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REVIEW

Autologous haematopoietic stem cell mobilisation in multiple myeloma and lymphoma patients: a position statement from the European Group for Blood and Marrow Transplantation

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Autologous haematopoietic SCT with PBSCs is regularly used to restore BM function in patients with multiple myeloma or lymphoma after myeloablative chemotherapy. Twenty-eight experts from the European Group for Blood and Marrow Transplantation developed a position statement on the best approaches to mobilising PBSCs and on possibilities of optimising graft yields in patients who mobilise poorly. Choosing the appropriate mobilisation regimen, based on patients' disease stage and condition, and optimising the apheresis protocol can improve mobilisation outcomes. Several factors may influence mobilisation outcomes, including older age, a more advanced disease stage, the type of prior chemotherapy (e.g., fludarabine or melphalan), prior irradiation or a higher number of prior treatment lines. The most robust predictive factor for poor PBSC collection is the $CD34^+$ cell count in PB before apheresis. Determination of the $CD34^+$ cell count in PB before apheresis helps to identify patients at risk of poor PBSC collection and allows pre-emptive intervention to rescue mobilisation in these patients. Such a proactive approach might help to overcome deficiencies in stem cell mobilisation and offers a rationale for the use of novel mobilisation agents.

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INTRODUCTION

Autologous haematopoietic SCT (auto-HSCT) aims to restore BM function after high-dose chemotherapy. In the context of auto-HSCT, mobilised PBSCs are currently the preferred source of HSCs worldwide for adult patients with multiple myeloma (MM) and lymphoma (non-Hodgkin's and Hodgkin's lymphoma).[1–3] Auto-HSCT with PBSCs is favoured because it leads to faster engraftment and haematologic reconstitution versus BM infusion, resulting in potentially improved patient outcomes.[1] Moreover, some studies demonstrated that the use of PBSCs was associated with better quality of life and reduced total costs.[1,2,4,5]

HSCs usually circulate in a very small number in PB;[6] therefore, their mobilisation from BM to PB is an essential part of auto-HSCT programs. Cytokines such as G-CSF, alone or in combination with chemotherapy, are typically used for PBSC mobilisation.[1,2,7] Compared with G-CSF-based mobilisation, chemo-mobilisation (i.e., chemotherapy+G-CSF) has advantages in terms of putative antitumour effect and higher probability of obtaining grafts with a sufficient $CD34^+$ cell count with lower numbers of aphereses.[1,7] However, disadvantages of chemo-mobilisation include increased toxicity and morbidity, and the need for hospitalisation (depending on the chemotherapy schedule; e.g., cyclophosphamide-based mobilisation is possible in an outpatient setting).[1,7]

Despite widespread and established practice, current mobilisation strategies vary between centres and differ in terms of feasibility and outcome.[2,7] Although the majority of patients are able to mobilise sufficient $CD34^+$ cells for at least a single autograft, approximately 15% fail to do so.[8] If two autografts are needed for a specific treatment strategy, even more patients fail to reach their individual collection goal. Newer approaches aiming to optimise mobilisation procedures include off-label use of pegylated G-CSF,[9–12] erythropoietin,[13] SCF[14,15] and plerixafor.[16–18] Nevertheless, it is necessary to optimise the current mobilisation approaches and to identify upfront the patients at risk of mobilisation failure.

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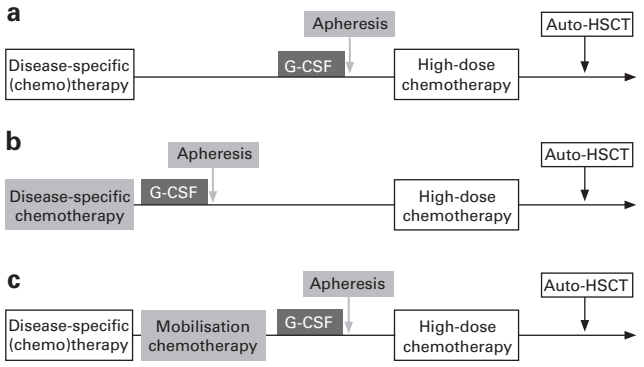

Figure 1. Current auto-HSCT mobilisation strategies: steady-state mobilisation (**a**; cytokines alone), chemotherapy-based mobilisation using disease-specific chemotherapy (**b**) or separate mobilisation chemotherapy (**c**).

