Conditioning

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13.1 Overview

HSCT is a therapeutic procedure that can cure and/or prolong life in a broad range of hematologic disorders including malignant and nonmalignant pathologies. Conditioning is the preparative regimen that is administered to the patients undergoing HSCT before the infusion of the stem cell grafts. Historically, the pre-HSCT conditioning had to:

1. Eradicate the hematologic malignancy in case of malignant indication for HSCT.
2. Provide sufficient IS to ensure engraftment and to prevent both rejection and GVHD.
3. Provide stem cell niches in the host BM for the new stem cells.

The third purpose is controversial as it was demonstrated in animal models that with mega doses of HSC and repeated administrations engraftment can be achieved without conditioning.

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From the theoretic point of view, the conditioning consisted of two components:

1. Myelo-depletion which targets the host stem cells
2. Lymphodepletion which targets the host lymphoid system, respectively

Some of the compounds used in the conditioning are more myeloablative (MA) in nature, for example, MEL or BU, while some are more lymphodepleting like FLU or CY. The pretransplant conditioning may include TBI or in rare and specific instances other types of irradiations like TLI that is applied, for example, in haplo-HSCT, or TAI that was used in the past in Fanconi anemia. Alternatively, the pre-HSCT conditioning can be radiation-free including only chemotherapy. In recent years, serotherapy, specific targeted novel compounds, and MoAb and radiolabeled Ab started to be incorporated into specific disease-oriented conditioning regimens.

Not just the constituents but also the schedule (days) of administration and doses may differ in the various conditioning regimen protocols. The pretransplantation conditioning regimens depend on the type of the HSC donor. For example, in auto-HSCT, the pre-HSCT conditioning consisted of chemotherapy alone, and in some transplant centers, it may include also irradiation, while, in allo-HSCT from unrelated or mismatched donors

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as well as in HSCT from alternative donors, the pre-HSCT conditioning usually includes serotherapy with ATG or ALEM (Campath; anti-CDW52 MoAb). Similarly, the intensity of the conditioning is traditionally higher in unrelated and mismatched transplants as well as in transplants from alternative donors in comparison to transplants from HLA MSD. The pre-HSCT conditioning regimen takes into account also the specific disease for which the HSCT is being performed, more so in auto-HSCT than in the allogeneic setting aiming to include an effective anti-disease-specific chemotherapy, for example, MEL for MM or BCNU and CY in lymphoma.

Other factors to be taken into account while choosing the optimal conditioning for a specific patient besides the disease he is afflicted with and the type of donor are age, comorbidities, and organ-specific toxicity risk. The conditioning protocols also differ between pediatrics and adults as in pediatric more emphasis should be given to growth and puberty issues. It also differs between nonmalignant and malignant disorders; the former are not just more frequent in pediatrics, but of major importance is the fact that in nonmalignant indications, there is no need for the GVL, and a main goal is to ensure absolutely no GVHD.

Historically, the conditioning protocols were MA in nature, and the two most popular ones were the CY/TBI (TBI 12Gy followed by IV CY 60 mg/kg × 2 days) and the BU/CY protocol (BU 4 mg/kg × 4 days and CY 60 mg/kg × 2 days). However, MAC is associated with significant organ- and transplant-related toxicity (TRT), limiting allo-HSCT to younger patients in good medical conditioning, typically up to age of 55 and 50 years old in allo-HSCT from sibling and URD, respectively. During the past two decades, non-MA (NMA), RIC, and reduced toxicity conditioning (RTC) regimens have been developed aiming in reducing the organ and TRM while keeping the anti-malignant effect and allowing allo-HSCT in elderly and medically infirm patients. These are relatively nontoxic and tolerable regimens designed not to maximally eradicate the malignancy but rather to provide sufficient IS to achieve engraftment and to allow induction of GVL as the primary treatment. Furthermore, special conditioning protocols have been developed for allo-HSCT from alternative donors including from MMUD, CB donors, and haploidentical family-related donors. These relatively new pre-HSCT conditioning typically includes new drug formulations like IV BU, compounds from the oncology field that are newcomers in HSCT like TREO or TT, new compounds like clofarabine (CLO), or new schedules sequentially administrating novel chemotherapy combination (FLAMSA) to be followed by RIC containing reduced doses of TBI.

