Crohn’s Allogeneic Transplant Study (CATS) for patients with treatment-refractory Crohn’s Disease

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Crohn’s Disease -- intestinal inflammation

earlier, more superficial ulcers

later, deeper, fibrotic ulcers
Crohn’s Disease -- colon strictures

colonoscopy – ulcers, edema, stricture

barium Xray – transverse colon stricture
Crohn’s Disease -- small intestinal strictures

barium Xray – long ileal narrowing

MRI– short jejunal stricture
Crohn’s Disease fistula

a tract from intestine to skin

opening of a fistula in peri-anal skin
Treatments for Crohn’s Disease

• Aminosalicylates

• Glucocorticoids (prednisone, topical budesonide)

• Antibiotics

• Anti-metabolites (methotrexate, 6-MP, azathioprine, cyclophosphamide)

• Biologic therapies (anti-TNF$_\alpha$, anti-$\alpha$4-integrin, anti-IL12, anti-IL6, anti-CD3, others)

• Surgery (resection, stricturoplasty, fistulectomy)
Crohn’s Disease and autologous hematopoietic cell transplantation

Northwestern University (Burt et al, Blood 2010)
• 9/24 elimination of CD to time of last follow-up (≤5 yrs)
• 15/24 recurrent CD before 5 yrs.

ASTIC Trial (Hawkey et al, Broad Foundation 2013)
• 17 autologous HCT vs. 17 mobilized only
• More clinical and endoscopic improvement after HCT
• 1 death (? Sinusoidal Obstruction Syndrome after CY)
Rationale for allogeneic bone marrow transplantation as a cure for Crohn’s Disease

• Crohn’s is a genetic disorder of immune regulation (see Elding et al, Am J Human Genetics 2013).

• Allogeneic bone marrow transplantation can cure many genetic disorders of immune regulation.

Thus, allogeneic bone marrow transplantation should be able to cure Crohn’s Disease by installing a normal immune system.
Examples of immune disorders with gut inflammation treated with allogeneic HCT

- SCID
- IPEX
- IL10-receptor defect or IL-10 deficiency
- CGD – chronic granulomatous disease
- WAS – Wiskott Aldrich syndrome
- CVID with severe autoimmune problems
- XIAP – X-linked lymphoproliferative disease
- XLA - X-linked Agammaglobulinemia
- Trisomy 8 mosaicism (Behcet’s like)
- NEMO (NF-κ-B essential modulator) deficiency
- STAT1 gain-of-function mutations
Crohn’s Disease and allogeneic hematopoietic cell transplantation

Seattle (Lopez Cubero et al, Gastroenterology 1998)
- 4/5 elimination of CD
- 1/5 graft rejection, recurrent CD

Essen (Ditschkowski et al, Transplantation 2003)
- 7/7 elimination of CD
Inclusion criteria

A diagnosis of CD
An adverse prognosis, failed all known therapies
Active intestinal inflammation
Severe CD as defined by one of the following:
   CD Activity Index (CDAI) ≥250
   Need for TPN to maintain weight
   Recurrent intestinal inflammation after resection
HLA-matched hematopoietic cell donor
Age from 18 through 60 years.
Some CATS exclusion criteria

Complication of CD that would jeopardize survival
History of Progressive Multifocal Leukoencephalopathy
Organ dysfunction that would jeopardize survival
Life expectancy severely limited by illness other than CD
History of a malignancy
Hematopoietic Cell Transplant Co-morbidity Index >2
Autologous stem cell collection

Peripheral blood stem cells after G-CSF 16 µg/kg/day
≥2.0 x 10^6 CD34+ cells/kg (CD34 selected)

Reduced intensity conditioning therapy

Fludarabine 150 mg/M^2
Cyclophosphamide 50 mg/kg
TBI 2 Gy
Pre- and post-transplant prevention of complications

N-acetyl cysteine (increases hepatocyte/SEC GSH)
Ursodiol (ameliorates cholestatic injury)
Trimethoprim-sulfamethoxazole
Antibiotic
Antifungal
Acyclovir
Pre-emptive antiviral (for CMV, Adenovirus)
Immune suppression (vs. rejection and GVHD)
GVHD prophylaxis

Rationale for prophylaxis choices:
  No biologic advantage at all to having GVHD
  Prevent severe acute GVHD
  Prevent extensive chronic GVHD

Bone marrow as cell source

Prophylaxis drugs:
  Cyclophosphamide 50 mg/kg x 2
  Tacrolimus
  Mycophenolic acid enteric coated
Assessment of Crohn’s Disease activity

Timing:
- Baseline
- Day 80
- One year
- Three years
- Five years

Methods:
- Endoscopy with biopsy
- Imaging
Statistical considerations

Number of patients = 12

Primary endpoint: Event-free survival at one year (alive and free of Crohn’s Disease)

Stop the study if Transplant Related Mortality >10%:

2 deaths in first 8 patients
or
3 deaths in 9 – 12 patients
Ethical equipoise

- Life-long CD misery
- Death from CD Rx
- GVHD or death after HCT
- Long CD remission
- Cure of CD
Crohn’s Disease before and after allogeneic transplant — child with IL10R defect

before

3 months after
Progress to date

Protocol approved, FDA IND application approved, posted www.clinicaltrials.gov

Website, newspaper, M.D. letters, blogs, CCFA posting

436 completed questionnaires from CATS website

117 patients met eligibility criteria, records requested

18 complete records received

7 patients examined in Seattle (all potentially eligible)
Screening visits show eligibility

Insurance coverage

Allogeneic donor search

Autologous stem cell collection

Reduced intensity conditioning

Allogeneic bone marrow

Follow-up to 5 years
Insurance Roadblocks
We do not cover clinical trials.

We exclude transplants for autoimmune diseases.

We cover transplants only for cancer.

Independent Medical Review needed.

Crohn’s is not life-threatening.

Your disease is not on the Medicare list of approved indications for transplant.

(Too expensive—never spoken, often implied)
Insurance Ripostes
Catch 22—to publish, one has to post in www.clinicaltrials.gov.

Crohn’s is a genetic disorder of immunity, just like Wiskott-Aldrich etc., which are covered.

Aplastic anemia, thalassemia, etc., are not cancer and they are covered.

Hazard of death in patients with severe CD is much higher than age-matched controls.

Too expensive? Compared to what? Biologics plus surgeries plus hospitalization X decades of care?
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