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ORIGINAL ARTICLE

Proposed definition of 'poor mobilizer' in lymphoma and multiple myeloma: an analytic hierarchy process by *ad hoc* working group Gruppo ItalianoTrapianto di Midollo Osseo

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Many lymphoma and myeloma patients fail to undergo ASCT owing to poor mobilization. Identification of poor mobilizers (PMs) would provide a tool for early intervention with new mobilization agents. The Gruppo italiano-Trapianto di Midollo Osseo working group proposed a definition of PMs applicable to clinical trials and clinical practice. The analytic hierarchy process, a method for group decision making, was used in setting prioritized criteria. Lymphoma or myeloma patients were defined as 'proven PM' when: (1) after adequate mobilization (G-CSF 10 μg/kg if used alone or ⩾5 μg/kg after chemotherapy) circulating $CD34^+$ cell peak is <20/μL up to 6 days after mobilization with G-CSF or up to 20 days after chemotherapy and G-CSF or (2) they yielded $<2.0 \times 10^6$ $CD34^+$ cells per kg in ⩽3 apheresis. Patients were defined as predicted PMs if: (1) they failed a previous collection attempt (not otherwise specified); (2) they previously received extensive radiotherapy or full courses of therapy affecting SC mobilization; and (3) they met two of the following criteria: advanced disease (⩾2 lines of chemotherapy), refractory disease, extensive BM involvement or cellularity <30% at the time of mobilization; age ⩾65 years. This definition of proven and predicted PMs should be validated in clinical trials and common clinical practice.

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Introduction

ASCT of PBSCs is the first option for patients with relapsed lymphoma or multiple myeloma (MM).[1–8] Successful engraftment correlates with the number of $CD34^+$ hemopoietic progenitors cells infused;[9–12] however, a proportion of MM or lymphoma patients fail to mobilize PBSCs and cannot proceed to ASCT.[12–18]

The definition of 'poor' mobilization varies, owing to the different parameters set to evaluate the extent of mobilization: peak of $CD34^+$ cells in PB, cumulative apheresis yield or simply percent of candidate patients undergoing ASCT. Various criteria have been proposed to define a successful $CD34^+$ cell mobilization and the adequate apheresis yield, but these data are difficult to analyse and compare with each other.[10,12,15,19,20] Therefore, a systematic review of the literature does not provide a clear definition of poor mobilization.

Standardization of criteria for diagnosis, prognosis and response is a major goal of the haematology community and may facilitate comparison among retrospective and prospective data. For these reasons, Gruppo italianoTrapianto di Midollo Osseo GITMO (Italian Group for Stem Cell Transplantation) convened a Working Group (WG) to clarify the definition of 'poor mobilizer' (PM). This is essential for the assessment of PBSCs' mobilization in clinical trials and as a decision criterion for streamlining mobilization strategies in clinical practice. To develop the criteria for the definition of the PM, GITMO-WG adopted a flexible decision-making method: the analytic hierarchy process (AHP) was developed to establish priorities and make the best decision when both the quantitative and qualitative aspects of a decision needed to be considered and a poor information base was available.[21] AHP is a multistep process, including four major phases: (1) defining the goal; (2) decomposing the problem and identifying critical issues; (3) categorizing/framing the main criteria; and (4) defining a hierarchy of the criteria. The participants' subjective judgment allows them to overcome the

scarcity or inconsistency of available information on the problem; finally, they are forced to quantify their subjective judgments by pairwise comparisons among the decided criteria. AHP has been successfully applied to develop the criteria of refractoriness, resistance or response in haematology.[22,23] The final definition of PM developed by the GITMO-WG is reported here, along with details with regard to the AHP method employed for defining criteria for poor PBSC mobilization.

Methods

A GITMO-WG of seven experts, with specific expertise in the field of PBSCs' mobilization, harvest, $CD34^+$ cell count and ASCT, was selected to develop a standard definition of patients with lymphoma or MM failing to mobilize adequate $CD34^+$ cells to proceed to ASCT (referred to as PM).

