# 5 Mobilization Strategies: HPC(A) Collections for Autologous Hematopoietic Cell Transplants

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## 5.1 Introduction

Autologous hematopoietic cell transplantation (auto-HCT) aims to restore bone marrow (BM) function after high-dose chemotherapy in patients with a variety of hemato-oncological diseases such as multiple myeloma (MM), non-Hodgkin's lymphoma (NHL), Hodgkin's lymphoma (HL), and other malignancies. For patients with MM and relapsed chemosensitive lymphomas, auto-HCT leads to improved progression-free survival (PFS) and overall survival (OS). Patients with MM achieve higher rates of complete remission with consolidative auto-HCT than with conventional induction therapy alone (Giralt et al. 2014; Passweg et al. 2016).

Under normal conditions, $CD34^+$ cells circulate only in a very small number in the peripheral blood (PB) (Pusic and DiPersio 2008). Therefore, their mobilization from the BM into the PB is an essential part of apheresis collection process. Since the introduction of hematopoietic growth factors, mobilized PB $CD34^+$ cells are the preferred source worldwide (Giralt et al. 2014; Mohty et al. 2014) as such growth factors allow enhanced $CD34^+$ cell mobilization and improved collection results (Gianni et al. 1989). Auto-HCT from PB is favored because it leads to faster neutrophil and platelet engraftment and hematologic reconstitution compared to BM, resulting in potentially improved patient outcomes. In addition, some studies demonstrate that the use of PB grafts in auto-HCT is associated with better quality of life and reduced hospital stays, less need for transfusions and antibiotics, and reduced total costs (Mohty and Ho 2011; Vellenga et al. 2001; Vose et al. 2002). Granulocyte-macrophage colony-stimulating factor (GM-CSF) has been largely replaced by granulocyte colony-stimulating factor (G-CSF) for $CD34^+$ cell mobilization.

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## 5.2 Mobilization Methods

Nowadays, there are two general approaches for autologous CD34+ cell mobilization: steady-state mobilization using growth factors such as G-CSF alone and chemo-mobilization (i.e., chemotherapy and G-CSF) using chemotherapy either as part or apart of the disease-specific treatment protocol followed by growth factor application (Giralt et al. 2014; Mohty et al. 2014; Bensinger et al. 2009). The use of chemotherapy generally produces higher CD34+ cell yields in a lower number of apheresis and, in theory, may reduce tumor contamination of the graft, although data to confirm this are still lacking (Mohty et al. 2014; Bensinger et al. 2009). Disadvantages of chemo-mobilization include increased toxicity and morbidity, the need for hospitalization, transfusion support, and anti-infectious treatment (Mohty et al. 2014; Bensinger et al. 2009).

Despite an established practice, current mobilization strategies vary between centers and differ in terms of feasibility and outcome (Mohty et al. 2014; Mohty and Ho 2011; Bensinger et al. 2009) (see Chap. 9). Although in the majority of patients sufficient CD34+ cells for at least a single autologous transplantation can be collected, approximately 5–25% fail to mobilize an adequate number of cells (Pusic et al. 2008; Wuchter et al. 2010). If patients are scheduled for >1 transplant, even higher failure rates are reported. A more recent approach to improve mobilization and collection procedures includes the use of cell-binding inhibitors like plerixafor (Calandra et al. 2008; Chabannon et al. 2015; Worel et al. 2017). Nevertheless, it is necessary to optimize the current mobilization approaches and to identify upfront patients who are at risk of G-CSF mobilization failure (see Chap. 4).

