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Pushing the envelope—nonmyeloablative and reduced intensity preparative regimens for allogeneic hematopoietic transplantation

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Abstract

Allogeneic hematopoietic cell transplantation (HCT) was originally developed to allow delivery of myeloablative doses of chemotherapy and radiotherapy. With better understanding of disease pathophysiology, the graft vs malignancy (GVM) effect of allogeneic hematopoietic transplantation and toxicities associated with myeloablative conditioning (MAC) regimens, the focus shifted to developing less toxic conditioning regimens to reduce treatment-related morbidity without compromising survival. Although HCT with MAC is preferred to reduced intensity conditioning (RIC) for most patients ≤ 60 years with AML/myelodysplastic syndrome and ALL, RIC and nonmyeloablative (NMA) regimens allow HCT for many otherwise ineligible patients. Reduced intensity preparative regimens have produced high rates of PFS for diagnoses, which are highly sensitive to GVM. Relapse of the malignancy is the major cause of treatment failure with RIC/NMA HCT. Incorporation of novel agents like bortezomib or lenalidomide, addition of cellular immunotherapy and use of targeted radiation therapies could further improve outcome. In this review, we discuss commonly used RIC/NMA regimens and promising novel regimens.

INTRODUCTION

Hematopoietic cell transplantation (HCT) is a potentially curative treatment option for a broad range of hematologic malignancies.[1–3] Patients undergoing HCT receive a preparative regimen, also known as conditioning, with the goal of cytoreducing the malignancy and providing sufficient immunosuppression to prevent rejection of transplanted stem cells.[4] Initial studies by Thomas *et al*.[5] used supra-lethal doses of TBI; this approach could induce durable remission in a fraction of patients with advanced hematologic malignancies, but at the cost of substantial toxicity and nonrelapse mortality (NRM). Significant progress has been made in optimizing conditioning regimens to decrease the toxicity without compromising outcomes.

Traditional conditioning regimens or myeloablative conditioning (MAC) regimens comprised maximally tolerated doses of chemotherapy with or without radiation therapy with infusion of donor hematopoietic cells to provide hematologic and immune recovery.

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CONFLICT OF INTEREST

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MAC regimens provide maximal direct anti-tumor activity, but at the expense of substantial nonhematopoietic toxicity. NRM with MAC regimens ranges from 10 to >50% depending on patient age, disease status, prior therapies, stem cell source and histocompatibility between the donor and the recipient.[6–11] High NRM from MAC regimens precludes their use in elderly patients and in patients with major comorbidities. With the median age of patients with hematologic malignancies in the seventh decade, there is a need to provide a well-tolerated approach for HCT for older and medically infirm recipients. The decision to perform HCT depends on patient goals, comorbidities, donor availability and social support. Most centers choose reduced intensity conditioning (RIC)/nonmyeloablative (NMA) regimens for patients >60 years or those with major comorbidities. The HCT comorbidity index has been developed based on objective assessment of various organ functions. Geriatric assessment should also be performed pre-HCT including functional assessment, frailty and mental status. The number and severity of comorbidities predict outcomes post HCT.[12,13]

The therapeutic benefit of allogeneic HCT is largely derived from the immune graft vs malignancy (GVM) effect where donor immune cells eradicate residual malignant cells that may survive the preparative regimen.[2,14–18] GVM is primarily mediated by donor T lymphocytes; however, it involves complex interaction between natural killer (NK) cells, dendritic cells and antibodies of donor origin.[19,20] NK cell activity is particularly evident in T-cell-depleted, mismatched HLA transplants.[21,22] Ab-mediated GVM is also described and may occur through C′-mediated cell death or by Ab-dependent cellular toxicity.[20] Sensitivity of malignancy to GVM effect varies among different diseases, and depends on the diagnosis, tumor burden immune escape mechanisms and proliferation rate. This is summarized in Table 1. GVM seems most potent in CML, follicular lymphoma and CLL, while AML is intermediate and ALL is relatively insensitive to this effect.[18,23,24] Pioneering work by Storb and McSweeney[25] in canine models established that 200 cGy TBI was sufficiently immunosuppressive to allow engraftment of MHC-matched allogeneic HCT. This regimen is nonmyeloablative and autologous marrow recovery in recipients with graft failure.[25] These preclinical studies led to the development of various RIC and NMA regimens to provide sufficient immunosuppression to achieve engraftment and allow GVM effects to eradicate the malignancy.

Champlin *et al*. suggested definitions of MAC, NMA and RIC preparative regimens. MAC regimens produce profound pancytopenia, which is usually irreversible and in most instances fatal, unless hematopoiesis is restored by HCT. In contrast, NMA regimens provide reversible myelosuppression, and autologous hematologic recovery would be expected to occur within 1 month without a HCT or if a graft is rejected. RIC regimens have intermediate intensity; they require a transplant for reliable hematopoietic recovery, but use a lower, less toxic dose of chemotherapy and radiation than traditional MAC regimens. Several forms of RIC regimens have been evaluated. The most common NMA regimens involve low-dose TBI, alone or in combination with fludarabine (Flu) or combinations of Flu and cyclophosphamide (Cy), with or without rituximab.[26–31] RIC regimens have generally included an alkylating agent busulfan (Bu) or melphalan (Mel) in combination with a purine analog, typically Flu. More recently monoclonal antibodies,

radioimmunotherapy or other agents have been incorporated into the conditioning regimens to better target and cytoreduce selected malignancies.