English-language articles were extracted focusing clinical studies of PBSC mobilization in lymphoma or MM patients and particularly the studies aimed at defining the adequate dose of $CD34^+$ cells for ASCT; AHP was used to identify the values and criteria that define poor mobilization. The participants first framed the conceptual criteria, and then the operational criteria: they are qualitative and quantitative, respectively. For instance, 'old age' is a conceptual criterion, whereas 'older than 65 years' is an operational criterion. Conceptual criteria were selected by the first questionnaire, if there was $>80\%$ agreement among the participants. Rank of the core set criteria was assigned through a number from 1 to 9 and the geometric mean of the ranks was calculated. Framing of operational criteria was obtained through the second questionnaire and by consensus through the Nominal Group Technique.[24] The participants set the hierarchy of the operational criteria by pairwise comparison. Each participant analysed 55 couples of operational criteria and assigned a relative weight of one criterion with respect to the other one: if the former criterion was judged to have a higher importance than the latter, a weight from 1 to 9 was indicated; if the former criterion was less important than the latter, a weight from 1/9 to 1 was indicated. Inter-participant standardized geometric means of the weights for each criterion were calculated, and subsequently, inter-participant means were also calculated.

Finally, 36 scenarios were built by the combination of operational criteria: for each scenario, the participants were requested to check whether the definition of 'predicted PM' held. A representative scenario is: 'The patient is a predicted PM if he or she is older than 65 years and shows extensive BM involvement at mobilization'. Each scenario received approval by each participant. The percent agreement of each scenario was compared with the sum of weights (obtained by pairwise comparison) of the criteria composing the scenario itself, and plotted.[21]

Results

The GITMO-WG agreed that establishing a clear definition of PM would help to optimize mobilization and transplant strategies (Figure 1); this might eventually reduce the need for: (1) repeated mobilization procedures; (2) SC harvest from BM; and (3) switch to allogeneic transplantation or other strategies.

Decomposition of the problem

GITMO-WG deemed that the issue of 'poor mobilization' may pertain to three sequential phases:

(i) before the mobilizing treatment, when the mobilization procedure is planned;
(ii) during the mobilization procedure; and
(iii) at the completion of the whole PBSCs collection process.

The criteria supporting a prediction of 'poor mobilization' in the first phase may help one to identify patients at 'high risk' of 'poor mobilization' (predicted PM) and cannot be amended because they pertain to a patient's history, age or disease status. The criteria supporting a judgment of 'poor mobilization' during the second phase are markers of the biological capability of the patient to mobilize SC. They are dynamic and subject to change while mobilization is ongoing (for example, increase in the dose of G-CSF or addition of a new drug). The third phase involves both the host (history and mobilization ability) and the performance of the apheresis procedure (apheresis volumes, timing of collections, efficiency, and so on). Keeping in mind an operational definition of poor mobilization, GITMO-WG agreed that the criteria for defining a 'proven PM' pertain both to the second and third phase. However, even if an adequate $CD34^+$ cell peak after mobilization predicts a successful collection, it cannot be considered a sufficient condition for a good harvest, as the latter is dependent on correct timing and performance of the apheresis procedure.

Framing of criteria

Through the first questionnaire, the GITMO-WG analysed 33 candidate conceptual criteria (Table 1); among them two (nos. 2 and 7) were selected for 'proven PM' and 'proven poor mobilization' (PPM) and 10 for 'predicted PM' (nos. 14–19 and 21–24); these latter were reduced to eight as 'disease status' was split into 'advanced disease' and 'refractory disease'; 'previous therapy with lenalidomide'

