Original Article

Plerixafor stem cell mobilization in Japanese children: A post-marketing study

Hiroaki Goto, Rie Kanamori, Satoshi Nishina and Takashi Seto

1Division of Hematology/Oncology, Kanagawa Children’s Medical Center, Yokohama, 2Specialty Care, Oncology Medical, 3Medical Affairs, Post-Authorization Regulatory Studies, Sanofi K.K., Tokyo, Japan

Abstract  Background: Plerixafor is approved in Japan for hematopoietic stem cell mobilization prior to autologous transplant, but limited data are available on the use in children. This study evaluates the safety and effectiveness of plerixafor in Japanese children aged <15 years.

Methods: A multicenter, post-marketing surveillance study was conducted in Japan to evaluate the safety and effectiveness of plerixafor in routine clinical practice. This subgroup analysis examined the safety and effectiveness of plerixafor administered as a once-daily, subcutaneous injection in children aged <15 years. The primary effectiveness outcome was the proportion of patients with $2 \times 10^6$ cells CD34+ cells/kg collected via apheresis within 4 days.

Results: Eighteen patients with solid tumors were included in this analysis; (median age 6.0 years, range, 1–13 years). In addition to granulocyte colony-stimulating factor, all patients had received chemotherapy immediately prior to plerixafor administration. The mean (SD) daily dose of plerixafor was 0.24 (0.01) mg/kg. Seven of the 18 patients (38.9%) developed adverse drug reactions (ADRs), all occurring in patients aged ≥6 years and weighing ≥16 kg. The most common ADRs were pyrexia ($n = 4$), vomiting ($n = 3$), nausea ($n = 2$), and abdominal pain ($n = 2$). Twelve patients (66.7%) achieved a CD34+ cell count ≥$2 \times 10^6$ cells/kg within 4 days after the start of plerixafor administration.

Conclusions: The results provide an encouraging sign that plerixafor 0.24 mg/kg may be safe and effective in pediatric patients in routine clinical practice in Japan, but further research in larger studies is needed.

Key words  autologous stem cell transplantation, children, plerixafor, post-marketing surveillance, solid tumors.
proportion of patients who achieved target CD34+ cell levels in ≤4 days of apheresis when treated with plerixafor compared with G-CSF alone.18,19 Plerixafor has also received regulatory approval in Japan for HSC mobilization in combination with G-CSF on the basis of these studies18,19 and two phase II studies conducted in adult Japanese patients with NHL or MM.20,21 In the Japanese studies, substantially higher proportions of patients receiving plerixafor plus G-CSF achieved CD34+ cell target levels in ≤2–4 days of apheresis compared with patients receiving G-CSF alone.20,21

While the efficacy and safety of plerixafor is well established in adults, relatively limited data are available on the use of plerixafor for HSC mobilization in children, particularly Asian children. Direct extrapolation of adult data is not possible because of inherent differences between adult and pediatric populations, including different underlying malignancies requiring different chemotherapy and radiotherapy regimens.14 The international phase I/II MOZAIC study was conducted in children (1 to <18 years) with solid tumors, including neuroblastoma, sarcoma, medulloblastoma, or lymphoma, and found that plerixafor plus standard mobilization (G-CSF ± chemotherapy) significantly increased the proportion of patients achieving a doubling of the peripheral CD34+ cell count in the 24 h before first apheresis compared with standard mobilization alone.22 This study, which was conducted mainly in Europe, determined that the optimal pediatric dose of plerixafor is the same as that recommended for adults (0.24 mg/kg administered 8–12 h before apheresis),22 and led to approval of plerixafor for pediatric use in the EU.14 Plerixafor is already used in pediatric patients at 0.24 mg/kg according to the adult dose, but its safety and efficacy have not been fully tested.

In order to confirm the safety and effectiveness of plerixafor in Japanese patients, a post-marketing surveillance (PMS) study that included children was undertaken in Japanese patients who were undergoing A-PBSCT and received plerixafor for HSC mobilization.23 This report describes the safety and efficacy data for plerixafor in a subgroup of pediatric patients from a PMS study.

Methods

Design and patients

Details of the study design have been previously published.23 Briefly, this was an observational, multicenter, PMS study conducted in patients in Japan who received plerixafor for HSC mobilization prior to A-PBSCT. The surveillance period was between February 2017 and March 2019, with patient registration undertaken between February and December 2017.