13.2 Total Body Irradiation

TBI is a major constituent of MAC regimens. Historically, TBI combined with CY has been the standard regimen used to condition patients with acute leukemia prior to HSCT. TBI is typically given at a dose of 12 Gy (Thomas et al. 1982). Higher doses of TBI up to 14.25 Gy resulted in improved antileukemic effect, but this was counterbalanced by increased toxicity and TRM (Clift et al. 1990). TBI provides both MA and IS ensuring engraftment in combination with optimal antileukemic effect. It provides homogeneous dose distribution in the whole body including sanctuaries for systemic chemotherapy such as the CNS and testicles. Fractionation of 12 Gy TBI in six doses of 2 Gy delivered twice a day over 3 days became the standard over time (Thomas et al. 1982).

The Acute Leukemia Working Party (ALWP) of the EBMT recently showed that 12 Gy fractionated TBI dose delivered either in two fractions or in one fraction per day over 3 or 4 days prior to HSCT resulted in similar outcome, in both ALL and AML patients (Belkacemi et al. 2018). Dose fractionation and dose rate have been shown to be of importance determining both efficacy and toxicity which includes mucositis, interstitial pneumonia, SOS/VOD, hemorrhagic cystitis, and long-term toxicity including growth retardation, endocrine problems, cataracts, and secondary malignancies.

As for mode of TBI administration across Europe, the ALWP of the EBMT performed a

questionnaire-based study focusing on technical practices across 56 EBMT centers and 23 countries demonstrating an extremely high heterogeneity of fractionation schedules. The total doses delivered ranged between 8 and 14.4 Gy with dose per fraction varying between 1.65 and 8 Gy. The dose rate at the source ranged between 2.25 and 37.5 Gy/min. This resulted in 40 different reported schedules, to which variations in beam energy, dosimetry, in vivo techniques, and organ shielding disparities had to be added (Giebel et al. 2014). Regarding TBI-mediated antileukemic effect, most studies have shown the equivalence of chemotherapy-based MAC mostly BU/CY and CY/TBI conditioning for AML (Nagler et al. 2013). In contrast, despite the absence of consensus, TBI has remained the first choice in many centers for ALL (Cahu et al. 2016).

13.3 Myeloablative Non-TBI-Containing Conditioning

The MAC are a high-dose chemotherapy mostly alkylating agent-based regimens used in both auto- and allo-HSCT. They cause by definition profound and prolong cytopenia that lasts up to 21 days and necessitates stem cell graft in order to recover (Bacigalupo et al. 2009). Historically, BU/CY is the prototype of chemotherapy-based MAC. It was developed by the Johns Hopkins group as early as 1983 as an alternative to TBI in an effort to reduce the incidence of long-term radiation-induced toxicities and improve the planning of HSCT in institutions lacking easy availability of linear accelerators (Tutschka et al. 1987). A considerable number of studies have shown the equivalence of BU/CY and CY/TBI for allo-HSCT in AML (Nagler et al. 2013) and recently also in ALL (Mohty et al. 2010) although most centers still use TBI-based MAC as the preferred pre-HSCT conditioning for ALL in fit patients with low comorbidities.

The original studies used oral BU that has an erratic and unpredictable absorption with wide inter- and also intra-patient variability with the risk of increased toxicity mainly SOS/VOD in patients with a high area under the curve of BU plasma concentration versus time, while low BU concentrations may be associated with a higher risk of graft rejection and relapse (Hassan 1999). The common solution was monitoring of BU levels and dose adjustments that allowed for better control of the dose administered and reduction of the abovementioned risks (Deeg et al. 2002). The development of the IV BU with more predictable pharmacokinetics, achieving tight control of plasma levels, and less need for plasma level testing and dose adjustments significantly reduced BU-mediated SOS/VOD and TRM (Nagler et al. 2014).