PURPOSE AND METHOD

This review generated by 28 experts from the European Group for Blood and Marrow Transplantation (EBMT) attempted to develop a position statement on best approaches for auto-HSC mobilisation in patients with MM and lymphoma, on factors predictive of poor mobilisation or mobilisation failure and on potential optimisation options for poor mobilisers. The position statement is based on currently available literature and clinical practice of the expert group.

OVERVIEW OF CURRENT AUTO-HSC MOBILISATION APPROACHES

Steady-state (cytokines only)

Monotherapy with G-CSFs remains the only available option for steady-state mobilisation, as GM-CSF is no longer available in many countries after commercial failure and withdrawal. G-CSF treatment leads to granulocyte activation/expansion and release of various proteases, eventually resulting in cleavage of cell–extracellular adhesion molecules that retain HSCs in BM.[6] Currently, the G-CSF cytokines filgrastim and lenograstim have marketing authorisation for mobilisation of auto-HSCs in Europe.[19,20] The approved doses/schedules are filgrastim 10 μg/kg per day subcutaneously for 5–7 consecutive days and lenograstim 10 μg/kg per day subcutaneously for 4–6 days; leukapheresis should be performed on days 5 or 6 (filgrastim) and between days 5 and 7 (lenograstim). Mobilisation with cytokines alone (Figure 1a) is well tolerated, but their use can be limited by the feasibility of embedding them into individual, study-based treatment plans or by suboptimal PBSC yields.

Chemo-mobilisation

Adding chemotherapeutic agents to cytokines may increase PBSC yields and can further decrease tumour burden.[1,7] However, the PBSC mobilisation window is less predictable compared with steady-state approaches,[1,7] causing potential problems with apheresis scheduling. In addition, the incidence and severity of side effects with chemotherapy+G-CSF is increased compared with G-CSF alone.[21–23] The approved doses for PBSC mobilisation after myelosuppressive chemotherapy are filgrastim 5 μg/kg per day subcutaneously and lenograstim 150 μg/m^2 per day (i.e., therapeutically equivalent of 5 μg/kg per day subcutaneously), starting within 1–5 days after completion of chemotherapy until last leukapheresis.[19,20]

Chemotherapy-based mobilisation may be part of the disease-specific chemotherapy (Figure 1b) or of separate chemo-therapeutic course(s) in addition to disease-specific treatment (Figure 1c). The choice of a specific chemo-mobilisation approach is based on patient disease characteristics and on local clinical practice guidelines (Table 1). In MM patients, high-dose cyclophosphamide+G-CSF is probably the most commonly used chemo-mobilisation strategy,[21,23] whereas some studies also suggest etoposide-based mobilisation approaches.[24] With the advent of new therapeutic agents, such as proteasome inhibitors and immunomodulatory drugs,[25] the role of high-dose cyclophosphamide as therapeutic agent in MM now becomes more questionable given its relatively small antitumour effect.[26] In lymphoma patients, chemotherapy+G-CSF as part of the disease-specific induction and salvage regimens has always been the preferred method. Such approach can eliminate the need for additional chemo-mobilisation or steady-state mobilisation before auto-HSCT in these heavily treated patients.[27–30] Furthermore, these disease-specific chemotherapy combinations have been shown to be more effective than cyclophosphamide-based chemo-mobilisation.[29,30]

Table 1. Current chemo-mobilisation approaches (selection based on clinical practice of the expert group)