## 5.3 Steady-State Cytokines Alone CD34+ Cell Mobilization

### 5.3.1 Dose and Schedule

Administration of G-CSF (filgrastim and lenograstim) remains the only available treatment option for steady-state mobilization, as GM-CSF is no longer available in many countries and other growth factors (e.g., pegylated G-CSF) have no label for PB CD34+ cell mobilization. G-CSF treatment leads to granulocyte activation and expansion and release of various proteases into the marrow, which then cleave adhesion molecules such as stromal-derived factor-1 (SDF-1), releasing hematopoietic stem and progenitor cells (specifically CD34+ cells) into the PB (Giralt et al. 2014; Pusic and DiPersio 2008; Petit et al. 2002). Filgrastim and lenograstim are usually injected at a daily dose of 10 μg/kg of body weight subcutaneously. Doses can be divided in two applications of 5 μg/kg body weight and administered twice daily. The approved schedules of G-CSF are 5–7 consecutive days for filgrastim and 4–6 days for lenograstim (Fig. 5.1a). Leukapheresis normally is initiated if CD34+ cells exceed a threshold of 20 μL or maybe lower (>10–15 CD34+ cells/μL)

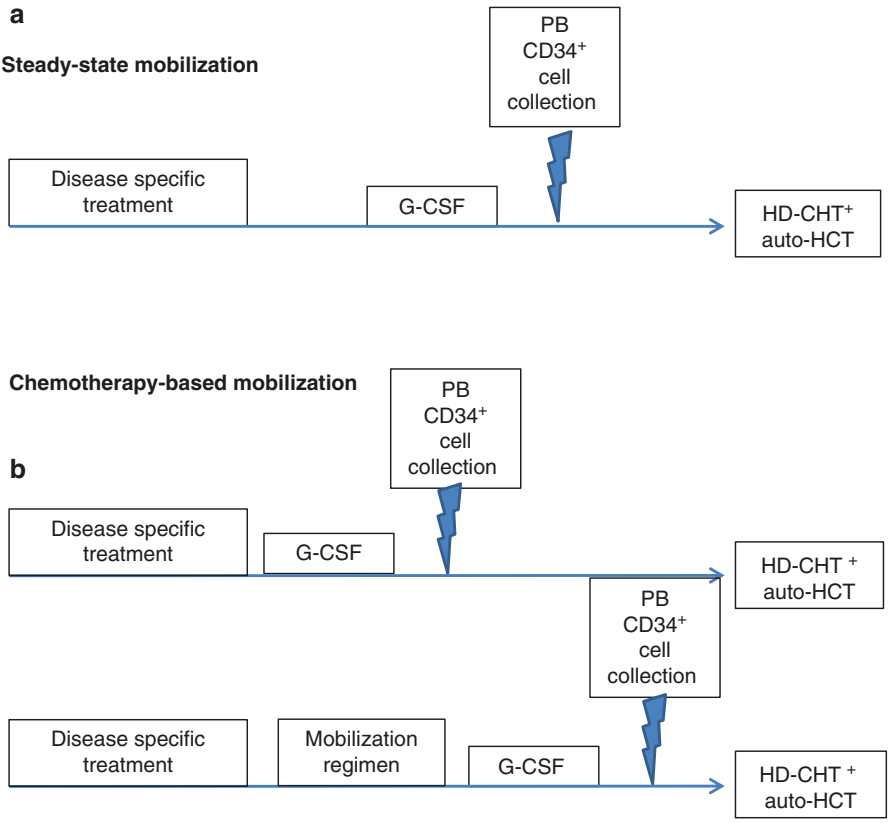


**Fig. 5.1** Mobilization strategies for autologous PB CD34+ cell collection. *Auto-HCT* autologous hematopoietic cell transplantation, *CHT* chemotherapy, *HD* high dose, *G-CSF* granulocyte colony-stimulating factor, *PB* peripheral blood

according to institutional guidelines but should be started at least on days 5 or 6 after filgrastim and between days 5 and 7 after lenograstim. However, collection can also be started on day 4 of G-CSF if the institutional defined threshold of CD34+ is exceeded.

