Slide 1	# The Target Concentration Approach to Dosing in Children and Adults -- Application to Busulfan Nick Holford Department of Pharmacology and Clinical Pharmacology, University of Auckland, Auckland, New Zealand	Results first presented at PAGANZ 2013, University of Queensland, Brisbane, Australia on Feb 15 2013. http://www.paganz.org/wp-content/uploads/2013/03/PAGANZ_2013_busulfan_integrated_PK.pdf
Slide 2	# Clinical Pharmacology Pharmacokinetics Pharmacodynamics CL V Emax EC50 Dose Concentration Effect	Clinical pharmacology describes the effects of drugs in humans. One way to think about the scope of clinical pharmacology is to understand the factors linking dose to effect. Drug concentration is not as easily observable as doses and effects. It is believed to be the linking factor that explains the time course of effects after a drug dose. The science linking dose and concentration is pharmacokinetics. The two main pharmacokinetic properties of a drug are clearance (CL) and volume of distribution (V). The science linking concentration and effect is pharmacodynamics. The two main pharmacodynamic properties of a drug are the maximum effect (Emax) and the concentration producing 50% of the maximum effect (EC50).
Slide 3	 # Target Concentration in Clinical Use of Medicines Target Conc = Target Effect x EC50 / (Emax –Target Effect) | Target Conc	Dose Model
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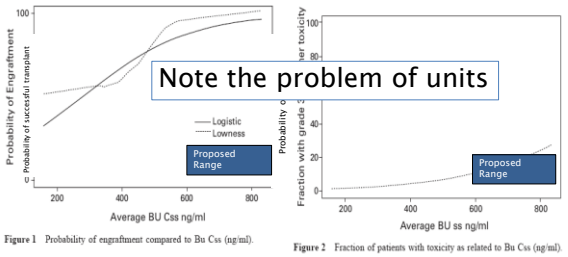
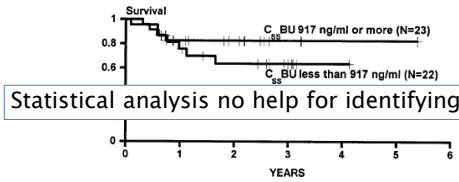
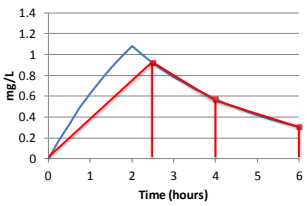
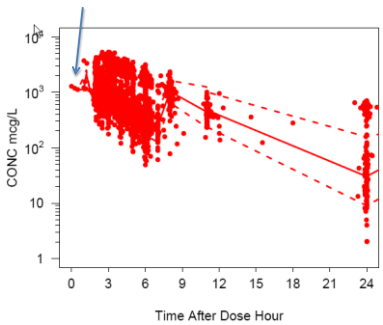
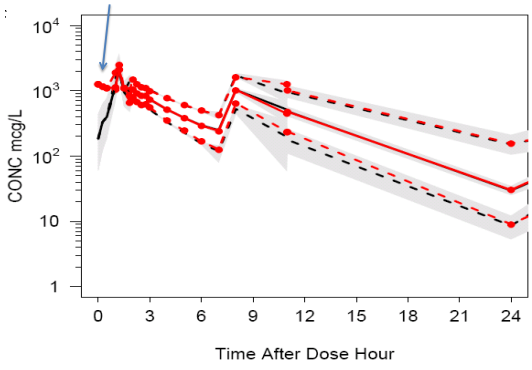
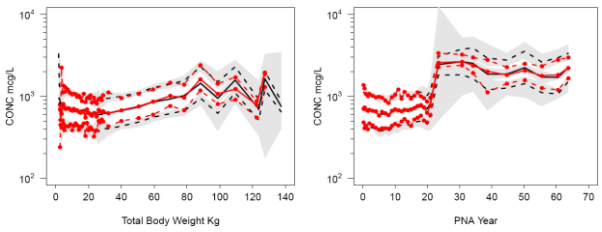
Initial Peak	Loading Dose = Target Conc x Volume of distribution
Average Steady State	Maintenance Dose Rate = Target Conc x Clearance | Ideal dose prediction requires individual estimates of Emax, EC50, Volume and Clearance	The target concentration approach links PKPD to prediction of the right dose for a patient.

