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Effect of Age on the Pharmacokinetics of Busulfan in Patients Undergoing Hematopoietic Cell Transplantation; an Alliance study (CALGB 10503, 19808, and 100103)

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Abstract

Purpose—Older patients with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) have often been excluded from myeloablative conditioning regimens containing busulfan because of non-disease related morbidity and mortality. We hypothesized that busulfan clearance (BuCL) in older patients (>60 years) would be reduced compared to that in younger patients, potentially explaining observed differences in busulfan tolerability.

Methods—AML patients in three CALGB hematopoietic cell transplantation studies were treated with a conditioning regimen using IV busulfan, dosed at 0.8 mg/kg. Plasma busulfan concentrations were determined by LC-MS, and analyzed by non-compartmental methods. BuCL was normalized to actual (ABW), ideal (IBW) or corrected (CBW) body weight (kg). Differences in BuCL between age groups were examined using the Wilcoxon rank sum test.

Results—185 patients were accrued; 174 provided useable pharmacokinetic data. Twenty-nine patients ≥ 60 years old (median 66; range 60–74) had a significantly higher BuCL vs those <60 years old (median 50; range 18–60): BuCL 236 vs 168 mL/min, p=0.0002; BuCL/ABW 3.0 vs 2.1 mL/min/kg, p=0.0001; BuCL/IBW 3.8 vs 2.6 mL/min/kg, p=0.0035; BuCL/CBW 3.4 vs 2.6 mL/min/kg, p=0.0005. Inter-patient variability in clearance (CV%) was up to 48% in both age groups. Phenytoin administration, a potential confounder, did not affect BuCL, regardless of weight normalization (p>0.34).

Conclusions—Contrary to our hypothesis, BuCL was significantly higher in older patients compared to younger patients in these studies and does not explain the previously reported increase in busulfan toxicity observed in older patients.

Keywords

busulfan; bone marrow transplant; elderly; pharmacokinetics

INTRODUCTION

While the incidence of cancer increases with age and the average age of the US population continues to rise, inclusion of older patients in clinical trials remains low [1]. The paucity of information about the pharmacokinetics and pharmacodynamics of anticancer drugs in older patients is an impediment to oncologists making optimal therapeutic decisions in this patient group, and may negatively affect treatment outcomes [2]. The number of people over 65 years of age in the US is projected to double from 35 million persons to 70 million by 2030, and thus account for an estimated 20% of Americans. Cancer rates for people aged 50–64 years are 7- to 16-fold higher than those for younger persons, and rates for persons aged 65–74 years are another 2- to 3-fold higher still [3,4].

Ageing is associated with several physiological changes which can affect drug pharmacokinetics and pharmacodynamics [5–13]. It is evident that there is a need for a

better understanding of the interaction between age and anti-cancer drug toxicity and efficacy [14].

Busulfan is an alkylating agent commonly used in preparative regimens for patients undergoing hematopoietic cell transplantation for a variety of malignancies, including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) [15]. Studies of myeloablative conditioning for AML and MDS have shown a poorer outcome in older patients due to causes other than relapse, such as transplant-related morbidity and mortality [16–19]. As a result, it has become routine practice to exclude older AML and MDS patients from treatment with myeloablative conditioning regimens [15] or alternatively, to lower the dose or number of doses of busulfan for older patients [20].

Both oral and intravenous busulfan are associated with wide interpatient variability in the busulfan area under the plasma concentration-time curve (AUC) achieved [4,21,22]. A high AUC (> 1,500 μmol/L • min) has been associated with a high risk of fatal veno-occlusive disease of the liver, especially in the context of allogeneic transplantation [23]. Other pharmacokinetic-pharmacodynamic correlations for busulfan include: C_{ss} and the risk for graft rejection and/or leukemic relapse with a matched sibling graft or HLA–partially mismatched related or HLA matched unrelated donor; Css / AUC and the risk of leukemia recurrence after hematopoietic cell transplantation for CML; Css / AUC and disease-free survival in older MDS patients undergoing allogeneic hematopoietic cell transplantation [24].

Because of the concern for treatment-related morbidity and mortality, older AML and MDS patients have generally been excluded from many myeloablative treatment regimens, and thus may receive less efficient cytoreduction [25]. Information on busulfan pharmacokinetics in older patients would allow better informed treatment decisions and potentially improve outcome. The goal of this study was to investigate whether older age is associated with lower busulfan clearance by pooling extensive pharmacokinetic data from three CALGB transplant studies using busulfan-containing conditioning regimens.