Disease-specific chemo-mobilisation	*Separate mobilisation chemotherapy*
MM	Cyclophosphamide-based
CAD, DPACE, VDT-PACE	
(Relapsed) lymphoma	Etoposide-based
ABVD, BEACOPP, (R)-CHOP, (R)-DA-EPOCH, (R)-DHAP, carbo-DHAP, dexa-BEAM, (R)-ESHAP, (R)-mini-BEAM, (R)-ICE, IVE, R-ACVBP, R-bendamustine, VIM	

Abbreviations: ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; ACVBP = doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone; BEACOPP = bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; BEAM = BCNU, etoposide, ara-C (cytarabine), melphalan; CAD = cyclophosphamide, doxorubicin, dexamethasone; carbo = carboplatin; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; DA-EPOCH = dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; Dexa = dexamethasone; DHAP = dexamethasone, ara-C, cisplatin; DPACE = dexamethasone, platinum, doxorubicin, cyclophosphamide, etoposide; ESHAP = etoposide, methylprednisolone, ara-C, cisplatin; ICE = ifosfamide, carboplatin, etoposide; IVE = ifosfamide, etoposide, epirubicin; MM = multiple myeloma; R = rituximab; VDT-PACE = bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, etoposide; VIM = etoposide, ifosfamide, mitoxantrone.

Plerixafor

Plerixafor, a novel chemokine-receptor (CXCR4) antagonist, disrupts the interaction between stromal-deriving factor 1 and CXCR4, thereby enhancing the HSC mobilisation effect of G-CSF.[31] In Europe, plerixafor is approved for use in combination with G-CSF for auto-HSC mobilisation in patients with lymphoma or MM whose cells mobilise poorly.[32] The approved dose is 240 μg/kg per day subcutaneously 6–11 h before initiation of apheresis following 4-day G-CSF pretreatment.

Plerixafor plus G-CSF alone or G-CSF+chemotherapy has been shown to be effective and well tolerated in patients with MM or lymphoma, including poor mobilisers, with superior efficacy to G-CSF alone or G-CSF+chemotherapy.[13,16,17,33–37] Numerous studies reported that plerixafor plus G-CSF is effective as rescue therapy during HSC mobilisation.[36,38–41] Whether the addition of plerixafor results in a benefit for patients in terms of clinical outcomes is still under investigation.

