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Busulfan disposition and hepatic veno-occlusive disease in children undergoing bone marrow transplantation

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Abstract Hepatic veno-occlusive disease (HVOD) is a frequent life-threatening toxicity in patients undergoing bone marrow transplantation (BMT) after the administration of a high-dose busulfan-containing regimen. Recent studies have shown that the morbidity and mortality of HVOD may be reduced in adults by pharmacologically guided dose adjustment of busulfan. We analyzed the pharmacodynamic relationship between busulfan disposition and HVOD in 61 children (median age, 5.9 years) with malignant disease. Busulfan, given at a dose ranging from 16 mg/kg to 600 mg/m², was combined with one or two other alkylating agents (cyclophosphamide, melphalan, thiotepa). Only 3 patients received the standard busulfan/cyclophosphamide (BUCY) regimen. A total of 24 patients (40%) developed HVOD, which resolved in all cases. A pharmacokinetics study confirmed the previously reported wide interpatient variability in busulfan disposition but did not reveal any significant alteration in children with HVOD. The mean area under the concentration-time curve (AUC) after the first dose of busulfan was higher in patients with HVOD (6,811 ± 2,943 ng h ml⁻¹) than in patients without HVOD (5,760 ± 1,891 ng h ml⁻¹; P = 0.10). This difference reflects the higher dose of busulfan given to patients with HVOD. No toxic level could be defined and, moreover, none of the toxic levels identified in adults were relevant. The high incidence of HVOD in children given 600 mg/m² busulfan may be linked to the use of more intensive than usual high-dose chemotherapy regimens and/or drug interactions. Before the prospective evaluation of busulfan dose adjustment in children, further studies are required to demonstrate firmly the existence of a pharmacodynamic relationship in terms of toxicity and allogeneic engraftment, especially when busulfan is combined with cyclophosphamide. The maximal tolerated and minimal effective AUCs in children undergoing BMT are likely to depend mainly upon the disease, the nature of the combined high-dose regimen, and the type of bone marrow transplant.

Key words Busulfan · Pharmacodynamics · Hepatic veno-occlusive disease

Introduction

In bone marrow transplantation (BMT) settings, hepatic veno-occlusive disease (HVOD) is the most frequent life-threatening complication among high-dose chemotherapy-related toxicities. After the administration of a busulfan-containing regimen, the incidence of HVOD ranges from 0 in children with a genetic disease [17] up to 52% in adults with hematological malignancies [11, 16]. No HVOD was observed in patients receiving single-agent high-dose busulfan [12, 15]. However, busulfan seems to be involved in HVOD, since the incidence of the latter was found to be 4% after high-dose chemotherapy without busulfan versus 22% after treatment with a busulfan-containing regimen before BMT in children [26].

Busulfan pharmacokinetics display wide interpatient variability in adults and children [5–7, 8, 24, 27, 28]. With the standard dose of busulfan (16 mg/kg), the incidence of HVOD proved to be lower in children than in adults [2, 17, 19]. This difference could be due to the age-dependent pharmacokinetics of the drug: busulfan clearance is higher in children than in adults [6, 8, 28]. We investigated a new busulfan dose level
(600 mg/m²) that eliminates the differences in systemic exposure between adults and children [27]. This new dose was expected to enhance the drug's antitumor and antileukemic activity. However, it has given rise to an increased incidence of HVOD [25]. We have recently demonstrated that the major independent risk factors for the occurrence of HVOD in children undergoing autologous BMT for malignant disease after the administration of a busulfan-containing regimen were the dose of busulfan, the intensity of the high-dose chemotherapy regimen, the timing of busulfan dosing within three-drug regimens, and the use of ketoconazole [13].

Grochow et al. [5] demonstrated that the occurrence of HVOD was significantly correlated with high systemic exposure after the first dose of busulfan in adults receiving busulfan and cyclophosphamide (BUCY regimen) before BMT. HVOD might be linked to an altered busulfan disposition of an unknown origin. The definition of a toxic level led these authors to propose dose adjustment as a means of decreasing the incidence of lethal HVOD in adults [4]. Since HVOD is dose-dependent in children, we studied the relationship between busulfan disposition and HVOD in 61 children undergoing BMT for malignant disease.

### Patients and methods

#### Patients

From 1987 to 1991, plasma busulfan pharmacokinetics were studied in 61 children with a median age of 5.9 years (range, 1–15 years) in a single institution. There were 30 boys and 31 girls. In all, 59 patients were treated for a malignant solid tumor (28 neuroblastomas, 13 brain tumors, 5 non-Hodgkin's lymphomas, and 3 Ewing's sarcomas) and 2 patients were treated for acute leukemia. At the time of BMT, 40 patients had measurable refractory disease or a relapse and 21 were in complete remission. Altogether, 53 patients had received conventional multidrug chemotherapy and 8 patients had received only CNS radiation therapy. In all, 58 and 3 patients underwent autologous and allogeneic BMT, respectively. All the patients had normal liver and kidney functions before receiving high-dose chemotherapy.

#### Treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Busulfan, melphalan (140 mg/m²)</td>
<td>6</td>
</tr>
<tr>
<td>Busulfan, thiotepa (900 mg/m²)</td>
<td>13</td>
</tr>
<tr>
<td>Melphalan (140 mg/m²), busulfan, cyclophosphamide (200 mg/kg)</td>
<td>7</td>
</tr>
<tr>
<td>Busulfan, cyclophosphamide (4.4 g/m²), melphalan (140 mg/m²)</td>
<td>30</td>
</tr>
<tr>
<td>Busulfan, cyclophosphamide (4.4 g/m²), thiotepa (900 mg/m²)</td>
<td>2</td>
</tr>
</tbody>
</table>

### Evaluation of liver toxicity

The diagnosis of veno-occlusive disease of the liver was based on MacDonald's criteria [10] as follows: (1) hepatomegaly, (2) jaundice or hyperbilirubinemia of ≥ 25 µM, and (3) ascites and/or a weight gain of ≥ 5%. Other biological symptoms [elevated levels of aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT), reversible renal dysfunction, changes in coagulation factors, platelet consumption] were often present but were not considered for the diagnosis. Abdominal ultrasonography confirmed the presence of ascites and frequently showed obscuring of major hepatic veins. No liver biopsy was performed. At least two of the three MacDonald's criteria had to be fulfilled for the diagnosis of HVOD. The day of onset was not taken into account since all but three patients received an autologous bone marrow transplant. For this retrospective study the clinical records of all the patients were reviewed by a clinician blinded for the pharmacokinetic findings. A total of 60 patients were evaluable for liver toxicity. One patient died on day 2 post-BMT of septicemia due to Candida albicans and was not included in the pharmacodynamics study.

### Blood sampling and busulfan assay

Heparinized whole-blood samples (2 ml) were drawn through the central line after the first dose of busulfan. Samples were obtained from 11 patients before busulfan administration and at 20 and 40 min as well as 1, 1.5, 2, 3, 4, and 6 h. Samples were obtained from 50 patients before busulfan dosing and at 30 min as well as 1, 2, 3, 4, and 6 h. Plasma was separated and frozen at −80°C until analysis. The study was designed in accordance with the requirements and recommendations of the ethics committee and parental consent was obtained. Busulfan plasma levels were measured in a gas chromatography-mass spectrometry assay using a deuterated analog as an internal standard, as previously described [23].

### Pharmacokinetic and statistical analysis

The decrease in the plasma concentration-time curve after the first dose was mono- and biexponential in 53 and 5 patients, respectively. The time required for maximal plasma concentration was 6 h, i.e.,