

Reduced Intensity Conditioning (RIC) Allogeneic Stem Cell Transplantation for LLM: Hype, Reality or Time for a Rethink

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Abstract

Reduced-intensity conditioning has been increasingly used before allogeneic SCT in a growing number of indications. It is well established that the first goal, allowing SCT for elderly and medically infirm patients has been achieved. RIC regimens result in consistent engraftment of allografts from related and unrelated donors. TRM rates have been markedly reduced, thus SCT can be administered relatively safely with no upper age limit, after prior autologous SCT, and in certain malignancies, such as lymphomas and myelomas, in which TRM rates were exceedingly high. However, toxicity may still be substantial with some regimens and in patients with a high comorbidity score. GVHD continues to be a major cause of morbidity and mortality after RIC and its incidence may not be lower than after myeloablative SCT. Invasive fungal infections are a second common cause of TRM, which are closely associated with GVHD, did not reduce in incidence. Novel approaches to further, reduce these two complications are required to further improve outcome. In-vivo T-cell depletion reduces initial rates of GVHD, but because DLI is required more often for increased risk of disease persistence and MC, the ultimate rate of GVHD remains unchanged. With gained experience, DLI is used more carefully after RIC, limiting its use to patients with persistent MRD after SCT or imminent graft rejection and delaying administration in other patients, may reduce the risk for GVHD. Methods to deliver cellular immune therapy without GVHD would be a major step forward. The development of tumor or minor histocompatibility antigen-restricted DLI and the combination with targeted therapy and tumor vaccines are promising. Despite initial data, there is no firm evidence for advantage of any of the regimens over the other regimens. Although TRM may reduce, with RIC, relapse rates may increase compared with ablative SCT, thus the net effects on disease-free survival are yet to be determined. Prospective comparative studies to determine the best NST regimen and randomized studies comparing RIC and ablative SCT are urgently required before RIC can be accepted as standard therapy and to better define its role.

Background

Allogeneic hematopoietic stem cell transplantation (SCT) is an effective potentially curative treatment of advanced or high-risk hematologic malignancies. High-dose chemo- radiotherapy with allogeneic SCT is associated with significant morbidity and mortality because of the toxicity of the preparative regimen, graft-versus-host disease (GVHD), and the immune deficiency state that accompanies the procedure. These risks are significantly increased with advanced age, concurrent medical problems, or extensive prior therapy, limiting standard SCT to younger patients in good medical condition. Hematologic malignancies are more common and have a worse prognosis in the elderly and disease and prior therapy may result in comorbidities precluding further intensive therapy. Extensive research has been directed toward the development of safer and less toxic approaches to allogeneic SCT. The introduction of reduced-intensity conditioning (RIC)

regimens is a major step toward achieving this goal. Much experience has been gained with this approach over the past decade.

Rationale for RIC Stem Cell Transplantation

Stem cell transplantation was initially developed as a means to deliver high-dose chemotherapy and radiation for elimination of the underlying disorder. Escalation of treatment doses results in better tumor kill, but it leads to irreversible myelosuppression. SCT was viewed as a supportive-care modality to restore hematopoiesis after treatment. However, it has subsequently become apparent that high-dose chemoradiotherapy does not eradicate the disease in many patients and that much of the therapeutic benefit of SCT relates to an associated, immune-mediated, graft-versus-leukemia (GVL), or graft-versus-malignancy (GVM) effect, which led to a novel therapeutic approach. Low-dose relatively nontoxic and tolerable conditioning regimens have been designed, not to eradicate

the malignancy, but rather to provide sufficient immunosuppression to achieve donor cell engraftment and to allow induction of GVL as the primary treatment.

