Bone Marrow Transplantation in Crohn's Disease

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- Basics of BMT
- Rationale for how BMT might work for IBD
- Data on autologous and allogeneic transplants
- Lessons from monogenic diseases
- CHP experience
- State of the art

Inflammatory Bowel Disease

- Progress in treatment of Crohn's disease
  - TNF-α inhibitors e.g. infliximab
- Persists for life
- Current therapies are not curative
- In patients with refractory disease
  - Significantly impair quality of life
  - May be life threatening

IBD: Pathophysiology

- An **abnormal host immune response** to intraluminal antigens occurring in a **genetically predisposed individual**, with the production of chronic inflammation of the gastrointestinal tract, accompanied by tissue destruction

Martínez-Montiel et al, WJG 2014

BMT Basics

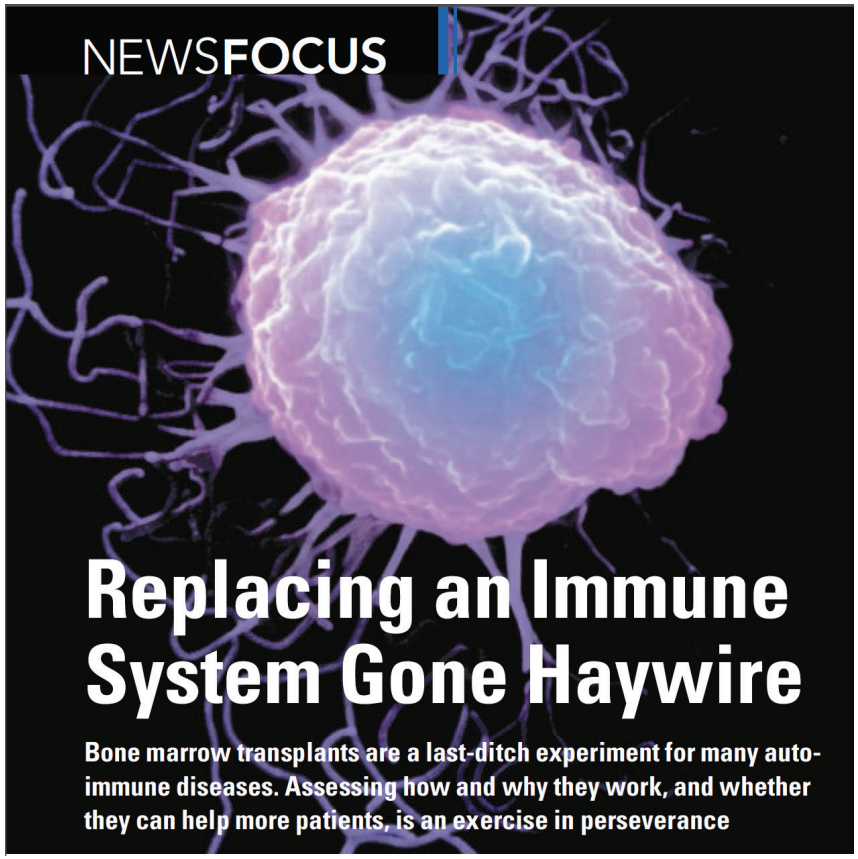
- Terminology
  - **B**lood and **M**arrow **T**ransplantation (BMT)
  - SCT, HSCT, HCT, PSCT…
- Type
  - Autologous
  - Allogeneic
- Source
  - Peripheral blood
    - G-CSF, Cyclophosphamide
  - Bone marrow
  - Umbilical cord blood
- *In vitro* manipulation
  - T-cell depletion
  - Mesenchymal stem cells

BMT Procedure

- Conditioning regimen
  - Chemotherapy, radiation, antibodies
    - Eradicate underlying disease
    - Immunosuppress the recipient
- Infusion (transplantation) of progenitor or stem cells
  - Reconstitution of hematopoiesis
    - Reset the immune system
  - Replace an abnormal but nonmalignant lymphohematopoietic system with one from a healthy donor

AUTOLOGOUS BMT

Transplants for Autoimmune Diseases: "Resetting" the Immune System



Couzin-Frankel, Science, 2010

- Thymic output generates a new and diverse TCR repertoire
- Reprogramming of autoreactive T cells
- Restoration of the $CD4^+CD25^+FoxP3^+$ lymphocytes

Auto-BMT for Coincidental Malignancy

- 1993: 41 y old woman with >20 y. fistulizing CD
  - Non-Hodgkin's Lymphoma
    - Chemotherapy and autologous BMT
      - Clinical remission at six months
- Isolated case reports of achieving remission from CD (4) and UC (1) after auto-transplanted for NHL, HD, Breast Cancer, AML
  - Remission from IBD for 2-7 years f.u.

Auto-transplant for CD

- 2003: Richard Burt et al
  - Severe CD (n =4), refractory (n=2)
  - Stem cell collection
    - Cyclophosphamide 2 g/m^2 + G-CSF
    - $CD34^+$ enrichment
  - BMT
    - Cyclophosphamide 50 mg/kg/d x4 days
    - Anti-thymocyte globulin 30 mg/kg/d x 3 days and Solu-Medrol
    - Prophylactic antimicrobials
    - Prompt blood count recovery
  - Clinical and endoscopic improvement

Autologous haematopoietic stem cell transplantation without CD34+ cell selection in refractory Crohn's disease

A Cassinotti,[1] C Annaloro,[2] S Ardizzone,[1] F Onida,[2] A Della Volpe,[2] M Clerici,[1] P Usardi,[2] S Greco,[1] G Maconi,[1] G Bianchi Porro,[1] G Lambertenghi Deliliers[2]

Gut, 2008

- Four adults with refractory CD
- Similar regimen for stem cell collection and transplant except no *in vitro* manipulation
- Clinical and endoscopic remission in 3 of 4 cases at 16.5 month follow-up

