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Hematopoietic stem cell transplantation for severe autoimmune diseases: Progress and perspectives

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Abstract

Two different sets of investigation are at the origin of hematopoietic stem cell transplantation (HSCT) for severe autoimmune diseases (SADs). The experimental evidence consisted in the transfer/cure of animal SADs as murine lupus by means of allogeneic but also, almost paradoxically, autologous HSCT. The clinical arm comes from serendipitous reports of patients allotransplanted for coincidental diseases, and ultimately cured of both conditions. Important multicentric prospective trials are ongoing to compare ASCT to the best available non-transplant therapies, but it may be argued that in the end both approaches will be integrated for single patients, and that new agents will possibly alter present strategies. Allogeneic STC is eliciting great expectations, but the burden of higher mortality and morbidity as a result of GVHD in the first place must be considered, even when making recourse to reduced conditioning regimens (RIC).

Keywords: autoimmune diseases, hematopoietic stem cell transplantation

Introduction

Stem cell therapy for severe autoimmune diseases (AD), generally as hematopoietic stem cell transplantation (HSCT), both allogeneic and autologous, but also more recently as gene therapy-assisted autologous HSCT, has become one of the hottest areas of clinical immunology. It has been developing progressively in the last decades, and has generated "excitement and promise as well as confusion and at times contradictory results in the lay and scientific literature" [6]. The utilization of stem cells to promote regenerative medicine must be distinguished from the purpose of suppressing autoimmune cellular and humoral aggression. This does not mean that both areas aren't tightly connected, since supplying new pancreatic beta cells to patients with type I diabetes, whether by islet cell transplantation or by boosting their numbers by reprogramming pancreatic acinar cells, cannot resolve the disease if the autoimmune process is not eliminated [61]. In some clinical entities both effects coincide. An appropriate example is aplastic anemia (AA) and some of its minor variants (pure red cell aplasia-PRCA, pure white cell aplasia-PWCA), in which allogeneic HSCT both suppresses autoimmunity and provides new HSC [62]. In all the other autoimmune conditions this double effect has not been demonstrated conclusively.

The utilization of HSCT, overwhelmingly of the autologous modality, has been growing impressively in the last few years, and is still increasing steadily [28,47]. Autologous HSCT (ASCT) relies on an extensive debulking of the autoaggressive immune system, followed by the re-infusion of the patients' HSC (commonly identified as CD34+ cells). The allogeneic procedure is based on the substitution of the faulty immune system by a new healthy one, theoretically capable of eradicating the autoimmune clones by means of the classical combination of high-dose immunosuppressive therapy and a Graft-versus-Autoimmunity (GVA) effect, which will be discussed later. Whether this last intervention will be ca-

pable of achieving the Holy Grail of self-tolerance [15] is still not established, given the complexity of the pathogenesis of ADs, including the persisting antigenicity of altered "self" proteins [12] and some paradoxical post-transplant relapses despite full donor chimerism, which will be discussed later.

A brief historical recapitulation

Two streams of research, experimental and clinical, are at the origin of the increasing utilization of HSCT, autologous and allogeneic, for SADs [34]. The first animal studies had shown that the transfer of spleen and/or whole marrow cells to immunosuppressed mice could reproduce murine lupus. The culprit cells were shown to be stem or lymphoid progenitors. The next step was to ascertain whether, contrarily, healthy HSC were capable of curing experimental ADs. Human blood SC were capable of suppressing antibody production in lupus mice, perhaps the first demonstration of a curative effect by xenogeneic HSCT. More recently, it has elegantly been shown that the nonmyeloablative transplantation of purified allogeneic HSC not only prevented, but also induced stabilization or reversal of lupus symptoms in NZB mice [50]. Durable mixed chimerism was also efficacious, a point that will be discussed later. A further experimental improvement has been the intra-bone injection of HSC [21].