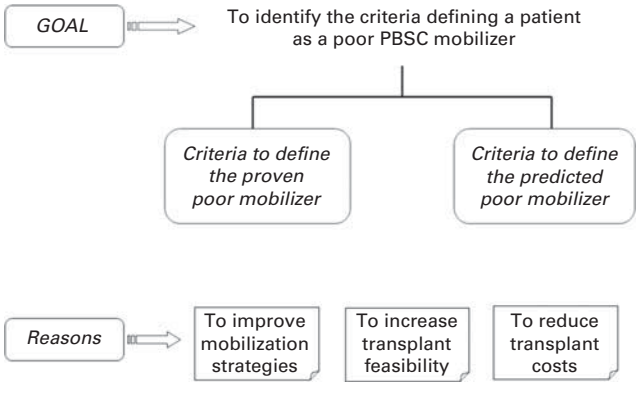

Figure 1 Goals and reasons of the GITMO-WG project.

Table 1 Candidate conceptual criteria evaluated in the first questionnaire; the core set criteria selected after the first questionnaire are represented in italic bold characters

	Conceptual criteria	*Percentage of agreement*	*Main references*
1	Harvested CD34+ cells	86	9,11,12,19,20,25–29
2	***Harvested CD34$^+$ cells per planned SCT***	***100***	
3	No. of planned ASCT	57	
4	Overall harvested CD34$^+$ cells after two aphereses	71	20,30,31,28
5	Harvested CD34+ cells at first apheresis	57	
6	Pre- and post-apheresis CD34$^+$ cell count	57	30–35
7	***Absolute number of circulating CD34$^+$ cells per μL***	***100***	
8	Overall number of nucleated cells harvested	14	26,35,36
9	Overall number of nucleated cells harvested per planned SCT	14	
10	Planned volumes of apheresis	57	30,37–40
11	Chemo-mobilization	71	41–50
12	Mobilizing G-CSF dose	71	
13	Diagnosis of underlying disease	71	49,50,51–67
14	***Age***	**100**	
15	***Disease status***	**100**	9,10,12,14,52,56,59,60,68
16	***BM involvement***	**86**	
17	***Pre-mobilization BM cellularity***	**86**	
18	***No. of previous cytotoxic therapy lines***	**100**	17,18,52–55,59,62,63,69,70
19	***Duration of previous chemotherapy***	***71***	
20	Interval elapsed since previous chemotherapy	29	
21	***Previous extensive radiotherapy***	***100***	36,48,52,65,67,68,71,72
22	***Previous alkylating therapy***	***86***	
23	***Previous therapy with lenalidomide***	***86***	73–76
24	***Previous therapy with fludarabine***	***86***	77–82
25	Platelet count at first apheresis	29	12,14,15,17,30,33–35,38–40,49,56,50,83–86
26	Time to platelet recovery after chemo-mobilization	57	
27	Pre-mobilization WBC/Plt count	14	
28	Circulating CD34$^+$ cells in steady-state previous PBSC mobilization	14	
29	Fold-increase of circulating CD34$^+$ cells per μL with respect to baseline	43	10,12,14,15,19,20,30–35,83,84,87,88
30	Absolute number of circulating CD34$^+$ cells per μL at a predetermined timing after the start of mobilization	86	
31	Kinetics of mobilization of CD34$^+$ cells	43	
32	Time to reach the CD34$^+$ cell peak	57	
33	Kinetics of mobilization of MNC cells	43	

Abbreviation: MNC = multinucleate cells.

