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Stem Cell Mobılızatıon in Multıple Myeloma

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1. Introduction

High dose melphalan supported by autologous hematopoietic cell transplantation (AHCT) has been shown to prolong survival and decrease relapse rates compared to conventional chemotherapies in elligible patients with plasma cell myeloma (PCM) (Attal et al., 1996; Child et al., 2003; Fermand et al., 2005; Koreth et al., 2007; Palumbo et al., 2004). Patients who are considered candidates for high dose therapy receive 2-4 cycles of non-melphalan containing induction therapies followed by peripheral blood progenitor cell(PBPC) mobilization and collection. Pateints proceed to high dose melphalan (200 mg/m^2) supported with AHCT. High dose melphalan and AHCT has been the gold standard treatment approach in patients with PCM younger than 65 but can be extended to mid-70's in patients otherwise in good performance status. Second AHCT has been shown to increase survival, especially those who could not achieve very good partial response (VGPR) after the first AHCT (Attal et al., 2003, Barlogie et al., 2006). Additionally, patients who had a long progression free survival after the first transplantation may benefit from salvage transplantation at relapse (Ljungman et al., 2010). These advances have mandated the mobilization and collection of PBPCs adequate for double transplants. Although not prospectively studied, the traditional minimum and optimum CD34+ cell dose limits have been 2 x 10^6/kg and ≥ 4 x 10^6/kg for single ; 4 x 10^6/kg and ≥ 8-10 x10^6/kg for double AHCT, respectively (Bensinger et al., 1995, Giralt et al., 2009). Therefore, successfull stem cell mobilization and collection are crucial for treatment of PCM. Risk factors such as age >60 years, the extend of prior chemotherapy or radiotherapy and prolonged disease duration are recognized predictors for poor mobilization. The induction treatment given before the process of PBPC mobilization and collection should not be toxic to the bone marrow. It has been clearly revealed over the past decades that the traditional induction regimens; vincristine, adriamycin, dexamathasone (VAD) or single agent dexamathasone have no impact on PBPC mobilization. However, today, they have been completely replaced with novel agents which are associated with better response rates. During the recent years, the impact of these novel induction agents (thalidomide, lenalidomide and bortezomib) on PBPC mobilization have been of major concern. Although the classical PBPC mobilization methods (G-CSF alone or G-CSF after chemotherapy) have been generally successful in PCM, there is still a considerable amount of mobilization failures. Studies have been focused on the investigational agents alone or in conjunction with G-CSF to imrove PBPC mobilization efficiency, prevent mobilization failures and the need for second or subsequent

mobilization attempts which often delay the timely performance of the transplantation and increase the morbidity and the cost. In this chapter, we will focus on the current stem cell mobilization strategies as well as the novel mobilizing agents in PCM and the impact of novel anti-myeloma drugs on PBPC mobilization.

2. Mobilization approaches in PCM

2.1 G-CSF alone

The optimal PBPC mobilization strategy in PCM is unclear. Both growth factor alone or chemotherapy followed by growth factor (chemomobilization) have been the most frequently used approaches. In growth factor-only mobilization, recombinant human granulocyte-colony stimulating factor (G-CSF) is commonly administered at 10 µg/kg/day s.c. for 4 days , PBPCs are collected from day 5 onwards and G-CSF continued until the last day of apheresis. PBPCs are collected by continuous flow apheresis procedure often processing 2-2.5 times the patient's blood volume. CD34+ cell enumeration is performed by flow cytometry according to the ISHAGE guidelines(Sutherland et al., 1996). The stem cell product is then cryopreseved until use for AHCT. Recombinant human G-CSF is reliable, with predictable mobilization efficiency. The most common toxicities observed during G-CSF administration such as bone pain, low grade fever, headache, are generally managable. However, G-CSF may be associated with rare serious adverse events such as spontaneous splenic rupture, thrombosis, flare of autoimmune disease and precipitation of sickle crisis (Cashen et al., 2007).

2.2 G-CSF analogs

2.2.1 Filgrastim and lenograstim

Filgrastim (Neupogen, F Hoffmann-La Roche, Basel, Switzerland) and lenograstim (Granocyte, Chugai-Aventis Pharmaceuticals, France) are nonglycosylated and glycosylated analogs of recombinant human G-CSF approved for PBPC mobilization. Studies investigating the patients with hematological malignancies who underwent PBSC mobilization for AHCT could not demonstrate any difference between glycosylated and non-glycosylated G-CSF in terms of both efficacy and toxicity (Kopf et al., 2006; Lefrere et al., 1999). The glycosylation of G-CSF contributes to a greater chemical-physical stability of lenograstim: the glycosylated G-CSF is more stable and resistant to degradation. The recommended dosage of lenograstim when used alone for PBPC mobilization is 5 µ/kg/day (s.c./i.v.). On the other hand, equal doses of 10 µ/kg/day of filgrastim and lenograstim have been recommended for mobilization of CD34+ cells without associated chemotherapy. However, a recent study has suggested that lower dose (7.5 µ/kg/day) of glycosylated G-CSF may be as effective as the standard dose of non-glycosylated G-CSF for PBPC mobilization in patients undergoing AHCT (Ataergin et al., 2008).