Slide 4	**TDM or TCI?** • Therapeutic Drug Monitoring – TDM Therapeutic Range ☹ **Imprecise** – Sub-optimal at borders of the range Toxic Ineffective • Target Concentration Intervention » TCI Single Target ☺ **Accurate** » Optimal – do the best you can Ideal !	
Slide 5	**What do we need to learn?** • Pharmacokinetics – Influence of body composition – Influence of young age • Dose Adjustment – AUC or Bayesian? • Target Concentration – Still just 'best guess'	
Slide 6	**Busulfan Pharmacodynamics**  Note the problem of units Figure 1 Probability of engraftment compared to Bu Css (ng/ml). Figure 2 Fraction of patients with toxicity as related to Bu Css (ng/ml). Proposed Range 0.6 to 0.9 mg/L; Target Concentration 0.77 mg/L Corresponds to Target AUC of 1125 umoL*min q6h dosing Bolinger AM, Zangwill AB, Slattery JT, Glidden D, DeSantes K, Heyn L, et al. An evaluation of engraftment, toxicity and busulfan concentration in children receiving bone marrow transplantation for leukemia or genetic disease. Bone Marrow Transplant. 2000;25(9):925-30.	Bolinger AM, Zangwill AB, Slattery JT, Glidden D, DeSantes K, Heyn L, et al. An evaluation of engraftment, toxicity and busulfan concentration in children receiving bone marrow transplantation for leukemia or genetic disease. Bone Marrow Transplant. 2000;25(9):925-30.

