



Fundamentals of Hematopoietic Stem Cell Transplantation Training Course

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Brought to you by the National Marrow Donor Program (NMDP) System Capacity Initiative Pharmacy Workgroup in Partnership with the American Society of Blood and Marrow Transplantation (ASBMT) Pharmacy Specialty Interest Group (SIG)

The field of hematopoietic stem cell transplantation (HCT) continues to advance rapidly. Starting work in this area can be quite intimidating for new practitioners. The "Fundamentals of Hematopoietic Stem Cell Transplantation" training program is designed to provide a new practitioner with the rudimentary skills required to care for patients undergoing HCT. This course will focus on therapeutic management of HCT patients. Practitioners new to the field of HCT will derive benefit from this coursework, including pharmacists, registered nurses, advanced practice professionals, and medical oncology fellows.

The course will be held in conjunction with the BMT Tandem Meetings on February 13th - 14th, 2013 at the Salt Palace Convention Center, Salt Lake City, Utah.

The registration cost to participate in the 2-day meeting is \$400 for ASBMT members and \$600 for non-ASBMT members.

Attendees will be provided with detailed printed materials from each session. The registration cost includes breakfast, beverages during the breaks, and lunch each day. Participants are responsible for their own travel and hotel arrangements. This meeting is a stand-alone meeting from the BMT Tandem Meetings and does not provide admittance to that meeting which requires a separate registration.

You can register for the course at:

<https://www.eiseverywhere.com/ereg/newreg.php?eventid=43345&>

If you are unable to attend the meeting, but would like a copy of the printed materials, they will be available for \$275 (ASBMT members) and \$375 (non-ASBMT members) following the live program. The printed materials will include slides and detailed handouts from the live program, as well as, topics not covered during the live program.



Fundamentals of Hematopoietic Stem Cell Transplantation

Course Agenda

Time	Day 1	
Meeting Moderator AM Day 1: Helen Leather, B.Pharm		
08:00 – 10:00	Introduction to HCT	Susannah Koontz
10:00 – 10:15	BREAK	
10:15 – 11:15	Mobilization	Kelly Gregory
11:15 – 11:45	Preparative Regimens	Cathryn Jennison
11:45 – 12:15	Antiemetics	Amber Bradley
12:15 – 13:00	LUNCH	
Meeting Moderator PM Day 1: Tippu Khan, Pharm D, BCOP		
13:00 – 14:00	Indications for HCT	LeAnne Kennedy
14:00 – 14:30	Mucositis/Nutrition	Kristin Held
14:30 – 14:45	BREAK	
14:45 – 15:15	SOS	Angela Hsieh
15:15 – 15:45	TA-TMA	Kelly Gregory
15:45 – 17:00	Infections – Bacterial	Rebecca Tombleson

Time	Day 2	
Meeting Moderator Day 2: Ashley Morris Engemann, Pharm D, BCOP		
08:00 – 09:00	Infections – Fungal	Zahra Mahmoudjafari
09:00 – 10:00	Infections – Viral	Kristin Held
10:00 – 10:15	BREAK	
10:15 – 12:15	GVH D – Acute	Ryan Bookout
12:15 – 13:00	LUNCH	
Meeting Moderator Day 2: Helen Leather, B.Pharm		
13:00 – 14:00	GVHD – Chronic	Ryan Bookout
14:00 – 15:00	Pulmonary Complications (DAH/IPS/BOOP/BOS)	Amber Bradley
15:00 – 15:15	BREAK	
15:15 – 17:15	Long Term Complications	Angela Hsieh
17:15 – 17:45	Post HCT Strategies (including DLI)	Kamakshi Rao

Chronic Graft-Versus-Host Disease
Ryan N. Bookout, PharmD, BCOP, BCPS
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I. Objectives

