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A Real Time Pharmacokinetic Assay to Allow for Targeted Melphalan Dosing in Multiple Myeloma Patients Undergoing Autologous Transplant

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Disclosures

- I have no conflict of interest to disclose in regards to the content of this presentation.

- I will not be discussing any off-label use of drugs during this presentation.

Learning Objective

- Outline the methods required to perform real-time melphalan pharmacokinetic testing in multiple myeloma patients undergoing autologous stem cell transplantation

Multiple Myeloma

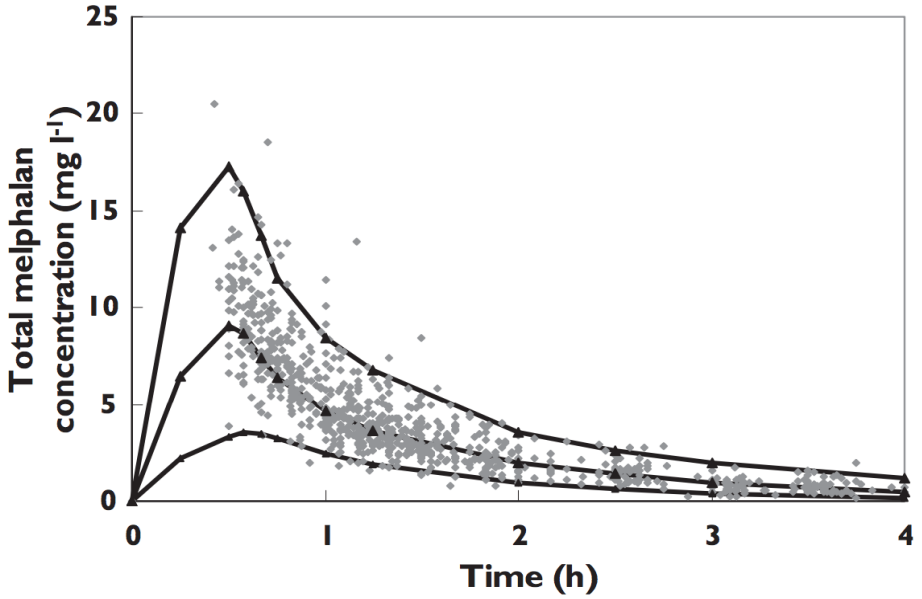
- Second most common hematologic malignancy
- Plasma cell disorder characterized by bone lytic lesions, hypercalcemia, and kidney dysfunction
- Remains incurable and relapse is inevitable despite the addition of newer immunomodulator and proteasome inhibitor drugs
- Autologous stem cell transplant remains standard of care in upfront treatment based on randomized trials demonstrating improved PFS

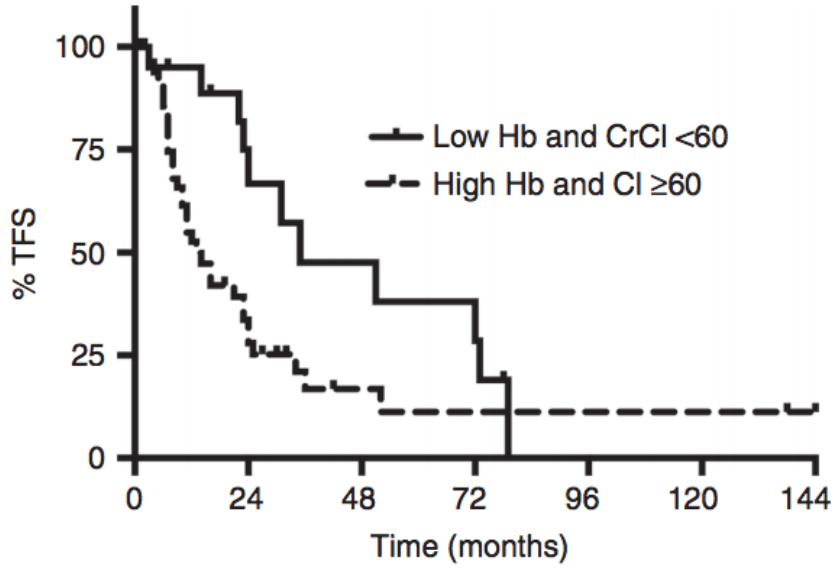
Attal M, et al. N Engl J Med 2017. 376(14):1311-20.
Palumbo, A, and Rajkumar SV. Leukemia 2009. 23(3):449-56.
Robak P, et al.Cancer Treat Rev 2018. 70:199-208.