2.2.2 Pegfilgrastim

Pegylated G-CSF (pegfilgrastim, Neulasta, Amgen Inc.,CA, USA) is currently approved by the US FDA for prevention of prolonged neutropenia after chemotherapy for nonmyeloid malignancies (Neulasta; package insert). Its potential in PBPC mobilization is currently

being explored. Due to its long plasma half-life compared to unconjugated G-CSF (33 vs 4-6 hours), it has the advantage of maintaining clinically effective serum levels over about two weeks after a single 6mg s.c. administration and achieving patient compliance. Its effect is self-limited and is terminated with cellular uptake by the recovering neutrophils (Hunter et al., 2003; Molineux et al., 1999). Clinical studies have demonstrated that pegfilgrastim is at least as efficient as filgrastim in mobilizing PBPCs after chemotherapy and this effect was not dose dependent. Pegfilgrastim was associated with a more rapid leukocyte recovery and an earlier performance of the first apheresis procedure in comparison to unconjugated G-CSF in PCM patients (Bruns et al., 2006; Fruehauf et al., 2007; Stiedl et al., 2005). Additionally, in a tandem transplant study, PBPC mobilization with chemotherapy plus pegfilgrastim in 237 PCM patients, a second booster injection of 6mg pegfilgrastim on day 13 after an initial administration on day 6, improved the serum G-CSF concentrations and the mobilization results (Tricot et al., 2008). In contrast to mobilization after chemotherapy, growth factor-only mobilization requires higher doses of pegfilgrastim to provide effective serum G-CSF levels (Hosing et al., 2006; Willis et al., 2009). However, this approach is not cost-effective when compared with unconjugated G-CSF. Pegfilgrastim is well tolerated with an advese event profile similar to that of unconjugated G-CSF. Bone pain is the most common complaint and a case of splenic rupture that may not have been related to pegfilgrastim was reported in one trial (Fenk et al., 2006).

2.3 Chemomobilization

The standard chemomobilization in myeloma consists of cyclophosphamide(CY) plus growth factor (Goldschmidt et al., 1996). High dose CY has been prefered in patients who fail initial mobilization attempt with growth factor only or for patients who could not achieve at least partial remission after induction regimens with the hope to control the high tumor burden before transplantation. However, it has been demonstrated that high dose CY does not increase overall complete remission rates or improve the time to progression for patients with myeloma undergoing AHCT (Dingli et al., 2006). At our center, CY 4 gr/m^2 with the same dose MESNA to prevent hemorrhagic cystitis is administered on day 1 and recombinant human G-CSF (10 µg/kg/day, in two divided doses) is started either on day 4 or day 7. The optimal timing for G-CSF initiation has not been determined conclusively. We have demonstrated that late (day 7) administration of G-CSF was as efficient and more cost-effective than early administration (Ozcelik et al., 2009). Flow cytometric quantification of peripheral blood(PB) CD34+ cells is performed when the WBC count reaches >1000/µl from the chemotherapy induced nadir. The apheresis is started when PB CD34+ cell count exceeds 10 cells/µl and continued until adequate number of CD34+ cells are collected usually for 1-3 apheresis procedures. Transfusion support should be given to keep the pre-apheresis Hb and platelet counts at ≥ 10gr/dl and ≥ 20 000-30 000/µl, respectively.

The dose of CY reported for mobilization has ranged from 1.5 to 7 gr/m^2. Retrospective studies comparing CY doses of 4 gr/m^2 versus 7 gr/m^2 and 1.2-2 gr/m^2 versus 4 gr/m^2 have favored lower doses because of similar stem cell mobilization efficiency but with considerably lower toxicity (Fitoussi et al., 2001; Jantunen et al., 2003). In a randomized study in myeloma patients comparing single dose 7 g/m^2 with 2.4 g/m^2 , higher number CD34+ cells were collected on the first apheresis day and there was a lower consumption of

G-CSF with the lower-dose CY regimen, which also permitted collection to occur as an outpatient procedure and was more cost-effective (Petrucci et al., 2003). Hiwase et al in their retrospective analysis have demonstrated that compared with low dose (1-2 gr/m^2) CY, patients receiving intermediate dose (3-4 gr/m^2) CY were more likely to collect the CD34+ cell number (≥4 x10^6/kg) adequate for tandem transplant. Febrile neutropenia was more frequent in intermediate dose CY group (38% vs 13%) but the increased toxicity was managable and acceptable (Hiwase et al., 2007). In the light of these studies, most centers prefer 3-4 gr/m^2 CY in their chemomobilization protocol (Gertz et al., 2010a).

