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# Hematopoietic stem cell transplantation for severe Crohn's disease

RM Craig, A Traynor, Y Oyama and RK Burt

*Division of Immunotherapy, Northwestern University Medical Center, Chicago, IL, USA*

**Summary:**

**It is clear that some patients with severe Crohn's disease (CD) fail to respond favorably to the standard treatment, including antibody to Tumor Necrosis Factor alpha (TNFα). We have embarked on a unique therapy for this group of patients, intense immune suppression followed by autologous hematopoietic stem cell transplantation (HSCT). The response to this approach in our first four patients has been excellent, with there being no significant untoward event from the transplantation and with each patient entering clinical remission in terms of the Crohn's Disease Activity Index off all therapy for CD and no diarrhea or abdominal pain. However, some evidence of minor laboratory abnormalities and slight inflammation of the colon on colonoscopic evaluation persist up to 1 year post-transplant. It is suggested that HSCT should be considered a reasonable option for patients who have failed standard CD therapy, although long-term follow-up will be necessary to confirm the duration of the induced clinical remission.**
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Approximately 4 years ago, Northwestern University opened a protocol for hematopoietic stem cell transplantation (HSCT) in severe Crohn's disease (CD). Although the proposal was approved by the FDA and local Institutional Review Board, the first suitable candidate underwent this procedure 1 year ago. Since then, three additional patients have undergone this treatment. The response has been excellent, with the patients rapidly going into clinical remission, although the two longest-duration patients still have superficial ulcerations seen on colonoscopy.

While CD is an immune-mediated disease, it is not at all clear that autoimmunity is the underlying pathogenesis. It may, instead, be an unbalanced reaction towards gut flora. Standard therapy for CD includes: five-aminosalicylic acid products that are anti-inflammatory and work locally;[1] corticosteroids that are broad-spectrum anti-inflammatory agents;[2–9] cytokine suppression or stimulation that work on the expression of inflammation rather than at the pathogenesis of the inflammation;[10–12] and antibiotics, such as metronidazole and quinolones that may perhaps decrease exposure to responsible antigens.[13] None of these therapies gets at the fundamental nature of the inflammatory process. Standard therapies suppress until a spontaneous remission ensues.

Although there are little data on CD mortality, it is clear that CD has a mortality in and of itself, supported by one of the largest series of CD which reported a 6% mortality rate.[14,15] In a selected series such as patients with severe and refractory disease, the mortality rate is probably higher, perhaps in the 10% range. Serious morbidity accompanies Crohn's disease including fistulae, abscesses, eye, skin joint and hepatic problems, the need for recurrent surgery and eventual short bowel syndrome necessitating home parenteral nutrition and its complications, and abdominal pain with resultant drug addiction.[15–17] Support for HSCT comes from reported patients who had undergone either allogeneic or autologous HSCT and had incidental CD.[18–21]

## HSCT

Candidates for HSCT must have failed prednisone, azathioprine, azulfidine, metronidazole, and remicade (TNF inhibitor) with failure defined as a Crohn's Disease Activity Index (CDAI) greater than 250 on a scale of 0 to 400 (Table 1).[22] We have found the CDAI to be an imperfect assessment of CD morbidity and are in the process of evaluating the Craig Crohn's Severity Score (Table 2) for future trials. As an example of the type of candidate, our first patient, a 22-year-old female had continuous disease for 10 years, with up to 25 bowel movements daily, requiring an ileo colonic resection at one point. She had been on total parenteral nutrition for 2 years. She was also addicted to narcotics, receiving 3 mg/h intravenous hydromorphone. Her CDAI was 305. She had severe colitis and ileitis on both colonoscopy and small bowel X-ray.