PFS, progression-free survival

Variability in High Dose Melphalan

- High interpatient variability in melphalan exposure (AUC) is observed when using BSA-based dosing, resulting in suboptimal exposure and response.
- Highly bound to proteins in red cell membranes and undergoes 40% renal elimination.
- Low creatinine clearance and hemoglobin, mediators of melphalan PK, are strong predictors of improved survival an increased toxicity.

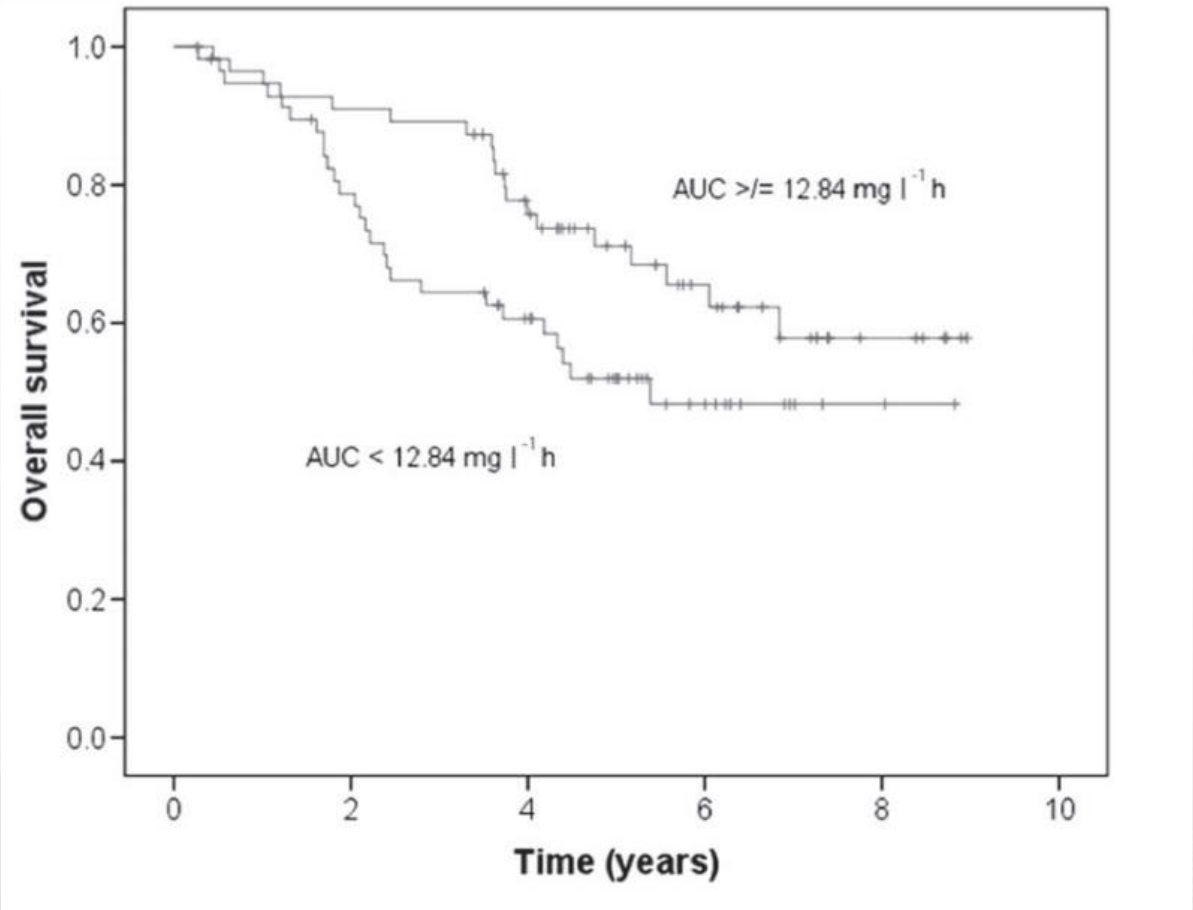




1. Nath CE, et al. Bone Marrow Transplant 2007. 40(7):707-8.
2. Nath CE, et al. Br J Clin Pharmacol 2010. 69(5): 484-97.
3. Sweiss K, et al. Bone Marrow Transplant 2019; 54(12):2018-7.

