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1 Drug description

Generic/Brand name:

Plerixafor (Mozobil ®)

Plerixafor

Mozobil ®

Developer/Company:

Genzyme Europe B.V., Netherlands

Description:

The active substance in Mozobil is plerixafor. It is used to mobilize hematopoietic stem cells from the bone marrow by blocking the activity of the protein CXCR4/SDF-1α a chemokine receptor. This protein is responsible for the homing of the hematopoietic stem cells (HSC) within the bone marrow (BM). Details about this process are described elsewhere [1]. As plerixafor blocks the activity of CXCR4/SDF-1α, stem cells can be released into the peripheral blood and can then be collected by aphaeresis [2-4].

blocks the activity of a protein keeping the HSC within the BM

The advantages of adding plerixafor to G-CSF compared to G-CSF alone are increased mobilization of CD34+ cells from the bone marrow into the peripheral blood and a decreased number of aphaeresis sessions needed to reach the target CD34+ stem cell dose in most patients [4]. CD34+ is a protein located at the surface of hematopoietic stem and progenitor cells. It is used as a marker to assess whether an adequate number of HSC are circulating in the peripheral blood for HSCT [5].

increases the amount of CD34+ cells mobilized in the PB

The recommended dose of plerixafor is 0.24 mg/kg body weight/day administered subcutaneously (sc) 6 -11 hours prior to aphaeresis on the evening of the fourth day of pre-treatment with the cytokine granulocyte colony-stimulating factor (G-CSF). G-CSF is given at a dose of 0.01mg/kg daily in the morning. The combination of G-CSF and plerixafor was given in clinical trials on 2-4 consecutive days, resulting in a maximum of 8 days of G-CSF and 4 days of plerixafor administration [2]. In patients with renal impairment (creatinine clearance ≤50 mL/min) the dose of plerixafor should be reduced by one third to 0.16 mg/kg [6-7]. Although the dosage of plerixafor is linked to the actual body weight of the patient the maximum daily dose of plerixafor should not exceed 40 mg [2].

dosing and administration

dose reduction in pts with renal impairment

2 Indication

Mozobil is indicated in combination with G-CSF to enhance mobilization of haematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with lymphoma and multiple myeloma whose cells mobilize poorly [2].

enhance mobilization of HSC in poor mobilizers

Only patients in first or second complete or partial remission are considered for high-dose chemotherapy and therefore for autologous hematopoietic stem cell transplantation (HSCT) [8-9].

pts in 1st or 2nd complete or partial remission

3 Current regulatory status

approved in Europe since 2009

In July 2009, the EMA granted market authorisation for Mozobil ® (plerixafor, AMD3100) in combination with G-CSF (filgrastim, Ratiograstim ®) for the mobilization of HSC in patients suffering from lymphoma or multiple myeloma who are eligible for autologous HSCT and whose cells mobilize poorly [2].

FDA approval since 2008

In the US, the FDA approved plerixafor in combination with G-CSF for the mobilization of HSC to the peripheral blood for the collection and subsequent autologous transplantation for patients with Non-Hodgkin's Lymphoma (NHL) and multiple myeloma (MM) in December 2008 [3].

orphan drug designation

Orphan drug designation for plerixafor was granted by the EMA in 2004 and by the FDA in 2003 [10-11].

4 Burden of disease

HSCT to support high-dose chemotherapy

harvesting methods: BM, autologous or allogenic HSCT of the PB)

Plerixafor is intended to be used in patients suffering from haematological malignancies such NHL, Hodgkin Lymphoma (HL) and MM who are eligible for high-dose chemotherapy supported by autologous HSCT and who are considered to be poor mobilizers. Stem cells can be harvested with different methods such as mobilization of the progenitor cells from the bone marrow into the peripheral blood (autologous or allogenic transplantation) or by collecting the stem cells directly from the bone marrow [1, 5]. The use of stem cells collected by aphaeresis of peripheral blood is widely predominant in the world [12].

NHL and MM most common indication for autologous HSCT

HSCT prevalence in EU: <0.6 per 10.000

Approximately 35,000 autologous HSCTs are currently performed worldwide each year to treat a variety of malignant and non-malignant conditions. According to Uy et al. (2008) NHL and MM are the most common indications for autologous transplantation. Also NHL and MM patients are sometimes considered to be poor mobilizers and are therefore eligible for the stem cell mobilization with plerixafor [5]. Plerixafor is intended to be used for the mobilization of stem cells in NHL, HL and MM patients either in first or second complete or partial remission. Within the European Public Assessment Report (EPAR) for plerixafor, a calculated prevalence for mobilizing progenitor cells prior to HSCT was <0.6 per 10,000 EU population stated [2]. Applying the estimates of the EMA the number of patients eligible for the mobilization of hematopoietic stem cells would result in a maximum of 480 in Austria, if plerixafor would be used upfront to mobilize all NHL and MM patients. If only patients mobilizing poorly at day 4 of G-CSF with or without chemotherapy would be treated with plerixafor, this number would be estimated to be much lower. Furthermore, the role of autologous HSCT in myeloma is questioned by the introduction of highly active new drugs (Bortezomib, Lenalidomide, etc.) [13] and needs to be re-explored in future studies [4].