High dose CY plus G-CSF is very efficient for PBPC mobilization in PCM patients but when compared with growth factor-only mobilization, chemotherapy plus growth factor mobilizes higher number of PBPCs in lower number of apheresis procedures but with the cost of increased toxicity; nausea- emesis, neutropenic fever, non-staphylococal bacteremia, sepsis, hemorrhagic cystitis, cardiac toxicity, hospitalization, requirement for transfusion support and with mortality rate of 1-2%. Moreover, there is increased possibility of delayed engraftment after AHCT if transplanted early after (e.g. <30 days) stem cell procurement (Gertz et al., 2009; To et al., 1990).

With the purpose of decreasing toxicity and at least preserving the efficiency, various alternative chemomobilization protocols with or without CY have also been investigated. Addition of etoposide (2 gr/m^2) to CY (4.5 gr/m^2) mobilization in a non-randomized study, resulted in increased toxicity without significant improvement in CD34+ cell yield (Gojo et al., 2004). In CAD protocol, CY (1gr/m^2, day 1) was combined with doxorubicin (15 mg/m2, day 1-4) and dexamethasone (40 mg, day 1-4) followed by a single dose 12 mg pegfilgrastim on day 5. Eighty-eight percent of patients achieved their CD34+ cell harvest target of 7.5 x 10^6 CD34/kg following a median of two apheresis. Mobilization efficiency and engraftment following transplantation using pegfilgrastim was comparable to filgrastim and patients mobilized with CAD plus pegfilgrastim had decreased time to first apheresis (13 vs 15 days)(Fruehauf et al., 2007). The former common induction protocol VAD followed by daily G-CSF 10 μg/kg from day 10 to day 15 was found to be as effective and less toxic than high-dose CY followed by daily G-CSF 5 μg/kg from day 8 in newly diagnosed myeloma patients (Lefrère et al., 2006). Blood stem cell collection results after mobilization with combination chemotherapy containing ifosfamide, epirubicin, and etoposide (IEV) followed by G-CSF in myeloma were favorable and allowed to support a tandem transplantation procedure in younger and elder patients in 97 and 95%, respectively. Grade ¾ hematological toxicity was observed in majority of patients and extramedullary toxicity including nephrotoxicity and neurotoxicity in 5–10% (Straka et al., 2003). IEV mobilized peripheral blood stem cells more efficiently than cyclophosphamide and etoposide, achieving a threshold of 6 x 10^6 CD34/kg in 97 vs. 71% with comparable major toxicities and similar tumor response rates, although there was one treatment-related death due to septic shock in the IEV chemotherapy group (Hart et al., 2007). DCEP protocol includes dexamethasone (40 mg/d, day 1-4) , CY 400 mg/m^2, etoposide 40 mg/m^2 and cisplatin 10 mg/m^2, daily continuous infusion for 4 days and has proved to be an effective salvage therapy for relapsed/refractory myeloma patients. G-CSF 5 μg/kg/day starting 48 h after the end of DCEP has been an effective mobilization protocol with 87 and 75% of patients achieving ≥ 2 x 10^6 and >4 x 10^6 /kg CD34+ cells, respectively (Lazzarino et al., 2001). The same group of investigators compared DCEP with CY (4 g/m^2) followed by G-CSF and concluded that DCEP is better tolerated and

more effective than CY for PBPC mobilization. Moreover, high-dose CY has limited anti-myeloma activity compared to DCEP. One study demonstrated the comparable efficiency and lower toxicity of shorter-infusional schedule of DCEP with respect to full-infusional schedule (Corso et al., 2002, 2005). Another study combined DCEP-short with a single dose 6mg s.c. pegfilgrastim and reported promising results (Zappasodi et al., 2008). In a pilot study, vinorelbin combined with CY 1.5 g/m² had similar efficiency compared to CY 4 g/m² in PBPC mobilization and less toxicity and no requirement for hospitalization (Annunziata et al., 2006). Melphalan i.v. 60mg/m² plus G-CSF 10 µg/kg/day was successful in mobilizing PBPC from myeloma patients. However, toxicity was notable and duration of mobilization was longer compared with CY 3 g/m² (16.5 days vs 10 days)(Gupta et al., 2005). Melphalan is a highly effective anti-myeloma drug but due to its stem cell toxicity, it is neither used for PBSC mobilization, nor recommended as an initial therapy for patients elligible for AHCT. In a retrospective analysis, single agent etoposide (1.5 g/m²) plus G-CSF was most potent at mobilizing PBPCs compared to CY (2-4 g/m²) plus G-CSF or G-CSF alone. Although the success rate for collecting the minimum CD34+ dose was similar in all groups, higher proportion of patients mobilized with etoposide could achieve the optimum dose required for tandem transplant. There was no difference in the progression free survival among the groups (Nakasone et al., 2009). Recently, in a retrospective single center review, intermediate dose etoposide (375 mg/m², day 1 and 2) followed by G-CSF was found to be highly effective in myeloma patients including the high risk patients for mobilization failure (Wood et al., 2011). However, myelosuppressive mobilization regimens neither seem to have any anti-myeloma effects nor appear to improve outcome (Attal et al., 2003). And most centers no longer routinely use CY for patients in first plateau.