The resolution of experimental ADs by means of healthy, compatible allo-SCT was to be expected, considering the overwhelming genetic predisposition of inbred strains of mice, which differs from the intricacies of human ADs, in which there is a complex relationship between genetic, environmental and regulatory factors, and where impaired mechanisms of thymic selection interact, in still poorly elucidated ways, with genetic factors. As already mentioned, a GVA effect has been postulated [33], and theoretically dissected in 6 different mechanisms [53], with immune-mediated abrogation of autoreactive clones in the foreground. In practice, donor-derived immune cells are capable of mediating an anti-autoimmune effect either specifically, or as a part of a more general alloimmune reaction. In experimental autoimmune encephalomyelitis (EAE) it was shown that active alloreactivity was associated with the greatest GVA effect [60]. The second stream in favor of allo-SCT came from the clinical observation of patients affected by coincidental diseases, that is patients with ADs having developed a hematologic malignancy for which they received an allo-SCT, and were ultimately cured of both diseases [35]. There were even cases in which allo-BMT transferred the AD of the donor to the recipient, but cured the latter of his former AD.

The rationale for an apparently paradoxical procedure such as autologous HSCT, in which the patients' immune cells, despite varying degrees of HSC depletion in vitro and/or in vivo, are administered back to them, came from the pioneering studies by van Bekkum and his group, who were able to cure EAE and adjuvant arthritis (AA), both models of human multiple sclerosis (MS) and rheumatoid arthritis (RA), by means of autologous ("pseudoautologous") HSCT [58]. These results considerably strengthened the philosophy of autologous HSCT for human ADs, even if it was pointed out later that in animal models the abnormality of the antigen-induced type seems to reside in immunocompetent T/B cells but not in the HSC, and therefore ASCT may be curative, while in spontaneous ADs new, unaffected HSC were necessary to achieve a cure [22]. In any case, the utilization of ASCT is now widely accepted for treating severe, refractory ADs.

A powerful immunosuppressive therapy for SADs has been developed at Johns Hopkins University in Baltimore, where such patients are treated with high-dose cyclophosphamide (CY) alone, with an inevitable delay of marrow and blood reconstitution, but with results that do not differ significantly from those obtained by ASCT [5].

Finally, two new approaches appear to be integrating this area. Mesenchymal stem cells (MSC) possess several immunomodulatory properties [44], have been shown to significantly ameliorate Graft-versus-Host Disease [25] (GVHD), and have been considered a valuable therapeutic option for SADs [56]. However the role of this kind of cellular therapy in human AD, whether associated with ASCT or not, is still to be established. Another fascinating approach is based on the idea of achieving antigen-specific tolerance to treat refractory ADs, even if translating such therapies from bench to bedside is still mainly theoretical. An approach combining HSCT and transduction of the culprit self-antigens in autologous HSCs in order to achieve central (thymic) tolerance has been developed by Alderuccio and his group [2], although only in animal experiments with organ-specific autoimmune conditions at this stage.

Autologous transplantation: progress and questions

In contrast to the long interval having taken place between the first allogeneic transplants for animal ADs and translational clinical trials, ASCT quickly followed the experimental investigations. It was proposed by myself for severe SLE in 1993 [36], and then for ADs in general in 1995 [30]. The first transplants were performed for a connective tissue disease [54] and for severe SLE [32]. The following utilization of ASCT for SADs grew almost exponentially, so much so that, besides the continually increasing registered transplants in the EBMT and CIBMTR registries, a recent study by Dominique Farge et al has analyzed 900 patients [14]. Excellent reviews of specific diseases have been published recently, and a monographic issue of Autoimmunity has just been devoted to this theme [28]. Here, I shall focus on the most significant and contemporary questions.

1. Autologous HSCT for ADs has been considered a relatively safe procedure from its inception, but is it becoming safer?

Autoimmune diseases represent an extremely heterogenous spectrum of diseases, and in most of them severe-refractory forms have a poor prognosis and a greatly impaired quality of life. One cannot disagree, however, with Burt's statement that "Treatment-related mortality needs to be very low for non-malignant diseases"1. Treatment-Related Mortality (TRM) reached 12% in the initial EBMT Registry, decreased to 7 +3% in 2005, and finally did not exceed 5% in the most recent EBMT study [14]. In this last study evidence was also

