Utilizing Intravenous Busulfan Pharmacokinetics for Dosing Busulfan And Fludarabine Conditioning Regimens In Institutions Where The Capability Of Doing Pharmacokinetics Is Not Present

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Disclosure

- The speaker has no actual or potential conflict of interest in relation to this presentation.

Learning Objective

- Describe a method by which pharmacokinetically guided IV busulfan-based conditioning regimens may be implemented in institutions where the ability to perform in-house pharmacokinetics is not present.

Question 1

At your institution how are busulfan pharmacokinetics (PK) addressed?

A. PK is not routinely performed
B. PK on samples performed in-house
C. PK on samples sent to outside laboratory for analysis

Overview

- Background
- Study rationale
- Methods
- Results
- Conclusions

Busulfan

- Busulfan has been effectively used for hematopoietic stem cell transplant for decades[1-4]
- Safety and efficacy of busulfan appears to be influenced by the PK parameters of the patient[5]
- IV busulfan reduces PK variability and improved outcomes have been linked with precise targeting of busulfan systemic exposure with PK based dose adjustment[6-10]
- Toxicities commonly associated with busulfan:
  - Myelosuppression
  - Gastrointestinal
  - Hepatic sinusoidal obstruction syndrome

PK – Pharmacokinetics; IV - Intravenous

Pharmacokinetics

- Busulfan pharmacokinetics are described by a 1-compartment model[11]
- Aim to achieve a constant AUC
  - Clearance = Dose/ AUC
  - Established AUC target levels are based on mg/m^2 daily dosing schedule
  - At our institution:
    - Myeloablative AUC target ~ 5000 - 6000μM*min
    - Reduced intensity AUC target ~ 4000μM*min

AUC - Area under the curve

Question 2

Q- Which of the following is a well described non-hematologic dose limiting toxicity of busulfan?

A: Sinusoidal Obstruction Syndrome (SOS)
B: Cardiomyopathy
C: Encephalopathy
D: Progressive Multifocal leucoencephalopathy (PML)

Study Rationale and Hypothesis

- Rationale: Lack of data describing the use of IV busulfan in institutions where the ability to perform in-house PK is not present
- Hypothesis: We propose that IV busulfan may be safely and effectively used in institutions where in-house busulfan assay is not available

PK – Pharmacokinetics; IV - Intravenous

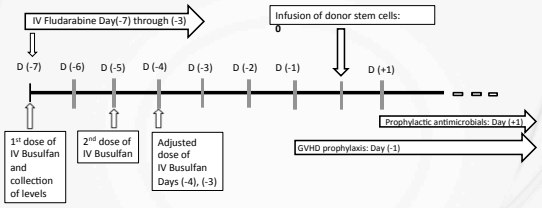
Study Design

Retrospective study

- Adult allogeneic stem cell transplants performed at University of Kentucky Markey Cancer Center between November 2012 - September 2013
- Patients who received a conditioning regimen comprising of IV busulfan and IV fludarabine
  - Actual body weight used to calculate BSA
  - Corrected body weight used if weight >125% of actual body weight
- Busulfan PK calculations performed by the Seattle Cancer Care Alliance Pharmacokinetics Laboratory, Seattle, WA

PK – Pharmacokinetics; IV – Intravenous; BSA – Body surface area

Dosing Strategy



Dosing Scheme:
RIC: IV Busulfan 100mg/m² Days (-7), (-5)
MAC: IV Busulfan 130-150mg/m² Days (-7), (-5)
IV Busulfan dose adjusted for targeted AUC Days (-4), (-3)
IV Fludarabine 30 mg /m² Days (-7), (-6), (-5), (-4), (-3)
Rabbit antithymocyte globulin at a dose of 1.5 mg/kg on Day (-3), (-2), (-1)

IV Busulfan levels drawn at:
- End of busulfan infusion
- 15 minutes after completion of busulfan infusion
- 4 hours after START of busulfan infusion
- 5 hours after START of busulfan infusion
- 6 hours after START of busulfan infusion
- 8 hours after START of busulfan infusion

Data Analysis

Patient Characteristics

Number of patients	14
Age at the time of transplant (years)	48.5 (range: 23-61)
Diagnosis	
AML	8
HLH	1
MDS	3
ALL	2
Disease Status	
CR	11
N/A	3
Regimen	
IV Busulfan/ IV Fludarabine	9
IV Busulfan/ IV Fludarabine + Thymoglobulin	5
CD34 Cells Infused (10^6 cells/kg)	7 (range: 2.7-15)

AML- Acute myeloid leukemia; HLH - Hemophagocytic lymphohistiocytosis; ALL- Acute lymphocytic leukemia; CR – Complete remission
Data are represented as median (range)

Patient Characteristics

Donors	
Related	5
Unrelated	9
HLA Match	
9/10	2
10/10	12
Regimen Intensity	
AUC 6000 μM*min	8
AUC 4500 μM*min	1
AUC 4000 μM*min	5
Body Surface Area (m^2)	1.825 (range: 1.5 – 2.1)

PK – Pharmacokinetics; AUC - Area under the curve; Data are represented as median (range)

Results

	For patients with target of 6000μM*min	**For patients with target of 4000μM*min**
AUC Achieved prior to PK adjustment	4482.5 (range: 3652 - 5771)	3221 (range: 2556 - 4579)
Daily AUC Estimate	5380.5 (range: 4821 - 5978)	4004 (range: 3732 - 4155)
Dose Adjustment (mg/m^2)	53.3 (range: 5 - 91)	47.9 (range: -25 - 85)

AUC - Area under the curve; Data are represented as median (range)

Results

Incidence of acute GVHD Acute grade I Acute grade II – IV	 2 (14.3%) 4 (28.6%)
Incidence of chronic GVHD	2 (14.3%)
Median time to achieve engraftment (days) ANC > 500/uL Platelets > 20,000/uL	 15 (range: 10 - 19) 17 (range: 11 - 25)
Cytomegalovirus viremia	2 (14.3%)
Relapse	1 patient (Day + 88 post- transplant)
Median follow-up period	6 months

GVHD – Graft versus host disease; Data are represented as median (range)

Conclusion

- PK guided IV busulfan-based conditioning regimens may be implemented at institutions where the ability to perform in-house PK is not present
- Larger sample size and longer follow-up period are necessary to definitively determine the effect of our strategy on patient outcomes

Limitations

- Retrospective study
- Single center data
  - Small group of patients
- Limited follow-up period
- Post dose PK levels were not collected
  - Data based on projected AUC

AUC - Area under the curve; PK - Pharmacokinetics

Thank you

Questions?

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