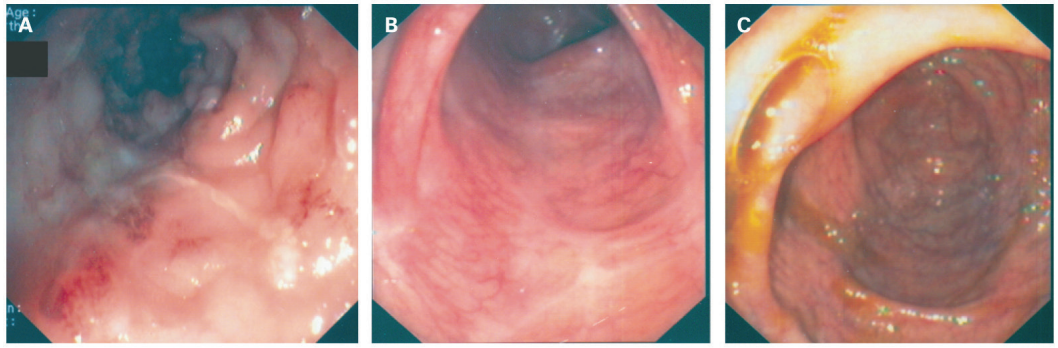


Figure 4 Endoscopic remission in case 3. A = pre-transplantation. B = 3 months post-transplantation. C = 12 months post-transplantation.

Autologous nonmyeloablative hematopoietic stem cell transplantation in patients with severe anti-TNF refractory Crohn disease: long-term follow-up

Richard K. Burt,[1] Robert M. Craig,[1,2] Francesca Milanetti,[1] Kathleen Quigley,[1] Paula Gozdziak,[1] Jurate Bucha,[1] Alessandro Testori,[1] Amy Halverson,[3] Larissa Verda,[1] Willem J. S. de Villiers,[4] Borko Jovanovic,[5] and Yu Oyama[1]

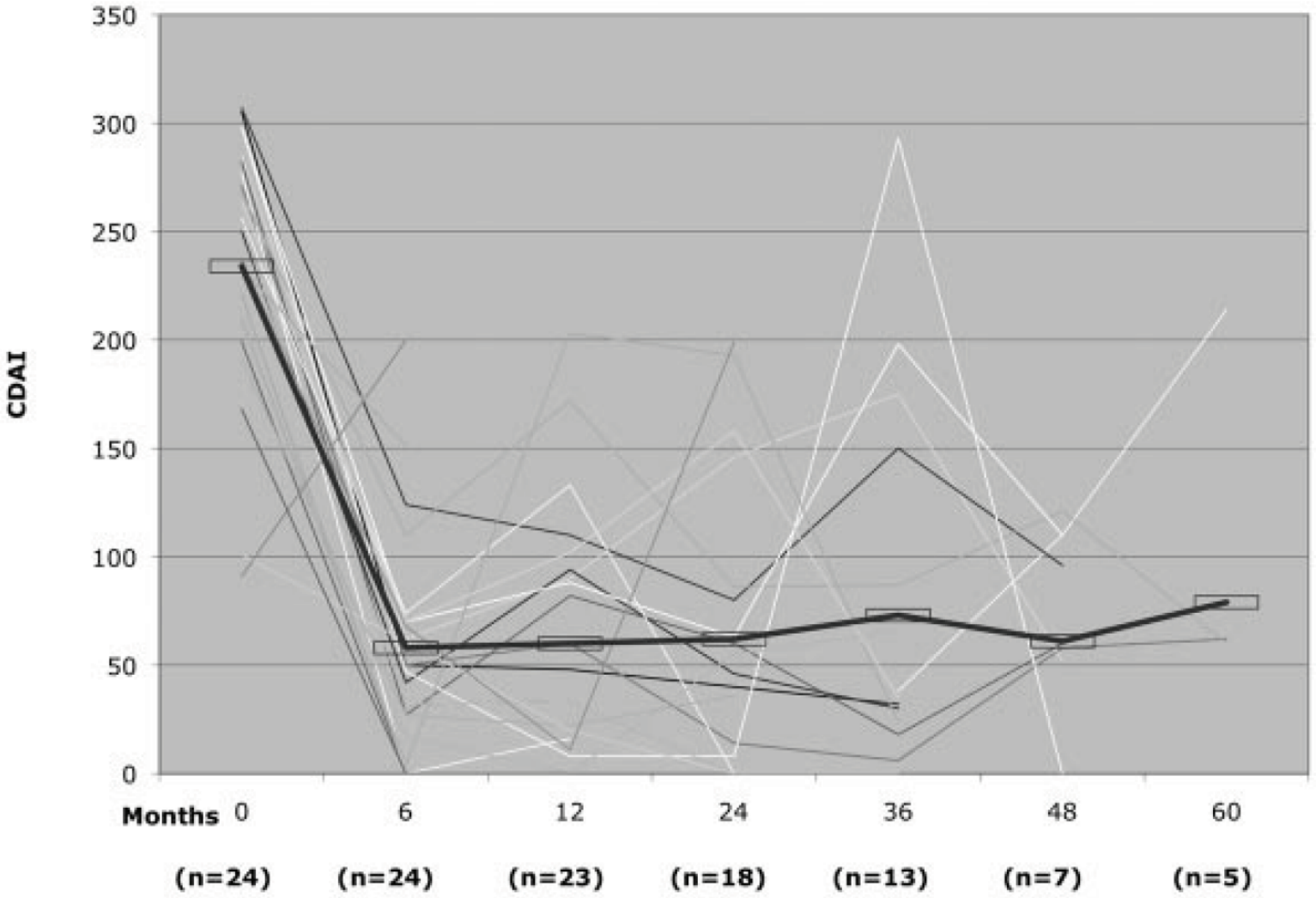
Divisions of [1]Immunotherapy and [2]Gastroenterology, Department of Medicine, and [3]Department of Surgery, Northwestern University Feinberg School of Medicine, Chicago, IL; [4]Division of Digestive Diseases and Nutrition, University of Kentucky Medical Center, Lexington, KY; and [5]Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL

