Current state and future directions of autologous hematopoietic stem cell transplantation in systemic lupus erythematosus

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ABSTRACT

Autologous haematopoietic stem cell transplantation (AHSCT) has been proposed as a treatment modality which may arrest the autoimmune disease process and lead to sustained treatment-free remissions. Since the first consensus statement in 1997, approximately 200 autologous bone marrow or haematopoietic stem cell transplantations (HSCTs) have been reported worldwide for systemic lupus erythematosus (SLE). The current state of AHSCT in SLE was reviewed at a recent meeting of the autoimmune working party of the European Group for Blood and Marrow Transplantation. There was general agreement among experts in this field that in patients with severe SLE refractory to conventional immunosuppressive treatments, AHSCT can achieve sustained clinical remissions (ranging from 50% to 70% disease-free survival at 5 years) associated with qualitative immunological changes not seen with other forms of treatment. However, this clinical benefit is associated with an increase in short-term mortality in most studies. Improving patient selection, long-term follow-up of patients after AHSCT, optimisation of induction and maintenance treatment together with detailed analysis of the immune system are identified as key areas for future research. Optimally, AHSCT should be compared with conventional treatment in randomised controlled trials. Development of stronger transplant registries, defining a core set of clinical data and standardising biological sample collections would make future collaborations and comparison of studies more feasible.

Systemic lupus erythematosus (SLE) is a severe, potentially life-threatening, disease. Overall 10-year survival rates range from 83% to 93% in recent studies, but the 15 and 20 year survival is much lower—between 76–80% and 77–78%, respectively.[1] Major organ involvement and persistent overall disease activity are predictors of poor outcome.[2 3] It is important to note that at the time of death, at least 50% of patients had active lupus in one study,[4] suggesting it contributed to mortality in a large proportion of patients. In a large international study (23 centres, 9547 patients) the standardised mortality rate (SMR), which compares mortality with that in the general population, was 2.4 (95% CI 2.3 to 2.5).[5] The increased risk of mortality was highest in people aged <40 years (SMR=10.7 (9.5 to 11.9)), in patients with <1 year of disease duration and was slightly higher in female subjects. African–American ethnicity was also associated with increased risk.[5]

The survival rate in the Euro-Lupus cohort was 95% at 5[6] and 93% at 10 years.[7] Only nephropathy had prognostic significance for a lower survival probability; however, 92% of patients with nephropathy at the beginning of the study survived after a 5-year follow-up period. Thrombotic events were responsible for 26.5% of the deaths.[8]

Survival curves were similar for the first 10–15 years for patients with mild–moderate versus severe disease in an Italian cohort,[9] but diverged significantly after that, demonstrating the need for a long-term perspective when assessing the real risk of lupus and its treatments. A Chinese study identified three distinct clusters with very different risks of mortality. The SMR was not increased in patients with mucocutaneous manifestations only (SMR=0.95 (0.5 to 1.7), p=0.86), but increased sevenfold (SMR=7.23 (6.7 to 7.7), p<0.001) in those with mainly renal and haematological manifestations. The third cluster with a heterogeneous clinical presentation had a 25% increase in mortality (SMR=1.27 (1.1 to 1.5), p=0.005).[10]

Protracted immunosuppressive treatment controls disease activity and prevents or minimises immediate organ damage in the majority of patients but is associated with significant treatment-related morbidities.[11] The ultimate long-term goal of treatment-free remission or cure has been elusive so far. In contrast to some other systemic autoimmune diseases, new biological treatments have not yet delivered the much anticipated breakthrough in the treatment of severe lupus. Therefore, for patients with the most severe lupus, there is a need for more efficacious treatments, preferably with fewer long-term side effects. Autologous haematopoietic stem cell transplantation (AHSCT) has been proposed as a treatment modality, which may arrest the autoimmune disease process and lead to sustained remissions.[12] Experimental transfer of lupus with bone marrow (BM) from SLE-prone mice into normal recipients[13] and the observed clinical remission of SLE after allogeneic or autologous BM transplantation (BMT) in humans[14–16] strongly supported the rationale for exploring BMT.[17] Because of the high mortality associated with allogeneic BMT, autologous haematopoietic stem cells (HSCs) or BMT were preferred for preliminary studies in autoimmune diseases.