and 'previous therapy with fludarabine' were included in the same category, and the new criteria 'previous exposure to other therapies potentially affecting SC mobilization' include criteria numbers 18,19,22. The reasons for excluding the remaining criteria included characteristics of the mobilization strategy (nos. 10–12), redundancy, scarce clinical application or poor predictive value (that is, mononuclear cell count). As for the mobilization strategy, GITMO-WG deemed it necessary to include the optimal dose of G-CSF in the definition of PM: G-CSF dose $\geqslant 10\,\mu g/kg$ if used alone or $\geqslant 5\,\mu g/kg$ after mobilizing chemotherapy. Through a second questionnaire, GITMO-WG ranked the 10 conceptual criteria from the core set and chose among 2–4 operational definitions for each conceptual criterion (Table 2). Among predicting criteria, a high rank was assigned to previous extensive radiotherapy and exposure to drugs known to affect the mobilization capacity. The operational definitions of the two criteria for the proven PM (CD34$^+$ cells peak in PB) and PPM (the final CD34$^+$ cell harvest) were scored and discussed by Nominal Group Technique.[24] As both the criteria concurred to the definition, harmonization of their operational wording was requested. Moreover, GITMO-WG established that the cutoff of $\geqslant 2.0 \times 10^6$ CD34$^+$ cells per kg harvested must be integrated with a pre-fixed number of apheresis procedures performed: $\leqslant 3$ apheresis days within a single mobilization attempt, after G-CSF alone or after chemo-mobilization. Finally, the peak of PB CD34$^+$ cells was timed according to the mobilization strategy adopted, as a larger variability in PB CD34$^+$ kinetics is expected after chemo-mobilization. Operational criteria for defining 'predicted PM' require some adjustments about the age cutoff and BM cellularity; there was major disagreement with regard to exposure to drugs or therapies potentially affecting SC mobilization, as a larger body of evidence supports a detrimental effect of selected alkylating drugs, that is, melphalan and fludarabine, whereas fewer reports were published on the detrimental effect of lenalidomide. Finally, GITMO-WG expressed the requirement to consider only full-course therapies damaging SC mobilization, as lower doses or shorter therapies are not ascertained detrimental factors.

Hierarchy of the operational criteria

The GITMO-WG compared the 10 operational criteria by pairs and elaborated the relative importance weight of one criterion to another (Table 2). Pairwise comparison of the

Table 2 Relative importance of the selected core set criteria, expressed both as conceptual and by operational definitions

Conceptual criteria	*Operational criteria*	*Rank (1–9)*	*Pairwise comparison*	*Variability (%)*
Harvested $CD34^+$ cells	Less than 2.0×10^6 harvested $CD34^+$ cells per kg per planned SCT by no more than three aphereses	8.7	0.26	47
Peak of $CD34^+$ cells	Peak $CD34^+$ cell count $<20/\mu L$ on days 4–6 after the start of mobilization with G-CSF alone or up to 18–20 days after chemotherapy and G-CSF	8.0	0.25	36
Refractory disease		6.0	0.08	74
Advanced disease	Advanced disease, that is, at least two previous cytotoxic lines	5.8	0.12	38
Extensive radiotherapy	Extensive radiotherapy to marrow bearing tissue	7.2	0.08	54
Previous exposure to fludarabine, melphalan, lenalidomide		6.6	0.06	47
Previous exposure to other therapies potentially affecting SC mobilization		4.8	0.03	67
Extensive BM involvement at mobilization		5.4	0.04	47
Poor BM cellularity at mobilization	BM cellularity $<30\%$ at mobilization	4.8	0.04	42
Old age	Age older than 65 years	5.1	0.02	50

Although the $CD34^+$ cell count reflects the biological mobilization ability, whereas the $CD34^+$ cell harvest in a pre-fixed number of apheresis days defines a poor mobilization, the terms of poor mobilizer and poor mobilization have been pragmatically considered equivalent. Inter-participant geometric means are reported. Inter-participants' variability of pairwise comparison is also reported in the fourth column.

two criteria defining 'proven PM' and PPM (harvested $CD34^+$ cells and peak $CD34^+$ cells) showed two similar scores, thus confirming similar ranks. Indeed, GITMO-WG considered each of the two criteria itself sufficient to sustain a judgment of 'predicted PM', but recognized that a poor harvest may be caused by technical problems affecting the extraction efficiency and the final yield of circulating $CD34^+$ cells. These problems may consist of delayed or anticipated timing of apheresis, small volume of processed blood and any troubles during the procedure that may prejudice the harvesting, even though the patient achieved a satisfactory peak of $CD34^+$ cells in PB. Pairwise comparison was particularly important to rank the importance of the eight criteria for defining 'predicted PM'. Advanced disease, refractory disease and previous extensive radiotherapy were the three criteria that decidedly had a higher importance. However, GITMO-WG observed that the criteria were biologically and clinically dependent on the others and, therefore, covariate.