We evaluated the safety and clinical outcome of autologous nonmyeloablative hematopoietic stem cell transplantation (HSCT) in patients with severe Crohn disease (CD) defined as a Crohn Disease Activity Index (CDAI) greater than 250, and/or Crohn Severity Index greater than 16 despite anti–tumor necrosis factor therapy. Stem cells were mobilized from the peripheral blood using cyclophosphamide (2.0 g/m^2) and G-CSF (10 μg/kg/day), enriched ex vivo by CD34$^+$ selection, and reinfused after immune suppressive conditioning with cyclophosphamide (200 mg/kg) and either equine antithymocyte globulin (ATG, 90 mg/kg) or rabbit ATG (6 mg/kg). Eighteen of 24 patients are 5 or more years after transplantation. All patients went into remission with a CDAI less than 150. The percentage of clinical relapse-free survival defined as the percent free of restarting CD medical therapy after transplantation is 91% at 1 year, 63% at 2 years, 57% at 3 years, 39% at 4 years, and 19% at 5 years. The percentage of patients in remission (CDAI < 150), steroid-free, or medication-free at any posttransplantation evaluation interval more than 5 years after transplantation has remained at or greater than 70%, 80%, and 60%, respectively. This trial was registered at www.clinicaltrials.gov as NCT0027853. (*Blood*. 2010;116(26): 6123-6132)

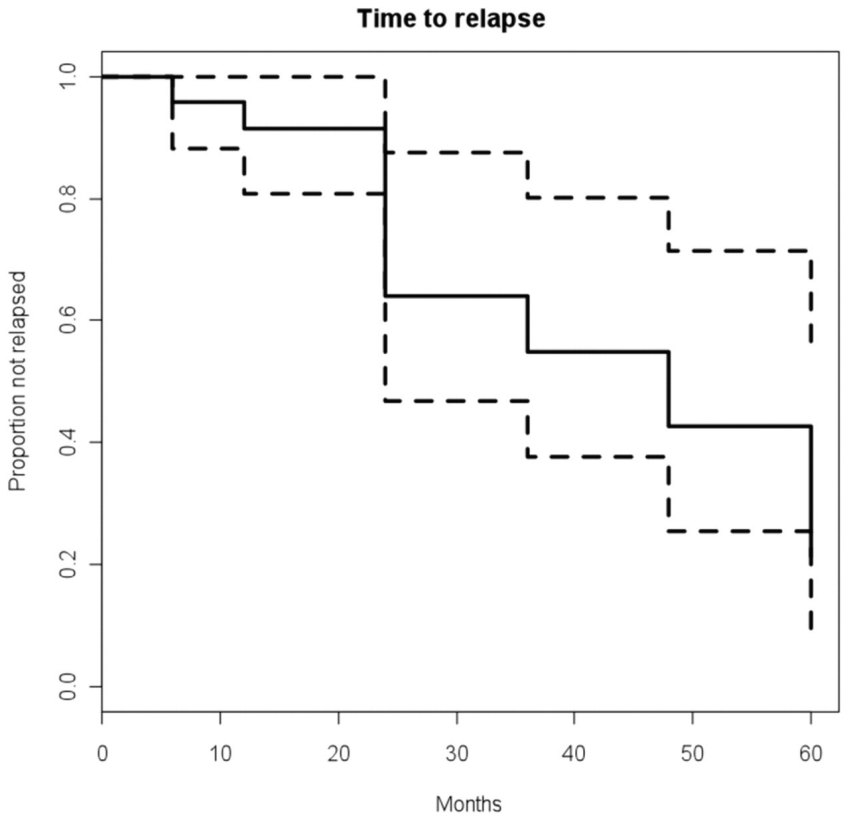
Burt et al: Methods & Results

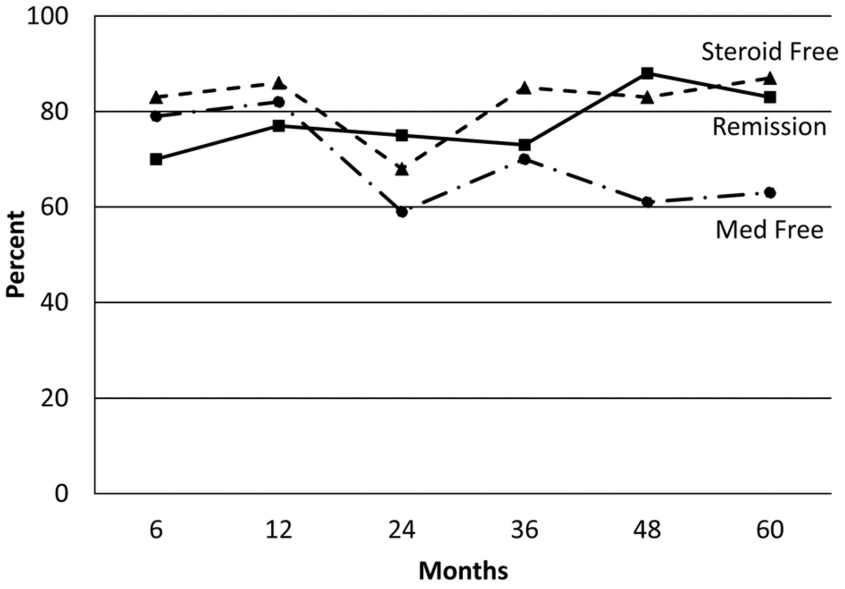
- Chronic active CD patients refractory to conventional therapies including anti-TNF inhibitor
- 24 patients
  - Age 15-52 years (mean, 27 y)
  - 17/24 (71%) prior surgeries
  - 18/24 (75%) fistulae
- Mean: duration 10 y, CDAI 253, CSI 23
- $CD34^{+}$ cell dose: 6.35 million/kg
- ANC and platelet engraftment: 9 days
- Transplant course: fevers, bacteremia, transfusions
- No transplant-related deaths (one death from accident)

