

Autologous stem-cell transplantation in treatment-refractory Crohn's disease: an analysis of pooled data from the ASTIC trial

James O Lindsay, Mathieu Allez*, Miranda Clark, Myriam Labopin, Elenor Ricart, Gerhard Rogler, Montserrat Rovira, Jack Satsangi, Dominique Farge, Christopher J Hawkey, on behalf of the ASTIC trial group†, European Society for Blood and Marrow Transplantation Autoimmune Disease Working Party, and European Crohn's and Colitis Organisation*

Summary

Background The randomised controlled ASTIC trial showed no benefit of mobilisation and autologous haematopoietic stem-cell transplantation (HSCT) compared with mobilisation followed by conventional therapy using a stringent primary endpoint (steroid-free clinical remission for 3 months with no endoscopic or radiological evidence of intestinal inflammation) in patients with treatment-refractory Crohn's disease. We now assess HSCT in patients enrolled in the ASTIC trial using endpoints that are traditional for clinical trials in Crohn's disease, and identify factors that predict benefit or harm.

Methods Patients who underwent mobilisation and were randomly assigned to conventional therapy in the ASTIC trial were offered HSCT at 1 year and underwent complete assessment for a further year. We report analyses of the combined cohort of patients who underwent HSCT at any time during the ASTIC trial programme. The primary outcome for this analysis was 3-month steroid-free clinical remission at 1 year after HSCT (Crohn's Disease Activity Index [CDAI] <150). We also examined the degree of endoscopic healing at 1 year. Multivariate analysis was performed to identify factors associated with achieving the primary endpoint by using logistic regression, and factors associated with experiencing a serious adverse event using Poisson regression. Participants were not masked to treatment, but the adjudication panel that reviewed radiology and endoscopy was masked to allocation and visits. All patients who underwent HSCT and had data available at baseline and 1-year follow-up were included in the primary and safety analysis. This trial is registered with ClinicalTrials.gov, number NCT00297193.

Findings Between June 28, 2007, and Sept 1, 2011, 45 patients were enrolled in the ASTIC trial from 11 European transplant units. 23 patients were randomly assigned to immediate HSCT, and 22 patients were assigned to mobilisation followed by conventional care. After completion of the ASTIC trial, 17 patients from the conventional care group received HSCT. In the combined cohort, data were available for 40 patients at baseline and 38 patients at 1 year after HSCT (one patient died, one withdrew). At 1 year after HSCT, 3-month steroid-free clinical remission was seen in 13 (38%, 95% CI 22–55) of 34 patients with available data for the whole year. Complete endoscopic healing was noted in 19 (50%, 34–66) of 38 patients. On multivariate analyses, factors associated with the primary outcome were short disease duration (odds ratio [OR] 0·64, 95% CI 0·41–0·997 per year; $p=0·048$) and low baseline CDAI (0·82, 0·74–0·98 per 10 units; $p=0·031$). 76 serious adverse events occurred in 23 of 40 patients with available data. The most common serious adverse event was infection, most of which were treatment related. Smoking and perianal disease at baseline were independent factors associated with the number of serious adverse events (OR 3·07 [95% CI 1·75–5·38; $p=0·0001$] for smoking and 3·97 [2·17–7·25; $p<0·0001$] for perianal disease) on multivariate analysis.

Interpretation When assessed using endpoints traditional for clinical trials of conventional therapy in Crohn's disease, HSCT resulted in clinical and endoscopic benefit, although it was associated with a high burden of adverse events. The prognostic factors identified could allow the therapy to be targeted to patients most likely to benefit and not experience serious adverse events.

