Launching a Busulfan Kinetic Pharmacy Service: Real-World Case in Community Hospital Setting

ONCOLOGY PHARMACOTHERAPY MAY 20, 2023

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Objectives

Review importance of therapeutic drug monitoring for busulfan in allogeneic stem cell transplantation

Describe our process for training and implementation of in house busulfan pharmacokinetic monitoring

Apply knowledge learned to a patient case

Background

Busulfan is a bifunctional alkylating agent utilized during chemotherapy conditioning prior to stem cell transplantation (SCT)

- Dose limiting toxicity is veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS)
- Considerable interpatient variability in busulfan pharmacokinetics (PK)
- Narrow therapeutic index of busulfan systemic exposure

Individualized busulfan dosing should be considered depending on the regimen and is based on harmonized busulfan plasma exposure unit (BPEU) using area under the curve (AUC)

Significant advancements have been made over the past 30 years since initial reports of busulfan therapeutic drug monitoring (TDM)

Palmer J et al. Biol Blood Marrow Transpl. 2016;22:1915–1925.
McCune JS, et al. Biol Blood Marrow Transplant. 2019 Sep;25(9):1890-1897.
McCune JS, et al. Ther Drug Monit. 2021 Oct 1;43(5):657-663.

Background

TDM or PK-directed dosing of busulfan in SCT conditioning is associated with improved patient outcomes

- ↑ Engraftment rates
- ↓ Hepatotoxicity (VOD/SOS) rates
- ↓ Relapse rates in chronic phase chronic myeloid leukemia

ELSEVIER

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT American Society for Blood and Marrow Transplantation

Guideline

Personalizing Busulfan-Based Conditioning: Considerations from the American Society for Blood and Marrow Transplantation Practice Guidelines Committee

Jeanne Palmer [1,*], Jeannine S. McCune [2,†], Miguel-Angel Perales [3], David Marks [4], Joseph Bubalo [5], Mohamad Mohty [6], John R. Wingard [7], Angelo Paci [8], Moustapha Hassan [9], Christopher Bredeson [10], Joseph Pidala [11], Nina Shah [12], Paul Shaughnessy [13], Navneet Majhail [14], Jeff Schriber [15], Bipin N. Savani [16], Paul A. Carpenter [17]

Background

Busulfan undergoes rapid degradation at room temperature

- Requires strict adherence to storage/shipping on ice

Turnaround time for send outs ~36 hrs vs. ~12 hrs after 1st dose with in-house lab testing and PK analysis

In-house busulfan PK analysis eliminates the need to send out samples which increases efficiency and accuracy of dosing recommendations

Potential over-dosing could lead to increased toxicities (VOD/SOS, seizure, etc.) while under-dosing may reduce efficacy

Palmer J et al. Biol Blood Marrow Transpl. 2016;22:1915–1925.
Hassan M, et al. J Pharm Biomed Anal. 1986;4:95–101.

Implementation and Training

Implementation

- This was a multidisciplinary collaboration between lab, pharmacy, and nursing teams at Baptist Hospital of Miami
- Laboratory
  - LC-MS/MS technology procured to determine and analyze busulfan plasma concentrations
  - Busulfan lab order set created for ordering and reporting results through electronic health record (EHR)
  - Specialized equipment required for processing and storage of samples and controls

Implementation (continued)

- Nursing
  - Internal busulfan requisition form created
- Pharmacy
  - Software license for Phoenix WinNonlin program purchased for PK analysis
  - End users completed training and competency on program and calculations
- Administrative
  - Proactive risk analysis completed to comply with FACT requirements
  - Standardized operating procedure (SOP) and competency developed

Baptist Hospital

BAPTIST HEALTH SOUTH FLORIDA

IV EVERY 6 HOURS BUSULFAN REQUISITION

PATIENT INFORMATION

Patient Name: _____

Medical Record Number: _____ Date of Birth: _____

Actual Weight (kg): _____ Genetic Sex *(check one)*: ☐ Male ☐ Female

Dosing Weight (kg): _____ Diagnosis: _____

Height (cm): _____ ICD-10 Code: _____

DOSE INFORMATION

Date of Dose: _____

Dose Given (mg): _____

Busulfan Manufacturer/Lot Number (if generic Busulfan):

