Preparative Regimens: Dosing Considerations in Special Populations

Saturday, February 14
11:00 am – 12:00 pm

ASBMT CIBMTR

Faculty

- Megan Bodge, Pharm.D.

Clinical Pharmacy Specialist, Stem Cell Transplant
VA Tennessee Valley Healthcare System
Nashville, Tennessee

- Joseph S. Bubalo, Pharm.D., MBA, BCPS, BCOP

Oncology Clinical Pharmacist
Assistant Professor of Medicine
Department of Pharmacy Services
Oregon Health & Science University Hospital
Portland, Oregon

ASBMT CIBMTR

Disclosures

- Dr. Bodge reports having no conflicts of interest
- Dr. Bubalo reports having no conflicts of interest

ASBMT CIBMTR

Objectives

- Interpret pertinent patient specific parameters and recognize the need for dose adjustments in patients with renal or hepatic impairment.
- Interpret pertinent patient specific parameters and recognize the need for dose adjustments in obese patients.
- Apply available literature on optimizing preparative regimen dosing in unique patient populations to challenging patient cases.
- Describe current gaps in the literature and opportunities for future research on preparative regimen dosing in unique patient populations.

ASBMT CIBMTR

Preparative Regimen Dosing in Patients with Renal or Hepatic Impairment: Parameters, Dosing Adjustments, and Patient Cases

Megan Bodge, Pharm.D.
Clinical Pharmacy Specialist, Stem Cell Transplant
VA Tennessee Valley Healthcare System
Nashville, Tennessee

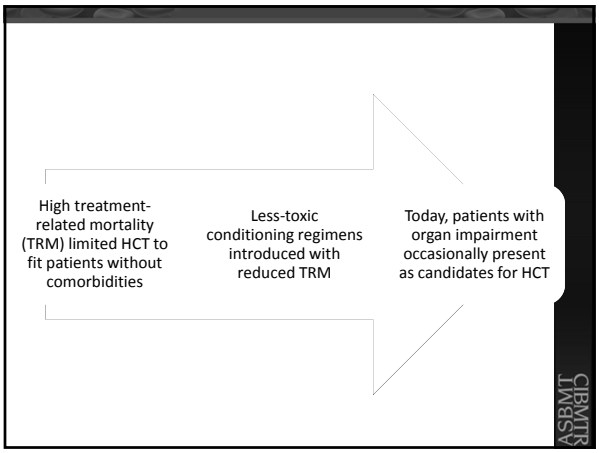
ASBMT CIBMTR

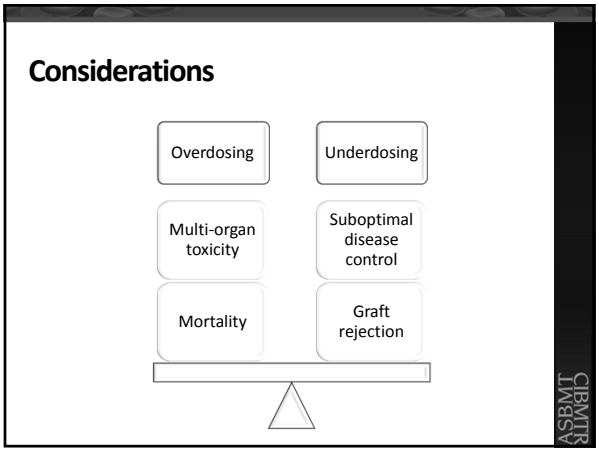
Preparative Regimens

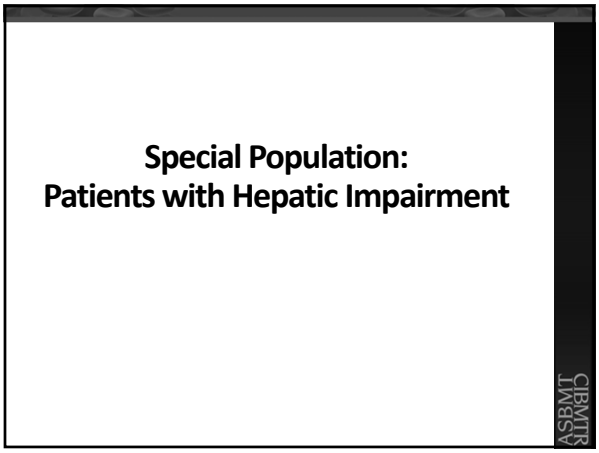
- Patients undergoing hematopoietic cell transplantation (HCT) are prepared with chemotherapy alone ± total body irradiation (TBI)
- Objective is two-fold:
  - Eradicate malignancy
  - Induce immunosuppression to permit engraftment
- Several workshops have convened to define conditioning regimens based on intensity, but no standard consensus reached
  - Myeloablative
  - Nonmyeloablative
  - Reduced-intensity

Copelan EA. *N Engl J Med.* 2006;354;17: 1813-1826.
Bacigalupo A, et al. *Biol Blood Marrow Transplant.* 2009;15: 1628-1633.