A third questionnaire was finally completed including 36 scenarios combining the above eight criteria (Figure 2) and identified previous extensive radiotherapy as the most powerful independent criterion. The scenarios also identified previous exposure to therapies potentially affecting SC mobilization as synergic independent factors, whereas disease status itself was not sufficient to fulfil the definition of 'predicted PM'. Therefore, the panel decided to join two conceptual criteria into a unique exhaustive one, which included therapies definitely proven to affect mobilization and all the other therapies that have been or will be proven to negatively affect SC mobilization. Finally, GITMO-WG decided to extend the definition of predicted 'PM' to those patients with a history of failure, not otherwise specified, and listed an additional specific criterion. On the basis of the above information, GITMO-WG separated the criteria for defining 'predicted PM' into two categories: major and minor. The former category included the three most powerful criteria, which are: previous failed mobilization, not otherwise specified, previous extensive radiotherapy and previous therapies detrimental to SC mobilization. The second category included: advanced phase disease, refractory disease, extensive BM involvement, BM cellularity $<30\%$ (before mobilization) and age >65 years. Although one major criterion was sufficient to qualify a patient as 'predicted PM', the presence of at least two minor criteria was requested to qualify a patient as 'predicted PM' (Table 3).

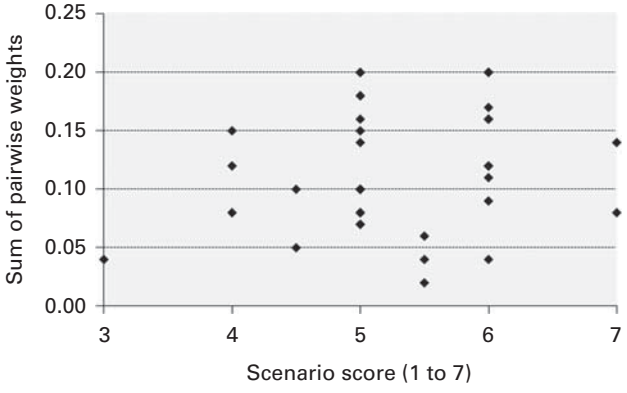

Figure 2 Scoring of 36 scenarios by sum of pairwise weights of direct judgment after the third questionnaire evaluation; all the scenarios have been framed by combining different operational definitions, generated from the selected conceptual criteria. The best scored scenarios concurred to the final definition of proven and predicted poor mobilizer.

Discussion

In this paper, GITMO-WG applied the AHP methods to select the operational criteria useful to identify the PM in current medical practice; at least 15% of lymphoma or MM patients fail to produce the target cell dose of $\geqslant 2 \times 10^6$/kg $CD34^+$ cells and cannot proceed to ASCT.[10,12,15,16,89]

Table 3 Final definitions of proven and predicted poor mobilizer

A patient with MM or lymphoma candidate to ASCT is a:	
Proven poor mobilizer	If he/she received adequate mobilization (G-CSF dose $\geqslant 10\,\mu g/kg$ if used alone or $\geqslant 5\,\mu g/kg$ after chemo) and he/she shows: peak $CD34^+$ circulating cell count $<20/\mu L$ on days 4–6 after the start of mobilization with G-CSF alone or up to 20 days after chemotherapy and G-CSF OR in the case of proven poor mobilization, that is: $<2.0 \times 10^6$ harvested $CD34^+$ cells per kg (that is, minimum safe dose for each planned ASCT) by $\leqslant 3$ aphereses
Predicted poor mobilizer	If he/she holds at least one major criterion or at least two minor criteria. Major criteria: Failed previous mobilization attempt, not otherwise specified. Previous extensive radiotherapy to marrow bearing tissue. Full courses of previous therapy, including melphalan, fludarabine or other therapies potentially affecting stem cell mobilization. Minor criteria: Advanced phase disease, that is, at least two previous cytotoxic lines Refractory disease Extensive BM involvement at mobilization BM cellularity <30% at mobilization Age >65 years

Re-infusion of high doses of $CD34^+$ cells is associated with fast platelet and neutrophil engraftment, leading to a significant cost sparing[25,26,51,90–94] and increased survival rates.[52,95–100] GITMO-WG selected two conceptual criteria to identify proven PM and/or PPM: (I) peak of $CD34^+$ cells in PB and (II) harvested $CD34^+$ cells.