3. High risk patients for mobilization failure

Although there may be variations in each center's definition of mobilization failure, generally it can be defined as lack of achievement of ≥ 2 x10⁶/kg CD34+ yield after 3 consecutive apheresis procedure or inability to start apheresis because of not reaching to >10 CD34+ cells/µl of PB . Extensive BM involvement with malignancy, prior radiotherapy especially to marrow-rich sites, prior treatment with alkylating agents, prior multiple chemotherapy regimens and older age have been associated with increased risk of mobilization failure (Bensinger et al., 2009; Demirer et al., 1996; Leung et al., 2010). Although the number of CD34+ cells collected decreases with increasing age, the experience has revealed that sufficient stem cell yield for ≥ 1 AHCT can be safely obtained in elderly patients up to 69-72 years (Roncon et al., 2011; Tempescul et al., 2010). On the other hand, in one retrospective study including myeloma and lymphoma patients, the total number of cycles of previous chemotherapy and previous treatment with melphalan were more significant predictors of poor mobilization than sex, age or body weight (Wuchter et al., 2010). Recently, prior prolonged exposure to novel agent lenalidomide has also been considered as a risk factor, which will be discussed later. With the current mobilization strategies about 5-10% of patients with PCM still end up with mobilization failure (Bensinger et al., 2009; Pusic et al., 2008). The classical strategy when patients fail G-CSF only mobilizations has been CY followed by G-CSF. However, this results in unnecessary exposure of the patients to chemotherapy toxicity for sole mobilization purposes, which means that novel PBPC mobilization approaches are required.

4. Novel agents for PBPC mobilization

Historically, attempts to increase the mobilization efficiency concentrated on using high doses of G-CSF or combining G-CSF with other cytokines and growth factors some of which are currently used in other indications. However, either due to inefficiency or AEs, most of these agents could not become a part of the standart mobilization. In recent years, several cytokines and chemokines have been investigated that may prove useful for amplifying yields of CD34+ cells without introducing additional toxicity. There are also investigational agents which are yet in preclinical and phase I clinical trials (Table 1) (Bakanay & Demirer, 2011).

Growth Factors Granulocyte-Macrophage Colony Stimulating Factor Recombinant human erythropoietin Recombinant human stem cell factor Recombinant human thrombopoietin Parathyroid hormone Recombinant human growth hormone
Chemokine axis mobilizers AMD3100 GRO-β analogs (SB-251353)
Other small molecules and peptides Very Late Antigen-1 antibodies Retinoic acid receptor alpha agonists Thrombopoietin receptor agonists

Table 1. Agents investigated as adjunct to G-CSF for PBPC mobilization

4.1 Plerixafor

Plerixafor (AMD3100, Mozobil, Genzyme Corporation, Cambridge, MA, USA) is a bicyclam molecule which selectively and reversibly antagonizes CXCR4 and disrupts its interaction with stromal cell derived factor-1 (SDF-1), thereby releasing hematopoietic stem cells into the circulation (Gerlach et al., 2001; Hendrix et al., 2000). Plerixafor has received approval by the US FDA and the European Medicines Evaluation Agency for use in combination with G-CSF to mobilize PBPCs for collection and subsequent AHCT in patients with NHL and PCM who previously failed mobilization with G-CSF alone (DiPersio et al. 2009a,2009b; Mozobil package insert). Plerixafor results in rapid mobilization of PBPC, which peaks at approximately 10 hours. Plerixafor has been shown to synergize with G-CSF for mobilizing stem cells in patients with PCM in various clinical conditions (Calandra et al., 2008; DiPersio et al., 2009a; Flomenberg et al., 2005; Stiff et al., 2009; Tricot et al., 2010). The results from phase II studies indicated that plerixafor added to G-CSF for PBPC mobilization from

myeloma patients mobilized more CD34+ cells per day of apheresis than G-CSF alone (4.4 vs 3-3.5 fold) with 95 to 100% of the patients achieving the minimum number (≥ 2 x10^6/kg) of target CD34+ cells in a median of 1-2 apheresis days. Even the heavily pretreated patients had the median 2.5 fold increase in the PB CD34+ cells and could proceed with high dose therapy and AHCT (Stewart et al., 2009; Stiff et al., 2009). In a randomized, placebo-controlled phase III study the proportion of patients from whom ≥ 6 x10^6 CD34+ cells/kg were collected in ≤2 days of apheresis served as the primary end point. The protocol for plerixafor plus G-CSF mobilization has been summarized(Table 2). The results demonstrated that the addition of plerixafor to G-CSF resulted in a significantly higher probability of achieving the optimal CD34+ cell target for tandem transplantation in fewer days of apheresis in PCM patients without any additional toxicity(Table 3). Peripheral blood stem cells mobilized by plerixafor and G-CSF resulted in prompt and durable engraftment after AHCT(DiPersio et al., 2009a).