### 5.3.2 Adverse Events of Cytokine Administration

The most common adverse events of cytokine mobilization are bone pain in 52–84% of patients, which can be treated with common analgesics, such as acetaminophen, paracetamol, or ibuprofen (Anderlini et al. 1999; Tigue et al. 2007). Other associated symptoms include fatigue, headache, and fever. There have been reports of

development or flare up of autoimmune events associated with G-CSF administration (e.g., autoimmune hyperthyroidism). A very rare but serious adverse event is splenic rupture which has been reported after G-CSF administration in healthy donors and patients and occurred in the majority of subjects at day 6 of G-CSF (Tigue et al. 2007). Several studies evaluated effects of short-term administration of G-CSF on the spleen. Spleen size was studied in healthy CD34⁺ cell donors receiving G-CSF at a dose of 7.5 mg/kg b.w./day for 5 days. An average increase of 11 mm in spleen length and 10% increase in volume were noted, but baseline values normally are reached within 10 days after stop of G-CSF administration (Platzbecker et al. 2001; Stroncek et al. 2003). Until now, no increased risk for hematologic malignancies has been observed in healthy donors (Anderlini et al. 1999; Tigue et al. 2007) (see Chap. 6).

### 5.3.3 Practice Points

Mobilization with cytokines alone is generally well tolerated, needs less resources, and can be optimally timed. If the underlying disease does not necessarily need cytotoxic therapy and is treated with immunomodulatory drugs (i.e., MM with novel induction therapy) or antibodies, or patients are in remission, steady-state mobilization with cytokines alone would be the preferred option.

## 5.4 Chemotherapy-Based Mobilization

It is a matter of fact that chemotherapy decreases tumor burden and may increase PB CD34⁺ cell yields in combination with growth factors (cytokines) (Mohty et al. 2014; Bensinger et al. 2009; Gertz 2010). However, compared to cytokine alone mobilization, chemotherapy-based regimens are associated with a higher incidence and severity of adverse events as neutropenic fever, sepsis, need for antibiotics and blood products, and hospital admission (Pusic et al. 2008; Gertz et al. 2009).

It is important to emphasize that DNA-topoisomerase II (i.e., etoposide) and alkylating agents (i.e., cyclophosphamide) are known to increase the risk of therapy-related myeloid neoplasms; hence, it is best to avoid them in a setting where such agents are solely being used to mobilize CD34⁺ cells (Arber et al. 2016). Chemotherapy may be given as disease-specific treatment (e.g., R-CHOP; rituximab, cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone in NHL patients) or apart from the treatment protocol (e.g., cyclophosphamide in MM patients treated with new therapeutic agents). The choice of a chemotherapy-based mobilization regimen depends on the disease entity and institutional guidelines. After myelosuppressive chemotherapy, G-CSF is given at doses of 5–10 μg/kg b.w. per day starting between days 1 and 7 after initiation of chemotherapy and continues until the last day of apheresis (Fig. 5.1b).

There is doubt that especially in MM patients, in the era of novel induction therapy (e.g., proteasome inhibitors and immunomodulatory agents), chemotherapeutic drugs used for CD34⁺ cell mobilization as cyclophosphamide or etoposide have an

additional antitumor effect. In contrast in lymphoma patients, the myelosuppressive chemotherapy given as standard first-line or salvage therapy has a positive impact on CD34+ cell mobilization and eliminates the need for additional chemo- or steady-state mobilization in these heavily pretreated patients (Mohty et al. 2014; Pavone et al. 2002). In addition, disease-specific chemotherapy protocols using a combination of cytotoxic drugs (e.g., D-PACE for MM consisting of dexamethasone, platinum, doxorubicin, cyclophosphamide, etoposide or CHOP for NHL consisting of cyclophosphamide, doxorubicin, vincristine, prednisone) have been shown to be more effective than cyclophosphamide alone (Mohty et al. 2014; Pavone et al. 2002).

