Citation: Cellular Therapy and Transplantation, Vol. 2, No. 6

Please cite this article as follows: *Gratwohl A. Theoretical and practical issues of autologous versus allogeneic stem cell transplantation in multiple sclerosis. Cell Ther Transplant. 2011;2:e.000058.01. doi:10.3205/ctt-2011-en-000058.01*

Submitted: 9 June 2010, accepted: 27 August 2010, published: 14 January 2011

Theoretical and practical issues of autologous versus allogeneic stem cell transplantation in multiple sclerosis

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Abstract

Autologous and allogeneic hematopoietic stem cell transplantation (HSCT) have some common and some clearly distinct goals. All current available information suggests that autologous HSCT should remain the standard approach to clinical HSCT for patients with severe autoimmune disorders, including multiple sclerosis. Allogeneic HSCT should be considered in rare patients with specific features that they are likely to benefit more from an allogeneic HSCT, e.g. young patients with no comorbidities and hematological autoimmune cytopenias.

Keywords: autologous hematopoietic stem cell transplantation, auto-HSCT, allogeneic hematopoietic stem cell transplantation, allo-HSCT, multiple sclerosis

Autologous versus allogeneic hematopoietic stem cell transplantation

Autologous and allogeneic hematopoietic stem cell transplantation (HSCT) have some common and some clearly distinct goals. Both permit the application of high dose chemo-radiotherapy up to the dose limiting extramedullary toxicity; allogeneic HSCT in addition can replace a diseased host hematopoiesis, including the immune system, with a healthy donor hemopoiesis. In the case of an autoimmune disease, the necessary goal to be achieved still remains a matter of debate. High dose immunoablation can reset ontogenesis of the immune system in animal models of experimental encephalomyelitis as well as in clinical HSCT for multiple sclerosis in humans. In view of its significantly lower transplant-related mortality, autologous HSCT currently remains the preferred choice in clinical studies.

Hematopoietic stem cell transplantation (HSCT) has become the treatment of choice for many patients with severe congenital or acquired malignant or non-malignant disorders of the hematopoietic system, and for chemo-, radio-, or immunosensitive malignancies [1,2]. Experimental animal studies, incidental reports from patients with HSCT for another indication but concomitant autoimmune disorders, and results from pilot studies have documented that complete remissions can be obtained in situations of severe treatment-refractory autoimmune disorders [3-6]. Animal data give clear indications that some forms of congenital autoimmune diseases can only be cured by allogeneic HSCT. Other forms of animal autoimmune diseases, considered as acquired immune disorders can just as clearly be cured by autologous HSCT alone [4,5]. The situation is less clear in humans. Generally, autoimmune disorders in humans are considered to be induced by three independent components: a) inherited factors such as certain defined HLA-antigens, b) environmental factors such as smoking in rheumatoid arthritis and, c) chance phenomena [7].

These considerations make it clear that autologous HSCT cannot eradicate the congenital factor; it might, however, be sufficient to control the inflammatory component that was induced by chance through environmental factors in an individual patient. As such, the situation in autoimmune disorders is not so much different from the case of clonally aberrant lymphoid reactions in patients with lymphoid malignancies. In some of these high dose chemotherapy is sufficient for control of the disease; in others, an allogeneic healthy novel immune system might be required. These concepts were

already well known more than ten years ago, when the European Group for Blood and Marrow Transplantation (EBMT) and the European League Against Rheumatism (EULAR) released a joint statement on the potential use of HSCT for treatment of patients with severe autoimmune disorders: the disease should be severe enough to justify the risk, the disease should not be so advanced not to permit clinical benefit for the patient, autologous HSCT should be the preferred choice, and standard techniques should be used [6,9].

This view has not changed since. The experience from more than 200,000 HSCT procedures worldwide give some clear indications as to the potential benefits and risks of both allogeneic and autologous HSCT. Allogeneic HSCT is always linked with immunological complications, graft rejection (Host-versus-Graft reaction; HvG) and the reverse, rejection of the recipient by the immunocompetent transplanted immune system (Graft-versus-Host disease; GvHD). Furthermore, time to recovery of complete immuno-competence is considerably longer in allogeneic HSCT than in autologous HSCT. The reasons for this delayed immune recovery are probably manifold: donor-host interaction is required for competent immune response, and immunosuppression is needed to suppress both HvG reaction and GvHD. This combined and prolonged immuno-incompetence is associated with a prolonged higher risk for bacterial, fungal, viral, and parasitic infections in allogeneic, compared to autologous HSCT. For these reasons, allogeneic HSCT is associated with higher transplant related mortality (TRM) in the early as well as in the late post-transplantation period. As a benefit, allogeneic HSCT is devoid of malignant (in the case of HSCT for a malignant disease) or autoreactive (in the case of autoimmune disease) stem, precursor, or effector cells. The risk of relapse is significantly higher after autologous HSCT in all disease categories examined. The net balance of benefit and detrimental effects between autologous and allogeneic HSCT is not easy to assess. It can be very clear in some congenital or high-risk malignancies. In others, years may elapse until the beneficial effects of reduced relapse become higher than the early years of life lost after allogeneic HSCT. Overall, the best results are always obtained with syngeneic HSCT; if there is a syngeneic donor, HSCT is the preferred choice. This is true despite the fact that syngeneic twins possess an inherent risk of developing the same disease as their twin. This disease concordance for twins has clearly been shown in autoimmune disorders and in hematological malignancies [1,10,11].

