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REVIEWS

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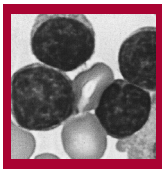
Reducing Intensity Does Not Necessarily Mean Reducing Potency

Maxim Norkin, John R. Wingard

Pre-transplant conditioning can significantly influence post-transplant outcomes. A strong anti-tumor effect achieved by myeloablative conditioning (MAC) is frequently counterbalanced by higher morbidity and non-relapse mortality, particularly in older adults. On the other hand, reduced intensity conditioning (RIC) is associated with lower post-transplant mortality, but may not be sufficient enough to prevent relapse, particularly in patients with persistent and aggressive malignances.

The role of RIC transplantation for patients with acute leukemia (AL), myelodysplastic syndromes (MDS) and lymphoma was addressed in the satellite symposium held in February 2013 at the Tandem BMT meeting in Salt Lake City, Utah. Dr. Forman focused on patients with AL and MDS. He reviewed studies suggesting that RIC can be as effective as MAC in patients in certain subgroups, particularly older adults with AL and MDS. Importantly, RIC was shown to be a reasonable alternative to MAC even in patients with poor risk myeloid malignances and in patients with Philadelphia chromosome-negative acute lymphoblastic leukemia (ALL), in whom MAC historically considered the standard of care. However, across all studies, the relapse rate following RIC transplant remains unacceptably high, particularly in patients with poorly controlled or advanced disease. Dr. Forman reviewed multiple attempts that are being evaluated to enhance the anti-leukemic potential of RIC without increasing its toxicity. Integration of targeted radiation (radioimmunoconjugates and intensity modulated radiation therapy) or clofarabine can augment the anti-leukemic activity of RIC. The relapse rate after RIC transplant can be further reduced by post-transplant maintenance therapy with hypomethylating agents (in patients with myeloid malignances) or tyrosine kinase inhibitors (in patients with Philadelphia chromosome-positive ALL). Adoptive T-cell immunotherapies with chimeric antigen receptor transduced T cells or bispecific T-cell engaging antibodies also have shown promising activity in decreasing the relapse rate following RIC transplants. Dr. Champlin focused on RIC transplants in lymphoma. RIC transplants are widely used in lymphoid malignances and often considered preferable to MAC regimens, particularly for patients with indolent lymphomas or relapsing after an autologous transplant. However, in the presence of chemoresistant or bulky disease the relapse rate following RIC continues to be high. Addition of rituximab or radioimmunotherapy to the RIC can improve post-transplant outcomes by minimizing risk of relapse via variety of mechanisms, including direct anti-tumor activity or enhancement of the graft versus leukemia effect.

RIC transplantation makes many elderly and less fit patents eligible for this potentially curative procedure. The controversy remains regarding the role of RIC transplant in younger patients who are eligible for MAC. Retrospective analyses comparing RIC vs. MAC are universally flawed by significant selection bias. Prospective studies evaluating MAC vs. RIC in younger patients with acute leukemia, MDS and lymphoma are urgently needed. A large prospective study comparing RIC vs. MAC in AML and MDS patients is currently being conducted by Blood and Marrow Transplant Clinical Trials Network. Ongoing research to enhance anti-tumor potency of RIC without worsening of organ toxicity has great potential to further improve outcomes of RIC and if successful potentially make MAC obsolete.



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Blood and Marrow TRANSPLANTATION REVIEWS

Symposium Report

The Impact of Reduced-Intensity Conditioning Regimens in Transplant Outcomes

Adapted from a continuing medical education symposium presented at the 2013 BMT Tandem Meetings on February 14, 2013, in Salt Lake City, Utah.
This program is supported by an educational grant from Otsuka America Pharmaceutical, Inc.

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Needs Assessment

Patients with hematologic malignancies who are not in remission before allogeneic hematopoietic stem cell transplantation (allo-HSCT) have poor prognosis. While effective, myeloablative transplants are associated with high transplant-related mortality. For this reason, transplant centers routinely establish criteria that restrict myeloablative transplants to patients who are below 60 years of age and without significant comorbidities. However, since the peak incidence rate of most hematologic malignancies is at age 50 and older, the majority of these patients are not eligible for high-dose treatment.

This standard approach to treating hematologic malignancies was challenged when researchers identified the phenomenon known as graft-versus-leukemia (GVL) effect, in which patients who experienced allograft rejection also had lower relapse rates. This discovery suggested that perhaps myeloablation was not the only approach to eradicating tumor cells, which led to the development of RIC regimens, which are nonmyeloablative and therefore rely on the GVL effect for tumor eradication.

Learning Objectives

Upon completion of the program, participants should be able to:

- Compare outcomes of RIC and conventional ablative conditioning prior to HSCT among lymphoma and leukemia patients
- Evaluate the usefulness of different conditioning regimens with certain illnesses and patient populations

Target Audience

The program will be oriented to a targeted audience of physicians and medical care professionals specializing in oncology, hematology, immunology, and microbiology.

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John R. Wingard, MD, has no relevant financial relationships to disclose.

Stephen J. Forman, MD (Chair), has no relevant financial relationships to disclose.

Richard E. Champlin, MD, has no relevant financial relationships to disclose.

Reduced-Intensity Transplantation for Acute Leukemia and Myelodysplasia

Stephen J. Forman, MD

Leukemia is generally understood to be a disease that affects older patients. In many leukemic malignancies, older age is a risk factor for disease characteristics associated with worse prognosis. In acute myelogenous leukemia (AML), for instance, older age is associated with worse cytogenetics. Moreover, AML often develops in patients with a background of myelodysplastic syndrome (MDS), which itself is a disease of aging. In acute lymphoblastic leukemia (ALL), the Philadelphia chromosome-positive (Ph+) cytogenetic aberration occurs more commonly in older patients, while cure rates decrease with increasing age.

Despite the clear association between older age and leukemia, conventional approaches to allogeneic hematopoietic stem cell transplantation (HSCT) have historically favored younger patients. The risks of treatment-related morbidity and mortality were high, limiting treatment to relatively young patients in good medical condition. In an analysis of the Surveillance, Epidemiology and End Results (SEER) database, the average age at diagnosis for most leukemic malignancies ranged from 65 to 71 years [1]. By comparison, the average age of allogeneic HSCT recipients ranged from 35 years for those with unrelated donors to 40 years for those with related donors. Less intensive HSCT protocols were necessary to overcome the age restrictions of standard ablative transplantation.

Development of Reduced-Intensity Regimens

Fully ablative transplants were developed with the dual goals of maximizing the elimination of residual disease and preventing rejection by inducing host immunosuppression. Various regimens were developed for this purpose, including a radiation-based regimen that combined total body irradiation (TBI) with either cyclophosphamide or etoposide or a non-TBI regimen utilizing busulfan and cyclophosphamide. These regimens were predominantly used in patients under the age of 50 years.

Investigators developed reduced-intensity regimens after recognizing that the graft-versus-leukemia/lymphoma (GVL) effect was both important and necessary in the cure of all cancers derived from the cells of the hematopoietic organ. Dr. Rainer Storb and colleagues at the University of Washington in Seattle were the first to observe that a minimally myelosuppressive regimen that reduced rejection and facilitated engraftment of donor immunity could be curative in some patients with hematologic malignancy. Now, with additional evidence and clinical experience, it is apparent that all malignancies of hematologic origin can be treated with this approach.

Acute Myelogenous Leukemia

Gyurkocza and colleagues at the Fred Hutchinson Cancer Research Center in Seattle, Washington, evaluated a nonmyeloablative allogeneic HSCT protocol for patients with high-risk AML who were older or had comorbid conditions [2]. The multicenter study included 274 patients (mean age, 60 years) with primary or secondary AML. All patients were conditioned with a single fraction of 2 Gy TBI, with or without fludarabine as additional immunosuppression. Most patients (n = 246) received TBI in combination with fludarabine at 30 mg/m^2 per day on days –4 through –2 before HSCT. A calcineurin inhibitor (cyclosporine or tacrolimus) and mycophenolate mofetil were given for postgraft immunosuppression. After conditioning, patients underwent allogeneic HSCT from related (n = 118) or unrelated (n = 156) donors.

