Technical Appendix: Principles of personalized busulfan (BU) dosing using therapeutic drug monitoring (TDM) in hematopoietic cell transplant (HCT) recipients

\*\*Legal disclaimer\*\*: Health care professionals who are personalizing BU doses based on pharmacokinetics (called therapeutic drug monitoring or targeted BU (TBU) dosing) should be knowledgeable regarding pharmacokinetics and the clinical care of HCT recipients. This technical appendix includes a non-exhaustive list of examples of technical issues that must be addressed for BU dosing using TDM.

1. References:
   1. Basic pharmacokinetics
      1. Shargel L, Wu-Pong S, Yu ABC, eds. Applied Pharmaceutics & Pharmacokinetics. Fifth Edition. New York: McGraw-Hill. 2005.
      2. David Bourne, PhD, University of Oklahoma’s website

<http://www.boomer.org/c/p4/index.php?Loc=OUHSC33>

* 1. BU pharmacokinetics: Slattery JT, Risler LJ. Therapeutic monitoring of BU in hematopoietic stem cell transplantation. Ther Drug Monit. 1998 Oct;20(5):543-9.

1. The following should be done before a center implements BU dosing using TDM:
   1. Identify an approved laboratory to quantitate BU plasma concentrations (called “BU lab”).

To quantitate the BU concentrations in plasma, a Clinical Laboratory Improvement Amendments (CLIA)- & College of American Pathology (CAP)-approved analytical method for BU must be established at the treating HCT center or must be obtained with a BU laboratory outside the treating HCT center.

* 1. Identify qualified health care professionals to interpret the BU plasma concentration-time data.

The interpretation of the BU concentration-time data involves two parts: pharmacokinetic modeling and dose recommendation. The HCT center must ensure that a group of clinical pharmacologists, physicians, or pharmacists are adequately trained to do the pharmacokinetic modeling and make dose recommendations in a timely fashion after obtaining the BU concentration-time data from the CLIA- & CAP- approved analytical laboratory.

* 1. Decide the optimal logistics for the entire team involved in BU dosing using TDM. The optimal logistics for BU dose targeting must be worked out well before the first patient has their BU dose personalized. Close collaboration must occur with
     1. with the nurses regarding consistent administration of BU and drawing the BU pharmacokinetic samples;
        1. For administration: With IV BU, a standardized procedure should be developed for consistently priming the IV BU tubing, infusing the IV BU dose, and completely flushing the IV line to ensure the entire BU dose is administered. This is especially important in infants, as the IV tubing volume could represent a significant portion of their dose. This standardized procedure should be developed before the pharmacokinetic sampling is started.
        2. For pharmacokinetic sampling: see 3.c.iii and 3.c.iv.
     2. with the pharmacists preparing the BU doses;
     3. with the relevant laboratory staff involved in the sample transport including quantity assurance of its cold chain, the (often separate) laboratory staff involved in quantitating the BU plasma concentrations; and
     4. with the clinical pharmacologists, physicians, and pharmacists responsible for conducting the pharmacokinetic modeling and dose adjustment.
  2. The BU dose must be administered early enough to allow for adequate time for the pharmacokinetic samples to be drawn and transported to the BU laboratory, allowing for sufficient time for quantitation, pharmacokinetic modeling, and targeted dose recommendation to achieve the target exposure prior to administration of the subsequent BU dose.