## 5.5 Binding Inhibitors: Plerixafor

### 5.5.1 Dose and Schedule

Plerixafor, a novel CD34+ cell-mobilizing agent, was launched in 2008 for use in the United States in combination with G-CSF for mobilization in patients with MM and lymphomas. In Europe, plerixafor was approved by the European Medicines Agency (EMA) with the restriction for patients whose CD34+ cells mobilize poorly (Genzyme Ltd: Suffolk U. Mozobil [Product information] 2009). Plerixafor is a reversible chemokine receptor 4 (CXCR4) antagonist that in combination with G-CSF augments the release of CD34+ cells from the BM by disrupting the binding site of CXCR4 with stromal cell-derived factor-1 (SDF-1). The recommended dose is 240 μg/kg b.w. subcutaneously approximately 6–11 h before initiation of leukapheresis following at least 4 days of G-CSF pretreatment. In patients with impaired renal function (creatinine clearance ≤50 mL/min), dose adjustment to 160 μg/kg b.w. is recommended (Genzyme Ltd: Suffolk U. Mozobil [Product information] 2009; DiPersio et al. 2009a, b). Until now, numerous studies have confirmed the efficacy of plerixafor in combination not only with G-CSF but also with G-CSF and chemotherapy, including poor mobilizing patients, with superior efficacy to other mobilization regimens (G-CSF alone or G-CSF and chemotherapy) without plerixafor (Calandra et al. 2008; Worel et al. 2017, 2011; DiPersio et al. 2009a, b; D'Addio et al. 2011). If plerixafor is given to improve or rescue chemotherapy-based mobilization, we prefer patients to have leukocyte counts of 5 G/L after at least 4 days of G-CSF pretreatment. Plerixafor can be used for remobilization in patents failing to collect a sufficient number of CD34+ cells, as immediate rescue in an ongoing mobilization attempt to prevent failure or preemptive in patients at risk for poor mobilization (Mohty et al. 2014; Chabannon et al. 2015; Worel et al. 2017, 2011; D'Addio et al. 2011).

### 5.5.2 Adverse Events of Plerixafor Administration

The most common adverse events observed are erythema at the injection site in 30% of patients and gastrointestinal disturbances (stomach discomfort, nausea, and diarrhea) in 30% of patients.

## 5.6 Suboptimal CD34+ Cell Mobilization: "Poor Mobilizers"

Factors adversely influencing PB CD34+ mobilization and collection include older age, female gender, diagnosis (lymphomas more likely than MM), longer disease duration and therapy, more advanced disease, previous intensive radio- and/or chemotherapy (especially treatment with purine analogues, melphalan, and lenalidomide), and low platelet counts prior to collection (Mohty et al. 2014; Kumar et al. 2007) (Table 5.1). The definition of "poor" CD34+ cell mobilization is heterogeneous. Parameters used to define poor mobilization range from the peak of CD34+ cells in the PB to the cumulative apheresis yield or the percent of patients in whom CD34+ cells

**Table 5.1** Risk factors for suboptimal CD34+ cell mobilization and mobilization failure

| Risk factor | Proposed mechanism | Strategy for CD34+ cell mobilization |
|---|---|---|
| Low platelet counts (Olivieri et al. 2012) | Reflects CD34+ cell reserve | Regimens that support HSPC proliferation |
| Age (>60–65 years old) (Olivieri et al. 2012; Stiff 1999) | Reduced HSPC reserve:<br>• HSPC senescence<br>• Loss or dysfunction of the HSPC niche<br>• Bone loss or altered bone metabolism | Regimens that support HSPC proliferation |
| Underlying disease (Pusic et al. 2008) | • Paraneoplastic dysfunction of the HSPC niche<br>• Reduction of niches due to tumor mass | Reduce bone marrow infiltration before HSPC mobilization. |
| Extensive irradiation of marrow-bearing sites (Olivieri et al. 2012) | Direct HSPC toxicity, impairment of HSPC niche | Consider plerixafor. |
| Previous chemotherapy: | | |
| • Melphalan (Olivieri et al. 2012) | Direct HSPC toxicity | Avoid melphalan before PB CD34+ cell collection. |
| • Fludarabine (Olivieri et al. 2012; Berger et al. 2008) | Direct HSPC toxicity, impairment of HSPC niche | PB CD34+ cell collection before 4 cycles of fludarabine |
| • Intensive CTH (Olivieri et al. 2012; Hill et al. 2011) | Impairment of HSPC niches, increased HSPC renewal with exhaustion | Consider plerixafor. |
| Previous prolong (>4 cycles) lenalidomide treatment (Kumar et al. 2007; Olivieri et al. 2012) | Possible effect on HSPC mobility (upregulation of CXCR4 expression), dysregulation of HSPC niche due to antiangiogenetic effects | PB CD34+ cell collection before 4 cycles of lenalidomide. Stop lenalidomide during HSPC mobilization and collection, and consider plerixafor. |
| Diabetes (Fadini and Avogaro 2013) | Possible effect on BM microenvironment, impaired HSPC mobilization due to mobilopathy | Consider plerixafor. |