The overall 5-year risk of relapse/disease progression was 42%, indicating that many patients with AML who otherwise would not be candidates for transplantation, based on age or comorbidities, can achieve long-term remission with this approach. The 5-year risk of relapse/progression was 39% for patients in first remission, 41% for those in second remission, and 52% for patients with advanced/refractory AML (Figure 1). Patients with truly advanced disease did not do well, suggesting that the larger leukemia burden may have overwhelmed the therapeutic potential of the GVL effect. In addition, unfavorable cytogenetic risk status was associated with an increased risk of relapse and mortality. The faster proliferation rates that are characteristic of unfavorable cytogenetics may allow leukemic cells to outgrow the GVL effect.

Acute Lymphoblastic Leukemia

Reduced-intensity transplantation is also associated with high remission and overall survival rates in patients with ALL and high-risk features. At the City of Hope National Medical Center in Duarte, California, Stein and colleagues evaluated a regimen of reduced-intensity conditioning (RIC) with fludarabine/melphalan prior to allogeneic transplantation in a study of 24 adult patients with high-risk ALL [3]. Reasons for utilizing the RIC regimen in this patient group included age 50 years or older (42%), compromised organ function (54%), or previous HSCT (37.5%). The conditioning regimen consisted of fludarabine 25 mg/m^2 for 5 days, followed by melphalan 140 mg/m^2 for 1 day. At 2 years, overall survival and disease-free survival were both 61.5%.

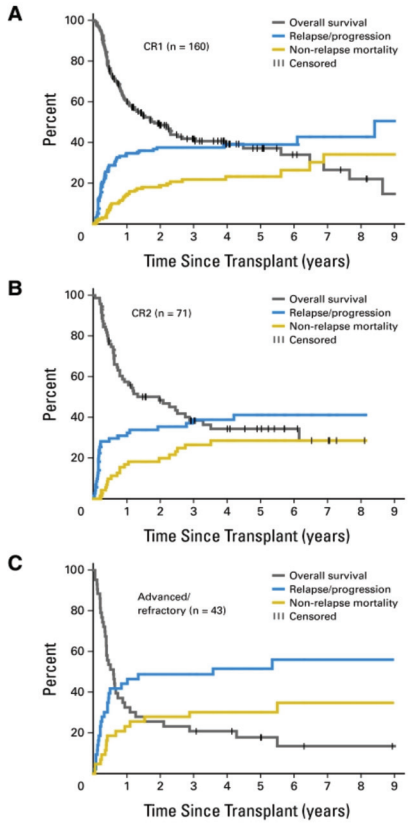

Figure 1. Long-term outcomes after nonmyeloablative allogeneic transplantation in patients with acute myelogenous leukemia (AML) in first remission, second remission, and with more advanced/refractory disease [2].

Myelodysplastic Syndrome

Nakamura and colleagues recently described the use of a fludarabine/melphalan conditioning regimen in combination with tacrolimus/sirolimus-based prophylaxis against graft-versus-host disease (GVHD) for 59 patients with

MDS undergoing reduced-intensity allogeneic transplantation at City of Hope National Medical Center [4]. Patients had a median age of 56 years (range, 20 to 73 years) and a median time from diagnosis of 8.2 months. The MDS subtypes included refractory anemia (RA) in 25 patients, RA with excess blasts (RAEB)-1 in 14 patients, RAEB-2 in 19 patients, and RA with ringed sideroblasts in 1 patient. The majority of patients (61%) were classified as high risk based on International Prognostic Scoring System (IPSS) scores (Intermediate-2 or high). At the time of HSCT, 15 patients (25%) had >10% blasts in the bone marrow.

All patients received intravenous (IV) fludarabine 25 mg/m^2 daily for 5 days, followed by 140 mg/m^2 for conditioning. GVHD prophylaxis consisted of a loading dose on day –3 (oral sirolimus 12 mg or IV tacrolimus 0.02 mg/kg), followed by daily oral dosing adjusted to maintain targeted serum levels (3 to 12 ng/mL sirolimus or 5 to 10 ng/mL tacrolimus). Twenty-one patients (35.6%) received sibling donor transplantations, and 38 patients (64.4%) received unrelated donor transplantations. Five patients (8.5%) received bone marrow grafts, and 54 patients (91.5%) received PBSC grafts. After a median follow-up of 25 months, results suggested promising outcomes with RIC HSCT and tacrolimus/sirolimus-based GVHD prophylaxis for patients with MDS. At 2 years, the overall survival was 75.1%, event-free survival was 65.2%, and relapse incidence was 20.9%. In a univariate analysis, bone marrow blasts >10% at the time of transplantation significantly predicted worse event-free survival (hazard ratio [HR], 2.52; P = .03) and worse overall survival (HR, 3.72; P = .006).

Together, these findings demonstrate the role of RIC allogeneic HSCT in the 3 major hematologic malignancies that affect primarily older adults, namely ALL, AML, and MDS. A reduced-intensity approach appears to be an effective treatment approach for many of these patients, including those with characteristics of poor prognosis.

Reduced-Intensity Conditioning in Younger Transplant Recipients

Prior to the discovery of the GVL effect, high-intensity conditioning regimens were thought to be solely responsible for the anti-leukemia effect of HSCT. The recognition of a substantial anti-leukemia effect mediated by donor lymphocytes, however, led to reductions in the intensity and toxicity of conditioning regimens. The introduction of RIC regimens allowed HSCT to be performed in patients older than the standard upper age limit (age 45 to 50 years) with acceptable toxicity and non-relapse mortality rates. Accordingly, RIC has extended the reach of HSCT for older patients with hematologic malignancies.

Even among younger patients, however, the persistent risk of non-relapse mortality and toxicity associated with high-intensity conditioning has prompted interest in the potential role of RIC in patients who are candidates for standard conditioning before allogeneic HSCT. Concerns about utilizing RIC in this patient population include a potential increase in the risk of relapse, which is the major cause of death following HSCT even in patients who undergo intense conditioning.

Acute Myelogenous Leukemia

To compare the safety of these approaches, Bornhäuser and colleagues conducted a phase III trial of RIC versus standard conditioning before allogeneic HSCT in patients with AML in first complete remission [5]. The trial included 195 patients aged 18 to 60 years with intermediate-risk or high-risk AML. Patients were randomly assigned to an RIC regimen consisting of 4 doses of 2 Gy of TBI (8 Gy) and 150 mg/m^2 fludarabine (n = 99) or a standard conditioning regimen consisting of 6 doses of 2 Gy of TBI (12 Gy) and 120 mg/kg cyclophosphamide (n = 96). The primary endpoint was non-relapse mortality.

The per-protocol analysis showed that non-relapse mortality was slightly lower following RIC compared with standard conditioning in the overall study population (HR, 0.42; P = .05) (Figure 2). When patients were grouped into age cohorts, however, significant differences in non-relapse mortality emerged. For patients aged 41 to 60 years, RIC significantly reduced the risk of non-relapse mortality compared with standard conditioning (HR, 0.23; P = .02). In contrast, non-relapse mortality was similar for patients aged 18 to 40 years, regardless of conditioning regimen (HR, 1.19; P = .82).

In the intent-to-treat analysis, there was no significant difference between conditioning regimens in overall survival (HR, 0.77; P = .29) or disease-free survival (HR, 0.85; P = .47). At 36 months, overall survival and disease-free survival were 61% and 58%, respectively, for patients who received the RIC regimen, compared with 57% and 56%, respectively, for those who received standard conditioning. No differences in overall survival or disease-free survival were observed between treatment groups when evaluated by patient age cohort, graft source, or cytogenetic risk group.

Findings from this phase III trial show similar outcomes in terms of early toxic effects and mortality with reduced-intensity versus standard conditioning in adult patients with AML in first remission undergoing allogeneic HSCT. Based on these results, RIC appears to be a safe and effective alternative for patients with AML in first complete remission, particularly when the toxicity and late effects of fully intensive regimens are a concern.

Acute Lymphoblastic Leukemia

The role of RIC HSCT in younger adult patients with ALL in first or second complete remission has been evaluated in a retrospective study [6]. The analysis included 93 patients who received RIC and 1428 patients who received standard full-intensity conditioning prior to allogeneic HSCT for Ph-negative ALL. The RIC regimens included busulfan 9 mg/kg or less (n = 27), melphalan 150 mg/m^2 or less (n = 23), low-dose TBI (n = 36), and others (n = 7). Patients in the RIC cohort were older than those in the standard conditioning group (median age, 45 years versus 28 years, respectively; P < .001) and more likely to receive peripheral blood grafts (73% versus 43%, respectively; P < .001). All other prognostic factors were similar in both treatment groups.

