Optimization of Busulfan Dosage in Children Undergoing Bone Marrow Transplantation: A Pharmacokinetic Study of Dose Escalation

By Andrew M. Yeager, John E. Wagner, Jr, Michael L. Graham, Richard J. Jones, George W. Santos, and Louise B. Grochow

Busulfan (BU) is a widely used myeloablative and antineoplastic agent in clinical bone marrow transplantation (BMT). The lower incidence of BU-associated toxicities and lower therapeutic effectiveness in young children given BU doses based on body weight (ie, 16 mg/kg) is associated with altered pharmacokinetics of BU; the area under the curve (AUC) of BU concentration versus time is significantly less in these patients than those observed in older children and adults. To optimize BU dosage in young BMT recipients, we developed a dosage regimen based on body surface area (BSA) and determined BU pharmacokinetics and BU-associated toxicities. Seven children (median age, 3.9 years; range, 1.1 to 5.7) undergoing allogeneic or autologous BMT for leukemia received 40 mg/m²/dose of BU every 6 hours for 16 doses; BU concentrations were measured in the plasma, and AUCs were determined for each patient after the first and 13th doses. Expressed as a function of body weight, the median concentration was significantly lower than that in adults given BU in a dosage regimen based on body surface area (BSA) and determined BU pharmacokinetics and BU-associated toxicities. The mean BU AUCs were 1.105 µmol/L·min (range, 0.790 to 2.080) after the first dose and 1.022 µmol/L·min (range, 0.632 to 1.860) after the 13th dose of BU, comparable to the AUCs in adults given 16 mg/kg of BU. These studies suggest that, in young children, BSA-based dosing of BU (40 mg/m²) provides drug exposures (AUCs) closer to adult values with acceptable toxicities and may improve therapeutic effects.

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BU dosage. The median actual dosage of BU calculated from BSA was 38.9 mg/m² (range, 36.7 to 41.7); these variations from the ideal study dosage of 40 mg/m² were due to rounding off the BU dosage from the 2-mg tablet size. When BU doses were expressed as a function of body weight, the median was 26.4 mg/kg (range, 24.3 to 28.2), approximately a 60% increase over the standard BU dosage of 16 mg/kg (Table 1).

Clinical course. All patients became aplastic within 2 to 8 days after BMT. Four patients developed mucositis, which required narcotic analgesia in two. In contrast, hepatic dysfunction was less frequently observed: in five patients, bilirubin did not exceed 1.9 mg/dL in the post-BMT period. In two patients undergoing allogeneic BMT for acute myeloid leukemia (AML) in remission, bilirubin elevation was observed. In patient 4, modest hyperbilirubinemia (maximum, 2.4 mg/dL at 23 days after BMT) was associated with weight gain, ascites, and tender hepatomegaly, consistent with the diagnosis of hepatic VOD; with fluid restriction and diuretics, symptoms resolved and bilirubin fell below 1.5 mg/dL within 7 days. In patient 7, bilirubin increased to 4.4 mg/dL 33 days after allogeneic BMT, but there was no evidence for VOD; the course was felt to be most consistent with hepatic acute graft-versus-host disease, and hyperbilirubinemia slowly resolved within 2 weeks on cyclosporine and methylprednisolone therapy. No patients developed pulmonary insufficiency or manifestations of interstitial pneumonitis (Table 1).

Pharmacokinetic data. Table 2 shows the AUC after the first and 13th doses of BU and the mean trough BU concentration (Cₘ₉) for each patient. The median and

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Type of BMT</th>
<th>Mean AUC (µmol/L·min)</th>
<th>Mean Cₘ₉ (µmol/L)</th>
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<td>1</td>
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<tr>
<td>7</td>
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<td>800</td>
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</table>