AUC, area under the plasma drug concentration-time curve; BSA, body-surface area; PK, pharmacokinetics

Melphalan Exposure Impacts Outcomes



A high melphalan AUC (above the median of 12.84 mg*h/L in this cohort) is associated with improved survival

1. Nath, C.E., et al., Br J Clin Pharmacol 2016. 82(1):149-59.

Melphalan PK Testing

- Differences in PK testing methodology
  - Variability in melphalan infusion times
  - No standardized procedures for proper handling and delivery of blood samples
  - No standard PK sampling window established
  - HPLC versus LC-MS/MS analysis

- Melphalan test dose strategies have failed to achieve therapeutic melphalan concentrations above the limit of assay detection, leading to variable AUC levels.

- Melphalan, 100mg/m^2 on day -2 and -1, allows for potential day -1 dose modification if day -2 PK testing with rapid turnaround is performed.

Shah, G., Blood, 2017. 130: p. 2023.

HPLC, high performance liquid chromatography; LC-MS/MS, liquid chromatography-mass spectrometry

Our goal was to develop a clinically feasible, reproducible and rapid method of measuring melphalan PK that allows for real-time dose adjustments in clinical practice.

PK Study Schema

Assay development and validation

- SOPs for sample collection and processing
- Preparation of calibration standards
- Optimization of HPLC conditions and MS parameters
- Development and validation calibrations curves

Melphalan 140 or 200 mg/m2

- Divided over days −2 and -1
- Infusion times ranged from 30 to 40 minutes, depending on the final dose
- A 14-mL NS flush administered through the primary tubing (start of infusion time).
- After melphalan infusion, a second 14-mL flush was administered (end of infusion)

PK blood draws

Blood drawn at 0, 5, 15, 30, 40, 75, 150, 240, 360, and 480 minutes after end of infusion on day-2 (n=20) and day -1 (n=5)

Blood draw logistics

Samples immediately collected in pre-chilled, pre-labeled heparinized tubes, placed in specimen bags on ice, and delivered to PK lab within 5 minutes of blood draw.