Crohn's Disease Activity Index



Relapse-free Survival





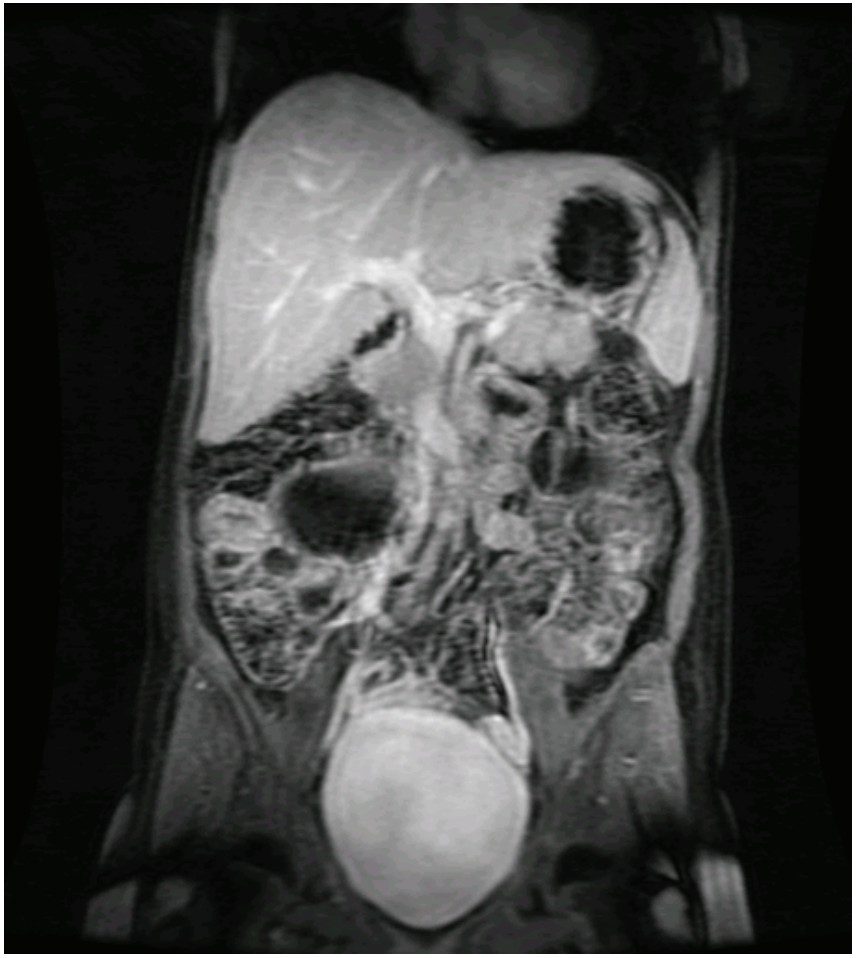
ASTIC Trial

(Hawkey et al, Broad Foundation 2013)

- Autologous Stem Cell Transplantation International Crohn's Disease trial (n=47)
  - 23 early and 24 late transplant
- Cytoxan 4 g/m^2 mobilization, unselected graft, rabbit ATG
- One death after Cy, neutropenic sepsis, organ failure, VOD
- CDAI 324 >161 vs. 351 >272
- CDEIS 18>5 vs. 14 >9
- Normal CDAI, CDEIS, no drugs at one y , 3 vs. 1 pt.

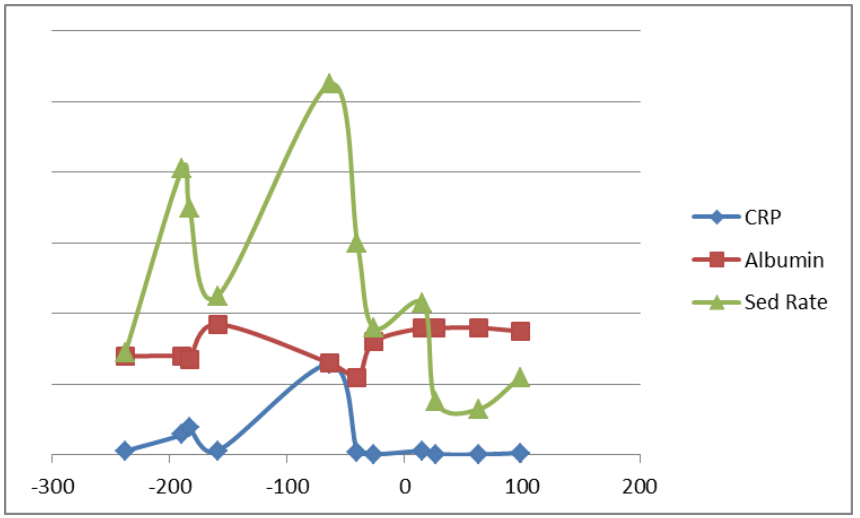
CHP: Refractory Crohn's Disease

- 16-year old
- 6 years history: Duodenitis, gastritis, ileitis, colitis
- Steroids, 6-MP, infliximab, adalimumab, certolizumab, natalizumab
- Volvulus, stricture, small and large bowel resection



Autologous Transplant

- Pancytopenia
  - Neutropenia x 9 days
  - Red cell and platelet transfusions
- No fevers
  - Bacillus species
- Fluconazole
- Pentamidine
- CMV –asymptomatic reactivation



CHP Experience: Preliminary

- Pediatric trial
  - Chicago study design
  - Miltenyi $CD34^+$ enrichment
  - Stringent eligibility, GI decision
    - Referrals 28
    - Evaluated 11
    - Transplanted 3

- 16 y, F. Clinical remission 16 months. Partially responsive to infliximab
- 25 y, M. Persistence disease. Very good response to infliximab
- 11 y, F. Transient improvement. Colectomy. Still severe perianal disease

Autologous BMT: Place in therapy

- Chronic active refractory
- High early response rate
- May again become responsive to anti-TNF therapy
- Life-threatening disease
- Acute toxicity
- Mortality
- Late potential effects
  - Fertility
  - SMNs
- Loss of response over time
  - Not curative
- Definitive study
  - Best patients for response
  - Cost, insurance approval
  - Competition!