1. Caution should be exercised at each step, with some relevant examples and troubleshooting below.
   1. The equations to target BU doses are below. Essentially, the area under the curve (AUC) must be accurately estimated to provide the individual patient’s clearance of BU based on their first dose. The steps below describe most of the steps and where troubleshooting often must occur.
   2. Preparation and administration of BU: A precise estimate of the BU dose is essential to estimate an individual patient’s BU clearance, using equation 1.
      1. The appropriate safety measures should be in place for the preparation of BU doses by pharmacy staff.
      2. With IV BU, it is not uncommon to have inconsistent data shortly after the end of the IV infusion (EOI). If an end of infusion (EOI) sample is obtained, a second sample shortly thereafter (e.g., EOI + 15 minute sample) can both be obtained to ascertain any IV BU administration or drawing blood errors.
      3. With oral BU, it should be ensured the patient has had proper prophylactic antiemetics to prevent emesis and that a procedure is established to re-dose if emesis does occur shortly after drug dosing. Infants and small children may need placement of a nasogastric tube in order to ensure proper administration of oral BU.
   3. Drawing the BU pharmacokinetic samples:
      1. An acceptable time period for BU pharmacokinetic sampling must balance the half-life of the drug (typically 2-3 hours), the dosing frequency (see FAQ7), and the practical logistical issue of obtaining the TDM results in a timely fashion to personalize the BU dose. For BU personalized dosing, an acceptable time period for BU pharmacokinetic sampling can be as short as 4 hours, which occurs with a 2 hour BU infusion and every 6 hour (Q6H) dosing, or as long as 8 hours, which occurs with a 3 hour BU infusion and every 24 hour (daily) dosing. However, the acceptable time period for BU pharmacokinetic sampling can be shortened if population pharmacokinetic modeling is used instead of the traditional noncompartmental analysis. For instance, 3-6 hours in a 3 hour BU infusion and every 24 hour (daily) dosing.
      2. The nursing staff should ensure the correct blood collection tube and sample processing are used per the analytical laboratory’s specification.
      3. With IV BU, the nursing staff should NOT draw from the same lumen that the IV BU was infused in. This could cause artificially elevated BU concentrations.
      4. With IV BU and oral BU, the dead space blood volume must be addressed by either wasting 3-5 mL of blood per sample or using the push-pull method to clear out the blood volume in the catheter.
      5. The precise time of the blood draw should be written upon the BU pharmacokinetic worksheet (for an example, please see <http://www.seattlecca.org/client/documents/Req_Q6-IV_Oral_BU_v2.pdf>).
      6. Examples of when pharmacokinetic samples could be drawn:
         1. Q6H oral BU: Samples are obtained at 15, 30, 60, and 90 minutes, and 2, 3, 4, 5, and 6 hours after oral administration. The 6 hour sample is just before starting the next dose.
         2. Daily IV BU: Samples are obtained at EOI, EOI + 15 minutes after the EOI, and at 4, 5, 6, 8, and 24 hours after the start of the infusion. The 24 hour sample is just before starting the next dose.
         3. If pharmacokinetic samples are obtained after dose 2 or later, then a pharmacokinetic sample before busulfan administration should be obtained.
   4. Sample analysis: Use a CLIA- & CAP- certified BU analytical laboratory that participates in the North American or the European proficiency exchange. As part of the CAP certification, the methods to troubleshoot analytical difficulties should be well described. After the concentrations are known, the pharmacokinetic modeling can be conducted
      * 1. When the BU concentration data is generated, it should be clear when (i.e., which time point) each concentration was obtained so there will be a list of concentration-time data.
        2. A visual inspection of the data should occur for the following:
           1. Cmax (ng/mL): highest quantitated plasma BU concentration of an AUC
           2. Tmax (min): time of Cmax
           3. Cmin (ng/mL): lowest quantitated plasma BU concentration of an AUC
           4. Tmin (min): time of Cmin
           5. Clearance (ml/min/kg)
           6. Volume of distribution (l/kg): Susceptible to infusion errors
           7. ke (/hr): elimination rate constant, which is based on clearance and volume
           8. Elimination half-life (hr): time for BU concentrations to decrease by 50%. Estimated from ke
        3. Suggestions for approaching an individual patient’s concentration-time dataset after one BU dose:

Ensure the target BU exposure is known before the BU concentration-time results are obtained.

Understand patient data (age, disease, etc).

Know what dose number you’re getting pharmacokinetic data from, what is the earliest dose you can target, and the total number of doses.

Get a sense of the patient’s BU pharmacokinetics – half-life, clearance.

Double-check data entry from MS Excel from the laboratory staff to pharmacokinetic modeling software used by the pharmacology staff.

Quickly estimate the half-life just from the laboratory concentration-time data– does it fit with the estimate from the pharmacokinetic modeling?

Analyze the concentration-time data using 2-3 different pharmacokinetic models. Currently noncompartmental or one compartment modeling is common, *but the use of population pharmacokinetic modeling to personalize dose recommendations is strongly encouraged.*

Make sure the modeling output fits with your sense of the patient’s BU pharmacokinetics.

Compare patient’s clearance to age and AIBW-population normal values.