In patients receiving G-CSF, plerixafor was administered subcutaneously at the recommended adult dose of 0.24 mg/kg (dosage calculated on actual body weight) once daily until the completion of PBSC collection with apheresis. Eligible patients were observed from the start of the plerixafor treatment until 30 days after the first dose, or the day prior to radiotherapy, or chemotherapy, whichever occurred first.

The study was conducted in accordance with Good Post-Marketing Study Practice requirements defined by the Japanese Ministry of Health, Labor and Welfare (Ministry of Health, Labour and Welfare, Ministerial Ordinance on Good Post-marketing Study Practice for Drugs. No. 171, December 20, 2004). Under these regulations, informed consent from individual patients was not required. The study protocol was reviewed and approved by the institutional review boards of each institution.

This subgroup analysis included patients aged <15 years old.

Data collection and assessments

Physicians recorded patient data on case report forms or using an electronic data capture system.

Baseline data were collected included disease characteristics, performance status, complications, prior treatments, concomitant medications, renal and hepatic function, white blood cell count, creatinine clearance, and CD34+ cell count in peripheral blood samples obtained before apheresis. The average plerixafor dose, the total number of plerixafor doses, and the number of days G-CSF was used were also recorded.

Adverse events (AEs), serious AEs, and adverse drug reactions (ADRs) were recorded and categorized by system organ class (SOC) and preferred term (PT) using MedDRA/J version 22.1 (Medical Dictionary for Regulatory Activities of Japanese Maintenance Organization [MedDRA/J], Tokyo, Japan). ADRs were AEs for which a causal relationship with plerixafor could not be ruled out. ADRs of special interest, including allergic and hypersensitivity reactions, leukocytosis, thrombocytopenia, interstitial lung disease, myocardial infarction, tumor cell mobilization, and splenomegaly/splenic rupture, were also evaluated. Vital signs and laboratory parameters were recorded.

The primary effectiveness outcome was the proportion of patients with a CD34+ cell count of 2 × 10⁶ cells/kg within 4 days of apheresis. The number of days of apheresis required to collect 2 × 10⁶ CD34+ cells/kg was also determined.

Statistical analysis

The safety analysis group comprised all pediatric patients who received plerixafor treatment and had no registration violations. The effectiveness analysis group included all pediatric patients in the safety analysis group who received plerixafor according to the approved dosage and administration schedule and had CD34+ data available.

Baseline demographics were summarized using descriptive statistics. Continuous variables were analyzed using mean ± SD, and median (range) and categorical variables were summarized using the number and proportion. The frequency of AEs was summarized descriptively overall and for each individual event (by SOC and PT).
All statistical analyses were conducted using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Patient disposition

Eighteen patients at 10 centers (6 boys and 12 girls) aged <15 years received plerixafor and all 18 patients were included in the safety and effectiveness analysis groups (Fig. 1). Seventeen patients were observed until the initiation of chemotherapy (n = 16; 88.9%) or 30 days after plerixafor administration (n = 1; 5.6%). One patient (5.6%) discontinued the study before the protocol-defined endpoint because they required closure of a cerebrospinal fluid leak caused by their primary disease.

Patients were aged between 1 and 13 years (median 6 years), including seven patients aged <6 years (median 3 years) and 11 patients aged 6 to <15 years (median 8 years; Table 1). The most common diagnosis was neuroblastoma (n = 8; 44.4%), followed by medulloblastoma (n = 5; 27.8%), Ewing sarcoma (n = 2; 11.1%), and germ cell tumor (n = 2; 11.1%). One patient (5.6%) had rhabdomyosarcoma. Most patients (n = 16; 88.9%) had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, but two patients (11.1%) had an ECOG performance status of 3. None of the patients had hepatic or renal dysfunction at baseline. White blood cell count was unknown in 17 of the 18 patients. Fifteen patients (83.3%) received a single injection of plerixafor and three patients (16.7%) received two injections. The mean ± SD plerixafor dose was 0.24 ± 0.01 mg/kg, in accordance with the prescribing information. Patients were treated with G-CSF for ≥4 days and all patients received chemotherapy before administration of plerixafor.