found of a clear center effect, indicating that experienced teams that are well acquainted with the multi-organ involvement of SADs produce superior results. In the case of a single disease such as SLE, a collection of 162 patients transplanted in 30 Centers showed a TRM of 11% [29], However of 200 patients transplanted at Northwestern University, Chicago, the TRM using non-myeloablative conditioning regimens in 200 patients was 1.5% [8]. This does not mean, of course, that TRM cannot grow much higher in very severe conditions such as advanced scleroderma. Scleroderma-related organ disfunction contributed to treatment-related deaths [43]. In conclusion, the answer to this first question is that ASCT may be considered reasonably safe when performed by experienced teams, appropriate conditioning regimens, and on patients who are not too disease-compromised. These data need to be counterbalanced by mortality from disease progression, and require the adoption of inclusion and exclusion criteria for each category of diseases, which cannot be detailed here. Although the inclusion of patients within approved or investigational protocols is the best policy, it must be realized that, in selected patients with advanced, refractory SADs, the decision to perform ASCT will ultimately rely on a combination of clinical acumen, experienced teams, and a good patient-doctor relationship.

2. Which are the most appropriate mobilization and conditioning regimens?

The source of HSCs was initially the bone marrow (BM), but has now changed to the peripheral blood (PB) following mobilization procedures. In the previously mentioned EBMT study of 900 patients the source was PB in 827 cases [43]. The most popular mobilizing regimens generally consist of combinations of cyclophosphamide (CY) and G-CSF [47]. Mobilizing regimens incorporating CY (from 2 to 4g/m^2) have the additional, significant advantage of acting as an important therapeutic procedure per se (therapeutic mobilization). In our own experience of 9 SLE patients the achievement of a complete remission (CR) following mobilization with CY 4g/m^2 enabled us, in 2 cases, to dispense from performing the initially programmed ASCT.

A variety of conditioning regimens have been utilized, but it could be shown that high-intensity protocols were followed by a lower probability of disease progression, albeit with a higher risk of TRM [16]. The strategy of performing intense immunosuppression without affecting the whole of the hematopoietic system is most generally accepted, taking into account that biologics such as Rituximab have a longer immunosuppressive activity than any chemotherapeutic agent. A combination of both strategies, in which Rituximab 500 mg is given before and after the regular 200 mg/kg CY protocol (the "sandwich technique"), is being currently utilized at Northwestern University, Chicago (USA). Anti-CD20 immunotherapy for the control of relapse following ASCT in patients with rheumatoid arthritis (RA) had been already utilized with success [41], and the strategy of using an additional immunotherapy in this area is attractive. Unfortunately a devastating complication, progressive multifocal leukoencephalopathy (PML), due to the activation of the John Cunningham virus (JCV), has been reported in a disquieting proportion of patients having been immunosuppressed with biological agents (Natalizumab, Rituximab). A recent review reported 52 patients as having developed PML, 7 of which had received HSCT (3 allogeneic, 4 autologous) for lymphoproliferative diseases [9]. Awareness is obviously needed of the potential for PML among Rituximab-treated patients. Maximal immunosuppression produces greater benefits, but may at the same time be associated with unforeseen iatrogenic complications.

