Hematopoietic Cell Transplantation

basal findings

Miroslav Tomíška

Internal Medicine, Block 4

5th year students

Interní hematologická
a onkologická klinika
FN Brno a LF MU

Terminology
of hematopoietic cell transplantation

- **Originally Bone Marrow Transplantation, BMT**
  - the source of hematopoietic cells was bone marrow
  - BMT has remained the title of scientific journal
- **Hematopoietic cell transplantation, HCT**
  - reflects the availability of peripheral blood stem cells
  - HCT covers other sources of stem cells
  - hematopoietic stem cell transplantation, HSCT
- **Autologous stem cell transplantation**
  - autologous peripheral blood stem cell transplantation, auto-PBSCT

History of HCT

- **Research to treat radiation sickness in 1950s**
  - potential of total body irradiation to treat leukemia
- **Discovery of HLA-system 1960s**
- **Discovery of cyclosporin A 1970s**
- **First publication of 100 transplanted patients from Seattle 1977** (Edward Donnall Thomas)
- **Allogeneic HCT routinly used from 1980s**
- **Autologous PBSCT from 1990s**

Main features of autologous and allogeneic HCT

Autologous	Allogeneic
donor and recipient is the same person	donor is another person, related or unrelated
no immune problem no immunosupression	immune difference immunosupresion necessary
high-dose chemotherapy is the main effect	immune treatment effect graft versus tumor efect, GvT
	risk of GvHD higher risk of infection
frozen graft	mostly native graft

Other types of HCT

- **Syngeneic transplantation (allogeneic)**
  - from identical twin
  - no GvT, higher risk of relaps
- **Haploidentical transplantation**
  - family donor, identical in only 1 haplotype
  - mainly if no other donor is available
  - requires specific immunosupression
- **Cord blood transplantation**
  - low number of hematopoietic cells for adult transplantation

Collection of hematopoietic cells

preparation of the graft

- **Bone marrow collection** (from illiac bones)
  - no stimulation, general anesthesia, 1 night hospital stay
  - 1000 mL of bloody marrow: centrifugation
  - collection of buffy coat (between red cells and plasma)
  - return of red cell mass to the donor
- **Peripheral blood stem cell collection**
  - bone marrow stimulation necessary (several days)
    - G-CSF (healthy donors for allogeneic HCT)
    - cytotoxic regimenn + G-CSF (for autologous SCT)
  - blood cell separation (extracorporal centrifugation)
  - buffy coat removal (CD34+ cells), plasma and RC return

Different types of allogeneic HCT

Various combinations for transplant treatment	
related family donor typically sibling	unrelated donor from a register
HLA identical donor 5/5 identity	HLA non-identical donor 1 or 2 missmatches
myeloablative conditioning	non-myeloblative needs more immunosupression
peripheral blood stem cells	bone marrow cells

Total Body Irradiation, TBI

as part of conditioning prior HCT

- **Effects** of **TBI** in conditioning prior to **alloHCT**
  - cytotoxic effect (anticancer tratment effect)
  - imunosupression
  - spacing effect in bone marrow
- **Doses of TBI in HCT**
  - **myeloablative dose 12-15 Gy**, 8-12 fractions, 4 days
  - **low-dose TBI 2-8 Gy**, 1-4 fractions
- **Regimens currently used in this dept**
  - myeloablative 10 Gy (5 fractions by 2 Gy)
  - non-myeloablative 4 Gy or only 2 Gy
- **Conditioning need not contain TBI**