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Introduction

Treatment-refractory Crohn's disease results in chronic ill health and reduced life expectancy, and often requires surgery.^{1–3} Progressive inflammation and surgery result in digestive tract damage that manifests with strictures, short bowel syndrome, and stoma formation, and is associated with refractory non-inflammatory gastro-intestinal symptoms.^{1,4} Although appropriate use of conventional and biological therapies can induce mucosal healing, many patients have primary or secondary non-response.^{1,5} Patients with treatment refractory Crohn's disease are prepared to expose themselves to significant treatment-related risk to achieve remission.⁶ There has been considerable interest in case reports that autologous haematopoietic stem-cell transplantation (HSCT) can induce sustained disease remission in such patients.^{7–13}

The ASTIC trial compared outcomes at 1 year in 23 patients with refractory Crohn's disease after autologous HSCT with 22 patients undergoing stem-cell mobilisation alone followed by conventional therapy.¹⁴ The results of this trial were negative, and few patients in either group achieved the ambitious primary endpoint of steroid-free clinical remission for 3 months with no endoscopic or radiological evidence of intestinal inflammation. However, exploratory analyses revealed that more patients on HSCT came off immuno-suppressive therapy, achieved clinical remission, and were free of endoscopic disease than did those who had mobilisation alone. HSCT was associated with many serious adverse events, including one death. Substantial morbidity was also associated with conventional therapy, although this therapy was associated with fewer serious adverse events.

The benefits and risks of HSCT must be balanced against ongoing, partly effective conventional therapy. Patients who underwent mobilisation and were then randomly assigned to conventional therapy in the ASTIC trial were offered HSCT at 1

year and underwent complete assessment for a further year. We report the clinical and safety analyses of the combined cohort of patients who underwent HSCT at any time during the ASTIC trial programme, and establish factors associated with clinically relevant outcomes that are used in conventional drug trials in this disease. This report provides additional information that could inform future clinical trials of HSCT in refractory Crohn's disease.

Methods

Study design and participants

ASTIC was a parallel group, randomised controlled trial designed to assess the benefit and safety of autologous stem-cell mobilisation and HSCT compared with mobilisation followed by conventional therapy at 1 year in patients with refractory Crohn's disease.¹⁴ Patients randomly assigned to conventional therapy after mobilisation were offered HSCT after primary outcome assessment and end of follow-up. The trial was done in six European countries at 11 centres approved for allo-geneic transplantation by Joint Accreditation Committee of the International Society for Cellular Therapy (JACIE) and the European Society for Blood and Marrow Transplantation (EBMT).¹⁵ We report the clinical, radio-logical, and endoscopic outcomes from the combined cohort of all patients with assessable data at 1 year after HSCT. This includes patients initially assigned to an early transplantation and those who subsequently underwent HSCT after conventional therapy.

The inclusion and exclusion criteria and recruitment process for the ASTIC trial have been reported previously.¹⁴ Briefly, participants were aged 18–50 years with continuing treatment-refractory Crohn's disease not amenable to surgery and with impaired quality of life (Inflammatory Bowel Disease Questionnaire [IBDQ]¹⁶ or European Quality of Life Visual analogue scale [EQ-VAS])¹⁷ despite at least three immunosuppressive or biological agents and corticosteroids.

A multidisciplinary trial steering group accepted patients for inclusion and all patients provided written informed consent. The protocol was approved by the institutional review board at each site and complied with country-specific regulatory requirements. The study was done in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.¹⁸ An independent data and safety monitoring committee reviewed safety data after every ten patients randomly assigned or in the event of death or other concerns.

Procedures

Patients underwent protocol-designated screening investigations that were reviewed by the trial steering group. Eligible patients underwent stem-cell mobilisation using cyclophosphamide 2 g/m² for 2 days and non-glycosylated granulocyte colony stimulating factor (G-CSF, filgrastim) 10 µg/kg per day.¹⁴ Patients underwent leukapheresis when the CD34-positive cell count exceeded 20 × 10⁴ cells per mL to a target of 3–8 × 10⁶ CD34-positive cells per kg bodyweight and, if successful, underwent HSCT immediately or after a delay of 1 year. An intermediate-intensity conditioning regimen was used, made up of intravenous cyclophosphamide 50 mg/kg per day for 4 days, rabbit anti-thymocyte globulin (Genzyme, Cambridge, MA) 2.5 mg/kg per day, and methylprednisolone 1 mg/kg per day for 3 days from day 3, with infusion of unselected autologous stem cells (minimum 3 × 10⁶ CD34-positive cells per kg) on day 7.¹⁵ All patients were followed up for 1 year after HSCT and could receive standard care for Crohn's disease during this period, including corticosteroids, immunosuppressive agents, and biological therapy, which were subsequently withdrawn in accordance with the protocol if appropriate.