GCSF 10 µg/kg/day s.c. on days 1-4
Plerixafor 240 µg/kg/day s.c. started on the evening of day 4
Apheresis initiated 10 h after the first dose of plerixafor on the morning of day 5
Daily GCSF before apheresis in the morning and plerixafor in the evening
Continued until the target CD34+ cells ≥ 6 x 10^6/kg was collected or a predetermined maximum number of apheresis (4-5) was reached

Table 2. Mobilization protocol of Plerixafor plus GCSF

	Plerixafor + G-CSF N=148	Placebo + G-CSF N=154
Achieved primary end point (%)	71.6	34.4
Achieved min. collection (%)	95.9	92.9
Fold increase PB CD34/µl	4.8	1.7
Median number of apheresis days to collect the target	1	4
Median(range) collected CD34 cells x10^6/kg	10.96 (0.66-104.57)	6.18 (0.11-42.66)
Failed mobilization (%)	0	4.6

Table 3. Phase III Clinical trial of PBPC mobilization with Plerixafor plus G-CSF in PCM

There is lack of sufficient information on direct comparison of mobilization with G-CSF and plerixafor to mobilization with chemotherapy and G-CSF. In a retrospective comparison, both G-CSF plus plerixafor and CY plus G-CSF resulted in similar numbers of cells collected as well as costs of mobilization and clinical outcomes (Shaughnessy et al., 2011). For the patients from whom sufficient number of CD34+ cells could not be collected after the first mobilization attempt with G-CSF alone, a second(rescue) mobilization has been traditionally attempted with chemotherapy plus G-CSF. However, instead of chemomobilization, a rescue stem cell mobilization with G-CSF and plerixafor can be offered in patients who only require PBPC mobilization and collection without any need for further tumor reduction. In compassionate use programs, plerixafor has been used successfully in myeloma patients who were either proven or predicted to be poor mobilizers. About 75% of the patients could

be rescued after failure from chemotherapy (Basak et al., 2011a; Calandra et al., 2008; Duarte et al., 2011). Plerixafor plus G-CSF can also be an option for myeloma patients who had received a previous AHCT and who require a repeated mobilization for a second transplantation. In a recent study, successful mobilization of PBPCs was performed in a similar proportion of the previously transplanted patients and other patients who had not undergone ASCT (70% vs 82.6%) (Basak et al., 2011b).

Plerixafor combined with chemotherapy and G-CSF in a recent open-label, multicenter trial on 40 patients with PCM and NHL, also proved to be a feasible method of stem cell mobilization. However, further studies are warranted to evaluate the exact timing of incorporating plerixafor into chemomobilization (Dugan et al., 2010). Table 4 gives a single center approach to mobilization in the era of novel mobilizing agent, plerixafor (Gertz, 2010b). In one single center experience, preemptive use of plerixafor was successful in patients who had either PB CD34+ counts <10/μl at the time of marrow recovery or poor yield of first apheresis CD34+ <1x 10^6 /kg (Jantunen et al., 2011). Similarly, a promising approach with growth factor and patient-adapted use of plerixafor has been recently suggested to be superior to chemotherapy and growth factor for autologous PBPC mobilization. The preemptive use of plerixafor using the PB CD34+ cell count on day 4 of G-CSF administration and the collection target to decide between continuing G-CSF only or adding plerixafor to the mobilization regimen may potentially reduce the percentage of failure in first-line mobilizations (Costa et al., 2011a, 2011b). A recent study demonstrated that the quantity of CD34+ cells collected on day 1, rather than the PB CD34+ cell count, might identify patients unlikely to achieve adequate stem cell collection for AHCT and suggested that patients who collect <0.70 x10^6 CD34+ cells/kg on day 1 could be considered for treatment modifications such as adding plerixafor (Duong et al., 2011).