LC-MS/MS analysis

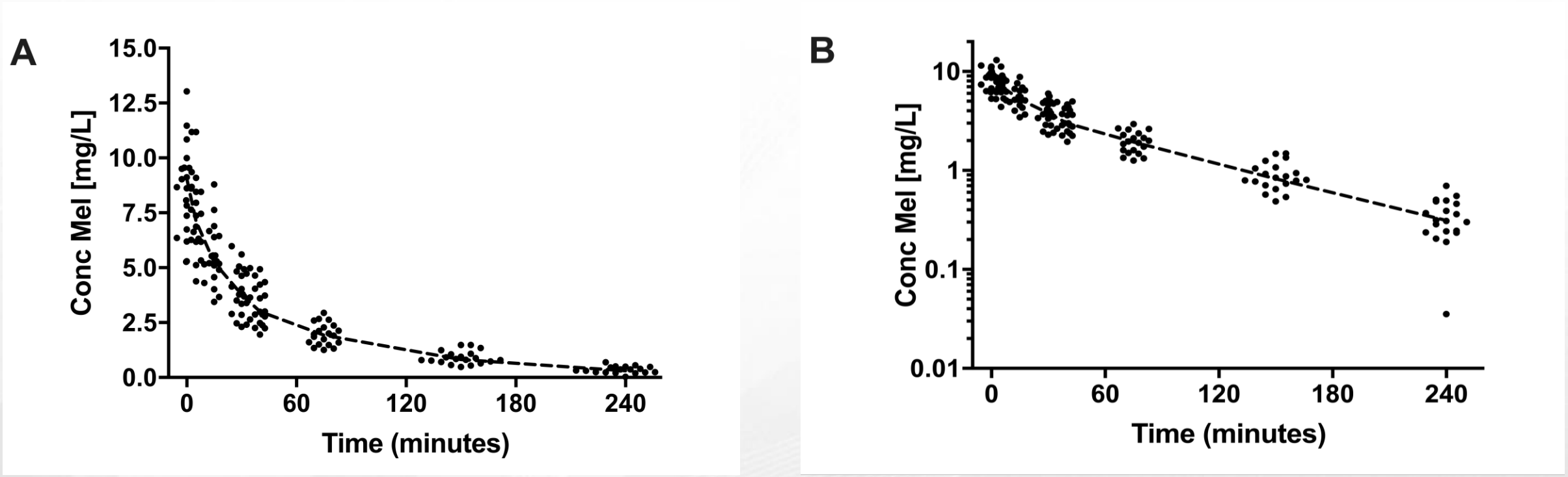
6-12 months after start of study

Day - 2 | Day - 1 | Day 0 | Day + 90

SOP, standard operating procedures

Results-Median AUC

Median single-day AUC on day -2 was 7.49 (4.95-11.28) mg*h/L



Data are presented in A) linear and B) log scale.

Results – No Intrapatient Variability Observed

- In the first 5 patients, we performed PK analysis on days -2 and -1
- AUC from day -2 correlated with day -1 (r=0.8), establishing that day -2 PK could be used to adjust the day -1 dose using a linear, dose-proportional calculation for future PK-directed studies .

Results- Dosing Simulations

- In patients whose day -2 AUC fell below the median, a day -1 dose increase to target the total target AUC would be required.
- In patients whose day -2 AUC fell above the median, a day -1 decrease to target the total target AUC would be required.

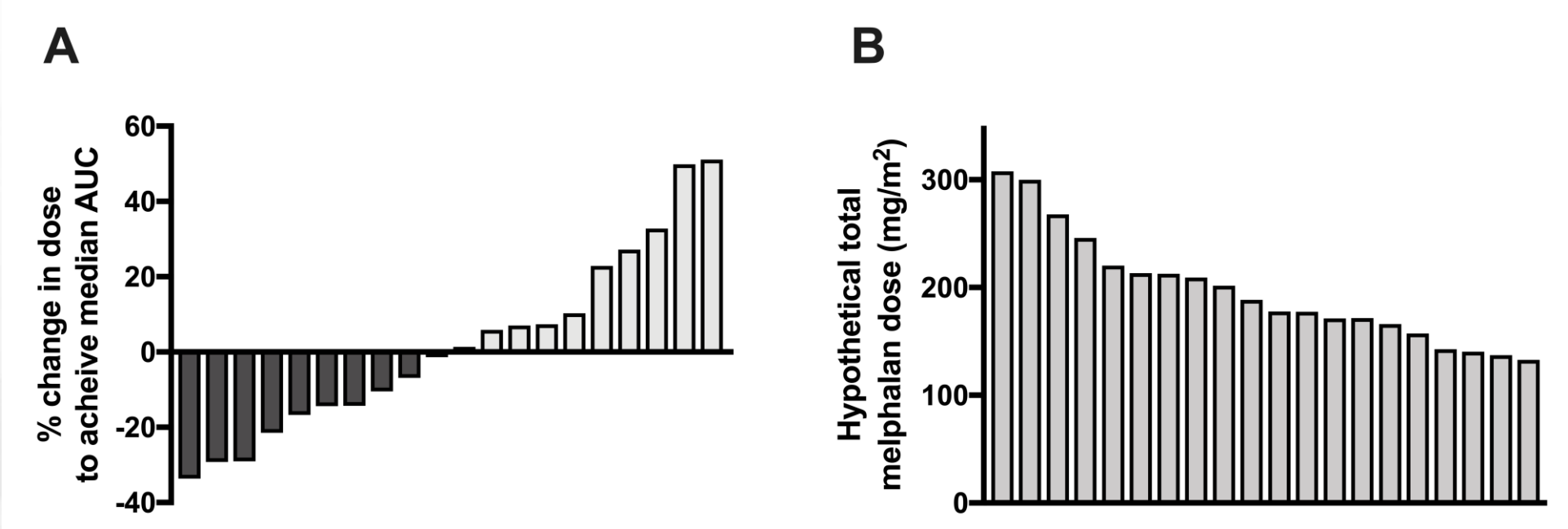
Equation 1: $\text{Clearance (L/h)} = \frac{\text{Administered Day -2 dose (mg)}}{\text{AUC}_{0-\infty}\ \text{(mg*h/L)}}$

Equation 2: Personalized Day -1 dose (mg) = Clearance (L/h) x target AUC (mg*h/L)

L, liter; h, hour; mg, milligram

Results – Dose Change Simulations

Based on each patient's day -2 PK profile, we calculated the theoretical dose for day -1 in order to target the total median melphalan AUC and compared it to the BSA-based dose received.



