Folinic Acid Rescue after Methotrexate Graft Versus Host Disease Prophylaxis to Reduce Mucositis and Improve the Probability of Day +11 Methotrexate Administration – Role of the Hematopoietic Cell Transplant Pharmacist in Development of Program Guidelines

Jeffrey Betcher, BSPharm, BCOP
Clinical Pharmacy Specialist
Cancer Center Pharmacy Supervisor
Mayo Clinic
Phoenix, Arizona

ASBMT CIBMTR

Disclosures

No relevant financial relationships

ASBMT CIBMTR

Learning Objectives

- Describe the impact of folinic acid rescue after methotrexate graft versus host disease prophylaxis on the incidence of mucositis, graft versus host disease, relapse and survival
- Outline the role of HCT pharmacists in the development of practice guidelines

ASBMT CIBMTR

Background

- MTX has additive toxicity
  - Mucositis
  - Hepatotoxicity
  - Delayed engraftment
- Only 62-73% receive day +11 MTX[1, 2]
- Omission of day +11 MTX increases risk of aGVHD[3, 4]

1.Ratanatharothorn V et al. *Blood* 1998;92:2303-2314.
2.Nash RA et al. *Blood* 2000;96:2062-2068.
3.Nash RA et al. Blood 1992; 80:1838-1845.
4.Kumar S et al. *Bone Marrow Transplant* 2002;31:73-75.

ASBMT CIBMTR

Background – How to Reduce Mucositis

- Reduced or omitted doses of MTX
- FA rescue
  - Limited data in HCT setting
  - Concern it may reduce MTX efficacy, therefore increasing the risk of aGVHD
  - Concern it may increase risk of relapse
- Supportive care management
  - Steroids
  - Opioids
  - Miracle mouthwash, topical anesthetics
  - TPN

ASBMT CIBMTR

HCT Pharmacist Role

- Assist in development and review of program guidelines and standard operating procedures
- Volunteered to review the data and present to the multidisciplinary HCT team
  - Rationale for FA use
  - Review of the literature
  - Present options and recommendations
  - Plan follow-up in 1 year, retrospective review

ASBMT CIBMTR

Rationale for Folinic Acid

- Canine unrelated histoincompatible BM graft
- No immunosuppression (IS) vs MTX + FA vs historical control (MTX only)
- Citrovorum factor 6 hours after each MTX dose
- MTX levels > 10^{-6} M completely abrogated thymidine uptake in lymphocytes on stimulation for 6 hours
- Results
  - MTX + FA dogs lived significantly longer than no IS
  - Incidence of early deaths was significant in the MTX only group
- MTX + FA completely abrogated antibodies without signs of toxicity

Gratwohl AA, et al. Acta Haematol. 1978;60(4):233-43.

ASBMT CIBMTR

Summary of Surveys

Source	N	FA Use	FA Dose	FA Started
Ruutu 1997	81	46%	24 centers 1:1 MTX 11 centers: 3 to 15 mg/kg total dose	Started at 4, 6, 12, 24, 36 and 48 hours 10 centers – 12hrs 21 centers – 24hrs
Peters 2000	NR	85-90% agree with use of FA	15 mg/m^2/day	24 hours after each MTX
Bhurani 2008	18	66% 2/3 routine	Dose 10 to 15 mg/m^2	24 hours after each MTX

Reasons FA Utilized

To avoid side effects such as:
- Myelosuppression
- Mucosal damage

Reasons FA not utilized

- No evidence of efficacy
- Possibility of increased risk of aGVHD

Ruutu T, et al. *Bone Marrow Transplant* 1997;19:759-64.
Peters C, et al. *Bone Marrow Transplant* 2000;26:405-11.
Bhurani D, et al. *Bone Marrow Transplant* 2008;42:547-50.

