Update on Non-myeloablative Stem Cell Transplantation for Hematologic Malignancies

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Abstract

Allogeneic stem cell transplantation is an established treatment modality for a variety of hematologic malignancies. Unfortunately it carries a high risk of complications and toxicities related to the intensive preparative regimen which is traditionally used for pre-transplant myeloablation and the graft versus host disease, which may be life threatening. Thus allogeneic stem cell transplantation has been used only for younger patients with a good performance status, excluding many other potential candidates due to advanced age or comorbid conditions. Non ablative or reduced intensity preparative regimens for allogeneic stem cell transplantation (NST) have been proposed as a strategy that would allow exploiting the graft versus tumor effect of allogeneic transplantation without the toxicity of myeloablative therapy. After more than five years of cumulative clinical experience, it is now well established that NST is a feasible treatment option for patients with suboptimal performance status and is mostly effective in slow proliferating malignancies, which gives time for a graft versus malignancy effect to take place. Additionally achievement of stable donor cell engraftment with NSTs provides a platform for adoptive immune cell treatments and may allow to extend indications of stem cell transplantation in the future.

Key words: Allogeneic transplantation; Non-ablative transplantation; Reduced intensity preparative regimen; Mini-transplant; Graft versus malignancy effect

1. Introduction

High dose chemoradiotherapy (HDCR) followed by allogeneic hematopoietic stem cell (HSC) transplantation is an effective and potentially curative treatment for patients with hematological malignancies. It has also been successful in the treatment of non-malignant hematological or metabolic diseases [1,2]. The curative effect of this treatment, traditionally was thought to be mediated by the tumoricidal effect of chemotherapy. The stem cell transplantation was considered a means to overcome the myelotoxic effects of the chemo and radiation, providing reconstitution of hemopoiesis.

As early as 1960, using a murine leukemia model, it was shown that hematologic malignancies could be cured only with doses of total body irradiation that would be incompatible with life [3]. Barnes and Mathe using animal models and clinical observations respectively, hypothesized that beyond hematopoietic reconstitution, allogeneic transplantation provides an anti-leukemic effect, mediated through the transplanted donor cells [4,5]. Until recently the existence of a graft versus malignancy effect in man was based on indirect evidence [6,7]. Direct evidence for a graft versus leukemia effect comes from the observation that donor lymphocytes infusion can reinduce remission in patients relapsing after allogeneic transplant, especially in patients with CML [8-13].

Allogeneic HSC transplant after myeloablative conditioning, is a curative option for many hematologic malignancies, however this modality is usually reserved for younger patients without serious comorbid conditions. The increased morbidity and mortality associated with older age, are the main reasons for not transplanting older patients or medically debilitated patients [14]. In animal models the incidence of GVHD mortality and morbidity is related to the intensity of the preparative regimen, and non ablative regimens in animal models...
have been developed that allow stable engraftment of donor stem cells [15-18]. Thus a strategy utilizing a less intensive, non-myeloablatove preparative regimen that was sufficiently immunosuppressive to prevent graft rejection and allow engraftment of HSC would be a rational clinical model to explore the efficacy of the graft versus malignancy effect in patients with hematologic malignancies ineligible for high dose chemotherapy or radiation because of age or concurrent medical conditions. In this review we summarize the published experience in the field of NST, its current applications and future areas for development.

2. Development of Conditioning Regimens and Post Transplant Immunotherapy in Nonmyeloablative Stem Cell Transplantation (NST)

Non-myeloablative stem cell transplantation, has shown that engraftment can occur with immunosuppression and minimal myelosuppression. However the optimum doses and the best agents required to achieve engraftment in different clinical situations has not yet been defined and is probably not the same for all patients. Depending on the aggressiveness of the underlying malignancy and the genetic disparity between donor and recipient there is a continuum of non-ablative, reduced intensity and full ablative regimens that have been used in the context of stem cell transplantation. Most NST regimens reported to date have included been either purine analogue based or low dose TBI based [23-35].