1. Discern the differences between “classic” acute graft-versus-host disease (aGVHD), persistent aGVHD, “classic” chronic graft-versus-host disease (cGVHD) and overlap syndrome
2. Identify risk factors for cGVHD
3. Compare and contrast the proposed differences in pathophysiology of acute graft-versus host disease aGVHD and cGVHD
4. Differentiate between the clinical manifestations and presentation of cGVHD
5. Understand the differences between the Seattle classification system and the current National Institute of Health (NIH) Clinical and Global Scoring System
6. Devise treatment plans for organ specific cGVHD
7. Devise ancillary and supportive care treatment plan for organ specific cGVHD
8. Differentiate toxicities associated with cGVHD therapies
9. Identify monitoring plan for cGVHD complications

II. Self-Assessment Question(s)

HF is a 46 year-old female currently day +205 status post a matched unrelated donor hematopoietic stem cell transplant (HSCT) for acute lymphoblastic leukemia. Her donor was a 25 year-old female with a 10/10 match. Both HF and the donor were CMV negative and HF’s course is without any signs/symptoms of acute GVHD (aGVHD). In clinic today, she is noted to have sclerotic changes to her bilateral forearms covering palm-sized areas. She complains that she just doesn’t sweat like she used to when she bikes her 10 miles daily. Her husband relays that she is using lubricating drops all the time. HF confesses to new onset excessive dry eyes with some photophobia to bright sunlight.

1. What classification of GVHD does she have?
 - a. Classic acute GVHD
 - b. Persistent recurrent acute GVHD
 - c. Classic chronic GVHD
 - d. Overlap syndrome
2. What risk factors dose HF that may reduce her risk of developing cGVHD?
 - a. Previous acute GVHD
 - b. Bone marrow HSCT
 - c. CMV positive
 - d. HLA mismatched unrelated donor

Table 1. Time frame of Acute GVHD²

Category	Time of symptoms post HSCT or Donor Lymphocyte Infusion (DLI)	Presence of Acute GVHD features	Presence of Chronic GVHD features
Acute GVHD			
Classic acute GVHD^A	≤ 100 days	Yes	No
Persistent, recurrent, or late-onset GVHD (no cGVHD diagnosis)^B	>100 days	Yes	No
Chronic GVHD			
Classic chronic GVHD (no current aGVHD diagnosis)^C	No time frame	No	Yes
Overlap syndrome^D	No time frame	Yes	Yes
<p>A. Characterized by maculopapular rash, nausea, vomiting, diarrhea, ileus, anorexia or cholestatic hepatitis occurring within 100 days of transplantation or DLI (without signs or symptoms of cGVHD)</p> <p>B. Features of classic aGVHD without distinctive manifestations of cGVHD occurring beyond day 100 after HSCT or DLI</p> <p>C. Classic cGVHD without features of aGVHD</p> <p>D. Features of both acute and chronic GVHD appearing together</p>			

2. Although acute GVHD does not differ significantly among recipients of HLA-identical sibling bone marrow (BM) versus PBSC, the cumulative incidence of chronic GVHD (and extensive GVHD) is higher in those who received PBSC (73% vs. 55%)⁴
3. Chronic GVHD is observed in:⁵
 - i. 33% of HLA-identical sibling transplantations
 - ii. 49% of HLA-identical related transplantations
 - iii. 64% of matched unrelated donor transplantations
 - iv. As high as 80% in 1-antigen HLA-nonidentical unrelated transplantations
4. Improvements in prevention and treatment of aGVHD have not borne out protection for patient developing cGVHD²

V. *Risk Factors/Predisposing Factors^{6,7}

1. Established risk factors
 - i. Prior acute GVHD (Hazard Ratio [HR] 1.42)
 - ii. HLA disparity between host and donor; incidence and severity increase with greater disparity between donor and graft
 - a. HLA matched donor (HR 1)
 - b. HLA matched unrelated donors (HR 1.3)
 - c. HLA mismatched related donors (HR 1.24)
 - d. HLA mismatched unrelated donors (HR 1.57)
 - iii. Source of stem cells
 1. PBSCs > BM