* 1. After the pharmacokinetic modeling, chose the appropriate dose and discuss with the treating physician.
     1. If clearance estimates are very different, evaluate different BU dose recommendations based on typical BU clearance for that patient population to get a sense of the potential error in the recommendation.
     2. Be careful with pharmacokinetic modeling output units and your target exposure units. Is the AUC as min xng/mL since the concentration-time data is entered that way?
     3. \*\*USE EXTREME CAUTION – the units differ between AUC & Css\*\* Below are equations for converting between the three most common ways of expressing busulfan exposure. Below are conversions for Q24H busulfan administration.
     4. The AUC used depends on which dose is being evaluated (i.e. first or subsequent) \*\*USE EXTREME CAUTION\*\*
        1. With first dose and all daily IV BU doses, use AUC extrapolated to infinity.
           1. Classical steady state conditions with daily IV BU will not be attained because each dose is almost completely eliminated (i.e., the 24 hour sample is below limit of quantitation).
        2. At steady state, use AUC to end of dosing frequency (AUClast).
           1. When are you at steady state? 5-6 half-lives or 10-18 hours with BU since it has a 2-3 hour half-life.
  2. Troubleshooting the pharmacokinetic modeling and dose recommendations
     1. After oral administration, those patients with a delayed Tmax will have very few (if any) concentration-time points to estimate their elimination half-life and thus it may be difficult to estimate their AUC0-∞ after the first dose. Consider troubleshooting using typical half-lives of BU.
     2. IV administration
        1. Low concentration in end of infusion (EOI) blood sample suggests inadequate dose administration or contamination with IV flush solution. Therefore, actual dose administered is lower than you’re using in equations, artificially increasing the BU clearance.
           1. Consider it low if the EOI concentration is <800 ng/mL for 0.8 mg/kg IV BU dose and <3200 ng/mL for 3.2 mg/kg IV BU dose.
           2. This can be difficult to interpret in obese patients with a large difference between adjusted ideal body weight and actual body weight.
        2. High concentration in last blood sample suggests the blood was drawn from the same port used for drug administration.
        3. Too few concentration-time points can provide poor estimations of the AUC and the BU clearance, thus leading to inaccurate dose adjustment.
     3. Either administration route
        1. If a high percentage of an AUC (i.e., >33%) is extrapolated using the equation AUC=Clast/ke, then the pharmacokinetic sampling should have occurred over a longer time interval and it is suggested to report the clearance as an equivocal BU clearance.
        2. If there is very ‘wobbly’ data that has concentration-time data going up and down, it is suggested to report the clearance as an equivocal BU clearance
     4. If there are concerns regarding the pharmacokinetic modeling and dose recommendation, then obtain busulfan pharmacokinetic data with the subsequent morning busulfan dose. And perform a day+1 TDM-based BU dose adjustment

BU AUC to Css Equivalency Table.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| AUC | AUC | Css | AUC | AUC |
| μMolar×min Q6H | μMolar×min Q24H | ng/mL | mg×h/L Q6H | mg×h/L Q24H |
| 750 | 3000 | 513 | 3.08 | 12.3 |
| 875 | 3500 | 599 | 3.59 | 14.4 |
| 877 | 3508 | 600 | 3.60 | 14.4 |
| 950 | 3800 | 650 | 3.90 | 15.6 |
| 1000 | 4000 | 684 | 4.11 | 16.4 |
| 1023 | 4093 | 700 | 4.20 | 16.8 |
| 1096 | 4385 | 750 | 4.50 | 18.0 |
| 1125 | 4500 | 770 | 4.62 | 18.5 |
| 1169 | 4677 | 800 | 4.80 | 19.2 |
| 1243 | 4970 | 850 | 5.10 | 20.4 |
| 1250 | 5000 | 855 | 5.13 | 20.5 |
| 1316 | 5262 | 900 | 5.40 | 21.6 |
| 1375 | 5500 | 941 | 5.64 | 22.6 |
| 1389 | 5554 | 950 | 5.70 | 22.8 |
| 1462 | 5847 | 1000 | 6.00 | 24.0 |
| 1500 | 6000 | 1026 | 6.16 | 24.6 |
| 1875 | 7500 | 1283 | 7.70 | 30.8 |

Css = AUC divided by the dosing frequency. When the AUC is expressed in micromolar quantities the BU molar mass (246.292 g/mol) must be used to calculate the AUC in mg/L quantities.

Equations:

Equation for changing AUC from mg×h/L to µM×min:

Equation for changing AUC from µM×min to mg×h/L:

Equation for changing Css in ng/mL to AUC in mg × h/L with 24 houra dosing frequency:

Equation for changing Css in ng/mL to AUC in µM×min with 24 houra dosing frequency:

Equation for changing AUC in µM×min to Css in ng/ml with 24 houra dosing frequency:

Equation for changing AUC in mg×h/L to Css in ng/mL with 24 houra dosing frequency:

If a different dosing frequency is used, removed 24 h and replace with the dosing frequency in hours.