Personalizing Busulfan Exposure in Hematopoietic Cell Transplantation: Current consensus and discrepancies

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Scope of the lecture:
After a brief introduction of the clinical pharmacology of BU (BU), this lecture will cover current BU dosing and therapeutic drug monitoring (TDM) practices. As many discrepancies exist between local and even international guidelines of BU dosing and TDM, the hematopoietic stem cell transplantation (HCT) community has started to realize that reaching consensus is the way forward to improve global HCT care. The talk will elaborate on the launch of of a worldwide collaborative initiative towards harmonization of BU dosing and TDM.

Learning objectives:
1. Gain knowledge on the clinical pharmacology of BU
2. Explain current BU TDM practices
3. Understand the need for harmonization of BU dosing and TDM

Extended abstract:
Busulfan (BU), administered either orally or intravenously, is an alkylating agent routinely used in conditioning regimens prior to HCT for various non-malignant and malignant diseases.[1] BU has a narrow therapeutic index. BU plasma exposure is a predictive biomarker that forecasts the likely response to BU-containing conditioning regimens.[2-6] On one hand low BU exposure, primarily caused by rapid BU clearance, is associated with an increased risk of rejection or relapse, while on the other hand high BU exposure is associated with an increased risk of hepatotoxicity and nonrelapse mortality (NRM).[7-14] BU has a narrow therapeutic range, which is acknowledge by inclusion of specific exposure targets on its package inserts. A BU AUC of 900 to 1500 μM*min or 900 to 1350 μM*min for a 4 times daily regimen are the current target exposures included in the EMA and FDA labels for intravenous BU, respectively. The latter AUC values were confirmed in recent large retrospective analysis including 674 pediatric patients from 15 centers in the Netherlands, USA, Canada, Switzerland, UK, Italy, Germany, and Australia who received a BU-based conditioning regimen. This study showed that improved clinical outcomes are likely to be achieved by targeting the BU AUC to 80-100 mg*h/L (equal to 21.6 mM*min total, or 5400 μM*min/day) using a new validated pharmacokinetic model.[15] Of note, in this study exposure-outcome associations were independent of concomitant conditioning agents and indication. Nevertheless, the Practice Guidelines Committee of the American Society of Blood or Marrow Transplantation (ASBMT) recently sought to develop evidence-based guidelines for personalized BU dosing but found that the published literature was too heterogeneous and lacked the necessarily controlled studies for this to be feasible.[16] Thus, the optimal BU exposure for a specific patient population based depends on age, diagnosis, concomitant agents in conditioning regimen and donor source remains elusive and should be addressed by prospective studies and through international collaboration.
For BU dosing multiple guidelines exist to achieve the target exposure in individual patients. In a recent study an "in silico" simulation was performed to describe the achieved AUCs of 12 published pediatric BU dosing guidelines using pharmacokinetic data of one hundred

eleven patients.[17] Initial BU doses were determined for all patients using each dosing guideline and total body weight. Of note, once, twice and four times daily dosing as common in clinical practice were included. Simulation revealed the proportion of patients with an AUC within the target range varied roughly from 40-75%. It is apparent that current BU dosing guidelines aim for different targets and vary in their capacity to achieve AUCs within the target window. Therefore, TDM is essential to verify achievement of the target AUC regardless of the dosing guideline used. As clinical acceptance of BU TDM is rapidly increasing, TDM of BU for optimal dose individualization is applied more frequently in patients undergoing HCT worldwide, especially in pediatric populations. Also, many contemporary HCT regimens are now developed with BU TDM.[18,19] Next to evidence of the importance of Bu TDM in children, a recent randomized controlled trial by Anderson and coworkers including 218 patients revealed that TDM was associated with a lower risk of relapse or treatment-related mortality compared the fixed-dose group using a dosing nomogram without TDM throughout an 80-month observation period in patients diagnosed with acute myeloid leukemia and myelodysplastic syndrome.[20] These results indicate that also adult patients benefit significantly from TDM of Bu. Unfortunately, characterizing the proportion of BU-conditioned HCT recipients whose dose is personalized using BU TDM is impeded by the exclusion of BU exposure data into international databases.