The discordant effects of major histocompatibility antigens holds true as well for minor histocompatibility antigens (mHAg). This has been shown for the H-Y encoded mHAg. Male stem cells are more likely to be rejected by female recipients; female donors are more likely to induce more GvHD in male recipients. The detrimental effects of increased TRM in the female donor-male recipient situation never outweigh the benefits of a reduced relapse rate. Hence it is unlikely that beneficial allogeneic effects, whatever their mechanism, will outweigh the negative impact [12]. The situation in severe autoimmune disorders is even more complicated than after allogeneic HSCT for a malignancy. Some clinical features of chronic GvHD are indistinguishable from some autoimmune disorders [13]. Specifically, chronic GvHD was first described based on its resemblance with Sjögren's syndrome, systemic sclerosis, or primary biliary cirrhosis [14]. Last but not least, late altered immunity has recently been described as a new late effect after allogeneic HSCT [15]. This syndrome includes some clinical and laboratory aspects of autoimmunity.

The introduction of reduced intensity conditioning transplants (RIC HSCT) has revolutionized clinical HSCT, expanded HSCT to patients with co-morbidities, and has abolished age limits [16]. It has also created big expectations that RIC HSCT might favor the clinical applicability of allogeneic HSCT for patients with severe autoimmune disorders. Indeed, RIC HSCT was recommended via a joint statement on allogeneic HSCT by an international panel [17]. However, experience over the last ten years with RIC HSCT for hematological malignancies does not support such expectations. Explanations are simple. The main reasons for death after an allogeneic HSCT are relapse, immunological complications (HvG and GvHD), infectious complications, and the toxicity of the conditioning regimen.

Conditioning regimens

The contribution to toxicity of the conditioning regimen is therefore just about one quarter of all toxicity. Earlier experience had clearly shown that increased conditioning intensity could reduce relapse risk, but only at the expense of higher TRM. The reverse is now the case. Reduced conditioning can reduce deaths from toxicity of the conditioning; it cannot reduce the risk of immunological complications. It does so at the expense of an increased relapse rate. The net benefit is in favor of the RIC HSCT early on, e.g., at day 100. It is lost at five-year follow up. RIC HSCT does not alter the inherent risk of the key pre-transplant patient factors as established by the EBMT risk score: age of the patient, disease stage, time interval from diagnosis to transplant, donor type, and donor recipient gender combination [11].

In summary, all current available information suggests that autologous HSCT should remain the standard approach to clinical HSCT for patients with severe autoimmune disorders including multiple sclerosis[18]. Syngeneic twin donors, if they exist, are preferred. Allogeneic HSCT can be discussed in rare patients with specific features that they are likely to benefit more, e.g., young patients with no co-morbidities and hematological autoimmune cytopenias [19].

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Ссылка: Клеточная терапия и трансплантация, 2011;2:e.000058.01. doi:10.3205/ctt-2011-en-000058.01

Теоретические и практические проблемы аутологичной трансплантации в сравнении с аллогенной трансплантацией стволовых клеток при рассеянном склерозе

Алоис Грэтвол

Резюме

Проведение аутологичных и аллогенных трансплантаций гемопоэтических стволовых клеток (ТГСК) имеет ряд общих целей, а также некоторые четкие различия по задачам их применения. Вся имеющаяся в настоящее время информация предполагает, что аутологичные ТГСК должны оставаться стандартным подходом в клинической трансплантации для лечения больных с тяжелыми аутоиммунными заболеваниями, в том числе - при рассеянном склерозе. Выбор в пользу аллогенных ТГСК должен рассматриваться у немногих больных с особыми характеристиками, при которых, возможно, выгоднее использовать аллогенную ТГСК, например, для молодых пациентов без сопутствующих заболеваний и гематологических аутоиммунных цитопений.

Ключевые слова: аутологичная трансплантация гемопоэтических стволовых клеток, ауто-ТГСК, аллогенная трансплантация гемопоэтических стволовых клеток, алло-ТГСК, рассеянный склероз

Ссылка: Клеточная терапия и трансплантация, 2011;2:e.000058.01. doi:10.3205/ctt-2011-en-000058.01