10-30% are poor mobilizers

The main indication for plerixafor are poor mobilizers. Out of the patients eligible for HSCT an estimated 10-30% are poor mobilizers and therefore eligible for HSC mobilization with plerixafor. Poor mobilizers are defined as

not being able to collect at least 2 x 10^6 CD34+ cells/kg with current standard of care [5-6, 14-15]. Factors predicting poor mobilization of HSC are advanced age, amount of previous myelosuppressive chemotherapy and radiation, number of chemotherapy regimen, interval from last chemotherapy, refractory disease and hypocellular marrow [1, 5].

The three indications, NHL, HL and MM are briefly described below:

Non-Hodgkin's Lymphoma

NHL: heterogeneous group of haematological diseases

NHLs encompass a heterogeneous group of diseases originating from cells of the lymphatic system such as B-lymphocytes, T-lymphocytes or natural killer (NK)-lymphocytes [8, 16]. About 90% of NHL are B-cell lymphomas and about 10% of NHL cases are T-cell and NK lymphomas [16]. According to Statistik Austria 514 peopled died of NH disease and 1057 new cases were diagnosed in 2007 in Austria [17]. Thus, in 2007 the incidence of NHL was 7.6 per 100,000 (9.5 for men and 6.1 for women) [17].

incidence: 7.6 per 100.000

Ann-Arbor Staging System

Since 2001 the World Health Organization (WHO) classification is the internationally accepted classification of NHL, which is a refinement of the REAL (Revised European-American Classification of Lymphoid neoplasm) classification. Further, the stages of NHL follow the Ann-Arbor-Staging system (stages I-IV and addition of the letters A or B; A=no common symptom observed, B=common symptom observed) where existence, frequency and localisation of extra-lymphatic involvement are observed [9]. The Ann-Arbor Staging system is primarily used to describe the extension of the diagnosed lymphoma and to choose the right therapy option. Further, information on prognosis of the disease development can be given [16].

histological subtypes

According to the international lymphoma classification project the most common histological types, comprising about 90% of the NHL cases in the United States are diffuse large B-cell (DLBCL, 31%), follicular lymphoma (FL, 22%), small lymphocytic lymphoma/chronic lymphocytic leukaemia (SLL/CLL, 6%), mantle cell lymphoma (MCL, 6%), peripheral T-cell lymphoma (PTCL, 6%), marginal zone B-cell lymphoma (MZL), mucosa-associated lymphoid tissue (MALT) lymphoma (5%) [8].

Morbus Hodgkin/Hodgkin Lymphoma

incidence in A: 1.7 per 100.000

According to Statistik Austria the incidence of HL was 1.7 per 100,000 (2 for men and 1.4 for women) in Austria in 2007 [18]. The classification and staging of HL follows like NHL the WHO classification or the Ann-Abor Staging [16, 19]. The distribution of HL is bimodal with peaks at the age of 20-30 years and at 70 years [9, 19].

bimodal distribution

>50% stage III/IV disease at diagnosis

HLs are very sensitive to chemo- and radiation therapy. About 50-60% for patients suffering from advanced disease and up to 90% for patients with localized HL can be cured [9]. Relapse is observed in about 25-30% of HL patients. Choice of therapy for early relapsed patients is high-dose chemotherapy supported by autologous HSCT four younger patients [9]. Assuming 136 cases of HL in Austria per year, a relapse rate of 27% and that only patients <65 years of age are eligible for HSCT, less than 37 HL patients are eligible for autologous HSCT.

relapse therapy: high-dose chemotherapy

Multiple Myeloma

incidence: ~2.5 per 100.000

no curative treatment

Durie-Salmon staging system

OS: depending on treatment and stage of disease

The incidence of MM was about 2.5 per 100,000 (2.8 for men and 2.1 for women) in 2007 in Austria. In absolute numbers 180 men and 198 women were diagnosed with plasmacytoma in Austria in 2007 [20]. Median age at time of diagnosis is 65 years [16]. MM is considered to be very sensitive to cytotoxic drugs. However, no curative treatment approach for this disease exists yet [13]. At diagnosis smoldering (asymptomatic) and active (symptomatic) disease can be distinguished. Further, the symptomatic disease is classified according to stages following the Durie-Salmon staging system or the International Staging System. Both staging systems have three different levels (stage I-III) and Durie-Salmon uses the letters A (normal renal function; serum creatinine level <2.0 mg/dL) and B (serum creatinine level ≥2.0 mg/dL) for sub-classification within the different stages [13]. Besides the dissemination of tumour mass the Durie-Salmon staging system gives prognostic information regarding survival of MM patients [21]. The overall survival had varied between a few months and a couple of years not at last depending on treatment with standard-dose chemotherapy (mean 3 years) and high-dose therapy (4-5 years) [21], until the introduction of novel agents (thalidomide, bortezomib, lenalidomid) initiating at least a doubling of these figures in the last years [13].