Since the first consensus statement in 1997,[18] approximately 200 autologous BM or HSC transplantations have been reported worldwide for SLE. The two largest experiences so far come from the European Group for Blood and Marrow Transplantation (EBMT) data registry (n=85; mean follow-up 25 months, range 2–123 months),[19] and from the single-centre study by Northwestern University (n=50; mean follow-up: 29 months, range 6–90 months).[20] The probability of 5-year disease-free survival was 50% in both studies, consistent with similar results from smaller pilot studies (table 1). These are remarkable response rates in a patient population refractory to conventional immunosuppressive treatment. Importantly, even patients not achieving sustained remission had significant clinical benefit as reflected by increased responsiveness to conventional treatment which had previously failed. In addition to a decrease in overall lupus activity and serological responses, AHSCT reversed pulmonary dysfunction[21] and antiphospholipid syndrome[22] and was associated with durable treatment-free responses lasting ≥5 years on minimal[20] or no treatment.[23 24]

These encouraging results have to be weighed against the increased risk of short-term mortality associated with AHSCT. In contrast to the fairly uniform efficacy outcomes, data on overall and transplant-related mortality are much more variable ranging from 0% to 25%, as shown in table 1. The reason for these different mortality results is unclear, but patient selection, conditioning regimen and centre effect may all contribute. Only randomised controlled studies can provide a definite answer as to how these mortality figures compare with mortality in the same population of patients receiving standard treatment. However, it is important to point out that about half (47%) of the deaths observed across all studies were not transplant related and that one-third (33%) were due to active lupus. This indicates that the population receiving a transplant represents a subset of lupus patients at high risk of mortality. Since standard treatment failed for most patients, it is reasonable to assume that lupus-related mortality would have been higher in this cohort had they not received AHSCT.

Several recent publications support the notion that AHSCT fundamentally changes the abnormal immune response in SLE. Autoantibody levels (including anti-dsDNA, anticardiolipin, antinuclear antibodies and lupus anticoagulant) decreased or disappeared consistently in all studies. A careful analysis of the regenerating adaptive immune system[23] confirmed the previously described normalisation of the restricted T-cell repertoire[26] and showed a sustained dramatic shift in B-cell subpopulations from memory to a naïve B-cell dominance after HSCT with disappearance of circulating plasmablasts, a hallmark of lupus. In addition, a return of CD4 regulatory T cells to the range seen in healthy controls was also observed.[23] This was confirmed in another study,[27] also describing an unusual CD8FoxP3+ regulatory T-cell subset in patients after transplant, which inhibited the pathogenic T-cell response to autoepitopes in nucleosomes. Importantly, these cells were not detected in lupus patients in clinical remission after conventional immunosuppressive treatments.[23 27]

Together these studies provide evidence that in patients with severe SLE refractory to conventional immunosuppressive treatments, AHSCT can achieve sustained clinical remissions associated with qualitative immunological changes not seen with other forms of treatment. However, these beneficial effects are limited by the increased short-term mortality. It is of utmost importance therefore that we optimise the risk:benefit ratio. The first consensus statement about the use of haematopoietic stem cell transplantation (HSCT) for treating severe autoimmune diseases stipulated some basic principles.[18] Briefly, patients should be considered for HSCT if (*a*) they have an increased risk of mortality from their autoimmune disease; (*b*) have been unresponsive to conventional treatments and (*c*) the HSCT can be undertaken before irreversible organ damage to achieve clinical benefit.[18] Based on these principles, the ideal candidates for AHSCT would be relatively young patients—who have the highest increase in SLE-related mortality risk and best post-transplantation outcomes—with major organ involvement and good vital organ functions, after failure of conventional immunosuppression.