ASBMT CIBMTR


High treatment-related mortality (TRM) limited HCT to fit patients without comorbidities
Less-toxic conditioning regimens introduced with reduced TRM
Today, patients with organ impairment occasionally present as candidates for HCT
ASBMT CIBMTR


Considerations
Overdosing
Underdosing
Multi-organ toxicity
Suboptimal disease control
Mortality
Graft rejection
ASBMT CIBMTR


Special Population:
Patients with Hepatic Impairment
ASBMT CIBMTR

Clinical Assessment of Hepatic Function

- Patient history and physical exam
- Comprehensive liver panel
- Hepatitis work-up
  - Hepatitis B antigen
  - Anti-hepatitis B antibody
  - Hepatitis B virus (HBV) DNA
- Further work-up for patients with identified impairment
  - Liver imaging and biopsy

ASBMT CIBMTR

Chronic Hepatic Impairment

- Dose adaptation more difficult to perform than in setting of impaired renal function due to lack of endogenous marker to guide dose adjustments
- Several aspects of drug absorption and distribution influenced by the liver:
  - Hepatic blood flow
  - Protein binding
  - Intrinsic capacity of the liver to activate/eliminate drugs

Powis G. *Cancer Treat Rev.* 1982;9:85-124.
Tchambazi L. *Drug Safety.* 2006;29: 509-522.

ASBMT CIBMTR

Hepatic Clearance

- Hepatic drug clearance (Cl_H) dependent on ability of the liver to extract a drug from the blood and the rate at which a drug is delivered to the liver by the hepatic blood flow (Q)
- Drugs typically stratified according to hepatic extraction (E) which may have implications for drug bioavailability and clearance

$$Cl_H = Q \bullet E$$

Powis G. *Cancer Treat Rev.* 1982;9:85-124.
Tchambazi L. *Drug Safety.* 2006;29: 509-522.

ASBMT CIBMTR

Hepatic Clearance in Disease

Liver Dysfunction Present	Implications
Cirrhosis	Portal blood flow may be decreased leading to reduced hepatic clearance. High extraction drugs may have increased bioavailability, which may lead to adverse effects. Decrease in activity of cytochrome P450 isozymes and/or glucuronyl transferases
Porto-systemic shunts	Increase in drug bioavailability may be observed, particularly for drugs with high hepatic extraction (i.e., cyclosporine, tacrolimus)
Low serum albumin levels	Drugs with high binding to albumin (> 90%) may be present in higher free concentrations leading to toxicity (i.e., etoposide, mycophenolate) Serum albumin ≤ 3 g/ml has been suggested as the most reliable indication of a decrease in liver function
Cholestatic patients	Clearance of drugs with predominant biliary elimination may be impaired (i.e., doxorubicin, vinca alkaloids)

Powis G. *Cancer Treat Rev*. 1982;9:85-124.
Tchambazi L. *Drug Safety*. 2006;29: 509-522.

ASBMT CIBMTR

Potential Approaches to Drug Dosing

- Extrapolation from the literature
  - Adjustments may be recommended based on liver function tests such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), or serum bilirubin
- Pharmacokinetic (PK) analysis of specific agents in order to determine empiric dose adjustments which may be warranted
- Therapeutic drug monitoring (TDM) in real time
  - Busulfan(BU)
  - Cyclophosphamide (CY)

ASBMT CIBMTR

Liver Function Tests

Biochemical Indices	Normal Serum Levels	Underlying Pathophysiological Condition	Relationship with Impairment of Liver Function
Bilirubin	≤ 1.2 mg/dL	Severe cholestasis; Impaired liver function	Moderate: 2-3 mg/dL Severe: > 3 mg/dL
Transaminase: ALT/AST Alkaline phosphatase	< 45 IU/L < 279 IU/L	Inflammation; Cytolysis Cholestasis	No quantitative relationship
Albumin	> 3.5 g/mL	Impaired liver function	Moderate: 3-3.5 g/mL Severe: < 3.0 g/mL
Prothrombin activity	80-100%	Impaired liver function	Moderate: 40-70% Severe: < 40%

Donelli MG, et al. *European Journal of Cancer*. 1998;34: 33-46.