Slide 7	 **Pharmacodynamics Adults**  Statistical analysis no help for identifying target Slattery et al. 1997 **Fig 2. Kaplan Meier statistics on the survival of patients transplanted for CML in CP or AP categorized on the basis of BU steady state concentrations (C_{ss}BU) greater than or less than the median (917 ng/mL) during conditioning. Patients were censored on the date of last contact. Tic marks denote survivors. The difference between the groups is not statistically significant (P = .33)**	Slattery JT, Clift RA, Buckner CD, Radich J, Storer B, Bensinger WI, et al. Marrow Transplantation for Chronic Myeloid Leukemia: The Influence of Plasma Busulfan Levels on the Outcome of Transplantation. Blood. 1997;89(8):3055-60. Naïve analysis based on categorical split of concentrations around the median does not give any information about choosing the target concentration.
Slide 8	 **AUC Dose Adjustment** **from Busulfex label (PDL 2006)** **Dose Adjustment Based on Therapeutic Drug Monitoring** Instructions for measuring the AUC of busulfan at dose 1 (see Blood Sample Collection for AUC Determination), and the formula for adjustment of subsequent doses to achieve the desired target AUC (1125 µM•min), are provided below. Adjusted dose (mg) = Actual Dose (mg) x Target AUC (µM•min)/Actual AUC (µM•min) For example, if a patient received a dose of 11 mg busulfan and if the corresponding AUC measured was 800 µM•min, for a target AUC of 1125 µM•min, the target mg dose would be: Mg dose = 11 mg x 1125 µM•min / 800 µM•min = 15.5 mg Busulfex dose adjustment may be made using this formula and instructions below. ***Blood Sample Collection for AUC Determination:*** Calculate the AUC (µM•min) based on blood samples collected at the following time points: For dose 1: 2 hr (end of infusion), 4 hr and 6 hr (immediately prior to the next scheduled BUSULFEX administration). Actual sampling times should be recorded. For doses other than dose 1: Pre-infusion (baseline), 2 hr (end of infusion), 4 hr and 6 hr (immediately prior to the next scheduled BUSULFEX administration). AUC calculations based on fewer than the three specified samples may result in inaccurate AUC determinations. For each scheduled blood sample, collect one to three mL of blood into heparinized (Na or Li heparin) Vacutainer® tubes. The blood samples should be placed on wet ice immediately after collection and should be centrifuged (at 4°C) within one hour. The plasma, harvested into appropriate cryovial storage tubes, is to be frozen immediately at -20°C. All plasma samples are to be sent in a frozen state (i.e., on dry ice) to the assay laboratory for the determination of plasma busulfan concentrations. **Calculation of AUC:** BUSULFEX AUC calculations may be made using the following instructions and appropriate standard pharmacokinetic formula: Dose 1 AUC_{0-6hr} Calculation: $AUC_{0-6hr} = AUC_{0-6hr} + AUC_{extrapolated}$, where AUC_{0-6hr} is to be estimated using the linear trapezoidal rule and AUC extrapolated can be computed by taking the ratio of the busulfan concentration at Hour 6 and the terminal elimination rate constant, λ_z. The λ_z must be calculated from the terminal elimination phase of the busulfan concentration vs. time curve. A "0" pre-dose busulfan concentration should be assumed, and used in the calculation of AUC. If the AUC is assessed subsequent to Dose 1, steady-state AUC_{ss} (AUC_{0-6hr}) is to be estimated from the trough, 2 hr, 4 hr and 6 hr concentrations using the linear trapezoidal rule. ***Instructions for Drug Administration and Blood Sample Collection for Therapeutic Drug Monitoring:*** An administration set with minimal residual hold up (priming) volume (1-3 mL) should be used for drug infusion to ensure accurate delivery of the entire prescribed dose and to ensure accurate collection of blood samples for therapeutic drug monitoring and dose adjustment. Prime the administration set tubing with drug solution to allow accurate documentation of the start time of BUSULFEX infusion. Collect the blood sample from a peripheral IV line to avoid contamination with infusing drug. If the blood sample is taken directly from the existing central venous catheter (CVC), DO NOT COLLECT THE BLOOD SAMPLE WHILE THE DRUG IS INFUSING to ensure that the end of infusion sample is not contaminated with any residual drug. At the end of infusion (2 hr), disconnect the administration tubing and flush the CVC line with 5 cc of normal saline prior to the collection of the end of infusion sample from the CVC port. Collect the blood samples from a different port than that used for the BUSULFEX infusion. When recording the BUSULFEX infusion stop time, do not include the time required to flush the indwelling catheter line. Discard the administration tubing at the end of the two-hour infusion.	
Slide 9	 **Bayesian Dose Adjustment** • Well established methodology for TDM based dose prediction – Sheiner 1977 – Applied to busulfan paedatric BMT (Bleyzac 2001, Salinger 2010) • Flexible – Not affected by sampling times (provided they are accurate) – First dose can be loading dose > maintenance dose • Output – Estimate of patient's clearance (CL) and dose – Any dosing interval (e.g. q6h, daily, continuous infusion) Dose mg q interval h = TargetConc (mg/L) * CL (L/h) * interval (h) 265 mg q 24 h = 0.770 mg/L * 14.3 L/h * 24 h	Sheiner LB, Rosenburg B, Marathe VV. Estimation of population characteristics of pharmacokinetic parameters from routine clinical data. J Pharmacokinet Biopharm. 1977;5:445-79. Bleyzac N, Souillet G, Magron P, Janoly A, Martin P, Bertrand Y, et al. Improved clinical outcome of paediatric bone marrow recipients using a test dose and Bayesian pharmacokinetic individualization of busulfan dosage regimens. Bone Marrow Transplant. 2001;28(8):743-51.