The WG agreed about the definition of PM also for those patients who did not achieve at least 2.0×10^6 $CD34^+$ during 3 apheresis days. Previous reports on the remobilization in this setting show that only a minority of patients was able to achieve the 2.0×10^6 $CD34^+$ threshold after a second mobilization attempt;[12,15] in particular, Pusic *et al.*[16] reports that among 269 patients remobilized, only 62 (23%) yielded $\geqslant 2.0 \times 10^6$ $CD34^+$.

In the past, the quality of PB harvest has been evaluated both as CFU-GM and as $CD34^+$ cell content, whereas limited data suggest a relationship between mononuclear cell count and $CD34^+$ cell content in mobilized PB.[27,32] Despite persistence of controversies about the most reliable technique for enumerating the $CD34^+$ cell content both in PB and in the harvest,[101–103] GITMO-WG agreed that pre-apheresis $CD34^+$ cell count in PB is the best predictor of $CD34^+$ cells in the apheresis products[12,16,30,31,33–35,83,84] and pragmatically considered a peak of $CD34^+$ cells $>20\,\mu L$ in PB, as a reliable indicator of a satisfactory mobilization ability; on the other hand, the strong correlation between the pre-apheresis $CD34^+$ cell count and the final harvest also indicates that a PPM could be considered a reliable marker of a proven PM.[12,16,30,31,33–35,83,84]

The GITMO-WG agreed on 2.0×10^6 $CD34^+$ cells per kg as the minimum safe dose for ensuring rapid neutrophil and platelet recovery both in lymphoma and in MM patients;[10–12,16,25,26,93,94] others suggested a different dose, such as 2.5 (refs. 9,11,26,28,29,104) or 1.5×10^6 $CD34^+$ cells per kg,[105] but below 1×10^6/kg $CD34^+$ cells, a high risk of delayed platelet recovery has been reported.[28]

GITMO-WG reviewed the current mobilization strategies as they can influence the SC mobilization, but cannot be considered the criteria for the definition of PM. When G-CSF alone is used, it is administered at doses ranging from 10 to $16\,\mu g/kg$ daily;[10] higher doses resulted in better harvest,[106–108] not confirmed in subsequent experiences,[109] as well the combination of G-CSF plus GM-CSF.[110,41,42] After the demonstration of the synergistic effect of CY and GM-CSF,[111] G-CSF followed by chemotherapy has been reported to mobilize similar number of $CD34^+$ cells;[42–44] therefore, as this cytokine has a better safety profile, at present the mobilization with CY and G-CSF at $5\,\mu g/kg$ is widespread.[44] A randomized study comparing different doses of G-CSF after chemotherapy did not show substantial benefit with higher doses.[45] The use of disease-oriented chemo-mobilization in the context of a well-designed treatment[98,112–114] resulted in better harvest compared with G-CSF alone,[10,16] but this did not translate into a better clinical outcome.[46,47] As regards these two mobilization strategies, GITMO-WG deemed that the same criteria for identifying the PM should be employed, even if the different timing of $CD34^+$ cell peaks and the different doses of G-CSF must be taken in account. GITMO-WG excluded from definition of PMs those patients who cannot reach a $CD34^+$ cell peak $\geqslant 20/\mu L$, but who were equally able to achieve the target $CD34^+$ cell dose by means of $\leqslant 3$ large-volume aphereses.[37]

