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Development of a phase III trial of hematopoietic stem cell transplantation for systemic lupus erythematosus

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Summary:

At Northwestern University, a phase I/II trial of hematopoietic stem cell transplant (HSCT) for systemic lupus erythematosus (SLE) has shown promising results. A phase III HSCT trial is being developed to confirm efficacy of HSCT *vs* continuing the currently accepted standard of care, intravenous pulse cyclophosphamide.
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Taken together all patients with systemic lupus erythematosus have a mortality of approximately 1% per year.[1–8] High-risk patients are at greater risk with a 20% 1-year, 35% 5-year and 45% 10-year mortality (Figure 1). Patients at high risk for lethal complications may be identified by renal disease, hypertension, lung involvement, anemia, thrombocytopenia, and antibodies to phospholipids, or active disease demonstrated by a high disease activity index score despite therapy.[1–8] For this group of patients who have failed pulse intravenous cyclophosphamide, autologous hematopoietic stem cell transplanation (HSCT) has induced drug-free, clinical and serologic remission for more than 4 years.[9–11]

Mobilization and conditioning regimen

Mobilization of stem cells from the blood with G-CSF alone has been demonstrated to precipitate a flare of some autoimmune diseases.[12] Before these clinical results were available, concern lingered that proinflammatory cytokines could induce disease exacerbation or reactivation. For this reason, in designing the phase I study, PBSCs were mobilized with cyclophosphamide (2.0 g/m^2) followed 48–72 h later by daily G-CSF (10 μg/kg/day). This approach not only prevented disease exacerbation but induced partial amelioration of disease activity. Mobilization with this dose of cyclophosphamide induced 1–2 days of an ANC $<1000/\mu$l. Since system lupus erythematosus (SLE) patients are heavily immune suppressed for many years prior to hematopoietic stem cell transplanation (HSCT), pre-emptive lipid amphotercin and broad spectrum antibiotics are used during any period of neutropenia independent of fever.

Since SLE is a cyclophosphamide-responsive disease, a cyclophosphamide-based conditioning regimen was employed. Candidates chosen for active and refractory disease would have significant visceral organ dysfunction such as renal failure or pulmonary disease. Such patients would tolerate most high-dose chemotherapy regimens poorly. Therefore, the conditioning regimen was limited to cyclophosphamide (200 mg/kg) and equine ATG (90 mg/kg). While not a myeloablative regimen, the infusion of mobilized CD34-enriched PBSC would minimize the resulting cytopenic interval, decreasing infectious risks in candidates who pretransplant are already highly immune compromised. Although a few patients have relapsed, this regimen has resulted in drug-free, clinical and serologic remission of greater than 4 years.[9–11] As presented by Dr Traynor, 34 SLE patients have undergone HSCT at Northwestern University using this regimen with remarkable improvements. Of patients undergoing HSCT, there has been no mortality. For this reason, the same mobilization and conditioning regimen will be used in the phase III trial.

Disease activity index

Multiple indices exist to measure or characterize disease activity. Activity instruments include the British Isles Lupus Assessment Group (BILAG) scale,[13] Systemic Lupus Erythematosus Disease Activity Index (SLEDAI),[14] Systemic Lupus Activity Measure (SLAM),[15] and the Lupus Activity Index (LAI).[16] The instrument employed depends on institutional and investigator familiarity. The BILAG is one of the more useful instruments for characterizing disease stage because the BILAG score correlates with intention to treat. The BILAG has been validated as an instrument to measure disease activity.[16,17]

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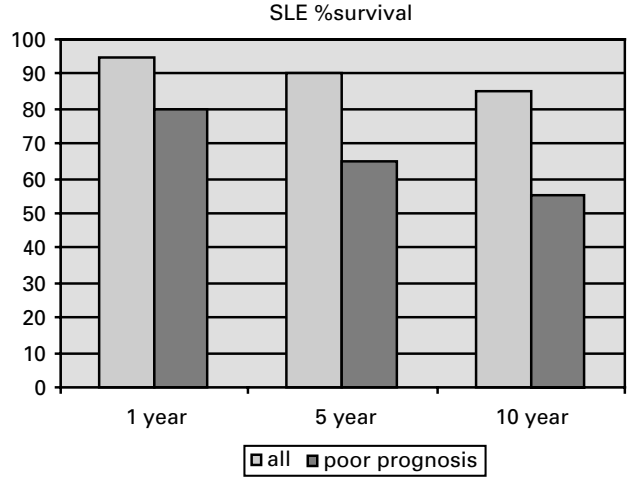

Figure 1 Current survival for SLE for all patients (light) and high-risk patients (dark) at 1, 5, and 10 years.