Clinical outcomes were not statistically different between the treatment groups. Compared with full-intensity conditioning, RIC showed trends toward slightly less acute grade II-IV GVHD (46% versus 39%, respectively; P = .16) and chronic GVHD (42% versus 34%, respectively; P = .16). Despite these differences, transplantation-related mortality at 3 years was similar with standard conditioning or RIC (33% versus 32%, respectively; P = .86). The relapse rate was slightly lower in the standard conditioning group compared with RIC at 3 years (26% versus 35%; P = .08), but overall survival was similar in both groups (43% versus 39%; P = .39). In a multivariate analysis, conditioning intensity had no effect on transplantation-related mortality (P = .92) or relapse risk (P = .14). Thus, the use of RIC may be just as effective as standard conditioning for patients with ALL who are in remission and going into allogeneic transplantation.

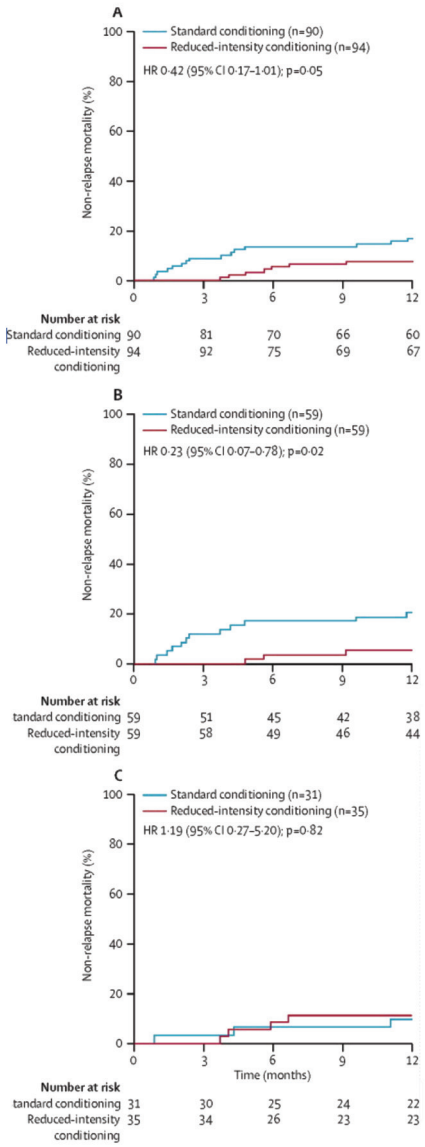

Figure 2. Non-relapse mortality following reduced-intensity or standard conditioning in patients with acute myelogenous leukemia (AML) by age cohort [5].

Novel Approaches to Radiation Therapy

Several therapeutic innovations have contributed to the development of more effective transplantation regimens. Recognition of the dose-response of radiation therapy—specifically, that radiation is effective earlier in the dose-response curve for patients with leukemia than for those with solid tumors—has enabled the use of lower radiation doses that still provide effective disease control. In addition, there is sufficient clinical evidence to conclude that reduced-intensity transplantations are of limited efficacy in patients with advanced, relapsed disease. The GVL effect is not strong enough to result in a cure in patients with a high tumor burden and aggressive disease kinetics.

For patients undergoing TBI, it is possible to nearly eliminate the risk of leukemia relapse by increasing the radiation dose, but at the expense of increased toxicity to the lungs and other organs. Research in this area is currently focused on strategies to deliver higher radiation levels to targeted tissues without increasing toxicity to non-target organs and incorporating this approach into a reduced-intensity regimen. Two promising strategies include the use of radioimmunoconjugates and intensity-modulated total marrow irradiation.

Radioimmunoconjugates

Radiolabeled monoclonal antibodies are novel tools used to deliver supplemental radiation to targeted sites. The 131-I-labeled anti-CD45 antibody delivers targeted hematopoietic radiation that is 3-fold stronger to the bone marrow and spleen compared with TBI and 10-fold stronger to the lymph nodes. In 2009, Pagel evaluated the feasibility of preconditioning with a 131-I-labeled anti-CD45 antibody plus fludarabine and low-dose TBI (2 Gy) in a study of 50 patients older than 50 years with advanced AML or high-risk MDS [7]. At the time of transplantation, 86% of patients had AML or MDS with >5% marrow blasts. Following treatment, all patients had a complete remission, and all patients had 100% donor-derived CD3+ and CD33+ cells in the peripheral blood by day 28 after allogeneic HSCT. The median overall survival and disease-free survival were 199 days and 159 days, respectively. At 1 year, the estimated probabilities of relapse and nonrelapse mortality were 40% and 22%, respectively.

Certain patients with hematologic malignancies, including those with multiple disease relapses and high disease burdens, are not likely to benefit from standard non-myeloablative regimens. Incorporating radioimmunotherapy is an opportunity to preserve the tolerability of reduced-intensity preparative regimens while delivering more radiation to malignant cells, thereby increasing the efficacy of treatment. Findings from the Pagel study support the use of radiolabeled monoclonal antibodies to enhance the efficacy of RIC allogeneic HSCT in older patients with AML or MDS who are not candidates for high-dose conditioning [7]. Ongoing trials of novel radioimmunoconjugates in autologous and allogeneic HSCT are underway.

Intensity-Modulated Radiation Therapy

Another option involves the use of helical tomotherapy to deliver radiation to the bone marrow via computed tomography (CT)-guided intensity modulated radiation therapy (IMRT). This amplifies the anti-leukemia activity of the RIC regimen and allows patients with higher burden of disease to receive transplantation. Specifically, helical tomotherapy uses spiral CT technology to deliver IMTR using a rotating multi-leaf collimator to "sculpt" radiation doses to large, complex-shaped target regions while simultaneously reducing radiation doses to non-target organs. Compared with TBI, helical tomotherapy substantially reduces the median radiation dose to surrounding organs. Thus, helical tomotherapy increases the efficacy of RIC regimens while decreasing the late effects of radiation by minimizing the total dose delivered to critical structures. Augmenting fludarabine and melphalan-based RIC regimens by adding total marrow and lymph irradiation (TMLI) is safe and well tolerated.

In 2011, Rosenthal evaluated the feasibility of augmenting RIC with TMLI at the City of Hope National Medical Center in a phase I/II trial of 33 patients with advanced hematologic malignancies [8]. All patients had factors that precluded fully myeloablative conditioning regimens, including older age (median age, 55.2 years) and/or compromised organ function. The conditioning regimen included fludarabine 25 mg/m^2 for 5 days, melphalan 140 mg/m^2 for 1 day, and TMLI delivered at 150cGy in 8 fractions over 4 days. All patients achieved engraftment at a median of 14 days after HSCT. Overall survival, event-free survival, and nonrelapse mortality at 1 year were 75%, 65%, and 19%, respectively. In this study, the use of RIC with TMLI enabled patients with advanced hematologic malignancies, who were not otherwise candidates for RIC, to undergo allogeneic HSCT transplantation with a low risk of toxicity.

Clofarabine as an Alternative to Fludarabine

Nearly all reduced-intensity regimens contain fludarabine, a nucleoside analogue. Fludarabine-based regimens are known to be immunosuppressive with some anti-leukemic efficacy.

Clofarabine, by comparison, appears to be more active in patients with leukemia. Several trials have been initiated to evaluate whether clofarabine, substituted for fludarabine, can successfully facilitate engraftment and increase leukemia control. In these ongoing studies, investigational regimens typically combine clofarabine with either busulfan or melphalan.

Clofarabine-based regimens may have a role in improving outcomes for patients who are not in remission at the time of HSCT. In a phase I/II study, Magenau and colleagues evaluated the use of clofarabine in combination with myeloablative doses of busulfan in 46 patients with nonremission hematologic malignancies [9]. Most of the enrolled patients (68%) were diagnosed with AML. Of these patients, 58% had high-risk cytogenetics and 71% had peripheral blood blasts present at HSCT. The conditioning regimen consisted of IV busulfan 3.2 mg/kg administered over 3 hours on days –5 to –2, adjusted if necessary to target an area under the curve (AUC) of 4800 mol/min. Patients were also assigned to 1 of 3 dosing cohorts of IV clofarabine (20, 30, or 40 mg/m^2) administered over 1 hour on days –6 to –2.

