, Hodgkin's disease, and ovarian cancer); age >60; bone marrow involvement by tumor; prior radiotherapy to marrow-producing sites; and more than six courses of chemotherapy. In addition, CD34$^+$ cell dose appears to be related to the mobilization regimen (ie, cytokines alone *vs* cytokines following intensive myelosuppressive chemotherapy). Multivariate analy-

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ses also have demonstrated that the number of chemotherapy cycles (with or without prior radiotherapy) and prior use of specific alkylating agents such as BCNU are associated with poor $CD34^+$ mobilization.[2,3,9,10]

These risk groups have been defined through retrospective analyses, and there are little published data on strategies to manage patients who mobilize poorly. To date, strategies have focused on management of individual patients who did not mobilize well. Prospective trials provide little data regarding novel approaches to managing patient groups that consist primarily of hard-to-mobilize patients (ie patients with Hodgkin's disease, leukemia, ovarian cancer, etc). However, several recent prospective studies have identified strategies that increase (and, conversely, that do *not* increase) $CD34^+$ mobilization and collection. This paper reviews the detriments and benefits of the existing management strategies, which are: (1) bone marrow harvesting; (2) remobilization with the same or a more intensive regimen (cytokines plus chemotherapy for patients initially mobilized with cytokines alone, or higher dose chemotherapy for patients mobilized primarily with chemotherapy); (3) dose-escalation of available cytokines; and (4) combination of cytokines that include one acting primarily on the primitive stem cell pool.

## Bone marrow harvesting

Anecdotal evidence seems to suggest that bone marrow harvesting is of benefit in patients who mobilize poorly. Recent data, however, have shown that this approach has limited value. Watts *et al*[11] prospectively evaluated the efficacy of adding marrow cells to PBPC for patients who mobilize $<1 \times 10^6$ $CD34^+$/kg. This group comprised 51 of 324 patients (16%) undergoing PBPC transplants at their center. This group was further subdivided into patients mobilizing $<1 \times 10^5$ CFU-GM/kg – felt to be a minimally acceptable cell dose for proceeding to transplant – and patients mobilizing $>1 \times 10^5$ CFU-GM/kg. Of the 51 patients who had $<1 \times 10^6$ $CD34^+$/kg, 23 (45%) had $>1 \times 10^5$ CFU-GM/kg. These 23 patients were transplanted using PBPC only. Although neutrophil engraftment was rapid, 40% of these patients experienced delayed platelet engraftment. Six of 27 patients who mobilized $<1 \times 10^6$ $CD34^+$/kg and $<1 \times 10^5$ CFU-GM/kg were transplanted with PBPC alone. One-half (3/6) experienced neutrophil engraftment and five of six experienced delayed platelet engraftment. Twelve of 27 patients in this group ($<1 \times 10^6$ $CD34^+$/kg and $<1 \times 10^5$ CFU-GM/kg) received both PBPC and marrow cells from an autologous bone marrow harvest. Four of 10 evaluable patients experienced delayed neutrophil engraftment and six of 10 had delayed platelet engraftment. These data suggest that bone marrow harvests are of little value in patients who mobilize poorly, and confirms the extremely poor outcome for patients who mobilize $<1 \times 10^6$ $CD34^+$/kg and $<1 \times 10^5$ CFU-GM/kg. When fewer than $1 \times 10^6$ $CD34^+$ cells/kg are mobilized, a different mobilizing technique or deferral of the transplant should be considered.

## Remobilization

Several studies indicate that, in general, remobilization with the same regimen yields the same poor results, unless the initial mobilization occurred before complete hematopoietic recovery from prior chemotherapy.[12,13] For instance, if patients are mobilized with cytokines alone, mobilization should not occur until 4–5 weeks after chemotherapy has been completed. If mobilization is performed too early and the yield is poor, a second mobilization with the same regimen may be of value. Another strategy is to remobilize with escalated doses of G-CSF alone, which in our experience is effective in approximately one-third of patients; however, no confirmatory data demonstrating this approach have been published to date.