- iv. Older age of donor or host
 - v. Sex mismatching
 - a. Parous females to males > females to females > males to males
 - vi. Donor leukocyte infusions
2. Controversial risk factors
- i. CMV seropositive
 - ii. CMV reactivation
 - iii. Splenectomy
 - iv. Ethnic diversity between donor and host
 - v. Higher infused CD34+ dose in peripheral blood stem cell transplantation
 - vi. Lower infused CD34+ dose in bone marrow transplantation
 - vii. Lower incidence in umbilical cord transplantation

VI. Pathophysiology

1. Development of aGVHD (well understood)⁷
- i. Initial phase
 - 1. Damage in host tissues caused by transplant regimen
 - 2. Injured tissues secrete inflammatory cytokines
 - 3. Interleukin-1
 - 4. Tumor necrosis factor- α
 - 5. Interferon- γ
 - ii. Second phase
 - 1. Antigen presenting cells (APCs) and inflammatory cytokines stimulate the activation of donor alloreactive T-cells
 - 2. T-cell expansion and differentiation occurs
 - 3. T-helper, T-cytotoxic, NK cells production
 - iii. Third (Effector) phase
 - 1. T-cell mediated cytotoxicity against host cells
 - 2. Production of more cytokines to direct and continue GVHD pathway
2. Development of chronic graft versus host disease (less understood) – donor T-cells play an important role in its development, but humoral immunity is also implicated^{8,9,10}
- i. Alloreactive T-cells are part of the initiation of cGVHD as donor derived T-cells target host immunocompatibility antigens
 - ii. Activated immune system cells (T-cells, B-cells, NK Cells) are not regulated by the thymus and immunologic attack of the host goes unchecked
 - iii. Cytolytic mechanisms, secretion of inflammatory cytokines, secretion of fibrosing cytokines and B-cell pathways result in immune response attack of target tissues
 - iv. B-cell involvement produces antibody production, antigen presentation, cytokine production and immune misregulation against the host tissues
 - v. Regulatory T-cells are impaired allowing a loss of tolerance of the graft to host resulting in autoimmunity and resulting cGVHD
 - vi. Inflammatory processes as well as fibrosing processes leading to tissue damage of the host

VII. *Diagnosis/*Signs and Symptoms/Clinical Manifestations

1. Historically (before 2005), the diagnosis of cGVHD was made if there were signs and

symptoms of GVHD following day 100 post-transplant (even if it was indistinguishable from aGVHD)^{2,11}

- i. Because of this confusion, reclassification of cGVHD was completed¹¹
2. Diagnosis of cGVHD requires the following (Table 2)^{2,12,13}
 - i. Distinction from acute GVHD
 - ii. Presence of at least one diagnostic clinical sign/symptom of cGVHD or the presence of at least one distinctive manifestation confirmed by tissue biopsy or other relevant testing in the same or other organ
 - iii. Exclusion of other differential diagnoses
3. Organ specific manifestations²
 - i. Clinical manifestations (Table 2)
 1. Incidence of clinical presentation
 - a. Skin 75%
 - b. Mouth 51-63%
 - c. Liver 29-51%
 - d. Eye 22-33%
 - e. GI tract 23-45%
 - f. Lung 4-19%
 - g. Esophagus 7%
 - h. Joints 6%
 - ii. Histopathologic findings can be similar to various auto-immune disorders (Table 4)¹²
 - iii. Accompanied by profound, prolonged immunodeficiency

Table 6. Global Scoring for cGVHD^{2, 12}

Severity of cGVHD	Description
Mild cGVHD	<ul style="list-style-type: none"> • Involves only 1 or 2 organs/sites (EXCEPT lung) with no clinically significant functional impairment (maximum score of 1 in all affected organs/sites)
Moderate cGVHD	<ul style="list-style-type: none"> • Involves at least 1 organ/site with clinically significant but no major disability (maximum score of 2 in any affected organ/site OR • 3 or more organs/sites with no clinically significant functional impairment (maximum score of 1 in all affected organs or sites). • A lung score of 1 will also be considered moderate cGVHD
Severe cGVHD	<ul style="list-style-type: none"> • Indicates major disability caused by cGVHD – score of 3 in any organ or site. • A lung score of ≥ 2 will also be considered severe cGVHD