The complete remission rate was 94% for all patients, and 100% for those without prior HSCT. In the overall study population, the 2-year nonrelapse mortality rate was 31%, and overall survival was 28%. For patients with AML, overall survival was 48% at 1 year and 35% at 2 years. Based on these promising findings, additional trials are underway to evaluate clofarabine/busulfan conditioning in nonremission AML and other aggressive hematologic malignancies.

The combination of clofarabine/busulfan as an RIC regimen was also evaluated in a study of 51 adult patients with ALL undergoing allogeneic HSCT [10]. The study cohort (median age, 36 years) included 30 patients in first complete remission, 13 in second complete remission, and 8 patients with active disease. The conditioning regimen consisted of IV clofarabine 40 mg/m^2 administered once daily, followed by IV busulfan infused over 3 hours daily for 4 days. The busulfan dose was adjusted to target a daily AUC of 5500 M/min for patients younger than 60 years and 4000 M/min for those aged 60 years and older. At 1 year, overall survival was 67%, disease-free survival was 54%, and nonrelapse mortality was 32%. For patients in first complete remission at the time of transplantation, the 1-year overall survival, disease-free survival, and nonrelapse mortality rates were 74%, 64%, and 25%, respectively.

The combination of clofarabine with high-dose melphalan also shows efficacy as a conditioning regimen for patients undergoing allogeneic HSCT. In 2012, Kirschbaum and colleagues at the City of Hope National Medical Center described preliminary findings from a phase I study of this RIC regimen in 16 patients with AML (median age, 62.8 years) [11]. Patients received IV clofarabine administered over 30 minutes on day –9 to day –5 and IV melphalan administered over 30 minutes on day –4. Patients were assigned to 1 of 3 dosing groups with escalating doses of clofarabine/melphalan (30/100 mg/m^2, 40/100 mg/m^2, or 40/140 mg/m^2) to determine the optimal RIC regimen. GVHD prophylaxis consisted of tacrolimus 0.02 mg/kg per day continuous IV infusion beginning on day –3, and sirolimus was administered as a 12 mg oral loading dose on day –3, followed by 4 mg/day in a single morning dose. At the time of transplantation, 7 patients were in complete first remission, 2 were in complete second remission, 4 had primary induction failure, and 3 were in first relapse.

The clofarabine/melphalan regimen was well tolerated and showed promising activity against advanced AML. Most patients (n = 12) were treated with clofarabine 40 mg/m^2 and melphalan 100 mg/m^2. In this group, the estimated 1-year overall survival and disease-free survival were 73% and 61%, respectively. In 2013, the City of Hope investigators presented updated findings in a total of 20 patients with high-risk leukemia, including 5 patients who received the highest-dose combination of 40 mg/m^2 clofarabine and 140 mg/m^2 melphalan [12]. In this analysis, the clofarabine/melphalan conditioning regimen resulted in durable remission, with a 2-year event-free survival of 70.7%. The updated overall survival rates were 77% and 70% at 1 year and 2 years, respectively. Building on these findings, a phase 2 trial is planned to evaluate the combination of clofarabine 40 mg/m^2 and melphalan 140 mg/m^2 in patients with high-risk AML undergoing allogeneic HSCT in first or second complete remission.

Posttransplantation Maintenance Therapy

Relapse is a major cause of treatment failure after transplantation, and options for treating disease recurrence are poor. Therefore, there is great interest in the use of posttransplantation strategies to reduce the risk of relapse. Investigational posttransplantation treatment regimens are designed to supplement the GVL effect, which occurs over time after HSCT. Moreover, because most recurrences occur early after transplantation, posttransplantation therapy must be given during the first 3 months after HSCT to be effective in maintaining remission.

Hypomethylating Agents

Hypomethylating agents, including decitabine and azacitidine, have an established role in the treatment of patients with high-risk MDS and provide important treatment options for elderly patients with leukemia. In 2010, de Lima and colleagues described the use of low-dose azacitidine as maintenance therapy after allogeneic HSCT at the University of Texas M.D. Anderson Cancer Center in Houston [13]. The analysis included 74 patients with high-risk AML or MDS who were eligible to receive azacitidine posttransplantation. Of these, 45 patients (median age, 60.6 years) actually received treatment. Thus, approximately 60% of this cohort of heavily pretreated patients was able to receive at least 1 cycle of the drug. Among those who received azacitidine, 30 patients (67%) were not in complete remission at the time of HSCT.

To determine the optimal maintenance regimen, investigators evaluated 5 daily azacitidine doses (8, 16, 24, 32, and 40 mg/m^2) and 4 treatment schedules (1, 2, 3, or 4 cycles). Cycle 1 started on HSCT Day +40, and each cycle was defined as 5 days of drug followed by 25 days of rest. Patients received a total of 105 cycles of low-dose azacitidine. After a median follow-up of 20.5 months, results demonstrated the feasibility of using posttransplantation azacitidine as a strategy for remission consolidation/maintenance. The median overall survival was 30.8 months, and the median event-free survival was 18.2 months. Although remission status did not influence overall survival outcomes, the median event-free survival was significantly higher for patients in complete remission than for those with active disease at the time of HSCT (27.2 months versus 12.0 months, respectively; $P = .05$).

Eighteen patients (37%) developed chronic GVHD, although the probability of developing chronic GVHD decreased significantly with the number of treatment cycles and was unaffected by azacitidine dose. Reversible thrombocytopenia was the major dose-limiting toxicity. The regimen with the lowest overall risk of toxicity was 32 mg/m^2 given for 4 cycles. The study authors noted that the optimal schedule

was unclear, however, and 4 to 6 cycles may be appropriate for maintenance. Moreover, in the relapse setting, treatment should continue until disease progression. Findings from this phase I/II study provide the basis for an ongoing randomized trial comparing azacitidine given for 1 year after allogeneic HSCT versus no maintenance therapy in patients with high-risk MDS/AML.

Tyrosine Kinase Inhibitors

Tyrosine kinase inhibitors (TKIs), including imatinib, dasatinib, and nilotinib, have been used in combination with chemotherapy to induce disease remission in patients with Ph+ ALL. Imatinib has also been used after myeloablative allogeneic HSCT to improve relapse-free survival in patients with Ph+ ALL and high-risk CML [14]. Used in the post-transplantation setting, TKIs are thought to improve disease control while the GVL effect is developing [15].

Ram and colleagues at the Fred Hutchinson Cancer Center in Seattle, Washington, recently led a multicenter study evaluating the use of posttransplantation imatinib following non-myeloablative allogeneic HSCT in patients with high-risk ALL [15]. The study included 51 patients (median age, 56 years) who underwent allogeneic HSCT after fludarabine (30 mg/m^2 per day on days –4 through –2) and 2 Gy TBI. All patients had high-risk ALL, including 19 patients who were beyond first complete remission at the time of transplantation. Of the 25 patients with Ph+ ALL, 18 received post-grafting imatinib. The recommended dosing schedule of imatinib was 400 to 600 mg daily for at least 1 year after HSCT or until unacceptable toxicity or disease progression. The median duration of post-HSCT imatinib was 11.5 months (range, 3 to 50 months).

The median follow-up was 43 months. For the full cohort of 51 patients, the estimated 3-year risk of relapse/progression was 40%, and the 3-year overall survival rate was 34%. Independent predictors of improved survival included HSCT in first complete remission (P = .005) and post-grafting imatinib therapy (P = .03). For patients with Ph+ ALL in first remission who received post-grafting imatinib, the 3-year overall survival rate was 62%. Within this group, the overall survival at 3 years was 73% for those without evidence of minimal residual disease at HSCT (n = 12). These findings support the role of non-myeloablative conditioning and allogeneic HSCT as a potentially curative treatment strategy for older patients with high-risk ALL in first complete remission. For patients beyond complete remission, posttransplantation maintenance therapy with imatinib is associated with favorable long-term survival.