Specific definitions were adopted at the 1st International Workshop of Non-myeloablative Stem Cell Transplantation and adopted in 2006, at a workshop conducted by Center for International Blood and Marrow Transplant Research (CIBMTR).[32] Bacigalupo *et al*.[33] defined the intensity of various conditioning regimens in 2009. The intensities of most commonly used regimens are shown in Table 2. The relative myelosuppressive and immunosuppressive effects of various regimens are depicted in Figure 1.

ADVANTAGES OF RIC AND NMA REGIMENS

RIC and NMA regimens allow HCT for patients considered ineligible for MAC because of advanced age or presence of comorbidities.[34–38] RIC and NMA HCTs are generally better tolerated with lower rates of toxicity and NRM than occur with MAC HCTs.[37,39–41]

These regimens may also be associated with a reduced incidence and severity of acute GvHD.[42] Several factors contribute to this observation. The clinical manifestations of acute GvHD reflect alloreactivity superimposed on the toxicity of the preparative regimen and subsequent cytokine release by damaged cells.[43] Residual host T cells may produce a veto effect that inhibits the development of GvHD, which may be less severe in the setting of mixed chimerism. T-cell depletion with antithymocyte globulin (ATG) or alemtuzumab has been studied with RIC transplants using fludarabine and busulfan or melphalan. These agents decrease the incidence and severity of GvHD, but this benefit is offset by an increased risk of relapse and infections and overall survival has not improved.[44]

The same types of infectious complications occur as with MAC, but the severity appears to be reduced. Neutropenia is reduced or eliminated by NMA regimens.[45] In addition, as the NMA preparative regimen does not immediately eliminate host-derived immunocompetent cells, these cells can contribute to host defense in the early post-transplant period.

A general recommendation is to utilize the least toxic regimen that can achieve the optimal therapeutic result. Thus, RIC and NMA regimens are indicated for diagnoses that are highly sensitive to GVM effects. In diagnoses where higher-dose intensity improves eradication of malignancy, RIC regimens should be reserved for elderly patients or those with comorbidities who could not tolerate an ablative regimen.[24] The decision to use ablative or RIC should consider the patient's age, performance status, frailty and comorbid conditions. There is no clearly defined age cutoff. Most centers recommend RIC or NMA regimens for patients over age 60 and most centers consider patients up to 75 years of age.

In this review, we summarize transplant outcomes with various RIC and NMA conditioning regimens in various hematologic malignancies and discuss novel conditioning regimens. Although most studies show comparable outcomes with RIC vs MAC for various diseases, they are generally retrospective studies with inherent selection bias. Bornhauser *et al*.[46] published the first randomized study comparing outcomes of RIC vs MAC HCTs in patients with AML with the groups balanced for age, cytogenetic risk, induction therapy and donor type. Outcomes were similar in both groups with NRM, relapse, PFS and survival of 13 vs

18%, 28 vs 26%, 58 vs 56 and 61 vs 58%, respectively. Contrary to this study, BMT CTN 0901 was recently closed early in favor of MAC for AML/myelodysplastic syndrome (MDS) patients; detailed results have not yet been released. Results from a multicenter study by EBMT evaluating RIC vs MAC HCTs for MDS/secondary AML patients are eagerly awaited. Ideally, well-designed randomized trials for individual diseases comparing RIC vs MAC HCTs should be performed. Available single-arm studies and retrospective data must be interpreted with caution.

AML/MDS

HCT is a curative option for high-risk AML/MDS.[47] AML is the most common indication for adult allogeneic transplants.[48,49] Elderly age by itself and increased incidence of high-risk cytogenetics in elderly patients confer a poor prognosis. A study by CIBMTR and CALGB reported improvement in PFS in elderly patients receiving RIC hematopoietic transplantation compared with those receiving chemotherapy alone.[50] Age did not independently affect outcomes of elderly patients with AML and MDS undergoing HCT with RIC regimens.[51] Several studies have shown that RIC transplantation is a feasible option for otherwise transplant ineligible patients and outcomes primarily depend on the disease status at the time of HCT. RIC improved overall and disease-free survival compared with patients treated with conventional chemotherapy regimens as summarized in Table 3.[52–67] The overall survival ranged from 42 to 79%, PFS from 37 to 76% and NRM from 4 to 33%. Patients receiving RIC transplants had similar outcomes compared with patients who had transplant with MAC regimens for AML and MDS are summarized in Table 4.[68–71]

In an attempt to further reduce NRM, NMA transplants have been evaluated. NMA regimen transplants can achieve long-term remission in elderly patients with poor performance status, but the results appear inferior when compared with RIC regimen transplants for patients who are not in remission.[72,73] All these studies had heterogeneous groups of patients, inherent bias of retrospective studies and comorbidities were not taken into account during analyses and they must be interpreted with caution. Prospective multicenter studies randomizing patients to RIC vs MAC regimen transplantation are currently ongoing in Europe.

