Bone Marrow Transplantation (2017) **52,** 1504–1511

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REVIEW

Conditioning regimens for allogeneic hematopoietic stem cell transplants in acute myeloid leukemia

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AML is currently the first indication for allogeneic hematopoietic stem cell transplantation (allo-HSCT), as shown by international transplant registries. The conditioning regimens are classified as myeloablative conditioning, non-myeloablative or reduced intensity conditioning. Targeted radioimmunotherapy such as anti-CD45 antibody have also been added to the conditioning regimen in an attempt to improve tumor cell kill. Refinement of standard regimens has led to a reduction of non-relapse mortality, also in the older age group over 60 or 70 years of age. Relapse post allo-HSCT remains an important issue, especially for patients who undergo transplant with residual or refractory disease. In these patients, pre- and post-transplant interventions need to be considered.

Bone Marrow Transplantation (2017) **52,** 1504–1511; doi:10.1038/bmt.2017.83; published online 15 May 2017

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) offers the only chance of long-term remission and possibly cure for AML patients. Most patients with newly diagnosed AML should be considered for allo-HSCT in first remission, unless they are classified as good risk, as identified by specific markers such as t(15;17), t(8;21), inversion 16 or normal cytogenetics with a mutated nucleophosmin 1 gene (NPM1) without the presence of FMS-like tyrosine kinase-internal tandem duplication (FLT3-ITD).[1] Allo-HSCT is considered in AML patients who do not enter remission after one or two courses of induction chemotherapy, and over 65 years of age, irrespective of the remission status, because of the short duration of first remission.[2] Since various donor sources are available such as an identical sibling (SIB), a matched unrelated donor (MUD), a cord blood unit (CB) or a family haploidentical donor (HAPLO), over 80% of eligible patients can undergo an allo-HSCT.[3] Conditioning regimens play important role and its choice is influenced by various factors, such as, age of patient, disease risk, performance status and remission status at the time of transplantation. The purpose of this review is to summarize important principles of conditioning regimens and possibly outline a tailored approach for patients in different age groups.

DEFINITION OF INTENSITY

Presently conditioning regimens are divided into three categories: (a) myeloablative conditioning (MA), (b) reduced intensity conditioning (RIC) and (c) non-myeloablative (NMA) conditioning. While MA regimens cause irreversible cytopenia and stem cell support is mandatory, NMA regimens cause minimal cytopenia and can be given also without stem cell support. RIC regimens do not fit criteria for MA or NMA regimens: they cause cytopenia of variable duration and should be given with stem cell support, although cytopenia may not be irreversible.[4]

CONDITIONING REGIMEN FOR AML PATIENTS WITHOUT CO-MORBIDITIES AND GOOD PERFORMANCE STATUS

The AML patients who are < 45 years of age or patients between 45 and 65 years without any comorbidities are effectively treated by myeloablative TBI-based conditioning or myeloablative non-TBI-based regimens.

Myeloablative conditioning with TBI

A myeloablative dose of TBI can be delivered in different regimens: single dose TBI: 5–10 Gy total dose; fractionated dose TBI (fTBI): 5–6 fractions over 3 days to a total of 10–14 Gy and 'Hyperfractionated' TBI: 10–12 fraction over 4 days, usually to a total of 14–15 Gy. TBI is most commonly combined with cyclophosphamide; however, it can be combined with various other chemotherapy agents.

Common chemotherapeutic agents used with TBI. Cyclophosphamide (CY) with fTBI (CY-TBI) is the most commonly used radiation-based regimen. The standard dose of CY is 120 mg/kg and standard dose of TBI delivered is 12 Gy, TBI doses ranging from 10 to 16 Gy are used. In addition to CY, busulfan (BU) and etoposide (VP-16) have also been combined with TBI to increase the leukemia cell kill.[4] A prospective randomized study has compared 12 Gy with 15.75 Gy TBI, relapse rate (RR) was lower with 15.75 Gy TBI, but non relapse mortality (NRM) and GVHD were higher, leading to comparable overall survival (OS).[5] Combinations of TBI-based regimens are summarized in Table 1.