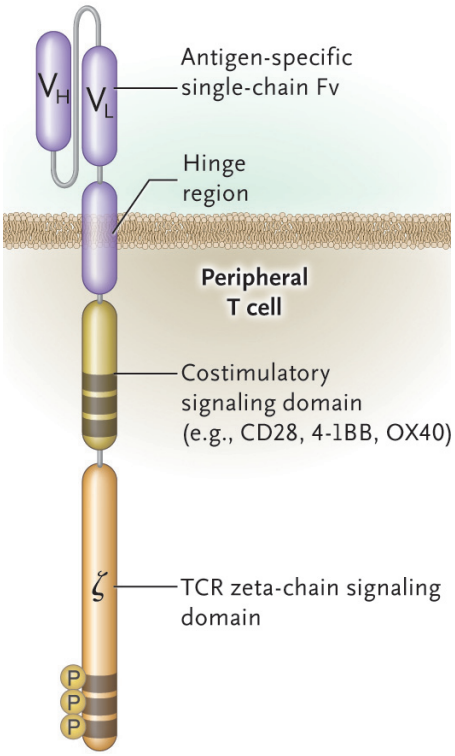

Figure 3. Design of a chimeric antigen receptor [16].

Adoptive T-Cell Immunotherapy

Adoptive T-cell immunotherapy is a new class of therapy designed to improve tumor control in patients with hematologic malignancies. Researchers have used gene-transfer techniques to genetically modify T-cells to stably express antibodies on their surface, thereby conferring new antigen specificity. The introduction of a chimeric antigen receptor (CAR) redirects the T-cell antigen specificity to target tumor-associated antigens (TAAs) expressed on malignant cells. The CARs typically include a targeting moiety, such as an antigen-specific single-chain Fv variable fragment from a monoclonal antibody, a trans-membrane hinge region, and a costimulatory signaling domain, such as CD28 (Figure 3) [16]. The costimulatory domain improves T-cell activation and expansion, as well as the proliferation, survival, and development of memory cells, all of which are key to successful adoptive T-cell immunotherapy [16].

Treatment with CARs has several theoretical advantages over other T-cell–based therapies. For instance, using the patient's own lymphocytes avoids the risk of developing GVHD and eliminates the requirement for major histocompatibility complex (MHC) restriction. Some of the evasion strategies that tumor cells use to escape recognition by the immune system, such as altered antigen presentation or MHC loss, are not effective against CARs. The ability to produce a large quantity of tumor-specific T-cells relatively quickly makes this approach feasible for use in the clinical setting. Although early CARs were developed to target tumor cells, it may be possible to broaden the repertoire of cell-surface targets to include cell-surface proteins, carbohydrates, glycolipids, and other molecular determinants relevant to a range of disease states [16].

One investigational application of adoptive T-cell therapy includes the use of CD19-specific CAR-transduced T-cells for the treatment of B-cell malignancies [17]. CD19 is an attractive target for CAR-based therapy because its expression is restricted to normal mature B-cells, malignant B-cells, and B-cell precursors. In the allogeneic setting, the goal of anti-CD19 CAR treatment is to induce a GVL effect in the absence of GVHD, despite the allogeneic nature of the T-cells. The choice of T-cell viral specificity may influence the risk of allo-reactivity from endogenous T-cell receptors. Current studies are using CD19-specific, CAR-modified T-cells with specificity against the Epstein–Barr virus (EBV), cytomegalovirus (CMV), and adenovirus [17].

Another novel approach to boosting the tumor-specific T-cell response involves the bispecific T-cell engaging (BiTE) antibodies. These antibodies have 2 variable regions, one for targeting a leukemic or neoplastic membrane antigen (e.g., CD19, CD33), and one specific to CD3 for T-cell recruitment and activation. Blinatumomab in a BiTE antibody that simultaneously targets CD19+ ALL cells and normal CD3+ T-cells, inducing T-cell mediated toxicity exerted on CD19+ blast cells. In a phase 2 study, treatment with blinatumomab was effective in achieving durable hematologic and molecular remission in B-lineage ALL patients with persistent or relapsed minimal residual disease [18]. In another study of blinatumomab for relapsed B-lineage ALL after allogeneic HSCT, treatment with the BiTE antibody rapidly induced complete responses

without any evidence of GVHD, suggesting a potential role for posttransplantation immunotherapy in high-risk patients [19].

Adoptive T-cell immunotherapy is also a promising strategy for myeloid malignancies. Researchers recently developed a new CAR molecule specific for the CD123 antigen, which is overexpressed on AML blasts from all phenotypes and genotypes [20]. CD123-specific CAR-redirected T-cells mediate the killing of CD123+ cell lines and cells from patients with relapsed or high-risk AML, but with limited effects on normal monocytes and low-CD123-expressing endothelial cells, suggesting a mild impact on normal hematopoiesis and a low toxicity profile [20,21]. The CD123-specific CARs can be produced from T-cells in patients with AML not in remission, which may broaden therapeutic options for AML treatment.

Summary

The development of reduced-intensity and nonmyeloablative preparative regimens has extended the reach of allogeneic HSCT to many patients who, until recently, were deemed ineligible for potentially curative therapy. Reduced-intensity and nonmyeloablative conditioning regimens are most commonly used in older patients and in those with comorbidities, although younger patients are also taking advantage of these alternatives to conventional myeloablative allogeneic HSCT. New approaches to allogeneic HSCT for patients with leukemia or high-risk MDS include novel radiation therapies such as radiolabeled antibodies and IMRT, the use of clofarabine as a more potent alternative to fludarabine, posttransplantation maintenance therapy with hypomethylating agents and TKIs, and the use of adoptive T-cell immunotherapy to improve long-term disease control. Ongoing research in the area of reduced-intensity and nonmyeloablative allogeneic HSCT will further expand treatment options for patients with hematologic malignancies.

Reduced Intensity Transplants for Lymphoma: Reduced Intensity versus Full Transplant

Richard E. Champlin, MD

Allogeneic transplantation is widely applied for the treatment of leukemia, including AML, MDS, and even chronic lymphocytic leukemia (CLL), and is covered by Medicare for these indications. By comparison, the role of allogenic HSCT in lymphoma is more controversial. At this time, Medicare does not cover allogeneic transplantation for lymphoma. Recent evidence, however, supports a role for allogeneic HSCT in the management of low-grade lymphoma.

Historically, conditioning regimens were developed with dual goals: to provide immune suppression to prevent graft rejection and to eradicate the malignancy. The most effective high-dose chemotherapeutic and radiation-based treatments for hematologic malignancies also kill normal myeloid and lymphoid cells, as well as malignant stem cells. Initial ablative approaches to allogeneic HSCT were associated with a high risk of toxicity and treatment-related mortality, particularly for patients with heavily pretreated lymphoma.

The discovery that much of the benefit of allogeneic HSCT is due to immune GVL effect, and that maximally ablative therapy may not be needed, changed the approach to transplantation for this patient population. In particular, researchers hypothesized that a lower-dose nonmyeloablative preparative regimen might be sufficient to prevent rejection. Moreover, a reduced-intensity, nonmyeloablative allogeneic transplantation may reduce toxicity and allow successful treatment of older patients with lymphoma and those with major comorbidities.

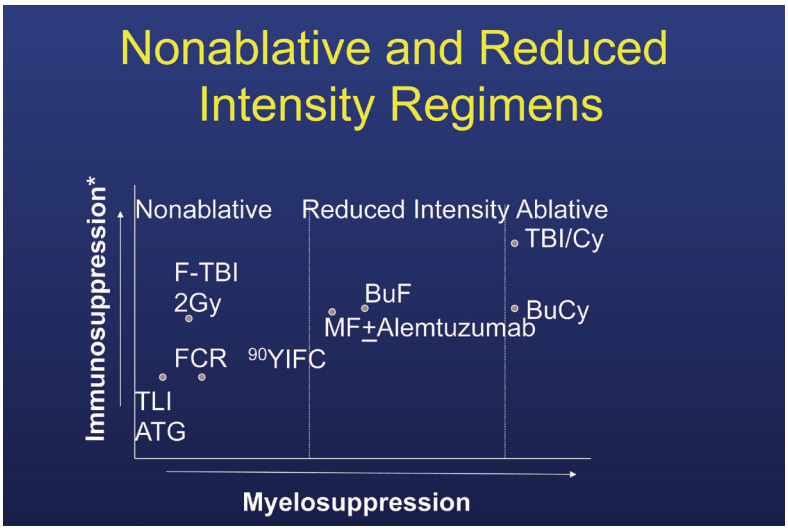

Figure 1. Nonmyeloablative, reduced-intensity, and ablative regimens in hematopoietic stem cell transplantation. ^{90}YFC indicates ^{90}Yttrium-ibritumomab tiuxetan, fludarabine, and cyclophosphamide; BuCy, busulfan and cyclophosphamide; BuF, busulfan and fludarabine; F-TBI, fludarabine and total body irradiation; FCR, fludarabine/cyclophosphamide and rituximab; MF, melphalan and fludarabine; TBI/Cy, cyclophosphamide and total body irradiation; TLI/ATG, total lymphoid irradiation and antithymocyte globulin.