ASBMT CIBMTR

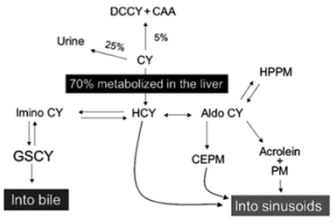
Busulfan

- Wide inter- and intra-patient variability in high dose BU disposition
  - Identified factors include age, alteration in hepatic function, disease, circadian rhythm, and drug interactions
- May contribute to liver injury by inducing oxidative stress, reducing glutathione levels, and altering CY metabolism
  - Primarily eliminated by conjugation with glutathione
  - Toxicity requires glutathione S-transferase (GST)-mediated conjugation to glutathione (GSH), which leads to oxidative stress
- Liver toxicity may be reduced if CY is given before targeted BU, or if dosing of CY is delayed for 1-2 days after completion of BU dosing

SD Taylor-Robinson. Cancer Chemotherapy. In: Drug Induced Liver Disease. 2013: 541-567.
Rezvani AR, et al. *Biol Blood Marrow Transplant*. 2013;19: 1033-1039.

Cyclophosphamide

- Prodrug with extensive, complex metabolism by the liver
  - Autoinduction and inhibition of its own metabolism
- Wide inter-individual variation in metabolism



SD Taylor-Robinson. Cancer Chemotherapy. In: Drug Induced Liver Disease. 2013: 541-567.
McDonald GB. *Aliment Pharmacol Ther*. 2006;24: 441-452.

CY Pharmacokinetics

- PK study conducted in patients with Hodgkin lymphoma
- Blood collected after 15 and 30 min and 1, 2, 3, 4, 6, 10, 20, 22, and 24 hours after CY infusion

	Dose of CY (mg/kg)	Elimination constant (B) [h^{-1}]	Half-life ($t_{1/2}$) [h]	Total body clearance Cl_t [l kg^{-1}]	Protein binding [%]	Renal clearance [m/min^{-1}]
Severe liver failure (n=7)	15	0.055	12.5 ± 1.0	44.8 ± 8.6	12.5 ± 2.5	11 ± 2
Normal liver function (n=10)	15	0.099	7.6 ± 1.4	62.98 ± 7.6	12.5 ± 2.0	10 ± 1.5
P-value			$P < 0.001$			

Juma FD. *Eur J Clin Pharmacol*. 1984;26: 591-593.

Therapeutic Drug Monitoring - BU

- Toxicity and lack of efficacy have been associated with systemic exposure of BU
  - High levels of BU may be achieved in the setting of hepatic impairment leading to toxicity
- TDM is conducted by obtaining blood samples after a weight-based dose of BU
  - Samples are quantitated and then the individual concentration-time data is modeled to estimate the individual patient's BU exposure and clearance
  - Subsequent doses are adjusted to achieve desired BU exposure (i.e., targeted steady state concentration 800-1000 ng/mL)
- TDM for BU incorporated into many centers, but not without challenges

McDonald GB, et al. *Gut.* 2008;57: 987-1003.
Hassan M, et al. *Cancer Chemother Pharmacol.* 1991;28: 130-134.
Sandstrom M, et al. *Bone Marrow Transplant.* 2001;28: 657-664.

Therapeutic Drug Monitoring - CY

- TDM for CY less well-established, but potentially promising
  - Centers on exposure to CY metabolites 4-hydroxyCY and carboxyethylphosphoramide mustard (CEPM)
    - Exposure to CEPM significantly related to SOS, bilirubin elevation, nonrelapse mortality, and survival in patients receiving CY/TBI conditioning
    - 5.9-fold increase in mortality rate reported for patients in the highest quartile of AUC_{CEPM} as compared with the lowest quartile
- CY doses can be adjusted in real-time via a regression model to achieve a target AUC of CEPM and HCY
  - Target AUC of CEPM and HCY of 325 ± 25 and > 50 µmol/L h
- Bayesian modeling of CY metabolism using HCY and CEPM plasma concentrations from 0-16 hours after the first CY dose leads to accurate dose adjustment

McDonald GB, et al. *Clin Pharmacol Ther.* 2005;78: 298-308.
Salinger DH, et al. *Clin Cancer Res.* 2006;12: 4888-4898.

Potential Methods to Reduce Liver Toxicity

- Ursodeoxycholic acid (UDCA)
  - Hydrophilic bile acid which constitutes 5% of bile acids in healthy individuals
  - UDCA reduces the concentration of hydrophobic bile acids which are more toxic to liver cells than hydrophilic bile acids
  - Stabilizes hepatocyte cell membranes by altering lipid composition and reduces release and expression of inflammatory cytokines
  - Studies have been conflicting as to true benefit of the agent
- Reduction of additional hepatotoxic agents
- Aggressive diuresis when intake exceeds output (goal weight change of -2% to 5% from baseline by Day 0)

McCune J. *Expert Opin Drug Metab Toxicol.* 2009;5: 957-969.
Johnson DB, et al. *Exp Hematol.* 2012 Jul;40(7):513-7.