Does the sequence of TBI and chemotherapy matter?. There is not much literature available regarding the sequencing of chemotherapy and TBI. The CIBMTR study examined this and found that the sequence of CY and TBI does not impact outcomes in acute leukemia patients undergoing allo-HSCT with MA conditioning.[6]

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Received 7 November 2016; revised 6 February 2017; accepted 24 February 2017; published online 15 May 2017

Table 1. Myeloablative TBI-based conditioning

Regimen	*Total dose*	*Ref.*
CY/TBI	120 mg/kg; 10 Gy	58
CY/fTBI	200 mg/kg; 12–16 Gy	59,60
CY/TBI	120 mg/kg with 12 Gy TBI or 120 mg/kg with 15.75 Gy TBI	5
TBI/ARA-C/CY	12 Gy; 36 g/m^2; 60 mg/kg	61
TMI/VP-16/ CY or TMI/ BU	12–15 Gy/60 mg/kg/100 mg/kg or 12–13.5 Gy/Busulfan targeted dose for AUC 800 μM min	8,9
FLAMSA;FLU/ARA-C/ AMSACRINE +TBI	80–120 mg/kg 100–200 mg/m^2 10 mg/kg+4 Gy	10

Abbreviations: ARA-C = cytosine arabinoside; AUC, area under the curve; CY = cyclophosphamide; fTBI = fractionated TBI.

Technical issues of dose and frequency with TBI. The delivery of chemotherapy is relatively easy, however applying uniform TBI has been challenging. The European Group for Blood and Marrow Transplantation (EBMT) survey in 56 European centers showed that there was considerable heterogeneity in delivery of TBI. The total maximum dose of TBI used for MA regimen ranged from 8 to 14.4 Gy, whereas the dose per fraction was 1.65–8 Gy. A total of 16 dose/fractionation modalities were identified. The dose rate ranged from 2.25 to 37.5 cGy/min. The treatment unit was a linear accelerator (LINAC) (91%) or a cobalt unit (9%). Beams (photons) used for LINAC were reported to range from 6 to 25 MV. The most frequent technique used for irradiation was 'patient in 1 field,' in which two fields and two patient positions per fraction are used (64%). In 41% of centers, patients were immobilized during TBI. Approximately 93% of centers used *in vivo* dosimetry with accepted discrepancies between the planned and measured doses of 1.5 to 10. In 84% of centers, the lungs were shielded during irradiation and the maximum accepted dose for the lungs was 6–14.4 Gy. These findings suggest that there is a considerable amount of heterogeneity in the delivery of TBI.[7]

Persistent disease at the time of allo-HSCT, newer TBI-based strategies/FLAMSA. Recently, total marrow irradiation (TMI) with tomotherapy has been proposed, with the aim of increasing the dose of radiation delivered to the marrow. Wong *et al.* reported preliminary results of two Phase I trials using TMI combined with high-intensity regimens in refractory AML patients. TMI (dose ranging from 12 to 15 Gy given at 1.5 Gy twice daily) was combined with VP-16 (60 mg/kg)/CY (100 mg/kg) or targeted IV busulfan (area under the curve of 800 mM per min for 7 days) and VP-16 (30 mg/kg).[8,9] In these highly refractory patients, the results were encouraging with 5 out of 12 patients achieving long-term CR. The usefulness of TMI needs to be tested in a prospective trial. For the persistent and refractory disease, both TBI and chemotherapy can be incorporated in a high-dose sequential treatment program. A promising approach proposed by the German group with the FLUDARABINE/AMSACRINE/ARA-C/4 Gy TBI sequential conditioning regimen showed promising results for high-risk AML and myelodysplastic syndrome (MDS) patients, including patients with primary induction failure and adverse risk cytogenetics.[10] A total of 23 AML patients were treated with this regimen, 22 engrafted, LFS at 4 years was 72.7%.[11]

In conclusion, TBI remains an important component of the conditioning regimen in patients with AML. It has been difficult to assess whether one given combination is superior to another. The standard myeloablative regimen, with more patients and longer follow-up, remains CY 120+fTBI 12 Gy. For patients with persistent disease or refractory disease, newer strategy with FLUDARABINE/ AMSACRINE/ARA-C/4 Gy TBI sequential conditioning regimen showed promising results for high-risk AML and MDS patients. For patients with advanced or refractory AML, the outcome is poor, with long-term survival in the order of 20%: for these patients interventions before the conditioning regimen, as proposed by the German group (FLAMSA) or after transplantation, such as early donor lymphocyte infusion (DLI) or panobinostat[12], should be further explored. There is heterogeneity in the delivery of TBI and hence every effort should be made to perform large retrospective and prospective studies to analyze the outcome. TMI approach appears promising; however, it is limited by lack of wider availability.

Myeloablative regimens without TBI

The most important factors limiting the use of TBI are age, previous radiation therapy, comorbidities and logistical problems with delivering TBI. The incidence of acute GVHD (aGVHD) is also higher with high-dose TBI due to direct organ toxicity, and possibly also to indirect upregulation of donor T-cell response.[13] The use of busulfan has revolutionized the approach towards conditioning and has become alternative to TBI.