PATIENTS AND METHODS

Patients

Patients were enrolled on one of three studies at CALGB institutions, all of which were approved by the institutional review board of participating institutions. Each participant signed an IRB-approved, protocol-specific informed consent in accordance with federal and institutional guidelines. Two studies, CALGB 19808 (NCT00006363) and 10503 (NCT00416598) used autologous transplant as treatment for AML in first remission in patients under age 60, and CALGB 100103 (NCT00070135) used allogeneic transplant as treatment for AML in first remission for patients between age 60 and 74. All trials required patients to have adequate organ function [26,27]. The CALGB 19808 end date was March 2006. CALGB 10503 and 100103 were performed over the similar time span of 2004–2011.

Treatment

All study patients received 2 h infusions of busulfan at 0.8 mg/kg corrected bodyweight (CBW), every 6 h for a total of 16 doses (CALGB 10503 and 19808) or 8 doses (CALGB 100103). CBW was calculated from ideal bodyweight (IBW) and actual bodyweight (ABW) as follows: CBW = IBW + 0.25*(ABW - IBW). If ABW >150% IBW, 150% of IBW was used as the ABW (IBW would be 112.5% IBW). If ABW < IBW, ABW was used [28]. Supportive care included the use of anti-seizure medication (phenytoin) and anti-emetics, which was recorded. CALGB 10503 and CALGB 19808 involved remission induction with cytarabine, daunorubicin, and etoposide, PBSC mobilization with etoposide, high dose cytarabine and G-CSF, and transplant was preceded by sequential busulfan (days -7 through -4) and etoposide (day -3). In CALGB 100103, the transplant was preceded by 30 mg/m^2/day fludarabine (days -7 through -3), busulfan (days -4 through -3), and thymoglobulin (days -4 through -2).

Pharmacokinetic sampling schedule and quantitation of busulfan concentrations

In CALGB 10503 and 19808, blood samples (5 mL collected in heparin anti-coagulated tubes) were obtained prior to, and at 125, 135 min, 4 h, and 6 h after the start of the first 2 h busulfan infusion. Samples were immediately placed on wet ice, refrigerated until processed, and processed within 1 h of collecting the last sample. Plasma was then separated by centrifugation at 1000 × g, for 10 min at 4 °C. Plasma aliquots were transferred to a cryovial and stored at −70 °C until analysis for busulfan concentrations. In CALGB 100103, samples were obtained prior to, and 115 min, 3, 4, 5, and 6 h after the start of the busulfan infusion. Peripheral blood sampling was preferred. If central line blood draws were performed, the central venous catheter was flushed with 5 mL of saline, and the initial 2 mL of blood drawn was discarded.

Plasma busulfan concentrations were quantitated with an LC-MS assay. Briefly, 0.2 mL aliquots of plasma sample, calibrator, or quality control were taken into preparation. Ten microliter of 1 μg/mL [D_8]-busulfan in methanol:0.2% formic acid in 10 mM ammonium acetate (50:50, v/v) were added, followed by a double extraction with 1 mL of ethyl acetate. The pooled supernatants were evaporated to dryness at 40 °C under a gentle stream of nitrogen. Dried residues were reconstituted in 50 μL methanol, sonicated, and diluted with 50 μL 0.2% formic acid in 10 mM ammonium acetate. Reconstituted residues were then transferred to Spin-X centrifuge tubes and centrifuged for 2 minutes at 16,000 × g. Ultrafiltrates were transferred to autosampler vials, and 10 μL were injected. The LC system consisted of an Agilent (Palo Alto, CA, USA) 1100 autosampler and binary pump, a Phenomenex (Torrance, CA, USA) hydro-Synergi (4 μm, 100 mm × 2 mm) column at ambient temperature, and a gradient mobile phase of methanol (A) and 0.2% formic acid in 10 mM ammonium acetate buffer (B) pumped at 0.2 mL/min. Between 0 and 4 min, A was increased linearly from 25% to 50%, and kept at 50% for 1 min. Between 5 and 6 min, A was increased linearly from 50% to 99% and then maintained at 99% from 6–8 min at a flow rate of 0.4 mL/min, followed by re-equilibration for a total run-time of 15 min. Mass spectrometric detection was carried out using a ThermoFinnigan (San Jose, CA, USA) MSQ mass spectrometer with electrospray ionization in positive-ion mode. The settings of the mass spectrometer were as follows: capillary voltage 4.0 kV; cone voltage 10 V; probe

temperature 400 °C. In single ion monitoring mode, the m/z values monitored were 263.9, and 271.9 for busulfan and [D_8]-busulfan, respectively. The LC system and mass spectrometer were controlled by ThermoFinnigan Excalibur software (version 1.4), and data were collected with the same software. The analyte-to-internal standard ratio (response) was calculated for each standard by dividing the area of the analyte peak by the area of the internal standard peak. The assay was accurate (between 96.5 and 106.0 %) and precise (CV <9.3%) over the busulfan concentration range of 1 to 300 ng/mL. Any samples above the upper limit of quantitation (300 ng/mL) was diluted to within the concentration range and re-assayed. During the study period, the assay was externally assessed by participation in the North American Busulfan Proficiency Exchange.