Lie *et al*[12] recently evaluated several remobilization strategies for individual patients who mobilized poorly. Using CFU-GM as the marker for stem cell yields, they demonstrated that, for patients initially mobilized with cyclophosphamide alone, the same chemotherapy dose yielded the same CFU-GM dose/kg for the first and second mobilizations (23.0 *vs* $15.4 \times 10^4$ CFU-GM/kg). However, a higher dose of cyclophosphamide for the second mobilization yielded significantly more CFU-GM/kg (14.8 *vs* $32.5 \times 10^4$/kg). Finally, for patients initially mobilized with GM-CSF plus IL-3, the use of cyclophosphamide and GM-CSF yielded both a higher CFU-GM dose/kg (18.3 *vs* $29.0 \times 10^4$/kg), and a significantly higher $CD34^+$ dose/kg (1.5 *vs* $4.1 \times 10^6$/kg). Taken together, these data suggest that an intensive chemotherapy with cytokine remobilization may yield increased stem cells for patients who mobilize poorly. Obviously, this benefit must be balanced against the resulting morbidity and costs.

## Mobilization with cytokines and chemotherapy

Data from a number of centers have suggested that chemotherapy and cytokines mobilize more stem cells than cytokines alone.[1,5,14] Several reports suggest that the intensity (measured as a total dose) of chemotherapy (eg, 7 g/m$^2$ *vs* 4 g/m$^2$ of cyclophosphamide or combination chemotherapy) is superior to single-agent chemotherapy with cytokines.[5,14] Data from centers using the combined modality approach that appear to include significant numbers of hard-to-mobilize patients suggest that there may be an advantage to chemotherapy plus cytokines. No comparative trials of various mobilization regimens have been performed, however, in groups consisting only of hard-to-mobilize patients.

## Dose-escalation of cytokines

Several studies have explored G-CSF dose in stem cell mobilization (Table 1). These studies demonstrate a $CD34^+$ dose response at doses of G-CSF ranging between 5 and 24 $\mu$g/kg.[15–17] For example, Grigg *et al*[17] demonstrated that the $CD34^+$ yield increased when G-CSF was used at 10 $\mu$g/kg *vs* 5 $\mu$g/kg or 3 $\mu$g/kg. The yield for those receiving 10 $\mu$g/kg was $4.6 \times 10^6$ $CD34^+$ cells/kg/apheresis *vs* 1.2 and $0.7 \times 10^6$ $CD34^+$ cells/kg for the 5 $\mu$g/kg and 3 $\mu$g/kg

**Table 1** $CD34^+$ apheresis yields ($\times 10^6$/kg) by G-CSF mobilizing dose

| *Ref.* | *G-CSF dose (μg/kg/day)* | | | |
|---|---|---|---|---|
| | *3* | *5* | *10* | *20–24* |
| Waller[15] | ND | ND | 2.0 | 4.6 |
| Zeller[16] | ND | ND | 4.1 | 9.2 |
| Grigg[17] | 0.7 | 1.2 | 4.6 | ND |

doses, respectively. Zeller *et al*, who explored a higher dose range, found that while 10 μg/kg yielded a similar $CD34^+$ dose/kg to that found by Grigg *et al* (ie $4.1 \times 10^6$ $CD34^+$/kg), escalating the dose to 24 μg/kg yielded $9.2 \times 10^6$ $CD34^+$ cells/kg. It should be noted, however, that all of the studies demonstrating a dose response to G-CSF were in either normal allogeneic stem cell transplant donors or in patients who would be considered easy to mobilize.