5 Current treatment

high-dose chemotherapy + HSCT standard of care in 1st or 2nd complete or partial remission

For haematological malignancies such as NHL, HL and MM high-dose chemotherapy supported by autologous HSCT is considered to be standard of care in patients under the age of 65 years in first or second complete or partial remission [6, 8]. The amount of CD34+ cells in the peripheral blood is currently the most widely used indicator for adequate stem cell mobilization. A consensus on the minimum amount of CD34+ cells needed for autologous HSCT has not been established yet between different research groups. The total CD34+ cell count in the peripheral blood should be at least 2 x 10^6 cells/kg. The target cell count of ≥5 x 10^6 cells/kg is associated with faster neutrophil and platelet engraftment and a decreased need for supportive measures such as antibiotics and transfusions. Therefore, the preferred target cell count for HSCT is ≥5 x 10^6 CD34+cells/kg [1, 22]. However, as it is difficult to collect ≥5 x 10^6 cells/kg in heavily pre-treated patients the collection of at least 2 x 10^6 cells/kg is necessary for autologous HSCT [1-2, 22].

mobilizing HSC from the BM to the PB

Different options exist for mobilizing HSC from the bone marrow into the peripheral blood for aphaeresis:

cytokines

- Cytokine (G-CSF or granulocyte macrophage colony-stimulating factor (GM-CSF)) monotherapy: sc 0.01 mg/kg per day for up to 5 days followed by leukaphaeresis daily (mean 1-5 days) until the target number of stem cells has been collected [1, 6].

cytokines + chemotherapy

- Cytokines plus chemotherapy (mainly cyclophosphamid [4]): The use of this combination requires fewer leukaphaeresis but also increases the risk of complications and shows significantly higher toxicities compared to G-CSF alone. These toxicities include increased risk for secondary malignancies, impairment of fertility, cardiac

toxicity, hemorrhagic cystitis and anaphylactic reactions. Further, the addition of chemotherapy to G-CSF does not reduce the risk of mobilizing and collecting tumour cells[1] and does not show a survival benefit after 12 months in comparison to patients treated with G-CSF [1].

treatment options for poor mobilizers

Currently, no uniform strategy exists for the management of poor mobilizers, whose initial mobilization attempt failed. Though, several options for remobilization exist [1, 5]:

- Dose escalation of G-CSF,
- addition of other cytokines (GM-CSF) to G-CSF,
- mobilization with chemotherapy and cytokines,
- harvesting cells directly from the bone marrow (BM) and
- use of novel agents alone or in combination with G-CSF [1].

still 30% not suitable for HSCT

Despite these strategies up to 30% of patients failing the initial mobilization still do not reach the minimum amount of CD34+ cells required for transplantation after remobilization [5].

6 Evidence

2 phase III, 4 phase II studies, CUP

According to the EPAR of the EMA 22 studies (two phase II studies, two phase III studies, eight clinical pharmacology and ten supportive studies) and one compassionate use program (CUP) for the use of plerixafor were considered in the marketing authorisation application process. Out of these 22 studies two phase III studies assessing the safety and efficacy of plerixafor in the mobilization of progenitor stells for HSCT, four phase II studies as well as major findings of the CUP are discussed in this report.

effectiveness and safety in NHL and MM patients

One of the phase III studies observed the clinical effectiveness of plerixafor in patients with MM and the other one in patients with NHL, both compared to placebo [14, 23]. Of the 600 (Intervention 298 vs Control 302) patients recruited in these phase III trials 544 (I 91.6% vs C 89.7%) were alive at the 12 months follow-up.

tumour cell mobilization with plerixafor

One phase II [24] study assessed, besides the efficacy of plerixafor, the possibility of tumour cell contamination of the aphaeresis product in patients with MM who are proven or predicted poor mobilizers. Flomenberg et al.

[1] The protein CXCR4, to which plerixafor is binding is not only expressed on the cell surface of, but also on the surface of cells of solid tumour malignancies. Therefore the potential for tumour cell mobilization is currently clinically investigated 1. Pusics, I. and J. DiPersio, *The Use od Growth Factors in Hematopoietic Stem Cell Transplantation.* Current Pharmaceutical Design, 2008. **14**: p. 1950-1961, 5. Uy, G.L., et al., *Plerixafor, a CXCR4 antagonist for the mobilization of hematopoietic stem cells.* Expert Opinion on Biological Therapy, 2008. **8**(11): p. 1797-804, 22. Tricot, G., M. Cottler-Fox, and G. Calandra, *Safety and efficacy assessment of plerixafor in patients with multiple myeloma proven or predicted to be poor mobilizers, including assessment of tumour cell mobilization.* Bone Marrow Transplantation, 2010. **45**: p. 63-68..

(2005) [25] investigated the superiority of plerixafor to G-CSF in MM and NHL patients and Cashen et al. (2008) [26] in patients with HL. Stewart et al. (2009) [22] conducted a phase II trial to investigate the safety, efficacy, pharmacokinetic and pharmacodynamic of plerixafor in NHL and MM patients.