*BM* bone marrow, *HSPC* hematopoietic stem and progenitor cell, *PB* peripheral blood, *CXCR4* CXC chemokine receptor 4

cannot be collected. Criteria to define a successful $CD34^+$ cell mobilization and an adequate apheresis yield have been proposed by several authors, but criteria vary between experts and centers. In a recent study of the Gruppo Italiano Trapianto di Midollo Osseo (GITMO), patients are defined as *proven poor mobilizers* when (1) after adequate mobilization (G-CSF 10 μg/kg body weight if used alone or ≥5 μg/kg body weight after chemotherapy), circulating $CD34^+$ cell peak is <20 cells/μL up to 6 days after mobilization with G-CSF alone or up to 20 days after chemotherapy and G-CSF, or (2) less than $2.0 \times 10^6$ $CD34^+$ cells per kg body weight in ≤3 apheresis are collected. Patients were defined as *predicted poor mobilizers* if (1) patients failed a previous collection attempt (not otherwise specified), (2) patients previously received extensive radiotherapy or full courses of chemotherapy affecting $CD34^+$ cell mobilization, and (3) patients 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, and age ≥65 years (Olivieri et al. 2012). Besides these definitions, several other groups have developed algorithms to guide the use of the optimal mobilization regimen including "correct" timing of plerixafor application (Giralt et al. 2014; Olivieri et al. 2012; Chen et al. 2012; Costa et al. 2011). A very important finding is that the use of plerixafor as an immediate rescue approach also results in very high success rates (Worel et al. 2017; Costa et al. 2011). In one study, 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 was developed to guide cost-effective use of plerixafor (continuing G-CSF only or adding plerixafor). The authors showed that patient-adapted plerixafor use based on this algorithm was superior to cyclophosphamide plus growth factor and successfully mobilized PB $CD34^+$ cells in MM patients previously treated with lenalidomide (Costa et al. 2011). Another study describes a risk-based approach to optimize PB $CD34^+$ cell collection with plerixafor by identifying potential poor mobilizers upfront. The algorithm takes into account the number of PB $CD34^+$ cells on day 5 of G-CSF mobilization, the desired amount of PB $CD34^+$ cells needed per transplant (≥$2.5 \times 10^6$/kg of recipient body weight for 1 transplant and ≥$5 \times 10^6$/kg of recipient body weight for 2 transplants), and $CD34^+$ collection yield on the first apheresis day. The use of plerixafor was triggered by PB $CD34^+$ cells of ≤10/μL (for 1 transplant), or ≤20 cells per μL (for 2 transplants) on day 5 of G-CSF, or a $CD34^+$ collection yield of less than 50% of the total $CD34^+$ cell dose needed in the first leukapheresis (Abhyankar et al. 2012) (see Chap. 9).

