

Table 1
Clinical and Disease Characteristics at Diagnosis of 5 AML Patients With Imminent Mobilization Failure

| Parameters | n=5 |
|--|---|
| Age, median, y (range) | 59 (23–69) |
| Males:females | 2:3 |
| Laboratory values, median (range) | |
| Hb, g/L | 88 (63–107) |
| WBC, G/L | 4.84 (1.3–26.3) |
| Peripheral blasts, % | 15 (1–68) |
| Marrow blasts, % | 80 (30–90) |
| Platelets, G/L | 85 (26–138) |
| LDH, IU/L | 712 (440–1512) |
| FAB classification | |
| M1 | 1 |
| M2 | 2 |
| M4 | 2 |
| Cytogenetics | |
| Normal karyotype | 5 |
| Mutation profiles | |
| Mutated <i>NPM1</i> only | 1 |
| Mutated <i>NPM1</i> , <i>IDH1</i> | 1 |
| Mutated <i>NPM1</i> , <i>FLT3</i> -ITD low | 1 |
| Mutated <i>NPM1</i> , <i>FLT3</i> -ITD high | 1 |
| Biallelic mutations of <i>CEBPA</i> | 1 |
| MRD diagnostics | <i>Technique/sensitivity at follow-up</i> |
| Mutated <i>NPM1</i> , subtype A | Real-time PCR (10^{-4} to 10^{-6}) |
| Mutated <i>IDH1</i> | NGS (~1%) |
| Mutated <i>CEBPA</i> | NGS (~1%) |
| Mutated <i>FLT3</i> -ITD | Fragment analysis (5%) |
| ELN risk group (2017) | |
| Favorable | 4 |
| Intermediate | 1 |
| WHO subtypes (2016) | |
| AML with mutated <i>NPM1</i> | 4 |
| AML with biallelic mutations of <i>CEBPA</i> | 1 |

AML = acute myeloid leukemia, ELN = European Leukemia Net, FAB = French-American-British, Hb = hemoglobin, LDH = lactate dehydrogenase, MRD = minimal residual disease, NGS = next-generation sequencing, PCR = polymerase chain reaction, WBC = white blood cells.

The collection procedure in 3 patients was accomplished in a single day following plerixafor administration, whereas 2 patients needed 2 consecutive apheresis days with plerixafor given only at the first day. The median number of circulating peripheral CD34⁺ cells at the first day of PBSC collection was 3.8 cells/mL (range 1.6–6.0) before plerixafor, and it was 24.9 cells/mL 4 hours after plerixafor administration. The median harvest of collected CD34⁺ PBSC was 4.05×10^6 /kg (2.05–6.29), respectively (Table 2).

All patients undergoing HDCT before ASCT received full-dosed busulfan 4 mg/kg per day p.o. (days –6 to –3) and cyclophosphamide 60 mg/kg per day i.v. (days –2/–1), with PBSC reinfusion at day 0. A median of 2.94×10^6 /kg b.w. CD34⁺ PBSC was transfused (2.06 – 4.30×10^6 /kg). Patients received a median of 3 red blood cell transfusions and 4 platelet transfusions. Neutrophils recovered >0.5 G/L after a median of 12 days (11–13 days), and the median time until platelets increased >20 G/L was 45 days (14–106 days). All patients ultimately achieved complete hematologic recovery. The median hospitalization duration was 24 days (21–36 days). After a median follow-up of 14 months (9–17 months), all patients were alive in ongoing CR1.

Whereas available data suggest that ASCT with PBSC can be recommended to distinct subgroups of AML patients, there

Table 2
Mobilization of Peripheral CD34⁺ Cells and Stem Cell Collection in Acute Myeloid Leukemia Patients With Rescue Plerixafor Administration, Engraftment, Hospitalization, and Outcome