6.1 Efficacy and safety - Phase III studies

Table 6.1-1: Evidence table of Phase III trials

Reference	DiPersio et al. 2009 [23] (multiple myeloma, protocol AMD3100-3102)		DiPersio et al. 2009 [14] (non-hodgkin's lymphoma, protocol AMD3100-3101)
Sponsor	Genzyme Corporation		Genzyme Corporation, Cambridge, MA (formerly AnorMED Inc.)
Country	Multicenter, 40 sites in 3 countries (United States, Canada, Germany)		Multicenter, 32 sites
Design	Randomized, double-blind, placebo-controlled		Randomized, double-blind, placebo-controlled
Participants characteristics	302 patients (pts) I(ntervention) 148 pts, median age 58.2 ±8.4 years C(ontrol) 154 pts, median age 58.4 ±8.6 years		298 pts I(ntervention) 150 pts, median age, years: 56 (range 29-75;) C(ontrol) 148 pts, median age, years: 59 (range 22-75)
Treatments	I(ntervention): G-CSF + plerixafor (AMD3100) 0.24 mg/kg (actual body weight) sc daily for up to 4 days or until ≥6 x 10^6 CD34+ cells/kg were collected. C(ontrol): G-CSF + placebo sc daily for up to 4 days or until ≥6 x 10^6 CD34+ cells/kg were collected. Aphaeresis began on day 5 and continued daily for up to 4 days or until ≥6 x 10^6 CD34+ cells/kg were collected.		I(ntervention): G-CSF + plerixafor 0.24 mg/kg (actual body weight) sc daily for up to 4 days or until ≥5 x 10^6 CD34+ cells/kg were collected. C(ontrol): G-CSF + placebo sc daily in the evening for up to 4 days or until ≥5 x 10^6 CD34+ cells/kg were collected. Aphaeresis began on the morning of day 5 and continued daily for up to 4 days or until ≥5 x 10^6 CD34+ cells/kg were collected.
In-/exclusion criteria	Inclusion: age 18-78, biopsy confirmed multiple myeloma, first or second complete or partial remission, ≥4 weeks since last cycle of chemotherapy, eligible for autologous HSCT[3], ECOG PS[4] 0 or 1 Exclusion: comorbid condition which rendered pts at high risk from treatment complication, st.p. autologous or allogeneic transplantation, failed previous hematopoetic stem cell collections or attempts		Inclusion: age 18-78, biopsy confirmed NHL, first or second complete or partial remission, ≥4 weeks since last cycle of chemotherapy, eligible for autologous HSCT, ECOG PS 0 or 1, WBC[7] count higher than 2.5 x 10^9/L, Exclusion: comorbid condition which rendered pts at high risk from treatment complication, failed previous HSC collections or collection attempts
Follow-up	12 months after transplantation		12 months after transplantation
Outcomes	Primary: proportion of pts collecting ≥6 x 10^6 CD34+ cells/kg (actual body weight) in ≤ 2 aphaeresis days. Secondary: proportion of pts collecting ≥6 x 10^6 CD34+ cells/kg in ≤ 4 aphaeresis days; proportion of pts collecting ≥2 x 10^6 CD34+ cells/kg in ≤ 4 aphaeresis days; number of aphaeresis days required to reach ≥6 x 10^6 CD34+ cells/kg; proportion of pts maintaining a durable graft at 12 m(on)ths; number of days to neutrophil and platelet engraftment; number of fold-increase in the number of PB CD34+ cells on each aphaeresis day.		Primary: proportion of pts able to mobilize ≥5 x 10^6 CD34+ cells/kg (actual body weight) in ≤ 4 aphaeresis days. Secondary: proportion of pts able to mobilize ≥2 x 10^6 CD34+ cells/kg in ≤ 4 aphaeresis days; number of aphaeresis days required to reach ≥5 x 10^6 CD34+ cells/kg; fold-increase in the number of PB CD34+ cells before and after study treatment; number of days to neutrophil and platelet engraftment; proportion of pts maintaining a durable graft at 12 mths.