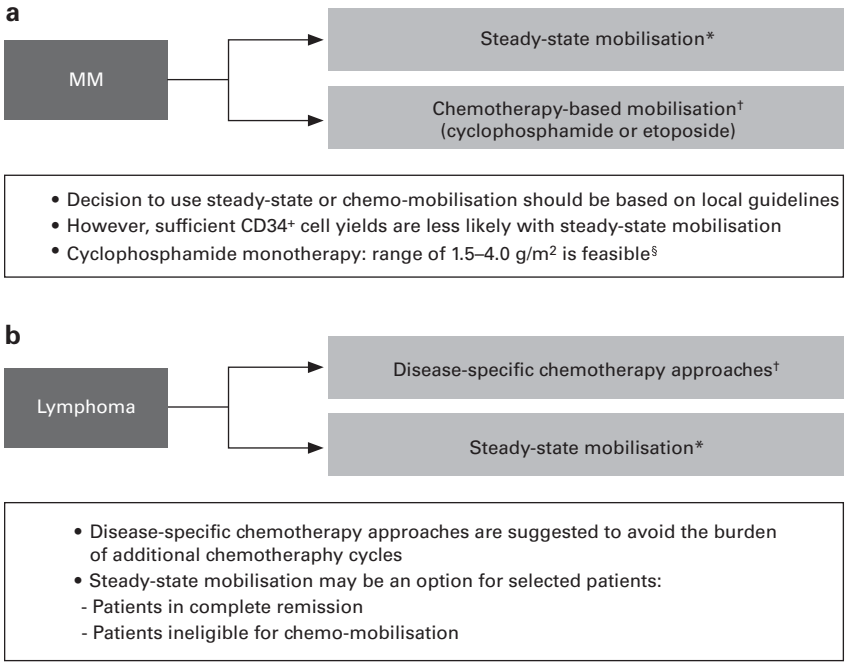

Figure 2. Position statement: PBSC mobilisation strategies for MM (**a**) and lymphoma patients (**b**). *G-CSF only; †G-CSF+chemotherapy; §higher doses of cyclophosphamide may be used based on available data; however, the aim should be to keep the duration of neutropenia as short as possible.

OPTIMISING GRAFT 'QUANTITY' (CD34$^+$ CELL YIELD)

Mobilisation regimen

In clinical practice, filgrastim and lenograstim may be used interchangeably and modifications of the approved label may be applied depending on local guidelines and treatment plans. Higher G-CSF doses (⩾10 μg/kg per day) or alternate application schedules (two times 5 μg/kg per day instead of one time 10 μg/kg per day) have been investigated to further enhance the number of harvested auto-HSCs.[42,43] However, further research is required. In addition, high G-CSF doses may increase the risk of splenic rupture.[44] As mentioned above, CD34$^+$ cell yields can be further increased by mobilisation with chemotherapy+G-CSF compared with G-CSF monotherapy.[21–23] The addition of plerixafor to standard mobilisation strategies has been shown to increase CD34$^+$ cell yields in known or predicted poor mobilisers.[13,16,17,33–37,39,40]

Timing

The timing of mobilisation regimen administration and apheresis may also influence CD34$^+$ cell yields. Recent data suggest that auto-HSC collection efficacy is higher and the proportion of patients with optimal harvest is larger when G-CSF is given 3 h before apheresis versus administration on the evening before apheresis.[45] Nevertheless, further research is needed to confirm these data. Plerixafor was shown to mobilise adequate auto-HSC yields when administered as rescue treatment before or during apheresis in patients with insufficient auto-HSC mobilisation after G-CSF monotherapy or chemo-mobilisation.[38–41] Earlier detection of PBSC mobilisation (based on CD34$^+$ cell-count assessments on day 4 versus 5) can help determine whether plerixafor should be administered, and has been suggested to further decrease the risk of mobilisation failure.[46]

Technical aspects

The flow cytometry protocol for CD34$^+$ cell measurement is a critical step in monitoring the HSC mobilisation process.[47] A validated protocol and external quality control are recommended.[48] CD34$^+$ cell collection has been shown to be more efficient with larger apheresis volumes (4.0–5.3 times the patient's total blood volume)[49,50] and no difference in CD34$^+$ cell viability was observed compared with normal-volume apheresis (2.7–3.5 times the patient's total blood volume).[49] Therefore, enhanced volumes are recommended for apheresis in relatively poor mobilisers or patients with high individual CD34$^+$ cell collection goal (⩾3 transplants). For patients who still mobilise poorly with larger-volume approaches, plerixafor addition to standard mobilisation strategies may sufficiently enhance mobilisation efficacy.[51] Nevertheless, not all patients are eligible for enhanced volume strategies. Larger transfusion volumes and related higher DMSO contents have been associated with increased risk of cardiac side effects.[52]

Position statement on current auto-HSC mobilisation approaches and their optimisation

Auto-HSC mobilisation approaches for MM and lymphoma patients suggested by the expert group are shown in Figure 2. If required, strategies are recommended to be optimised by remobilising with cytokines alone or by changing the previously chosen chemo-mobilisation approach (e.g., switch from steady-state to chemo-mobilisation, or choose an alternative chemo-mobilisation strategy if patients failed to mobilise after an initial chemotherapy-based approach). In addition, new agents such as plerixafor or the use of large-volume apheresis can further improve mobilisation outcomes. For the latter, processing of up to three times the total blood volume is suggested as feasible without impairing the patient's tolerance.