Busulfan. BU has myelotoxic and antileukemic properties, and has been extensively used in conditioning regimens. Two preparations of BU are available: oral BU and IV BU. IV BU has better bioavailability and the mean clearance of IV BU is typically 3.3 ml/min/kg in adults and 4–5 ml/min/kg in children. Mean estimates for volume of distribution range from 0.62 to 0.84 L/kg. Therapeutic drug monitoring of IV BU is feasible in most patients except for children with nonmalignant diseases.[14]

Myeloablative BU vs TBI. MA doses of BU have been directly compared with TBI. In a prospective study by Bredeson *et al.*,[15] MA BU vs MA TBI-based regimens in myeloid malignancies were compared. A total of 1483 patients undergoing transplantation for myeloid malignancies (IV-BU, $N = 1025$; TBI, $N = 458$) were enrolled. Cohorts were similar with respect to age, gender, race, performance score, disease and disease stage at transplantation. Most patients had AML (68% IV-BU, 78% TBI). Two-year probabilities of survival (95% confidence interval) were 56% and 48% for IV-BU and TBI, respectively. Corresponding incidences of TRM were 18% and 19% and disease progression were 34% and 39%, respectively. The incidence of hepatic veno-occlusive disease was 5% for IV BU and 1% with TBI ($P < 0.001$). There were no differences in PFS and GvHD. Compared with TBI, IV BU resulted in superior survival with no increased risk for relapse or transplant-related mortality (TRM). These results support the use of MA IV BU vs TBI-based conditioning regimens for treatment of myeloid malignancies.[15] The commonest combination of BU is with CY. Socie *et al.*[16] compare the outcomes of BU-CY vs CY-TBI in the landmark meta-analysis.

Busulfan, cyclophosphamide (BU-CY) vs cyclophosphamide, TBI (CY-TBI). The most common MA regimens used are CY-TBI and BU-CY. Four randomized studies have been carried out, to compare CY-TBI vs BU-CY in patients undergoing an allo-HSCT. Socie *et al.*[16] reported the long-term follow-up and outcome of these four studies in 172 AML patients. Although CY-TBI had a somewhat superior survival as compared with BU-CY, this did not reach statistical significance (63% vs 51%, respectively). The corresponding disease-free survival (DFS) estimates were 57% vs 47%. The 5-year cumulative incidence of clinically extensive chronic GVHD (cGVHD) reached 20 and 19% with BU-CY vs CY-TBI, respectively.[16] The retrospective EBMT study by Nagler *et al.* compared outcomes of patients with AML in first or second remission after allo-HSCT from sibling donors who underwent BU-CY ($n = 795$) or CY-TBI ($n = 864$) conditioning. Engraftment rate was 98% and 99% after BU-CY and CY-TBI, respectively. Grades 2 to 4 aGVHD was significantly lower in the BU-CY compared with the CY-TBI group ($P < 001$). Similarly, cGVHD was significantly lower in

Table 2. Summary of BU-CY vs CY-TBI based regimen

Regimen	*Follow-up*	*TRM (%)*	*LFS (%)*	*OS (%)*	*Relapse*	*Ref.*
BU/CY2 ($n=51$) vs	2 years	27	47%	51%	34%	62
CY/TBI ($n=50$)		8%	72%	75%	14%	
BU/CY2 ($n=25$) vs	3 years	NR	83	NR	NR	63
CY/TBI ($n=26$)		BR	58	NR	NR	
BU/CY ($n=381$)	5 years	27	54	55	19	18
vs CY/TBI ($n=200$)		33	58	60	12	
BU/CY2 (134)	2 years	15	65	NR	23	64
BU/CY4 (89)		18	6	NR	24	
CY/TBI (223)		19	266	NR	19	

Abbreviations: BU = busulfan; CY = cyclophosphamide; TBI = total body irradiation.

the BU-CY compared with the CY-TBI group ($P=0.003$). Cumulative incidence of 2-year NRM was 12 ± 1% in the BU-CY group and 15 ± 2% in the CY-TBI group ($P=0.14$), and 2-year relapse incidence was 26 ± 3% in the BU-CY and 21 ± 1% in the CY-TBI group ($P=0.012$).[17]

In a registry study, Litzow *et al.*[18] analyzed 381 patients with AML in first remission treated with either CY-TBI or BU-CY, and found no significant difference in TRM, DFS or OS (Table 2).

In conclusion, BU-CY and CY-TBI lead to similar long-term outcomes in patients with myeloid AML patients, although TBI-based conditioning provided better long-term OS. Various combinations of BU were tried; however, BU-CY appears to be best combination for the young fit patients.