ALLOGENEIC BMT

Allogeneic HCT: Rationale

- The risk of Crohn's disease has a large genetic component
  - Many identified genes are involved in immune or inflammatory processes
- Allogeneic BMT successful to treat primary immunodeficiency diseases with colitis
- Case reports of benefit with transplant for malignancies

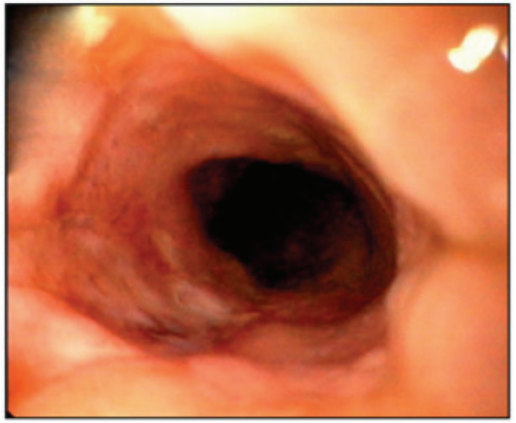
Allogeneic BMT can cure patients with Crohn's disease by immune reconstitution from a healthy donor

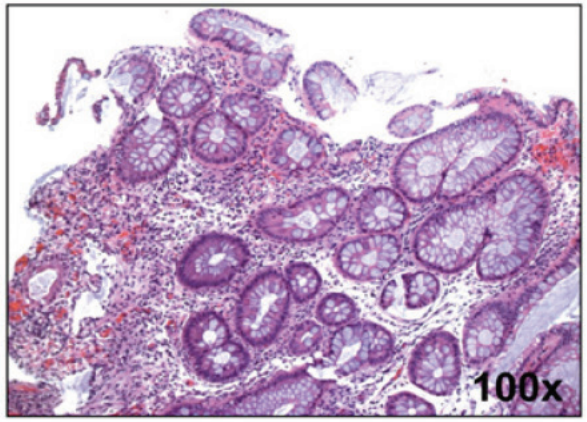
Allotransplants for Malignancies

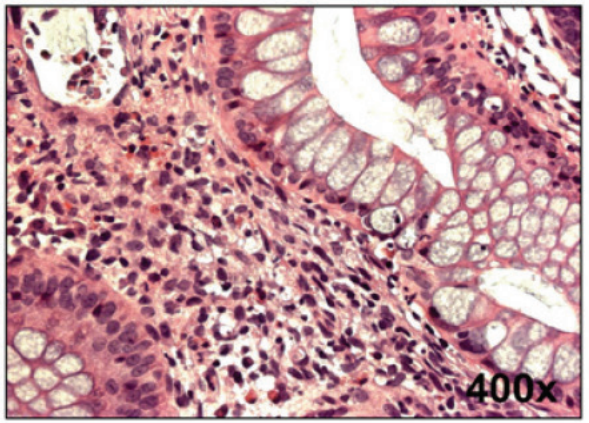
- Seattle (Lopez Cubero et al, Gastroenterology 1998)
  - 4/5 elimination of CD
  - 1/5 graft rejection, recurrent CD
- Essen (Ditschkowski et al, Transplantation 2003)
  - 7/7 elimination of CD

IL-10 Deficiency, n=16, Kotlarz et al.

- Onset in first three mo.
  - IL-10 (3), IL-10RA (5), IL-10RB (8)
- Failure to thrive, recurrent fevers and infection, bloody diarrhea, abscesses, perianal fistula, oral aphthous lesions, folliculitis, arthritis
- Normal T- and B-cell functions
- IST, ileostomy, colostomy, resections, no sustained remission







Allogeneic BMT, n=5

- Alemtuzumab, fludarabine, treosulfan, and thiotepa
- GVHD: CsA + MMF
- Gut decolonization
- Sib (2), Unrelated (3)
- Bone marrow (4)

  PB (1)

- One 2nd BMT, one DLI for mixed chimerism, one stem cell boost
- Viral infections
- Three acute GVHD
- No deaths
- Four sustained remission at 2 years f.u.

IL-10 Deficiency, n=9, Engelhardt, et al.

- 6 of 9 identified patients with IL-10 / IL-10R deficiency DID NOT undergo HSCT:
  - Severe IBD with perianal disease refractory to immunosuppressive therapy, all requires surgical interventions
- 3 of 9 underwent HSCT:
  - Sustained IBD remission including resolution of fistulas, improved general nutrition/weight gain, all survived