ASBMT CIBMTR

Summary of Literature

	N	MTX Dose (mg/m^2)	FA Dose	Outcomes
Torres 1989	57	15/10/10/10	1:1 x 1 24 hr after MTX	↓ toxicity GVHD(NS)
Nevill 1992	82	15/10/10/10	1:1 D1 x 3, D3 x 6, D6 & D9 x 8 (24 hr after MTX)	↓ toxicity GVHD/EFS(NS)
Russell1 994	69	15/10/10/10	5 mg q6h, 24 hr after MTX thru 12hr before next MTX	GVHD(NS)
Sugita 2012	118	D1: 15 or 10, D3 & D6:10 or 7	1:1 D1 & 3: 12h, 18h, 24h D6: 24h, 30h, 36h	↓ mucositis GVHD(NS)
Huspeth 2013	47	15/10/10/10	10 mg/m^2 IV 12 hr after each MTX	↓ mucositis RFS(NS)

Torres A, et al. *Blut* 1989;58:63-68.
Nevill TJ, et al. *Bone Marrow Transplant* 1992;9:349-54.
Russell JA, et al. *Bone Marrow Transplant* 1994;14:397-401.
Sugita J, et al. *Bone Marrow Transplant* 2012;47:258-64.
Hudspeth, MP, et al. *Bone Marrow Transplant* 2013;48:46-9.

ASBMT CIBMTR

Many Options for FA Use, No Consensus

- Patient Selection
  - Prophylaxis for all HCT
  - Prophylaxis for risk of severe mucositis only
  - Treatment if significant mucositis only
- Dose 5 mg to 15 mg/m^2
- When to start – 6, 12, 18, or 24 hours
- Schedule and number of doses
  - Once after each MTX dose
  - q6h after each MTX dose
  - # of doses may vary due to time between

ASBMT CIBMTR

HCT Pharmacist's Recommendation

- Myeloablative regimens only
  - CyTBI
  - VPCyTBI
  - Big BuFlu
  - BuCy and CyBu
- Leucovorin 10mg/m^2 IV q6h x 3 doses, starting 12 hours post each dose of MTX
- RIC , RT and NMA
  - Same as above only if severe mucositis with day +6 and/or +11 or at provider discretion

ASBMT CIBMTR

Methods

- Hypothesis – Utilizing FA after each dose of MTX will improve likelihood of administering day +11 MTX by reducing mucositis
- Compare pre-guideline (prior year 2012) with post-guideline implementation
  - Consecutive patients
  - Leucovorin 10 mg/m^2 IV q6h x 3 doses
  - Starting 12 hours post each dose of MTX
- Myeloablative regimens only
- First transplants only

ASBMT CIBMTR

Methods - Endpoints

- Primary endpoint(Statistical test: Chi-Square)
  - Ability to administer full dose day +11 MTX
- Secondary endpoints
  - Incidence (Statistical test: Chi-Square)
    - — TPN and PCA use (Statistical test: Chi-Square)
    - — Length of stay
    - — Maximum grade mucositis (Statistical test: Mann-Whitney U)
  - Cumulative incidence (Statistical test: Log-rank)
    - — aGVHD and cGVHD
    - — NRM, Relapse and OS at 1 year

ASBMT CIBMTR

Patient Characteristics

	Pre-guideline	Post-guideline	p-value
N	31	27	
Age	42 (18-60)	34 (21-55)	0.1899
Gender			0.2643
Male	15	17	
Female	16	10	
MTX Dose			0.8686
Standard (15/10/10/10)	20	19	
Int (10/10/10/10)	1	1	
Mini (5-10/5/5/5)	10	7	
Disease			0.4170
ALL/AML	25 (8, 17)	21 (9, 12)	
CLL/CML	3 (1,2)	3 (0, 3)	
MPD	0	1	
NHL/HD	3	2	
Donor Match			0.4859
MRD	12	7	
MMRD	0	1	
MUD	13	13	
MMUD	6	6	
rATG			**0.0185**
Yes	10	17	
No	21	10	
DRI			0.9365
Low	2	3	
Int	23	19	
High	6	5	
HCT-CI			0.5534
0-2	22	21	
>/= 3	9	6	
Regimens			0.7847
BuCy or CyBu	15	13	
Busulfan/Fludarabine	5	4	
TBI-based (CyTBI, VPCyTBI)	11	10	