- iii. thrombocytopenia
- iv. HLA-nonidentical marrow donors
- 2. The overall survival rate is 42%
 - i. Patients with progressive onset of chronic GVHD have a survival rate of 10%

***Patient Case 1 continued**

BM's chief complaint of new onset skin depigmentation on her thighs gives her a skin score of 1. Her increased xerostomia and aversion to spicy foods yield a mouth score of 1. Her gritty dry eyes with use of drops five times daily gives an eye score of 2. Her joint stiffness of her bilateral knees without loss of range of motion gives her a joint score of 1. Her Global cGVHD score is determined as moderate cGVHD.

XI. *Treatment

- 3. Indications for treatment (when to start and what to do)
 - i. Mild cGVHD – topical therapy (Table 8)^{18,19,20}
 - ii. Moderate to severe cGVHD involving 3 or more organs or with a score of 2 or greater in any one organ system- systemic therapy
 - 1. Some clinicians incorporate the delineation of high risk features into their determination for treatment
 - a. Thrombocytopenia
 - b. Progressive onset of cGVHD from patients with aGVHD
 - c. Bilirubin > 2 mg/dL
 - 2. Underlying disease indication (malignant vs. non- malignant) will also factor into a clinician's decision making process (What is the risk of disease relapse with use of systemic therapy?)
 - iii. First line systemic therapy^{11,18,19,21,22}
 - 1. Corticosteroids have been used as first-line treatment since the 1980s
 - 2. Effect likely due to lymphocytic effects and anti-inflammatory properties
 - 3. Standard dose 1 mg/kg of methylprednisolone per day alone or in combination with other agents (no Randomized Controlled Trials [RCT] to compare higher doses)
 - a. Approximately 33% of patients respond to initial therapy
 - b. Stable or improving after 2 weeks
 - 25% dose reduction targeting 1 mg/kg every other day over the next 6-8 weeks
 - Severe or not obtaining a CR hold dose at 1 mg/kg every other day for 2-3 months, then taper by 10-20% per month for a total of 9 months
 - 4. Prednisone 1 mg/kg/day tapering to every other day regimen²³
 - 5. Prednisone + calcineurin inhibitor^{24,25}
 - 6. Not additional benefit
 - a. Mycophenolate + calcineurin inhibitor + prednisone²⁵
 - b. Thalidomide + calcineurin inhibitor + prednisone²⁶
 - c. Hydroxychloroquine + calcineurin inhibitor + prednisone
 - iv. Second line therapy (what to do after steroids fail)²¹
 - 1. Definition for steroid refractory²²
 - a. Progression on prednisone 1 mg/kg/day for 2 weeks

- b. Stable disease on ≥ 0.5 mg/kg/day of prednisone for 4-8 weeks
- c. Inability to taper prednisone below 0.5 mg/kg/day
- 2. Secondary treatment^{17,18,22}
 - a. Initial second line treatment should include agents with adequate safety profile and well-documented activity in GVHD like
 - Calcineurin inhibitors
 - Extracorporeal photophoresis (ECP)
 - mTOR inhibitors
 - Mycophenolate mofetil (MMF)
 - b. Third and fourth line agents can have significant side effects pharmacologically and financially
 - c. Goal of secondary therapy is steroid sparing
 - d. Assessment of response to salvage therapy at 8-12 weeks after initiation of new therapy
 - Sclerotic skin lesion patients require longer assessment of response to new therapy (up to 6 months)
 - e. If progression occurs after 4 weeks, a new treatment option should be offered **(with discontinuation of the most recently added therapy)**
 - f. Currently, there is no valid recommendation or consensus on which second/third/fourth line agents should be initiated first.
 - Assess patient's prior immunosuppressive therapies and responses to them
 - Avoid overlapping toxicities (e.g., myelosuppression, renal dysfunction, etc)
 - Patient preference to therapy

L.