Safety

Seven of the 18 pediatric patients (38.9%) developed AEs, all of which were considered to be ADRs (Table 2) and all occurring in the subgroup of patients aged 6 to <15 years and weighing ≥16 kg. ADRs occurred in three patients with medulloblastoma, two patients with Ewing sarcoma, and two patients with a germ cell tumor. Two patients (11.1%) developed serious ADRs: hypoxia in one patient and nausea/vomiting in another. Both these events resolved without sequelae. The most common types of ADR in children by SOC were gastrointestinal ADRs (n = 4), general disorders and administration site conditions (n = 4). The most common ADRs by PT were pyrexia (n = 4; 22.2%), followed by vomiting (n = 3; 16.7%), nausea (n = 2; 11.1%), and abdominal pain (n = 2; 11.1%).

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Fig. 1 Flow chart of patient disposition.
11.1%). One patient each developed diarrhea, frequent bowel motions, oral hypoesthesia, abnormal hepatic function, back pain, hypoxia, and inflammation.

No ADRs of special interest were reported during the survey period.

**Effectiveness**

Overall, 12 of the 18 patients (66.7%) achieved a CD34+ cell count of \(2 \times 10^6\) cells/kg within 4 days of apheresis, including five of seven patients (71.4%) aged <6 years and weighing <16 kg, and seven of 11 patients (63.6%) aged 6 to <15 years and weighing \(\geq 16\) kg. The primary effectiveness endpoint was met in five of eight patients with neuroblastoma (62.5%), four of five patients with medulloblastoma (80.0%), one of the two patients with Ewing’s sarcoma (50.0%), one of the two germ cell tumor patients (50.0%), and in the one patient with rhabdomyosarcoma (100.0%).

In the 12 patients who met the primary effectiveness target, \(2 \times 10^6\) CD34+ cells/kg was reached after 1 day of apheresis in 10 patients and after 2 days of apheresis in two patients. The target was reached after 1 day of apheresis in all five of the responding patients aged <6 years and weighing <16 kg. In the seven responding patients aged 6 to <15 years and weighing \(\geq 16\) kg, the target was reached after 1 day of apheresis in five patients and after 2 days in two patients.

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**Table 1 Patient baseline demographic and clinical characteristics**

| Overall safety analysis group (n = 18) | Age <6 years (n = 7) | Age 6 to <15 years (n = 11) |
|--------------------------------------|---------------------|-----------------------------|
| Age, years, mean ± SD                | 6.5 ± 3.8           | 2.7 ± 1.1                   | 8.9 ± 2.7                   |
| Sex n (%)                            | Male 6 (33.3)       | 2 (28.6)                    | 4 (36.4)                    |
|                                      | Female 12 (66.7)    | 5 (71.4)                    | 7 (63.6)                    |
| Body weight (kg), mean ± SD          | 21.1 ± 9.2          | 13.4 ± 2.9                  | 26.0 ± 8.4                  |
| Diagnosis, n (%)                     | Neuroblastoma 8 (44.4) | 6 (85.7)                        | 2 (18.2)                       |
|                                      | Medulloblastoma 5 (27.8) | 0                              | 5 (45.5)                       |
|                                      | Ewing’s sarcoma 2 (11.1) | 0                              | 2 (18.2)                       |
|                                      | Germ cell tumor 2 (11.1) | 0                              | 2 (18.2)                       |
|                                      | Rhabdomyosarcoma 1 (5.6) | 1 (14.3)                       | 0                              |
| ECOG PS at study drug initiation, n (%) | 0 7 (38.9)                   | 2 (28.6)                        | 5 (45.5)                       |
|                                      | 1 9 (50.0)          | 5 (71.4)                     | 4 (36.4)                       |
|                                      | 2 0                  | 0                            | 0                              |
|                                      | 3 2 (11.1)          | 0                            | 2 (18.2)                       |
|                                      | 4 0                  | 0                            | 0                              |
| Chemotherapy prior to study drug administration, n (%) | 18 (100.0)         | 7 (100.0)                    | 11 (100.0)                    |
| Previous collection of hematopoietic stem cells, n (%) | No 7 (38.9)         | 2 (28.6)                     | 5 (45.5)                       |
|                                      | Yes 11 (61.1)       | 5 (71.4)                     | 6 (54.5)                       |
| Daily dose of plerixafor, (mg/kg), mean ± SD | 0.24 ± 0.01                  | 0.24 ± 0.01                  | 0.24 ± 0.01                  |
| Number of administrations of plerixafor, mean ± SD | 1.2 ± 0.4                   | 1.1 ± 0.4                     | 1.2 ± 0.4                     |
| Number of administrations of plerixafor, category, n (%) | 15 (83.3)          | 6 (85.7)                     | 9 (81.8)                       |
|                                      | 2 3 (16.7)          | 1 (14.3)                     | 2 (18.2)                       |
| Total number of days of G-CSF administration, category, n (%) | ≤3 0               | 0                            | 0                              |
|                                      | 4 6 (33.3)          | 3 (42.9)                     | 3 (27.3)                       |
|                                      | ≥5 12 (66.7)        | 4 (57.1)                     | 8 (72.7)                       |
| Number of days of administration of G-CSF prior to plerixafor administration, category, n (%) | 1–3 0               | 0                            | 0                              |
|                                      | 4 1 (5.6)           | 0                            | 1 (9.1)                        |
|                                      | 5 6 (33.3)          | 3 (42.9)                     | 3 (27.3)                       |
|                                      | ≥6 11 (61.1)        | 4 (57.1)                     | 7 (63.6)                       |
| CD34+ cell count prior to apheresis, cells/μL, category, n (%) | 0–<5 2 (11.1)        | 0                            | 2 (18.2)                       |
|                                      | 5–<10 1 (5.6)       | 1 (14.3)                     | 0                              |
|                                      | 10–<20 0            | 0                            | 0                              |
|                                      | ≥20 4 (22.2)        | 2 (28.6)                     | 2 (18.2)                       |
| Not implemented                      | 11 (61.1)          | 4 (57.1)                     | 7 (63.6)                       |