Some other MAC regimens include MEL in combination with BU (Vey et al. 1996), while others incorporated VP (Czyz et al. 2018). Subsequently, in an attempt to further reduce regimen-related toxicity, CY was replaced with FLU, a nucleoside analog with considerable IS properties that also has a synergizing effect with alkylators by inhibiting DNA repair. The combination of BU and FLU used in patients with AML was found to have more favorable toxicity profile with similar efficacy. Recently a well-designed two-arm study compared BU/CY to BU/FLU, demonstrating a significant reduction of TRM in the FLU/BU arm with no difference in RI (Rambaldi et al. 2015). Recently, other alkylators like TT (Eder et al. 2017) and CLO (Chevallier et al. 2012) have been incorporated into MAC protocols for both AML and ALL in an attempt to reduce risk of relapse with equivalent results to TBI-containing conditioning protocols.

13.4 Nonmyeloablative, Reduced Intensity and Reduced Toxicity Conditioning

NMA and RIC have been widely introduced over the past 20 years in an attempt to reduce organ toxicity and TRM allowing HSCT in elderly and medically infirm patients not eligible for standard MAC (Slavin et al. 1998). In addition, RTC based on FLU and MA alkylating agent doses were designed to allow safer administration of dose-intensive therapy. Multiple such protocols have been reported over the years with somewhat

overlapping dose intensity and to a certain extent unclear categorization among NMA versus RIC and RTC.

A group of experts had an attempt to define and dissect the conditioning regimen intensity based on the expected duration and reversibility of cytopenia after HSCT (Bacigalupo et al. 2009). MAC was defined as a conditioning regimen that results in irreversible cytopenia in most patients, and stem cell support after HSCT is required. Truly NMA regimens cause minimal cytopenia and can theoretically be given without stem cell support. RIC regimens cause profound cytopenia and should be given with stem cells, but cytopenia may not be irreversible. The original NMA conditioning protocols were the TBI 2 Gy in combination with MMF and CSA (the so-called Seattle protocol that subsequently incorporated FLU 90 mg because of high non-engraftment in the original protocol) (McSweeney et al. 2001) and the FLAG conditioning protocol (FLU, Ara-C, idarubicin, and G-CSF) pioneered in MD Anderson (Giralt et al. 1997).

Additional very popular protocol is the FLU/BU conditioning regimen we pioneered in Jerusalem initially with oral but subsequently with the IV formulation of BU that is given 2–4 days determining the intensity of the conditioning being NMA, RIC/RTC, and MAC, respectively (Kharfan-Dabaja et al. 2014). Overall multiple studies indicated that the conditioning dose intensity is highly correlated with outcome after HSCT. Increased dose intensity is associated with reduced RI but also with higher NRM (Aoudjhane et al. 2005). For example, few studies compared the FLU/BU RIC to another frequently used RIC regimen, namely, the FLU/MEL protocol demonstrating lower RI but higher toxicity with the FLU/MEL protocol which is more intense (Shimoni et al. 2007). Subsequently TREO (L-threitol-1,4-bis-methanesulfonate, dihydroxybusulfan) with activity against both on committed and noncommitted stem cells as well as potent IS properties (Danylesko et al. 2012) was combined with FLU as an effective conditioning regimen pre-HSCT for both myeloid and lymphatic malignancies with a favorable toxicity profile with little extramedullary toxicity (Nagler et al. 2017).

