Intensive Immunosuppression with Autologous Hematopoietic Stem Cell Reconstitution as Therapy for Rheumatoid Arthritis

The potential relationship of histocompatible hematopoietic stem cells (HSC) in the pathogenesis of autoimmune diseases was first suggested by classic studies performed by Dr. Morton and Dr. Denman and their associates[1,2]. The ability to transfer autoimmune disease to normal animals by the infusion of HSC opened new avenues for investigating the pathophysiology of autoimmunity, as well as for considering the application of hematopoietic stem cell transplantation (HSCT) as a therapeutic intervention in established autoimmune processes. The significant reduction in both the morbidity and mortality of performing HSCT for malignant disease has also increased the enthusiasm for utilizing such therapeutic approaches in autoimmune disease states. In addition, clinical observations have suggested that autoimmunity could be transferred from donors to recipients following HSCT, and that the reversal of autoimmune diseases was sometimes seen in HSCT recipients[3-5].

Changes in the basic understanding of both the pathophysiology and clinical course of rheumatoid arthritis (RA) have suggested that more intensive therapy is reasonable. This has led to many different approaches that emphasize more aggressive and earlier treatment of patients with RA, often utilizing multiple disease modifying agents at the same time. The use of combination therapy, multiple different immunosuppressive agents, and biologic agents has all suggested that more intensive therapy may change both the disease course and manifestations. It is, therefore, natural to suggest intensive immunosuppression followed by HSC reconstitution might both alter the disease process and initiate longstanding clinical responses. This has led to multiple efforts by various investigational groups to apply HSCT for patients with refractory RA. While this therapeutic approach remains investigational, current concepts of pathogenesis of RA provide a strong underlying rationale for aggressive immunosuppressive therapy followed by the infusion of myeloprotective HSC. While the specific techniques used in autologous HSCT treatment programs for RA differ significantly, the overall immunological goals remain fairly consistent. It is anticipated that use of HSCT in RA may cause disease alteration by:

1. Destroying autoreactive mature and progenitor cells that contribute to rheumatoid arthritis, replacing them with a normal immune system.
2. Reducing the number of autoreactive cells to low levels that allow for self-tolerance to be reestablished as the lymphoid population reexpands.
3. Altering immunoregulatory circuits by the use of cytotoxic agents to reestablish more efficient immune control mechanisms.

IDENTIFICATION OF CANDIDATES FOR HEMATOPOIETIC STEM CELL TRANSPLANTATION

The major issue in applying HSCT remains patient selection, with reference to the specific group being studied as well as the development of clinical criteria for specific patient selection. Ideally, HSCT would be offered to patients at high risk for progression to significant disease morbidity and mortality, who have not or will not respond to effective conventional therapies, who are rather early in the disease before irreversible major organ damage, and who have evidence that any existing structural tissue damage is reversible. Unfortunately, RA is notoriously unpredictable in its clinical course and the ability to predict clear-cut prognostic factors early in a patient's disease is still in its infancy. It would be ideal to have clinical, genetic, or laboratory markers that could differentiate patients with poor prognoses. Adult patients with RA who have a DRß1 subtype marker (04-04) have a more destructive course, but only recently have such genetic markers been used to identify patients who would have differential clinical responses to specific therapies[6]. The dilemma remains that the best potential candidates for disease remission following HSCT are those with early disease, while the preferred candidates based on toxicity are those with advanced and far less reversible disease process. As clearly shown in the early experience with HSCT for malignancy, limiting patient selection to those with severe disease having few therapeutic options will result in an initial experience characterized by relatively high toxicity and low therapeutic responses. Fiscal considerations also become directly involved in patient selection. While the initial costs of HSCT are quite high, a curative regimen could certainly be cost effective over the long term when compared with currently used multidrug regimens and biological therapies.

It is often tempting to apply aggressive therapeutic modalities to patients who have no other options. This leads to the

real possibility that patients will be selected for intensive therapeutic regimens without the appropriate consideration of the therapeutic goals and the biologic rationale for suggesting that such therapy might be effective in the setting of RA. The fact that reasonable intensive therapies do exist that are less toxic than HSCT must be strongly considered in the development of any investigative protocols. On the other hand, patients who have failed earlier therapy with combination disease modifying agents, with or without biologic disease modifying agents, do present a unique opportunity to apply more intensive immunomodulation to patients with well established and progressive RA. With the above concepts in mind, the following questions could be used to select individual patients with RA for consideration of hematopoietic stem cell transplantation:

1. Does the patient have definable RA with factors that reasonably predict for a progressive, destructive clinical course?
2. Has the patient failed appropriately aggressive conventional therapies?
3. Is there a reasonable suggestion from pathogenetic studies, preclinical models, and/or anecdotal clinical reports that the specific immunosuppressive protocol being used might cause a clinical response in patients with RA?
4. Is the patient free of serious major organ failure that would limit the application of aggressive immunosuppressive regimens, or significantly increase post-transplant complications?
5. Has there been a realistic consideration of the financial issues?
6. Is there a clearly defined treatment protocol that has undergone prior ethical investigative review?

It is obvious that offering HSCT to high risk patients will predict a worse overall clinical response to the therapeutic intervention itself. However, until the specific toxicity issues of HSCT have been defined in patients with RA, the application of this intensive therapy in patients with early disease is premature.

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