Combination of BU with other agents. BU has been combined with various chemotherapy agents. Oral BU, 4 mg/kg per day for 4 days and CY 120 mg/kg, has been combined with VP-16 60 mg/kg or VP-16 30 mg/kg, without showing an advantage over standard BU/CY2.[19–21] BU (1 mg/kg administered orally per 6 h on days −8 to −5), VP-16 (20 mg/kg administered on days −4 and −3), ARA-C (3 g/m^2 administered per 12 h on days −3 and −2) and 10 μg/kg G-CSF (administered SC from day −9 to day −2) were assessed in 42 AML patients in first CR. In this particular regimen of BU/VP-16/ARA-C, the NRM was very low and the RR and DFS rates were 21% and 79%, respectively.[22]

Lee *et al.*[23] compared MA doses of BU-CY with BU-fludarabine (FLU) in younger patients. In this phase III randomized study, 64 patients received BU (3.2 mg/kg per day × 4 days) plus CY (60 mg/kg per day × 2 days; BU-CY), and 62 patients received BU (same dose and schedule) plus FLU (30 mg/m^2 per day × 5 days; BU-FLU). Nonrelapse mortality was similar in the two arms, but the BU-CY arm had better OS, and event-free survival at 2 years, 67.4% vs 41.4% ($P=0.014$) and relapse-free survival, 60.7% vs 36.0% ($P=0.014$), respectively. These results indicated that the BU-CY might be better in younger adults who are eligible for MA conditioning therapy for allo-HSCT.[23]

In conclusion, BU-CY still remains the most studied regimen and achieves high degree of remission in younger patients.

Long-term complications after MA conditioning regimen

Late effects have been analyzed in the four randomized trials comparing BU-CY vs CY-TBI: the 7-year cumulative incidence of cataracts was 12.3% and 12.4% for AML ($P=0.82$), avascular necrosis was 6% and 7% for BU-CY vs CY-TBI, respectively. There was increased risk of cataract after CY-TBI and of alopecia with BU-CY conditioning. The secondary malignancies account for up to 5–10% of late deaths.[16]

CONDITIONING REGIMEN FOR AML PATIENTS WITH CO-MORBIDITIES AND ELDERLY PATIENTS

Sixty percent of newly diagnosed AML patients are elderly and hence it may be difficult to deliver MA conditioning prior to transplant. The development of NMA conditioning has facilitated the allo-HSCT in elderly patients.

NMA conditioning regimens with TBI

In the past decade, the Seattle team has introduced TBI (2 Gy) in combination with fludarabine (FLU) for allo-HSCT in older patients. This dose of TBI is NMA and produces little or no cytopenia. A report on 274 AML patients, conditioned with FLU-TBI 2 Gy has shown 26% NRM, 42% relapse and 37% survival in remission patients.[24] Similar results were seen in 122 AML patients who had undergone FLU-TBI conditioning.[25] St Louis group has explored low-dose TBI-based conditioning. Twenty-seven good-risk (AML in first remission and chronic-phase CML) and 53 poor-risk (other) patients underwent allo-HSCT with low-dose TBI (550 cGy) and CY. The TRM at 2 years in good risk and poor risk group was 7% and 19% respectively. The DFS and OS at 3 years in good risk group was 77% and 85%, respectively, and of the poor-risk group were 34% and 36%, respectively.[26] It is currently thought that TBI 2 Gy is a suboptimal regimen for AML, and exposes the patient to a high risk of relapse; however, it is well suited for elderly and patients with comorbidities.

In conclusion, the standard TBI-based NMA regimen is TBI 2 Gy in combination with FLU and can be adopted for older patients (over the age of 45, or patients unfit to receive full-dose TBI).

NMA conditioning without TBI

FLU was introduced in the preparative regimens for allo-HSCT by the Perugia group in the 1990s, in the context of NMA allo-HSCT. Thereafter, FLU has been one of the key components of RIC/NMA regimens, usually in association with an alkylating agent, such as BU, melphalan or THIO. FLU has also been used together with MA doses of IV BU, initially by the Alberta group in Canada. The first published NMA conditioning 1998 includes FLU, anti-thymocyte globulin (ATG) and low-dose IV BU (8 mg/kg) in 26 patients (AML = 10 patients).[27] This regimen was very well tolerated and at the median follow-up of 8 months, 22 of 26 patients (85%) are alive and 21 (81%) were disease-free. The calculated actuarial probability of DFS at 14 months was 77.5% (95% confidence interval, 53–90%). A recent randomized study in AML patients aged 45–65 comparing BU-CY with FLU-BU has shown that the combination of FLU-BU significantly reduced NRM.[28] In this randomized, phase 3 trial, patients were randomly assigned 1:1 to receive either BU-CY ($n=125$) or BU FLU ($n=127$). The 1 year NRM was 17.2% (95% CI 11.6–25.4) in the BU-CY arm and 7.9% (4.3–14.3) in the FLU-BU arm ($P=0.026$). The most frequently reported grade 3 or higher side effects were gastrointestinal events in 23% of 121 patients in the BU-CY group and 1% of 124 patients in the FLU-BU group. The infection rates were 17% in the BU-CY group and 10% FLU-BU group.[28] The editorial comment of this study suggested that 'whenever possible, FLU-BU should be the conditioning regimen of choice for patients with acute myeloid leukemia undergoing matched sibling or unrelated donor hematopoietic stem-cell transplantation', in patients aged 45–65.[29]

NMA and RIC regimens are well tolerated and can achieve long-term remission in older AML patients with medical comorbidities. FLU has a synergistic effect with other alkylating agents, is well tolerated and is backbone of various RIC regimens. The French group has extensively used FLU (150–180 mg/m^2 total dose), IV BU (8 mg/kg) (the so-called FB2 regimen) and ATG for GVHD prophylaxis with quite promising results. Several combinations of FLU are available and few are listed in Table 3.