Data Integrity and Statistical Analysis

Patient registration and data collection was managed by the Cancer and Leukemia Group B (CALGB) Statistical Center. Statistical analyses were performed by CALGB statisticians and were based on the study database that was locked on Dec 10, 2011.

The busulfan plasma concentration *versus* time data was analyzed non-compartmentally using the LaGrange function as implemented by the LAGRAN computer program [29]. Clearance was calculated from $AUC_{0\text{-inf}}$. The percentage of the AUC that was extrapolated was on average 29%, with a median and SD of 27% and 15%, respectively.

The two-sided Fisher's Exact test was utilized to test for a difference in BMI between age patients <60 years vs ≥60 years old. The Wilcoxon rank sum test [30] was used to test the effect of age <60 years vs ≥60 years old on busulfan clearance (BuCL) as calculated non-compartmentally (mL/min), normalized to actual (ABW), ideal (IBW), or corrected (CBW) body weight (in kg). The effect of body size category (BMI normal 18–26 kg/m^2; obese 27–35 kg/m^2; severely obese >35 kg/m^2), was tested by Kruskal-Wallis rank sum test.

RESULTS

Patient characteristics

A total of 185 subjects were enrolled between August 2003 and July 2010, of which 11 were inevaluable for one or more of the following reasons: original blood sample drawn from busulfan infusion site, inadequate documentation of body weight or dose administered, and inadequate busulfan concentration–time data to perform the non-compartmental pharmacokinetic analysis. Detailed patient demographics are listed in Table 1.

Busulfan pharmacokinetics and age

BuCL values of individual patients are shown in Fig. 1. Patients over the age of 60 had a significantly higher clearance than younger patients, regardless of how clearance was expressed (Fig. 2 and Table 2). Inter-patient variability in clearance (CV%) was up to 48% in those <60 years old and up to 47% in the patients ≥60 years old.

The elimination half-life was comparable between the studies in patients <60 years old and ≥60 years old. The volume of distribution was statistically higher in the older patients.

The use of phenytoin in our study population was more prevalent in the younger population, and did not affect busulfan clearance, regardless of normalization ($p>0.34$), as tested by the wilcoxon rank test.

Other co-medications documented in our study population included fluconazole, voriconazole, levofloxacin, flucloxacillin, co-trimoxazole, caspofungin, ondansetron, levetiracetam, lamotrigine, ibuprofen, and oxycodone, but these were not considered likely to be of relevance in modifying busulfan pharmacokinetics, as described previously [31].

Analysis of clearance across age and BMI categories showed that ABW normalized clearance is a function of BMI, while AIBW normalized clearance is not, see Table 3.

DISCUSSION

The goal of this study was to investigate the relationship between busulfan pharmacokinetics and age. Age-dependent differences in the pharmacokinetics of busulfan have been reported previously with children having a higher distribution volume and clearance compared with adults after oral busulfan, resulting in both reduced toxicity and reduced efficacy [32]. When comparable exposures were achieved, toxicity and efficacy were more comparable in children and adults [33]. More recently, a potential age-related difference in pharmacodynamics susceptibility to busulfan was reported. Oral busulfan exposure determined graft rejection in children as had been documented in adults. However, severe regimen-related toxicity appeared unrelated to exposure in children, in contrast to reports in adults[34,23,35]. Our hypothesis was that older patients had a lower busulfan clearance than young patients.

Our study showed that patients older than 60 years did not have a lower busulfan clearance than the patients younger than 60 years. The pharmacokinetic disposition of busulfan in our study was concordant with previous published reports (mean busulfan clearance = 2.74 mL/min/kg ABW; mean $t_{½}$ = 2.83 h) [24]. The slightly (but statistically significant) higher volume of distribution of busulfan in older patients might be explained by the older subjects having a body composition with more adipose tissue compared to younger study participants, in line with the higher proportion high BMI subjects in the older group. Previously, in both pediatrics and adults, the volume of distribution was shown to be a function of actual body weight [36–38]