IL-10 Deficiency: Summary

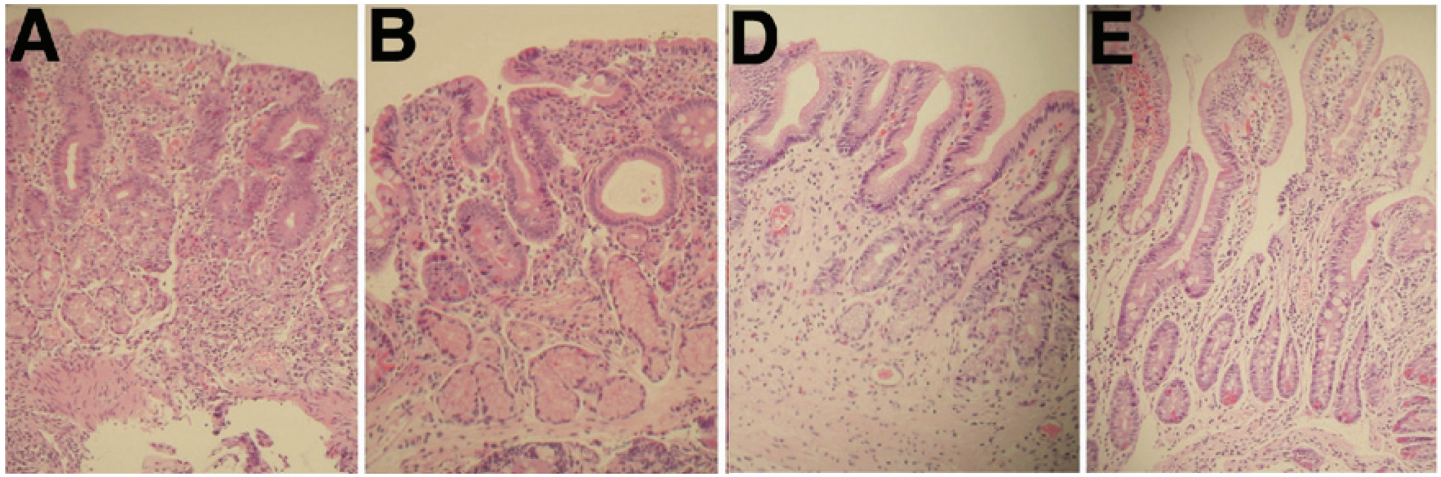
- Very-early-onset IBD
  - Severe colitis, perianal, fistulizing disease
  - Refractory to Rx
  - Risk of lymphoma
- Allogeneic BMT
  - IL-10 signaling in hematopoietic cells is to control gut inflammation
  - Should be considered early in the course
- North American experience: majority not consanguineous, IL-10 deficiency not as apparent, look for other monogenic diseases
  - A recent case with fistulizing Crohn's, DLBCL, Relapse, plan for auto-
    - IL-10RB mutations, MUD BMT

Immune Dysregulation Can Present with Enteropathy, Colitis

- Chronic granulomatous disease: Recurrent sinopulmonary infections and/or skin abscesses
- IPEX syndrome (Immune dysregulation, polyendocrinopathy, enteropathy, X-linked): autoimmune symptoms such as rash, abnormal pancreatic or thyroid function
- XIAP/XLP-2 (X-linked inhibitor of apoptosis / X-linked lymphoproliferative disease): can manifest as IBD, HLH, abnormal lymphoproliferation, lymphoma
- NEMO (NFκB essential modifier) deficiency: ectodermal dysplasia, recurrent infections, hypogammaglobulinemia

Intractable Ulcerating Enterocolitis of Infancy

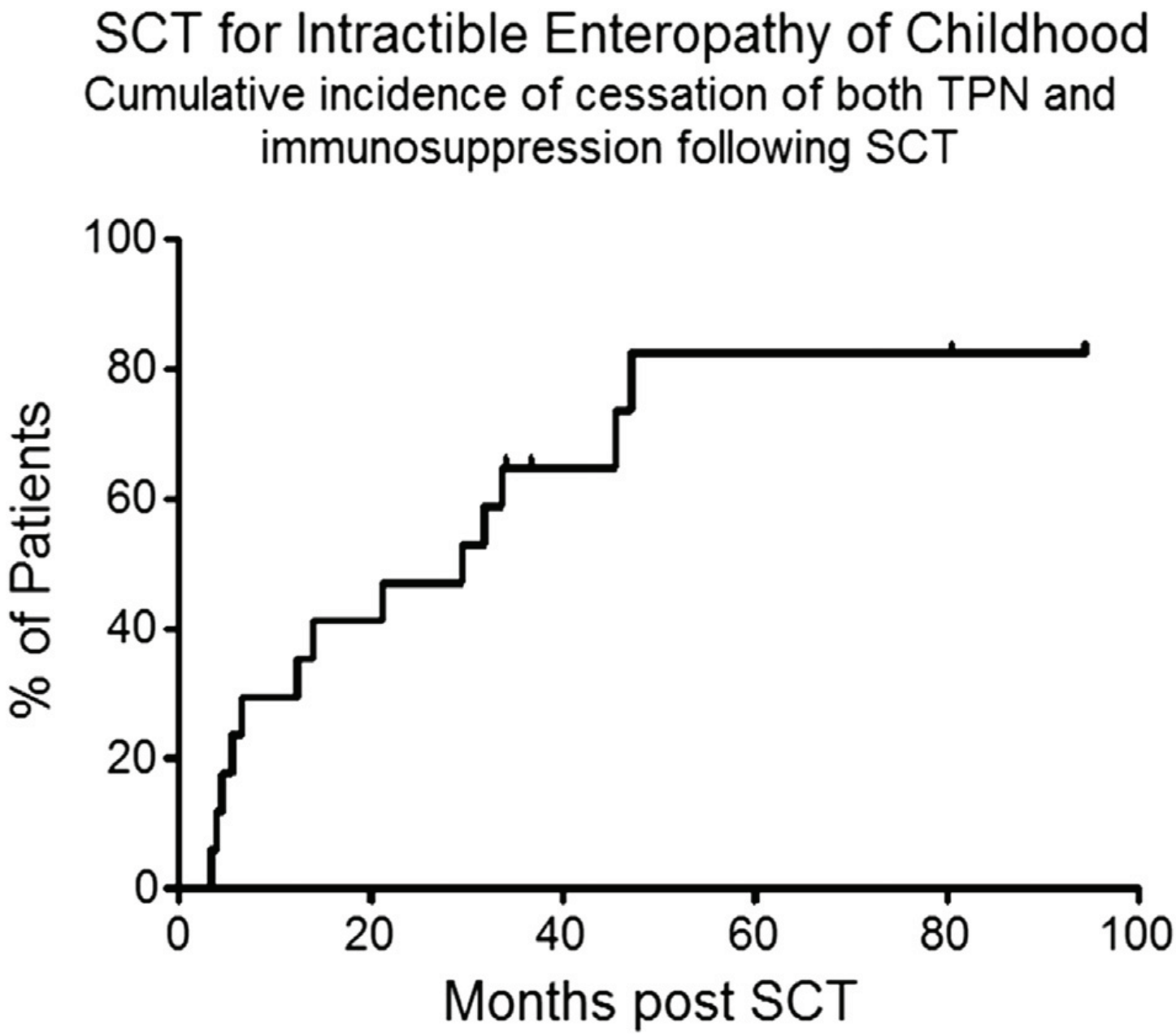
- Onset at 6 months, EBV-PTLD at 4 y, URD BMT after fludarabine-melphalan-alemtuzumab
  - All donor, reversal of ileostomy, remission at 5 y
- Similar outcome in sibling, at 3 y