A) Percent change in day -1 melphalan dose necessary to achieve the median AUC
B) Hypothetical total melphalan dose (mg/m^2) required to target the median AUC

Results- Developing Alternative Sampling Strategies

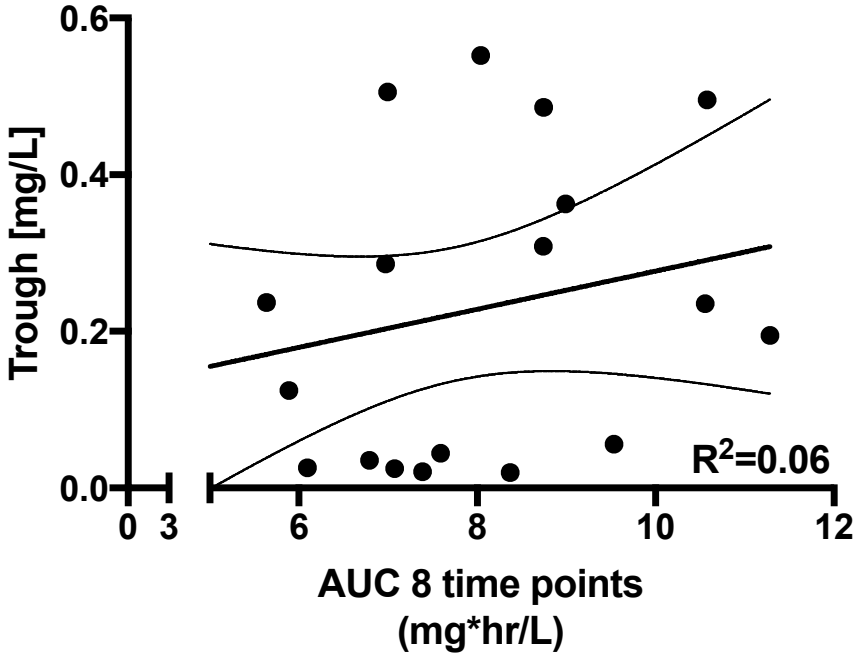
- Clinically applicable sampling strategy needed
  - —Blood draws at 8 or 10 time points (0, 5, 15, 30, 40, 75, 150, 240, 360, and 480 minutes) is not feasible in clinical practice

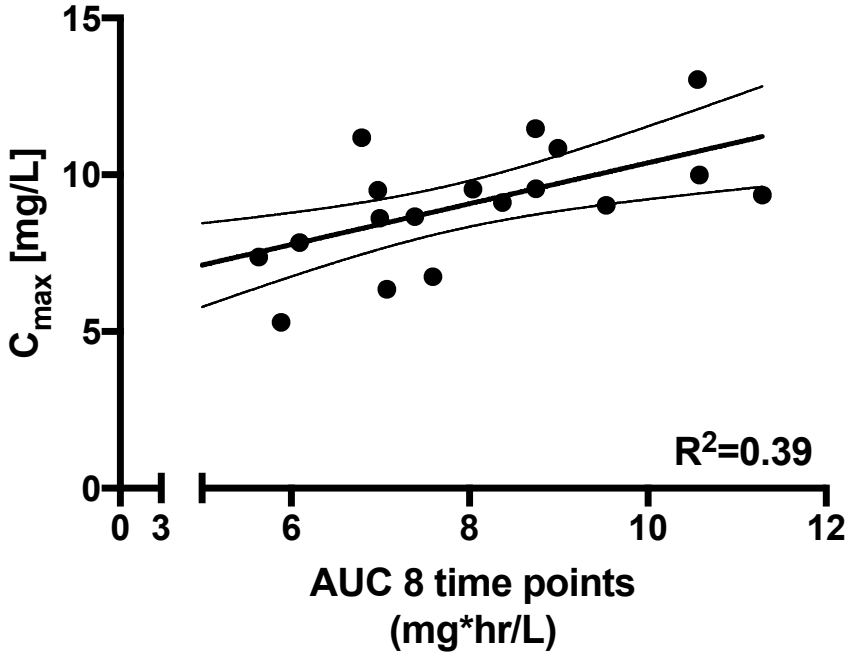
- To maximize clinical application, we sought to determine an abbreviated blood sampling schedule using D-optimality analyses