## 5.7 What Is the Optimal $CD34^+$ Cell Dose/Kg for Successful Transplantation?

The infused $CD34^+$ cell dose influences the time to neutrophil and platelet engraftment, need for platelet and red blood cell transfusion, occurrence of febrile complications, need for antibiotics, and graft stability. Low $CD34^+$ cell doses (<$2.0 \times 10^6$ $CD34^+$ cells/kg of recipient body weight) are associated with delayed engraftment and increased transfusion requirements, mostly for platelets (Table 5.2). However, a delay in platelet recovery also can be explained by other factors, such as intensive pretreatment, including irradiation to marrow-bearing sites, altering the matrix of the marrow, and the use of growth factors after transplantation, which could reflect

**Table 5.2** Studies focusing on $CD34^+$ cell doses in autologous hematopoietic cell transplants

| References | Cohort | Mobilization | Focus | Outcome |
|---|---|---|---|---|
| Weaver et al. (1995) *(Blood 1995)* | 320 breast cancers 137 lymphomas 10 MM, 52 solid tumors | CHT ± HGF | Engraftment kinetics | $<2.5 \times 10^6$/kg $CD34^+$ cells (2%) delayed PLT and ANC engraftment |
| Pérez-Simón et al. (1998) *(Transfusion 1998)* | 38 breast cancers 23 lymphomas 6 MM, 4 solid tumors | Steady state, 5 μg/kg HGF | Collection, engraftment | $0.75 \times 10^6$/kg $CD34^+$ cells/kg (13%) necessary to ensure engraftment |
| Pérez-Simón et al. (1999) *(BMT 1999)* | 51 breast cancers 31 lymphomas 15 MM, 3 solid tumors | Not stated | Late engraftment Hospitalization, AB, transfusions, 1-year follow-up | $>1.1 \times 10^6$/kg $CD34^+$ cells/kg stable engraftment $>2.2 \times 10^6$/kg $CD34^+$ cells/kg reduced transfusions |
| Siena S. (2000) *(JCO 2000)* | MEDLINE search was conducted to identify relevant publications. | Different | Clinical outcomes | $\geq 8 \times 10^6$ $CD34^+$ cells/kg associated with better clinical outcome |

*AB* antibiotic treatment, *ANC* absolute neutrophil count, *CHT* chemotherapy, *FU* follow-up, *HGF* hematopoietic growth factor, *MM* multiple myeloma, *PLT* platelets

the ability of cytokines to influence cells of intermediate lineage that have the potential to become either neutrophils or platelets, leading to an accelerated neutrophil maturation and later platelets recovery (Jillella and Ustun 2004).

Clinical studies investigating the optimal $CD34^+$ cell dose to be reinfused in patients undergoing autologous transplantation showed that using high $CD34^+$ cell doses (>5 to $>10 \times 10^6$/kg) is associated with faster neutrophil and platelet recovery, but, apart from a reduced need for platelet transfusions, the full effect and real clinical benefit of this strategy is unknown (Table 5.2). Indeed, studies investigating the effect of the $CD34^+$ cell dose on engraftment have yielded contrary results. More recent studies have found a correlation between $CD34^+$ cell dose, progression-free survival (PFS), and overall survival (OS) in patients with MM and non-Hodgkin's lymphoma (NHL). Possible reasons for better PFS and OS in this good or "super"-mobilizers are a sustained and more rapid hematopoietic reconstitution that leads to a lower non-relapse mortality (NRM) and the fact that higher numbers of $CD34^+$ cells in the graft coincide with an increased number of T cells, which may accelerate immune reconstitution after auto-HCT and, therefore, induce tumor-specific T cells (Bolwell et al. 2007). In contrast, another study in NHL patients demonstrated that higher $CD3^+$ T-cell doses infused with the graft, and not $CD34^+$ numbers, have an effect on absolute lymphocyte and natural killer (NK) cell count at day +15, thereby positively influencing PFS and OS. Patients with lymphocytes of at least 500 cells/μL and NK cells greater than 80 cells/μL on day 15 after auto-HCT had significantly better PFS and OS in this study (Porrata et al. 2008).