Slide 10	 **AUC vs Bayesian Dose Adjustment**  • Simulated concentrations without error • AUC linear or linear/log trapezoidal • Bayesian pharmacokinetic model **AUC method sensitive to sampling time but Bayesian PK is not**	
Slide 11	 **Busulfan in infants to adult hematopoietic cell transplant recipients: A population pharmacokinetic model for initial and Bayesian dose personalization** Jeannine S. McCune[1,3], Meagan J. Bemer[1], Jeffrey S. Barrett[4], K. Scott Baker[2, 3, 5], Alan S. Gamis[6], Nicholas H.G. Holford[7] University of Washington Schools of [1]Pharmacy and [2]Medicine, Seattle, WA; [3]Fred Hutchinson Cancer Research Center, Seattle, WA; [4]Division of Clinical Pharmacology & Therapeutics, The Children's Hospital of Philadelphia, Philadelphia, PA; [5]Seattle Children's Hospital, Seattle, WA; [6]Children's Mercy Hospitals and Clinics, Kansas City, MO; [7]University of Auckland Department of Pharmacology and Clinical Pharmacology, Auckland, New Zealand.	Presented at PAGANZ 2013, University of Queensland, Brisbane, Australia on Feb 15 2013. http://www.paganz.org/wp-content/uploads/2013/03/PAGANZ_2013_busulfan_integrated_PK.pdf
Slide 12	 **The Data** • Routinely collected busulfan concentration profiles were obtained at a national center for measuring busulfan concentrations • Dosing and demographic data was matched with 12,182 concentrations in 1610 patients • 92% of patients were under the age of 20 Handful of Concs before end of infusion  	

Slide 13	 ## Pharmacokinetic and Random Effect Models • Zero order input using dose and input duration recorded by clinical staff • Two compartment distribution • First order elimination • Between subject and within subject variability estimated with exponential model for random effect • Combined additive and proportional residual error • NONMEM 7.2 FOCE Interaction	
Slide 14	 ## The Weight Problem • Clinical tradition has been to record 'dosing weight' (DWT) which is then used to predict the dose on a mg/kg basis • There are many 'dosing weight' formulas but the formula was not recorded and actual body weight was not known • 133 patients (108 adults and 25 children) had actual body weight (AWT) recorded	It is hoped that future studies of busulfan will record actual weight and use actual weight to predict doses using normal fat mass (see below).
Slide 15	 ## A Solution... $TBW_i = DWT \times FFEM_{DW} \times \exp(\eta_{DW})$ TBW=Total body weight prediction DWT=Dosing weight covariate $FFEM_{DW}$=Factor in women relative to men that predicts TBW	No systematic difference between TBW and DWT was found in males. Females had a slightly higher TBW.

Slide 16	**Size and Maturation** • Body Size – Fat mass was accounted for by using total body weight and fat free mass to predict normal fat mass NFM=FFM + Ffat*(TBW – FFM) – Theory based allometry was used to determine the best body size metric • Maturation – Maturation of clearance was described using a sigmoid Emax maturation model $Fmat = \frac{1}{1+\left(\frac{PMA}{TM50}\right)^{-Hill}}$ $CL_{PREDICTED_{NFM,PMA}} = CL_{NFM} \cdot Fmat$ TM50=PMA at 50% maturation	Details of calculation of body size and maturation can be found in Holford N 2010. Dosing in children. Clin Pharmacol Ther 87(3):367-370.
Slide 17	**Model Evaluation** Handful of Concs before end of infusion  	The VPC shows excellent predictions of observed concentrations except samples taken before the end of the (usually) 2 hour infusion. It is probable that these samples were contaminated because there were drawn from the same catheter used to infuse busulfan without adequate flushing.
Slide 18	**Covariate Evaluation** Weight Age  	The two main covariates, weight and age, show no residual mis-specification of the model. The higher concentrations in adults reflect the use of daily rather than 6 h dosing with samples drawn mainly in the first 6 hours after the dose.