The optimal time to start apheresis is more predictable for patients mobilised with G-CSF alone than for those mobilised with chemotherapy+G-CSF. For patients who were mobilised with chemotherapy+G-CSF and showed too low CD34$^+$ counts on the estimated day of apheresis, the expert group suggests reassessing CD34$^+$ counts after 1 day. This ensures that leukapheresis is started on the optimal day. Up to four leukapheresis sessions can be recommended as feasible. However, the group raised the issue of cost-effectiveness of such practice.

AUTOGRAFT 'QUALITY'

Cell subsets other than CD34$^+$ cells

Recent data suggest that the quality of CD34$^+$ cells from poor mobilisers is comparable to those from adequate mobilisers in patients treated with filgrastim;[53] the dose of mobilised CD34$^+$ cells per kg mainly determines neutrophil and platelet engraftment after auto-HSCT.[54] The addition of plerixafor to G-CSF alone or G-CSF+chemotherapy not only mobilises more CD34$^+$ cells but also seems to increase the proportion of more-primitive HSC subsets, the absolute lymphocyte count and the numbers of various lymphocyte subsets (CD19$^+$ B lymphocytes, CD3$^+$ T cells and natural killer (NK) cells) in the autograft.[55–59] Preliminary data suggest a positive correlation between the number of reinfused NK cells and early absolute lymphocyte recovery after auto-HSCT.[60] However, further investigation is needed to evaluate potential effects of autograft cell subsets on the patients' clinical outcomes.

Tumour cell contamination

Auto-HSCT is associated with the risk of tumour cell contamination of the graft. Current mobilisation strategies with G-CSF or G-CSF +chemotherapy vary not only in auto-HSC yields and safety, but also in levels of autograft contamination with tumour cells.[61–66] Whether the antitumour effect of chemo-mobilisation also translates into a lower risk of tumour cell contamination, compared to steady-state mobilisation, remains controversial.[62] The integration of novel agents into mobilisation regimens so far does not appear to increase tumour cell contamination of the graft.[67,68] A large currently ongoing trial (Collaboration between EBMT and Genzyme to collect Autologous transplant outcomes in Lymphoma and Myeloma patients (CALM)) will compare the outcomes of patients transplanted with plerixafor-mobilised cells between 2008 and 2011 to those of equivalent patients transplanted without plerixafor to determine whether plerixafor mobilises increased rates of malignant cells (data to be published; patients will be followed until 2014). The impact of autograft tumour cell contamination on long-term safety and clinical outcome is still controversial.[62] Randomised phase III studies suggest that tumour cell contamination of the graft does not significantly affect PFS or OS.[5,62–64,69–71] On the other hand, results from a report of the Centre for International Blood and Marrow Transplant Research indicate that syngeneic transplants lead to better outcome than autologous transplants, suggesting that contamination is a problem in myeloma and probably also in lymphoma.[72,73] It should also be noted that most clinical trials in MM patients were performed before the recent implementation of novel treatments. Therefore, *in vivo* tumour debulking may be much higher today, resulting in a higher potential of contaminated autografts and reinfused tumour cells inducing relapse. This makes it difficult to draw definitive conclusions on the role of residual plasma cells and *ex vivo* purging.

Position statement on autograft 'quality'

Determination of cell subsets other than CD34$^+$ cells is not routinely performed in clinical practice, but only in clinical trials. Accordingly, assessment of tumour cell contamination in routine clinical practice may not be valuable but can be of interest in clinical trials.