_____

Dose Number: _____ (write "test" if test dose)

Total # of regimen doses: _____

Desired Target Range: _____ (AUC) mg*h/L

Dosing interval (check one): ☐ every 6 ☐ every 8 ☐ every 12 ☐ every 24

CONTACT INFORMATION

Attending MD: _____

FOR RESULTS CONTACT

Verbal report recipient: _____

Contact Number: _____

Email address: _____

Fax Number (if app): _____

IV Every 6 Hours Busulfan Dose 1 or Test Dose

Infusion Time is Typically 120 minutes

Infusion Start Time: _____ Infusion Stop Time: _____

	Actual sample Collection Time	Initials
End of Infusion		
End of Infusion **+ 15 min**		
End of Infusion **+ 30 min**		
End of Infusion **+ 2 hours**		
End of Infusion **+ 3 hours**		
End of Infusion **+ 4 hours**		

DRUG INTERACTIONS

Please indicate if the patient has taken any of the following drugs within the past 30 days: Deferasirox, Metronidazole, Itraconazole, Isavuconazole, Voriconazole, Posaconazole, Azithromycin, TKIs, Acetaminophen, Ivosidenib, Enasidenib

Drug: _____ Date of last dose: _____

Drug: _____ Date of last dose: _____

Drug: _____ Date of last dose: _____

Drug: _____ Date of last dose: _____

CONDITIONING REGIMENS

Please indicate any other drug/treatment the patient has taken/will take as part of their current conditioning regimen:

☐ Cyclophosphamide ☐ ATG ☐ Etoposide

☐ Fludarabine ☐ Thiotepa ☐ TBI

☐ Melphalan ☐ Other: _____

1. Please draw a **minimum of 6 mL** of blood in a dark green top tube (sodium heparin).
2. Label each sample with **exact time of collection**
3. **Place samples immediately on ice.** Busulfan degrades quickly at room temperature.
4. Send samples in **separate bags** to the lab with a copy of this Requisition form. Samples MUST be received in the lab **within 45 minutes after sample drawn.**
5. Centrifuge at 4 °C. Separate plasma into a plastic tube labeled with Patient name, MR Number, Date, and exact time of draw. **Keep the samples refrigerated.**

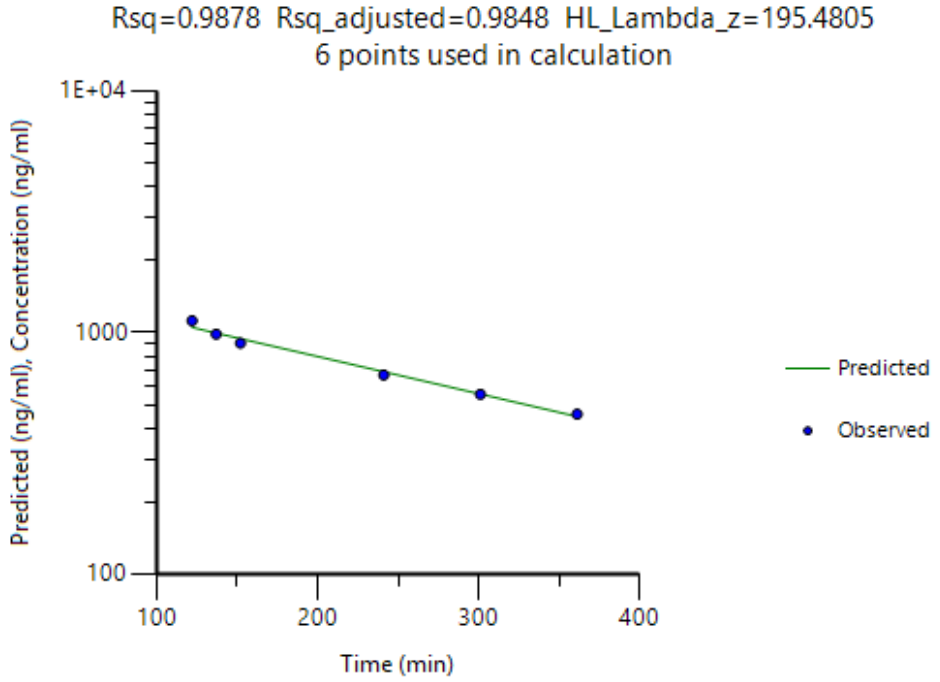
IMPORTANT:

- Accurate blood draw and infusion start/stop times are critical to busulfan PK analysis.
- Send to the Lab the original Requisition. A physician or designee MUST sign the requisition and contain all the information completed.