In addition, the IDEC trial and the Systemic Lupus International Collaborating Clinics (SLICC) group are currently using the BILAG system. For these reasons, the BILAG is a reasonable instrument to measure disease activity in the phase III trial.

The BILAG is a scoring system to evaluate the current disease activity and the changes in disease activity from the last assessment. The evaluation is based on a five-category classification characterizing the degree of symptoms attributed to active lupus for 86 questions based on the patient's history, examination, and laboratory results. The 86 questions are grouped into eight systems: general, mucocutaneous, neurological, musculoskeletal, cardiovascular and respiratory, vasculitis, renal, and hematological. For each of the eight systems, a severity grade (A–E) is calculated based on the scores. The following list indicates interpretation of each of the grades for each system:

A: disease is active enough to need treatment;
B: disease has the potential to need treatment soon;
C: disease currently does not meet grade A or B criterion;
D: disease has satisfactorily resolved;
E: disease has never occurred in this system.

Control arm

Historically, mortality from SLE markedly improved because of more aggressive immune suppression as well as improved supportive care from dialysis, and newer antihypertensive medications. For patients with lupus nephritis, 5-year survival in the 1950s was almost zero.[18] With the introduction of high-dose corticosteroids in the 1960s, the 5-year survival remained a dismal 25%.[19] Following addition of oral cyclophosphamide and azathioprine, 5-year survival improved to 40–70%. In the 1980s, introduction of intravenous pulse cyclophosphamide (500–1000 mg/m^2 monthly) improved 5-year survival to 80%.[20] It must be cautioned that most of the published pulse cyclophosphamide literature is restricted to lupus nephritis that has an easily defined end point, time to dialysis. Evaluating the outcome for other lupus-affected organ systems, for example, pneumonitis, cerebritis, etc was more difficult before the development and validation of disease activity instruments such as the BILAG.

Newer immune-suppressive agents have more recently been used to treat SLE including cyclosporine and mycophenolate mofetil (CellCept). The efficacy of Cellcept has only been shown in small studies. In a study from Hong Kong, 12-month survival rates and response rates were similar in patients with lupus nephritis (approximately 80%) treated with either daily oral cyclophosphamide for 6 months (followed by daily oral azathioprine for 6 months) compared to oral mycophenolate mofetil daily for 12 months.[21] However, there are no comparative trials demonstrating superiority of cyclosporine, mycophenolate mofetil or oral cyclophosphamide to pulse cyclophosphamide. The current standard of care in the USA for patients with SLE nephritis or organ-threatening disease is intravenous pulse cyclophosphamide (500–1000 mg/m^2) monthly for 6 months and then every 3 months. This is based on the historical improvement in survival of patients with SLE given i.v. pulse cyclophosphamide compared to oral cyclophosphamide.

If the question is 'What is the best salvage therapy for cyclophosphamide refractory SLE?' then comparison between HSCT *vs* mycophenolate mofetil or cyclosporine or even transplant doses of cyclophosphamide without stem cell infusion may be appropriate. However, the question is: 'Is there a therapy better than the current standard of care, i.e. pulse cyclophosphamide?' Currently, patients with active disease despite pulse cyclophosphamide are often continued on pulse therapy. If patients with lupus are offered HSCT at the onset of disease, many patients who would otherwise have been successfully treated with pulse cyclophosphamide would be unnecessarily exposed to the more dangerous and aggressive procedure of HSCT. On the other hand, it would be difficult to enroll patients into a trial of continued 'failed therapy' *vs* HSCT. Therefore, candidates must have active SLE despite exposure to some pulse cyclophosphamide therapy but yet be able to remit with continued pulse cyclophosphamide.

The next trial

Brodsky *et al*[22] have reported efficacy from high-dose cyclophosphamide given in the same doses as for transplantation (200 mg/kg) but without stem cell infusion.[22] If the HSCT arm proves superior to the current standard of care, that is, monthly pulse cyclophosphamide, the next study would probably compare 200 mg/kg cyclophosphamide without stem cells to 200 mg/kg cyclophosphamide and ATG with infusion of cyclophosphamide mobilized and selected CD34$^+$ stem cells.

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