FACTORS PREDICTIVE OF POOR MOBILISATION OR MOBILISATION FAILURE

Factors described as predictive of impaired HSC collection or mobilisation failure include: older age; female sex; diagnosis (lymphoma worse than MM); longer time since diagnosis; more advanced disease; previous radiotherapy and/or chemotherapy (especially fludarabine and other purine analogues, and melphalan); higher number of previous therapy lines; longer time from last chemotherapy to mobilisation initiation; previous auto-HSCT; low haemoglobin, WBC, or platelet levels before mobilisation; and low CD34$^+$ cell counts in BM before mobilisation and in PB before apheresis.[74–88] Whether prior treatment with new therapies such as lenalidomide and rituximab negatively affects the mobilisation outcomes in MM and lymphoma patients, respectively, is controversial.[77,78,82,84,89–91] Adaptation of the mobilisation strategy and/or the addition of novel agents (e.g., plerixafor) to conventional regimens may overcome the negative effect of prognostic factors for poor mobilisation.[24,27,34–36,92–94] Nevertheless, there is an urgent need to define which patient population might benefit from optimised mobilisation approaches to help clinical decision-making.

Algorithms to define poor mobilisers

In a retrospective analysis of 840 patients with MM or non-Hodgkin's lymphoma, 129 patients (15%) were identified as poor mobilisers and divided into three categories based on CD34$^+$ levels in PB before leukapheresis: 'borderline' poor mobilisers (11–19/μL at maximum stimulation), 'relative' poor mobilisers (6–10/μL) and 'absolute' poor mobilisers (<5/μL).[8] Diagnosis, sex, age, body weight and previous irradiation made no significant difference in HSC mobilisation capacity. Only the number of previous chemotherapy cycles and prior melphalan treatment had a significant impact on the ability to mobilise HSCs. In another retrospective analysis of 1556 patients with lymphoproliferative disorders initially mobilised with G-CSF alone, sensitivity–specificity analysis was used to identify ideal PB CD34$^+$ count cut-points that would allow early intervention and prevent collection failure.[86] In patients with plasma cell disorders, PB CD34$^+$ counts of 11, 17, 21 and 28/μL by day 4 or 5 were required to collect a minimum of 2, 4, 8 or 12×10^6 CD34$^+$ cells per kg, respectively. A CD34$^+$ yield $<0.8\times10^6$ cells per kg on day 1 of apheresis was predictive of $<2\times10^6$ CD34$^+$ cells per kg. For patients with non-Hodgkin's or Hodgkin's lymphoma, PB CD34$^+$ counts of <6 and <15/μL on day 4 or 5 predicted failure to achieve a target collection of 2 and 4×10^6 cells per kg, respectively.

The Gruppo Italiano Trapianto di Midollo Osseo proposed a definition of poor mobilisers in lymphoma and MM patients using an analytic hierarchical process.[94] Patients are defined as 'proven' poor mobilisers when (1) after adequate mobilisation (G-CSF 10 μg/kg if used alone or $\geqslant5$ μg/kg after chemotherapy), the circulating CD34$^+$ cell peak is <20/μL for up to 6 days after mobilisation with G-CSF or up to 20 days after G-CSF +chemotherapy, or (2) they yield $<2.0\times10^6$ CD34$^+$ cells per kg in $\leqslant3$ aphereses. Patients are 'predicted' poor mobilisers if they (1) failed a previous collection attempt, (2) previously received extensive radiotherapy or full courses of therapy affecting HSC mobilisation and (3) meet two of the following criteria: advanced disease ($\geqslant2$ lines of chemotherapy), refractory disease, extensive BM involvement or cellularity $<30\%$ at the time of mobilisation, and age $\geqslant65$ years.