Several preparative regimens have been utilized for allogeneic HSCT, with a range of myelosuppressive and immunosuppressive effects (Figure 1). On one end of the spectrum of myelosuppression, cyclophosphamide and high-dose TBI (e.g., 1000 to 1200 rad) is an example of fully ablative therapy. Reduced-intensity regimens, such as melphalan and fludarabine (MF) or busulfan and fludarabine (BuF) are associated with a lower risk of toxicity. These regimens are considered ablative—i.e., transplantation is necessary to recover hematopoiesis—but they are less toxic and better tolerated that fully ablative strategies, particularly in older patients. On the other end

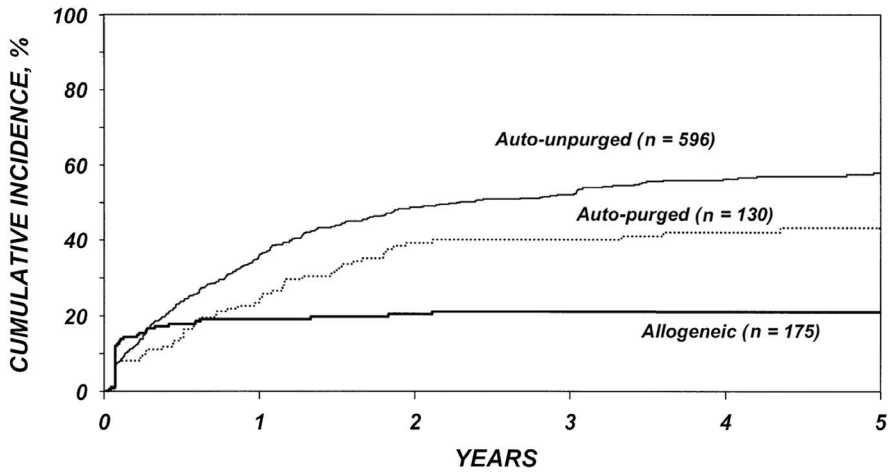

Figure 2. Cumulative incidence of relapse by type of transplant for follicular lymphoma [22].

of the spectrum are the truly nonmyeloablative preparative regimens, such as fludarabine and low-dose TBI (F-TBI) or fludarabine/cyclophosphamide and rituximab (FCR). Although non-ablative, these regimens provide sufficient immune suppression to facilitate engraftment and induce the GVL effect. In addition, the incorporation of agents such as ^{90}Yttrium-ibritumomab tiuxetan (^{90}Y) to non-ablative regimens improves disease control, particularly in patients with chemoresistant disease.

Transplantation in Follicular Lymphoma: A Historical Perspective

To better understand the mechanisms of disease control associated with different transplantation strategies for lymphoma, van Besien and colleagues analyzed outcomes from 904 patients undergoing allogeneic or autologous transplantation for follicular lymphoma [22]. All patients were treated between 1990 and 1999, and had transplantation information reported to the International Bone Marrow Transplant Registry (IBMTR) or the Autologous Blood and Marrow Transplant Registry (ABMTR). Within this cohort, 176 patients (19%) received allogeneic transplants, 131 patients (14%) received purged autologous transplants, and 597 patients (67%) received unpurged autologous transplants. The median follow-up was 36 months for allograft recipients, 49 months for purged autograft recipients, and 41 months for unpurged autograft recipients.

Both allogenic HSCT and autologous transplantation induced durable remissions for patients with follicular lymphoma. The major difference between these approaches to transplantation, however, relates to the risk of relapse. The risk for disease recurrence was 54% lower for allogeneic HSCT recipients ($P < .001$) and 26% lower for recipients of purged autotransplants ($P = .04$) than for recipients of unpurged autotransplants. At 5 years, the cumulative risk of recurrence for allogeneic HSCT, purged autotransplantation, and unpurged autotransplantation was 21%, 43%, and 58%, respectively (Figure 2).

Allogeneic HSCT was also associated with a low early recurrence rate (19% at 1 year) and near absence of recurrences beyond 1 year after transplantation, confirming the curative potential of this treatment approach. However, it is unclear whether cure is a result of the GVL effect, a tumor-purging effect induced by high-dose chemotherapy, or a combination of both. For patients undergoing allogeneic HSCT, there was no association between acute or chronic GVHD and disease recurrence.

Counterbalancing the reduced risk of recurrence with allogeneic transplantation, however, is a greater risk of treatment-related mortality. Adjusting for other variables, the risk of treatment-related mortality was 4.4 times higher after allogeneic transplantation than autologous transplantation ($P < .001$). At 5 years, the treatment-related mortality rates for allogeneic HSCT, purged autotransplantation, and unpurged autotransplantation were 30%, 14%, and 8%, respectively. The 5-year overall survival rates for these groups were 51%, 62%, and 55%, respectively.

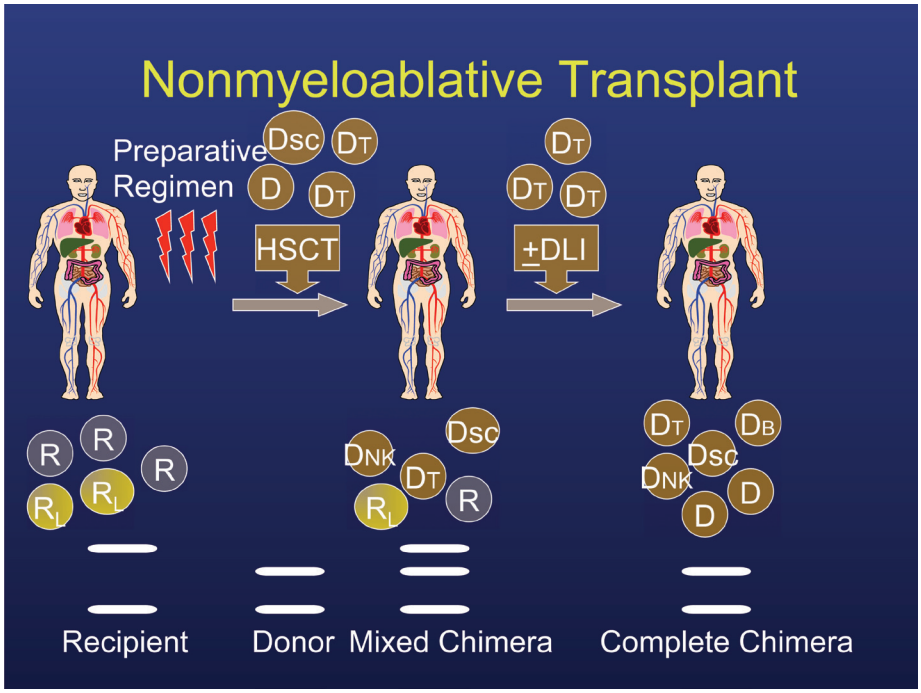

Figure 3. Nonmyeloablative hematopoietic transplantation.

Regardless of transplantation type, several factors predicted adverse outcomes, including age older than 40 years, prolonged interval (> 1 year) from diagnosis to transplantation, high serum lactate dehydrogenase (LDH) at transplantation, refractory disease, bone marrow involvement, and low performance scores. Treatment between 1990 and 1993 also predicted worse outcomes compared with later treatment, suggesting an improvement in transplantation outcomes over time. The use of TBI was associated with an increased risk of treatment-related mortality but a lower risk of recurrence.

Overall, findings from this analysis of IBMTR and ABMTR registry data confirm that transplantation has its major benefit when performed early in the course of disease. For patients who have an HLA-matched sibling donor, the choice of autologous or allogeneic HSCT remains a matter of physician and patient preference. The presence of poor prognostic factors has similar adverse effects on long-term outcomes for patients with follicular lymphoma who undergo either allogeneic or autologous transplantation.

Reduced-Intensity Conditioning in Lymphoma

One of the earliest approaches to reduced-intensity transplantation in the lymphoma population involved the addition of alemtuzumab to reduce the risk of GVHD associated with standard fludarabine/melphalan conditioning. In 2004, Morris and colleagues described the used of this alemtuzumab-based reduced-intensity allogeneic HSCT regimen in 88 patients with relapsed and refractory non-Hodgkin lymphoma (NHL) [23]. All patients (median age, 48 years) received alemtuzumab 20 mg/day by IV infusion over 8 hours on days –8 to –4; fludarabine 30 mg/m^2 by IV infusion over 30 minutes on days –7 to –3; and melphalan 140 mg/m^2 by IV infusion over 30 minutes on day –2.