RIC stem cell transplantation does not eliminate all host hematopoiesis and commonly leads to a state of mixed chimerism (MC). MC describes persistence of donor cells with normal host hematopoietic cells and cells of the underlying malignancy. Stable long lived MC has been reported in animal models and in patients having RIC SCT for nonmalignant disorders. However, in patients with malignancies, MC is most often transient and conversion to complete chimerism (CC), autologous recoRIC SCT itution, or relapse occurs spontaneously or after immune manipulations within the first few months after RIC SCT. The initial nonmyeloablative treatment is expected to produce only transient suppression of the underlying malignancy, but it allows time for the immune GVM effect to develop. Patients with MC or with detected or minimal residual disease (MRD) after RIC SCT may require additional immune-therapeutic approaches. Immunosuppressive therapy administered after SCT for the prevention of GVHD can also suppress GVL. Early withdrawal of immunosuppressive therapy allows the occurrence of potent GVL effect that can potentially eliminate residual disease and host hematopoiesis producing complete remission and CC, respectively. If this does not occur, donor lymphocyte infusions (DLI) may harness this effect and switch the balance toward CC/complete remission. The GVL and graft-versus-hematopoietic tissue effects are highly associated with GVHD, although they may also occur in its absence. Therefore, the initial RIC SCT serves as a platform for additional allogeneic cellular therapy.

RIC Stem Cell Transplantation Regimens

Nonmyeloablative stem cell transplantation regimens comprise of a spectrum of regimens with different immunosuppressive and myelosuppressive properties. The kinetics of engraftment, chimerism, and eradication of residual disease differ accordingly. Conditioning regimens have been referred to as nonmyeloablative if they do not completely eradicate host hematopoiesis and immunity. A few of these regimens have been administered as chemotherapeutic regimens with no stem cell support and allow relatively prompt hematologic recovery. Autologous recoRIC SCT itution of hematopoiesis is expected if the allograft is rejected. These regi-

mens are only mildly myelosuppressive and commonly result in induction of MC. CC and GVL may develop slowly, spontaneously, or after immune interventions. The Seattle regimen consisting of low-dose total body irradiation (TBI: 200 cGy) with (or initially without) fludarabine and intensive pre and post transplant immunosuppression is the prototype of these regimens.

More intensive regimens have also been developed. These regimens have been referred to as reduced intensity conditioning regimens. They have not been administered without stem cell support and autologous recovery may be slow, if at all. These regimens often combine immuno suppressive agents, such as fludarabine with or without sero-therapy (antithymocyte globulin [ATG] or alemtuzumab), and agents with moderate myelosuppressive effects, such as busulfan or melphalan. Although these regimens are more intensive than the nonmyeloablative regimens, dose intensity is still reduced compared to ablative regimens, allowing reduction of toxicity. Reduced intensity regimens, in similarity to myeloablative regimens, rapidly induce CC and antitumor responses, but they are more toxic and are associated with a higher risk for GVHD. A third approach is using a double-step strategy. High-dose chemotherapy supported by autologous SCT is used for cytoreduction and also as an immunosuppressive platform for the second stage of allogeneic SCT with nonmyeloablative or reduced-intensity conditioning administered 2 to 3 months later. The separation of high-dose chemotherapy and allogeneic effects results in reduced toxicity and better tolerability compared to when allogeneic SCT immediately follows high-dose chemotherapy. A novel approach is to combine RIC SCT with targeted therapy. Imatinib mesylate has been explored as adjuvant to RIC SCT before SCT, allowing reduction of conditioning intensity, and after SCT to eliminate MRD .Rituximab has been used in conjunction with RIC SCT in lymphoid malignancies and by us after SCT to target MRD. Radio-labeled immune conjugates, such as radio-labeled anti-CD20 monoclonal antibodies, may be used with SCT to target lymphoma cells, allowing the use of less intensive conditioning.