ECOG PS, Eastern Cooperative Oncology Group Performance Status; G-CSF, granulocyte stimulating factor; WBC, white blood cell.
Discussion

This subgroup analysis of a PMS study supports the safety and effectiveness of plerixafor 0.24 mg/kg for HSC mobilization in Japanese children with solid tumors who are scheduled to undergo A-PBSCT. This is the first study of plerixafor in a Japanese pediatric population.

The overall results from the study indicated that patients aged <15 years were more likely to experience ADRs compared with those aged ≥15 years (P = 0.0005).23 The reason for this is not clear; however, the rate of ADRs in patients aged <15 years in this study was similar to the procedure-related AE rate reported previously among children undergoing PBSC harvests using protocols that did not include plerixafor.24 It was also similar to the rate among Japanese adolescents and young adult patients aged 15 to 29 years (data not shown) in the wider population of the current PMS study. The chemotherapy for pediatric solid tumors prior to PBSC harvest is usually intensive, which probably contributes to the high rate of ADRs seen in this population. Our study had no control group, so it is impossible to determine which AEs resulted from plerixafor and which were caused by chemotherapy or other treatments.

In the phase I/II MOZAIC study in pediatric patients, treatment-emergent AEs occurred in 76.7% of 30 patients in the plerixafor treatment arm and 66.7% of 15 patients in the standard therapy arm.22 Compared with our study, in which 38.9% of the 18 pediatric patients receiving plerixafor developed ADRs, the MOZAIC study showed a low rate of treatment-related AEs with plerixafor (13.3%) and none with standard mobilization.22 This is somewhat unexpected because post-marketing analyses often report a lower rate of AEs than clinical trials do, since post-marketing research relies on the judgment of the attending physician, whereas clinical trials use protocol-defined AE assessment. Patient age may have contributed to the difference in ADR incidence between the current PMS study and the MOZAIC study. We found that ADRs occurred only in patients aged ≥6 years and weighing ≥16 kg, but the MOZAIC study included a higher proportion of plerixafor-treated patients aged <6 years (53.3%) than our PMS study, in which 38.9% of patients were aged <6 years and weighed <16 kg. All seven patients with ADRs in our study had tumor types that were not present in the subgroup of children aged <6 years (Ewing sarcoma, germ cell tumor, medulloblastoma), so the relatively high incidence of ADRs observed in older children may reflect different tumor types and treatment histories, including previous chemotherapy cycles or radiotherapy. However, another possible reason for the higher rate of ADRs in patients aged 6–15 years is that ADRs may be overlooked in infants and young children who are less able to communicate.