Our hypothesis was based on a decreased metabolic capacity for busulfan in older subjects. Busulfan is predominantly conjugated to glutathione by glutathione-S-transferase 1A1 (GST1A1), and metabolized to a lesser extent by CYP3A4 [39]. The rate-limiting factor for glutathione conjugation via GST1A1 is the availability of the cofactor glutathione, the availability of which decreases with age, as reported in human lymphocytes, gastric mucosa, and erythrocytes, and rodent liver, kidney and heart [40–42]. This presumably explains shifts of human acetaminophen glutathionylation to oxidative metabolism with older age [43]. Therefore, we hypothesized that busulfan clearance would be lower in older patients, resulting in higher busulfan exposures, increasing non-disease related morbidity and mortality in older AML patients. The data from our studies suggested that busulfan

clearance is increased (not lower) in patients ≥60 years old compared with patients <60 years. The effect of age on clearance appears opposite to our hypothesis, but the absolute difference in clearance of −68 mL/min (−127 to −27 mL/min 95% CI of the difference) equals 40% of the median clearance in patients <60 years. This effect is small relative to the observed inter-individual coefficient of variability in BuCL of 47%. The relatively large variability in clearance observed in our study relative to the 19–34% variability previously reported [44,4,45–49]is likely a reflection of the diverse population of patients participating in this multi-institutional cooperative group trial, as opposed to the previous, mostly single institution, studies.

Based on a recent report by Yeh *et al.*[50], we analyzed our data after categorizing patients based on BMI category and confirmed the previous report that ABW normalized clearance is a function of BMI, and that AIBW normalized clearance is not. Indeed, BMI was higher in the older group of patients (p=0.024). Although this could partially explain the observed difference in CL/ABW between patients age <60 years vs ≥60 years old, it does not explain the difference when expressed as CL/AIBW. The effect of body size on busulfan pharmacology deserves further characterization [50,44].

A number of medications may bias busulfan pharmacokinetics studies. Itraconazole, but not fluconazole, decreased busulfan clearance by 20% [51]. Metronidazole co-administration doubled busulfan trough concentrations, increasing toxicity, including multi-organ failure, veno-occlusive disease and hemorrhagic cystitis, likely through inhibition of CYP3A metabolism [52]. Risk factors for veno-occlusive disease of the liver included concomitant ketoconazole, a known pan-CYP450 inhibitor [53]. Phenytoin increased oral busulfan clearance by approximately 20% [54,55], likely due to induction of CYP3A4 [56], which may have predominated any reduction in glutathione conjugation [57–59]. Blood glutathione concentrations have been positively correlated with Bu clearance (adjusted $R^2 = 0.45$; P = 0.009) [49]. The toxicological relevance of the shift of busulfan clearance from conjugation to oxidative metabolism is uncertain. Phenytoin use was documented in our study population, but could not explain the increased clearance in the older patients because its use was slightly more prevalent in the younger patients studied rather than the older patients. In addition, more recent data with intravenous busulfan has failed to confirm the interaction observed with oral busulfan [31,60,38,36]. Fluconazole and voriconazole were documented as administered concomitant medications, but neither ketoconazole nor itraconazole, the more potent inhibitors of CYP450 enzymes, were administered in our study populations [61]. No other co-medication was deemed able to explain the observed difference in busulfan clearance. Yeh et al. previously reported that concomitant fludarabine (used in the study of patients >60 years old) might decrease busulfan clearance from day 1 to day 4, though busulfan preceded by fludarabine did not result in any change in busulfan clearance [50]. Unfortunately data were only presented as relative change between days, not allowing comparison of absolute clearance values between these two scenarios. Furthermore, Bartelink et al. did not observe a changes in busulfan clearance between patients with or without fludarabine[31].

Previously, McCune et al. reported in a dataset of 1610 patients (92% children; 128 adults with a maximum age of 66 years old) that busulfan clearance normalized by body size

essentially plateaued at age 2.5 years. However, their dataset did not have nearly as many elderly patients as the current study and utilized “size-standardized clearance”, which utilized “normal fat mass” as the size-metric, itself derived through a series of estimates and formulae. Visually, the cluster of patients age 32–66 years old might display higher clearances than the model estimated [44].

Busulfan exposure is correlated with both efficacy and toxicity in patients. The considerable differences in study design of the three trials from which the patients’ busulfan pharmacokinetic data were obtained, precluded a rigorous evaluation of the effect of age on non-disease related toxicities.

The increased clearance that we observed in the older patients should be interpreted with caution, and clearly needs to be confirmed in future studies. Potential limitations of our findings are that the pharmacokinetic studies were performed on the first day of busulfan dosing, which may not be reflective of the entire treatment period (usually 16 or 8 doses at 6-hourly intervals) with busulfan. Possibly, clearance may decrease as glutathione levels are depleted upon repeated doses, and it is not inconceivable that this effect would be more pronounced in older patients. The slightly different pharmacokinetic sampling in the studies is unlikely to have had an impact on calculated busulfan pharmacokinetic parameters. Potentially, there exists a selection bias in the older subjects for good performance status, with a better physiological state than less selected subjects of <60 years old. This notion is supported by the higher percentage of older patients with good performance status. An unplanned sub-analysis of the effect of age on BuCl within each of the three individual studies did not result in a significant effect (P-value>0.162).