| | |
|---|------------------|
| Mobilization and apheresis, n | 5 |
| Apheresis procedures, total number, n | 7 |
| Single day of apheresis, n (%) | 3 (60) |
| Two days of apheresis, n (%) | 2 (40) |
| Laboratory values, median (range) | |
| WBC, at 1st day of apheresis, G/L | 35.4 (12.1–63.6) |
| CD34 ⁺ cells, $\times 10^6$ /L | |
| in PB before plerixafor administration | 3.8 (1.6–6.0) |
| in PB after plerixafor administration | 24.9 (3.0–46.8) |
| Collected CD34 ⁺ cells/kg | 4.05 (2.05–6.29) |
| Vitality of CD34 ⁺ cells, % | 99 (97–99) |
| Transfused CD34 ⁺ cells/kg | 2.94 (2.06–4.30) |
| Engraftment, median (range) | |
| Red cells transfusions, n | 3 (2–7) |
| Platelet transfusions, n | 4 (1–8) |
| Neutrophil recovery (>0.5 G/L), d | 12 (11–13) |
| Platelet recovery (>20 G/L), d | 45 (14–106) |
| Hospitalization, d, median (range) | 24 (21–36) |
| Outcome | |
| Follow-up, mo, median (range) | 14 (9–17) |
| Complete remission at last follow-up | 5/5 |
| Relapse during follow-up | 0/5 |

PB = peripheral blood, WBC = white blood cells.

is little information on the mobilization failure rate and on rescue strategies for AML patients with a failed attempt of autologous PBSC collection.^{12,13} In AML patients, chemosensitivity of colony-forming units of granulocytes and monocytes derived from BM cells were described to correlate inversely with the peripheral maximum CD34⁺ cells peak during SC mobilization.¹⁴

Plerixafor, a small-molecule inhibitor of the CXCR4 chemokine receptor, has been approved in combination with G-CSF for PBSC mobilization for lymphoma and myeloma patients.¹⁰ However, plerixafor is so far not recommended for PBSC mobilization in AML patients due to the risk of mobilization of leukemic cells and potential autograft contamination. We report in this single-center study for the first time the safe and successful second-line mobilization of PBSC with plerixafor in AML patients who failed conventional mobilization with G-CSF after the second induction. Despite its limitations, our study suggests that the rescue administration of plerixafor induced significant additional mobilization of CD34⁺ cells from the BM to the peripheral blood, thereby allowing collecting sufficient CD34⁺ cells in all 5 patients. In fact, the median number of circulating peripheral CD34⁺ cells stimulated by G-CSF increased from 3.8 to 24.9×10^6 /L before and after plerixafor infusion. Consequently, plerixafor administration enabled these patients to proceed to subsequent consolidation with HDCT followed by ASCT.

Due to the potential of plerixafor for comobilization of leukemia stem cells,⁸ only MRD-negative patients combining different molecular techniques (Table 1) were selected for plerixafor application in this study, and MRD was excluded in the autografts. Acknowledging these strict conditions, all patients in this study maintained CR1 after a median follow-up of 14 months. Importantly, our data are limited to AML patients with MRD-negative CR1 in the BM and in the autografts as candidates for plerixafor administration after

mobilization failure with G-CSF. Molecular MRD techniques should be comprehensive, including real-time PCR in the case of appropriate mutations, fragment analysis, and, increasingly, NGS.

Hematologic recovery after ASCT using plerixafor and G-CSF stimulation for collection of CD34⁺ PBSC is of obvious interest. Neutrophil recovery >0.5 G/L after ASCT occurred after a median of 12 days, and, thus, was identical as in a previous large study in AML patients receiving G-CSF only.¹² Platelet recovery >20 G/L seemed prolonged in plerixafor mobilized AML patients, with a median of 45 days versus 16 days in G-CSF-only mobilized patients in our previous series.¹² Possibly, this delayed platelet recovery in plerixafor mobilized AML patients reflects the background of primary mobilization failure and a poor stem cell pool in these particular patients.

In conclusion, rescue mobilization of PBSC with plerixafor was highly effective and safe in our small series of AML patients with primary mobilization failure. However, others have reported the development of secondary myelodysplastic syndromes or AML following rescue mobilization by plerixafor and subsequent HDCT/ASCT in 5 out of 43 patients with lymphomas or multiple myeloma after a median of 29 months after ASCT.¹⁵ Acknowledging the fact that these patients were heavily pretreated with 80% of them having received more than 2 prior chemotherapeutic regimens and with 20% having a history of previous radiotherapy, the question may arise whether plerixafor or rather the preceding intensive anticancer treatment truly contributed to the development of myeloid malignancies in these patients.¹⁵ Nevertheless, further studies should aim to better characterize the potential of plerixafor for reliable and safe PBSC mobilization combined with G-CSF in AML patients planned for ASCT.

Acknowledgments

The authors wish to thank the data management, the apheresis, the flow cytometry, and the stem cell laboratory teams of the ASCT program at the University Hospital of Bern and its associated partner hospitals and collaborators for documentation of data relevant for this study.

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