Process Workflow

PK Report

Subject	Nominal_Time (min)	Time (min)	Concentration (ng/ml)	Dosing_Weight (kg)	Dose (mg)	Infusion_length (min)
	0	0	0	72.5	58	122
	120	122	1121			
	135	137	987			
	150	152	906			
	240	241	669			
	300	301	557			
	360	361	461			



Subject	Dose (mg)	Dosing_Weight (kg)	AUCINF (hr*mg/L)	Css (ng/ml)	CL (ml/min)	CLperKg (ml/min/kg)
[redacted]	58.00	72.50	6.39	1065.54	151.20	2.09

Pharmacist Training

Objectives

- Explain the rationale for therapeutic drug monitoring for busulfan
- Identify important drug interactions with busulfan
- Utilize the Phoenix WinNonlin program to determine individualized patient clearance
- Calculate recommended dose of busulfan to achieve the target AUC

Process

- Review of educational materials including literature and webinars
- Watch Phoenix WinNonlin demo
- Practice with patient case examples
- Complete and successfully pass internal competency assessment

Competency Assessment

General Questions

- Busulfan PK
- Drug interactions
- TDM range and harmonized units (AUC)

$$CL = \frac{\text{Administered dose 1}}{AUC_{0-\infty}}$$

$$\text{Personalized dose} = CL \times \text{target AUC}$$

$$Css = \frac{AUC_{0-\infty}}{\text{dosing frequency}}$$

Patient Case Examples

- Knowledge of equations and calculations
- Unit conversions
- Software exercises
- Interpretation of results

$$\frac{\text{Css in } \frac{ng}{mL} \times \text{dosing frequency in hours}}{1000} = \text{AUC in } \frac{mg \times h}{L} \text{ per dose}$$

Patient Case

Patient Case

68 y/o male with relapsed AML s/p salvage chemotherapy

- Bone marrow biopsy after 1 cycle demonstrates persistent disease

Decision is made to proceed with conditioning chemotherapy Busulfan/ Melphalan/ Fludarabine + Anti-thymocyte globulin (ATG) followed by matched related donor T-cell depleted allogeneic peripheral blood stem cell transplant

Pre-transplant assessment reveals patient to be at risk for VOD/SOS post transplantation

Opportunities to mitigate VOD/SOS risk include

- Busulfan therapeutic drug monitoring
- Avoiding hepatotoxic medications
- Avoiding potential drug interactions
- Close monitoring to prompt early diagnosis and treatment (daily weights, liver function tests, fluid status)
- Ursodiol prophylaxis

Patient Case (continued)

Patient Case (continued)

Busulfan target ranges

- Average AUC target 4.2-5.4 mg*hr/L per dose (Css 700-900 ng/mL)
- Cumulative AUC target 50.4-64.8 mg*hr/L (for 12 dose regimen)

Dose was adjusted to target an estimated average AUC 4.2 mg*hr/L per dose

- Lower end of therapeutic range due to VOD/SOS risk factors

Patient was discharged on D+15 post transplant with no signs or symptoms of VOD/SOS

Baptist Health South Florida

Miami Cancer Institute

Baptist health south Florida

8900 N Kendall Dr, Miami, FL 33176 - Phone: 786 . 596 . 2000

Pharmacokinetics Report - Busulfan

Subject	Dose (mg)	Dosing_Weight (kg)	AUCINF (hr*mg/L)	Css (ng/ml)	CL (ml/min)	CLperKg (ml/min/kg)
10	58	72.5	6.39	1065.54	151.2	2.09