In summary, we observed that there was increased BuCL in a study of patients ≥60 with AML undergoing transplantation compared to younger patients (<60 years) with AML in two other studies where busulfan was used as part of a myeloablative regimen. Future studies of this kind should recruit all age groups in a single protocol with a uniform study plan, and use measures to prevent selection bias. In addition, other possible covariates, such as functional age [62], and its relationship with drug tolerability, need to be studied in older patients to better optimize busulfan therapy for individuals ≥60 years old. Subsequently, potential differences in exposure-response relationships between these age-cohorts can be addressed. Population pharmacokinetic approaches and limited sampling strategies may then play a role in further optimizing therapy in this increasingly prevalent type of patient.

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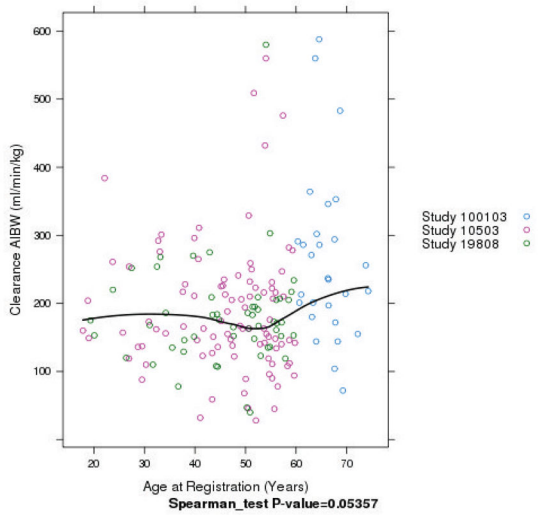
1a



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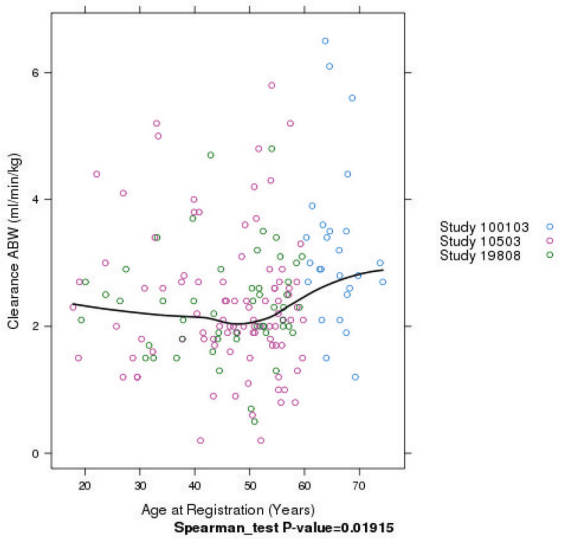

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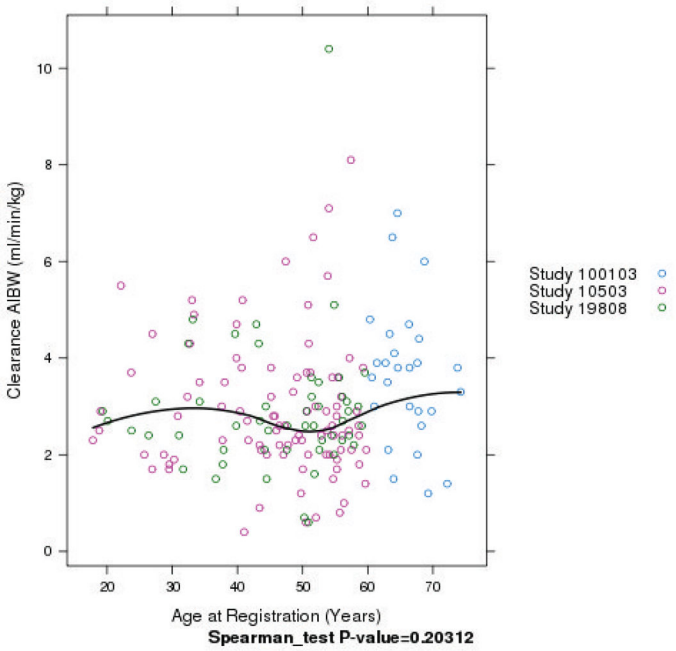