Newer strategies with treosulfan and clofarabine. Treosulfan (TREO) is a prodrug of a bifunctional alkylating agent and possesses myelotoxic and immunosuppressive properties. TREO-based conditioning regimens can be considered as 'low-toxicity' combinations and its anti-leukemic property is comparable to conventional myeloablative regimens. TREO is combined with FLU, at a dose of 12–14 g/m^2. Michallet *et al.* reported the results on 56 patients with hematological malignancies (of whom 29 were AML), transplanted from a 10/10 HLA identical MUD, using a TREO/FLU/ATG conditioning regimen. The cumulative incidence of grade >2 aGVHD at 100 days was 31%, the incidence of extensive chronic GVHD (cGVHD) at 18 months was 8% and 3-year OS was 52%. The cumulative incidence of relapse was 25% at 3 years and the NRM at 12 and 24 months was 20% and 23%, respectively.[30] The studies from groups in Germany and Israel has shown promising efficacy with TREO-based regimens.[31,32] Kroger *et al.*[31] investigated a dose-reduced conditioning regimen consisting of TREO and FLU followed by allo-HSCT in 26 patients with secondary AML or MDS. Twenty patients were transplanted from matched or mismatched unrelated donors and 6 from HLA-identical sibling donors. The median age of the patients was 60 years (range, 44–70). Grade 2–4 aGVHD was seen in 23% and severe grade 3 aGVHD was seen in 12%, NRM at day 100 was 28% and 2-year estimated OS and DFS were 36% and 34%, respectively. None of the patients experienced grade 4 aGVHD and cGVHD was noted in 36% patients' with 18% having extensive cGVHD.[31] Shimoni *et al.*[32] explored a regimen of FLU (30 mg/m$^2\times5$) and TREO (12 g/m$^2\times3$) in 24 patients with AML ($n=19$) or MDS ($n=5$), not eligible for MA regimen. Two-year DFS was 60%, the CI of relapse was only 15%, while NRM was 25%.[32] Gyurkocza *et al.*[33] prospectively investigated a regimen that consisted of: TREO (14 g/m^2 per day) on day −6 to −4, FLU 30 mg/m^2 per day and 2 Gy TBI in AML and MDS patients. The patient population consisted of AML patients in CR ($n=60$) and intermediate or high risk MDS ($n=36$) with a median age of 50 years. At the median follow-up of 12.8 months, the estimated 2-year PFS and OS was 59% and 68%, respectively.[33] Chevallier *et al.*[34] reported the results of a clofarabine-based regimen on 90 patients with hematologic malignancies that included AML ($n=69$) or ALL ($n=21$). The majority of cases ($n=66$) presented with an active disease at transplant while 38 patients had received previous transplantation. Engraftment was achieved in 97% of evaluable patients. With a median follow-up of 14 months (range 1–45), the 2-year OS, LFS and RR were 28%, 23% and 41%, respectively.[34] When comparing AML and ALL patients, OS and LFS were significantly higher for AML.

In conclusion, the TREO/FLU/ATG and Clofarabine/BU/ATG conditioning regimen produces long-term remission in a high proportion of patients with high-risk AML transplanted in CR and deserves further evaluation.[39–41] But none of these has been shown to be superior to a conventional CY-TBI or BU-CY.

Table 3. Combinations with FLU

FLU ± others
FLU/TBI ± others
FLU+CY ± others
FLU+BU ± others
FLU+MEL ± others

BU = busulfan; CY = cyclophosphamide; FLU = fludarabine; MEL = melphalan; TBI = total body irradiation.