Key results	Primary: collection of ≥6 x 10^6 CD34+ cells/kg in ≤ 2 aphaeresis days: I 71.6% vs. C 34.4%, p<0.001; Secondary: collection of ≥6 x 10^6 CD34+ cells/kg in ≤ 4 aphaeresis days: I 75.7% vs C 51.3%, p<0.001; collection of ≥2 x 106 CD34+ cells/kg in ≤ 4 aphaeresis days: I 95.3% vs C 88.3%, p=0.031; Median number of aphaeresis days required to reach ≥6 x 10^6 CD34+ cells/kg: I 1 day vs C 4 days; number of fold-increase in the number of PB CD34+ cells from day 4 to day 5: I 4.8-fold vs C 1.7-fold, p<0.001. pts undergoing transplantation: I 148 (95.9%) vs C 136 (88.3%) successful neutrophil engraftment: I 99.3% vs C 100%, median time to engraftment was 11 days in both groups; successful platelet engraftment: 99.3% in each group after a median time of 18 days. graft failures at 12 mths: none identified in both groups OS at 12 mths: I 141 (95.3%) vs C 148 (96.1%)		Primary: proportion of pts able to mobilize ≥5 x 10^6 CD34+ cells/kg : I 59.3 % vs. C 19.6%, p<0.001; Secondary: proportion of pts able to mobilize ≥2 x 10^6 CD34+ cells/kg: I 86.7% vs. C 47.3% p<0.001; median number of aphaeresis days required to reach ≥5 x 10^6 CD34+ cells/kg: I 3 days vs C not estimable; median fold increase in PB CD34+ cell count from day 4 to 5: I 5.0 (range 0.6 - 49.8) vs C 1.4 (range 0.0 – 13.0); all pts who underwent transplantation (I 90% vs C 55.4%) had successful neutrophil engraftment (median time to engraftment 10 days) and 98% had successful platelet engraftment (median time to engraftment 20 days). graft failures at 12 mths: I 2 vs C 0. OS at 12 mths: I 132 (88%) vs C 129 (87.2%). OS at 12 mths for pts who had undergone HSCT (I 135, C 82): I 119 (88.1%) vs C 71 (86.6%)
Adverse effects (AEs)	AEs related to study treatment (periode 1) were more frequent in the intervention group than in the control group, 64.6% vs 44.4%, respectively. Diarrhea: I 18.4% vs C 5.3% Nausea: I 16.3% vs C 7.3% Vomiting: I 5.4% vs C 2.7% Fatigue: I 8.2% vs C 3.3% Injection site erythema: I 20.4% vs C 3.3% Bone pain: I 9.5% vs C 7.9% Headache: I 5.4% vs C 8.6% Parestesia: I 7.5% vs C 7.3% AEs leading to discontinuation of study treatment: I 1 vs C 2; all 3 remained in the study. AES leading to study withdrawal: I 4 vs C none reported		AEs related to study treatment (period 1) were more frequent in the intervention group 65.3% vs 41.4% in control group. Diarrhea: I 38% vs C 6.2% Nausea: I 17.2% vs C 5.5% Abdominal pain: I 6% vs C 1.4% Injection site erythema: I 29.3% vs C 6.2% Bone pain: I 10.7% vs C 6.9% Headache: I 11.3% vs C 6.2 AEs leading to discontinuation of study treatment: I 3 vs C 3 serious AE by study period[5] (regardless of relatedness to study treatment): Period 1: I 5.3% vs C 6.9% Period 2: I 18.5% vs C 20.7% Period 3: I 20.0% vs C 17.1% Withdrawal from study (not study drug related): I 2 vs C 5
Commentary			No differences in early post-transplantation outcomes between the two study groups including engraftment, graft durability and patient survival. Long term follow-up of these pts will allow for the assessment of disease-free survival as the potential of tumour cell mobilization of plerixafor is not yet sufficiently investigated.

[2] *sc – subcutaneous*

[3] *HSCT – hematopoietic stem-cell transplantation*

[4] *ECOG PS – Eastern Cooperative Oncology Group Performance Status*

[5] *Study periods: this study consisted of 3 periods. Period 1, from random assignment to the day before high-dose chemotherapy; period 2, from first day of chemotherapy to the first day of platelet and neutrophil engraftment (whichever was later) after transplantation; period 3, from the first day after engraftment through 12 months after transplantation. In periods 2 and 3 adverse events were evaluated only in patients who underwent transplantation.*

[7] *WBC – white blood cells*

rescue procedure for pts not achieving primary or secondary study endpoints

I 10 vs C 52

For patients not collecting ≥2x10^6 CD34+ cells/kg in ≤4 aphaeresis days or <0.8x10^6 CD34+ cells/kg in 2 days for single or tandem transplantation, both studies provided an open-label rescue procedure consisting of a minimum 7-day rest period without treatment followed by a treatment strategy similar to the intervention group. Out of 62 (I 10 pts vs C 52 pts) NHL patients who received the rescue procedure, 37 (I 4 pts vs C 33 pts) achieved ≥2x10^6 CD34+ cells/kg in ≤4 aphaeresis days with the rescue procedure and 52 patients underwent transplantation [14]. In the other trial, the 7 MM patients entering the rescue procedure had been treated with placebo + G-CSF and mobilized enough CD34+ cells to undergo transplantation. All 7 MM patients had a successful neutrophil and platelet engraftment and were alive at 12 months' follow-up.

reporting of AEs organized in study periods

period 1: plerixafor administration

In order to conduct a reliable safety analysis the safety reporting of the two phase III studies was organized in study periods. Period one was from random assignment to the day before high-dose chemotherapy. In this period the study drug was administered. Periods 2-3 in NHL patients and periods 2-5 in MM patients involved the transplantation procedure and post-transplant time periods until 12 months follow-up [27].

SAEs period 1: hypotension, dizziness, thrombocytopenia, nonischemia, chest pain

AEs occurring in period 1 of each study are presented above in Table 6.1-1. The majority of AEs occurred in period 2-5 and were expected and common after high-dose therapy and HSCT. During period 1 three NHL patients experienced severe adverse events (SAEs; I hypotension and dizziness, thrombocytopenia vs C nonischemia chest pain). Within the MM study the most common AEs in period 1 considered to be study drug related were gastrointestinal disorders and injection site reactions.

12 months' OS: I 91.56% vs C 91.65%

At the 12 months follow-up 273 (91.56% of 298) patients treated with plerixafor + G-CSF and 277 (91.65% of 302) patients treated with G-CSF + placebo were alive. One trial did not report on the patients lost to follow-up [14], whereas the other phase III trial reported 13 deaths within the 12 months' follow-up period. The most common cause of death was due to disease progression (I 3 of 7 deaths vs C 5 of 6 deaths) [23].