Overall outcome comparing these low-intensity conditioning protocols versus MAC was determined by the net effect of the opposing effects, i.e., reduction in TRM, while higher RI, leading to similar LFS and OS with patient age, comorbidities, and disease status at transplantation being significant prognostic factors. Retrospective comparative trials showed that while outcome may be similar with the various regimens in patients given HSCT in remission, NMA/RIC are inferior when HSCT is given in advanced disease, due to high RI. These observations were confirmed in some of the long-term studies but not in others (Shimoni et al. 2016). Interestingly, no disadvantage was observed for the low-intensity protocols in comparison to MAC even in high-risk disease like AML with monosomal karyotype or secondary leukemia (Poiré et al. 2015). RTC regimens are typically with more intensive antileukemic activity but limited toxicity and thus better tolerated by patients not eligible for myeloablative conditioning (Shimoni et al. 2018).

New novel conditioning protocols that may be categorized in this family of conditioning although no consensus was established are the regimens that incorporate CLO and TT and especially the TBF regimen (TT, BU, FLU) (Saraceni et al. 2017). Another worth mentioning conditioning that was developed for high-risk leukemia with encouraging results is the FLAMSA conditioning which comprised sequential chemotherapy including FLU, Ara-C, and amsacrine followed by RIC pre-allo-HSCT (Malard et al. 2017). Only few randomized studies compared head-to-head MAC to RIC or RTC regimens mostly confirming the above findings. A French well-designed two-arm study compared BU/FLU to TBI (low dose)/FLU demonstrating less RI with the BU/FLU regimen but higher TRM resulting in similar LFS and OS (Blaise et al. 2013). Similarly, a German randomized study compared RIC regimen of four doses of 2 Gy of TBI and 150 mg/m^2 FLU versus MAC of six doses of 2 Gy of TBI and 120 mg/kg CY demon-

strating reduced toxicity in the RIC arm but similar RI, TRM, LFS, and OS between both study arms (Bornhäuser et al. 2012). These results were recently confirmed with longer follow-up.

Finally, a recent CTN phase III randomized trial compared MAC (BU/CY, FLU/BU, or CY/TBI) with RIC (FLU/BU or FLU/MEL) in patients with AML and MDS (Scott et al. 2017). RIC resulted in lower TRM but higher RI compared with MAC, with a statistically significant advantage in RFS and a trend to an advantage in OS with MAC. Another randomized study comparing RIC and MAC in patients with MDS demonstrated similar 2-year RFS and OS with no difference between the two conditioning regimens (Kröger et al. 2017). As for the issue of higher risk of RI post RIC, novel immunological and pharmacologic approaches are being currently explored (as will be discussed in Chap. 69). Treatment options include second HSCT or DLI with similar results (Kharfan-Dabaja et al. 2018).

13.5 Conditioning Regimens for Allo-HSCT from Alternative Donors: MMUD, CB, and Haploidentical

Historically, these types of allo-HSCT were the most challenging ones with relatively high incidence of non-engraftment and high TRM. Notably, recent development in the field of transplantation including novel conditioning regimens resulted in major improvement in the results of allo-HSCT from alternative donors with the haplo-HSCT being of the most interest (Lee et al. 2017). A key component of the conditioning regimen for MMUD and haplo-HSCT is ATG, recently reviewed for the ALWP of the EBMT (Baron et al. 2017). In previous well-designed randomized clinical trials in allo-HSCT from URD and in a single study also from MSD, ATG was demonstrated to reduce GVHD and TRM without jeopardizing the GVL effect, and thus there is no increase in RI (Baron et al. 2017). In contrast and somewhat still puzzling in CBT, ATG is a negative factor associated with decreased OS and EFS rates and a high incidence of NRM (Pascal et al. 2015).