In a report of plerixafor use in six Korean children aged 6–15 years, Hong et al. described spontaneous pneumomediastinum at 11 and 56 days after plerixafor in two children (aged 10 and 11 years) with medulloblastoma, so the relatively high incidence of ADRs observed in older children may reflect different tumor types and treatment histories, including previous chemotherapy cycles or radiotherapy. However, another possible reason for the higher rate of ADRs in patients aged 6–15 years is that ADRs may be overlooked in infants and young children who are less able to communicate.

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Table 2 Summary of adverse drug reactions reported in children during the survey period

| Adverse drug reactions, n (%) | Overall safety analysis set (n = 18) | Age <6 years (n = 7) | Age 6 to <15 years (n = 11) |
|------------------------------|-------------------------------------|---------------------|-----------------------------|
| Any ADRs                     | 7 (38.9)                            | 0                   | 7 (63.6)                    |
| Any serious ADRs             | 2 (11.1)                            | 0                   | 2 (18.2)                    |
| ADRs occurring in at least one patient by PT |                                     |                     |                             |
| System organ class           |                                     |                     |                             |
| Preferred term               |                                     |                     |                             |
| General disorders and administration site conditions | 4 (22.2) | 0 | 4 (36.4) |
| Pyrexia                      | 4 (22.2)                            | 0                   | 4 (36.4)                    |
| Inflammation                 | 1 (5.6)                             | 0                   | 1 (9.1)                     |
| Gastrointestinal disorders   | 4 (22.2)                            | 0                   | 4 (36.4)                    |
| Vomiting                     | 3 (16.7)                            | 0                   | 3 (27.3)                    |
| Abdominal pain               | 2 (11.1)                            | 0                   | 2 (18.2)                    |
| Nausea                       | 2 (11.1)                            | 0                   | 2 (18.2)                    |
| Diarrhea                     | 1 (5.6)                             | 0                   | 1 (9.1)                     |
| Frequent bowel movements     | 1 (5.6)                             | 0                   | 1 (9.1)                     |
| Hypoesthesia oral            | 1 (5.6)                             | 0                   | 1 (9.1)                     |
| Respiratory, thoracic and mediastinal disorders | 1 (5.6) | 0 | 1 (9.1) |
| Hypoxia                      | 1 (5.6)                             | 0                   | 1 (9.1)                     |
| Hepatobiliary disorders      | 1 (5.6)                             | 0                   | 1 (9.1)                     |
| Hepatic function abnormal    | 1 (5.6)                             | 0                   | 1 (9.1)                     |
| Musculoskeletal and connective tissue disorders | 1 (5.6) | 0 | 1 (9.1) |
| Back pain                    | 1 (5.6)                             | 0                   | 1 (9.1)                     |

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findings consistent with diffuse alveolar damage. In contrast to these findings, serious ADRs occurring in two patients in our population (hypoxia and nausea/vomiting) resolved without sequelae. The ADRs observed in our study were considered consistent with the known safety profile of plerixafor in children.26,28 Other studies in pediatric patients who had inadequate circulating CD34+ cell levels for harvesting achieved the 2×10⁶ CD34+ cells/kg target on the day of harvesting, whereas 50% of patients with a CD34+ pre-count of <10 cells/µL met this target.37 In the study of 33 pediatric patients who failed to achieve successful pre-apheresis mobilization (defined as a CD34+ count of ≥20 cells/µL) after 4 days of G-CSF administration, 93.9% of patients successfully mobilized CD34+ cells after treatment with plerixafor, with 81.8% of patients meeting the CD34+ cell target of 2×10⁶ cells/kg after one apheresis procedure.26 These findings suggest that a peripheral blood CD34+ cell count threshold of <10–20 cells/µL could be used to identify poor pediatric mobilizers who would benefit from the addition of plerixafor to standard mobilization. This should be studied in larger groups of patients.