- The mean AUC calculated from all 8 sampling points was sequentially compared to the AUC obtained from fewer sampling points in a descending manner while maintaining an R-squared value >90%

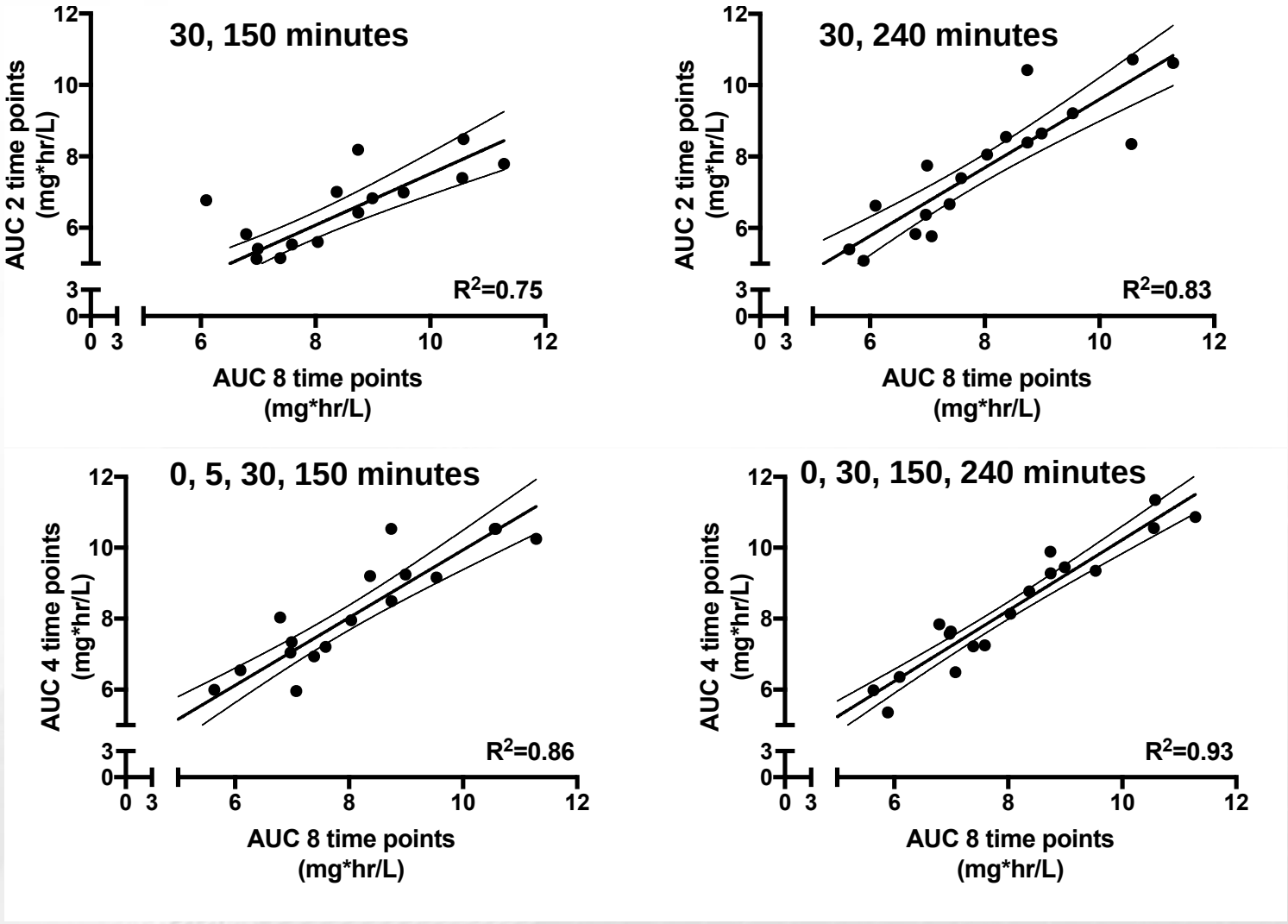
Results- Developing alternative sampling strategies

