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Case Discussion

Ruminating on rheumatoid arthritis and transplantation

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Introduction

A 40-year-old woman who works for a pharmaceutical company has a 5-year history of severe rheumatoid arthritis. She is currently maintained on a TNF alpha inhibitor, methotrexate, and a non-steroidal anti-inflammatory agent. On this regimen, she has continued to develop new erosions and progressive debility. She previously failed therapy with an alternative TNF alpha inhibitor and an IL-1 inhibitor. Her sister recently volunteered for HLA typing as part of a company program and the sister is a complete match for the patient. She has researched stem cell transplantation for severe rheumatoid arthritis and is interested in pursuing this option.

Recommendations of Dr. Richard Burt, MD

Most patients with rheumatoid arthritis (RA) have a normal life expectancy. However, a small number of RA patients suffer not only from significant disability with diminished quality of life, but also an increased risk of disease-related mortality. Poor prognostic patients may be identified by the number of swollen and/or affected joints as well as significant inability in performing normal activities of daily living. For such individuals who are failing standard therapies including a TNF-α inhibitor and methotrexate/leflunomide, hematopoietic stem cell transplantation (HSCT) is being offered as a treatment option.

Hematopoietic stem cells (HSCs) are adult stem cells that can be mobilized from the peripheral blood or harvested from the bone marrow. While the commonly accepted nomenclature uses the term "hematopoietic" to describe these cells, HSCs are also stem cells of the immune compartment and differentiate into new T and B lymphocytes, dendritic cells, macrophages, monocytes, and neutrophils. Therefore, autologous HSC may be used to regenerate a new or "antigen naive" immune system following treatment with a conditioning regimen designed to "immune ablate" the diseased immune compartment. Initial autologous HSC conditioning regimens were relatively mild and generally used either cyclophosphamide or cyclophosphamnide and ATG. These conditioning regimens were well tolerated as reported by Snowden et al. [1] with no mortality in approximately 70 patients treated in Australia, Europe, and North America. Disease recurrence within 1–2 years was common; however, disease manifestations were generally less severe and easily controlled with medications for which symptoms had previously been refractory. In addition, a more intense conditioning regimen of busulfan and cyclophosphamide performed in one patient provided a long-term remission exceeding 5 years. Therefore, in order to maintain long-term remissions, future autologous HSCT protocols for RA are using either busulfan/cyclophosphamide conditioning or continuing cyclophosphamide/ATG regimens but adding post HSCT maintenance immune suppression with either mycophenolate (cellcept) or methotrexate.

In contrast to an autologous HSCT, the rationale for allogeneic HSCT is to change genetic susceptibility to disease by regenerating the immune system from a brother's or sister's stem cells. In general, allogeneic HSCTs that are designed to result in full donor engraftment may cause graft versus host disease (GVHD) and changing one immune-mediated disease (RA) for another (GVHD)

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would not be an acceptable outcome. The risk of GVHD can be eliminated at the expense of establishing a mixed chimera (both donor and recipient immune systems coexisting together) by removing the donor's lymphocytes and antigen presenting cells from the graft before infusion. To this end, a current allogeneic HSCT study is designed to induce mixed chimerism without GVHD in patients with refractory and poor prognosis RA. In the first case report, a patient with 32 involved joints and 20 swollen joints entered a durable treatment free remission and has become rheumatoid factor negative without evidence of GVHD for more than 2 years post HSCT [2].

The majority of individuals will not have an available healthy HLA-matched sibling donor. For these individuals, embryonic stem cells (ESCs) are being investigated as an alternate marrow donor source [3]. ESCs are derived from the inner cell mass of the pre-implantation embryo (blastocyst). These blastocysts arise from in vitro fertilization and would otherwise be destroyed. Recently, it has been demonstrated in murine models that ESCs engraft across MHC barriers and establish stable mixed hematopoietic and immune chimerism without GVHD. In the future, ESC may become available for both immune regeneration as well as repair of cartilage within damaged joints.

Stem cell therapies offer hope for patients with severe RA. Autologous and allogeneic HSCTs are already ongoing in clinical trials, while ESC transplants are being investigated in animal models. Certainly this field should proceed in carefully designed University and US FDA approved clinical trials. For patients suffering otherwise intolerable and inhumane disease-related circumstances, there is hope.

Recommendations of Dr. Daniel E. Furst, MD

I believe that this patient is not the ideal candidate for high dose immunosuppressive therapy with stem cell transplantation for two basic reasons. (1) The treatment options for RA are increasing rapidly and the treatment options for this patient have not been exhausted, apparently. For example, there is no mention of combination therapy with methotrexate and leflunomide, the use of combinations such as methotrexate, sulfasalazine, and hydroxychloroquine, or the use of rituximab plus methotrexate or cyclophosphamide. These options should be tried before embarking on a regimen with a 1.5% transplant-related mortality and a cost of >$100,000 US. (2) An additional, although apparently contradictory, factor is the fact that this patient has already had her disease for 5 years and most regimens and studies to date require earlier disease ($\leq$3 years of disease) with the thought that the RA becomes less responsive to immunological intervention later on in the course, as its pathogenesis may "shift" from macrophage/T cell dependence to dendritic cell dependence.

Recommendations of Dr. Michael H. Weisman, MD

As a consultant rheumatologist, I see cases like this and they are, indeed, unfortunate situations. The first thing I will do is to determine if the patient had an adequate course of the drugs mentioned. Too often, rheumatologists will be so anxious to get a response that they will not push the dose or wait long enough for a therapeutic response. Next, I will explore if combinations of DMARDS and anti-TNF drugs have been used, and if not, I will try them. If that is not successful or not possible, I will look for alternate approaches such as the use of leflunomide or rituximab. Sometimes corticosteroids can be used carefully and successfully. A total re-examination of the patient's treatment history can be very useful and potentially helpful.

The question of stem cell transplantation is raised by this case and by the patient. Currently, this type of management is experimental, carried out under strict protocol use, and studied only at certain centers in the USA and worldwide. There are no guidelines at present for its implementation. Clearly, there are significant toxicity issues and potentially lethal consequences for this approach, and it is not recommended currently as part of aggressive management of RA. Alternatively, there are some very exciting new biologic agents on the horizon and emerging data on the use of Cytotoxic T-lymphocyte Antigen 4-Immunoglobulin (CTLA4-Ig) and anti IL-6 provide promising new treatment alternatives for RA.

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