3. What significant changes in the immune system take place following ASCT ? Are we really curing autoimmunity ?

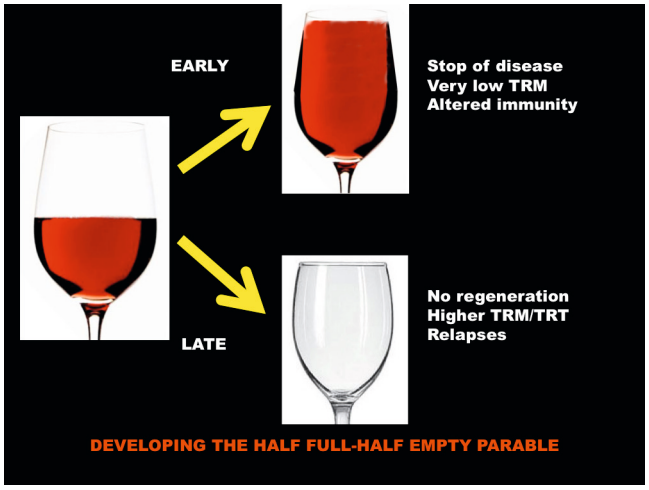
No other aspect of the ASCT-based procedures has been the object of so much research, controversy, enthusiasm, and skepticism. A prolonged depression of CD4+ CD45RA cells is a general finding, and takes place following both ASCT and high-dose immunosuppressive therapy (HDIS) alone. The type of immunomodulation which then follows has been called a "black box" by Muraro and Douek [42], but, thanks to their own and others' investigations, is becoming increasingly clear. High-dose immunosuppression reduces the population of autoimmune cells to minimal residual autoimmune disease (MRAD). While the cure of oncohematological disease requires the eradication of cancer SC, a different view is entertained for ADs. Two basic mechanisms have been postulated. The first has been defined as a "re-education" of the faulty immune system [1], obtained by restoring a diverse antigen-specific repertoire through reactivation of the thymic output ("thymic rebound"), which has also been shown to persist in adults, albeit in lesser measure. In a recent study of ASCT in 7 SLE patients the Berlin group has found evidence for an overwhelming regeneration of the adoptive immune system and of the B-cell lineage, which became apparently tolerant to self-antigens [3]. The second mechanism is closely related, and consists in the reconstitution of the regulatory T-cell pool following ASCT. Tregs (CD4+ CD25+) expressing the transcription factor Foxp3 are crucial in preventing autoreactivity and restraining autoimmunity throughout life. Experimental and clinical studies have demonstrated the impact of the T regulatory network in inducing post-transplant immune tolerance in SLE [63].

Are these changes sufficient and stable enough to guarantee a rebuilding of the immune system, configured in a way that is less likely to redevelop autoimmunity? The abundant and sophisticated studies undeniably display some controversies. In a first study in autotransplanted MS patients the T cells recognizing myelin basic protein were indeed initially depleted by immunoablation, but then rapidly expanded from the reconstituted T cell repertoire in 12 months [52]. More recently, an early recovery of CD4 T-cell receptor diversity was found after "lymphoablative" conditioning and autologous CD34 cell transplantation in systemic sclerosis (SSc) patients, suggesting that the treatment is not completely T-cell ablative (or, more generally immune SC-ablative), and thus not ultimately curative [51]. This contrasts with another recent study which found that CD34+-selected progenitor cells had limited survival capacity and are therefore unlikely to be a major source of carryover of autoimmune T-cell expansions [11]. However, in a comprehensive recent study analyzing original and pooled data from autotransplanted MS patients, Mondria et al

[40] found not only the previously known persistence of CSF oligoclonal bands in 88% of the reported cases, but also the persistence of the soluble lymphocyte activator CD27 thus concluding that complete eradication of activated lymphocytes from the CNS had not been established, despite an intensive immunosuppressive regimen including ATG, CY and total body irradiation (TBI), in two fractions of 5 Gy a day at days –2 and –1. Active demyelinization and axonal damage have been found to continue after ASCT [39]. Our own clinical experience has included late (and very late) relapses, in a way that suggested a recapitulation of the natural history of lupus. So whether pressing the reset button will turn out to be immunologically curative is still uncertain.

4. What type of benefit, if any, does ASCT confer to severe, progressive, relapsing-refractory ADs?

In a recent, provocative editorial commenting on the utilization of ASCT for SADs, and more specifically for the rheumatic diseases, Illei [23] has posed the question, whether "the glass is half full or half empty".



The effects of ASCT may be divided into two phases: the early suppression of ongoing, immuno-inflammatory events, and the later resetting of the autoimmune clock, which is closely related to the length and grade of remission. The first effect is clearly due to the immunosuppressive conditioning regimens, and is proportional to the dose intensity, and also independent from HSC rescue. No sophisticated dynamics occur here, besides the well-known combination of immunosuppression and abrogation of its attending inflammation. This first effect is responsible for its dramatic disease-arresting ("nosostatic") properties, which have been observed in practically all actively aggressive SADs, and most demonstratively in SLE. This change occurs in the aggressive phases of disease, where ASCT may well be the most potent salvage therapy available. A clear distinction of the diverse sensitivity to ASCT according to the phases of disease has been recently made by Shevchenko et al [49], who have divided the transplant strategies for MS into "early", "conventional" and "salvage-late" procedures. Among the many examples of this early, dramatic therapeutic effect are, besides the cancellation of systemic symptoms, the almost immediate clearance of inflammatory urinary sediments in lupus nephritis, the rapid improvement of nailfold capillaroscopy in SSc [4], and the early abrogation of Gadolinium-enhancing lesions in MS [27]. The striking disappearance of diffuse calcinosis in a child with overlap connective disease [13] and the regression of dermal fibrosis in patients with severe scleroderma [43] may be considered intermediate changes.