6.2 Efficacy and safety - further studies

4 phase II trials and one CUP

Additional to the phase III studies, four phase II trials and one Compassionate Use Protocol (CUP) including poor mobilizers were identified [22, 25-26, 28].

superiority of plerixafor + G-CSF compared to G-CSF

dose adaption

pts changed treatment arms

Flomenberg et al. 2005 [25] conducted a phase II trial (Protocol AMD3100-2101) to assess whether plerixafor in combination with G-CSF is able to mobilize more progenitor cells per unit of blood volume than G-CSF alone. 25 patients with MM or NHL (10 MM, 15 NHL), either in first or second complete or partial remission, were randomly assigned to receive either the combination of plerixafor and G-CSF or G-CSF as an initial mobilizing regimen. Plerixafor was given at a dose of 160 μg/kg for the first 8 patients and at an increased dose of 240 μg/kg for the following patients in the evening of day 4 and was also continued daily until day 8. After a washout period remobilization with the other treatment option followed. 24 patients underwent transplantation and one patient was excluded from transplantation for reasons not related to the study. After G-CSF administration alone 8 patients reached the target of ≥5x10^6 CD34+ cells/kg, whereas 20 patients

receiving the combination plerixafor + G-CSF reached this target. Generally, 12 patients required fewer aphaeresis sessions to reach ≥5x10^6 CD34+ cells/kg when treated with AMD3100 (plerixafor) + G-CSF in comparison to G-CSF alone. One patient died due to sepsis and hypotension, five other patients experienced severe AEs (abdominal pain, jugular vein thrombosis, hematuria, neutropenic colitis, catheter infection and gastroenteritis) none of these was felt to be study drug related. The most frequent study drug related AEs were mild and included diarrhoea, injection site redness and nausea and bone pain.

mobilization of HSC in HL pts

historical control group

Cashen et al. 2008 [26] conducted a phase II study to determine if the addition of plerixafor to mobilization regimens is also effective and safe in patients with HL. A mobilisation regimen consisting of G-CSF was given to each of the 22 relapsed and refractory HL patients included in the study. The results were compared with a historical control group composed of 98 patients with HL who underwent G-CSF mobilization and peripheral blood stem cell (PBSC) collection. The main outcome of collecting ≥5x10^6 CD34+ cells/kg was achieved by 15 patients (68%) in the combination arm and by 15 patients (15%, p>0.001) in the G-CSF alone arm. The target of ≥2x10^6 CD34+ cells/kg collection was reached by 21 (95%) patients treated with G-CSF + plerixafor and by 76 (78%, p=0.071) patients treated with G-CSF alone. The median number of CD34+ cells collected on days 1-2 was 6.2x10^6/kg and 3.0x10^6/kg (p<0.001) in the intervention group and in the historic control group, respectively. The mean number of aphaeresis session was 2.5 in the intervention group and 2.9 in the control group. AEs possibly related to plerixafor were injection site erythema or irritation (n=13), diarrhea (n=3), nausea (n=2), vomiting (n=1) and abdominal pain or discomfort (n=2).

assessment of PK and PD of plerixafor in NHL and MM pts

Stewart et al. (2009) [22] investigated the safety, efficacy, pharmacokinetic (PK) and pharmacodynamic (PD) in 22 (8 with NHL, 14 with MM) patients in a phase II, open-label single-arm study. Patients received the common mobilization regimen consisting of 10 μg/kg G-CSF every day in the morning and 240 μg/kg plerixafor in the evening of day 4 of G-CSF for up to 5 days or until ≥5x10^6 CD34+ cells/kg were collected. All 22 patients reached the primary outcome of ≥2-fold increase of CD34+ cells after plerixafor administration (from 16.6 to 52.1 cells/μL in NHL patients and from 30.0 to 86.9 cells/μL in MM patients; median increase of 2.9-fold (NHL 2.7 vs MM 3.1)). All patients underwent HSCT. Successful polymorphonuclear leukocyte engraftment was shown after a median of 11 days and the mean time for platelet engraftment was 18 days. All patients experienced at least one AE. AEs considered being study drug related are injection site erythema (36%), injection site pain (18%), upper abdominal pain (9%), diarrhea (9%) and headache (9%). All of these AEs were mild or moderate. Serious AEs occurred in 8 patients but none was considered to be study drug related.

assessment of tumour contamination in aphaeresis product of poor mobilizers

Tricot et al. [24] conducted a phase II trial to investigate the safety and efficacy of plerixafor for stem cell mobilization and tumour contamination of the aphaeresis product in 20 MM patients who were either proven (n=10) or predicted (n=10) poor mobilizers. Both groups had mobilized poorly with either G-CSF alone or G-CSF in combination with chemotherapy. The peripheral blood CD34+ cell count was measured pre- and post-plerixafor and showed a significant increase. 17 patients underwent transplantation (1 collected insufficient CD34+ cells for transplantation and two patients decided not to proceed with transplantation for the moment). Eight patients were transplanted with pooled cells from other collections. At the 12 months fol-

low-up 12 of the 17 patients who underwent transplantation showed durable graft, three died (2 due to disease progression and 1 because of cerebral infarction) and 2 patients were lost to follow-up. Adverse events occurred in all patients – 1 mild, 7 moderate and 12 experienced severe adverse events. Drug related AEs were erythema (17 pts), injection site reaction and diarrhea (each: 3 pts), fatigue, injection site pruritus, injection site swelling, hot flushes (each 2 pts). None of the 25 serious AEs occurring in 8 patients were considered to be study drug related. Tumour cell contamination of the aphaeresis product was assessed by using flow cytometry (sensitivity 1/100 cells to quantify tumour cells) in peripheral blood samples taken before the first dose of plerixafor and before the subsequent aphaeresis. For final analysis 9 paired samples (pre- and post first dose of plerixafor) were used. None, except one pre-plerixafor sample showed >1% of light-chain-restricted cells and no plasma cells with aneuploid DNA could be observed in any of the samples.