RIC Stem Cell Transplantation and Regimen-related Complications

Nonmyeloablative stem cell transplantation regimens were originally designed to enable treatment of older and medically infirm patients not eligible

for ablative conditioning. This goal has largely been achieved. Standard ablative regimens are often limited to patients up to age 55 years. Age was not found to be an adverse factor for prediction of outcome after related and unrelated donor RIC SCT and is no longer a contraindication for SCT. Standard SCT in certain high-risk settings, such as in patients failing a prior autologous SCT, and in patients with certain diagnoses, such as multiple myeloma, Hodgkin's, and non-Hodgkin's lymphoma, was associated with unacceptably high treatment related mortality (TRM) rates as high as 50%. TRM in the range of 10% to 20% can be observed in these settings using RIC SCT regimens. In particular, RIC SCT was able to reduce TRM after unrelated donor SCT.

Reduction of TRM is largely attributed to reduction in organ toxicity. The Seattle group has shown marked reduction in cardiovascular, gastrointestinal, hepatic, infectious, metabolic, neurologic, and pulmonary toxicity when comparing their low-dose TBI-based nonmyeloablative regimen to ablative regimens. Nonrelapse mortality within the first 100 days was 9% and 21%, respectively. The major therapy-related organ dysfunction syndromes are reduced in incidence. In particular, idiopathic pneumonia syndrome is less frequent after RIC SCT (2.2% vs 8.4% in one study), despite treatment of older patients. Hepatic toxicity may still be substantial, especially after some reduced intensity regimens. However, not all syndromes are reduced. We have shown that thrombotic microangiopathy is a frequent devastating complication after RIC SCT, more common in second SCTs and in association with acute GVHD. Diffuse alveolar hemorrhage is also relatively common in this setting. We have hypothesized based on experimental data that fludarabine-related endothelial and pulmonary epithelial toxicity may be associated with this unexpected observation. Other hemolytic complications associated with donor-recipient ABO incompatibility may be more common after RIC SCT. Although direct toxicities of high-dose chemotherapy are reduced with RIC SCT, toxicities involving immune mechanisms may not. Organ toxicities are largely associated with patient comorbidity score before SCT. Further research is required to define the relative organ toxicities in different regimens.

RIC stem cell transplantation is less myelosuppressive compared to ablative conditioning; which results in a shorter duration of neutropenia and less

transfusion requirements. Some of the nonmyeloablative regimens result in minimal myelosuppression and can be safely administered in the outpatient setting. Reduced-intensity regimens often result in more profound cytopenias more similar to ablative conditioning. The reduced duration of neutropenia and the limitation of mucosal injury result in reduced risk for severe infections in the immediate post-SCT period. However, the risk for invasive fungal infections is not reduced. These infections are often associated with GVHD and corticosteroid therapy and represent one of the major causes of TRM after NSI. In the Seattle study, invasive fungal infections occurred in 19% of RIC SCT recipients, relatively late in the course, and were the primary cause for 39% of non relapse-associated deaths.

RIC Stem Cell Transplantation and Graft-versus-host Disease

Graft-versus-host disease is one of the major causes of post-SCT morbidity and mortality. When RIC SCT was introduced, it was hoped that GVHD incidence would reduce. Acute GVHD results at least partially from tissue injury and cytokine release secondary to the toxicity of the preparative regimen, amplified by donor immune cells. The use of RIC SCT should theoretically limit tissue injury and cytokine release and reduce the incidence and severity of GVHD. MC that is more common after RIC SCT allows bilateral transplantation tolerance with some protection from GVHD. However, host-antigen presenting cells that have a major role in initiation of GVHD may persist after RIC SCT and contribute to GVHD. The duration of immunosuppressive therapy is usually shorter after RIC SCT and immune manipulations are often incorporated into RIC SCT programs, increasing the likelihood of GVHD, although delayed immune manipulations, once the toxicity of conditioning and cytokine release are already resolved, are less likely to produce severe GVHD. The net effect of these differences between RIC and ablative SCT on GVHD is still not well established. The Seattle group reported that the incidence of grade II/IV acute GVHD after RIC SCT was significantly lower than after ablative therapy, reaching 64% and 85%, respectively. However, the incidence of chronic GVHD was approximately 70% in both cohorts. Initiation of steroid therapy was delayed from an average of 1 to 3 months after SCT, corresponding to a new syndrome described as late-onset acute GVHD. This study suggests that GVHD is not reduced in incidence with RIC SCT, but it is only delayed. In

another study, The incidence of grade II/IV acute GVHD of 36% after myeloablative regimens, but only 12% after truly nonmyeloablative regimens. Chronic GVHD was also reduced. Further prospective studies are needed to determine the relative incidence of GVHD after RIC SCT. However, because it is still a major cause of morbidity and mortality, several approaches have been explored to decrease the risk.