The impact of ASCT on SADs in the long run has been discussed in several contributions. In the most important study, Progression Free Survival (PFS), which may be considered as the most accurate estimated outcome of a therapeutic procedure, was 43% at 3 years [14]. Three apparently contrasting aspects emerge: first, that in the overwhelming majority of patients no authentic immunological cure may be realistically expected; second, that dramatic remissions occur, may be life-saving, and even long term. Thirdly, in most relapses the utilization of conventional therapies, to which the patients were formerly refractory, is generally possible.

5. Is ASCT the best available treatment for SADs?

ASCT is a powerful therapeutic procedure for SADs. But can it be regarded as the best treatment available, considering the increasing utilization of new pharmacological, prospective (phase III) clinical trials, which are being actively pursued for SSc (the ASTIS trial in Europe and the SCOT trial in North America), MS (ASTIMS, which is probably the most advanced one), Crohn's disease (ASTIC), and SLE (ASTIL)? It is clear that this is the only way to obtain a scientifically correct answer. However, the pace of medical progress is such, that by the time that these laborious trials will have reached statistical significance, new agents may have superseded those utilized in the non-transplant arms. Furthermore, in a sizable proportion of these patients' ASCT may be integrated with other therapeutic interventions, including high-dose immunoglobulins (HDIG), biologics and possibly new, "intelligent" molecules.

Allogeneic transplantation facts and questions

More cogently than for the autologous procedure, animal experiments and results from coincidental disease patients had indicated a powerful instrument to cure autoimmunity in Allo-SCT. In an international workshop held in 2005, it was stated that "the potential for a 1-time delivery of a curative therapy is outstanding" [17]. But will it really be so? Many clinical trials are being pursued worldwide, but I shall confine myself only to published material and our personal experience.

Clinical results

A retrospective EBMT study [10] has collected 35 patients having received 38 allogeneic transplants for various ADs, hematological and non-hematological. The donors were identical siblings for 24 patients, matched unrelated donors (MUD) for 3, mismatched related for 2 and syngeneic for 3 patients. Treatment related mortality (TRM) was 22.1% at 2 years and 30.7 at 5, while death due to progression of disease was 3.2% at 2 years and 8.7% at 5. Of the 29 surviving patients 55% achieved complete clinical and laboratory remission, and 24% achieved a partial remission. The consensus is that nonmyeloablative (NST), reduced intensity conditioning regimens (RIC) should be utilized [46].

Immunological aspects

The substitution of an immune system which is behaving badly by a normal, healthy one is the rationale of the allogeneic approach, and its successful achievement is the prerequisite for embarking on a treatment which has been saddled with a 30% mortality after 5 years [17]. Although it is predictable that TRM following Allo-SCT, if further pursued, will probably become lower, both with an improvement of the learning curve and with optimized conditioning regimens, and effective GVHD control, the only legitimate motivation for performing it is achieving a cure.Allo-SCT is traditionally regarded as a "platform for immunotherapy" [24]. An exhaustive analysis of the mechanisms by which it might cure ADs has been performed by Sykes and Nikolic [53], who have placed the previously discussed GVA effect in the foreground. A retrospective study showed, in analogy to an established pattern in oncohematological diseases, that there were more relapses of coincidental ADs in patients transplanted for hematological malignancies with no GVHD, than in those who developed it [19]. However this effect could not be detected in the recent EBMT study [10], and a much greater clinical material would be necessary to obtain significant evidence. Efforts have been made, as already attempted in oncohematological diseases, to separate GVHD from GVA. A potent GVA effect was demonstrated in rat models of EAE. Clinically there is a group of patients who had been allotransplanted for SADs, in whom donor lymphocyte infusions (DLI) were necessary to achieve full donor chimerism, which ultimately ensured complete remissions of the SADs (lit in 11). These results are counterbalanced with others, which are in favor of the hypothesis that mixed chimerism might be capable of inducing long-term remissions [7]. However it has been shown that increasing mixed chimerism is conducive to graft loss in children transplanted for non-malignant disorders [45]. Full chimerism was present in two patients with rheumatoid arthritis [26] and in a 7-year old boy with Evans syndrome, in whom two autologous transplants had been previously unsuccessful [57].