G-CSF 10 μg/kg single dose x 4 days If collecting for 1 transplant: if CD34+ < 10 x 10^6/L, add plerixafor If collecting for >1 transplant: if CD34+ < 20 x10^6/L, add plerixafor
If relapsed or primary refractory myeloma or circulating plasma cells: CY 1.5 g/m^2 x 2 days, begin G-CSF 5 μg/kg on day 3 Check CD34+ when WBC >1000 x 10^6/L. If CD34+ < 10 x 10^6/L continue to check for three consecutive days. If CD34 remains < 10 x10^6/L, begin plerixafor

Table 4. The Mayo Clinic Rochester approach to PBPC mobilization in myeloma

Plerixafor is well tolerated and adverse events are usually mild and transient. The most common adverse events are diarrhea, nausea, vomiting, flatulance and injection-site reactions, fatigue, arthralgia, headache, dizziness and insomnia. Severe adverse events such as hypotension and dizziness after drug administration and thrombocytopenia after apheresis are very rare (DiPersio et al., 2009, Mozobil package insert). No case of splenic rupture due to plerixafor has been reported to date. No evidence of tumor cell mobilization could be demonstrated after plerixafor in PCM and NHL patients(Fruehauf et al., 2010). A

plerixafor dose reduction to 160 μg/kg in patients with a creatinine clearance value ≤ 50 mL/min is recommended (Douglas et al., 2011; MacFarland et al., 2010; Pinto et al., 2010). Plerixafor addition to G-CSF has undoubtedly increased the number of patients who could proceed with high dose therapy and AHCT. Plerixafor incorporation in the first line mobilization protocols in patients who are predicted poor mobilizers will eliminate the need for further mobilization attempts and the cost-effectiveness of such approaches should be clarified. Recently, the International Myeloma Working Group(IMWG) have proposed some strategies to overcome the risk factors for poor PBPC mobilization in PCM (Giralt et al., 2009) (Table 5).

Risk Factor	**Proposed strategy**
Age>60	Consider plerixafor
History of melphalan exposure	Consider upfront chemomobilization or plerixafor
Extensive prior therapy and prolonged disease duration	Harvest early between cycles 2-4 Consider upfront plerixafor or chemomobilization Assess marrow for secondary dysplastic changes before collection
Extensive radiotherapy to marrow bearing tissue	Consider collection before radiotherapy Consider upfront chemomobilization or plerixafor Assess marrow for secondary dysplastic changes before collection

Table 5. Strategies proposed by IMWG to overcome the risk factors for poor PBPC mobilization in PCM

5. The effect of novel induction protocols on PBPC mobilization in PCM

Until the last decade, the standard first line therapy for PCM has been either VAD or single agent dexamethasone. These therapies clearly do not have any adverse effects on PBPC mobilization from the bone marrow. However, they have been replaced by more efficient novel agents such as IMIDs (thalidomide and lenalidomide) and proteosome inhibitor bortezomib. Novel induction agents in myeloma are effective as first line therapy enhancing the quality of responses prior to AHCT and by controlling the tumor load at diagnosis they decrease the early mortality and prolong the overall survival. With the novel induction agents, the time from diagnosis to planned AHCT is shorter and most patients can achieve ≥ VGPR after the transplantation which eliminates the need for tandem AHCT for most patients. In fact it also neccesitates re-exploration of the role of first line AHCT in selected patients, moving AHCT to a second line position. The novel agents are also used as adjuncts to transplant conditioning regimen or as maintenance therapy after transplant (Dimopoulos et al., 2007; Harousseau et al., 2010; Kumar et al., 2009; Rajkumar et al., 2006).

5.1 Thalidomide

The IMIDs have antiangiogenesis, immunomodulatory activity and direct cyctotoxic affects on myeloma cells. Pretransplant treatment with IMIDs appear to have no impact on

engraftment kinetics suggesting that both thalidomide and lenolidomide do not have qualitative effects on stem cells. Thalidomide was the first IMID to be used in PCM and initial therapy with thalidomide-dexamethasone (thal/dex) was superior to dexamethasone alone (Rajkumar et al., 2006). Although there has been controversial reports, most studies have shown no impact of thalidomide on stem cell mobilization and >80% of patients who received thal/dex were able to collect adequate stem cells for tandem transplant (Cavo et al., 2005). In a phase III randomized study, patients treated with induction regimen TAD (Thalidomide, doxorubicine, dexamethasone) had fewer CD34+ cell collection following CAD plus G-CSF mobilization than patients who received VAD as induction. However, the number of CD34+ cells were sufficient to support double AHCT in 82% of TAD treated patients (Breitkreutz et al., 2007). However, in a recent study thalidomide in combination with CY and dexamethasone (CTD) as induction regimen had significantly (49%) lower PBPC yield and higher percentage of mobilization failures for one (25.4 vs 5.8%) or two (39.4 vs 15.9%) transplants compared with VAD and a VAD-like induction regimen. The authors have pointed that thalidomide and CY with no previously reported negative impact on stem cell mobilization can have substantial impact when used in combination (Auner et al., 2011).