Slide 19	**Structural Parameters** | Parameter	Description	Units	Bootstrap Estimate	Bootstrap RSE	2.5% ile	97.5% ile
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CL	Clearance	L/h/70kg	12.5	1.1%	12.2	12.7
V1	Central volume of distribution	L/70kg	15.8	6.6%	13.5	17.9
Q	Inter-compartmental clearance	L/h/70kg	148.1	7.2%	126.4	168.0
V2	Peripheral volume of distribution	L/70kg	33.9	3.0%	32.1	35.8
$FFAT_{CL}$	Fat fraction for clearance (from ABW data)	.	0.509	42.8%	0.110	0.950
$FFAT_{V}$	Fat fraction for volume (from ABW data)	.	0.203	51.6%	0.016	0.429
$TM50_{CL}$	PMA at 50% maturation	weeks	45.7	4.3%	41.6	49.2
$HILL_{CL}$	Hill coefficient for maturation	.	2.3	9.7%	1.93	2.74
$FFEM_{V}$	Fractional difference in total volume (V1+V2) in females		1.07	1.2%	1.05	1.10
$FFEM_{DW}$	Fractional difference in dosing weight in females		1.08	1.7%	1.05	1.11 | Weights are Normal Fat Mass for CL and V	Both clearance and volume were better related to normal fat mass than either predicted total body weight or fat free mass. Maturation of busulfan clearance reaches 50% of the predicted size standardized adult value around 6 weeks after full term (40 weeks) gestation. There is a slightly larger steady state volume of distribution in females. Predicted total body weight also tended to be slightly larger than dosing weight in females.
Slide 20	**Test of Allometric Theory** • Wide range (95% interval) of weight (5-90 kg) and large sample size (N=1610) • Allometric exponents estimated with starting value of 0.67 for CL and Q and 1.25 for V1 and V2 • Non-parametric bootstrap used to estimate average and 95% confidence interval for allometric exponents 	Parameter	Description	Bootstrap Estimate	Bootstrap RSE	2.5% ile	97.5% ile
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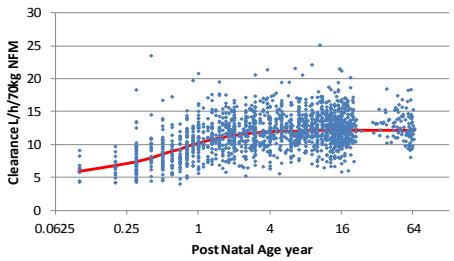
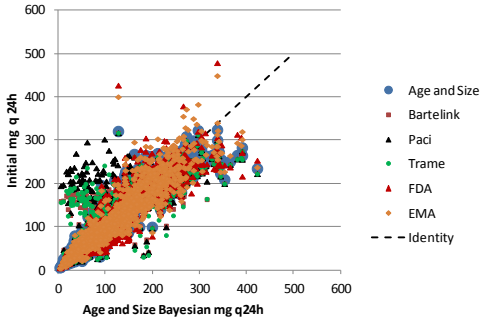
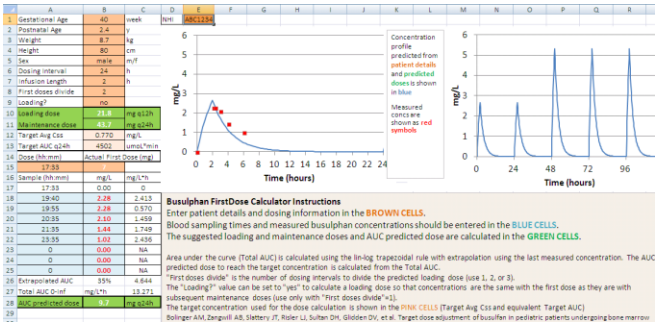
PWR_CL	Allometric exponent for CL	0.767	3.1%	0.724	0.817
PWR_V1	Allometric exponent for V1	1.059	9.1%	0.932	1.321
PWR_Q	Allometric exponent for Q	0.845	11.8%	0.695	1.065
PWR_V2	Allometric exponent for V2	0.993	4.0%	0.888	1.060		Wide range (95% interval) of weight (5-90 kg) and large sample size (N=1610) provides a design suitable for testing the predictions of theory based allometry. The 95% confidence interval of the estimate of the exponent for clearance is narrow and includes the theoretical value of ¾. Similar agreement between theory and observation is seen for V1 and V2 (theoretical value of 1). It is uncertain if intercompartmental clearance is more like elimination clearance or volume of distribution. The confidence interval is relatively wide and includes both ¾ and 1. There is no support for an allometric exponent of 2/3 for clearance which would be expected if body surface area was an appropriate size metric.
Slide 21	**Prediction of Maturation**  	The maturation of size standardized clearance shows about a 2 fold range from neonates to adults. There is clearly substantial unexplained between and within subject variability even after accounting for age and weight. The unpredictable, apparently random, between subject variability can be reduced by using target concentration intervention to improve individual estimates of clearance. This in turn can be used to predict the busulfan dosing regimen to achieve the target concentration.