ALL

Patients with ALL achieve high rates of CR with modern chemotherapy, but long-term disease remission is seen only in a one-third of patients. Consolidation treatment with HCT has improved outcomes.[74,75] ALL is a relatively insensitive disease to GVM effect;[24] however, patients who develop GvHD do have a reduced risk of relapse. A large prospective study by UK Medical Research Council (MRC)/Eastern Cooperative Oncology Group (ECOG), MRC UKALL XII/ECOG E2993 showed improvement in a 5-year survival for standard risk ALL patients receiving HCT 53 vs 45% for those with no donor and received conventional chemotherapy. However, in patients with high-risk ALL donor vs no donor 5-year survival was not significantly different (41 vs 35%, $P = 0.2$) due to high NRM of 36% at 2 years.[76] RIC regimen transplants are a reasonable option for patients who are not

candidates for MAC regimen transplants as shown in Table 3.[77–84] Flu-Mel conditioning regimen provided survival of >60% with NRM and relapse of around 20% each.

Outcomes of RIC transplants were compared with patients who had MAC regimens. Similar results occurred in patients with Philadelphia-negative ALL, while patients with Philadelphia-positive disease had a higher incidence of relapse with RIC. This is summarized in Table 4.[85–88] Incorporation of tyrosine kinase inhibitor (TKI) treatment may improve outcomes of patients with Philadelphia-positive ALL undergoing RIC. Bachanova *et al*.[88] reported superior survival 55 vs 33% with RIC compared with MAC with use of pre-HCT TKI in patients who have negative minimal residual disease.

CML

CML was the most common indication for HCT in the pre-TKI era and is the disease where there is best evidence of a potent graft vs tumor effect[17]. RIC regimen transplants are effective treatment options for CML patients refractory to TKI therapy.[89–94] Outcomes of CML with RIC HCT depend on stage of disease; best results are reported in patients in chronic phase where outcomes are similar compared with MAC transplants.[94] However, RIC transplants may not be adequate for advanced stage disease.[92,93] TKI treatment and donor lymphocyte infusions have been effective for patients with residual disease after RIC transplants.

CLL

CLL is also susceptible to the graft vs tumor effect.[17,95–102] RIC and NMA regimen HCTs have shown encouraging results with survival ranging between 50 and 65% as shown in Tables 3 and 4.[103–108] Khouri *et al*.[104] demonstrated Flu-Cy conditioning and immunomodulation with rituximab, withdrawal of immunosuppression and donor lymphocyte infusion (DLI) in patients with relapsed refractory CLL achieved survival of 51% and in certain HLA genotype patients the PFS was 68% at 5 years. This regimen was well tolerated with NRM of 17%.

PLASMA CELL MYELOMA

Allogeneic HCT has been extensively evaluated for treatment of plasma cell myeloma. These patients tend to be relatively frail and MAC HCTs have been associated with a high rate of NRM. RIC HCT has been the preferred approach for heavily pretreated patients eligible for allogeneic transplants in salvage settings post autologous HCT and summarized in Tables 3 and 4.[109–112] Outcomes of RIC and MAC are similar. There is a higher rate of relapse with RIC transplants, which offsets the benefit of decreased NRM.[113] Preliminary studies are examining incorporation of bortezomib and lenalidomide into conditioning regimens; prospective trials are needed.[114]

LYMPHOMA

Lymphomas have variable degrees of sensitivity to GVM effects, with low-grade lymphomas having highest sensitivity and large-cell lymphoma and Hodgkin’s disease being

relatively insensitive. There are data to support use of RIC transplant in patients with various non Hodgkin's lymphoma (NHL) and like most other conditions, outcomes of RIC transplants are similar to MAC transplants as summarized in Tables 3 and 4.[115–125] More recently, targeted therapies and radioimmunotherapy have been incorporated into RIC regimens to decrease the tumor burden of patients undergoing transplants, thereby decreasing risk of relapse and not adversely affecting NRM.

Relapsed refractory follicular lymphoma can be cured with NMA HCT. Khouri *et al.*[115] reported data of 47 patients treated at MD Anderson cancer center (MDACC) with Flu, Cy and rituximab (FCR) conditioning. At a median follow-up of 11 years survival was 78% and PFS was 72%. NRM was low at only 15 %. Two other studies, by Thompson *et al.*[126,127] and CALGB with RIC HCT using Flu-Mel conditioning, with or without Alemtuzumab showed survival of 76–81% and PFS of 75% with over 3-year median follow-up.

NMA HCT is feasible and effective for patients with relapsed refractory mantle cell lymphoma. With FCR conditioning, Khouri *et al.*[115] reported PFS of 43% and survival of 53% at 6 years. Results reported by CIBMTR and Cook *et al.*[119,128] showed less encouraging outcomes with survival ranging between 14 and 25% at 3-year follow-up, which could be related to differences in number of patients with chemosensitive disease and relapsed disease after autologous stem cell transplantation.

More recently, the group from MD Anderson Cancer Center presented phase II data with NMA conditioning HCT using bendamustine, Flu and rituximab in CLL and NHL Survival and PFS were 89 and 80% with NRM of 9% with a median follow-up of 1 year.[129] This regimen is well tolerated with a low incidence of cytopenias. It can be used as a conditioning for outpatient transplants.