ASBMT CIBMTR

Results – Primary Endpoint

	Pre-guideline	Post-guideline	P value
N	31	27	
Received day + 11 MTX 100%	**15 (48.4%)**	**23 (85.2%)**	**0.0025**
Reduced dose D3, D6 or D11	11 (35.5%)	2 (7.4%)	
FA 10mg IV q6h x 8 doses*	15 (48.4%)	NA	
FA added day +6 only	5	NA	
FA added day +11 only	8	NA	
FA added day +6 & +11	2	NA	

* 10mg flat dose

ASBMT CIBMTR

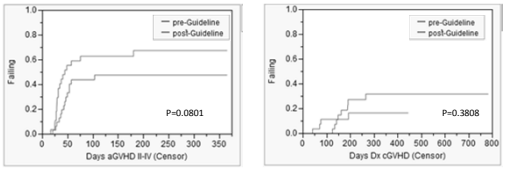
Results – Secondary Endpoints

	Pre-guideline	Post-guideline	P value
N	31	27	
Mucositis Grade (Median)	3	2	0.9984
Mucositis Grade 3/4	17 (54.8%)	10 (37%)	
TPN	18 (58.1%)	13 (48.2%)	0.4499
Median TPN days	11 (range 5-55 days)	5 (range 3-13 days)	
Median TPN Start Date	7	6	
PCA	27 (87.1%)	17 (63%)	**0.0306**
Median PCA days	10.5 (range 6-54 days)	7 (range 1-13 days)	
Median PCA Start Date	7	7	
Median LOS	27 (range 22-75 days)	24 (range 20-33 days)	

48.4 % of pre-guideline patients received some FA late, and post-guideline still better. Suggesting early FA use better.

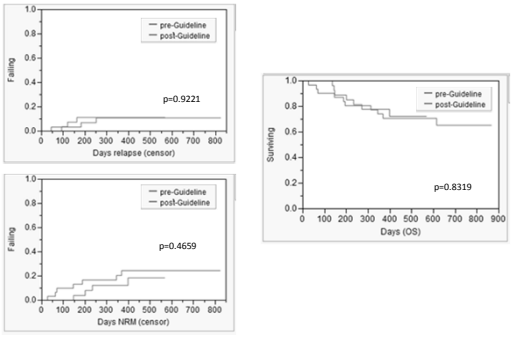
ASBMT CIBMTR

Secondary Endpoints: GVHD



ASBMT CIBMTR

Secondary Endpoints: Relapse, NRM & OS



ASBMT CIBMTR

ARS

In this study, the use of folinic acid (FA) after each dose of methotrexate for the prevention of GVHD resulted in:

a) Increased use of TPN
b) Increased incidence of cGVHD
c) Increased ability to receive day + 11 MTX
d) Increased NRM
e) All of the above

ASBMT CIBMTR

Conclusions

- FA rescue after MTX for GVHD prophylaxis significantly improves the probability of administering day +11 MTX and reduces mucositis as evidence by significantly less utilization of PCA and a trend towards less TPN use without adversely impacting GVHD, relapse and survival
- The HCT pharmacist plays an important role in the review of literature, research, development of guidelines and education of the HCT team

ASBMT CIBMTR

Coauthors

Travis Shelton, PharmD, BCPS, BCOP
James Slack, MD
Jose Leis, MD, PhD
Veena Fauble, MD
Lisa Sproat, MD
Jeanne Palmer, MD
Pierre Noel, MD (BMT Program Director)

Special thanks to Dr. James Slack for his assistance with our program database and statistics.

ASBMT CIBMTR