Slide 22	 **Three Ways to Dose** • Population – Same dose for everyone • The dream dosing method! • Group (Covariate guided) – Same dose for similar group • e.g. same weight, CLcr, genotype • Individual – Dose determined by individual response • e.g. BP, INR, blood conc	
Slide 23	 **Prediction of Initial Covariate Guided Doses**  	The integrated model developed from PK data from children and adults was used to obtain a Bayesian estimate of clearance for each patient. This estimate of clearance was used to make the best guess estimate of the daily dose required to reach a target steady state concentration of 0.77 mg/L. Initial dose predictions were made using just covariate based models for clearance according to the current integrated study and those reported in the literature (Bartelink 2012, Paci 2012, Trame 2011). In general all methods gave reasonable predictions of the required daily dose except when the non-integrated methods were applied in children (best guess doses less than 150 mg/day). There was one instance where the integrated model initial dose was just over twice as big as the required daily dose. Bartelink IH, Boelens JJ, Bredius RGM, Egberts ACG, Wang C, Bierings MB, Shaw PJ, Nath CE, Hempel G, Zwaveling J, Danhof M, Knibbe CAJ 2012. Body Weight-Dependent Pharmacokinetics of Busulfan in Paediatric Haematopoietic Stem Cell Transplantation Patients: Towards Individualized Dosing. Clin Pharmacokinet 51(5):331-345. Paci A, Vassal G, Moshous D, Dalle JH, Bleyzac N, Neven B, Galambrun C, Kemmel V, Abdi ZD, Broutin S, Petain A, Nguyen L 2012. Pharmacokinetic behavior and appraisal of intravenous busulfan dosing in infants and older children: the results of a population pharmacokinetic study from a large pediatric cohort undergoing hematopoietic stem-cell transplantation. Ther Drug Monit 34(2):198-208. Trame MN, Bergstrand M, Karlsson MO, Boos J, Hempel G 2011. Population pharmacokinetics of busulfan in children: increased evidence for body surface area and

		allometric body weight dosing of busulfan in children. Clin Cancer Res 17(21):6867-6877.
Slide 24	 **Initial Dosing Methods** Acceptable if within 80-125% of individual Bayesian predicted dose **Age & Size method overall better than EMA method. FDA and other published methods markedly inferior.** **Age Group** All Ages: Age & Size 72%, EMA 70%, FDA 57%, Bartelink 66%, Paci 66%, Trame 66% **Age Group** Age>=1 and <2: Age & Size 69%, EMA 72%, FDA 54%, Bartelink 60%, Paci 60%, Trame 60% **Age Group** Age>=5 and <10: Age & Size 78%, EMA 71%, FDA 49%, Bartelink 70%, Paci 69%, Trame 69% **Age Group** Age<1: Age & Size 62%, EMA 61%, FDA 54%, Bartelink 56%, Paci 56%, Trame 56%	
Slide 25	 **Busulfan FirstDose**  Excel Based Calculator for Children and Adults	FirstDose and AUC nh926.xls

Slide 26

But …

- At best only 2/3 of patients will get a suitable busulfan dose
- So 1/3 of patients will be either over-treated or undertreated
- What can we do for them?

Slide 27

Safe and Effective Variability

- CLINICAL JUDGMENT
  Suppose medicine use is safe and effective if:
  1. Individual Css is on average at the Target Conc
     - Aim for the optimum target
  2. 90% of the time Css is within 80%–125% of Target Conc
     - 'therapeutic range' with optimum target
- STATISTICS
  Assume log-normal distribution for Css
  90% of Css must lie within ± 1.64 x SD
  - Therefore SD must be 0.136

The Safe and Effective Variability (SEV) is 13.6%

Slide 28

Dosing Individualization Method Depends on Safe and Effective Variability (SEV)

Suppose total variability PPV_{total}=0.7, unexplained BSV_u=0.4, unexplained WSV_u=0.3

