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LETTER TO THE EDITOR

Mobilization and harvesting of PBPC in newly diagnosed type 1 diabetes mellitus

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Autologous hematopoietic stem cell (HSC) transplantation is an established treatment for hematological malignancies, and recently has been employed to treat severe chronic autoimmune diseases (CAID),[1] including newly diagnosed type 1 diabetes mellitus (T1DM).[2] The objective of this modality of treatment in autoimmune diseases is the elimination of autoreactive clones of T cells to allow the regeneration of a 'new' immune system from the HSC infused. At diagnosis most of β-cell mass has been destroyed. However, blocking autoimmune aggression could spare the remaining β-cells and confer a clinical remission.[2]

Mobilization and harvesting of HSC from PBSC is an essential part of autologous transplantation, but the optimal strategy for it remains unclear. Usually, HSC mobilization includes administration of G-CSF, alone or in combination with chemotherapy,[3] to harvest a minimum of 2.0×10^6 $CD34^+$ cells/kg for rapid engraftment after a myeloablative conditioning regimen. Nevertheless, it is estimated that 2–40% of patients fail to achieve the minimal cellular dose for transplant.[4]

This retrospective study has the purpose to unveil the characteristics of HSC mobilization in patients with T1DM. We reviewed the records of 25 patients with T1DM enrolled at our institution. All the patients were within 6 weeks from diagnosis, when they were submitted to mobilization and harvesting of HSC. Our hypothesis is that these patients are 'good mobilizers' as they were not previously exposed to drugs toxic to HSC or BM stroma.

$CD34^+$ cells were mobilized with CY (2 g/m^2) associated with G-CSF (median 9.4 μg/kg/day; range 4.9–12.5 μg/kg/day), initiated the day after the CY administration and continued daily until cell collection, and harvested through peripheral access from all the patients. Harvesting was initiated when the $CD34^+$ cell count reached a minimum of 10/μL in peripheral blood. Aphereses were performed using the continuous-flow blood cell separator COBE Spectra (Caridian BCT, Lakewood, CO, USA). The results were shown as median and range. To compare eventual differences Mann–Whitney test (significance set at $P<0.05$) was used. This study was approved by the local and National Research Ethics Committee.

Median age of the patients was 17 years (13–31). Eighteen (72%) of them were male (Table 1). Median $CD34^+$ cell concentration in peripheral blood was 80.9 (36.5–167.6)/μL on the day of apheresis, however, in males and females the $CD34^+$ cell concentrations were 88.3 (36.5–167.6)/μL and 66.8 (38.2–83.1)/μL, respectively ($P=0.1088$). All patients attained the target cell dose after a single apheresis session. The median $CD34^+$ cell number collected was 9.1 (5.0–22.5) $\times 10^6$/kg. Male patients had a marginally superior $CD34^+$ cell collection: 10.9 (5.0–22.5) $\times 10^6$/kg vs 7.9×10^6/kg (5.2–9.60) for female patients ($P=0.0566$), despite the similar total blood volumes processed (3 in female vs 2.5 in male patients; $P=0.1573$). The processed total blood volume was 2.6mL (2.2–3.4) in 215 (152–280) minutes. $CD34^+$ cell harvest was performed on day 8 (7–9) (Table 1). A total of seven patients (28%) presented adverse reactions that could be attributed to the mobilization regimen, such as headache, myalgia and malaise. One patient had febrile neutropenia. Eight patients (32%) had adverse reactions related to the apheresis procedure, especially due to citrate toxicity (Table 2). In two patients insulin could be discontinued during the conditioning regimen. No patients died before engraftment. Neutrophil engraftment occurred on day 11 (9–13) in both female and male patients.

HSC mobilization characteristics in patients with CAID are relatively well established.[5,6] The same cannot be asserted for patients with T1DM. Herein, we found that all 25 patients with T1DM had an efficient $CD34^+$ cell mobilization with CY and G-CSF, demonstrated by the high concentration and the early peak of $CD34^+$ cells in the peripheral blood. These phenomena are commonly observed in 'good mobilizers', and suggest that HSC and the BM microenvironment in T1DM patients are not damaged. According to Stiff,[7] patients can be stratified into three categories regarding mobilization efficiency: (A) easily mobilizable ($>5 \times 10^6$/kg), (B) difficult to mobilize ($1–5 \times 10^6$/kg) and (C) non-mobilizable ($<1 \times 10^6$/kg) after repeated apheresis attempts. The patients in this study can be considered easily mobilizable as all of them had a $CD34^+$ cell collection superior to 5×10^6/kg with a single apheresis. Mobilization characteristics are influenced by the strategies employed, patients' diagnoses and type of previous treatment.[8] Approximately 10% of patients with CAID failed to mobilize HSC.[6] Patients with systemic lupus erythematosus achieved the lowest $CD34^+$ number in peripheral blood and the lowest cell yield, whereas patients with multiple sclerosis or scleroderma achieved the highest. Furthermore, Statkute *et al*,[5] had to perform a mean of 1.8 apheresis sessions per patient with CAID (2.5 for those with lupus). Overall, patients with T1DM needed approximately half the apheresis sessions relative to patients with other autoimmune diseases, possibly because T1DM patients were 'healthier' than patients with CAID. The good mobilization observed resulted in an adequate neutrophil engraftment (on day 11).

Table 1 Patients' characteristics ($n = 25$)

Characteristics	*Median (range)*[a]
Age (years)	17 (13–31)
Gender (male)	18 (72%)
Number of apheresis procedures per patient	01
Day of cell harvest	8 (7–9)
Blood volume processed[b]	2.6 (2.2–3.4)
$CD34^+$ cells/μL at the morning of harvest	80.9 (36.5–167.6)
Total $CD34^+$ ($\times 10^6$/kg)	9.1 (5.0–22.5)

[a]Except for gender and number of apheresis procedures.
[b]Which corresponded to a median of 11 767 (7857–15 138) mL.

Table 2 Toxicity of mobilization and harvest ($n = 25$)[a]

Mobilization patients	
Headache	5 (20%)
Myalgia	5 (20%)
Malaise	3 (12%)
Fever[b]	2 (8%)
Harvest (apheresis)	
Paresthesia	5 (20%)
Chills	4 (16%)
Cold	2 (8%)
Venous access	1 (4%)

[a]A total of seven (28%) patients presented adverse reactions attributed to mobilization regimen, and eight (32%) had adverse reactions related to apheresis procedure.
[b]One patient had febrile neutropenia.

Only one patient presented a significant complication (febrile neutropenia) during mobilization. Approximately 30% (8/25) of the patients had a mild adverse effects that could be attributed to mobilization regimen or citrate toxicity (bone pain and paresthesia), which is lower than expected.[9] Possible explanations for this finding could be the younger age of our patients, and the fact that ~70% of them were of male gender, supposedly less prone to present some side effects[10] related to mobilization with G-CSF.

In conclusion, patients with T1DM mobilize HSC efficiently with CY and G-CSF. Toxicity associated with mobilization and cell harvest occurred in a minority of patients. These findings suggest that patients with T1DM could be safely submitted to HSC mobilization and harvest.

Conflict of interest

The authors declare no conflict of interest.

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