Comparison of RIC vs myeloablative conditioning conditioning

There are very few studies directly comparing RIC vs myeloablative conditioning (MAC). The BMT CTN 0901 randomized phase 3 trial by Scott *et al.*[35] compared outcomes by conditioning intensity, RIC vs MAC in patients with MDS or AML. The 18-month relapse was significantly higher in patients who received RIC in both the AML (50% vs 16.5%; $P<01$) and MDS (37% vs 3.7%) subgroups compared with the MAC arm. This translated to a significantly longer relapse-free survival for patients in the MAC arm (68.8% vs 47.3%; difference of 20.4%; $P<0.01$).[35] The prospective, open-label randomized phase 3 trial, Bornhouser and colleagues compared FLU-based RIC conditioning regimen with a standard CY-TBI MAC regimen in patients with AML in first CR. Ninety-nine patients were randomly assigned to receive RIC and 96 to receive standard MAC. The incidence of NRM did not differ between the RIC and MAC groups with cumulative incidence at 3 years 13% and 18%, respectively. At 3 years, the cumulative incidence of relapse was 28% and 26%, respectively; DFS was 58% and 56%, respectively, while OS was 61% and 58%, respectively. Grade 3–4 of oral mucositis was less common in the RIC group than in the standard MAC group (50 patients in the RIC vs 73 p-

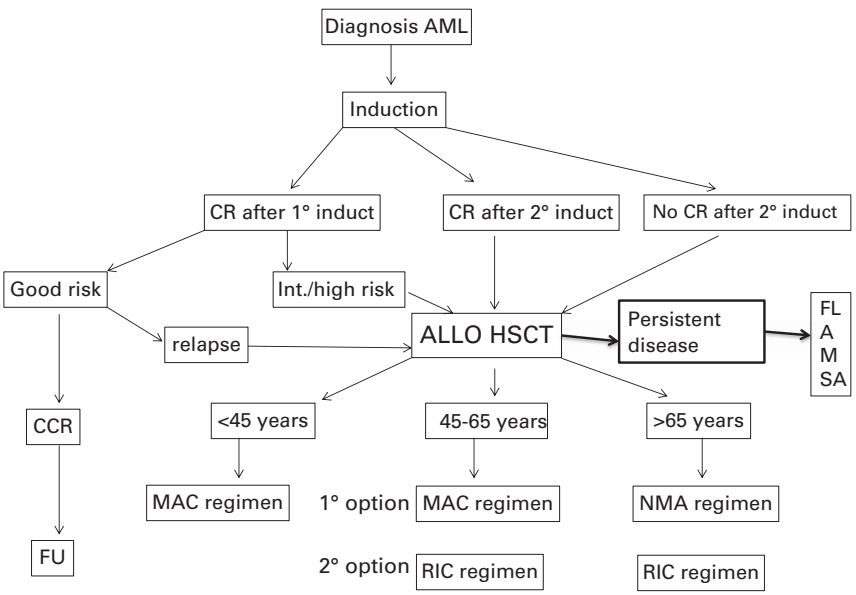

Figure 1. Proposed schema for conditioning regimen.

atients in the standard MAC group); the frequency of other side effects such as GVHD disease and increased concentrations of bilirubin and creatinine did not differ significantly between groups.[36] In a systematic review and meta-analysis of MAC and RIC trials, involving 5563 AML patients, the RIC arm had significantly less grade 2–4 aGVHD, but comparable OS and event-free survival. Relapse were higher in RIC arm (OR, 1.41; 95% CI, 1.24–1.59; $P < 0.00001$) and NRM was not significantly different between the two arms (OR, 0.99; 95% CI, 0.87–1.13; $P = 0.85$).[37]

In conclusion, it is difficult to draw definitive conclusions on the role of RIC vs MAC regimens in AML: this is due to the fact that numerous variables come in to play, and influence the outcome. It is clear that MA regimens offer better disease control and DFS in younger patients. It is probably reasonable to state that the choice of RIC or MAC regimen, will depend on patients' age, comorbidities, disease phase, donor type, GVHD prophylaxis, as suggested in Figure 1.

Long -term complications after RIC

RIC conditioning is also associated with long-term complications. In a retrospective analysis of 4269 patients with AML, MDS and lymphoma who underwent RIC-based allo-HSCT, there was higher risk of cancers of oral sites (lip, tonsil, oropharynx), bone, soft tissue, vulva and melanoma, with age (> 50 years) being the only independent risk factor for solid cancers (HR: 3.02, $P < 0.001$)[38] in AML and MDS patients. Similarly, a retrospective analysis of 931 patients, with MAC ($n = 257$), RIC ($n = 449$) or reduced toxicity conditioning (RTC) ($n = 225$), the incidence of secondary malignancies was 1.7%, 7.4% and 5.7% after MAC, RIC and RTC, respectively ($P = 0.02$). On multivariate analysis, FLU-based conditioning (hazard ratio (HR) 3.5, $P = 0.05$), moderate-severe cGVHD (HR 2.8, $P = 0.01$) and diagnosis of chronic myeloproliferative or non-malignant disease (HR 0.2, $P = 0.04$) were identified as a risk factors for secondary malignancy. The risk of secondary malignancies is not reduced in the era of RIC conditioning and the risk is lifelong.[39,40] Hypogonadism and infertility remains an important clinical problem after RIC or MAC transplant and all patients of reproductive age should be counseled on this important complication of transplantation.[41,42]

ALLO-HSCT FROM DONORS OTHER THAN HLA IDENTICAL SIBLINGS

Haploidentical donors (HAPLO) and umbilical cord blood (UCB) are immediately available and reduce the duration for donor search, especially for ethnic minorities and in developing countries.