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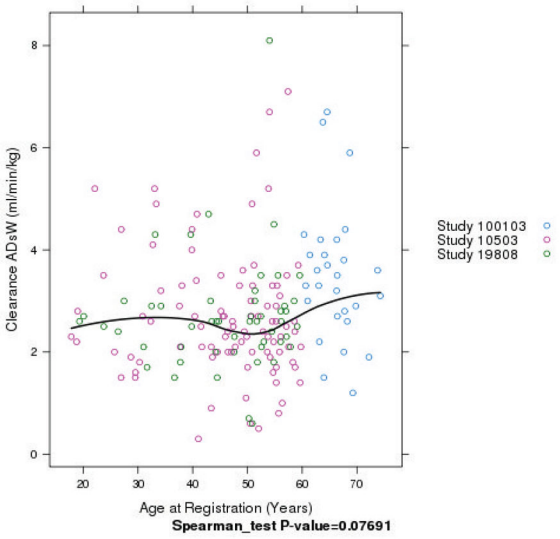
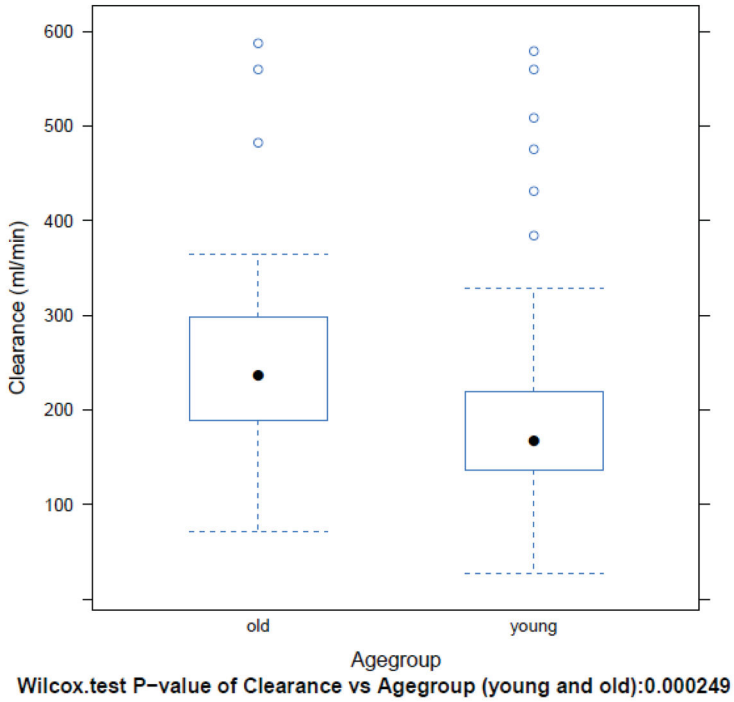


Fig. 1.

Relationship of patient age and busulfan clearance (BuCL). Points represent individual patient values of BuCL (a), BuCL/ABW (b), BuCL/IBW (c), and BuCL/CBW (d). A loess smoother spline was fitted to the data in each case and shows the trend of BuCL with age.

2a



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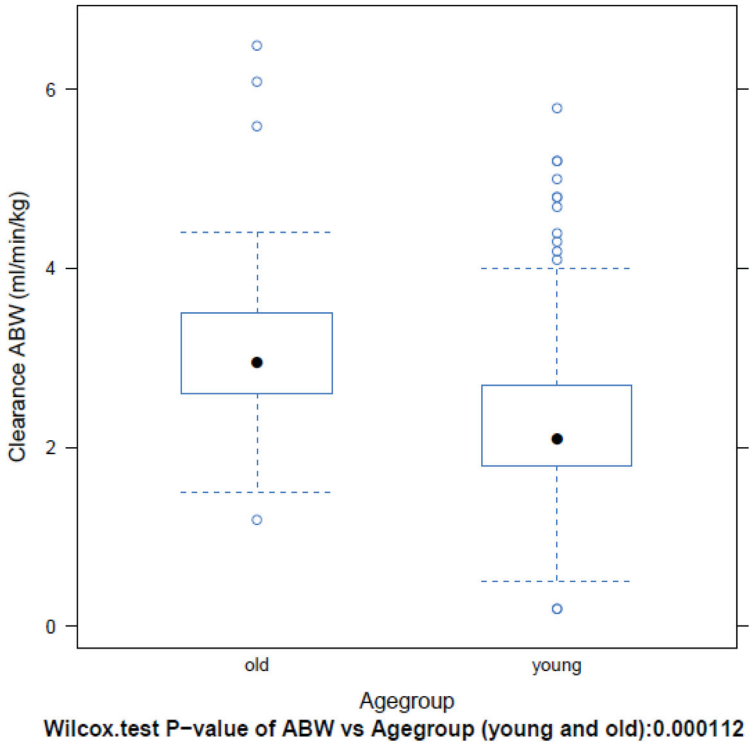