In an analysis performed by Eurocord, the MAC regimen for CBT included TBI 12 Gy—or BU—with or without FLU, TBI 12 Gy + CY, and more recently TBF (TT, BU, FLU) (Ruggeri et al. 2014). Comparing these regimens in single (s) (with >2.5 × 10^7 cells/kg) and double (d) CBT resulted in similar outcomes, NRM and RI incidence, which were not statistically different among the groups. LFS was 30% for sUCBT using TBI- or BU-based MAC compared with 48% for sUCBT TBF and 48% for dUCBT ($P = 0.02$ and $P = 0.03$, respectively), and it was not statistically different between sUCBT with TBF and dUCBT. They concluded that the choice of TBF conditioning regimen for sUCBT may improve results, and whether this regimen may be effective in dUCBT should be further analyzed (Ruggeri et al. 2014). In the haploidentical setting, the field moved from T-depleted to T-repleted haplo-HSCT and in recent years from ATG-based anti-GVHD prophylaxis to PT-CY pioneered by the Baltimore group (reviewed in Lee et al. 2017). Initial conditioning protocols in the Baltimore approach were RIC with BM grafts, but subsequently MAC regimens and PB grafts were introduced. In recent years, the TBF condoning is increasingly used for haplo-HSCT in Europe. Similarly, the PT-CY strategy for GVHD prophylaxis is being adopted to allo-HSCT from MUD, MMUD, and sibling donors (Ruggeri et al. 2018). In general comparing RIC to MAC for MMUD, CBT, and haplo-HSCT demonstrated in large similar transplantation global outcome for RIC versus MAC with some differences in the various alternative donors (Baron et al. 2016). For example, in the allo-HSCT from MMUD in patients >50 years, RIC resulted in reduced TRM and better LFS and OS in comparison to MAC, while in those <50 years, no difference was observed (Savani et al. 2016). In CBT, RIC resulted in a higher RI and a lower NRM, translating to comparable LFS, GVHD

and relapse-free survival (GRFS), and OS (Baron et al. 2016). In the haplo-setting, no significant difference was observed (Rubio et al. 2016).

13.6 Preparative Conditioning for Autologous HSCT

Auto-HSCT are performed mainly for malignant lymphoma and MM. The most popular conditioning protocol for auto-HSCT in lymphoma is BEAM (BCNU, VP, Ara-C, and MEL) (Mills et al. 1995) or BEAC (with CY instead of MEL), while some centers substitute the BCNU with TT (the so-called TEAM or TECAM protocol), especially in patients with pulmonary problems in order to prevent the BCNU-mediated lung toxicity. Others tried to replace the BCNU by bendamustine (the so-called BeEAM protocol). Adding anti-CD20 radiolabeled MoAb like yttrium-90-ibritumomab tiuxetan (Zevalin) to the condition improved results in some studies, but a large randomized multicenter study with 131I-tositumomab (Bexxar) was negative (Vose et al. 2013).

As for auto-HSCT in MM, high-dose MEL has been shown to be superior to TBI/MEL. Recently some centers incorporated IV BU into the auto-HSCT in MM, while others included BOR. The numbers of auto-HSCT in acute leukemia went down in the last two decades in parallel to the increase in the numbers of allo-HSCT with RIC and from alternative donors (Gorin et al. 2015). The most popular preparative regimen for AML is BU/CY. Recently on behalf of the ALWP of the EBMT, we demonstrated that BU/MEL is a better preparative regimen as compared to BU/CY with lower RI, better LFS and OS, and no difference in TRM. Similar results were obtained in the subgroup of patients with high-risk AML. Patients with negative MRD before auto-HSCT did better (Gorin et al. 2017).

Key Points

- Conditioning regimens are integral and important part of HSCT enabling engraftment and provide an antitumor effect.
- The conditioning regimen pretransplantation should take into consideration patient and disease characteristics including age, comorbidities, disease status, and most probably measurable residual disease.
- Conditioning regimens may include irradiation, chemotherapy, serotherapy, monoclonal antibodies, and targeted therapy which varied in different malignancies and types of donors.
- The dose intensity of the pre-HSCT conditioning varied between MAC, RTC, RIC, and NMA in decreasing intensity order.
- The NMA and RIC significantly reduced transplant-related organ toxicity and mortality enabling transplant in elderly and medically infirm patients.
- The conditioning regimens for allo-HSCT from cord blood and haploidentical donors are somewhat specific.

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