Haploidentical transplants (HAPLO)

A conditioning regimen used as a backbone of HAPLO transplants for AML includes: (1) THIO, FLU, single-dose TBI 8 Gy with *ex-vivo* T-cell depleted, mega-dose of CD34+ cells;[43] (2) high dose CCNU, BU, CY, ARA-C, with unmanipulated HAPLO marrow and G mobilized blood;[44] (3) thiotepa, BU, FLU with unmanipulated HAPLO marrow[45] and (4) FLU combined with full-dose TBI.[46]

Solomon *et al.*[47,48] and Bacigalupo *et al.*[4] have used a BU-based conditioning regimen with FLU and CY (BU/FLU/CY) or with THIO and FLU (THIO/BU/FLU), respectively, with very good results. The major HAPLO studies are summarized in Table 4. In all these studies, the incidence of grade 2–4 aGVHD was in the range of 10–40%, NRM was 10–20% at 1 year and DFS was 50–60% at 2 years.

MD Anderson results for HAPLO in myeloid malignancies were recently published. All patients received a uniform conditioning regimen of melphalan 140 mg/m^2 (dose-reduced to 100 mg/m^2 in

Table 4. Summary of the various HAPLO regimens and outcomes for AML and outcomes

Regimen	*Total dose*	*TRM/NRM (%)*	*EFS/DFS (%)*	*Follow-up*	*Relapse*	*Ref.*
FLU/BU/CY ($n = 5$)	180 mg/m^2; 520 mg/m^2; 29 mg/kg	10%	50%	1 yr	40%	46
FLU/BU/CY ($n = 15$)	125 mg/m^2; 440 mg/m^2; 29 mg/kg					
THIO/BU/FLU ($n = 35$)	10 mg/kg; 9.6 mg/kg; 150 mg/m^2	18% at 6 months	51%	18 months	22%	65
FLU/TBI ($n = 15$)	120 mg/m^2; 9.9 Gy					
BU/FLU/CY ($n = 18$)	110–130 mg/m^2; 125 mg/m^2; 29 mg/m^2	7%	60%	2 years	33%	47
FLU/CY/TBI ($n = 35$)	150 mg/m^2; 29 mg/m^2; 2 Gy					
FLU/MEL/THIO ($n = 66$)	160 mg/m^2; 100–140 mg/m^2; 5 mg/kg	11.8%	56.5%	3 years	30.1	51
FLU/TBI ($n = 30$)	75 mg/m^2; 12 Gy	5%	76%	2 years	19%	48

BU = busulfan; CY = cyclophosphamide; MEL = melphalan; TBI = total body irradiation; THIO = thiotepa.

Table 5. Summary of important RIC UCB studies and outcomes

Regimen for cord blood transplant	*Acute and chronic GVHD*	*TRM*	*LFS*	*OS*	*Relapse*	*Ref.*
FLU/CY/TBI	Acute GVHD: 50% at 100 days Chronic GVHD: 16/66 pts 12 limited 4 extensive	20% at 2 years	LFS: 35% at 2 years	OS not reported yet	20% at 2 years	50
FLU/BU/ATG	Not available	MDS: 18% MUD: 14% UCB: 24%	MSD: 48% MUD: 57% UCB: 33% At 3 years	MSD: 55% MUD: 45% UCB: 43% $P = 0.26\%$	No available	51
FLU/CY TBI at differential doses	RIC: 47% acute GVHD MAC: 67% acute and GVHD $P < 0.01$	RIC:19% MAC: 27% $P =$ not significant	RIC:30% MAC: 34% $P =$ not significant	RIC: 31% MAC: 55% $P = 0.02$	RIC: 43% MAC = 9% $P < 0.01$	48
FLU/CY/TBI	Acute: 25% Chronic: 5%	16% $N =$ not significant	25% $P =$ not significant	34% P not significant	UCB: 60%	52