The risk of GVHD after transplantation was low, as expected with this alemtuzumab-based conditioning regimen. Grades III and IV acute GVHD developed in 4 patients (4.5%). In addition, 6 patients (6.8%) developed limited (n = 2) or extensive (n = 4) chronic GVHD. Fifteen patients received donor lymphocyte infusion (DLI) for persistent mixed chimerism 6 months after transplantation. Of these, 8 patients (53%) converted to full donor hematopoiesis at a median of 14 weeks after infusion. Despite DLI, however, 6 patients maintained mixed hematopoietic chimera status throughout follow-up.

The relapse rates did not differ significantly by disease grade (P = .21). At 3 years, the cumulative relapse rates for patients with low-grade lymphoma (n = 41), mantle cell lymphoma (MCL; n = 10), and high-grade lymphoma (n = 37) were 44%, 50%, 52%, and 44%, respectively. In contrast with relapse rates, overall survival after RIC allogeneic HSCT varied significantly by disease grade. The 3-year overall survival rates were 73% for low-grade lymphoma, 60% for MCL, and 34% for high-grade disease (P < .001). Overall survival also varied significantly by disease status at the time of transplantation. Within the subgroup of patients with low-grade NHL only, the 3-year overall survival rates were 81% for those in complete remission at transplantation, 72% for partial remission, and 0% for refractory disease (P = .003). In summary, these findings demonstrate the feasibility of adding alemtuzumab to a fludarabine/melphalan-based RIC regimen prior to allogeneic HSCT in patients with relapsed and refractory NHL.

Rationale for Nonmyeloablative Transplantation in Lymphoma

The goal of nonmyeloablative transplantation is to attain engraftment, eradicate the malignancy, and provide full immune reconstitution without GVHD. Figure 3 illustrates one approach to nonmyeloablative allogeneic HSCT. In this model, patients receive a reduced-intensity preparative regimen that leaves residual lymphoma cells as well as normal hematopoietic cells at the time of transplantation. The donor graft includes immunocompetent cells that mediate the GVL effect. Ideally, the elimination of recipient lymphoid and myeloid cells results in a complete chimera with only donor-derived hematopoiesis. If necessary, DLI can be used to boost the GVL effect.

Compared with fully ablative transplantation, this approach is associated with a lower risk of GVHD because fewer cytokines are released in response to drug-related toxicities. The risk of posttransplantation infection is comparable, but recipients of nonmyeloablative conditioning regimens are less debilitated from the toxicity of transplantation than those who receive fully ablative regimens and are therefore more likely to respond to therapy. As a result, the risk of transplantation-related mortality is lower with reduced-intensity and nonmyeloablative transplantations, but this is counterbalanced by higher rates of relapse, particularly in patients with bulky or chemoresistant disease. Importantly, reduced-intensity and nonmyeloablative regimens have extended the use of HSCT to patients up to 75 years of age. Many transplantation centers around the United States are routinely treating patients in this age cohort with nonmyeloablative allogeneic HSCT.

With limited data from randomized controlled trials, it is difficult to compare ablative and nonmyeloablative HSCT in patients with lymphoma. Nonrandomized comparisons are typically confounded by the inclusion of different patients populations, such as young, fit patients in studies of ablative regimens and older patients with multiple comorbidities in trials of RIC transplantation. Published evidence to date, however, supports general conclusions about these approaches to allogeneic HSCT. Reduced-intensity regimens are associated with a higher rate of relapse, particularly in patients with active disease, but a lower risk of non-relapse mortality compared with ablative transplantation. Accounting for both of these factors, overall survival rates tend to be similar, regardless of conditioning regimen.

Options for Nonmyeloablative Allogeneic SCT

Research in allogeneic HSCT has recently focused on whether it is possible to refine the preparative regimen to enhance tumor control without increasing toxicity. Two competing schools of thought have dominated this research discussion. Some investigators believe that the preparative regimen does not significantly influence treatment outcomes, and that the only goal of therapy is to induce the GVL effect. In contrast, others believe that the choice of preparative regimen directly affects the extent of cytoreduction and, for patients with bulky disease or other high-risk features, the risk of relapse. Accordingly, the optimal conditioning regimen will depend on the diagnosis, disease stage, and sensitivity to the GVL effect.

Rituximab and the GVL Effect

Rituximab mediates antibody-dependent cell-mediated cytotoxicity. Specifically, rituximab enhances the GVL effect by coating target cells with anti-CD20 antibody, thereby augmenting the cytotoxic potential of the donor immune system through T-cells and natural killer (NK) cells [24,25]. The role of rituximab in facilitating a pronounced GLV effect was illustrated in a study of 17 patients with CLL that was refractory to fludarabine (n = 9) or whose disease recurred after prior responses to fludarabine-based regimens (n = 8) [26]. The median patient age was 54 years (range, 43 to 73 years). All patients received a nonmyeloablative preparative regimen

consisting of fludarabine 30 mg/m^2 on days -5 to -3 followed sequentially at 4-hour intervals by 750 mg/m^2 cyclophosphamide (FC). Ten patients also received rituximab (FCR) administered on day -13 (375 mg/m^2) and on days -6, +1, and +8 (1000 mg/m^2).

The response rate was 94%, including complete remission in 12 patients and partial remission in 4 patients. The experience of one patient, in particular, illustrates how the addition of rituximab facilitated the GVL effect after immunosuppression was withdrawn. The patient had an initial response that was associated with the development of GVHD, but the duration of response was short, lasting just 45 days. No further DLI was given due to active GVHD. Instead, the patient received posttransplant immune modulation with rituximab at a dose of 375 mg/m^2 followed by 1000 mg/m^2 weekly for 3 weeks. After rituximab was added, the patient achieved a complete response that lasted for 10 months.

Overall survival was 100% for patients who received rituximab as part of the conditioning regimen, compared with 14% for patients who received chemotherapy alone (P = .03). The major cause of death for patients in the FC group was GVHD. All patients received the same GVHD prophylaxis, yet the risk of chronic GVHD was significantly lower in the FCR group than in the FC group (36% vs. 81%, respectively; P = .04). In a non-randomized analysis, progression-free survival for the 17 patients in this study who received nonmyeloablative transplantation was comparable to that in historical group of 20 younger patients who received high-dose chemotherapy and allogeneic transplantation. Therefore, the early experience with nonmyeloablative HSCT and posttransplant immune modulation with rituximab demonstrated the strong GVL effect associated with this regimen in patients with CLL.

Rituximab-based therapy also shows activity in low-grade lymphoma. In 2008, Khouri and colleagues reported 8-year efficacy and safety findings from a prospective trial of nonmyeloablative HSCT in 47 patients with relapsed follicular lymphoma [27]. The conditioning regimen included fludarabine (30 mg/ m^2 daily for 3 days), cyclophosphamide (750 mg/m^2 daily for 3 days), and rituximab (375 mg/m^{2}for 1 day plus 1000 mg/ m^2 for 3 days). Patients were also given GVHD prophylaxis with tacrolimus and methotrexate. All patients experienced a complete remission, and 2 patients relapsed during the median follow-up of 60 months. The 5-year overall survival was 85%, and the 5-year progression free survival was 83%. According to the study authors, these findings represent significant progress toward curative treatment for relapsed follicular lymphoma.

Fludarabine and Total Body Irradiation

Another approach to nonmyeloablative allogeneic HSCT in patients with lymphoma involves the use of fludarabine and low-dose TBI. In a prospective study, 62 patients with relapsed or refractory indolent or transformed NHL underwent RIC with 2 Gy TBI with or without fludarabine followed by allogeneic HSCT [28]. In this heavily pretreated cohort, patients had received a median of 6 lines of treatment before HSCT, and 44% of patients received previous high-dose therapy with autologous HSCT. The 3-year overall survival rate was 52% for patients with indolent disease and 18% for those with transformed disease. The 3-year progression-free survival rate for indolent and transformed disease was 43% and 21%, respectively.