The low rate of serious ADRs in our study is consistent with the MOZAIIC study, in which all serious AEs were attributed to the effects of mobilizing chemotherapy22 as well as other studies describing real-world use of plerixafor in children.26–28 Case reports of plerixafor use in children have mostly reported no drug-related AEs.29–36 Teusink et al. reported no AEs (serious or otherwise) in 16 children with neuroblastoma, brain tumor, or relapsed malignancies aged 8 months to 15 years (median 6 years) who were receiving plerixafor,28 whereas Maschan et al. reported grade 1 or 2 AEs in eight of 33 (24.2%) children aged 1 to 18 years (median 9 years),26 and Sevilla et al. reported mild AEs in two of eight (25.0%) children aged 6–18 years (median 12.5 years).27 Although the latter two studies did not describe the age or underlying malignancies of the children with AEs,26, 27 the median age of the patients was older than that reported in the study by Teusink et al.,28 which may have contributed to the difference in AE rates between the studies. AEs reported in these studies included diarrhea, nausea, bone pain (possibly related to disease progression), pyrexia, and urticaria.26,27 Similarly, some of the most common ADRs in our study were gastrointestinal events (vomiting, nausea, abdominal pain, and diarrhea).

Consistent with the findings of studies in adult Japanese patients with MM or NHL,20,21 our study demonstrated that plerixafor is effective in achieving target CD34+ cell levels in Japanese children with solid tumors. Within 1 to 2 days of apheresis, almost 70% of our cohort of 18 pediatric patients achieved 2×10⁶ CD34+ cells/kg, which is the minimum recommended CD34+ cell level required for successful engraftment.1,2 Other studies in pediatric patients who had failed previous mobilization with G-CSF ± chemotherapy, or who had inadequate circulating CD34+ cell numbers to initiate apheresis, have demonstrated successful mobilization with plerixafor in ≥75% of patients.25–28 In the MOZAIIC study, significantly more children treated with plerixafor met the primary endpoint of doubling the CD34+ cell count in the 24 h before apheresis than those treated with standard mobilization alone, but high proportions of patients in both treatment arms reached ≥2×10⁶ CD34+ cells/kg within 1 to 2 days of apheresis (27/30 [94.4%] patients in the plerixafor arm and 15 of 15 [100.0%] patients in the standard treatment arm).22

Nakamura et al. have described their experience with pre-apheresis CD34+ cell count as a predictor of adequate G-CSF-induced mobilization for A-PBSCT in 42 Japanese children (≤17 years) with solid tumors.37 All the children with a peripheral blood CD34+ count of ≥10 cells/µL on the day before PBSCT harvesting achieved the 2×10⁶ CD34+ cells/kg target on the day of harvesting.

Conclusions

In summary, this study in 18 Japanese children with solid tumors who received plerixafor for HSC mobilization during routine clinical practice revealed no new safety concerns. ADRs, which occurred in seven patients (38.9%), were limited to the older patient subgroup (6 to <15 years), which may reflect different types of malignancies in older versus younger children. Adequate CD34+ cell levels for harvesting were achieved within 1 to 2 days of apheresis in 12 of the 18 patients (66.7%). These data provide encouraging preliminary support for the effectiveness, safety, and tolerability of plerixafor at the internationally accepted dose of 0.24 mg/kg in Japanese children. The data also suggest that plerixafor may facilitate successful A-PBSCT in Japanese children who are expected to be poor mobilizers. Further research in a larger cohort of patients with a wider range of malignancies, including lymphoma, is needed to verify this and to clarify the optimal timing of PBSCT harvest and of CD34+ cell monitoring in peripheral blood.

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Disclosure

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Author contributions
H.G. served as scientific advisor; S.N. contributed to study conception and design; T.S. contributed to enrollment of patients and operations; R.K. planned the pediatric subgroup analysis; all authors interpreted the results. All authors read and approved the final manuscript.