CUP for pts excluded from clinical trials

9 paired samples – no tumour cell contamination observed

The Compassionate Use Protocol (CUP) [28] was established because plerixafor trials have generally excluded patients who could not mobilize or collect sufficient cells for HSCT. The SPU[2] and CUP were initiated to allow requests for plerixafor treatment to be addressed in an urgent manner, such as when a patient required remobilization within 1-2 weeks. The data available from the CUP may be limited due to amount and quality of data sent by site. Further no comparison to a control group was made. Patients enrolled had previously received a conventional mobilization regimen, which resulted in mobilization of insufficient CD34+ cells for transplant. The entry to the CUP was limited to patients who had previously failed to proceed to aphaeresis due to low peripheral blood (PB) CD34+ cell counts. Calandra et al. (2008) reported results of 115 patients representing over 80% of the NHL, MM and Morbus Hodgkin patients enrolled in the CUP. More than 66% of patients included in the data audit reached the progenitor cell count $\geq 2x10^6$ CD34+ cells/kg. More than 75% of patients were able to proceed to transplantation. No follow-up data were reported. Of the plerixafor related AEs two (1.6%) were severe, 17 (13.6%) were moderate and 106 (84.8%) were mild. Most common AEs related to AMD3100 were gastrointestinal (diarrhoea 17.4%, nausea 9.6%), injection site (erythema 15.7%) and nervous system (paresthesia and oral paresthesia 6.9%). The two severe AEs that were study drug related were headache and nightmares. Out of the 115 pts included in this data analysis 15 died – deaths were not related to AMD3100.

7 Estimated costs

Cost estimates for 20 mg/ml Mozobil ® (plerixafor) are € 5,537.- [29]. Generally one vial consists of 24 mg plerixafor in 1.2ml solution [30] resulting in € 6,644 for one vial.

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[2] SPU Protocol allow patients who do not qualify for ongoing trials to have access to unlicensed drugs 7. Calandra, G., et al., *AMD3100 plus G-CSF can successfully mobilize CD34+ cells from non-Hodgkin's lymphoma, Hodgkin's disease and multiple myeloma patients previously failing mobilization with chemotherapy and/or cytokine treatment: Compassionate use data.* Bone Marrow Transplantation, 2008. **41**(4): p. 331-338.

Assuming an average weight of 75 kg for NHL, HL or MM patients the daily dose of plerixafor would be 18 mg. Therefore one dose of plerixafor would cost € 6,644. As plerixafor can be given up to four consecutive days, treatment costs can range between € 6,644 and € 26,576. Plerixafor is approved to be given in addition to G-CSF, therefore the costs for G-CSF have to be added. One injection of filgrastim consists of 0.48 mg in 0.8 ml solution and costs € 99.94 [31].

treatment costs with plerixafor range from € 6,644 – 26,576 + the costs of G-CSF

Additional, costs for high-dose chemotherapy and HSCT have to be considered. Plerixafor is intended to reduce hospitalization costs due to fewer aphaeresis sessions needed to harvest a sufficient amount of CD34+ cells in fewer aphaeresis sessions. Whether plerixafor reduces hospitalization rates or not, has not been addressed within the trials included in this report.

8 Ongoing research

According to ClinicalTrials.gov, a service of the U.S. National Institutes of Health, one phase III trial and several phase II trials are ongoing.

several ongoing trials registered

Phase III trial NCT00838357 – this trial is a multicenter, open label single-arm study evaluating the efficacy and safety of plerixafor in lymphoma (NHL, HD) and MM patients who are eligible for autologous HSCT. The study started in September 2008 and is estimated to be completed in September 2010. 100 patients are planned to be enrolled.

Phase II trials listed on the website www.clinicaltrials.gov are investigating different study aims such as

- identification of the ideal dose of plerixafor and other mobilization agents (G-CSF, chemotherapy) to increase the number of patients successfully collecting CD34+ cells,
- safety analysis whether plerixafor in combination with bortezomib may be able to stop myeloma cells attaching the bone marrow,
- safety of combining plerixafor with other chemotherapy agents for allogeneic stem cell transplantation in myeloid leukaemia patients, both when plerixafor is given subcutaneously or intravenous and
- to assess the ability of plerixafor to release chronic lymphoceutic leukaemia or small lymphocytic lymphoma cells into the peripheral blood to enhance the cytotoxic effect of chemotherapy (e.g., rituximab).