Melphalan AUC using single time points to determine PK did not correlate with observed AUC

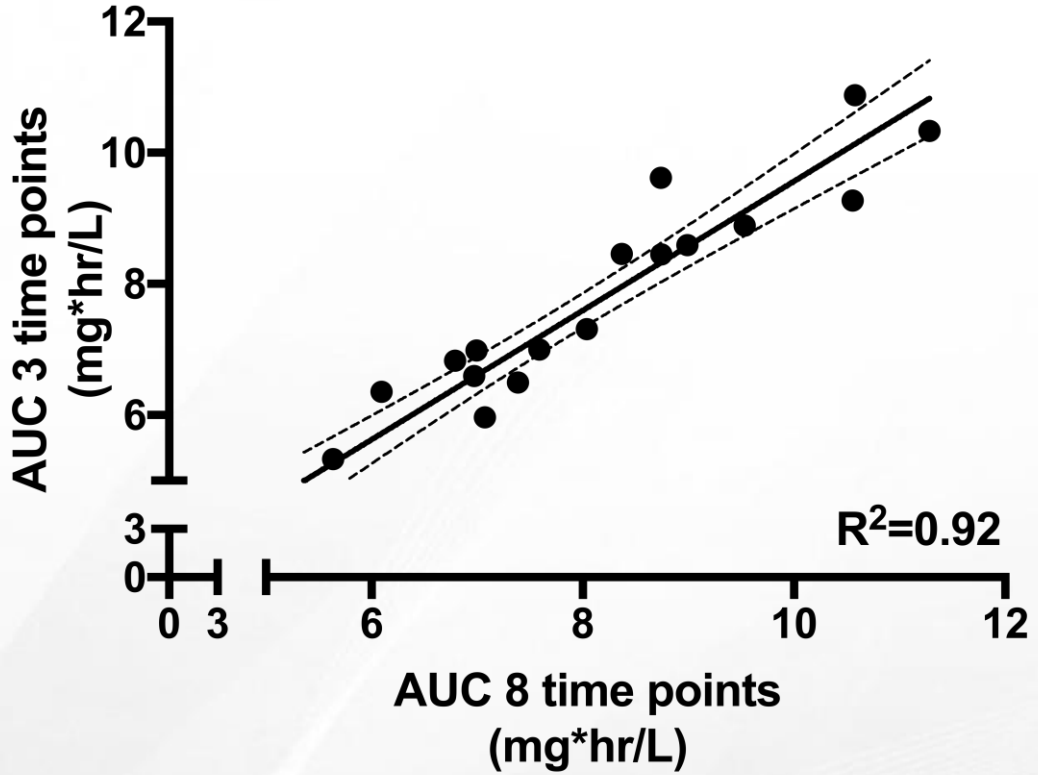




Melphalan AUC using 2- or 4- time point schedules to determine PK



Results – Modified PK Sampling for Clinical Application



3-time point sampling schedule (30, 150, and 240 minutes) correlated well with the original 8-time point sampling schedule

Conclusion

- We observed a higher median AUC compared to previous reports
  - Improved methods for melphalan detection (LC MS, immediate transport and freezing of samples)
- No intrapatient variability between day -2 and -1 PK, allowing for linear dose adjustments
- Simplified 3-time point sampling schedule is currently being used in a phase I/II study
- Personalized melphalan dosing will both decrease interpatient variability and has the potential to improve myeloma outcomes
- Application of PK-directed melphalan dosing at centers where a PK laboratory is not on site may require a novel dosing regimen with melphalan being administered on days -3 and -1 to allow for timely turnaround of PK results and dose adjustments

Acknowledgments

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  - —BMT nurses
- **Our patients!**

***Senior author**

ARS Question

- **Which of the following statements about melphalan PK-testing is true?**

A. Due to melphalan's extremely short half-life, PK-testing in the clinical setting cannot be performed.

B. Because there is significant intrapatient variability in melphalan AUC between doses, PK-directed dosing using a linear dose proportional calculation is not feasible/

C. A 3-time point blood sampling schedule at 30, 150, and 240 minutes after the end of infusion can be used to determine the melphalan AUC.

D. Melphalan exposure does not correlate with clinical outcomes after autologous transplant.

Future Reading/Learning References

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