5.2 Lenalidomide

Lenalidomide in combination with dexamethasone (Len/dex) have been associated with better outcomes and improved survival rates in patients with PCM (Rajkumar et al., 2005, Dimopuolos et al., 2007, Wang et al., 2008). However, lenalidomide can cause myelosuppression and concerns have been raised that its use may negatively impact the ability to mobilize stem cells in patients who received lenalidomide as part of their induction therapies (Kumar et al., 2007; Mazumder et al., 2008; Paripati et al., 2008; Popat et al., 2009). Kumar have indicated that among patients mobilized with G-CSF alone there was a significant decrease in total CD34+ cells collected, average daily collection, day 1 collection and increased number of apheresis in patients treated with lenalidomide compared to patients treated with other regimens(Kumar et al., 2007). One retrospective analysis demonstrated higher mobilization failure rates with filgrastim among lenalidomide- treated patients compared with patients who had not received lenalidomide (25% vs 4%, $p<0.001$). Failure rate was very high in patients who received >3 cycles of lenalidomide. Majority of the lenalidomide-treated patients(77%) could be rescued with chemotherapy plus filgrastim(Popat et al., 2009). A multicenter prospective study of 346 patients with newly diagnosed PCM, has demonstrated that 21% of the patientswho received 4 cycles of len/dex as induction regimen, could not achieve the target 4×10^6 CD34+ cells/kg after CY plus G-CSF mobilization whereas only 9% of patients failed after a second mobilization attempt with the same mobilization protocol. Lenalidomide as a part of the induction regimen did not adversely affect the PBPC mobilization and a second mobilization procedure with CY plus G-CSF may be an appropriate strategy to rescue poor mobilizers(Cavallo et al., 2011). In different studies where patients were mobilized after len/dex induction therapy, mobilization with CY plus G-CSF yielded clearly higher (range 6.3 to 14.2 x 10^6/kg) number of stem cells with respect to mobilization with G-CSF alone (range 3.1 to 7.9 x 10^6/kg) (Kumar et al., 2007; Mark et al., 2008; Mazumder et al., 2008; Paripati et al., 2008; Popat et al., 2009). Incorporation of lenalidomide into induction therapy for PCM did not have clinically significant impact on PBPC mobilization when CY plus G-CSF was used as mobilization protocol. Sufficient stem cells for tandem auto-HCT were collected from all patients

mobilized with CY plus G-CSF versus only 33% of patients mobilized with G-CSF alone. Some studies demonstarted lower stem cell yield with increasing duration of lenalidomide therapy but other studies could not demonstrate such correlation (Mark et al., 2008; Mazumder et al., 2008; Nazha et al., 2011). Since addition of CY + G-CSF does not increase the responses to myeloma therapy, exposing patients to the risks of chemomobilization for sole mobilization purposes should be avoided. Plerixafor is a promising alternative to chemomobilization in patients with PCM who received prior therapy with lenalidomide. Retrospective data analysis for 60 patients who received plerixafor plus G-CSF for front-line mobilization in a phase 3 clinical trial or for remobilization in a compassionate use program demonstrated that CD34+ cells can be successfully and predictably mobilized and collected in majority of patients with PCM who have been previously treated with lenalidomide (Micallef et al., 2010) (Table 6). The IMWG have published the consensus report focusing on the approach to stem cell mobilization in era of novel agents in PCM (Kumar et al., 2009)(Table 7).

	Frontline P + G-CSF	Remobilization P + G-CSF	Total
Minimal ≥ 2 x 10^6 CD34+ cells/kg	100%	80%	86.7%
Optimal ≥ 5 x 10^6 CD34+ cells/kg	95%	47.5%	63.3%

Table 6. Mobilization response to Plerixafor plus GCSF in lenalidomide-treated patients

5.3 Bortezomib

Bortezomib is effective in patients with relapsed or refractory disease as well as in untreated patients No definitive impact of initial therapy with bortezomib on stem cell harvest could be demonstrated (Benson et al., 2010; Corso et al., 2010; Horousseau et al., 2010; Jagannath et al., 2005). In the IFM2005/01 trial comparing bortezomib/dexamethasone to VAD, there was a trend towards lower CD34+ numbers among those receiving bortezomib. However, a single mobilization with G-CSF was adequate and allowed the harvest of sufficient number of CD34+ cells for a single transplant in 97% and for a tandem transplant 77% of the patients treated upfront with bortezomib/dexamethasone. Compared with VAD, a higher number of patients in bortezomib/dexamethasone arm required a second mobilization attempt to reach the target 5 x 10^6 CD34+ cells/kg for tandem transplantation (Horousseau et al., 2010; Moreau et al., 2010). HOVON65/GMMG-HD4 randomized phase 3 trial comparing bortezomib, adriamycin, dexamethasone (PAD) versus VAD, no impact of bortezomib was seen on ability to collect stem cells (Goldschmidt et al., 2008).