In the last decade radioimmunotherapy has emerged as a promising treatment option for hematological diseases especially chemoresistant NHL. Radiolabeled monoclonal antibodies allow for targeted therapy with low-toxicity rates and high-response rates when used as single agents. Addition of ^{90}Y-ibritumomab tiuxetan to Flu-TBI regimen was evaluated in heavily pretreated aggressive NHL patients by Gopal *et al.*[130] Overall Survival, PFS and NRM were 54.1, 31.1 and 15.9%, respectively, at 30 months. The NRM at day 100 was only 2.5% and this strategy could induce early responses in patients who otherwise had refractory disease. This strategy would allow adequate time for harnessing benefit from GVM effect.

Khouri *et al*. reported data with incorporation of ^{90}Y-ibritumomab tiuxetan to fludarabine and cyclophosphamide for chemorefractory follicular lymphoma. Results were encouraging with the 3-year PFS rates of 80 and 87% with chemorefractory or chemosensitive disease. This strategy could be attempted in other CD20-positive malignancies refractory to salvage chemotherapy regimen.

Promising new therapies like epratuzumab an anti-CD22 mAb conjugated with ^{90}Y showed excellent response in refractory follicular lymphoma patients. Inotuzumab ozogamicin, an antibody drug conjugate with anti-CD22 mAb in patients with ALL, produced an overall response rate of >50% in treatment-refractory patients. Addition of these agents to RIC is being evaluated in ongoing clinical trials.

HODGKIN'S LYMPHOMA

Despite a relatively low sensitivity to GVM, RIC transplants in Hodgkin's lymphoma have produced durable remissions in 30–40%, as summarized in the Tables 3 and 4.[131–134] Most patients had relapsed after autologous hematopoietic transplants, before being referred for allogeneic transplantation. Most long-term responders had chemosensitive low bulk disease. The Flu-Mel RIC regimen has been commonly used; this resulted in NRM <15% in matched related and unrelated transplants.[135] Relapse is the main cause of treatment failure in patients who have HCT, and risk of relapse depends on chemosensitivity of disease, poor performance status, age >45, relapse <6 months after autologous transplantation and transplantation before 2002.[136]

With the availability of brentuximab vedotin, salvage therapy was more effective in increasing CR rates before allogeneic transplantation. The addition of gemcitabine to fludarabine-melphalan conditioning showed encouraging results with PFS and survival at 2 years of 55 and 78%, respectively. Incidence of NRM was acceptable at 15%.[137]

SPECIFIC PREPARATIVE REGIMENS

Fludarabine melphalan (Flu-Mel)

This regimen was pioneered by Giralt *et al*.,[138] based on the idea that melphalan has activity in variety of hematological malignancies and is well tolerated in elderly patients even at high doses. Purine analogs exert a synergistic effect by inhibiting mechanisms of DNA repair from alkylating agent-induced DNA damage, and, in combination with the alkylating agent, have adequate immunosuppressive effect to allow engraftment. The median age of patients was 52 years (range, 22–70 years). AML patients in first remission or CML patients in chronic phase had 57% disease-free survival at 1 year. Grade III–IV aGvHD was seen in 19% of patients who had related donor transplants vs 39% in patients who had unrelated donor transplants. NRM rate was 37.4% at day 100. This regimen has activity in both lymphoid and myeloid malignancies.[139] Several other investigators have reported decreased NRM with Flu-Mel conditioning in patients, otherwise not eligible for HCT for various hematological malignancies as shown in disease-specific tables.

GvHD and treatment of GvHD causing mortality from various infections are a concern with RIC Flu-Mel conditioning. Alemtuzumab, a monoclonal antibody against CD52, has been combined with Flu-Mel conditioning to decrease incidence and severity of GvHD; however, several studies showed increased relapse rates needing donor lymphocyte infusion and also increased risk of infections.[140–142] Van Beisen *et al*. compared outcomes of AML/MDS patients treated with Flu-Mel regimen and Flu-Mel +alemtuzumab regimen treated at two different sites. NRM, relapse, survival and disease-free survival were similar in both groups. Grade II–IV acute GvHD and chronic GvHD was significantly lower in patients who received Flu-Mel+Alemtuzumab.[66] In a CIBMTR analysis, patients who received alemtuzumab for *in vivo* T-cell depletion effectively reduced GvHD compared with T-cell replete grafts, with grades 2–4 and 3–4 acute GvHD 40 vs 19%, $P = 0.001$, and 22 vs 11%, $P = 0.001$; however, this did not translate into better overall survival because of increased recurrence rates.[143] In another study, patients with AML treated with RIC and alemtuzumab

had worse overall survival compared with patients treated with T-cell-replete grafts despite lower rates of GvHD because of loss of GVM effect.[144] Recently Gartner *et al*.[145] reported quicker NK cell recovery with lower dose of alemtuzumab with sufficient GvHD prophylaxis, which might improve survival by decreasing risk of infections and relapse. For indolent diseases like follicular lymphoma where NRM is higher than risk of disease progression, use of donor lymphocyte infusion for patients with relapse has helped in decreasing risk of relapse with acceptable NRM of 15% at 4 years and PFS of 76%.[126]

Another *in vivo* T-cell depletion strategy is the use of ATG, which has been extensively studied in unrelated donor transplants with RIC regimens. In the CIBMTR study cited above, rates of grades 2–4 and grades 3–4 acute GvHD were similar with T-cell replete and ATG-containing regimens: 40 vs 38% and 22 vs 21%, respectively, and the overall survival rate was lowest in the patients receiving ATG compared with alemtuzumab and T-cell-replete grafts, 38 vs 50% and 46%. There was no advantage seen in the NRM rates with ATG-containing RIC regimens. Also patients who received ATG had a higher incidence of Epstein Barr virus post-transplant lymphoproliferative disorder unlike alemtuzumab, which effectively depletes B cells. Despite improvement of supportive care and decrease in infections with antimicrobial therapies we recommend cautious use of T-cell depletion strategies based on the disease status, chemosensitivity and pre-transplant therapies, given the above data.