Target AUC (hr*mg/L)	Target Css (ng/ml)	Number of doses given	remaining doses	total number of doses	New Css (ng/ml)	New AUC (hr*mg/L)	recommended dose (mg)
4.2	700	2	10	12	626.9	3.76	34

Harmonized AUC (dose 1)	6.39	mg x hr/L
Target Cumulative AUC	50.39	mg x hr/L
Target Average AUC	4.20	mg x hr/L
Css (Dose 1)	1065.5	ng/ml
Target Css average exposure	700	ng/ml
Clearance rate (per Kg)	2.09	ml/min/kg
Recommended dosing type	Q 6h	
recommended dose	34	mg
Dose change	-41.2	%
Dose recommended starts at dose #	3	
Dose recommended end at dose #	12	

	AUC (hr*mg/L)	Cumulative AUC (hr*mg/L)
Dose 1	6.39	6.39
Dose 2	6.39	12.78
Dose 3	**3.76**	16.54
Dose 4	**3.76**	20.30
Dose 5	**3.76**	24.06
Dose 6	**3.76**	27.83
Dose 7	**3.76**	31.59
Dose 8	**3.76**	35.35
Dose 9	**3.76**	39.11
Dose 10	**3.76**	42.87
Dose 11	**3.76**	46.63
Dose 12	**3.76**	50.39

SCHEDULED TIME FROM END OF INFUSION (EOI)	BUSULFAN LEVEL (ng/mL)
EOI	1121
EOI + 15 MINUTES	987
EOI + 30 MINUTES	906
EOI + 2 HRS	669
EOI + 3 HRS	557
EOI + 4 HRS	461

Patient Data (Aug 2022 – Apr 2023)

Patient	Starting Dose	Dose # Adjusted	Final Dose	% Dose Adjustment
1	52	3	46	-11.5%
2	68	4	45	-33.8%
3	52	3	43	-17.3%
4	52	3	52	0%
5	50	3	55	10%
6	68	3	72	5.9%
7	60	3	69	15%
8	50	3	41	-18%
9	56	3	49	-12.5%
10	64	3	76	18.8%
11	58	3	34	-41%
12	79	3	70	-11.4%

Doses are adjusted to target harmonized area under the curve (AUC) 4.2-5.4 mg*h/L.

Baptist Experience

Historically sent over 30 busulfan samples to outside lab

Dose adjustments on average completed at dose 7

Post-implementation dose adjustments on average performed by dose 3

In house PK resulted in dose adjustment on average 4 doses (24 hours) sooner

Patient data to date shows similar dosing to send out

With increased data we hope to show that in house PK is more accurate (less degradation in handling) and associated with improved tolerability and efficacy (preventing over- or under-dosing)

Summary and Future Directions

Personalized busulfan dosing has the potential to improve patient outcomes following stem cell transplant

Implementation of a busulfan PK pharmacy service was possible due to collaboration with other departments and development of a comprehensive training program

Further data analysis will be important to evaluate outcomes and identify opportunities for research and process improvement

Self Assessment Question

Which of the following is true as it relates to the importance of busulfan therapeutic drug monitoring?

a. Low busulfan plasma exposure is associated with higher rates of graft rejection and relapse
b. High busulfan plasma exposure is associated with increased hepatotoxicity and nonrelapse mortality
c. Busulfan has high inter- and intra- patient pharmacokinetic variability and a narrow therapeutic index
d. Busulfan TDM has been associated with improved engraftment rates
e. All of the above are true

Self Assessment Question

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c. Busulfan has high inter- and intra- patient pharmacokinetic variability and a narrow therapeutic index
d. Busulfan TDM has been associated with improved engraftment rates
e. **All of the above are true**

Acknowledgements

Samer Hay RPh, PhD, BCOP
Lela Hall PharmD, BCOP
Claudia Martin Diaz PharmD, BCPS, BCOP
Eduardo Guizan Corrales PharmD, BCOP
Leonette Kemp PharmD, BCOP
Tiba Al Sagheer PharmD BCOP, BCACP