Initially, RIC SCT regimens called for only a short course of immune suppression and early administration of DLI for disease eradication and conversion to CC. These interventions markedly increase the risk of GVHD. More recently, more careful approaches were introduced including the extension of the duration of immune suppression, especially after unrelated donor transplantation, up to 6 months. With better understanding of chimerism and MRD kinetics, the indications for DLI have been restricted, trying to reserve it only for patients destined to relapse or reject their graft, thus reducing the risk of GVHD in all other patients.

Another approach is the use of in-vivo T-cell depletion. Alemtuzumab is an effective agent in the prevention of GVHD. Alemtuzumab administered during conditioning depletes host T cells, thus reducing the risk of graft rejection reported with in-vitro T-cell depletion techniques. Alemtuzumab also depletes host-antigen presenting cells involved in GVHD. It persists after SCT and partially depletes donor T cells, thus alemtuzumab is very effective in the prevention of GVHD. However, patients administered alemtuzumab have a higher risk of opportunistic infections, in particular cytomegalovirus. Furthermore, alemtuzumab recipients have a higher risk of MC and residual disease and require more DLI, thus after DLI, the ultimate net risk of GVHD is not reduced and there is no improvement in survival. ATG administered before SCT has similar effects, although it may be less effective in the prevention of GVHD. Studies are being conducted to determine the dose of alemtuzumab or ATG that may result in net effects that would improve survival.

Immune-therapeutic Intervention After RIC Stem Cell Transplantation

In indolent malignancies, such as chronic myeloid leukemia (CML), chronic lymphocytic leukemia (CLL), follicular lymphoma, and multiple myeloma, MRD is often detected after SCT following ablative conditioning and reduced-intensity conditioning.

MRD can be followed and no intervention is indicated unless progression or plateau in response is observed or quantitative MRD is rising. In aggressive malignancies, such as acute leukemia, timing is more crucial. There may not be sufficient time to follow MRD because relapse may occur within weeks, whereas effective DLI response may take 2 to 3 months. The sensitivity of the test is important. DLI may be administered early or when using very sensitive tests, such as quantitative polymerase chain reaction, when applicable. MRD can be followed very closely (eg, every 1-2 weeks). If MRD is declining, no intervention is needed.

The kinetics of MRD after RIC SCT is not well established as after ablative conditioning. The same level of MRD, may not necessarily have the same significance. MRD surviving high-dose chemotherapy and, to a lesser extent, reduced-intensity conditioning represents highly resistant malignancy, whereas MRD is expected after RIC SCT. MRD remaining after T-cell depletion or the use of alemtuzumab is also highly predictive of relapse.

In the future, tumor-specific lymphocytes or DLI generated against hematopoietic-specific minor histocompatibility antigens, such as HA-1 and HA-2, may be used to harness anti-tumor responses without the risk of GVHD and follow SCT with T-cell depleted grafts.

Targeted therapy is another option for control of MRD. Imatinib mesylate may be effective in salvaging CML patients with relapse or persistent disease after SCT, frontline or after failure of DLI. Imatinib mesylate may be synergistic with DLI. We have shown that rituximab administered after SCT for aggressive lymphoma reduced relapse risk in very high-risk patients. Rituximab may have eliminated MRD and may have synergized with the donor immune system, providing effectors for antibody-dependant cytotoxicity. Similar effects of rituximab administered for residual CLL after RIC SCT. Future studies may identify other methods to target MRD, trying to reduce relapse risk after SCT.

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