2.1. NST in Acute Leukemia/MDS

From April 1996 to January 2000 31 patients received one of two preparative regimens depending on prior exposure to fludarabine [35]. Twenty patients who either had no prior exposure to fludarabine or had responded to fludarabine based chemotherapy, received fludarabine, cytarabine and idarubicin. Eleven patients with prior fludarabine exposure received cladribine 12 mg/m² for 5 days by continuous infusion with cytarabine 1 g/m² daily. All patients received bone marrow or mobilized peripheral stem cells from an HLA identical or 1 antigen mismatch related donor after completion of chemotherapy. GVHD prophylaxis consisted of cyclosporine or tacrolimus with either steroids or methotrexate. Neutrophil recovery occurred in 29 patients at a median of 13 days post-transplant (range 8-38 days) and 25 patients achieved platelet transfusion independence after a median of 17 days (range 8-78 days). Chimerism analysis on day 30 revealed that 20 patients had between 80% and 100% donor cells. 1 patient had 40% donor cells and 2 patients had no evidence of donor cell engraftment. Two patients with >95% engraftment had late autologous reconstitution by 3 months without evidence of relapse, all other patients in remission remained with >95% donor cell engraftment.

Toxicity was minimal with only one treatment related death. Acute GVHD grade ≥2 occurred in 6 patients, one patient died as a result of this complication. Four of these 6 patients were recipients of bone marrow from mismatched related donors.

Complete remission (as defined by <5% bone marrow blasts, neutrophil recovery and platelet transfusion independence) was obtained or continued in 24 patients. Thirteen of these patients relapsed at a median of 3.6 months (range 1.4-17.2 months). At one year the overall survival for the whole group is 47% and the disease free survival is 34%. The most important prognostic factor for survival was disease status at the time of transplant. Patients who were in remission or untreated first relapse when they received their transplant had a better outcome than those with refractory disease. Death resulted from disease (n=15), infection (n=3), toxicity (n=1), GVHD (n=1) and graft failure (n=1).

In an effort to improve outcomes for patients with refractory disease a more intensive combination of fludarabine with melphalan was explored [36]. The rational of this regimen was to provide more sufficient myelosuppresion for a better short-term leukemia control, which would allow successful engraftment and anti-leukemic effect of allogeneic stem cells, including those from unrelated donors. Forty-three AML/MDS patients were treated between 4/96 and 2/00. All were ineligible for conventional transplant due to age or co-morbid conditions. Only one patient was in 1st complete remission, 10 patients were in untreated 1st relapse, 5 patients were in 2nd or subsequent remission, and 27 were in refractory relapse.

Preparative regimen consisted of fludarabine with melphalan (180 or 140 mg/m²) for 37 patients or cladribine (12 mg/m² daily for 5 days) with melphalan for 6 patients. The latter preparative regimen was soon abandoned because of excessive toxicity. Patients received progenitor stem cells from HLA identical or 1 antigen mismatch related donors, or from HLA identical unrelated donors. GVHD prophylaxis consisted of tacrolimus and methotrexate for the majority of the patients. Two-year survival and disease free survival (DFS) was 36% and 34% respectively. Patients with sensitive disease had 55% long term survival and patients with refractory disease had 20% DFS at 2 years post transplant.

Data from the European Bone Marrow Transplant Registry (EBMTR) were recently presented by Rezvani et al. One hundred and forty-nine patients [37] with acute leukemia or MDS underwent non-myeloablative stem cell transplants from April 1994 to May 2000. Sixty-nine patients had AML, 40 ALL and 45 MDS.

Eighty-six percent of the patients received fludarabine based preparative regimens followed by allogeneic stem cells from an HLA identical sibling in 80%, an HLA matched unrelated donor in 12% and other donors in 8% of the cases. GVHD prophylaxis was consisted of cyclosporine and methotrexate in 91% of the cases.

Seven percent of the patients experienced primary graft failure and durable donor cell engraftment (>95% donor cells) was seen in over 77% of the patients. GVHD grade III or IV occurred in 18% of the patients with an overall survival of 35% at 18 months.