Controversial evidence, however, comes from the analysis of relapsed patients. There appear to be two types of relapses. An example of the first type is the report of a failure of Allo-SCT to arrest disease activity in a patient with MS having been successfully transplanted because of coincidental chronic myeloid leukemia [38]. Even more disquieting are the aforementioned reports of patients with SADs having received Allo-SCT, but having subsequently relapsed despite full donor chimerism. The first and widely acknowledged case was a female patient with rheumatoid arthritis (RA), who received an HLA-identical transplant because of gold-induced aplastic anemia [55] and the second another patient with RA and multiple myeloma (MM), in whom the myeloma was cured but the RA relapsed [31]. The most demonstrative case is the one of a patient with severe Evans syndrome, who was transplanted from his HLA-identical sister but needed a series of DLI in order to achieve full donor chimerism and complete hematological remission. This patient unfortunately relapsed and died with a terminal hemolytic-uremic syndrome 5 years later [20]. The patient was male and had received the bone marrow of his HLA-identical sister. The immunoglobulins (IgG, IgM) eluted from his 100% XX expanded B cells were not the ones eluted from his Coombs-positive cells. It was hypothesized that the autoantibodies might have been secreted by long-lived host plasmacytes surviving in postulated marrow niches [18]. Even allowing for the hypothesis that relapses in donor cells in patients transplanted for leukemia might be less uncommon than generally thought to be, it is still an extremely rare event, having been identified in 14 out of 10,489 transplants in a recent survey [37]. In contrast, 3 relapses in the much smaller group of autoimmune allotransplanted patients inevitably causes some perplexity. Only further careful investigations will hopefully elucidate this unexpected problem.

Syngeneic transplants are a niche event. Three patients with RA received syngeneic transplants following high-dose immunosuppression. The first was a patient with severe seronegative RA, who enjoyed a long-term remission [59]. However a second patient with progressively erosive, rheumatoid factor positive RA, who was treated with high-dose CY and received an unmanipulated peripheral blood graft (PBSCT) from her identical twin sister, had a poor clinical response, associated with serological persistence64. A still unpublished case is the one of 45 year old lady with severe seropositive RA who was transplanted in Genoa from her identical twin sister on July 29, 2005. The conditioning regimen consisted of CY, 160 mg/Kg. Both rheumatoid factor and anti-cyclic citrulline peptide (CCP) titres decreased significantly (CCP from 234 to 2), but there was a clinical relapse with fever, polyarthritis and elevation of ESR, requiring further treatment.

Concluding remarks

Is there, at the time of this writing, sufficient evidence to answer the question, as to whether HSCT, in its various paradigms, is and will be the best available therapy for SADs? There has been a tendency to place the cause of autoimmunity on a faulty immune system, thus assimilating ADs to the neoplastic lymphoproliferative diseases. However most ADs result from a combination of faulty immune systems and antigen (target organ) dysfunctions. The distinction between primary and secondary ADs, the first being sustained by primary immune defaults and the latter by a predominant antigenic trigger, has been considered as helpful for the evaluation of SCT interventions. However the interaction between immune system and target organ antigenicity is extremely tight.

The autologous procedure is being performed worldwide because of its combination of safety and efficacy. It is capable of arresting progressive, otherwise refractory ADs. In addition, if utilized early in appropriate patients, it favorably changes the course of disease, even allowing for varying degrees of regeneration. Whether the autoaggressive immune system is being re-educated or, more simply, reset, is still not fully clarified. With this background, I believe that Illei's glass [39] is more full than empty, when ASCT is performed in an early stage of disease (fig. 1). However , independently from the results, I believe that there ultimately will be an integration between the two approaches, with careful selection of individual patients.