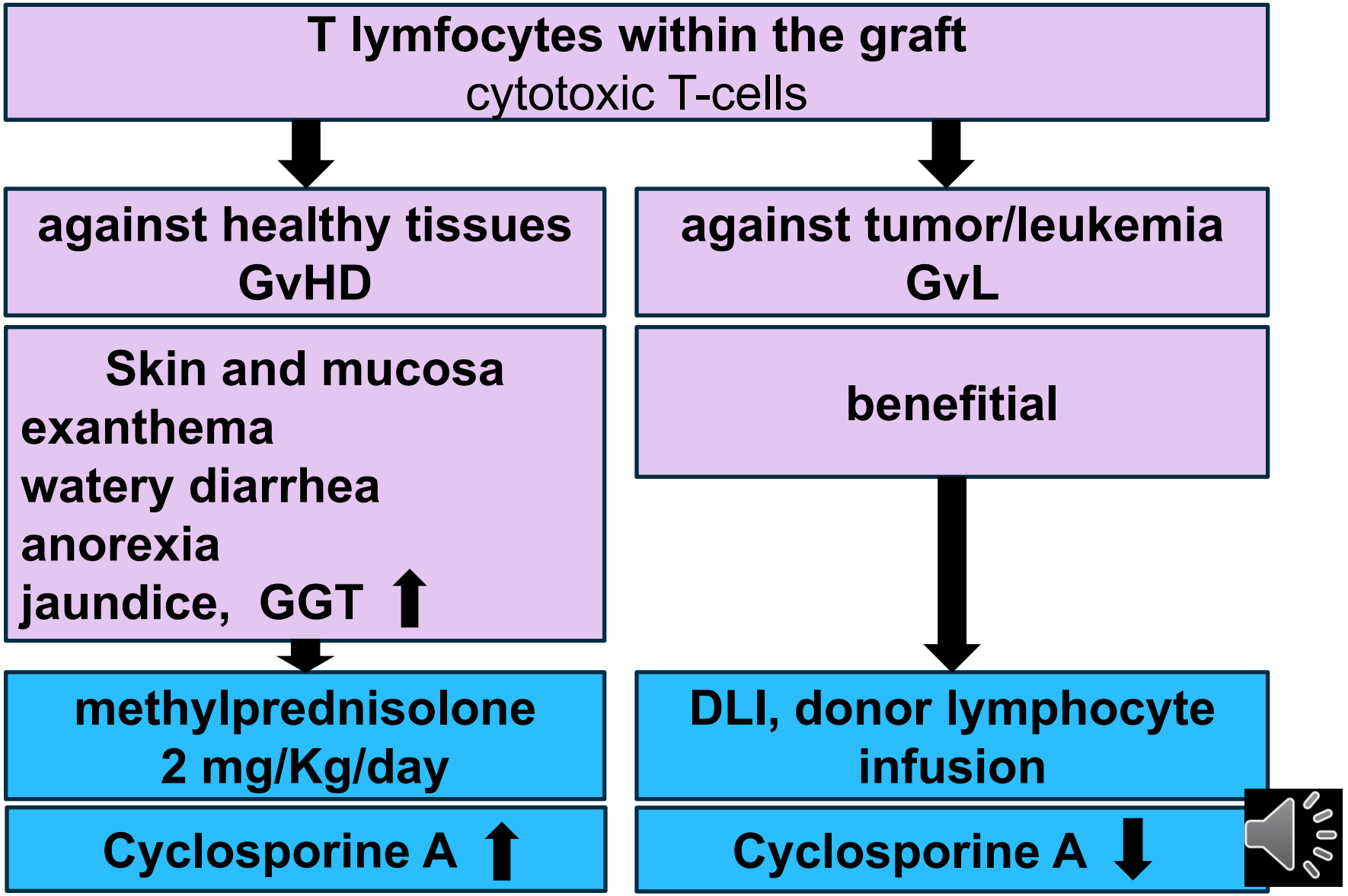
Immunosupression in alloHCT

starts as prophylaxis since conditioning

- **Anti-thymocyte globulin, ATG**
  - rabbit globulin, halflife 20 days
  - inhibition of human T-lymfocytes
  - i.v. infusion, risk of reaction - requires prophylaxis
  - part of conditioning
- **Cyclosporin A (CsA) i.v. or capsules**
  - calcineurin inhibitor, inhibits T-lymphocyte activation
  - starts prior to transfusion of the graft
  - continues for several months
- **CsA is usually combined** (2-drug regimen)
  - methotrexate (MTX) Day +1, +3, +6, +11
  - mycophenolate mofetil