Patient Case #1

- Mr. Doe is a 46 y/o M with a history of CML (T315I mutated), post-traumatic stress disorder, depression, and cirrhosis related to HBV infection. He is referred for HCT as a potentially curative option for his hematologic malignancy.

ASBMT CIBMTR

Patient Case #1

- Mr. Doe undergoes work-up to determine the extent of his liver impairment, including a liver biopsy.

Parameter	Value
Total bilirubin	1.6 mg/dL
Direct bilirubin	1.0 mg/dL
Alkaline phosphatase	184 IU/L
AST	62 IU/L
ALT	48 IU/L
Albumin	3.2 g/dL

ASBMT CIBMTR

Patient Case #1

- Mr. Doe is determined to be a candidate for HCT.
  - What preventative strategies can be employed to reduce the likelihood for toxicity post-HCT?

ASBMT CIBMTR

Patient Case #1

- Conditioning regimen should likely be modified:
  - Preferable to use a reduced-intensity or nonmyeloablative regimen
    - No specific data to support a specific regimen
  - Consider substitution of a less liver-toxic drug for CY
  - If CY is utilized, reduce the dose by 10-20%
  - Utilize TDM for both BU or CY, if possible
- Consider utilization of ursodiol prophylaxis
  - 300 mg by mouth three times daily
- Avoid other hepatotoxic medications (i.e., azoles, phenytoin)

Johnson DB, et al. *Exp Hematol*. 2012 Jul;40(7):513-7.
Strasser SI, et al. Gastrointestinal and Hepatic Complications. In: Thomas' Hematopoietic Cell Transplantation. 2004: 769-810.

Special Population: Patients with Renal Impairment

Chronic Kidney Disease (CKD)

- Well-documented that renal injury is a common complication of HCT
- Major risk scoring indices include renal insufficiency as a risk factor for post-HCT mortality
  - Hematopoietic cell transplantation-specific comorbidity index (HCT-CI) mild renal comorbidity: serum creatinine 1.2 – 2.0 mg/dL
  - HCT-CI moderate to severe renal comorbidity: serum creatinine > 2 mg/dL, renal dialysis, or renal transplant
- Reports in the literature detail successful autologous and allogeneic HCT for patients with CKD, including patients with end-stage renal disease (ESRD)
  - Limited information for alloHCT recipients regarding creatinine clearance (CrCl) and dialysis schedules for patients who were hemodialysis (HD)-dependent

Sorror et al., *Blood*. 2005; 106: 2912-2919
Bodge MN, et al. *Biol Blood Marrow Transplant*. 2014; 20: 908-919.

Melphalan (MEL)

- One of the most effective chemotherapeutic agents for treatment of multiple myeloma
  - Renal dysfunction is a presenting feature in up to 20-50% of patients
- Bi-functional alkylating agent which is both secreted and reabsorbed by the renal tubules
- Pharmacokinetics
  - Appear to be dose and age independent
    - Individual differences in metabolism poorly understood
  - 90% bound to plasma proteins
    - 60% to albumin
  - Primary route of elimination is spontaneous degradation
    - Renal excretion ~13-14%
  - Conflicting data on differences in renal dysfunction

Tricot G, et al. *Clin Cancer Res*. 1996;2(6):947-952.
Badros A, et al. *Br J Haematol*. 2001;114(4):822-829.
Canal P, et al. *Drugs*. 1998;56: 1019-1038.

ASBMT CIBMTR

Safety of Autotransplants with High-Dose Melphalan in Renal Failure: A Pharmacokinetic and Toxicity Study

- Prospective trial
- N=20; 6 patients with severe renal dysfunction
  - Defined as CrCl < 40 ml/min
  - 5 patients were receiving HD
- Dosing: 200 mg/m^2 for all patients
- No reported differences: post-transplant engraftment, transfusion requirements, incidence of severe mucositis, or overall survival
- Renal dysfunction associated with longer durations of fever (p = 0.0005) and hospitalization (p = 0.004)

Tricot G, et al. *Clin Cancer Res*. 1996;2(6):947-952.

ASBMT CIBMTR

Pharmacokinetics

	Median Half-Life	Area Under the Concentration Curve	MEL Clearance
No renal dysfunction (n=14)	1.9 h	7.9 mg h/liter	23.6 liter/h
CrCl < 40 mL/min (n=6)	1.1 h	5.5 mg h/liter	27.5 liter/h

- Plasma $t_{1/2}$ and area under the concentration curve differed by a factor of 10 between patients with the lowest and highest values
- MEL clearance differed by a factor of 5

Tricot G, et al. *Clin Cancer Res*. 1996;2(6):947-952.