An update of the clinical experience and the role of HSCT for SLE was recently considered by a panel of experts at a National Institutes of Health (NIH) and EBMT-sponsored meeting.[28] Although the optimal conditioning regimen has not been established, the available data support the use of lower-intensity

Table 1 Published experience with autologous hematopoietic stem cell transplant in SLE

		*Patients		Mortality				
Centre/source	Reference	N	Conditioning	Overall N (%)	Transplant related N (%)	SLE related N (%)	Overall survival	Relapse-free survival
EBMT registry (35 centres)†	19 25	85	Various	18 (21)	11 (13) (95% CI 5 to 17)	5 (6)	79% At 5 years (95% CI 66 to 86)	44% At 5 years (95% CI 32 to 56)
Northwestern University, USA	20	50	CY+ATG	8 (16)	2 (4)	4 (8)	84%	50% at 5 years
Zhengzhou, China	29	18	TLI+CY+ATG	NR	0 (0)	NR		72% (13/18) At median 12 (3–26) months' follow-up
Seoul, South Korea	30	7	CY+ATG	0 (0)	0 (0)	0 (0)		100% At median 13 (3–26) months' follow-up
Berlin, Germany	23	7	CY+ATG	2 (29)	1 (14)	1 (14)	71% (5/7)	72% At 60 months (range, 24–96 months)
National Institutes of Health, USA	24	8	CY+fludarabine +rituximab	2 (25)	2 (25)	0 (0)	75%	75% At a median 54 months (range, 36–60 months)

*An additional patient received two cycles of mobilisation and went into remission without conditioning and transplant.
†The registry data include the experience from two studies from Novosibirsk, Russia[31] and Genova, Italy[32] which were also published independently.
ATG, antithymocyte globulin; EBMT, European Group for Blood and Marrow Transplantation; CY, cyclophosphamide; NR, not reported; SLE, systemic lupus erythematosus; TLI, total lymphoid irradiation.

non-myeloablative conditioning rather than myeloablative conditioning for autologous HSCT. Another important determinant of outcome in HSCT, in general, is the so called 'centre effect'—namely, that better outcomes after HSCT transplants are in dedicated centres performing large number of procedures. This was shown in a recent EBMT analysis[25] and supported by the observation that the best outcomes in SLE come from the centre performing the largest number of HSCTs.[20] Therefore, studies of HSCT for SLE should be performed in centres experienced in both HSC transplant and lupus and be based on a close collaboration of the transplant and lupus specialists.

RESEARCH AGENDA

Patient selection

The most fundamental problem is to identify the ideal candidate for transplant. Various characteristics can define subpopulations of lupus patients with poor prognosis, but identifying the individuals with the worst prognosis early in their disease course is more difficult. Therefore, finding combinations of demographic, clinical and laboratory markers that reliably predict bad prognosis of patients with SLE or are associated with transplant-related mortality should be a priority. The rapid emergence of novel technologies and the availability of large lupus cohorts followed up longitudinally provide an opportunity to answer these questions.

Need for maintenance treatment

The ultimate treatment goal in SLE is to induce long-term, treatment-free remissions or cure. Although AHSCT can achieve this in some patients (at least up to 5–7 years), this is not universal after transplant. Therefore, further studies are needed to determine if refinements of the conditioning regimen or post-transplant maintenance treatments improve long-term outcomes.

Long-term follow-up

The ultimate benefit of AHSCT will only be determined after decades of follow-up when the initial increase in mortality can be balanced against any long-term benefit in mortality, comorbidities, quality of life and cost. Therefore, a formalised follow-up of all lupus patients who have undergone AHSCT is highly desirable. Establishment of more robust transplant registries for large patient cohort data analyses through existing mechanisms of international collaboration, such as Center for International Blood and Marrow Transplant Research and the EBMT, should be highest priority of any future research agenda.

Mechanistic studies

Careful analysis of the immune system and risk factors for disease recurrence, transplant complications or late effects, such as premature atherosclerosis or the risk of infections and malignancies should be an integral part of any transplant study in lupus.

The role of AHSCT in the treatment of severe SLE should optimally be established in adequately powered randomised controlled trials (RCTs). The failure of a recent randomised study to enrol subjects (http://clinicaltrials.gov/ct2/show/NCT00230035) was disappointing and calls into question the feasibility of launching such an RCT in SLE. Therefore, while smaller phase II studies are pursued and stronger registries are developed, defining a core set of clinical data to be collected in every study and standardising biological sample collection would make future collaborations and/or comparison of various studies more feasible. Nevertheless, it remains of critical importance for the SLE and transplant communities to identify expert interdisciplinary teams that can work together and re-examine the important question of conducting an international RCT of AHSCT for severe SLE.

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