Hematopoietic Stem Cell Transplantation-Associated Thrombotic Microangiopathy

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Learning Objectives

1. Describe the pathogenesis of transplant-associated thrombotic microangiopathy (TA-TMA).
2. Recognize risk factors associated with the development of TA-TMA.
3. Compare and contrast available diagnostic guidelines for TA-TMA.
4. Recommend appropriate treatment strategies for the management of TA-TMA.

Hematopoietic Stem Cell Transplantation-Associated Thrombotic Microangiopathy

Patient Case

JH is a 53 year old female with myelodysplastic syndrome (MDS) who underwent a myeloablative HLA-mismatched HSCT with busulfan, cyclophosphamide, and antithymocyte globulin. She received tacrolimus and methotrexate for graft-versus-host disease (GVHD) prophylaxis. Her inpatient transplant course was significant for an elevation in blood pressure for which she was started on amlodipine 10mg daily on day +8 and metoprolol 50 mg BID on day +16. Neutrophil engraftment occurred on day +21 and she was discharged to the outpatient HSCT clinic on day +24 with a platelet count of $210 \times 10^6/\text{mL}$. On day +43 JH presents to the outpatient SCT clinic with a maculopapular rash covering 60% of her body surface area. She also complains of abdominal cramping and diarrhea. Her laboratory work is significant for a platelet count of $52 \times 10^6/\text{mL}$, Hgb of 7.3 g/dL, SCr increased from a baseline of 0.6 mg/dL to 1.6 mg/dL, and a tacrolimus level of 11.5 ng/mL. Her coagulation tests are within normal limits.

What further work-up is needed to assess JH's current problems? What risk factors does JH have for developing TA-TMA?

I. Epidemiology of disease¹⁻³

- a. Reported incidence of TMA post hematopoietic stem cell transplantation (HSCT) is 0.5% to 70%. The wide range is indicative of inconsistencies in diagnostic criteria available and heterogeneity of patient populations studied
 - i. Most large, retrospective studies report an incidence between 10%-25%
- b. High mortality rate of 60-90%

II. Pathophysiology

- a. TMA encompasses primary processes such as idiopathic thrombotic thrombocytopenic purpura (TTP) and hemolytic uremia syndrome (HUS), as well as secondary disorders including TA-TMA.
- b. Thrombotic thrombocytopenic purpura⁴
 - i. TTP is attributed largely to deficient activity of a metalloproteinase (ADAMTS13) responsible for cleaving ultra large von Willebrand factor (vWF) multimers. The deficient ADAMTS13 activity is due to either a true deficiency of enzyme or an inhibitory antibody and is generally severe (<5% activity).
 - ii. The large, uncleaved vWF multimers clump platelets causing platelet thrombus formation within the microvasculature. This causes transient ischemia of the brain, kidneys, and other organs.
 - iii. TTP is often characterized by more significant thrombocytopenia and hemolytic anemia.
 - iv. ADAMTS13 is an acronym for a disintegrin-like and metalloprotease with thrombospondin type 1 motifs.

- c. Hemolytic uremic syndrome (HUS)⁴
 - i. HUS classically follows a diarrheal illness caused by gram negative bacilli producing Shiga toxin (D+HUS). Circulating Shiga toxin binds to renal endothelial cells resulting in injury and thrombin generation. Microvascular aggregation and thrombosis occurs primarily in the kidneys.
 - ii. In patients with non-Shiga toxin HUS or atypical HUS (aHUS), there are mutations in several proteins responsible for regulating the alternative complement pathway, including complement factor H (CFH), membrane cofactor protein (MCP) and factor I (IF).
 - iii. HUS is often characterized by more significant renal failure.
- d. Transplant-associated thrombotic microangiopathy^{2,4}
 - i. TA-TMA is defined by microvascular endothelial cell injury due to radiation therapy, high-dose chemotherapy, calcineurin inhibitor/sirolimus exposure, GVHD, and invasive fungal or viral infections.
 - ii. Release of cytokines (IL-1, TNF- α , IFN- γ) causes microvascular endothelial cell damage and apoptosis, leukocyte adhesion, activation of platelets and coagulation factors, and formation of thrombi.
 - iii. Similar to patients with non-Shiga toxin HUS, mutations in complement regulators may also contribute to the development of TA-TMA.
 - iv. Differs from de novo TTP, in that systemic microthrombus formation does not appear to play a major role and levels of the von Willebrand factor-cleaving protease ADAMTS13 are not markedly decreased.