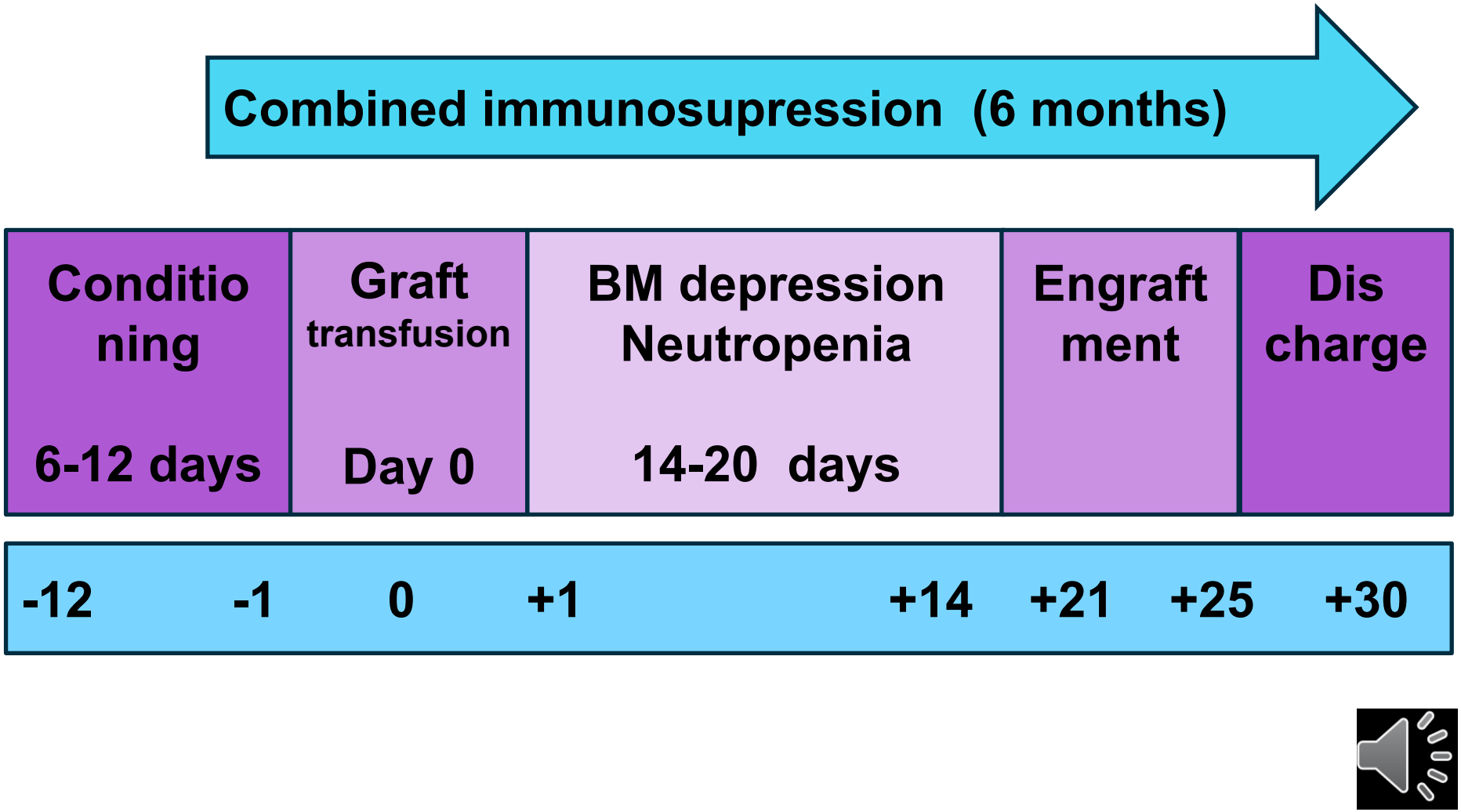
Immune effect of the graft

is mediated by cytotoxic T-lymfocytes



Arrangement of allogeneic HCT

model situation



Main reasons for allogeneic HCT

- **Acute leukemia (AML, ALL)**
  - after prior induction and consolidation chemotherapy
- **Myelodysplastic syndrome**
  - sometimes as first-line treatment
- **Chronic lymphoproliferation**
  - malignant lymphoma, CLL
  - mostly after failure of prior treatment
- **CML**
  - after failure of targeted therapy with TKIs
- **Aplastic anemia** (nonmalignant disease)