ASBMT CIBMTR

Results of Autologous Stem Cell Transplant in Multiple Myeloma Patients with Renal Failure

- Prospective trial
- 81 patients with renal dysfunction included; 38 patients were receiving dialysis
- Initial dosing: 200 mg/m^2 (n=60; 27 patients on dialysis)
  - Reduced to 140 mg/m^2 due to excessive toxicity
- MEL 140 mg/m^2 appeared to have equal efficacy with reduced toxicity for patients with renal dysfunction
  - Mucositis, pulmonary complications, and cardiac complications were more common in the MEL-200 group than the MEL-140 group
  - No statistically significant difference in treatment-related mortality between groups
- No impact on event-free survival or overall survival based on MEL dose or dialysis dependence

Badros A, et al. *Br J Haematol.* 2001;114(4):822-829.

ASBMT CIBMTR

Summary of Retrospective Trials

Study	Patients	MEL Dosing	Outcomes
Knudsen, et al.	29 patients with CrCl < 60 ml/min; 8 patients on hemodialysis	200 mg/m^2 (n=26) 140 mg/m^2 (n=3)	TRM 17% for patients with renal impairment; significantly longer hospitalization, increased use of blood products, and increased number of infections
San Miguel, et al.	14 patients; 4 on dialysis	200 mg/m^2	TRM 29% 43% had an improvement in renal function post-HCT
Bird, et al.	27 patients with CrCl < 20 ml/min; 23 patients on dialysis	60-200 mg/m^2 (Median dose: 140 mg/m^2; 10 patients received 200 mg/m^2)	TRM 18.5% 4/17 patients became dialysis-independent

Bird JM, et al. *Br J Haematol.* 2006 Aug;134(4):385-390.
Knudsen LM, et al. *Eur J Haematol.* 2005 Jul;75(1):27-33.
San Miguel JF, et al. *Hematol J.* 2000;1(1):28-36.

ASBMT CIBMTR

Cyclophosphamide

- Dose adjustment for reduced glomerular filtration rate (GFR) has been debated in the literature
  - Pharmacokinetic models suggest that clearance of two CY metabolites (4-OH CY and aldophosphamide) may be reduced in the presence of severe renal impairment
- Drug clearance and volume of distribution have been found to be decreased in patients with reduced GFR

ASBMT CIBMTR

Administration and Pharmacokinetics of High-Dose Cyclophosphamide with Hemodialysis Support for Allogeneic Bone Marrow Transplantation in Acute Leukemia and End-Stage Renal Disease

- Case report of a 42 yo dialysis-dependent M with AML who underwent HCT
- Conditioning regimen
  - CY 60 mg/kg IV on day -7 and -6
    - Pt had regular hemodialysis session (4 h) on day -7 before CY, then longer hemodialysis sessions (6 h) performed beginning 14 h after the end of each CY infusion
    - Continuous bladder irrigation employed for prevention of hemorrhagic cystitis from day -7 to day -5
    - IV hydration (100 ml/h) was used with CY administration
  - TBI 165 cGy twice daily x 4 days (day -4 to day -1)
- No acute cardiac effects detected and no hemorrhagic cystitis observed

Perry JJ, et al. *Bone Marrow Transplant*. 1999 Apr;23(8):839-842.

ASBMT CIBMTR

Pharmacokinetic Studies

- Parameters calculated based on venous blood samples collected at 0, 1, 2, 3, 4, 6, 12, and 24 h after the start of each CY infusion
- One-compartment model determined to best fit the CY and CY-alkylating plasma concentration-time data

	Elimination $t_{1/2}$	Cl_s	Vd_{ss}	CY-alkylating elimination $t_{1/2}$	CY CL_{HD} during HD	CY-alkylating metabolites CL_{HD}
Day 1	14.6 h	38.4 ml/min	49.5 l	22.4 h	178 ml/min	108 ml/min
Day 2	9.0 h	48.5 ml/min	40.5 l	16.5 h		
Normal range	3-12 h	51-100 ml/min	30-50 l			

Perry JJ, et al. *Bone Marrow Transplant*. 1999;23: 839-842.

ASBMT CIBMTR

Overall Conclusions from the Literature

- Few published comparisons of the relative efficacy of many conditioning regimens in the general population
- Most of the data for special populations is in the form of case reports or small retrospective analyses
- Must always consider nonmarrow dose-limiting toxicities when administering toxic agents to patients with organ impairment
- Additional literature detailing outcomes of patients with chronic liver impairment or CKD is ultimately needed

ASBMT CIBMTR

Patient Case #2

- Mr. Jones is a 63 year old male who is preparing to undergo haploidentical HCT utilizing the Hopkins protocol. Prior to Day +3 and +4 CY administration (50 mg/kg per dose), he develops renal failure necessitating initiation of hemodialysis on Day +2 with serum creatinine 4.8. His bilirubin level also increases, total bilirubin level 5.0 mg/dL.
  - What dose adjustments should be made to Mr. Jones' cyclophosphamide dose to account for his current organ function?
  - What supportive care measures should be implemented?