As the identification of the 'predicted PM' GITMO-WG defined three major and five minor criteria, the most important criteria were as follows: previous cytotoxic chemotherapy and irradiation. The average decrease estimated for each cycle of chemotherapy is of 0.2×10^6 $CD34^+$ cells per kg per apheresis and 1.8×10^6/kg $CD34^+$ cells after large-field radiotherapy, whereas a local irradiation is not associated with impaired mobilization.[36,48,68,69,71] Although underlying disease has been reported as a factor influencing mobilization,[49,53–56] GITMO-WG deemed that this is not an independent factor, being influenced by the previous treatment and by the disease status. Advanced disease is often associated with extensive BM involvement. In addition, in lymphoma patients BM involvement and platelet count before mobilization are associated with mobilization failure,[9,10,36,57–62] and although it was difficult to identify a clear age cutoff,[63,64] GITMO-WG deemed that older age is an important factor associated with poor mobilization.[65,50,66]

GITMO-WG agreed that the higher percentage of PM is characterized by either morphological or functional injury to BM, caused by extensive radiotherapy or/and chemotherapy, but also by the so-called stem cell poisons.[36]

This heterogeneous group of drugs includes purine analogues, melphalan,[67,72] and the list has recently included thalidomide[115] and lenalidomide.[73–76] Fludarabine negatively affects mobilization in patients with CLL;[77–80] however, some authors reported satisfactory collections,[81] whereas others recommend paying attention to the interval from last dose of fludarabine.[82]

Among the other factors associated with unsuccessful mobilization, including PB white cell count, platelet count, apheresis techniques, interval between last chemotherapy and mobilization attempt,[9,34,38–40,61,69,70,85–88,116,117] the platelet counts before mobilization seem a reliable indicator of adequate marrow function, but this factor has not been considered sufficiently powerful like the ones selected as conceptual criteria.

In conclusion, poor mobilization of SC is a major limitation to ASCT in lymphoma and MM, and the availability of new drugs, able to increase the SC mobilization, requires a stringent definition of the PM. Several patient- and disease-related factors have been retrospectively identified, but never prospectively validated. GITMO-WG recommend that patients previously failing at least one mobilization attempt should be candidates for new mobilizing strategies.[19,20,118] Excluding this selected group, the preventive identification of PM, by using the criteria established here, should be validated in a prospective trial. In the meantime, the GITMO-WG recommend using standard criteria for identifying both the 'proven and the predicted PM' before planning the use of new mobilizing agents. Recently, two large series of patients with lymphoma or MM have been retrospectively evaluated define PM, according to the standardized criteria: extensive previous chemotherapy, previous melphalan exposure and a previous failed mobilization attempt have been identified as predictive factors of poor mobilization. Pusic *et al*.[16] reports that 19% of patients yielding $<2\times10^6$ $CD34^+$ cells per kg during five apheresis after mobilization with G-CSF alone,[16] whereas Wuchter *et al*.[12] identified 15% of PMs by using the criterion of a peak concentration 20/μL of $CD34^+$ cells, after chemotherapy followed by G-CSF.[12] The International Myeloma Working Group also proposed some qualitative predictive risk factors for poor mobilization, without any ranking.[119] The GITMO-WG worked to define simple, but stringent operational criteria for the identification/prediction of the PM in the setting of MM and lymphoma patients. The decision to separate the criteria for defining 'predicted PM' into two categories (major and minor) could be questionable, but it keeps the advantage to be easy to use and to update. Recently, new mobilizing agents, such as plerixafor, proved to be effective in PM.[118,120,121] However, the scientific community has not still provided a standard definition of PM, who may potentially benefit from this drug; therefore, these criteria could help the selection of those patients who could benefit from new mobilizing drugs, waiting for a definitive validation by a prospective trial.

Conflict of interest

This paper has been completed after three Expert Meetings supported by Genzyme Corporation. The authors received a reimbursement and an honorarium. The authors declare that there are no competing financial interests in relation to this work.

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