Unexplaiined PPV_U=sqrt(BSV_u^2 + WSV_u^2)=0.5 Predictable BSV_P=sqrt(PPV_{total}^2 - BSV_u^2)=0.57

SEV	Method Criterion	Example	Dosing Strategy
0.9	SEV>PPV_{total}	**0.9>0.7**	Population dosing
0.55	PPV_{total} > SEV SEV>PPV_u	0.7>0.55 **0.55>0.5**	Group dosing (WT, CLcr, etc) (BSV_P ⇨ 0)
0.35	PPV_u > SEV SEV>WSV_u	0.5>0.35 **0.35>0.3**	Individual response dosing (TCI) (BSV_U ⇨ 0)

Holford NHG, Buclin TMD. Safe and effective variability – A criterion for dose individualization. Ther Drug Monit 2012; 34: 565-68

Slide 29

Key Busulfan Random Effect Parameters

Parameter	Description	Bootstrap Estimate	Bootstrap RSE	2.5% ile	97.5% ile
BSVu CL	Unexplained BSV in clearance	0.215	4.7%	0.195	0.234
WSVu CL	Unexplained WSV in clearance	0.113	14.8%	0.081	0.145
RUV_{ADD}	Additive RUV (ng/mL)	26.2	13.7%	18.9	32.8
RUV_{PROP}	Proportional RUV	0.0387	12.8%	0.0298	0.0468

BSV_{total} (predictable plus unpredictable BSV)=0.33
BSV_p (predictable BSV)=0.22 (55% of total BSV variability)

BSV = Between subject variability (sqrt(OMEGA))
WSV = Within subject variability (sqrt(OMEGA))
RUV= Residual unidentified variability (sqrt(SIGMA))

The between occasion variability in clearance is an estimate of the irreducible within subject variation in clearance from which cannot be improved by target concentration intervention.

Slide 30

Safe and Effective Variability (SEV) Busulfan

PPV_U	BSV_U	WSV_U
0.243	0.215	0.113

- Suggested Therapeutic Success Criterion
  95% of Concs Within 80%–125% of Target Css
  ∴ SEV is 0.114 (log normal SD)
- Unpredictable PPV_U is 0.243 and is >> SEV
  ∴ Covariate (WT, Age) prediction alone will be inadequate
- Unpredictable WSV_U is 0.113 and is < SEV (just!)
  ∴ TCI can achieve safe and effective target

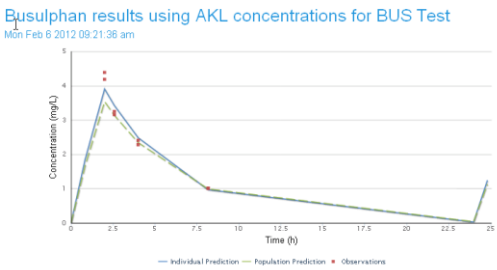
McCune JS, Bemer MJ, Barrett JS, Scott Baker K, Gamis AS, Holford NHG. Busulfan in Infant to Adult Hematopoietic Cell Transplant Recipients: A Population Pharmacokinetic Model for Initial and Bayesian Dose Personalization. Clin Cancer Res. 2014;20(3):754-63.PPV

PPVu=sqrt(BSVu^2 + WSVu^2)

Slide 31

Busulfan NextDose

http://www.nextdose.org



Report

busulphan Next Dose
2012-02-06-092136am_akl: Target conc 0.77 mg/L
Occasion 1: Predicted maintenance dose 258 mg every 1 day Actual dose 300 mg
Average (1): Proposed maintenance dose 258 mg every 1 day

Slide 32	 ## Why TCI is Necessary • The acceptable exposure range we propose for busulfan is based on a goal of 95% of patients lying within 80–125% of the target Css. • With TCI the unpredictable variability for busulfan can be reduced to the WSV of CL 11.3%. • This means that only 5% of patients will be under- or over-dosed. A major improvement over initial dosing based on size and age.	Holford NHG, Buclin TMD. Safe and effective variability - A criterion for dose individualization. Ther Drug Monit. 2012;34(5):565-8.
Slide 33	 ## Conclusion • Theory based allometry confirmed experimentally for CL, V1, (Q) and V2 • Normal fat mass describes allometric size better than other methods • Maturation of busulfan clearance reaches half of adult values around 6 weeks after full term delivery • TCI is essential to achieve exposure goals in 95% of treated patients	
Slide 34	 ## Practical Questions • Number and timing of blood samples for busulfan measurement? • Should doses be adjusted to achieve – target AUC ignoring whether first dose was too or too low? – The traditional goal or – total treatment period target AUC? – The pharmacological theory goal	