III. Etiology/Pathogenesis

- a. Etiology of TTP/HUS⁴
 - i. Idiopathic : Deficient ADAMTS13 activity
 - ii. Drug-induced: quinine, mitomycin C, cyclosporine, tacrolimus, sirolimus, ticlopidine, gemcitabine, pentostatin, carmustine
 - iii. Pregnancy/post-partum
 - iv. Diarrhea-associated HUS (D+HUS): Caused by Shiga toxin-producing *E. coli*
 - v. Atypical HUS (aHUS): Complement regulatory protein defects
- b. Etiology of TA-TMA³
 - i. Conditioning regimens
 - 1. Total body irradiation (TBI)
 - 2. Myeloablative conditioning with high dose busulfan, cyclophosphamide
 - 3. Non-myeloablative conditioning with fludarabine
 - ii. Infection
 - 1. Aspergillosis, cytomegalovirus (CMV), adenovirus, parvovirus B19, human herpes virus-6 (HHV6), BK virus

Anti-Emesis in Hematopoietic Stem Cell Transplantation (HSCT)

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1. Objectives

- a. Describe the pathophysiology and significance of chemotherapy-induced nausea and vomiting (CINV)
- b. Outline the risk assessment for CINV
- c. Apply the clinical data supporting therapeutic recommendations for the prevention and treatment of CINV within the hematopoietic stem cell (HSCT) population
- d. Outline appropriate monitoring parameters for CINV
- e. Devise appropriate plans for preventing, monitoring and treating adverse reactions associated with the therapeutic interventions for CINV

Patient Case 1

JR is a 25 year-old Caucasian female with Hodgkin's lymphoma. Her past medical history is significant for morning sickness during both of her pregnancies. She has no pertinent social history (no history of cigarette smoking or illicit drug use and only minor occasional alcohol consumption). She reports being very worried because she remembers having "severe" nausea with ABVD (doxorubicin, bleomycin, vinblastine, dexamethasone) in the past. Currently, she is being admitted for BEAM (carmustine, etoposide, cytarabine, melphalan) conditioning followed by autologous HSCT (aHSCT).

Part 1: List JR's risk factors for CINV.

Part 2: Provide an acceptable CINV prophylaxis strategy for JR's BEAM conditioning chemotherapy.

Part 3: On day + 4 JR is complaining of nausea and has had three episodes of emesis in the past 24 hours without relief from PRN prochlorperazine or lorazepam. List at least two options to address her breakthrough nausea/vomiting (N/V).

2. Self-Assessment Question(s)

- 1) Which of the following is FALSE regarding CINV?
 - A. Nausea is traditionally more difficult to control than vomiting
 - B. The majority of HSCT patients do not experience CINV with prophylaxis
 - C. The main neuroreceptor implicated in acute CINV is 5-HT₃
 - D. Total body irradiation-containing conditioning regimens are considered highly emetogenic