Special thanks to
Esther Lazo MS, MT and BHM lab team
Annette Caravia MSN, APRN, BMTCN, 6 Hope nursing leaders and nursing team
Moe Shwin PharmD, BCOP and Dina Dumercy McHenry PharmD, MBA, BCOP, CSSGB, CPh

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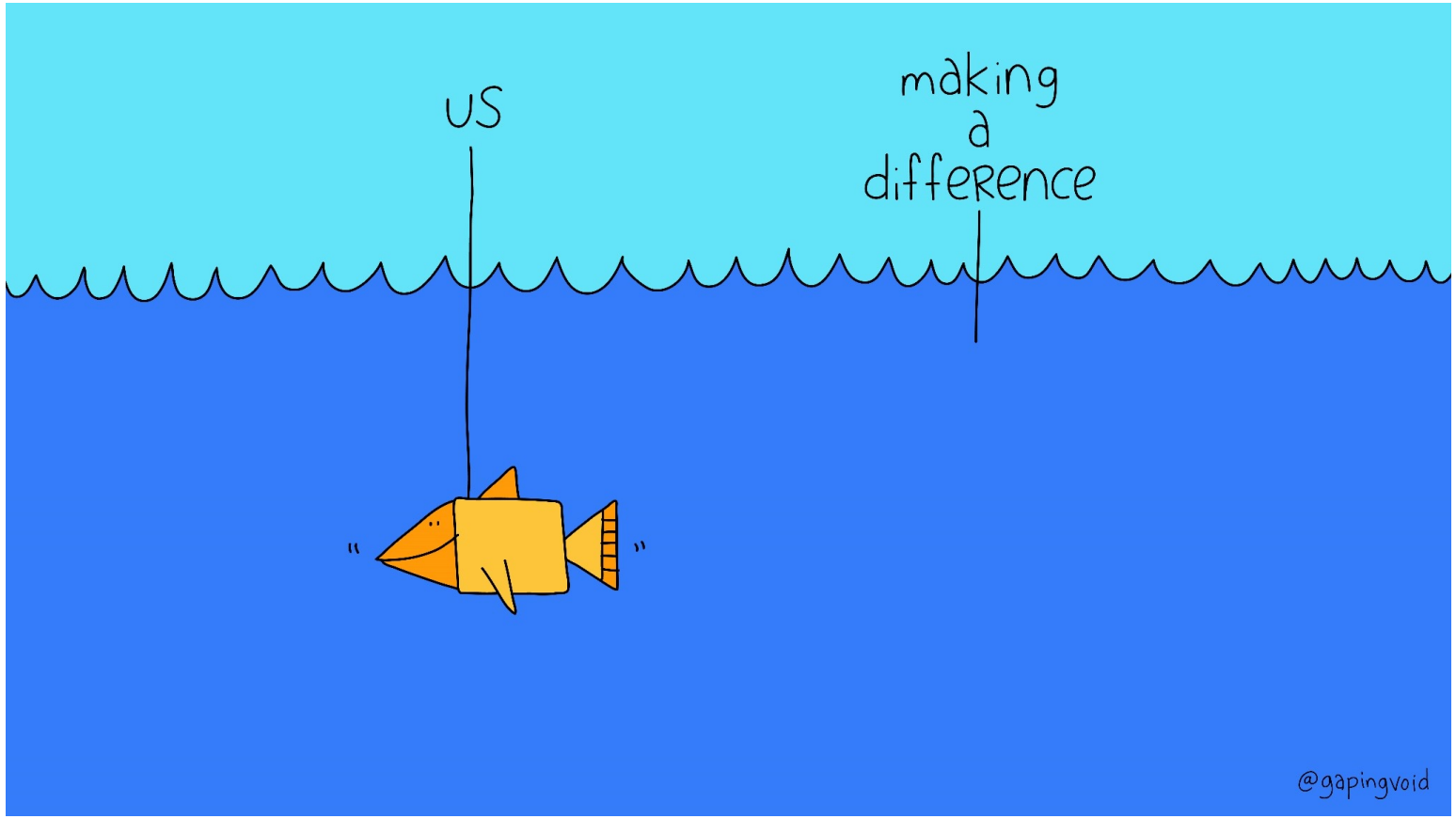
Thank You!



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