Fludarabine busulfan

Low-dose Bu with Flu was first developed as a conditioning regimen, with the Bu to achieve well-tolerated cytotoxicity against myeloid malignancies in combination with Flu and ATG as immunosuppressive agents to prevent rejection of infused stem cells.[97] Since then variations of this regimen have been studied extensively by several transplant groups for both myeloid and lymphoid malignancies and are summarized in disease-specific tables. This regimen was studied by Brenner *et al*.[146] in patients 70 years or older patients and the cumulative incidence of grades II to IV acute GvHD was 13% and grades III to IV was 9.3%. At 2 years the cumulative incidence of chronic GvHD was 36%, survival and PFS were 39%, with relapse rate of 56%. NRM was 3.7% at day 100 and 5.6% at one year. Within the RIC regimen two different doses of Bu, 3.2 and 6.4 mg/kg, IV were studied with Flu by Chen *et al*.[147] in patients with MDS/AML. The cumulative incidences of acute GvHD and chronic GvHD were similar. Two-year NRM rates were 8.9 vs 9.8%, respectively; PFS 40.6 vs 39.3% and survival 47.4 vs 48.8%, respectively, predicting dose of 3.2 mg/kg might be sufficient in most cases.

The Flu-Bu conditioning regimen was often used in combination with ATG with the goal of improving NRM and GvHD rates, A large French study with addition showed significant improvement in GvHD rates with addition of rabbit ATG 5mg/kg to Flu-Bu regimen for AML patients. At 4 years of follow-up grade III–IV acute GvHD was 9%, and extensive chronic GvHD occurred in 22%. The survival at 4 years was 54% with relapse rate of 36% and NRM of 22%.[148] These results are promising and further strategies to decrease relapse rates could improve outcomes further.

Low-dose TBI+/− fludarabine

TBI alone with or without Flu as a NMA conditioning regimen was pioneered by Storb and coworkers, primarily to transplant patients who are >60 years of age. They reported 372 patients between the ages 60 and 75; cumulative incidences of NRM and relapse at 5 years were 27 and 41%, respectively, with 5-year survival of 35% and PFS of 32%. Higher age was not associated with the higher incidence of acute GvHD or chronic GvHD. Analysis based on age did not significantly affect the outcomes and it was the disease risk and comorbidity index, which were the determinants.[149] Outcomes of patients who were treated with TBI alone vs TBI along with Flu were compared in a randomized phase III study. Outcomes were superior with addition of Flu to TBI regimen with 3-year survival 65 vs 54% in favor of Flu-TBI and they had lower relapse rate 40 vs 55%. Addition of Flu contributed to better T-cell and NK-cell chimerism at day 28 and less incidence of graft failure.[150] Transplant with Flu TBI conditioning is a reasonable option in elderly patients who would otherwise be not eligible for transplantation.

Total lymphoid irradiation/ATG

Investigators from Stanford university developed a novel RIC regimen with total lymphoid irradiation and ATG, which altered host immunity profile to favor regulatory NK T cells. A total of 111 (67 lymphoid/34 myeloid) patients were treated with total lymphoid irradiation/ATG and received G-CSF-mobilized grafts. Over a third of the patients in this study were >60 years of age, with half of the lymphoid malignancy patients having high risk of relapse after failing autologous transplantation. Fifty-one of these patients had mismatched donors. Cumulative incidence of grade II–IV GvHD was 2 and 10% for related and unrelated donors, and 1-year NRM was significantly improved at 4%. Probability of 3-year survival and PFS was 60 and 40%, respectively.[60]

Treosulfan-based regimens

Treosulfan is a prodrug of a bifunctional alkylating cytotoxic agent that is approved for the treatment of ovarian cancer in Europe. Treosulfan-based reduced toxicity regimens were well studied in the myeloablative setting, Michallet *et al*.[151] studied treosulfan fludarabine ATG RIC regimen in a phase II trial. This study included patients with acute and chronic leukemias. The regimen was well tolerated with NRM of 23% at 2 years and overall survival of 52% at 3 years. Cumulative incidence of relapse was 25%, and of acute and chronic GvHD was around 30%.

Clofarabine-based regimens

Clofarabine is a second generation, purine analog with activity in relapsed AML with favorable toxicity profile. It has been studied as an alternative to fludarabine for RIC. Debulking relapsed/refractory AML/MDS patients with clofarabine/cytarabine followed by RIC HCT with Cy TBI led to 2-year PFS and overall survival of 52 and 56%, respectively.[152] Small prospective study CLORIC trial with clofarabine busulfan RIC in high-risk AML/MDS, ALL and biphenotypic leukemia patients with median age of 59 years showed excellent 1-year PFS and overall survival of 63 and 57%, respectively.[153] Several other studies confirmed feasibility and efficacy of clofarabine-based conditioning.[154,155]

FUTURE DIRECTIONS

Better understanding of molecular pathways led to identification of treatment targets in various hematological malignancies and has improved response rates in frontline and relapse settings. Outcomes of RIC/NMA HCTs could be further improved by incorporation of novel agents to the disease-specific conditioning regimens without significant additional toxicities.