The Loyola Bone Marrow Transplant group recently conducted a phase II trial of high-dose G-CSF (32 μg/kg given in two divided doses) in 26 patients with advanced ovarian carcinoma[18] (Table 2). This patient group is known to have poor $CD34^+$ mobilization and slow platelet engraftment with standard doses of G-CSF.[8] Patients underwent apheresis starting on day 5 with the goal of collecting $4 \times 10^6$ $CD34^+$ cells/kg (all patients received a minimum of two aphereses, even if they achieved $4 \times 10^6$ $CD34^+$ cells/kg within one apheresis). These patients were compared retrospectively with 18 patients who were mobilized with 10 μg/kg of G-CSF. The groups were matched for median age, initial stage, response to initial chemotherapy, and the number of prior chemotherapy regimens. The results of this analysis are shown in Table 2. The number of aphereses required to collect the $4 \times 10^6$ $CD34^+$ cells/kg target was 1 *vs* 3.5 for the 32 and 10 μg/kg doses, respectively. Because both groups received identical $CD34^+$ cell doses ($4 \times 10^6$ cells/kg), neutrophil and platelet engraftment times following high-dose chemotherapy were similar for the two groups (median time to neutrophil engraftment was 13 and 11 days for the low- and high-dose groups, and time to platelet engraftment was 12 and 13.5 days, respectively).

**Table 2** $CD34^+$ mobilization with low- *vs* high-dose G-CSF in patients with advanced ovarian cancer[18]

| | *G-CSF dose (μg/kg/day)* | |
|---|---|---|
| | *10* | *32* |
| *n* | 18 | 26 |
| $CD34^+$/kg collected ($\times 10^6$) | | |
| 1st apheresis | 1.8 | 4.6 |
| 2nd apheresis | 1.1 | 2.3 |
| % patients collecting $4 \times 10^6$ $CD34^+$/kg | | |
| 1st apheresis | 11% | 55% |
| 2nd apheresis | 33% | 70% |
| % patients not reaching $2 \times 10^6$ $CD34^+$/kg in 3 collections | 17% | 4% |

However, none of the high-dose G-CSF patients had delayed platelet engraftment beyond day 35 post-transplant, compared to 22% of the low-dose patients ($P < 0.05$). Despite the higher cost associated with the intensive G-CSF mobilization schema, the total estimated costs for the two groups were similar (due to the cost of the additional aphereses and additional platelet and red cell transfusions required by the low-dose group).

It is interesting to examine the added costs (for cytokines and aphereses) of remobilizing the 22% of low-dose G-CSF patients who did not engraft platelets by day 35. If remobilized with high-dose G-CSF, the average cost per patient for those initially mobilized with 10 μg/kg would be $1300 more than the average cost per patient for those initially mobilized with 32 μg/kg. This suggests that optimal management of hard-to-mobilize patients is to target large patient groups at risk for poor mobilization and not individual patients, due to the significant costs of remobilization.

## Cytokine combinations

The goal of using a cytokine that primarily acts on the primitive stem cell pool (ie 'early-acting') in combination with a more lineage-specific cytokine (ie 'late-acting') is to increase the number of pluripotent stem cells mobilized into the peripheral blood. To date, the combination of G-CSF and SCF has been the most extensively studied.[7,10] The combination has mobilized more stem cells than either agent alone in both murine and non-human primate models.[19–21] In these models, the number of total cells needed to successfully reconstitute hematopoiesis after lethal injury was significantly reduced for the cells mobilized by the combination. Phase I/II data using a fixed dose of G-CSF (10 μg/kg) and escalating doses of SCF (5–20 μg/kg) showed a direct correlation between total $CD34^+$ cells mobilized and SCF dose in easy-to-mobilize breast cancer patients.[7] A similar trial in lymphoma patients did not show such a dose response;[10] however, there were a significant number of heavily pre-treated patients included in this trial. When results were examined based on extent of prior treatment, the combination was found to provide an advantage for both easy- and hard-to-mobilize patient groups (Table 3). These findings were not statistically significant due to the small number of patients treated. Additionally, a more rapid (although not statistically significant) engraftment of platelets was seen for the lymphoma patients mobilized with the combination *vs* those who were mobilized with G-CSF alone (13 *vs* 21 days, respectively).