All patients underwent the same schedule of assessments before and during the year after HSCT. This comprised disease activity, haematology, bio-chemistry, and adverse events according to EBMT guidelines,¹⁵ and concomitant medication, all every 6 weeks; quality of life (IBDQ, EQ-5D, and EQ-VAS) every 6 months; and endoscopic and radiological assessment of the entire intestine at baseline and 1 year. Baseline data were recorded before mobilisation in patients undergoing immediate HSCT and before conditioning in those undergoing HSCT at 1 year. Outcome data were recorded 1 year after conditioning for all patients. An adjudication committee who were masked to time of assessment and previous treatment assignment re-viewed all radiology and endoscopy reports to establish intestinal disease activity.

Outcomes

The primary endpoint for this analysis was steroid-free clinical remission. Steroid-free clinical remission was defined as a Crohn's Disease Activity Index (CDAI) less than 150 with no corticosteroids for at least 3 months.¹⁹ Secondary endpoints were clinical and endoscopic disease activity, quality of life and a two-point patient reported outcome (PRO-2; a measure that comprises the stool frequency and pain score from the CDAI).²⁰ Complete endoscopic healing was defined as an ulceration subscore of 0 in all segments using the Crohn's disease simple endoscopic score (SES-CD).²¹ Partial endoscopic healing was defined as an ulceration subscore of no more than 1 in two or fewer segments of all segments examined. Patients were defined as free from active disease if there was no ulceration on upper gastrointestinal endoscopy, colonoscopy, and small bowel imaging, assessed by the adjudication committee. Endoscopic disease regression was defined as an SES-CD score of 0 in all segments. Baseline factors that predicted clinical and endoscopic remission as well as the occurrence of one or more serious adverse events were identified.

Statistical analysis

Quantitative variables were described using mean and SD, and compared in univariate analysis using paired or non-paired *t* test. Categorical variables were compared using χ^2 test or Fisher's exact test. Multivariate analyses were done using logistic regression for all endpoints apart from the number of serious adverse events, which was analysed using Poisson regression. All associated factors in univariate analyses with a *p* value less than 0.10 and factors known from clinical experience to influence the outcome were entered in the model. A step-wise selection of the variables was applied to develop a score for the primary endpoint according to the number of risk factors present. The optimal threshold defining high versus low values for each continuous variable in the final model was obtained using the Hothorn and Zeileis method. All tests were two-sided and *p* values 0.05 or less were deemed to indicate a significant

association. Analyses were done using SPSS, version 22.0, and R, version 3.2.3. This trial is registered with ClinicalTrials.gov, number NCT00297193

Role of the funding source

The Broad Foundation reviewed and assessed the original grant application. Co-authors who were members of EBMT or ECCO had full access to all the data in the study and had final responsibility for the decision to submit the manuscript for publication.

Results

Between June 28, 2007, and Sept 1, 2011, 45 patients were enrolled and randomly assigned to either conditioning with stem cell rescue ($n=23$) or conventional care ($n=22$) in the ASTIC trial.¹⁴ Of 22 patients assigned to receive conventional therapy during the ASTIC trial, 17 went on to receive HSCT after completion of the trial (one patient withdrew, three underwent surgery, and one had improved on conventional therapy; figure 1). Of 23 patients who underwent HSCT in the ASTIC trial, 21 had available data at 1 year (one died at 20 days after conditioning and one withdrew at 26 weeks). Therefore, for this analysis, data were available for 40 patients at baseline and 38 patients at 1 year. The final date of follow-up included in this analysis was Feb 4, 2014. The median disease duration was 15.04 years (IQR 9.19–16.82; table 1). All but one patient (oesophageal disease only) had colonic or ileo-colonic involvement. At baseline, patients had markedly active disease with a mean CDAI of 332.6 (SD 111.36) and PRO-2 of 23.85 (10.35; table 1). There was evidence of active disease in all patients and the mean SES-CD was 14.03 (SD 8.96).