- ii. Other risk factors:
 - 1. Younger age, history of previous CINV, higher Hesketh's score for chemotherapy regimen
 - 2. Non-significant trend to lower response in females
- iii. Factors influencing CINV in HSCT patients
 - 1. Type of HSCT
 - a. aHSCT < allogeneic (allo) HSCT ^{11,12}
 - i. Nausea and vomiting rates
 - 1. 51 % & 18 % with aHSCT (auto)
 - 2. 78 % & 39 % with allo HSCT
 - 2. Disease state
 - a. In one retrospective study of patients undergoing highly emetogenic conditioning chemotherapy for aHSCT and allo HSCT, patients with leukemia had highest rate of nausea (85 %) and vomiting (45 %) ¹¹⁻¹²
 - 3. Conditioning regimen
 - a. Evaluation of CINV in various HSCT conditioning regimens ¹³
 - i. Study population:
 - 1. aHSCT and allo HSCT patients (n = 21)
 - 2. Conditioning regimens: melphalan, Cy/TBI, Bu/Cy/Etoposide, BEAM
 - ii. Overall results:
 - 1. Incidence vomiting peaked on day 5 (35 % patients)
 - 2. Nausea (any grade) was 71 % on days 3 and 4
 - 3. Nausea persisted on day 12 in > 50 % of patients
 - 4. Nausea persisted on day 25 in 4 patients (all had received melphalan conditioning)
 - 5. Prior CINV predicted at least one episode of emesis ($P = .01$)
 - iii. Conclusion:
 - 1. Melphalan conditioning regimens are highly emetogenic with significant delayed CINV
 - b. Retrospective, observational study of CINV in HSCT ¹⁴
 - i. Study population:
 - 1. aHSCT (n = 78) and allo HSCT (n = 38)
 - a. Number of patients per each type of conditioning regimen not reported
 - 2. CINV prophylaxis with 5-HT3 antagonist + dexamethasone
 - ii. Results:
 - 1. High CINV rates after administration of melphalan (both BEAM and high-dose melphalan regimens)
 - a. 90 % with no emesis prior to melphalan but only 45 % without emesis post-melphalan
 - 2. Low complete control rates for allo HSCT
 - a. Authors attributed this finding to use of cyclophosphamide-containing regimens (Flu/Cy, Bu/Cy and Cy/TBI)

	BEAM	Mel	Flu/Bu/ATG	Flu/Cy	Cy/TBI	Bu/Cy
No emesis (%)	59.6	29	66.7	38.5	0	33.3
No nausea (%)	25.5	6.5	50	15.4	0	0
No breakthrough medication use (%)	25.5	12.9	50	15.4	0	0

BEAM, carmustine, etoposide, cytarabine, melphalan; Mel, melphalan; Flu, fludarabine; Bu, busulfan; ATG, anti-thymocyte globulin; Cy, cyclophosphamide; TBI, total body irradiation.

- iii. Conclusion:
 - 1. Melphalan and cyclophosphamide conditioning regimens are highly emetogenic
- c. Prospective observational study of CINV in children undergoing HSCT (n = 15) ¹⁵
 - i. Study population:
 - 1. 15 children receiving cyclophosphamide (n=1) or + TBI (n=14); mean age: 8.6 yrs (2 to 17 yrs)
 - 2. CINV prophylaxis with ondansetron IV 5mg/m² (max 8mg) q8h
 - ii. Results
 - 1. Complete control defined as no vomits or retches; nausea severity not assessed
 - 2. On days that cyclophosphamide administered, 9 (60%) experienced complete control
 - 3. During entire acute phase (cyclophosphamide ± TBI), 33% experienced complete control
 - iii. Conclusion
 - 1. Ondansetron improved emetic control in children
 - 2. Further improvement in emetic control required
- d. Prospective observational study in children undergoing HSCT (n=25) ¹⁶
 - i. Study Population
 - 1. 25 children receiving autologous (n=14) or allogeneic (n=11) HSCT
 - 2. Various conditioning regimens including: cyclophosphamide + TBI (n=9); etoposide + carboplatin + cyclophosphamide (n=7); busulfan + cyclophosphamide (n=5)
 - 3. CINV prophylaxis with ondansetron + dexamethasone
 - 4. Nausea severity evaluated using non-validated tool
 - ii. Results
 - 1. Complete control defined as no vomits or retches per 24 hr; worst nausea severity per 24 hr reported separately
 - 2. 8% of children had complete control and no nausea during acute phase; 12% had complete control and no nausea during the delayed phase
 - iii. Conclusion
 - 1. Improvement in CINV control in children is needed