Several groups have developed algorithms to guide the use of plerixafor.[85,95–97] Costa *et al.*[97] developed and validated a decision-making algorithm based on the PB CD34$^+$ cell count on day 4 of G-CSF administration and the collection target of CD34$^+$ cells to guide cost-effective use of plerixafor for auto-HSC mobilisation (continuing G-CSF only or adding plerixafor). Subsequently, they showed that patient-adapted plerixafor use based on this algorithm was superior to cyclophosphamide plus growth factor[98] and successfully mobilised HSCs in MM patients previously treated with lenalidomide.[99] Abhyankar *et al.*[95] developed a risk-based approach to optimise HSC collection with plerixafor by identifying potential poor mobilisers upfront. The

Table 2. Factors described as predictive of poor mobilisation or mobilisation failure

Predictive factors	*References*
Age	
Older patients	81,83,100
Disease	
More advanced stage	83,85,100
Prior chemotherapy	
Higher no. of prior treatment lines	8,75,83,85,88,100
Type of chemotherapy (fludarabine, lenalidomide (controversial) or melphalan)	8,75–78,82–85,87,88,91,100
Prior irradiation	75,83,100
Low CD34$^+$ cell count in PB before apheresis	8,75,85,86
Low platelet count before mobilisation (controversial)	75,79–81,88

plerixafor algorithm takes into account the number of circulating CD34$^+$ cells per μL on day 5 of G-CSF mobilisation, the desired number of CD34$^+$ cells per kg needed per transplant ($\geqslant 2.5 \times 10^6$/kg for 1 transplant and $\geqslant 5 \times 10^6$/kg for >1 transplants), and the day-1 CD34$^+$ collection yield. A day-5 CD34$^+$ circulating level of < 10 cells per μL (for 1 transplant), or < 20 cells per μL (for >1 transplant), or a day-1 CD34$^+$ collection of less than one-half of the total CD34$^+$ dose needed, prompted the use of plerixafor. Data demonstrated that this approach helped decrease the need for remobilisation and reduce the number of collection days needed.

Position statement on predictive factors for poor mobilisation, CD34$^+$ cell-count determination and proactive intervention to rescue PBSC collection

Factors considered by the expert group to be predictive of poor mobilisation in MM and lymphoma patients in daily clinical practice are listed in Table 2. Of these, the CD34$^+$ cell count in PB before apheresis is the most robust predictor for poor PBSC collection.[8,85,86,100] Thus, determination of CD34$^+$ cell counts in PB before apheresis is suggested by the expert group to estimate the patient's risk of poor PBSC collection and to consider additional intervention for patients at risk (Figure 3). For patients with >20 CD34$^+$ cells per μL in PB before apheresis, no proactive intervention is needed, whereas the group suggests pre-emptive use of plerixafor to reach a minimum cell target of 2×10^6 CD34$^+$ cells per kg body weight for patients with < 10 CD34$^+$ cells per μL in PB before apheresis. For patients with 10–20 CD34$^+$ cells per μL at the mobilisation peak before apheresis (i.e., grey zone), a dynamic approach is suggested, also taking into account other previously published predictive factors (Table 2) and the target number of aphereses before applying plerixafor (e.g., when collecting PBSCs for $\geqslant 2$ transplants in MM patients, pre-emptive intervention with plerixafor may become mandatory for patients with 10–20 CD34$^+$ cells per μL before apheresis). These suggestions are to be considered the minimum number of CD34$^+$ cells for auto-HSCT. Higher CD34$^+$ cell counts before auto-HSCT may reduce the need of post-HSCT support. The EBMT 'Haematopoietic Stem Cell Mobilisation and Apheresis' handbook recommends optimal levels being $\geqslant 5 \times 10^6$ CD34$^+$ cells per kg for a single transplant (http://www.ebmt.org/Contents/Resources/Library/Resourcesfornurses/Documents/Haematopoietic%20Stem%20Cell%20Mobilisation%20and%20Apheresis%20Handbook.pdf; accessed on 19 November 2013).

In the opinion of the expert group robust validation of these factors in a prospective registration trial is desirable. Although several algorithms were recently proposed to predict PBSC collection failure using PB CD34$^+$ counts before leukapheresis as threshold to stratify patients at risk and to trigger proactive intervention with plerixafor,[8,85,86,95–97,100] there is a need for optimised algorithms to predict apheresis yields based on circulating CD34$^+$ cell numbers. Also, readily available, robust, and harmonised techniques for such CD34$^+$ cell number determination are required.