A word of caution must be said concerning the potential development not only of PML, as already discussed, but also of therapy-related myelodysplasia and leukemia (t-MDS, t-AML), which must be closely watched for when utilizing alkylating drugs and others. Fortunately, there haven't been such reports in this area, and recourse to ASCT in patients with SADs should not be hindered by the fear of late malignant complications, although careful long-term surveillance is mandatory.

Great expectations have been associated with allogeneic SCT, but its position is still uncertain. Ongoing trials will hopefully offer some answers to the question, or hope, whether the total eradication of a faulty immune system will be sufficient, and whether there is solid evidence of a clinically exploitable GVA effect. The unexpected relapses despite full donor chimerism are still a problem, but further experience is needed.

Summary

Two different sets of investigation are at the origin of hematopoietic stem cell transplantation (HSCT) for severe autoimmune diseases (SADs). The experimental evidence consisted in the transfer/cure of animal SADs as murine lupus by means of allogeneic but also, almost paradoxically, autologous HSCT. The clinical arm comes from serendipitous reports of patients allotransplanted for coincidental diseases, and finally cured of both conditions. The encouraging results of ASCT in experimental ADs were enthusiastically translated into human therapy by clinicians hoping to achieve great results without incurring into the rigors associated with the allogeneic procedure.

Well over 1000 ASCT for SADs have been performed worldwide at this time with multiple sclerosis (MS) and connective tissue diseases in the foreground. Transplant-related mortality (TRM) and morbidity have decreased to well under 5%. A dramatic disease-arresting effect is a constant benefit, but the whole course of the disease appears to be influenced favorably. Profound changes of the autoimmune circuitry have been demonstrated, but no authentic eradication of disease (cure?) should realistically be expected. Important multicentric prospective trials are ongoing to compare ASCT to the best available non-transplant therapies, but it may be argued that in the end both approaches will be integrated for single patients, and that new agents will possibly alter present strategies.

Allogeneic STC is eliciting great expectations, but the burden of higher mortality and morbidity with GVHD in the first place, must be considered, even when making recourse to reduced conditioning regimens (RIC). Paradoxical relapses despite complete donor chimerism have been reported. Further experience is clearly needed, but the early enthusiasm for an attractive one-shot therapy must be tempered with a realistic evaluation, at least until new significant breakthroughs have been attained.

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Трансплантация гемопоэтических стволовых клеток при тяжёлых аутоиммунных болезнях: успехи и перспективы

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Резюме

Для обоснования целесообразности трансплантации гемопоэтических стволовых клеток (ТГСК) при тяжёлых аутоиммунных болезнях (ТАБ) приводятся результаты двух различных серий исследований. Экспериментальные доказательства основываются на положительных результатах лечения ТАБ (волчанки) у мышей посредством трансплантации аллогенных, а также, что звучит почти невероятно, аутологичных гемопоэтических стволовых клеток. Клинические доказательства основываются на сообщениях о аллотрансплантациях, сделанных по поводу других заболеваний, в результате чего были успешно вылечены и сопуствующие ТАБ. В настоящее время продолжаются мультицентрические клинические исследования, результаты которых позволят сравнить лечебный эффект трансплантации аллогенных стволовых клеток (ТАСК) с уже наиболее положительно зарекомендовавшими себя схемами лечения ТАБ без применения ТГСК, хотя, не исключено, что в будущем, в каких-то конкретных клинических случаях могут быть использованы оба подхода, и существующая лечебная тактика будет скорректирована при появлении новых лечебных препаратов. На ТАСК возлагаются большие надежды, но никогда нельзя забывать о её последствиях - высокой смертности и осложнениях, прежде всего, в результате РТПХ, даже если для профилактики используют режимы предварительного кондиционирования.

Ключевые слова: аутоиммунные болезни, трансплантация гемопоэтических стволовых клеток, аллогенная трансплантация, аутологичная трансплантация

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