9 Commentary

2 phase III RCTs evaluating safety and efficacy of plerixafor

Up to date two phase III trials assessing the safety and efficacy of plerixafor in addition to G-CSF, the current standard agent for mobilization of hematologic stem cells, have been conducted. Both trials were multicenter RCTs sponsored by Genzyme Corporation and had similar in- and exclusion criteria and treatment regimens. Both defined the collection of CD34+ cells as primary and secondary outcomes (see Table 6.1-1) and showed that the CD34+ cell count increased when plerixafor was given additionally to G-CSF compared to placebo plus G-CSF, in MM patients 95.3% vs 88.3% (p=0.031) and in NHL patients 86.7% vs 47.3%, respectively. Also the percentage of patients undergoing transplantation was higher in the intervention group (MM 95.9%, NHL 90%) compared to the control group (MM 88.3%, NHL 55.4%).

primary outcome: collection of CD34+ cells

AEs in intervention group more frequent than in control group

The safety profile of the trials showed an increase in adverse events in the intervention group (64.6% - 65.3%) compared to the control group (41.4% - 44.4%). In the MM study three patients discontinued study treatment due to AEs (I 1 patients vs C 2 patients) and four other patients withdrew from the study due to AEs [23].

CD34+: indicator and predictor of neutrophil and platelet engrafment

The most commonly used indicator and predictor for neutrophil and platelet engraftment after transplantation is the CD34+ cell count in the peripheral blood [1, 26]. This indicator was used in the included phase II and III trials to assess the efficacy of plerixafor for mobilizing progenitor cells in NHL, HL and MM patients. Besides the mobilisation of a sufficient number of CD34+ cells for HSCT, it is expected that plerixafor can improve patients' quality of life, reduces hospitalization costs, allow for more efficient use of resources by eliminating the need for additional aphaeresis sessions (e.g., personal, blood bank resources) and improves transplant outcomes of infusion of a higher stem cell dose [4, 25-26]. Negative aspects of the addition of plerixafor to G-CSF may be the additional costs of plerixafor, increased risk of side effects (I 64.6%-65.3% vs C 41.4%-44.4%) and the inconvenience of giving an injection the evening prior to aphaeresis [26].

phase III studies excluded poor mobilizers

According to the summary for the public of plerixafor by EMA patients included in the two major phase III studies [14, 23] were adequate or good mobilizers [2], though the target population intended to be treated with G-CSF in combination with plerixafor are poor mobilizers [2, 14].

reduction of aphaeresis days required

no difference in 12 months survival

Event though the trials included have shown superiority regarding the reduction of aphaeresis days required to collect the pre-defined number of CD34+ cells (MM: I 1 day vs C 4 days; NHL: I 3 days vs C not estimable), no relevant difference in the 12 months overall survival has been shown, as could be expected in trials of this size. Regarding the potential of tumour cell mobilization (see below) FDA and EMA considered that a long-term follow-up regarding patient relevant outcomes (progression free survival (PFS), OS, relapse rates) is necessary. Thus, Genzyme Corporation committed to extending the long-term follow up for the two controlled Phase III studies to 5 years, including evaluation of relapse, PFS, and overall survival [2, 28].

patients' QoL needs to be assessed

Further, the assessment of quality of life in patients treated with plerixafor compared to those not treated with plerixafor is still lacking. Moreover, because data regarding hospitalization, blood bank and other resources are still missing, a possible reduction in resources needed due to harvesting higher

number of CD34+ cells in fewer aphaeresis sessions can not be demonstrated.

no head-to-head trials exist

The Scottish Medicines Consortium criticised that, at the moment, no comparative trials of plerixafor + G-CSF against other regimens such as chemotherapy + G-CSF (standard of care in HSCT eligible NHL patients in Scottland) do exist [32].

potential for tumour cell mobilization cannot be yet excluded

Another important concern that needs to be further addressed in clinical trials is the potential ability of plerixafor to mobilize tumour cells. It is reported that plerixafor mobilizes leukaemia cells [24]. Therefore, Mozobil cannot be used for mobilization of HSC for transplantation in leukaemia patients [23]. Tricot et al. address this concern in their phase II trial. They did not observe plasma cells with aneuploid DNA content within their 9 paired samples and further concluded that their sample size was too small to exclude the potential of tumour cell mobilization by plerixafor in MM patients [24]. Also, EMA concluded that this issue has not yet been sufficiently addressed to either confirm or exclude the potential of tumour cell mobilization. If plerixafor in combination with G-CSF mobilizes more tumour cells than G-CSF alone, the relapse rate within the intervention arm is expected to be higher than in the control arm. For this reason the long-term follow-up has been extended to 5 years evaluating relapse, progression-free survival and overall survival [2, 27].

role of plerixafor in the clinical practice needs to be defined

Although plerixafor added to G-CSF leads to an increase in CD34+ cells in the peripheral blood and a reduction in number of aphaeresis days required to collect a certain target count of CD34+ cells, there are still questions needed to be answered like the potential for tumour cell mobilization, quality of life in patients, potential for reduction of costs and when to decide to give plerixafor for stem cell mobilization to ameliorate the benefit for the patient. These concerns are funded especially concerning the upfront use of plerixafor in the stem cell collection procedure, while the “rescue” use in true poor mobilizers (as defined by low peripheral CD34 counts on day 4 of standard G-CSF with or without chemotherapy mobilization protocol) seems much less disputable because such patients do not possess a sensible treatment alternative.

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