## 5.8 Practice Points

Until now, there is no golden standard for the kind of mobilization regimen for autologous CD34⁺ cell collection. Both steady-state and chemotherapy-based regimens have their advantages and disadvantages. PB CD34⁺ cell mobilization can be optimized with an appropriate strategy adapted to each patient, based on the patient's disease, existing risk factors for poor mobilization, and the individual collection aim. A low PB CD34⁺ cell count before apheresis is a predictor for poor collection results. Therefore, CD34⁺ cell counts are an important factor helping to estimate the patient's risk for poor mobilization and collection and may allow immediate intervention to rescue mobilization failure. A possible algorithm of CD34⁺ cell mobilization in daily routine is given in Fig. 5.2.

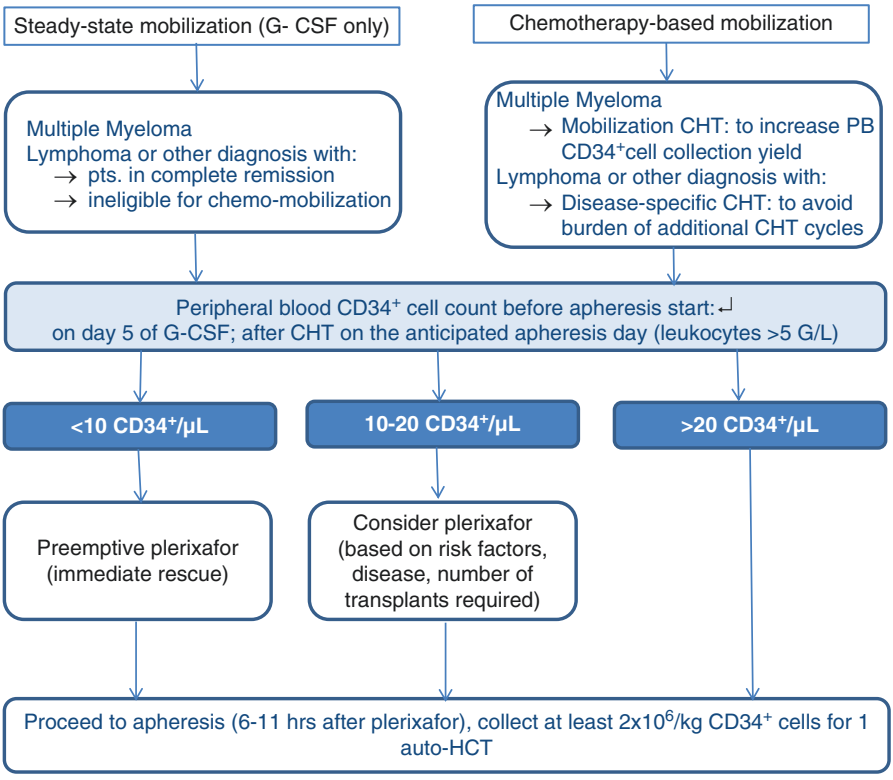


**Fig. 5.2** Possible algorithm of CD34⁺ cell mobilization in daily routine. *PB* peripheral blood, *auto-HCT* autologous hematopoietic cell transplantation, *CHT* chemotherapy, *hrs* hours, *G-CSF* granulocyte colony-stimulating factor, *pts* patients

The minimum recommended dose of $2.0 \times 10^6$ $CD34^+$ cells/kg b.w. is associated with regular and timely engraftment. Although doses less than $2.0 \times 10^6$ $CD34^+$ cells/kg b.w. result in hematopoietic engraftment, they are associated with a delay in neutrophil and platelet recovery and a risk for graft failure or transitory loss of engraftment. To determine the optimum dose of $CD34^+$ cells/kg of b.w. and possibly other cells, not only for regular and stable engraftment but also for improved PFS and OS, randomized studies with sufficient numbers of patients need to be conducted.

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