Fact Sheet

National Scleroderma Foundation

Stem Cell Transplants and Scleroderma

INTRODUCTION

The term "cellular therapy" refers to any type of treatment where the therapy involves the use of healthy human cells to replace potentially damaged or harmful cells to treat a disease.

The bulk of cellular therapy has been used to treat a variety of cancers such as leukemia or lymphomas, but in the last 20 years there has been increased use for treatment of autoimmune conditions such as scleroderma, lupus, multiple sclerosis and inflammatory bowel disease among others. Although frequently referred to as a "bone marrow transplant," this document will use the term "stem cell transplant" going forward to discuss how these types of therapies have been applied to patients with scleroderma. However, the future of other types of cellular treatments remains very promising.

WHAT IS A STEM CELL TRANSPLANT?

Briefly, stem cell transplantation refers to the replacement of one's blood cells (which includes red cells, platelets and the cells of the immune system) with a graft that comes from either the patient themselves (which is called an "autologous transplant") or from a donor (called an "allogeneic transplant"). Stem cells are the immune cells in the very earliest stages of development and thus have the ability to become a number of different types of cells.

The earliest stem cell transplants for scleroderma were allogeneic, however these types of transplants have two major concerns. First, is a complication known as graft-versus-host disease (GVHD). This is where the donor's immune system recognizes the patient's body as foreign and attacks it. GVHD is often manageable but can lead to debilitating acute and chronic issues including skin tightness that can mimic scleroderma itself. Second, because of the risk of GVHD, patients are placed on medications that lower their immune system which increases the risk for infection. Autologous transplants, on the other hand, do not have the risk of GVHD and thus there is no need for immunosuppression and thus have been the preferred method of transplant for patients with scleroderma. There is still a risk for infection due to the period of time where the patient's immune system is still regrowing after transplant.

WHAT ARE THE STEPS IN A STEM CELL TRANSPLANT

First, a patient's history is reviewed and the patient is evaluated by a rheumatologist as well as an oncologist that specializes in stem cell transplant. After the decision is made to undergo stem cell transplant, the first step is harvesting stem cells. While we previously used to harvest these from the bone marrow, these are now done from the blood. A catheter (also known as a "port" is placed and the patient will receive a medication that increases the amount of stem cells in the blood, a process called mobilization. This could be on or a combination of agents such as granulocyte colony stimulating factor (GCSF), cyclophosphamide or plerixafor. Some centers further select for cells that have a cell surface maker called CD34, which theoretically reduces the number of autoimmune cells.

After harvesting, the patient undergoes a process called conditioning where the goal is to significantly reduce the immune that are currently in the patient's body. There are many types of conditioning regimens that are used, but are broadly divided into 2 types: myeloablative/high intensity and non-myeloablative/reduced intensity. Myeloablative transplants use high

doses of chemotherapy as well as radiation to destroy immune cells. Non-myeloablative transplants use a lower dose of chemotherapy and no radiation. There are pros and cons to both regimens.

Following conditioning, the cells that were previously harvested are transfused back to the patient through the port. While harvested cells are always reinfused after conditioning, patients who undergo myeloablative regimens are unlikely to recover their immune systems without the reinfusion. There are typically residual cells (and thus potentially capable of causing autoimmune disease) remaining in the bone marrow after a nonmyeloablative regimen.

It can take between 10-14 days for the immune system to start recovering. During this vulnerable period, patients are given a combination of antibiotics to prevent against infections and remain in a hospital setting, usually a specialized stem cell transplant unit. Once the immune system begins to recover, patients may be discharged out of the hospital but may have daily outpatient visits for a couple of months to ensure that the immune system is continuing to recover and there are no other side effects.

WHAT ARE THE BENEFITS OF STEM CELL TRANSPLANT FOR PATIENTS WITH SCLERODERMA?

First and foremost, stem cell transplantation is NOT a cure for scleroderma. Our primary goal is to halt progression of the disease and over time hopefully see improvement in a number of areas including lung and skin involvement.

While hundreds of transplants have been done, it has only been in the last 15 years where relatively large randomized controlled trials have been done to compare autologous stem cell transplant to standard immunosuppressive therapy. 2 of these trials – the ASSIST trial (19 participants) and the ASTIS trials (156 participants) - utilized a non-myeloablative conditioning regimen, while the third – the SCOT trial (75 participants) used a myeloablative regimen incorporating total body irradiation. All of these trials demonstrated that stem cell transplant offered a greater chance of disease stability and improvement in skin/lung disease than immunosuppression with cyclophosphamide, which was the standard of care at the time these trials were designed. Additionally, long-term overall survival was greater in patients undergoing transplant than those receiving cyclophosphamide. While we cannot directly compare the results of the trials to each other, the need for restarting immunosuppression in the ASTIS trial was 22%, whereas it was 9% in the SCOT trial.

Transplant is not without risks, however. Death due to transplant itself occurred in 10% of patients in the ASTIS trial and 3% of those in the SCOT trial. Overall serious side effects were greater in transplant than in the immunosuppression group. Notably, cigarette smoking has been associated with poorer outcomes after transplant.

There are also unknowns in terms of stem cell transplant. We do not know if transplant can improve gastrointestinal disease or reduce the burden of Raynaud's phenomenon and finger ulcers. Our experience thus far is that it does not significant reduce symptoms such as heartburn/reflux or motility through the gastrointestinal tract. We also have not directly compared stem cell transplant to therapies that have been developed more recently such as mycophenolate mofetil (Cellcept), tocilizumab or nintedanib, however while these agents may offer less side effects than cyclophosphamide, they have not been shown to be more effective.

WHO BENEFITS FROM A STEM CELL TRANSPLANT?

To answer this question it is important to understand who were included in the clinical trials. All patients had less than 5 years of disease, significant skin involvement (with a modified Rodnan Skin Score of at least 14) and most had lung involvement. A small number of patients in the ASTIS trial had only skin disease, but had rapid progression and less than 2 years of disease. The average age of patients was between 41-47 years old. Additionally patients were excluded if they had heart disease, severe lung disease or a history of pulmonary artery hypertension (which can be seen in 15-20% of patients with scleroderma). The reasons for this is that the conditioning regimen can be toxic to the heart and transplant can do more harm than benefit. Thus the primary patients that

we see as good candidates for autologous stem cell transplant are patients with early, rapidly progressing diffuse skin disease, lung disease that has not progressed too far, and the absence of heart disease or pulmonary hypertension.

WHAT ARE THE FUTURE DIRECTIONS FOR STEM CELL TRANSPLANTS?

In the next several years we hope to improve the safety of stem cell transplant and refine the population that would most benefit from this treatment. We hope to see if transplant can prevent long term complications such as severe gastrointestinal disease or pulmonary hypertension. We also do not know if adding immunosuppression after transplant can reduce the risk of relapse.

We are also excited to see if other types of cellular therapy may benefit patients with scleroderma. With improved ways of preventing GVHD, we may rethink allogeneic stem cell transplant which may allow us to use a lower intensity conditioning regimen. Finally, CAR T therapy, which has been very successful in treating certain types of cancers, is currently being studied in patients with scleroderma and may offer greater effectiveness with less short and long term side effects than our current method of autologous stem cell transplant.

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