Peripheral blood stem cells are mobilized with cyclophosphamide 2.0 g/m$^2$ and G-CSF 10 $\mu$g/kg/day and enriched via an Isolex cell separator. Conditioning is cyclophosphamide 200 mg/kg and antithymocyte globulin (ATG 90 mg/1 kg & ATG 5.5 mg/kg). Post-transplant evaluation includes CDAI, Inflammatory Disease Bowel

Correspondence: Dr RK Burt, Division of Immunotherapy, Northwestern University Medical Centre, Chicago, IL 60611, USA. E-mail: rburt@nwu.edu

**Table 1** Crohn's Disease Activity Index (CDAI)

| *Variable* | *Quantity* | *Multiple* | *Total* |
|---|---|---|---|
| Number of liquid or soft stools per day | | 2 | |
| Abdominal pain (0 = none, 1 = mild, 2 = moderate, 3 = severe) | | 5 | |
| General well being (0 = well, 1 = slightly under par, 2 = poor, 3 = very poor, 4 = terrible) | | 7 | |
| Number of complications: arthralgias, iritis, erythema nodosum, pyoderma gangrenosa, aphthous ulcerations, anal fissure, anal fistula, anal abscess, fever >37° past week, intestinal obstruction | | 20 | |
| Opiates for diarrhea (no = 0, yes = 1,) | | 30 | |
| Abdominal mass (no = 0, questionable = 2, yes = 5) | | 10 | |
| Deviation from normal hematocrit ($N$ = 42 for female, 47 for male) | | 6 | |
| % deviation from standard weight | | 1 | |
| Total CDAI | | | |

From Best *et al*[22]: CDAI < 150 = remission; > 450 = severely ill.

**Table 2** Craig Crohn's Severity Score

| *Feature* | *Score* |
|---|---|
| Diarrhea | |
| 3–10/day | 1 |
| 10/day | 2 |
| Pain | |
| Intermittent cramping | 1 |
| Steady, mild to moderate | 2 |
| Steady, severe | 3 |
| Chronic opiate use for pain | 2 |
| Well being | |
| Fair | 1 |
| Poor | 2 |
| Terrible | 3 |
| Corticosteroid use | 2 |
| Immunosuppressives | 2 |
| 5-ASA or antibiotic use | 1 |
| Enteropathic arthritis/arthralgias | 1 |
| Hepatobiliary complication | 2 |
| Perianal fistula or abscess | 2 |
| Entero-entero fistula | 2 |
| Enterovaginal fistula | 2 |
| Enterovesicle fistula | 2 |
| Perianal fissure, anal pain | 1 |
| Vulvar inflammation | 1 |
| Intestinal obstruction | 2 |
| Abdominal mass | 2 |
| Erythema nodosum | 1 |
| Pyoderma gangrenosa | 2 |
| Aphthous stomatitis | 1 |
| Iritis | 2 |
| Fever >1 week | 2 |
| Weight loss | |
| 10% usual | 1 |
| 20% usual | 2 |
| Hematocrit | |
| 1–5 < normal | 1 |
| >5 < normal | 2 |
| CRP abnormal | 1 |
| Serum albumin | |
| 2.5–3.5 | 1 |
| <2.5 | 2 |
| Sedimentation rate >20 | 1 |
| Colonoscopy | 1–3 |
| Small bowel radiograph inflammation | 1–3 |

Questionnaire, colonoscopy, small bowel radiographs, CRP, sedimentation rate, albumin, weight, and anti-*Saccharomyces cerevisiae* antibody (ASCA).

Four patients have completed HSCT. One of these subjects is 1 year, one is 11 months, one is 2 months and the final is 2 weeks post-transplantation. The only toxicity in these patients was culture-negative fever for 24 to 48 hours.[23] Abdominal pain and diarrhea resolved for the most part during the hospitalization. In all patients, the CDAI and the severity index have normalized despite withdrawal of all therapy for CD. However, some of the colonoscopies show persistent but asymptomatic mild inflammation. While the depth of this remission and how long this remission will last remains uncertain, it is reasonable to consider HSCT in patients with severe CD so long as these patients have failed standard therapy.

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