Thapar, 2008

Allo-BMT for Intractable Childhood Enteropathy, Worth et al, 2014

- 26 patients (1999 -2013)
  - Failed IST (13), TPN (13), surgery (11)
- Mutations: IPEX, XIAP, IL10, IL10Ra (8), not known (18)
- 22 matched, 5 mismatched transplants
  - Flu-Mel-Alem
- Six deaths: Conditioning, GVHD, Viral infections, PTLD
- 19 alive, 17 sustained improvement, 89% off TPN and 100% off IST
- Cure even in in the absence of a defined genetic defect



Worth, Tandem 2014

CROHN'S ALLOGENEIC TRANSPLANT STUDY

www.CATS-FHCRC.org

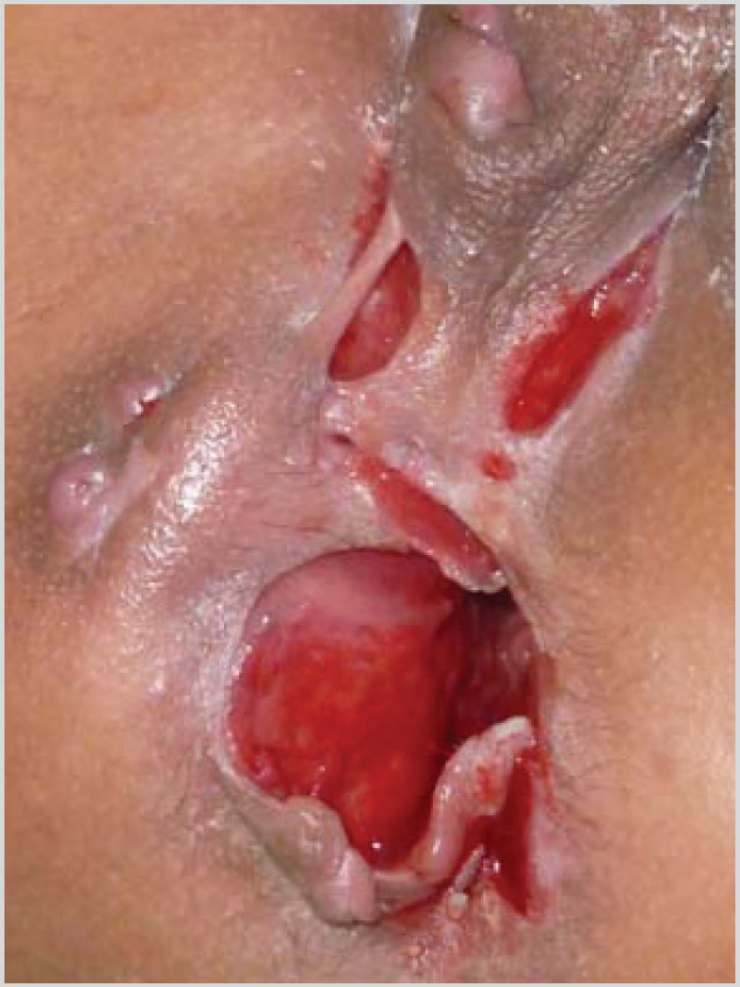
Dr. McDonald & Georges, 2013

Transplant Protocol

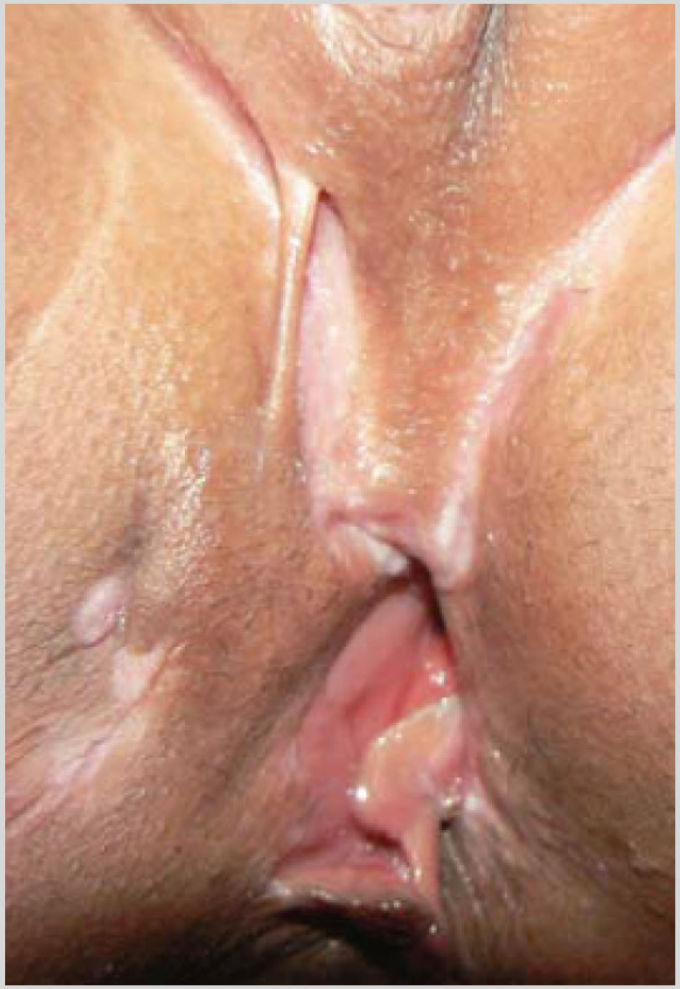
- Fludarabine, cyclophosphamide, 2 Gy TBI
- Bone marrow as stem cell source
- Posttransplant Cy, Tacrolimus, MPA, G-CSF