The primary outcome of steroid-free clinical remission for 3 months occurred in 13 (38%, 95% CI 22–55) of 34 patients. 12 (35%, 19–51) of 34 patients were in remission for 3 months off all medical therapies, and 16 (43%, 27–59) of 37 patients were in steroid-free remission at 1 year.

Complete endoscopic healing was achieved in 19 (50%; 95% CI 34–66) of 38 patients, and partial endoscopic healing was achieved in 31 (82%; 69–94) of 38 patients (figure 2). 18 (47%; 31–63) of 38 patients were judged free from evidence of intestinal ulceration on endoscopic and radiological assessment at 1 year.

HSCT resulted in a significant improvement in clinical disease activity with a reduction in mean CDAI from baseline to 1 year (336.7 [SD 112.26] to 196.0 [133.29]; $p<0.0001$). This improvement was evident at week 6 (CDAI 212.3 [SD 128.36]; $p<0.0001$ compared with baseline), at which time 15 (38%; 95% CI 21–54) of 39 patients were in clinical re-mission (CDAI <150; figure 3). HSCT improved disease-specific quality of life with a significant increase in mean IBDQ from baseline to 1 year (119.66 [SD 33.54] to 152.23 [45.15]; $p<0.0001$). There were similar significant improvements baseline to 1 year in EQ5D (0.75 [0.10] to 0.80 [0.16]; $p=0.0330$), EQ-VAS (53.55 [21.42] to 72.72 [22.50]; $p=0.00016$), and PRO-2 (24.03 [10.56] to 12.45 [9.78]; $p<0.0001$) scores (table 2).

There was a significant improvement in endoscopic disease activity with a reduction in mean total SES-CD from baseline to 1 year (14.1 [SD 9.03] to 5.4 [6.57]; $p<0.0001$, table 2). Complete endoscopic disease regression was seen in ten (26%; 95% CI 12–40) of 38 patients. The effect of HSCT on individual ileal and colonic segments is shown in the appendix (p 1). Disease in the small bowel proximal to the ileum was present in seven (18%; 95% CI 6–31) of 38 patients with data at 1 year, of whom five (71%; 39–100) were judged free from disease in this location at 1 year. HSCT had no effect on perianal disease (data not shown).

In the year after HSCT, reintroduction of anti-TNF therapy was required in seven (18%; 95% CI 6–31) of 38 patients who completed HSCT after a median of 18 weeks after HSCT (range 14–39). This treatment resulted in a significant reduction in mean CDAI (319 [SD 124.17] to 174 [87.52]; $p=0.016$), and five (71%; 95% CI 38–100) of seven patients who had anti-TNF treatment had a clinical response (reduction of CDAI >70 points).

On univariate analysis, categorical variables significantly associated with higher rate of 3-month steroid-free remission at 1 year were disease localisation (colonic disease) and disease behaviour at baseline (inflammatory phenotype; appendix p 2), and continuous variables were shorter time from diagnosis to HSCT, lower baseline CDAI, and higher baseline SES-CD (appendix p 3).

After multivariate analyses, factors associated with steroid-free remission for at least 3 months were shorter time from diagnosis to HSCT (odds ratio [OR] 0.64, 95% CI 0.41–0.997 per year; $p=0.048$), and lower baseline CDAI (0.82, 0.74–0.98 per 10 units; $p=0.031$). Higher baseline SES-CD (0.85, 95% CI 0.71–1.002; $p=0.053$ per unit) seemed to be associated with the primary endpoint but was not statistically significant. The optimal thresholds were 298.3 for CDAI, 17 for SES-CD, and 11.24 months for time from diagnosis to HSCT. This allowed a prognostic score to be devised based on the number of predictive factors present at baseline (appendix p 4), leading to a receiving operating characteristic area under the curve (ROC AUC) of 0.948 (0.874–1.0).