Radioimmunotherapy

Radioimmunotherapy, such as with an anti-CD20 antibody conjugated with ^{90}Y, delivers radiation to tumor cells that bind the antibody as well as to neighboring cells that are either inaccessible to the antibody or have insufficient antigen expression. For patients undergoing allogeneic HSCT, radioimmunotherapy has been added to nonmyeloablative conditioning regimens to enhance initial disease control.

In 2012, Khouri and colleagues presented updated results from their pivotal 2008 study of nonmyeloablative allogeneic HSCT after FCR in patients with relapsed and chemosensitive follicular lymphoma [29]. In the same update, investigators also described the addition of ^{90}Y to fludarabine and cyclophosphamide (^{90}YFC). The total FCR cohort included 47 patients and a median follow-up of 107 months (range, 72 to 142 months). In this group, the 11-year overall survival and progression-free survival rates were 78% and 72%, respectively. Given the low frequency of relapse over the long follow-up period, these patients were considered to be cured of their disease.

In the second cohort, a total of 26 patients were treated with the ^{90}YFC preparative regimen. In this group, patients received rituximab 250 mg/ m^2 on day –14 before transplantation, followed by an imaging dose of In-111-ibritumomab tiuxetan (111In) prior to tumor visualization. On day –7, patients were infused with rituximab 250 mg/m^2 followed by ^{90}Y-ibritumomab tiuxetan 0.4 mCi/ kg (maximum total dose, 32 mCi). On days –5 to –3, patients received fludarabine 30 mg/ m^2 per day and cyclophosphamide 750 mg/ m^{2}per day. The median follow-up period was 33 months (range, 17 to 94 months).

Patients treated with ^{90}YFC were more likely than those treated with FCR to have chemorefractory disease (38% versus 0%, respectively; P < .001). The 3-year progression-free survival rates were 80% for patients with chemorefractory disease and 87% for those with chemosensitive disease (P = .7). These findings indicate that the addition of radioimmunotherapy may improve outcomes for patients with chemoresistant disease, who do almost as well on the ^{90}YFC regimen as do chemosensitive patients treated with FCR alone (Figure 4).

Radioimmunotherapy has also been added to fludarabine and TBI-based conditioning regimens for patients with high-risk B-cell lymphoma, who would not be considered candidates for standard myeloablative or nonmyeloablative transplantation. Gopal and colleagues evaluated whether radioimmunotherapy-based nonmyeloablative allogeneic HSCT could provide effective cytoreduction and improve long-term disease control in a prospective phase II study of 40 patients with active residual B-cell lymphoma [30]. The median age was 58 years (range, 29 to 69 years), and at the time of enrollment, patients had a median of 6 prior treatment regimens (range, 3 to 12). Six patients (15%) had chemosensitive disease, and 17 (43%) had bulky disease, defined as >5 cm. Conditioning began on day –21 with rituximab 250 mg/ m^2 and an imaging dose of 111In. On day –14, patients received 250 mg/m^2 rituximab followed by 0.4 mCi/kg ^{90}Y (maximum total dose, 32 mCi). Fludarabine 30 mg/m^2 daily was administered on days –7 through –5, and a total of 2 Gy TBI was delivered on day 0. The median follow-up period was 1.7 years.

In this population of patients with high-risk disease, radioimmunotherapy-based RIC allogeneic HSCT induced early remissions in most patients, including those with chemoresistant and bulky disease. The estimated 2-year overall survival and progression-free survival were 54% and 31%, respectively. Patients with indolent histology had superior survival outcomes compared with patients with other histologic subtypes (P < .01). The estimated 6-month progression-free survival rates in patients with indolent lymphoma (n = 18), MCL (n = 8), and diffuse large B-cell lymphoma (DLBCL) (n = 14) were 89%, 50%, and 43%, respectively.

Nonmyeloablative Allogeneic Transplantation after ASCT

High-dose chemotherapy with autologous HSCT is an effective therapeutic strategy for many patients with relapsed or

refractory DLBCL. For those who develop disease recurrence after autologous HSCT, however, treatment choices have been limited. In 2011, van Kampen and colleagues analyzed outcomes in patients who underwent first allogeneic HSCT as salvage therapy for relapsed DLBCL after a previous ASCT [31]. The retrospective analysis included 101 patients (median age, 46 years) who participated in the European Group for Blood and Marrow Transplantation Registry. Of these, 37 patients were treated with a myeloablative conditioning regimen, and 64 patients received RIC followed by allogeneic HSCT. The median follow-up was 36 months (range, 3 to 112 months).

Progression-free survival at 1 and 3 years after allogeneic HSCT were 52% and 42%, respectively. Several factors predicted worse progression-free survival, including time to relapse after autologous transplantation < 12 months (response rate [RR], 1.8; P = .03), high LDH at diagnosis (RR, 2.3; P = .02), and the use of bone marrow stem cells (RR, 2.2; P = .02). Patients with chemorefractory disease also showed a trend toward worse progression-free survival compared with those with chemosensitive disease (P = .06).

The risk of non-relapse mortality was 16% at 3 months, 25% at 1 year, and 28% at 3 years. Patients treated with RIC regimens had a significantly lower risk of non-relapse mortality at 3 years compared with those who received fully ablative conditioning regimens (20% versus 41%, respective; P = .05). Overall survival was 65% at 1 year and 52% at 3 years. Predictors of worse overall survival included shorter time to relapse after autologous transplantation (RR, 2.0; P = .02) and high LDH at diagnosis (RR, 2.2; P = .03). Patients with refractory disease also showed a trend toward worse overall survival (P = .18). These findings suggest a role for allogeneic HSCT in patients with DLBCL relapsing after autologous transplantation. In addition, the results illustrate the potential for nonmyeloablative conditioning regimens to reduce the risk of non-relapse mortality in this heavily pretreated patient population.

Summary

Preparative regimens clearly affect disease control following reduced-intensity allogeneic HSCT, particularly for patients with active lymphoma. The choice of myeloablative versus reduced-intensity or nonmyeloablative conditioning regimen for patients with lymphoma depends on a careful consideration of both the potential risks and potential benefits of therapy. In general, patients should be treated with the least toxic regimen that can achieve maximal survival. Current evidence suggests that reduced-intensity or nonmyeloablative conditioning regimens are less toxic and at least as effective as myeloablative conditioning for follicular lymphoma. Indeed, these regimens should be considered the standard of care for indolent lymphoid malignancies and DLBCL relapsed post-autologous HSCT.

In the future, the development of novel reduced-intensity and nonmyeloablative strategies may further improve progression-free survival for this patient population. Prospective, randomized clinical trials are needed to determine the optimal preparative regimen for patients with various forms of lymphoma.

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The Impact of Reduced-Intensity Conditioning Regimens in Transplant Outcomes

CME Assessment Test

1. Clinical trial evidence supports the use of reduced-intensity conditioning followed by allogeneic HSCT in appropriate patients with which of the following?

A. ALL only
B. AML only
C. MDS only
D. ALL, AML, and MDS

2. In preparative regimens, clofarabine is an effective substitute for which of the following agents in studies of patients with AML undergoing allogeneic HSCT?

A. Busulfan
B. Melphalan
C. Fludarabine
D. Cyclophosphamide

3. Posttransplantation maintenance therapy with imatinib is associated with favorable long-term survival in patients with high-risk ALL.

A. True
B. False

4. Which of the following is NOT a standard component of chimeric antigen receptor (CAR) molecules used in adoptive T-cell immunotherapy?

A. Variable region that targets a specific neoplastic membrane antigen (e.g., CD19)
B. A trans-membrane hinge region
C. Costimulatory signaling domain (e.g., CD28)
D. A radiolabel (e.g., 131-I-labeled anti-CD45 antibody)

5. In a large registry study of patients with follicular lymphoma, allogeneic HSCT was associated with which of the following compared with autologous transplantation?

A. Reduced risk of disease recurrence
B. Reduced risk of treatment-related mortality
C. Prolonged overall survival
D. Increased risk of posttransplantation infection

6. Reduced-intensity and nonmyeloablative regimens have extended the use of HSCT to patients with hematologic malignancies up to what age?

A. 55 years
B. 65 years
C. 75 years
D. No upper age limit

7. Which of the following describes the effect of rituximab added to preconditioning therapy and posttransplantation immune modulation in patients undergoing allogeneic HSCT?

A. Enhanced GVL effect
B. Increased risk of chronic GVHD
C. Reduced risk of neutropenic fever

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