Abbreviations: ATG = anti-thymocyte globulin; BU = busulfan; CY = cyclophosphamide; TBI = total body irradiation.[66–68]

patients older than 55 years), FLU 160 mg/m^2 with or without THIO 5–10 mg/kg. GVHD prophylaxis consisted of post-transplant CY (PTCY), tacrolimus and mycophenolate mofetil (MMF). The 3-year PFS, 1-year NRM and cumulative incidence of relapse were 56.5%, 11.8% and 30.1%, respectively. The incidence of Grade 2–4 aGVHD was only 25%. Patients with morphologic CR at the time of allo-HSCT or with low-risk cytogenetics had a statistically significant improvement in PFS. Patients with intermediate or low-risk cytogenetics had a 3-year PFS of approximately 70%.[51] Wang *et al.* has compared outcome between HAPLO and SIB transplant. The conditioning used for HAPLO was cytarabine (4 g/m^2 per day) on days −10 to −9; BU (3.2 mg/kg per day) on days −8 to −6; CY (1.8 g/m^2 per day) on days −5 to −4; methyl chloride hexamethylene urea nitrate (Me-CCNU) (250 mg/m^2 per day), orally once on day −3; and ATG (2.5 mg/kg per day; Sang Stat, Lyon, France) on days −5 to −2. The 3-year DFS rate, OS rate and NRM in HAPLO were 74%, 79% and 13% respectively. The outcomes were similar to SIB transplant.[52]

In conclusion, the HAPLO approach offers a large donor pool for transplant eligible patients. It is clear that conditioning regimens for HAPLO transplant do not differ from the regimens used with other donor types. The relevant issue becomes graft manipulation (with or without T cells) and the phase of the disease. The outcomes are better in patients in CR at the time of transplantation (Table 4).

Umbilical cord blood stem cell transplant (UCBT)

The University of Minnesota pioneered the use of double UCB transplantation using the platform of MA conditioning regimen consisting of CY (120 mg/kg), FLU (75 mg/m^2) and TBI (1320 cGy).[53] The RIC UCB transplant approach is particularly important for AML patients in their late 60s. One of the most commonly used RIC for UCB is CY 50 mg/m^2, FLU 200 mg/m^2 divided in 5 days, and TBI 200 cGy with cyclosporine A and MMF for immune suppression.[53]

Variations on this include the use of TREO by the Seattle group and THIO by the Memorial Sloan Kettering group.[54] The Boston group has also reported promising RIC UCB conditioning regimen consisting of FLU, melphalan and rabbit ATG, and when sirolimus/tacrolimus was used for immune suppression, a very low risk of aGVHD was observed. The backbone of the conditioning platform (CY 50 mg/m^2, FLU 200 mg/m^2, TBI-200 cGy) has been shown to result in sustained donor engraftment in $>$90% of recipients, NRM between 20 and 30%, and long-term DFS in 25–50% of patients depending on disease stage and the presence of co-morbid conditions prior to transplantation.[55]

In conclusion, it appears that RIC UCB offers DFS ranging 25–35%; however, the patient numbers were limited. RIC UCB transplants can be explored as a reasonable option in patients without sibling donor, matched unrelated donor or HAPLO donor (Table 5).

FUTURE DIRECTIONS

The dose delivered to AML cells can be theoretically increased, by using radiolabeled antibodies. The 131-I-labeled anti-CD45 antibody (131-I-BC8) can deliver between 2- and 3-fold more irradiation to the bone marrow, spleen, lymph nodes and other sites of leukemia than to any normal organ. The phase I dose escalation study in 58 advanced AML and MDS patients using radioimmunotherapy-based conditioning, the estimated 1 year OS was 41% with no D30 mortality. The novel approach of pre-targeted radioimmunotherapy (PRIT) has been explored to improve the specificity of radioimmunotherapy.[56,57]

In conclusion, clinical results of radiolabeled anti-CD45 antibody combined with FLU and low-dose TBI already have shown some promise: however radiolabeled antibodies require a dedicated unit-specific dosimetry, and are expensive. In the absence of clear advantages, radiolabeled antibodies have failed to become a popular option for transplant programs.

CONCLUSION

A large number of different conditioning regimens have been tested in patients with AML, and can be classified as MAC, RIC or NMA (Figure 1). When an allo-HSCT is indicated, possibly in all intermediate-/high-risk AML patients (Figure 1), the conditioning regimen can be tailored according to the age and the comorbidities of the patient. Young patients under the age of 45 will most likely benefit from a MAC transplant with full-dose TBI, although BU-CY is also an acceptable alternative. Between 45 and 65 years of age, BUCY may be toxic, and FLU-BU would be the first choice, as shown in the recent randomized GITMO trial (Figure 1). In patients above the age of 65 a RIC or NMA regimen is probably the best option, and could be tested up to the age of 70 and over, possibly, but not necessarily preceded by a short course of chemotherapy. In these elderly patients, due to dismal current results of induction chemotherapy, upfront NMA transplantation may be worth a clinical trial.

SEARCH CRITERIA

PubMed/Medline search, identified studies for this review. Studies reporting conditioning regimens in AML with at least 20 patients in a disease-specific setting (e.g. complete remission or advanced disease) were included in the review.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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