Univariate analysis identified low haemoglobin (mean 12.0 g/dL [SD 1.33] vs 12.9 g/dL [1.17]; $p=0.029$), high CRP (31.95 mg/L [SD 31.78] vs 15.49 mg/L [13.63]; $p=0.063$), and a short time from diagnosis to HSCT (12.1 years [SD 3.9] vs 16.3 years [7.0]; $p=0.026$) as baseline factors positively associated with complete endoscopic healing. However, no factors remained significant in multivariate analysis. Likewise, by uni-variate analysis, low haemoglobin (12.0 g/dL [SD 1.37] vs 12.9 g/dL [1.16]; $p=0.038$), high CRP (31.95 mg/L [32.82] vs 16.42 mg/L [13.78]; $p=0.094$), and a short time from diagnosis to HSCT (11.88 years [3.93] vs 16.27 years [6.81]; $p=0.021$) were baseline factors associated with being adjudicated free of all active disease at 1 year. However, no factors remained significant in multivariate analysis.

Serious adverse events were common in patients undergoing HSCT (23 of 40 patients with available data had 76 serious adverse events. 48 out of the 76 events were designated as related to treatment; table 3). The most frequent serious adverse events both during the 100 days after conditioning and the subsequent follow up were infectious, related to treatment. There was a reduction in the incidence of serious adverse events during the course of the trial. Univariate analysis suggested that patients with perianal disease at baseline might be more likely to experience at least one serious adverse event, but this result was not statistically significant (81.8% vs 48.3%; $p=0.079$). By contrast, univariate analysis identified increased numbers of serious adverse events in

current smokers (4 [SD 3.96] vs 1.38 [SD 2.1]; $p=0.011$), patients with perianal disease at base-line (4.09 [3.96] vs 1.07 [1.49]; $p=0.0004$), and patients who received conditioning and HSCT immediately after mobilisation (2.61 [3.31] vs 0.94 [1.20]; $p=0.01$), compared with participants who did not meet these criteria. Multivariate analysis identified that smoking and perianal disease at baseline were independent factors associated with the number of serious adverse events (OR 3.07 [95% CI 1.75–5.38; $p=0.0001$] for smoking and 3.97 [2.17–7.25; $p<0.0001$] for perianal disease).

Discussion

Our results show significant improvements in 3-month steroid-free remission, quality of life, and both clinical and endoscopic disease activity 1 year after HSCT in patients with treatment-refractory Crohn's disease.

To our knowledge, these data represent the largest reported cohort of patients with treatment-refractory Crohn's disease to under-go HSCT to date. These data add important information to the randomised controlled ASTIC trial¹⁴ because we assessed endpoints that are more traditional for clinical trials in refractory Crohn's disease and include data from patients who underwent HSCT after the primary endpoint for the controlled trial had been assessed.

In the ASTIC controlled trial, few patients in either group achieved the ambitious primary endpoint of sustained disease remission at 1 year, with no use of corticosteroids, immunosuppressive drugs, or biological drugs, and no endoscopic or radiological evidence of active disease (ie, cure); there was a high burden of serious adverse events and one patient died from sinusoidal obstructive disease after conditioning. As such it has been reported as a negative trial.¹⁴ Several important issues have been raised that affect interpretation of the benefit of HSCT in the ASTIC trial.^{22,23} The predefined primary endpoint was the most stringent ever used for a clinical trial in Crohn's disease. The low number of patients who achieved this outcome indicates that cure is not a common outcome and that the trial might have been underpowered to detect a difference in this endpoint. However, a significant benefit of HSCT versus mobilisation alone was noted for individual components of the primary outcome. Finally, the ASTIC trial recruited a treatment refractory cohort with heterogeneous disease distribution, many of whom would not meet the inclusion criteria for conventional clinical trials (for example, six patients had diverting or permanent ileostomies).