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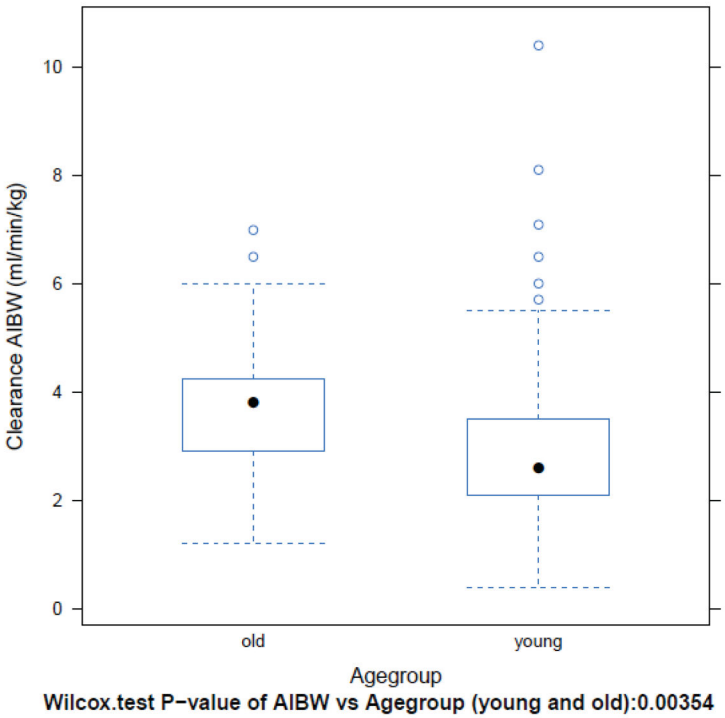

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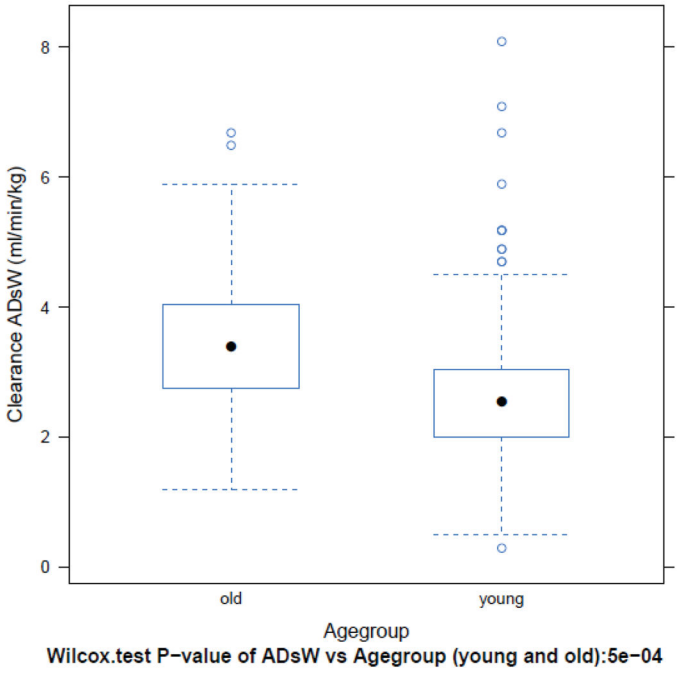

Fig. 2.

Box-plots of BuCL (a; p=0.0002), CL/ABW (b; p=0.0001), CL/IBW (c; p=0.0035), and CL/CBW (d, p=0.0005) in patients <60 years old and ≥60 years old.

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Table 1

Patient demographics of studies in subjects ≥60 years old (100103) and patients <60 years old (19808 and 10503).

CALGB Study	**19808**	**10503**	**19808+10503**	**100103**
Number of patients	56	100	156	32
Useable pharmacokinetic data	56	100	156	29
Median age (range)	50.3 (19.3–59.6)	49.6 (17.8–60.0)	49.8 (17.8–60.0)	66.3 (60.3–74.3)
Sex				
Male (%)	21 (37.5)	50 (50)	71 (45.5)	20 (69)
Race				
White n (%)	46 (82)	85 (85)	131 (84)	27 (93)
African n (%)	6 (11)	4 (4)	10 (6)	0
Asian n (%)	1 (2)	1 (1)	2 (1)	0
ECOG Performance Status *				
0 (%)	26 (46)	32 (32)	58 (37)	15 (52)
1 (%)	24 (43)	62 (62)	86 (55)	10 (34)
2 (%)	5 (9)	6 (6)	11 (7)	4 (14)
3 (%)	1 (2)	0	1 (0.6)	0
Phenytoin use (%)	49 (88)	55 (55)	104 (67)	13 (45)
Weight (kg)	76.1(49–172)	82.3(46.6–171)	79,8(46.6–172) **	84(54.1–124) **
BMI (kg/m^2)	27(18.9–57.9)	29.4(17–54.4)	28.4(17–57.9) ***	27.1(19.8–35.4) ***

* Performance status was recorded at the time of diagnosis for patients on the 2 studies with younger patients, but only at the time of transplantation in the older patient study.