Studies combining bortezomib with lenalidomide or thalidomide also did not reveal any adverse effect of bortezomib on stem cell mobilization (Richardson et al., 2010; Bensinger et al., 2010; Kaufman et al., 2010). Simultaneous use of bortezomib in combination with thalidomide and chemotherapy (DT-PACE; cisplatin, doxorubicin, CY, etoposide and dexamethasone) was also effective, safe and allowed for adequate stem cell collection (Badros et al., 2006). Addition of alkylating agents to initial therapy especially in combination, may increase the risk of mobilization failures but no comparative data is available. Phase 2 studies combining CY with lenalidomide and CY with thalidomide

reported mobilization failures while combination of CY with bortezomib did not reveal any failure (Reeder et al., 2009).

Condition	Recommended approach
Initial therapy with thalidomide or bortezomib plus dexamethasone Patients who received <4 cycles of lenalidomide plus dexamethasone and younger than 65 years	G-CSF alone
Patients who received ≥4 cycles of lenalidomide plus dexamethasone	CY + G-CSF
Patients who received ≥4 cycles of lenalidomide plus dexamethasone and older than 65 years	Reduced dose CY + G-CSF G-CSF alone with the addition of plerixafor before second apheresis if first apheresis yields <2 x 10^6 CD34+ cells/kg
Patients who received other myelosuppressive drugs in combination with lenalidomide	CY + G-CSF
Failed mobilization with G-CSF alone in lenalidomide-treated patients	CY + G-CSF G-CSF + Plerixafor G-CSF + GM-CSF

Table 7. Approach to stem cell mobilization in era of novel agents in PCM : IMWG consensus perspectives

6. Conclusions

As the novel anti-myeloma drugs (thalidomide, lenalidomide, bortezomib) in combination with dexamethasone or other agents have replaced the traditional VAD or single agent dexamethasone as first line therapy for myeloma, there has been concern about their impact on PBPC mobilization from the bone marrow. Studies could not demonstrate any deleretious effect of bortezomib on stem cell mobilization. There has been contraversy regarding thalidomide's impact especially when combined with other cytotoxic agents such as CY. However, the thal/dex combination has proved to allow for adequate PBPC yield for tandem transplantation. On the other hand, prolonged exposure to lenalidomide definitely affects the stem cell yield. Early PBPC mobilization with (<4 cycles) is recommended after lenalidomide-containing regimens. If this condition can not be satisfied, mobilization with CY+ G-CSF or addition of plerixafor to G-CSF should be considered. Although the integration of the novel anti-myeloma agents in the upfront treatment of PCM has started questioning the place of the high dose therapy supported with AHCT as first line approach, it is still the gold standard approach in elligible patients with PCM. This requires the mobilization and collection of adequate number of PBPCs following an initial induction threatment. Traditionally, G-CSF alone or after chemotherapy (mostly CY) have been the most commonly used protocols. Generally, CY plus G-CSF is used in the second mobilization attempt after failing G-CSF. However, this approach does not improve the overall outcome of the myeloma patients. So, it is unnecessary to expose the patients to toxic effects of chemotherapy for sole mobilization purposes. And the combined cytotoxic

chemotherapies are better reserved for relapsed or refractory cases. Current studies focus on the novel investigational agents as adjuncts to G-CSF to improve the PBPC yields. Plerixafor, which selectively and reversibly antagonizes CXCR4 and disrupts its interaction with SDF-1, has the ability of rapid mobilization of PBPCs from BM and gained approval as an adjunct to G-CSF for poor mobilizers. At the present, it is challenging to search for the best approach using the available drugs with appropriate timing to provide sufficient CD34+ yield after initial mobilization attempt and in a cost-effective manner avoiding further mobilization attempts and exposure to chemotherapy.

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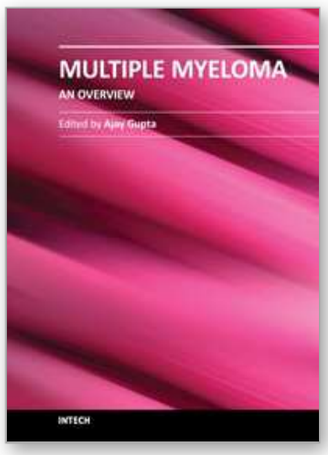

Multiple Myeloma - An Overview

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Multiple myeloma is a malignant disorder characterized by the proliferation of plasma cells. Much insight has been gained into the molecular pathways that lead to myeloma and indeed much more remains to be done. The understanding of these pathways is closely linked to their therapeutic implications and is stressed upon in the initial chapters. Recently, the introduction of newer agents such as bortezomib, lenalidomide, thalidomide, liposomal doxorubicin, etc. has led to a flurry of trials aimed at testing various combinations in order to improve survival. Higher response rates observed with these agents have led to their integration into induction therapies. The role of various new therapies vis a vis transplantation has also been examined. Recent advances in the management of plasmacytomas , renal dysfunction, dentistry as well as mobilization of stem cells in the context of myeloma have also found exclusive mention. Since brevity is the soul of wit our attempt has been to present before the reader a comprehensive yet brief text on this important subject.

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