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

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Abstract

Autologous hematopoietic 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 hematopoietic stem cell transplantations have been reported world-wide for 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 therapies, AHSCT can achieve sustained clinical remissions (ranging from 50–70% disease free survival at 5 years) associated with qualitative immunological changes not seen with other forms of therapy. However, this clinical benefit is associated with an increase in short-term mortality in most but not all studies. Improving patient selection, long-term follow up of patients after AHSCT, optimization of induction and maintenance therapy along with detailed analysis of the immune system are identified as key areas for future research. Optimally, AHSCT should be compared to conventional therapy in randomized controlled trials. Development of

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stronger transplant registries, defining a core set of clinical data and standardizing biologic sample collections would make future collaborations and comparison of various studies more feasible.

Systemic lupus erythematosus (SLE) is a severe potentially life-threatening disease. Overall 10-year survival rates range from 83–93% in recent studies, but the 15 and 20 year survival is much lower between 76–80% and 77–78%, respectively (reviewed in [1]). Major organ involvement and persistent overall disease activity are predictors of poor outcome [reviewed in [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 centers, 9,547 patients) standardized mortality rate (SMR), which compares mortality to the general population, was 2.4 (95% confidence interval 2.3–2.5) [5]. The increased risk of mortality was highest in people under 40 years [SMR 10.7 (9.5–11.9)], in patients with less than 1 year of disease duration and was slightly higher in females. African-American ethnicity was also associated with increased risk [5].

The survival rate in the Euro-Lupus cohort was 95% at five [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 five-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 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 (0.5–1.7), $p = 0.86$), but increased seven-fold (SMR 7.23 (6.7–7.7), $p < 0.001$) in those with mainly renal and hematological manifestations. The third cluster with a heterogeneous clinical presentation had a 25% increase in mortality (SMR 1.27 (1.1–1.5), $p = 0.005$) [10].

Protracted immunosuppressive therapy controls disease activity and prevents or minimizes 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, novel biologic therapies have not yet delivered the much anticipated breakthrough in the treatment of severe lupus. Therefore, for the most severe lupus patients, there is a need for more efficacious therapies preferably with fewer long-term side effects. Autologous hematopoietic 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 to explore BMT [17]. Because of the high mortality associated with allogeneic BMT, autologous hematopoietic stem cells 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 world-wide 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 center study by Northwestern University (n=50; mean follow up: 29 months, range: 6–90 months) [20]. The probability of five-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 therapy. Importantly, even patients not achieving

sustained remission had significant clinical benefit as reflected by increased responsiveness to previously failed conventional therapy. In addition to a decrease in overall lupus activity and serologic responses, AHSCT reversed pulmonary dysfunction [21] and antiphospholipid syndrome [22] and was associated with durable treatment-free responses lasting five or more 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 (TRM) are much more variable ranging from 0–25%, as shown in Table 1. The reason for these different mortality rates is unclear, but patient selection, conditioning regimen and center effect may all contribute. Only randomized controlled studies can provide a definite answer of how these compare to mortality rates in the same population of patients receiving standard therapy. 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 transplanted population represents a subset of lupus patients at high risk of mortality. Since most patients failed standard therapy, 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, anti-cardiolipin, 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 normalization 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 CD8+FoxP3+ 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 therapies [23, 27].

Together these studies provide evidence that in patients with severe SLE refractory to conventional immunosuppressive therapies, AHSCT can achieve sustained clinical remissions associated with qualitative immunological changes not seen with other forms of therapy. However, these beneficial effects are limited by the increased short-term mortality. It is of utmost importance therefore that we optimize the risk benefit ratio. The first consensus statement concerning the use of HSCT for treating severe autoimmune diseases stipulated the 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 of the role of HSCT for SLE was recently held by a panel of expert in a NIH- and EBMT-sponsored meeting [28]. Although the optimal conditioning regimen has not been established, the available data support the use of lower intensity non-myeloablative over myeloablative conditioning for autologous HSCT. Another important determinant of outcome in HSCT in general is the so called “center effect”, namely that better outcomes after HSCT transplants are in dedicated centers performing large number of procedures. This was shown in the recent EBMT

analysis [25] and supported by the fact that the best outcomes in SLE come from the center performing the largest number of HSCT [20]. Therefore, studies of HSCT for SLE should be performed in centers experienced in both hematopoetic stem cell 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 bad 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 SLE patients or are associated with TRM should be a priority. The rapid emergence of novel technologies and the availability of large, longitudinally followed lupus cohorts provide an opportunity to address these questions.

Need for maintenance therapy

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 therapy improves long-term outcomes.

Long-term follow up

The ultimate benefit of AHSCT will only be determined after decades of follow up when the upfront increase in mortality can be balanced against any long-term benefit in mortality, co-morbidities, quality of life and cost. Therefore, a formalized follow up of all lupus patients who underwent AHSCT is highly desirable. Establishment of more robust transplant registries for large patient cohort data analyses through existing mechanisms of international collaboration, such as CIBMTR and 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 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 randomized controlled trials (RCT). The failure of a recent randomized study to enroll subjects (http://clinicaltrials.gov/ct2/show/NCT00230035) was disappointing and calls in question the feasibility of launching such 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 standardizing biologic sample collection would make future collaborations and/or comparison of various studies more feasible. Nevertheless, it would remain of most critical importance for the SLE and transplant communities to identify expert interdisciplinary teams that can work together and re-visit the important question of conducting an international RCT of AHSCT for severe SLE.

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Table 1

Center/Source	Reference	#Patients	Conditioning	Mortality			Overall survival	Relapse free survival
		N		Overall N (%)	Transplant related N (%)	SLE related N (%)		
EBMT registry (35 Centers)*	[19, 25]	85	Various	18 (21%)	11 (13%) (95% CI 5%–17%)	5 (6%)	79% at 5 years (95% CI 66%–86%)	44% at 5 years (95%CI 32%–56%)
Northwestern University, USA	[20]	50	CY+ATG	8 (16%)	2 (4%)	4 (8%)	84%	50% at 5 year
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 (28%)	1 (14%)	1 (14%)	72% (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 mobilization 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.

CY: cyclophosphamide, ATG: anti-thymocyte globulin, TLI: total lymphoid irradiation, NR: not reported