Albeit the evidence on the optimal exposure and the value of TDM of BU in HCT conditioning is becoming more apparent, it is of concern that distinctly different methods to estimate the exposure are currently used in clinical practice. For instance, numeric integration or trapezoidal rule, AUC from 0 to infinity; ($AUC_{0\text{-infinity}}$), to the next dose ($AUC_{0\text{-tau}}$), the concentration at steady state (C_{ss}) are used as BU exposure parameter depending on HCT center and/or TDM site. The importance of the latter was illustrated by Bartelink and colleagues,[15] who showed that the BU AUC calculated using various approaches in use by individual centers had a poor correlation (r^2=0.35) with BU $AUC_{0\text{-infinity}}$ calculated post hoc from raw concentration-time-data using non-linear mixed effect modelling. Their findings are supported by example plots showing concentration observations derived in individuals (black dots), the individual predicted concentrations by NONMEM (blue shaded area) and non-compartmental analysis to calculate the exposure (AUC-tau; red shaded area and AUC-infinity; green shaded area) (Figure 1). Furthermore, many centers use the steady state concentration (Css) as BU exposure target in a four times daily dosing setting. In this respect, consensus regarding the use of Css versus AUC is lacking and there is no consensus of the units used to express AUC in micromole*min/L or AUC in mg*hr/L. At the same time, the AUC and Css targets, depending on the units used, may differ numerically with different dosing frequencies. First of all, this poses a patient safety issue, as the arithmetical conversions between units are prone to error. Secondly, international databases have omitted BU exposure due, in part, to these issues. As a result, databases with BU pharmacokinetic data are not easy to create by cooperative groups, which precludes mining large databases to optimize BU use. Preferably, a single BU exposure unit should be adopted internationally. Finally, administration protocols, analytical assays and the pharmacokinetic modeling to estimate BU exposure including the resulting BU dosing recommendations differ from center to center affecting accuracy and precision of attained BU exposure in individual patients.

Hence, there is an urgent medical need for harmonization of BU target exposures and TDM procedures in HCT conditioning. To address this unmet need, an international BU harmonization project initiative subsequently was started in November 2016. This project takes a two-pronged approach to achieve the goal of improving outcomes in HCT recipients. The first part aims to harmonize the quantitation, pharmacokinetic modeling and personalized dose recommendations of BU pharmacokinetic data by means of an international interproficiency testing program. The second part is the BU exposure unit harmonization with the ultimate goal

of reaching consensus on the optimal BU exposure in conditioning prior to HCT. Both these international projects seek to improve patient safety and improve the scientific rigor for BU TDM.

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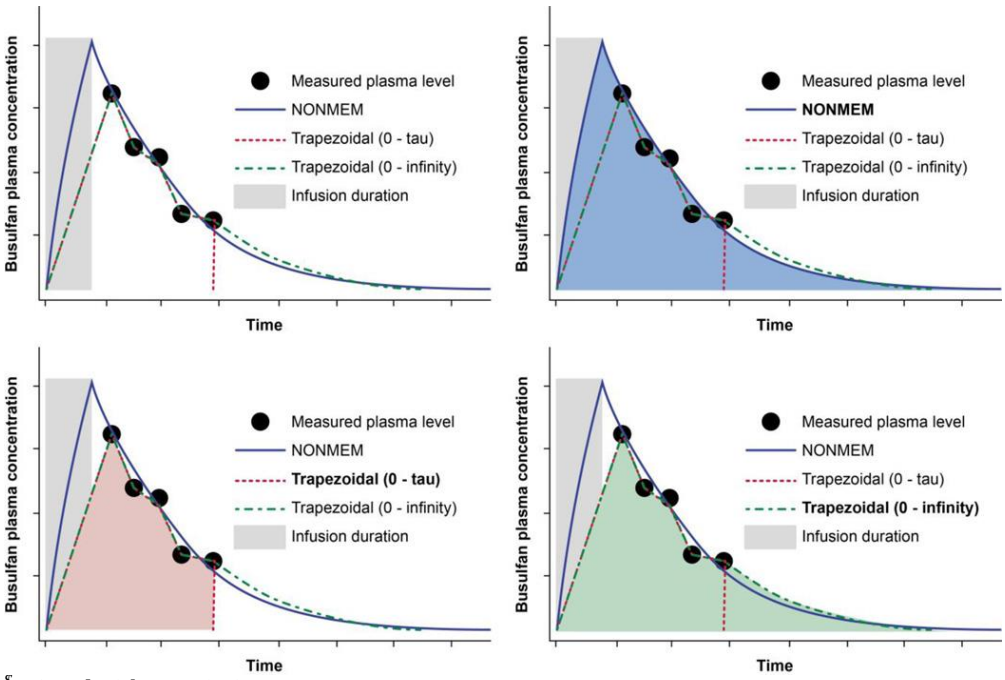
Figures

Figure 1[$]



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