Assessment of baseline and 1-year outcome from the combined group of patients in the ASTIC trial irrespective of timing of HSCT allowed a better assessment of the effect of stem-cell transplantation. Importantly, sufficient numbers of patients were included to identify factors that might predict clinical benefit. The potential for bias inherent in an open-label assessment is reduced by the robust nature of the data collection and monitoring that was required for a controlled trial. All endoscopic and radiological investigations were reviewed and scored by an adjudication panel that was masked to the timing of the assessment and the treatment assignment of the patient. The present analysis shows that HSCT is associated with an early and sustained reduction in clinical disease activity, and allowed withdrawal of steroid therapy. Patient-reported outcomes and assessment of both disease-specific and generic quality of life mirror the improvements in disease activity. Endoscopic disease activity was significantly reduced, and complete endoscopic healing was achieved in half the patients at 1 year. Complete healing throughout the entire intestine was observed in just under half the patients. These figures compare favourably with reports of clinical and endoscopic outcomes from currently licensed and emerging biological therapies.^{24–28}

Univariate analyses highlighted baseline factors associated with achieving steroid-free clinical remission for longer than 3 months. Associated factors included colonic disease, short disease duration, evidence of inflammatory rather than complex disease, and high endoscopic burden of disease activity. High baseline CDAI was a negative predictive factor, which might reflect the fact that patients with advanced disease have structural damage to the intestine that drives non-inflammatory symptoms. This concept is supported by the fact that several patients with no change in their CDAI during the trial had complete regression of intestinal ulceration on radiology and endoscopy at 1 year. Multivariate analysis confirmed the independence of disease duration, endoscopic evidence of disease activity, and a lower baseline CDAI. This confirmation allowed a predictive model to be constructed, although this is likely to be of little clinical utility because only patients with active disease refractory to available biological therapies would be likely to be considered for HSCT.

All patients were intolerant or refractory to at least one anti-TNF drug before entering the trial. Patients who had a disease flare after HSCT were able to recommence anti-TNF therapy, resulting in a significant reduction in disease activity and most patients having short-term clinical remission. Further study is required to establish the mechanism by which previous loss of response or intolerance to therapy is overcome, and assess the benefit of routine maintenance therapy after HSCT.

Many patients had serious adverse events throughout each phase of the trial, highlighting the importance of careful patient selection. The incidence of serious adverse events reduced during the course of the trial implying that centres became more proficient at managing HSCT with experience.²⁹ Patients in both groups received 4 g/m² cyclophosphamide at mobilisation. Although this was accepted practice at the start of the trial,¹⁵ lower intensity mobilisation regimens are recommended to reduce the toxicity of the procedure.^{10,22} Patients who proceeded immediately to conditioning and stem-cell rescue had a greater number of serious adverse events on univariate analysis, probably due to the additional doses of cyclophosphamide received within a short time frame. Smoking and perianal disease were independent risk factors for an increased number of serious adverse events. Studies of HSCT in other diseases have also reported that smoking is a risk factor for adverse events.³⁰ An understanding of factors that predict risk should influence the design of future research to establish whether lower-intensity regimens deliver similar benefits with reduced risks. Subsequent trials should consider straight randomisation between low-dose mobilisation and HSCT versus standard care to give an accurate comparison between HSCT and best medical therapy.

The data from this cohort represent the largest report of patients with refractory Crohn's disease undergoing autologous HSCT. These data show significant benefit from HSCT in terms of steroid-free clinical remission, enhanced quality of life, and mucosal healing. The large number of serious adverse events suggests that this treatment strategy should only be considered in patients who are refractory to biological therapies. Identification of factors that predict both benefit and harm will be invaluable in the

design of future trials. Such trials should assess whether the use of low-intensity mobilisation and conditioning regimens can maintain the observed benefit while reducing the risk of HSCT.

Contributors

JOL prepared the initial draft of the manuscript. JOL, MA, MMC, ML, ER, GR, JS, and CJH were responsible for study concept and design. JOL, MA, MMC, ML, ER, GR, MR, JS, DF, and CJH were responsible for acquisition, analysis, and interpretation of data. MMC and ML did statistical analysis. JOL, MA, MMC, ML, ER, GR, MR, JS, DF, and CJH were responsible for critical revision of the manuscript for important intellectual content. CJH and DF obtained funding.

Declaration of interests

CJH received a National Institute for Health Research Senior Investigator Award and funding from the University of Nottingham Medical School Dean's Fund and the Nottingham University Hospitals NHS Trust Research and Development Fund. All other authors declare no competing interests.

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