Non-myeloablative regimens, NMR
characteristics and advantages

- **Lower total dose of cytotoxic drugs/TBI**
  - lower side effects, lower toxicity
  - myeloablative regimens are suitable up to 40 yr
- **NMRs are good options for**
  - patients > 40 yr, up to 65 yr
    decreased organ function reserves compared to young pts.
  - comorbidity (chronic disease)

Specific complications after **allo HCT**
may be lifethreatening and may cause death

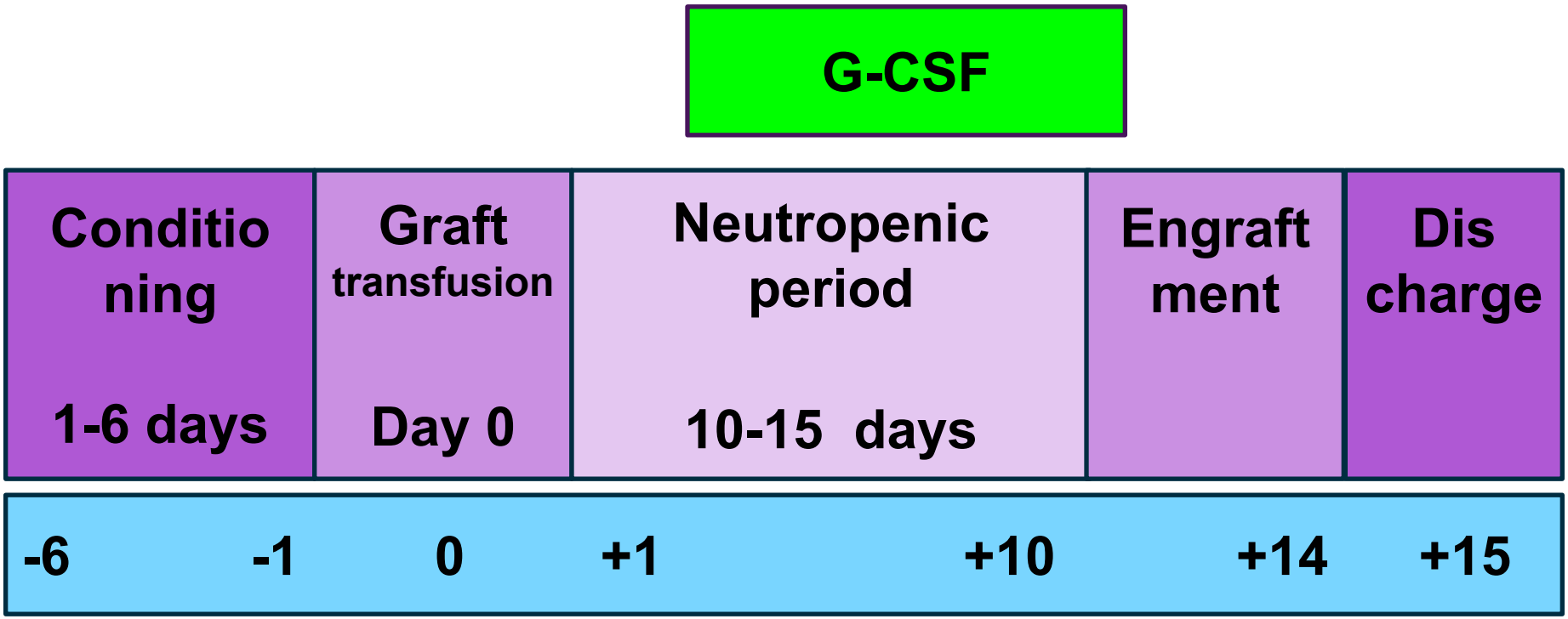
- **Mucositis** (mucosal toxicity of conditioning)
  - oropharyngeal
  - gastrointestial (both can be severe)
- **Veno-Occlusive Disease, VOD**
  - Sinusiodal Obstructive Syndrome, SOS
- **Infections owing to prolonged neutropenia and immunosuoression**
  - bacterial, including sepsis
  - deep fungal (tissue) infection (invasive)
  - viral
- **Acute Graft versus Host Disease, GvHD**