Targeted radioimmunotherapy

Pagel *et al*.[156] pioneered use of ^{131}I-labeled anti-CD45 antibody in combination with a NMA regimen of fludarabine and low-dose TBI to deliver targeted radiation to the bone marrow, spleen and lymph nodes in patients with AML or MDS who had >5% blasts before transplant. The authors demonstrated that the maximal tolerated dose (MTD) of radiation to the liver was 24 Gy by radio immunotherapy, which would otherwise be a supralethal dose when administered by conventional methods. A third of these patients had infusional reactions; however, they resolved at the end of infusion. Results of this study were encouraging with 100% T and myeloid donor engraftment at 1 month with NRM of 12% at 100 days. The relapse rate was 40% and overall survival of 41% at 1 year. Similarly Ringhoffer *et al*.[157] demonstrated that ^{188}Re or ^{90}Y-labeled anti-CD66 antibody delivered radiation dose of 21.9 (+/− 8.4) Gy to the marrow with a significantly higher dose using ^{90}Y conjugate and had encouraging results when used as a part of conditioning therapy. However, these agents are β-particle-emitting isotopes, which create a field radiation effect and target negative marrow tumor cells. These agents could also cause non-specific toxicity to normal cells. α-Particles have higher linear energy transfer and shorter range with less non-specific toxicity.[158] α-Emitters ^{213}Bi and ^{225}Ac in combination with targeting vehicle-humanized anti-CD33 mAb Lintuzumab are being evaluated in phase I/II studies alone and in combination in AML.[159–161] Preliminary results show encouraging reduction in bone marrow blast percentage. This strategy with ^{213}Bi-labeled Abs, against CD45 and T-cell receptor αβ before transplantation, is being tested in canine models to minimize the toxicity of NMA regimens.[162,163]

Pretargeted radioimmunotherapy

Pretargeted radioimmunotherapy is an interesting strategy, which could further reduce the systemic toxicities to normal organs with encouraging results in pre-clinical setting. Targeting molecule anti-CD45 mAb conjugated with streptavidin is infused to reach the target cells, and circulating Ab is removed by ‘Clearing agent’. This followed by infusion of ^{213}Bi- or ^{90}Y-DOTA-biotin led to leukemia-free survival in mouse models up to 100 days.[164] Other interesting strategies include incorporation of bispecific Ab-hapten in NHL patients and single-walled carbon nanotubes (SWNTs) with complementary morpholino oligonucleotide (MORF) sequences.[165,166] SWNT-MORF bind to cancer cells with significantly higher affinity than monoclonal Abs as they have been pretargeted with antibodies modified with oligonucleotide strands complementary to those on the nanotubes. Inclusion of these agents with conditioning could further improve outcomes especially in patients with residual disease at the time of HCT.

Helical tomotherapy

Helical tomotherapy involves delivery of radiation therapy from a rotating beam source and has the advantage of safe dose escalation to bone marrow, spleen and lymphoid tissues with significantly lower radiation damage to normal tissues. Chargari *et al.*[167] demonstrated the feasibility of HT as a preparative regimen for HCT to debulk patients with lymphoma.

CONCLUSIONS

RIC and NMA regimens provide the opportunity for hematopoietic transplants for elderly patients and in those with comorbidities who cannot tolerate MAC. The relative role of RIC vs MAC needs to be determined for each diagnosis, ideally by randomized clinical trials. Preliminary data suggest that RIC regimens are highly effective for indolent lymphoid malignancies and may be preferred for these diagnoses. In contrast, the intensity of the preparative regimen appears important in myeloid malignancies, particularly for those with active disease. The major causes of treatment failure with RIC transplants are relapse and GvHD. Novel approaches to selectively cytoreduce the malignancy or enhance GVM immune effects are needed to improve transplant outcome. Preclinical and early clinical data with targeted radiation therapy approaches are promising. Improved approaches to control GvHD and infections are also needed to improve overall survival. Controlled clinical trials are required to define optimal therapeutic strategies.

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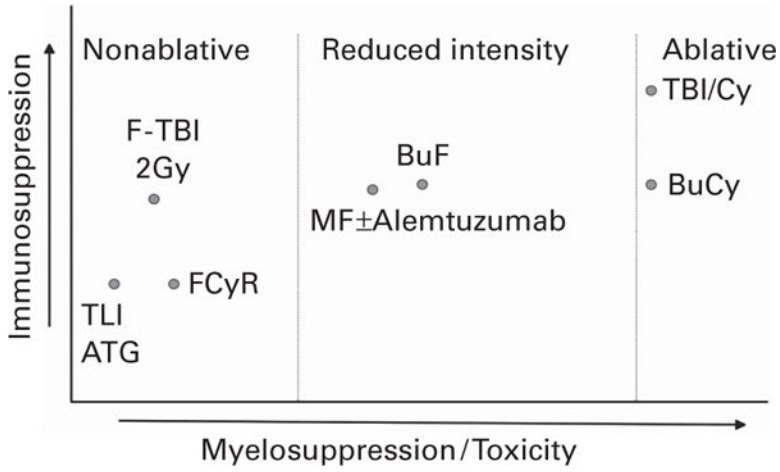

Figure 1.
Relative myelosuppressive and immunosuppressive effects of various regimens. Bu = busulfan; Cy = cyclophosphamide; F = fludarabine; Gy = grays; Mel = melphalan; R = rituximab.