A subsequent randomized phase II trial has recently been completed in patients with non-Hodgkin's lymphoma and Hodgkin's disease who were prospectively defined as hard-to-mobilize, based on prior chemotherapy and radiation therapy.[22] This trial was presented in preliminary form at the 1997 meeting of the American Society of Hematology. Heavy prior therapy was defined as two or more cycles of procarbazine, nitrosoureas, nitrogen mustard, and melphalan; ⩾7 g of high-dose Ara-C; ⩾10 cycles of chemotherapy; or radiation to the mediastinum, abdomen, or pelvis. Patients ($n = 102$) were randomized to mobilization

**Table 3** Phase I/II trial of SCF + G-CSF to mobilize stem cells in non-Hodgkin's lymphoma patients: time to engraftment[10]

| | *G-CSF* | *SCF + G-CSF* |
|---|---|---|
| *No heavy prior therapy* | | |
| *n* | 5 | 7 |
| Days to ANC >500 (median) | 9 | 10 |
| Days to platelets >20 000 (median) | 12 | 10 |
| *Heavy prior therapy* | | |
| *n* | 5 | 18 |
| Days to ANC >500 (median) | 14 | 11 |
| Days to platelets >20 000 (median) | 23 | 12.5 |

with G-CSF (10 $\mu$g/kg/day) or the combination of G-CSF (10 $\mu$g/kg/day) and SCF (20 $\mu$g/kg/day). Apheresis began on day 5 with the goal of collecting the optimal dose of $5 \times 10^6$ CD34$^+$/kg (Table 4). The total CD34$^+$ collection for the combination group was significantly higher than for the G-CSF alone group (3.6 *vs* $2.7 \times 10^6$/kg, respectively). In addition, 44% of the patients in the combination group reached the target dose of $5 \times 10^6$ CD34$^+$/kg compared with 17% in the G-CSF alone group. Most importantly, 26% of the patients in the G-CSF alone group did not reach the minimum dose of $1 \times 10^6$ CD34$^+$/kg compared with 15% in the group mobilized with combination SCF + G-CSF. Engraftment times were identical in the two groups; however, patients not reaching the minimum CD34$^+$ cell dose of $1 \times 10^6$/kg (most likely to occur in those mobilized with G-CSF alone as noted above) were removed from the study.

The results of this trial indicate that mobilization with the combination of SCF and G-CSF is a successful strategy, not only for patients who are easy to mobilize, but also for those who are hard to mobilize – such as heavily pre-treated patients with lymphoma and Hodgkin's disease.

## Conclusion

In summary, published data suggest that rapid engraftment of both neutrophils and platelets is correlated with a CD34$^+$ cell dose of $\geqslant 5 \times 10^6$/kg. Researchers currently are identifying patients who fail to consistently reach this cell dose. Strategies to improve stem cell collection should be aimed at these groups rather than at individual patients who mobilize poorly. Options, such as the use of cytokines plus chemotherapy or high-dose G-CSF are promising, but need to be subjected to randomized trials to determine their true value in hard-to-mobilize patients. The results of a recently completed randomized trial show that the combination of SCF + G-CSF appears to be superior to G-CSF alone for mobilizing heavily pre-treated patients with lymphoma and Hodgkin's disease. This study represents the first successful strategy to increase the safety of transplants performed in the hard-to-mobilize patient.

**Table 4** Randomized phase II trial of G-CSF *vs* G-CSF + SCF in heavily pre-treated patients with non-Hodgkin's lymphoma and Hodgkin's disease: percent reaching $5 \times 10^6$ CD34$^+$/kg after five aphereses[22]

| *Mobilization regimen* | *n* | *% reaching $5 \times 10^6$ CD34$^+$/kg* |
|---|---|---|
| G-CSF | 54 | 17 |
| G-CSF + SCF | 48 | 44* |

*$P = 0.002$.

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