- Target =12 patients (18-60 y)
  - 500 completed online questionnaire
    - 145 eligible
      - 18 complete records
        - » 11 evaluated

Dr. McDonald & Georges, 2013

Crohn's Disease before and after allogeneic transplant — child with IL10R defect



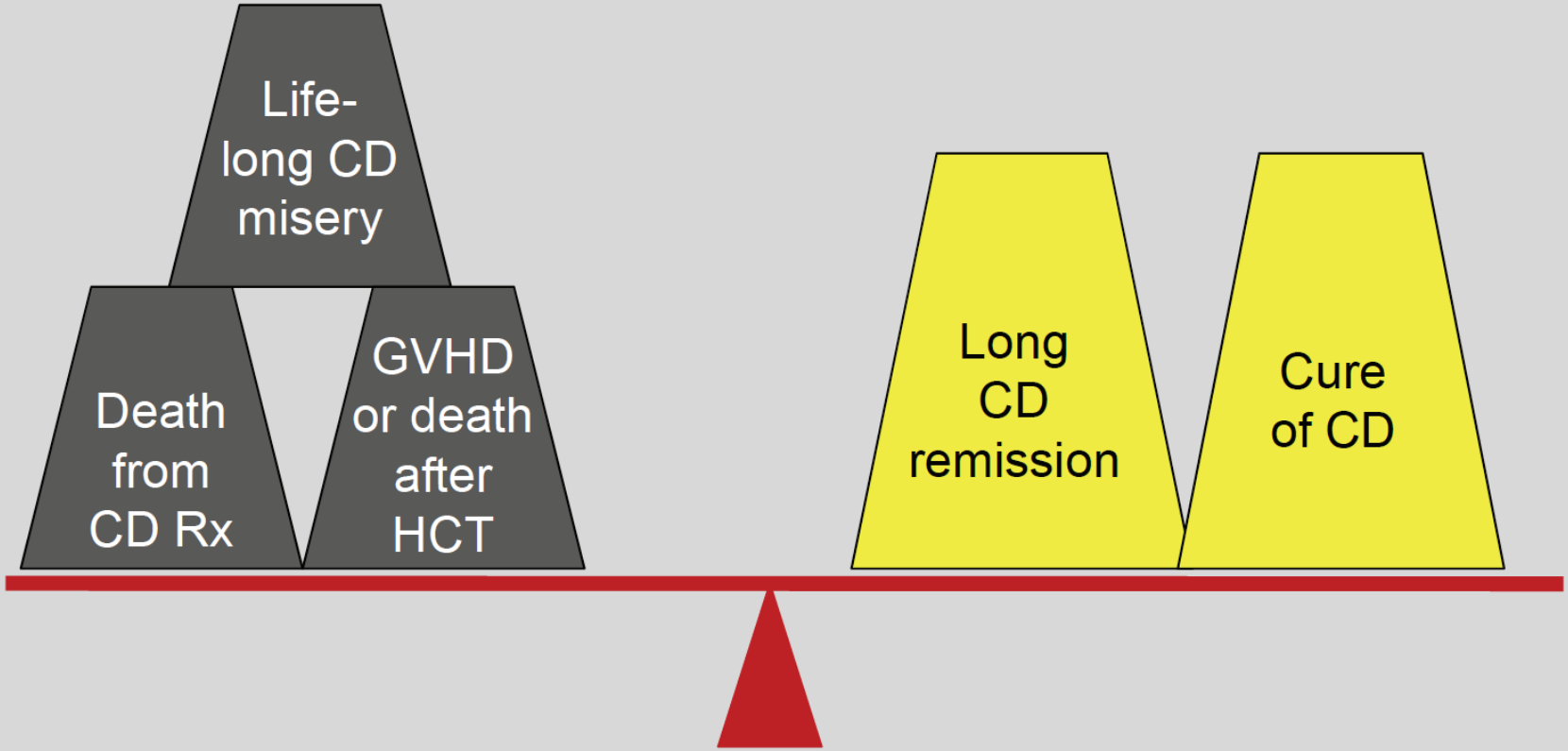
before



3 months after

Dr. McDonald & Georges, 2013

Ethical equipoise



Dr. McDonald and Georges, 2013

Allogeneic BMT: Place in Therapy

- Rare Mendelian variants with intestinal inflammation
  - IL-10 genes, XIAP, HLH, IPEX, WAS, CGD, CVID
  - NEMO?
- Intractable enteropathy, colitis without defined mutation
  - Early onset
  - Familial?
- Refractory Crohn's
  - Clinical trial to address
    - Disease control
    - Best candidates
    - Survival
    - Place in therapy

TEŞEKKÜR EDERİM