Table 1

Disease sensitivity to GVM effects

Highly sensitive	CML CLL Low-grade lymphoma Mantle cell lymphoma
Intermediate sensitivity	AML Intermediate-grade lymphoma Hodgkin's lymphoma Plasma cell myeloma
Relatively insensitive	ALL High-grade lymphoma

Abbreviation: GVM = graft versus malignancy.

Table 2

Intensity of various conditioning regimens

Myeloablative conditioning regimens	TBI ⩾ 5 Gy single dose or ⩾ 8 Gy fractionated Bu >8 mg/kg Cy200+ATG
Nonmyeloablative conditioning regimens	TBI ≤ 2 Gy ± purine analog Flu+Cy ± rituximab +ATG Flu+AraC+Ida Cladribine+AraC Total lymphoid irradiation+ATG Flu+bendamustine+rituximab
Reduced intensity conditioning regimens	Flu Mel ± alemtuzumab or ATG Bu Flu

Abbreviations: AraC = cytarabine; ATG = antithymocyte globulin; Bu = busulfan; Cy = cyclophosphamide; Flu = fludarabine; Gy = grays; Ida = idarubicin; Mel = melphalan.

Table 3

Summary of HCT studies with RIC/NMA regimens

Study	*Disease*	*Regimen*	*aGvHD 2–4 (%)*	*cGvHD (%)*	*TRM (%)*	*Relapse (%)*	*PFS (%)*	*OS (%)*
Van Besien[52]	AML/MDS	Flu Mel Ale	33	18	33	27	38	48 (1 yr)
Wong[53]	AML/MDS/CML	Flu Mel	41	63	55	NR	37	44 (27 mo)
Taussig[54]	AML/MDS	Flu Cy/Flu Mel	12	66	0(100 d)	NR	56%	69 (26 mo)
Alatrash[55]	AML/MDS	Flu Bu	41	43	26(3 yr)	NR	44	46 (2 yr)
Nakamura[56]	AML/MDS	Flu Mel	63	62	35	16	51	53 (2 yr)
Blaise[57]	AML	Flu Bu ATG	24	70	9	18	76	79 (18 mo)
Grigg[58]	AML	Flu Cy	30	67	15	37	56	68 (2 yr)
Valcarcel[59]	AML	Flu Bu	35	53	20	44	39	42 (4 yr)
Kohrt[60]	AML	TLI ATG	10	28	4(1 yr)	NR	48	50 (3 yr)
Martino[77]	ALL	Flu Mel/Flu Cy	63	72	23	49	NR	31 (2 yr)
Hamaki[78]	ALL	Flu Bu/Flu Mel	45	64	30	51	30	40 (1 yr)
Mohty[79]	ALL	Flu TBI/Flu Mel/Flu Cy	NR	NR	28	51	21	31 (2.8 yr)
Bachanova[80]	ALL	Flu Cy TBI	55	45	27	36	NR	50 (3 yr)
Ram[81]	ALL	Flu TBI	53	44	28	40	NR	34 (3 yr)
Stein[82]	ALL	Flu Mel	75	86	21	21	61	61 (2 yr)
Cho[83]	ALL	Flu Mel	43	65	18	20	63	64 (3 yr)
Sorror[103]	CLL	2 Gy TBI	55–66	49–53	23	38	39	50 (5 yr)
Khouri[104]	CLL	Flu Cy/Flu Mel R	37	56	17	39	36	51 (5 yr)
Dreger[105]	CLL	Flu Cy based	45	73	23	40	42	65 (4 yr)
Michallet[106]	CLL	Flu TBI	44	29	NR	22	46	55 (3 yr)
Giralt[109]	Myeloma	Flu Mel	46	28	40	NR	19	30 (2 yr)
Mohty[110]	Myeloma	Flu Bu ATG	36	41	17	51	41	62 (2 yr)
Gerull[111]	Myeloma	Flu TBI 2 Gy	37	70 (18 mo)	17	NR	29	41 (18 mo)
Kroger[112]	Myeloma	Flu Mel ATG	38	37	26	26/86	54	73 (2 yr)
Khouri[115]	FL	FCR	11	60	15	2	83	85 (5 yr)
Khouri[116]	FL	^{90}YFC	13	39	8	NR	85	88 (3 yr)
Pinana[117]	FL	Flu Mel	53	78	41	8	57	54 (4 yr)