ASBMT CIBMTR

Patient Case #2

- Cyclophosphamide dose
  - Expect decreased bioactivation due to liver impairment, but also decreased renal clearance based on PK studies
  - Can consider dosing at 75-100% normal dose
- Supportive care measures:
  - Pre- and post-dose HD
  - Increase mesna dosing (200% of Cy dose/day) and administer as a continuous infusion
  - Decreased hydration/furosemide as needed to maintain fluid balance
  - Closely monitor for cardiac toxicity post-Cy

ASBMT CIBMTR

Conditioning Agents - Summary

Agent	Major Nonmarrow Toxicities	Renal Clearance	Hepatic Metabolism
Busulfan	Pulmonary, seizures, dermatologic	Minimal	Extensive; glutathione conjugation followed by oxidation
Cyclophosphamide	Heart, mucosa, bladder, electrolytes (hyponatremia)	Yes; moderately dialyzable (20-50%)	Yes, requires hepatic biotransformation to alkylating metabolite
Melphalan	Mucosa, gastrointestinal, central nervous system	Yes; ~10% as unchanged drug; not removed by dialysis (short half-life in water)	Yes, but not thought to be hepatotoxic at standard doses
Fludarabine	Musculoskeletal (weakness), neurotoxicity	Metabolite F-ara-A is renally cleared (60%)	No, rapidly dephosphorylated in the plasma

Semin Nephrol. 2010;30: 602-14
McCune JS, et al. *Expert Opin Drug Metab Toxicol.* 2009;5: 957-969
Donelli MG, et al. *European Journal of Cancer.* 1998;34: 33-46

ASBMT CIBMTR

ARS Question #1

What implications should be considered for patients with low serum albumin levels related to liver cirrhosis who receive drugs with high protein binding, such as etoposide?

A. Decreased adverse effects related to increased bioavailability
B. Decreased adverse effects related to decreased bioavailability
C. Increased adverse effects related to increased bioavailability
D. Increased adverse effects related to decreased bioavailability

ASBMT CIBMTR

ARS Question #2

Mr. Young is a 64 year old male with IgG kappa multiple myeloma and chronic kidney disease. What melphalan dosing should be utilized prior to his autologous stem cell transplant based on available prospective literature?

A. 100 mg/m^2
B. 140 mg/m^2
C. 180 mg/m^2
D. 200 mg/m^2

ASBMT CIBMTR

Preparative Regimens: Dosing Considerations in Special Populations Obese Patient

ASBMT CIBMTR

Obesity in the General Population

- Prevalence of obesity in the US has risen significantly in the US since 1990
  - 34.9% of adults, > 20 year old (72 million)
  - ~17% of children and adolescents
    - — Birth to 2 years 8.1%
    - — 2-19 year olds 16.9%
- Prevalence stable between 2001 and 2012
- Recently classified as a disease state

Ogden C et al. JAMA 2014;311(8):806-14.
Ligibel JA et al. JCO 2014;32(31):3568-74.

ASBMT CIBMTR

Obesity and Cancer Risk

- Overtaking tobacco as leading cause of preventable cancer
  - Up to 84,000 cases per year attributed to it
  - Implicated in 15-20% of cancer related mortality
- Relevant to both solid tumor and hematologic malignancies
- Increased risk for second primary malignancies

Ligibel JA et al. JCO 2014;32(31):3568-74.

ASBMT CIBMTR

Obesity and Cancer Therapy

- May affect ability to deliver therapy
- Can contribute to associated morbidity
- Risk factor for
  - Poor wound healing
  - Increased co-morbid conditions
  - Post-operative infections
- >50% of non-cancer deaths in cancer survivors are cardiovascular related
- Diabetes related to additional mortality increase

Ligibel JA et al. JCO 2014;32(31):3568-74.

ASBMT CIBMTR

Obesity Defined

- Pediatrics
  - <2 years old – weight at or above the 95th percentile for recumbent length for age and gender
  - 2-19 years old – BMI at or above 95th percentile for age and gender. Overweight (85-95th percentile)
- Adults
  - Overweight – BMI 25-29.9 kg/m2
  - Obese BMI > 30 kg/m2
    - Grade I obesity - BMI 30-34
    - Grade II obesity - BMI 35-39
    - Grade III obesity - BMI > 40

Ogden C et al. JAMA 2014;311(8):806-14.