** P-value by wilcox rank test: 0.7307

*** P-value by two-sided Fisher's Exact test: 0.024

Table 2

Busulfan clearance in subjects ≥ 60 years old (100103) and patients <60 years old (19808 and 10503).

CALGB Study	**19808**	**10503**	**19808+10503**	**100103**
Median age (range)	50.3(19.3–59.6)	49.6(17.8–60.0)	49.8 (17.8–60.0)	66.3 (60.3–74.3)
CL (mL/min)				
Mean	180	190	186	263
Median	172	163	168	236
Range	40–580	28–560	28–580	72–588
P-value *				**0.0002**
CL/ABW (mL/min/kg)				
Mean	2.34	2.34	2.34	3.22
Median	2.3	2.1	2.1	3.0
Range	0.5–4.8	0.2–5.8	0.2–5.8	1.2–6.5
P-value *				**0.0001**
CL/IBW (mL/min/kg)				
Mean	2.91	2.90	2.91	3.63
Median	2.6	2.6	2.6	3.8
Range	0.6–10.4	0.4–8.1	0.4–10.4	1.2–7
P-value *				**0.0035**
CL/CBW (mL/min/kg)				
Mean	2.7	2.7	2.7	3.5
Median	2.6	2.5	2.6	3.4
Range	0.6–8.1		0.3–8.1	1.2–6.7
P-value *				**0.0005**
t½ (h)				
Mean	3.88	3.93	3.91	3.70
Median	3.00	2.77	2.82	2.62
Range	1.05–29.4	0.28–33.0	0.28–33.0	1.24–12.4
P-value *				**0.74**
Vd (L)				
Mean	49.4	50.9	50.4	77.6
Median	44.5	41.6	43.4	59.2
Range	20.5–125	7.3–302	7.3–302	15.5–228
P-value *				**0.0023**

* patients <60 years old and ≥60 years old i.e CALGB100103 vs CALGB 19808 + CALGB 10503.

ABW, actual bodyweight; IBW, ideal bodyweight, CBW, corrected bodyweight (used to dose)

Table 3

Busulfan clearance by different weight metrics and body mass index–based weight category, mean±SD (range).

Clearance metric	Normal	Obese	Severely Obese	P-value**
All patients				
N (%)	82 (44.3%)*	66 (35.7%)	37 (20.0%)	
CL (mL/min)	183±86.8 (45–560)	217±110 (40–588)	200±102 (28–580)	0.1411
CL/ABW (mL/min/kg)	2.64±1.1 (0.6–6.5)	2.56±1.12 (0.5–6.1)	1.95±0.94 (0.2–4.8)	0.00097
CL/IBW (mL/min/kg)	2.82±1.17 (0.6–6.5)	3.27±1.49 (0.6–8.1)	3.09±1.78 (0.4–10.4)	0.25
CL/CBW (mL/min/kg)	2.76±1.14 (0.6–6.5)	3.04±1.34 (0.6–7.1)	2.61±1.33 (0.3–8.1)	0.2
<60 years				
N (%)	68 (43.6%)	52 (33.3%)	36 (23.1%)	
CL (mL/min)	169±65.2 (45–384)	200±103 (40–560)	199±103 (28–580)	0.22
CL/ABW (mL/min/kg)	2.52±0.98 (0.6–5.2)	2.39±1.06 (0.5–5.8)	1.92±0.93 (0.2–4.8)	0.0022
CL/IBW (mL/min/kg)	2.71±1.06 (0.6–5.5)	3.07±1.49 (0.6–8.1)	3.09±1.81 (0.4–10.4)	0.60
CL/CBW (mL/min/kg)	2.64±1.02 (0.6–5.2)	2.86±1.34 (0.6–7.1)	2.6±1.35 (0.3–8.1)	0.60
≥60 years				
N (%)	14 (48.3%)	14 (48.3%)	1 (3.4%)	
CL (mL/min)	248±137 (72–560)	283±113 (144–588)	213	0.53
CL/ABW (mL/min/kg)	3.25±1.46 (1.2–6.5)	3.22±1.16 (1.5–6.1)	3	0.94
CL/IBW (mL/min/kg)	3.33±1.55(1.2–6.5)	4.04±1.29 (1.5–7)	3	0.23
CL/CBW (mL/min/kg)	3.31±1.48 (1.2–6.5)	3.73±1.18 (1.5–6.7)	3	0.38

*One patient had marginal low BMI and was placed in the normal cohort to allow testing across 3 categories.

**By Kruskal-Wallis rank sum test

ABW, actual bodyweight; IBW, ideal bodyweight, CBW, corrected bodyweight (used to dose)