Principals of autologous PBSCT

- **High-dose chemotherapy (HD chemo)**
  - brings all treatment effect
  - qualitatively higher as compared to conventional dose
  - overcomes heterogeneity od tumor tissue
    - areas/cells with lower chemosensitivity
  - high dose of cytotoxic agents kill much more cancer cells
  - alkylating agents are suitable for HD treatment
- **Transfusion of stem cells (graft) is supportive**
  - enables to overcome myelotoxicity of HD chemo
  - auto PBSCT is only suitable for chemosensitive tumors

Arrangement of autologous HCT

model situation



Main reasons for **autologous PBSCT**

transplantation is not the option for advanced disease

- **Malignant lymphoma**
  - only after failure of 1st line treatment
  - requires to use salvage regimen prior to autoPBSCT
  - reduction of tumor burden confirms chemosensitivity
- **Multiple myeloma**
  - used routinely after several cycles of 1st line treatment
  - up to 70 yr in good biological age
  - High Dose (HD) melphalan for conditioning
  - prolongs life, but is not curative
- **Exceptionally acute leukemia**
  - if unsuitable for allo HCT

Antimicrobial therapy in HCT

- **Prophylaxis in HCT**
  - pneumocystis jiroveci (carinii): co-trimoxazole
  - herpes viral infections: aciclovir
  - fungal infections: fluconazole or posaconazole
- **Preemptive treatment**
  - PCR confirmation of CMV reactivation
    positive laboratory tests with no clinical signs
- **Empirical treatment due to clinical sings**
  - antibacterial: from diagnosis of FN / sepsis
  - antifungal: Day 5-7 in persistent fever/signs
- **Treatment of proved infection**

Invasive Fungal Infections, IFIs

Invasive Fungal Disease IFD

- **Possible IFD**
  - host factors and clinical signs (without mycological evidence)
- **Probable IFD**
  - host factors identifying the patient at risk
  - clinical signs/symptoms consistent with IFD
    halo sign/air-crescent sign/cavity on pulmonary HRCT scan
  - mycological evidence
    culture or microscopic analysis
    indirect tests: antigen detection (galactomannan, glucan)
- **Proven IFD**
  - histological analysis
  - culture of a tissue specimen from the site of disease

Oropharyngeal mucositis in HCT

presentation and treatment

Symptoms/signs: mouth pain, stomatitis, mucosal ulceration, dysphagia, salivation, acumulation of mucus, aspiration

- **Pain management**
  - opioids, continuously
  - NSAIDs, short infusions (prior to meals), around the clock
- **Rinses of the mouth**
  - benzydamin (locally acting NSAID)
  - antiseptics (chlorhexidine, povidon iodine)
  - calcium phosphate precipitating formulation
- **Nutritional support**
  - ONS for sipping
  - parenteral nutrition

Gastrointestinal mucositis in HCT

presentation and treatment

Symptoms/signs: diarrhea, flatulence, abdominal pain, crampi, nausea, vomiting

- **Treatment of diarrhea**
  - loperamide, diphenoxylate
  - octreotide (somatostatin analgue)
  - fidaxomycin in Clostridium difficile infection
- **Pain management**
  - peripheral analgetics, spasmolytics
  - opioids
- **Nutritional support**
  - total parenteral nutrition

The End