ASBMT CIBMTR

Obesity and Hematopoietic Cell Transplantation (HCT)

- Obese patients are able to undergo HCT successfully
  - Similar overall survival (OS) and disease free survival (DFS)
- Indications that there is increased risk of non relapse mortality (NRM)
- Potential for increased and decreased peritransplant morbidity
  - Increased infections, drug specific toxicity, longer length of stay
  - Decreased drug specific toxicity – less mucositis, quicker engraftment

Bubalo et al BBMT 2014;20:600-16.

ASBMT CIBMTR

How do we measure the patient?

- Ideal Body weight (IBW)
- Total body weight (TBW)
- Adjusted body weight (ABW)
  - ABW = IBW + %(TBW-IBW)
  - 25% (ABW25), 40% (ABW40), 50% (ABW50) or other adjustment
- BSA based on TBW vs IBW or ABW
  - No preferred BSA formula

Bubalo et al BBMT 2014;20:600-16.

ASBMT CIBMTR

What is Ideal Body Weight?

Comparison of ideal Body weight Equations Using Height		
Reference	Gender	Equation
Devine (1974)	Men	50 kg + 2.3 kg/each inch over 5 feet
	Women	45.5 kg + 2.3 kg/each inch over 5 feet
Robinson et al.	Men	52 kg + 1.9 kg/each inch over 5 feet
(1983)	Women	49 kg + 1.7 kg/each inch over 5 feet
Miller et al.	Men	56.2 kg + 1.41 kg/each inch over 5 feet
(1983)	Women	53.1 kg + 1.36 kg/each inch over 5 feet

History of IBW

- Historical data comparing relative mortality of different height-weight combinations
- 1970s Devine formula developed

Pai MP, Paloucek FP. The origin of the "ideal" body weight equations. Ann Pharmacother 2000;34:1066-9.

ASBMT CIBMTR

Obesity recommendations for Preparative Regimens in the obese individual

Drug	Dose
Alemtuzumab	Flat dose(Adults)
Busulfan	Adult ABW25 or BSA based on TBW with PK monitoring for > 12 mg/kg PO equivalent. Pediatrics on TBW with monitoring
Carboplatin	BSA based on TBW(Adults)
Carmustine	BSA based on TBW unless >120% IBW then BSA based on ABW25(Adults)
Clofarabine	BSA based on TBW(Adults)
Cyclophosphamide	Dose on the lessor of TBW or IBW for CY200 Cy120 dose on IBW (adults) or TBW until > 120%IBW then ABW25 (pediatrics)
Cytarabine	BSA based on TBW(Adults)
Etoposide	Adults use ABW25 for mg/kg dosing or TBW for BSA based dosing

Bubalo et al BBMT 2014;20:600-16.

Cy120 – 60 mg/kg x 2 days, Cy200 – 50 mg/kg x 4 days

ASBMT CIBMTR

Obesity recommendations for Preparative Regimens in the obese individual

Drug	Dose
Fludarabine	BSA based on TBW(Adults)
Melphalan	BSA based on TBW(Adults)
Pentostatin	BSA based on TBW(Adults)
Thiotepa	BSA based on TBW unless >120% IBW then BSA based on ABW40(Adults)
Antithymocyte globulin - equine	Mg/kg based on TBW – Adults and Pediatrics
Antithymocyte globulin - rabbit	Mg/kg based on TBW – Adults and Pediatrics

Bubalo et al BBMT 2014;20:600-16.

ASBMT CIBMTR

What is the evidence?

- No level I or II evidence
  - Lack of prospective data
  - Historic or poorly matched case controls
  - Case series not detailed enough
  - Most studies had minimal pharmacokinetic (PK) information
  - Evolution of transplant types and supportive care
- Why did we proceed?
  - Can the drug titration series of the past be re-created?

ASBMT CIBMTR

What are the ramifications of not putting out a statement?

- Are we harming patients?
  - Will we continue to run up against dose limiting toxicities (DLT) that are already known?
  - Dosing parameters are currently unclear for obese individuals
  - Significant variation in dosing exists between institutions and countries
- Greater risk for harm than standard antineoplastic dosing?
  - Ongoing gap in understanding of the impact of body habitus on medications
  - Dosing at the limits of organ tolerance

ASBMT CIBMTR

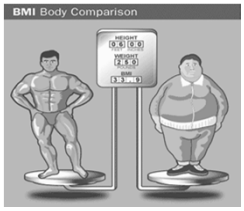
What has not been addressed?

- Different transplant types
  - Adult
    - Myeloablative (MA)
    - Reduced-intensity (RIC)
    - Non-myeloablative (NMA)
    - Autologous
  - Pediatric
    - Same types as adult
- Supportive medication dosing – methotrexate, calcineurin inhibitors, anti-infectives, etc.
- Effect of multiple agents on DLT

ASBMT CIBMTR

Challenging patient types

- The large fit individual
- The very obese – BMI >50
- Children (0-15 years old)
- The underweight patient



Where do we go from here?