Mean ± SD 1.105 ± 0.468 959 ± 413 1.08 ± 0.42

Abbreviations: AUC, area under the curve of BU concentration v time; Cₘ₉, minimum (trough) BU concentration.
mean BU AUC after the first dose were 850 and 1,105μmol/L-min, respectively (range, 790 to 2,080). There was no alteration in AUC after the 13th BU dose, at which time the median and mean AUCs were 904 and 1,022μmol/L-min, respectively (range, 632 to 1,860). These values are similar to the AUC in adults (ie, 1,200 to 1,600μmol/L-min) that are therapeutic but not associated with increased risks of VOD or other life-threatening extra- medullary toxicity. The range of trough plasma BU concentrations, times to peak BU levels, and clearance rates in these patients were all similar to those previously reported in children under age 6 years receiving standard doses (1.0mg/kg/dose) of BU.

**DISCUSSION**

In children under age 6 years receiving a standard dosage of BU based on body weight (16mg/kg), pharmacokinetic studies from this laboratory have shown that the mean AUC was 715μmol/L-min. Using the BSA-derived BU dosage regimen (40mg/m²), the AUC in our patients (1,105μmol/L-min) was significantly higher (P = .019; two-tailed Student’s t test) and is comparable to the target AUC in adults receiving dose-adjusted BU. Expressed as a function of body weight in this group, the BSA-based BU dosages (24.3 to 28.2mg/kg; median, 26.4mg/kg) are similar to those extrapolated from the studies of Shaw et al and Vassal et al in which BU dosage was based on 20mg/m² or 37.5mg/m², respectively. Taken together, these studies confirm that, in younger children, at least 50% higher doses of BU are needed than calculated on the basis of body weight (ie, 16mg/kg).

These pharmacokinetic data were corroborated by the increased incidence of mucositis in these children. Interestingly, neither the severity of mucositis nor the occurrence of VOD was correlated with elevated AUC in this series; the three patients with the most severe mucositis (no. 4, 5, and 6), one of whom also had VOD, had BU AUCs below the mean. No patients in this series had neurotoxicity, as previously attributed to BU, such as interstitial pneumonitis, were not observed in this or other series in which BU doses exceeding 1mg/kg (or 20mg/m²) were used. On balance, the observed toxicities, infrequent in children given conventional doses of BU, are acceptable and manageable consequences of attainment of higher BU dosages, which may improve therapeutic effect.

It has been suggested that both allograft rejection and higher relapse rates are more frequent in young children given BMT after regimens that use standard-dose BU, consistent with lower drug exposures to both normal stem cells and neoplastic cells. The differences in diagnoses, remission number, and types of BMT in this series preclude conclusions about improved therapeutic effectiveness in recipients of BSA-determined BU dosing. Nevertheless, donor cell engraftment was prompt in the three recipients of allogeneic marrow and one recipient of HLA-compatible allogeneic placental blood, and was complete and sustained. No episodes of late graft failure, as reported in children receiving standard-dose BU for allogeneic BMT from related donors, were observed.

The reasons for altered disposition of BU in young children are unknown, but are probably multifactorial. Altered gastric pH (higher in infants and very young children), relative differences in distribution and percentages of body adipose tissue and total body water, and alterations in first-pass hepatic clearance and metabolism may all contribute to the relative underdosing of BU when the drug is administered on the basis of body weight. These and other observations suggest that BSA-based dosage of BU and other antineoplastic agents is the most rational and reliable approach in children. However, in infants under age 6 months, drug dosage based on BSA may be inaccurate, and studies of adjusted BU dosage have not yet been conducted in this age group.

Although BSA-based BU dosage in children provides drug exposures closer to adult values, the wide range of AUC observed in this and other studies suggests that further studies are warranted; ultimately, therapeutic monitoring of BU levels and individualized adjustment of BU dosage may be used to provide optimal drug exposures for each patient. As high AUC for BU has been associated in adults with an increased risk of VOD, which has a high case-fatality rate, dose-adjustment strategies may retain or enhance the therapeutic effectiveness of high-dose BU and reduce the incidence of life-threatening drug-associated toxicities.

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