Slide 35

Slide 36

Demographics

Statistic	Units	average	2.5% ile	97.5% ile
PNA	year	9.8	0.3	58.4
PMAW	week	551	56	3089
AWT	kg	30.8	5.2	89.7
DWT	kg	30.2	5.2	84.4
FFMKG	kg	23.3	4.3	64.5
HTCM	cm	116	58	181
BMI	kg/m^2	18.9	12.6	30.8
IBW	kg	14.9	-38.3	76.1

The percentile are derived from the empirical distribution of baseline values for these demographic features.
Note that ideal body weight (IBW) is frequently negative in children because the empirical IBW formula was developed in adults and is not appropriate for children.

Slide 37

Busulfan Random Effect Parameters

Parameter	Description	Bootstrap Estimate	Bootstrap RSE	2.5% ile	97.5% ile
FDW	BSV in Fraction of Dosing Weight	0.166	7.8%	0.134	0.185
CL	BSV in clearance	0.215	4.7%	0.195	0.234
V1	BSV in central volume	0.410	10.8%	0.329	0.506
Q	BSV in intercompartmental clearance	0.922	9.1%	0.730	1.059
V2	BSV in peripheral volume	0.120	23.8%	0.059	0.183
CL	BOV in clearance	0.113	14.8%	0.081	0.145
V1	BOV in central volume	0.244	20.0%	0.147	0.327
Q	BOV in intercompartmental clearance	0.577	24.6%	0.330	0.903
V2	BOV in peripheral volume	0.212	12.4%	0.162	0.264
RUV_{ADD}	Additive RUV (mcg/L)	26.2	13.7%	18.9	32.8
RUV_{PROP}	Proportional RUV	0.0387	12.8%	0.0298	0.0468

BSV = Between subject variability (sqrt(OMEGA))
BSV = Between occasion variability (sqrt(OMEGA))
RUV= Residual unidentified variability (sqrt(SIGMA))

The between occasion variability in clearance is an estimate of the irreducible within subject variation in clearance from which cannot be improved by target concentration intervention.

BSVtotal (predictable plus unpredictable BSV)=0.33;
BSVp=0.22 (55% of total BSV variability)

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Published Busulfan PK Parameters

Clearance

Estimate	Units	Population	Source
12.2	L/h/70kg	173 adults oral (normal weight)	Gibbs 1999
10.3	L/h/70kg	24 children IV (allometric)	Booth 2006
12.6	L/h/70kg	37 adults IV (daily doses)	Salinger 2010
10.6	L/h/70kg	44 adults; 13 <18y IV	Abbasi 2011, PDL 2006
12.4	L/h/70kg	94 adults; 1 < 18y oral	Abbasi 2011

Volume

Estimate	Units	Population	Source
44.8	L/70kg	24 children IV	Booth 2006
50.6	L/70kg	37 adults IV	Salinger 2010
Not done		44 adults; 13 <18y IV	Abbasi 2011
Not done		94 adults; 1 < 18y oral	Abbasi 2011

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Published Busulfan PK Variability

Clearance

		Population	Source
BSV+BOV	25%	24 children IV (allometric)	Booth 2006
BSV	23%		
BOV	10%		
BSV+BOV	20%	94 adults; 1 < 18y oral	Salinger 2010

Limiting factor for dose prediction

Volume

		Population	Source
BSV+BOV	12%	24 children IV (allometric)	Booth 2006
BSV	11%		
BOV	6%		
BSV+BOV	16%	94 adults; 1 < 18y oral	Salinger 2010

BSV=Between Subject Variability BOV=Between Occasion Variability