- A baseline standard has been created
- Publish/require more complete demographics
  - Add analysis by BMI, Body weight
  - Prospective study of weight impacts
- Additional PK monitoring models
- Can we dose on BMI vs %IBW?
- Dose titration of immune modulation – antilymphocyte globulins, alemtuzumab

Where do we go from here (cont.)

- New endpoints or surrogates for efficacy that allow safer or attenuated dosing
- Organized way to manage multi-agent regimen risks.
- Improved toxicity management to support dose intensity where warranted.

Melphalan: the next drug to investigate PKs?

Pros

- Wide use in autologous (myeloma), ablative (BEAM), and RIC (FluMel) HCT
- Toxicity and efficacy associated with AUC
- Inter-individual variation common
- Linear association between dose and AUC

Cons

- Target AUC target not yet determined
- Dosed once in most regimens
- Requires development of test dose or split dose strategy
- Commercial testing not common
- New formulation may be required

Shaw PJ et al Bone Marrow Transplantation 2014;49:1457-1465

ASBMT CIBMTR

Melphalan: Moving Forward

- New maximum tolerated dose?
  - If myelosuppression and mucositis are managed
    - Next DLT atrial fibrillation, > 220 mg/m2
    - Hepatic toxicity > 280 mg/m2
- Addition of other agents in conditioning
  - Busulfan
  - Pazopanib
  - Bortezomib
  - Histone deacetylase inhibitors – vorinostat
  - Arsenic
- PK analysis could assist with therapy development

Shaw PJ et al Bone Marrow Transplantation 2014;49:1457-1465

ASBMT CIBMTR

Toxicity Management

- Fludarabine Neurotoxicity in HCT patients
  - Review of 1596 patients (624 adults, 972 children)
  - 39 cases (2.4%), age 3-60 (median 43)
  - Median total dose 200 mg/m2 (151-182)
  - Presenting symptoms - confusion/somnolence, generalized seizure, severe persistent headache, blurred vision
  - Posterior reversible encephalopathy syndrome (PRES) 17, acute toxic leukoencephalopathy (ATL) 11, and other leukoencephalopathy (OLE) 11

Beitinjaneh A, et al BBMT 2011;17:300-308.

ASBMT CIBMTR

Fludarabine encephalopathy

- Median survival 5.6 months, 43% (16) at 1 year
  - 15/37 died from neurologically unrelated causes
  - 10 longer term survivors with 6 having full neurologic recovery.
- Toxicity variables
  - Pathophysiology unclear
  - PRES preceded by hypertension, high CSA levels, more reversible
  - ATL – less reversible
  - Fludarabine most likely cause

Beitinjaneh A, et al BBMT 2011;17:300-308.

ASBMT CIBMTR

Fludarabine encephalopathy

- Previously seen in early phase trials
  - 36% at 90 mg/m2 x 5 days
- Product information recommends ≤125 mg/m2 per cycle (0.2% incidence)
- Was obesity a risk?
  - No review for a weight effect.
  - BMI/weights not reported
- What is the effect of combining with other neurotoxins?
- Age > 60 may be a risk factor
- Could Pk guidance have eliminated this toxicity?

Beitinjaneh A, et al BBMT 2011;17:300-308.

ASBMT CIBMTR

Conclusions

- Obese individuals can undergo HCT successfully
- The optimal dosing for most agents is unclear
- Additional study needed
  - Prospective assessment by BMI
  - Increased PK studies with associated efficacy and toxicity assessment
- Consider ASBMT guideline as a starting point
  - Consider intent of the dose when choosing the dose parameters
  - Consider known DLT and maximum tolerated doses

ASBMT CIBMTR

ARS Question 3 (polling)

Are you comfortable following the recommendations from the ASBMT obesity guideline paper?

- A: Sure, we have been waiting for information like this
- B: No, the evidence is too soft
- C: No, we are transplanters and we want dose intensity
- D: Will use some of the recommendations but not all
- E: Other

ASBMT CIBMTR

ARS Question 4

The correct initial dosing weight for busulfan in a 20 year old male with a BMI of 40 kg/m2 would be?

- A: Total body weight
- B: Ideal body weight
- C: Adjusted body weight 25% difference (ABW25)
- D: Adjusted body weight 40% difference (ABW40)

ASBMT CIBMTR

ARS Question 5

The patient type currently at greatest risk for toxicity if we do not adjust for BMI is:

- A: Children with BMI over 25
- B: Children over 15 years old
- C: Adults BMI 20 to 30
- D: Adults BMI over 50

ASBMT CIBMTR