References
1 Hsu YM, Cushing MM. Autologous stem cell mobilization and collection. Hematol. Oncol. Clin. North Am. 2016; 30: 573–89.
2 Kim JS. Hematopoietic stem cell mobilization: Current status and future perspective. Blood Res. 2017; 52: 79–81.
3 Anderlini P, Rizzo JD, Nugent ML, Schmitz N, Champlin RE, Horowitz MM. Peripheral blood stem cell donation: An analysis from the International Bone Marrow Transplant Registry (IBMTR) and European Group for Blood and Marrow Transplant (EBMT) databases. Bone Marrow Transplant. 2001; 27: 689–92.
4 Douglas KW, Gilleece M, Hayden P et al. UK consensus statement on the use of plerixafor to facilitate autologous peripheral blood stem cell collection to support high-dose chemoradiotherapy for patients with malignancy. J. Clin. Apher. 2018; 33: 46–59.
5 Haas R, Murea S. The role of granulocyte colony-stimulating factor in mobilization and transplantation of peripheral blood progenitor and stem cells. Cytokines Mol. Ther. 1995; 1: 249–70.
6 Perseghin P, Terruzzi E, Dassi M et al. Management of poor peripheral blood stem cell mobilization: incidence, predictive factors, alternative strategies and outcome. A retrospective analysis on 2177 patients from three major Italian institutions. Transfus. Apher. Sci. 2009; 41: 33–7.
7 Sevilla J, Guilién M, Castillo A et al. Defining "poor mobilizer" in pediatric patients who need an autologous peripheral blood progenitor cell transplantation. Cytotherapy 2013; 15(1): 132–7.
8 Wuchter P, Ran D, Bruckner T et al. Poor mobilization of hematopoietic stem cells–definitions, incidence, risk factors, and impact on outcome of autologous transplantation. Biol. Blood Marrow Transplant. 2010; 16: 490–9.
9 Pusic I, Jiang SY, Landau S et al. Impact of mobilization and remobilization strategies on achieving sufficient stem cell yields for autologous transplantation. Biol. Blood Marrow Transplant. 2008; 14(9): 1045–56.
10 Moreb JS, Byrne M, Shugarmann I et al. Poor peripheral blood stem cell mobilization affects long-term outcomes in multiple myeloma patients undergoing autologous stem cell transplantation. J. Clin. Apher. 2018; 33: 29–37.
11 Azar N, Ouazgoudh M, Choquet S, Leblond V. Impact of plerixafor (Mozobil) on hospital efficiency: A single center experience. J. Clin. Apher 2018; 33: 5–13.
12 Gertz MA, Wolf RC, Micallef IN, Gastineau DA. Clinical impact and resource utilization after stem cell mobilization failure in patients with multiple myeloma and lymphoma. Bone Marrow Transplant. 2010; 45(9): 1396–403.
13 Holmberg L, Maloney DG. The role of autologous and allogeneic hematopoietic stem cell transplantation for Hodgkin lymphoma. J. Natl. Compr. Canc. Netw. 2011; 9(9): 1060–71.
14 Karres D, Ali S, van Hennik PB et al. EMA recommendation for the pediatric indications of plerixafor (Mozobil) to enhance mobilization of hematopoietic stem cells for collection and subsequent autologous transplantation in children with lymphoma or malignant solid tumors. Oncologist 2020; 25: e976–81.
15 Fricker SP. Physiology and pharmacology of plerixafor. Transfus. Med. Hemother. 2013; 40: 237–45.
16 US Food and Drug Administration. Mozobil Prescribing information [Internet]; 2008 [Cited 3 November 2020]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/022311lbl.pdf
17 European Medicines Agency. CHMP Summary of Product Characteristics: Mozobil® [Internet]. 2014 [Cited 8 July 2020]. Available from: https://www.ema.europa.eu/en/documents/product-information/mozobil-epar-product-informat_i on_en.pdf
18 DiPersio JF, Micallef IN, Stiff PJ et al. Phase III prospective randomized double-blind placebo-controlled trial of plerixafor plus granulocyte colony-stimulating factor compared with placebo plus granulocyte colony-stimulating factor for autologous stem-cell mobilization and transplantation for patients with non-Hodgkin’s lymphoma. J. Clin. Oncol. 2009; 27: 4767–73.
19 DiPersio JF, Stadtmauer EA, Nademanee A et al. Plerixafor and G-CSF versus placebo and G-CSF to mobilize hematopoietic stem cells for autologous stem cell transplantation in patients with multiple myeloma. Blood 2009; 113: 5720–6.
20 Matsue K, Kumagai K, Sugiuura I et al. Plerixafor for mobilization and collection of haematopoietic stem cells for autologous transplantation in Japanese patients with non-Hodgkin lymphoma: A randomized phase 2 study. Int. J. Hematol. 2018; 108: 524–34.
21 Ri M, Matsue K, Sunami K et al. Efficacy and safety of plerixafor for the mobilization/collection of peripheral hematopoietic stem cells for autologous transplantation in Japanese patients with multiple myeloma. Int. J. Hematol. 2017; 106: 562–72.
22 Morland B, Kepak T, Dollorso S et al. Plerixafor combined with standard regimens for hematopoietic stem cell mobilization in pediatric patients with solid tumors eligible for autologous transplants: Two-arm phase I/II study (MOZAIC). Bone Marrow Transplant. 2020; 55(9): 1744–53.
23 Tsukada N, Nishikori M, Goto H et al. Safety and effectiveness of plerixafor for peripheral blood stem cell mobilization in autologous stem cell transplantation: Results of a post-marketing surveillance study. Drugs Real World Outcomes. https://pubmed.ncbi.nlm.nih.gov/34455570/. Online ahead of print.
24 Cooling L, Hoffmann S, Webb D et al. Procedure-related complications and adverse events associated with pediatric autologous peripheral blood stem cell collection. J. Clin. Apher. 2017; 32: 35–48.
25 Hong KT, Kang HJ, Kim NH et al. Successful mobilization using a combination of plerixafor and G-CSF in pediatric patients who failed previous chemomobilization with G-CSF alone and possible complications of the treatment. J. Hematol. Oncol. 2012; 5: 14.
26 Maschan AA, Balashov DN, Kurnikova EE et al. Efficacy of plerixafor in children with malignant tumors failing to
mobilize a sufficient number of hematopoietic progenitors with G-CSF. Bone Marrow Transplant. 2015; 50(8): 1089–91.

