

Autologous stem cell transplantation for Crohn's disease: same authors, different conclusions?

In the ASTIC trial,¹ patients with Crohn's disease refractory to corticosteroids and a minimum of three other immunosuppressive or biological drugs were randomly assigned to either stem cell mobilisation followed by immediate hematopoietic stem cell transplantation (HSCT), or stem cell mobilisation and continued conventional therapy.^{1,2} These same authors previously reported negative results, with one death in the transplantation group and no difference in primary outcome between the control and treatment group.¹ In the *Lancet Gastroenterology & Hepatology*, James O Lindsay and colleagues³ now report significant improvement in Crohn's disease activity index (CDAI),^{3,4} a patient-reported outcome score based on abdominal pain and stool frequency (PRO-2),⁵ quality of life, and simple endoscopic score for Crohn's disease (SES-CD).⁶ In this Article,² the authors attempt to correct a type II error in trial design that gave the impression that HSCT is not beneficial.

The complex primary endpoint of the ASTIC study—a medication-free, clinically asymptomatic, and radiological and endoscopic disease-free remission period¹—contributed to the type II error. This endpoint had never been attempted in any previous trial and was in reality a simple binary endpoint—ie, the treatment would either be a cure or a failure. Because no drug for Crohn's disease is curative, it seems plausible that all approved drugs would have also failed to meet such a stringent primary endpoint. Drug trials for Crohn's disease use much more realistic endpoints, such as CDAI, PRO-2, SES-CD, and quality of life.³⁻⁶ When the authors focused on these widely accepted drug trial endpoints, transplantation resulted in significant improvement.² This improvement was impressive, since drug trials usually enroll treatment-naïve patients without stricturing, penetrating, or fistulating disease. By contrast, patients enrolled to the ASTIC trial had not responded to at least four immune-based drugs, including some with fistulating and penetrating disease.

A second type II error in the ASTIC trial design arose because patients were randomly assigned to either HSCT with 200 mg/kg cyclophosphamide and antithymocyte globulin or mobilisation with cyclophosphamide (4 g/m² [100 mg/kg]), which is half the dose of

cyclophosphamide used in the transplantation regimen. Treatment efficacy in the ASTIC randomised trial was therefore obscured by comparing drug (transplant cyclophosphamide) to 50% of the drug (mobilisation cyclophosphamide). For autologous HSCT, the infused stem cells are merely a supportive blood product to accelerate hematopoietic recovery; both toxicity and efficacy are determined by the conditioning regimen.

In this Article, the authors attempt to correct this by reporting the outcomes of all transplantations, including patients initially in the mobilisation group who crossed over to HSCT. When re-analysed in this manner, the results of HSCT for treatment-refractory Crohn's disease are promising, with significant improvement in CDAI, PRO-2, SES-CD, and quality of life.

The theoretical concept behind autologous HSCT for Crohn's disease is to re-establish tolerance with a single treatment (conditioning regimen) that stops inflammation and induces transient cytopenias.⁷ Thereafter, it is hoped that rapid recovery within days of hematopoiesis and somewhat slower recovery over months of lymphopoiesis in a non-inflammatory environment will reset self-tolerance. Post-transplantation human immune analysis studies in patients with multiple sclerosis⁸ support the concept of immune regeneration, and studies in systemic lupus erythematosus⁹ support the concept of immune tolerance.

Crohn's disease is unique among autoimmune disorders because persistent inflammation from ulcers, fistulae, fissures, and strictures contaminated with faeces could prevent a complete reset of tolerance following HSCT. A possible simple approach to improve the efficacy of the regimen used in the ASTIC trial is to incorporate several months of post-transplantation oral gut cleansing antibiotics (eg, metronidazole, rifaximin, or ciprofloxacin), or an oral agent to decrease inflammatory cytokine release (eg, cyclosporine), or both, to facilitate a non-inflammatory environment during the first 6 months of post-transplantation lymphopoiesis.

In terms of safety, transplantation regimen doses of cyclophosphamide should not exceed 200 mg/kg due to risk of cardiac and liver damage.¹⁰ In ASTIC, the combined mobilisation and transplantation dose



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of cyclophosphamide was 300 mg/kg.^{1,2} The one death from hepatic veno-occlusive disease suggests that, when using 200 mg/kg cyclophosphamide in the conditioning regimen, the mobilisation dose of cyclophosphamide should have been reduced by half, to 50 mg/kg (2 g/m²). Alternatively, mobilisation can be performed with filgrastim (G-CSF) alone.

Autologous HSCT, done with the ASTIC approach, was not a cure. It did, however, define the maximum limit of combined mobilisation and transplantation cyclophosphamide dose, and resulted in significant improvements in patients with refractory Crohn's disease. Further investigation of autologous HSCT to define the optimal candidate, mobilisation, regimen, and standard of care during and after transplantation should continue within experienced centres. Before initiation of another randomised trial, further phase 1–2 studies of modified mobilisation and conditioning regimens should be performed to minimise unique Crohn's disease toxicity while also optimising efficacy.

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- 1 Hawkey CJ, Allez M, Clark MM, et al. Autologous hematopoietic stem cell transplantation for refractory Crohn disease: a randomized clinical trial. *JAMA* 2015; **314**: 2524–34.
- 2 Lindsay J, Allez M, Clark M, et al. A prospective analysis of the one-year outcome of autologous stem cell transplantation in treatment refractory Crohn's disease: identifying factors that predict benefit and harm. *Lancet Gastroenterol Hepatol* 2017; [details to be added].
- 3 Best WR, Beckett JM, Singleton JW, Kern F. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. *Gastroenterology* 1976; **70**: 439–44.
- 4 Thia KT, Sandborn WJ, Lewis JD, et al. Defining the optimal response criteria for the Crohn's disease activity index for induction studies in patients with mildly to moderately active Crohn's disease. *Am J Gastroenterol* 2008; **103**: 3123–31.
- 5 Khanna R, Zou G, D'Haens G, et al. A retrospective analysis: the development of patient reported outcome measures for the assessment of Crohn's disease activity. *Aliment Pharmacol Ther* 2015; **41**: 77–86.
- 6 Daperno M, D'Haens G, Van Assche G, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. *Gastrointest Endosc* 2004; **60**: 505–12.
- 7 Burt RK, Loh Y, Pearce W, et al. Clinical applications of blood-derived and marrow-derived stem cells for nonmalignant diseases. *JAMA* 2008; **299**: 925–36.
- 8 Muraro PA, Douek DC, Packer A, et al. Thymic output generates a new and diverse TCR repertoire after autologous stem cell transplantation in multiple sclerosis patients. *J Exp Med* 2005; **201**: 805–16.
- 9 Zhang L, Bertucci AM, Ramsey-Goldman R, Burt RK, Datta SK. Regulatory T cell (Treg) subsets return in patients with refractory lupus following stem cell transplantation, and TGF-beta-producing CD8+ Treg cells are associated with immunological remission of lupus. *J Immunol* 2009; **183**: 6346–58.
- 10 Santos GW. Preparative regimens: chemotherapy versus chemoradiotherapy. A historical perspective. *Ann NY Acad Sci* 1995; **770**: 1–7.