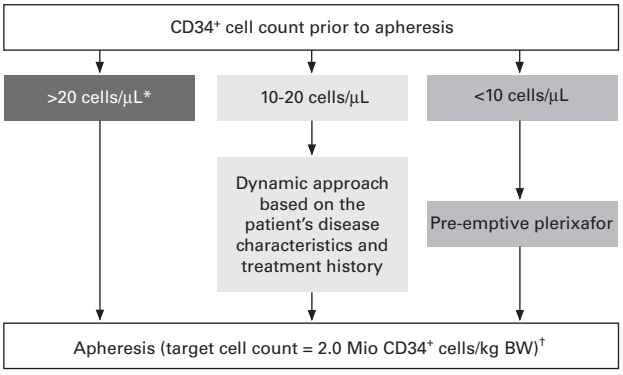

Figure 3. Position statement: proactive intervention to rescue mobilisation failure. *No proactive intervention required; †a target cell count of >2.0 Mio CD34$^+$ cells per kg body weight (BW) may be needed depending on the patient's disease and treatment features, and the individual collection goal.

CONCLUSIONS

PBSC mobilisation can be optimised with an appropriate strategy adapted to each patient, based on the patient's disease and treatment features and the individual collection goal. A low CD34$^+$ cell count in PB before apheresis is a candidate predictor for poor PBSC collection. The expert group suggested that determination of CD34$^+$ cell counts before apheresis may estimate the patient's risk for poor PBSC collection and may allow proactive intervention to rescue mobilisation failure.

CONFLICT OF INTEREST

MM: Research support and honoraria from Sanofi, Amgen and Chugai, whose products are discussed here. KH: Consulting fee or honorarium and support for travel to meetings from Genzyme/Sanofi; board membership for Pfizer and Noxxon; payment for lectures including service on speakers' bureaus from Janssen; and travel/accommodations/meeting expenses unrelated to activities listed from Roche. NK: Honorarium for lectures from Sanofi; and consultant fee from Noxxon. MA: Consulting fee or honorarium from ETICHO. GWB: Sponsorship for participation in scientific conferences from Sanofi; membership of Mozobil advisory boards for Sanofi; and reimbursements for trainings from Sanofi. AB: Honoraria from Sanofi whose products are discussed here. KD: Speaker's fees and honoraria for medical advisory board work from Genzyme and Sanofi Europe between 2009 and 2012 inclusive. GL: Consulting fee or honorarium from ETICHO. CG: None disclosed. OJ: Consulting fee or honorarium from ETICHO; and consultancy for Sanofi. MWK: consultancy for GlaxoSmithKline, Bayer and Merck. ZK: Consultancy for CEEOR; payment for lectures including service on speakers' bureaus from Sanofi-Aventis; and travel/accommodations/meeting expenses unrelated to activities listed from Sanofi-Aventis. RML: Payment for lectures including service on speakers' bureaus from Sanofi; and consultancy and board membership for Sanofi. GM: Grant and fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees and the like from ETICHO; support for travel to meetings or other purposes from Genzyme; expert testimony for Janssen and ETICHO; and payment for lectures including service on speakers' bureaus from Janssen. AN: Research grant from Genzyme/Sanofi; and honorarium for participating in a scientific advisory board. HCS: Membership of an advisory board for Sanofi. DS: Honoraria and research grants from Genzyme and Amgen; and membership of advisory boards for Genzyme and Amgen. AS: Participation in Sanofi-organised advisory boards. NW: Speaker's fee from Sanofi and membership of the advisory board. PW: Honorarium for lectures from Sanofi; and consulting fee or honorarium from ETICHO. CC: Consultancy for Terumo BCT, Novartis and Sanofi-Genzyme; and membership of an advisory board for

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