27 Sevilla J, Schiavello E, Madero L et al. Priming of hematopoietic progenitor cells by plerixafor and filgrastim in children with previous failure of mobilization with chemotherapy and/or cytokine treatment. J. Pediatr. Hematol. Oncol. 2012; 34: 146–50.

28 Teusink A, Pinkard S, Davies S, Mueller M, Jodele S. Plerixafor is safe and efficacious for mobilization of peripheral blood stem cells in pediatric patients. Transfusion 2016; 56(6): 1402–5.

29 Aabideen K, Anoop P, Ethell ME, Potter MN. The feasibility of plerixafor as a second-line stem cell mobilizing agent in children. J. Pediatr. Hematol. Oncol. 2011; 33: 65–7.

30 Emir S, Demir HA, Aksu T, Kara A, Ozgün厄 M, Tunç B. Use of plerixafor for peripheral blood stem cell mobilization failure in children. Transfus. Apher. Sci. 2014; 50: 214–8.

31 Vettenranta K, Mottonen M, Rikonen P. The use of plerixafor in harvesting autologous stem cells in the pediatric setting. Pediatr. Blood Cancer 2012; 59(1): 197–8.

32 Vives S, Sancho J-M, Almazåñ F, Juncå J, Grifols J-R, Ribera J-M. Plerixafor plus G-CSF in combination with chemotherapy for stem cell mobilization in a pediatric patient with Ewing’s sarcoma. J. Clin. Apher. 2012; 27: 260–2.

33 Worel N, Apperley JF, Basak GW et al. European data on stem cell mobilization with plerixafor in patients with nonhematologic diseases: An analysis of the European consortium of stem cell mobilization. Transfusion 2012; 52: 2395–400.

34 Chambon F, Merlin E, Rochette E et al. Mobilization of hematopoietic stem cells by plerixafor alone in children: A sequential Bayesian trial. Transfus. Apher. Sci. 2013; 49: 453–8.

35 Bitan M, Eshel R, Sadot E et al. Combined plerixafor and granulocyte colony-stimulating factor for harvesting high-dose hematopoietic stem cells: Possible niche for plerixafor use in pediatric patients. Pediatr. Transplant. 2016; 20: 565–71.

36 Patel B, Pearson H, Zacharoulis S. Mobilisation of haematopoietic stem cells in paediatric patients, prior to autologous transplantation following administration of plerixafor and G-CSF. Pediatr. Blood Cancer 2015; 62(8): 1477–80.

37 Nakamura Y, Okubo M, Furuta Y, Tokida M, Ichikawa K, Ohsaka A. Impact of CD34+ pre-counting and plerixafor on autologous peripheral blood stem cell collection in Japanese university hospitals in eight years. Transfus. Apher. Sci. 2019; 58(6): 102664.