Study	*Disease*	*Regimen*	*aGvHD 2–4 (%)*	*cGvHD (%)*	*TRM (%)*	*Relapse (%)*	*PFS (%)*	*OS (%)*
Vigouroux[118]	FL	Flu based	34	43	32	9.6	66	66 (3 yr)
Cook[119]	MCL	Flu Mel+/− Ale/Flu Bu +/− Ale	39	61	21	65	14	37 (5 yr)
Rezvani[120]	DLBCL	Flu TBI	53	47	25	41	35	45 (3 yr)
Thomson[121]	DLBCL	Flu Mel Ale	17	22	34	33	48	47 (4 yr)
Sirvent[122]	DLBCL	Flu Bu/Flu Cy/Flu Mel/Flu TBI	39	41	23	41	44	49 (2 yr)
Alvarez[131]	HL	Flu Mel	45	45	25	NR	32	48 (2 yr)
Sureda[132]	HL	Flu Mel +/− ATG	48	47	15	37	24	43 (4 yr)
Anderlini[137]	HL	Gem-Flu Mel	19	39	15	NR	55	78 (18 mo)

Abbreviations: aGvHD = acute GvHD; Ale = alemtuzumab; ATG = antithymocyte globulin; Bu = busulfan; cGvHD = chronic GvHD; Cy = cyclophosphamide; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; Flu = fludarabine; Gem = gemcitabine; HCT = hematopoietic cell transplantation; HL = Hodgkin's lymphoma; MAC = myeloablative conditioning; MDS = myelodysplastic syndrome; MCL = mantle cell lymphoma; Mel = melphalan; mo = months; NMA = nonmyeloablative; NR = not reported; OS = overall survival; RIC = reduced intensity conditioning; TRM = treatment-related mortality.

Table 4

Summary of studies comparing RIC with MAC regimens

Study	*Disease*	*RIC vs MAC aGvHD 2–4 (%)*	*RIC vs MAC cGvHD (%)*	*RIC vs MAC NRM (%)*	*RIC vs MAC Relapse (%)*	*RIC vs MAC PFS (%)*	*RIC vs MAC OS (%)*
Olle Ringden[68]	AML	31 vs 36	31 vs 38	HR 0.85	HR 1.46	HR 0.88	NR
	AML	29 vs 29	36 vs 46	HR 0.64	HR 1.34	HR 1.04	NR
Shimoni A[69]	AML	8 vs 22	31 vs 56	22 vs 8	14 vs 9	45 vs 49	50 vs 49 (2 yr) *P* = NS
Flynn CM[70]	AML	22 vs 17	13 vs 18	34 vs 33	RR 2.2	31 vs 30	33 vs 35 (2 yr) *P*>0.1
Aoudjhane M[71]	AML	22 vs 31	48 vs 56	32 vs 18	41 vs 24	40 vs 47	44 vs 46 (2 yr) *P* = NS
Martino[63]	AML/MDS	43 vs 58	45 vs 52	32 vs 22	26 vs 40	33 vs 39	41 vs 45 (3 yr) *P* = 0.8
Luger[64]	AML/MDS	41 vs 45	40 vs 35	RR 0.9	39 vs 32	NR	33 vs 34 (5 yr) *P* = NS
Scott[65]	AML/MDS	54 vs 78	55 vs 64	41 vs 34	31 vs 23	27 vs 44	28 vs 48 (3 yr) *P* = 0.56
Alyea[27]	AML/MDS	26 vs 27	33 vs 18	15 vs 32	61 vs 38	20 vs 31	34 vs 28 (2 yr) *P* = 0.056
Eom[85]	ALL	51 vs 52	61 vs 50	21 vs 24	34 vs 26	51 vs 55	HR 0.98 (5 yr) *P* = 0.30
Marks[86]	ALL	39 vs 46	34 vs 42	32 vs 33	35 vs 26	32 vs 41	38 vs 43 (3 yr) *P* = 0.39
Mohty[87]	ALL	Similar	Similar	21 vs 29	47 vs 31	32 vs 38	45 vs 48 (2 yr) *P* = 0.23
Bachanova[88]	ALL	46 vs 41	63 vs 45	13 vs 36	49 vs 28	26 vs28	39 vs 35 (3 yr) *P* = 0.62
Crawley[113]	Myeloma	35 vs 46	Similar	24 vs 37		19 vs 34	38 vs 51 (2 yr) *P* = NS
Hari[123]	FL	44 vs 36	62 vs 46	23 vs 23	RR 2.97	55 vs 67	62 vs 71 (3 yr) *P* = 0.15
Hamadani[128]	MCL	37 vs 36	43 vs 35	43 vs 47	32 vs 33	25 vs 20	30 vs 25 (3 yr) *P* = 0.45
Peres[107]	CLL	39 vs 55	38 vs 48	14 vs 27	15 vs 14	NR	63 vs 18 (5 yr) *P* = 0.006
Brown[108]	CLL	30 vs 50	NR	46 vs 9.5	7 vs 26	NR	63 vs 49 (5 yr) *P* = 0.003
Sureda[133]	HL	44 vs 53	38 vs 40	23 vs 46	57 vs 30	18 vs 20	28 vs 22 (5 yr) *P* = 0.04
Bacher[125]	DLBCL	43 vs 43	42 vs 37	47 vs 56	38 vs 26	15 vs 18	20 vs 18 (5 yr) *P* = NR

Abbreviations: aGvHD = acute GvHD; cGvHD = chronic GvHD; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; HL = Hodgkin's lymphoma; HR = hazard ratio; MAC = myeloablative conditioning; MCL = mantle cell lymphoma; MDS = myelodysplastic syndrome; mo = months; NR = not reported; NRM = nonrelapse mortality; OS = overall survival; RIC = reduced intensity conditioning; yr = years.