Unexpected Toxicity Associated with Use of Body Surface Area for Dosing Melphalan in the Dog

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ABSTRACT

A multistratal Phase I study using i.v. melphalan was conducted in dogs with spontaneously occurring neoplasia. Melphalan was administered at 7.5, 10, 11.25, 12.5, and 20 mg/m² of body surface area. Disproportionately greater toxicity was observed in small dogs. Seven of the eight dogs (88%) weighing less than 14 kg experienced severe myelosuppression (neutropenia, <1500/mm³; and/or thrombocytopenia, <80,000/mm³), whereas only three of 13 dogs (23%) weighing greater than 14 kg developed severe myelosuppression (P = 0.016). We concluded that small dogs are at greater risk of developing bone marrow toxicity from i.v. melphalan than large dogs if body surface area is used to calculate the dose. Although both body surface area and weight were found to be significantly correlated with severity of toxicity, melphalan-induced toxicity in dogs can be more accurately estimated by body weight than by surface area, P = 0.008 versus P = 0.022, respectively.

It may be necessary to prescribe antineoplastic agents that are eliminated by processes not primarily under metabolic influence or that produce side effects on tissue not correlated to basal metabolic rate on a parameter other than body surface area. In dogs, melphalan should be dosed on a weight basis, and treatment groups should be stratified by weight in randomized clinical studies, particularly when the weight range of treated subjects is great.

INTRODUCTION

Chemotherapeutic agents have a low therapeutic index and therefore require a precise means of prescription. In the past, antineoplastic drugs have been administered on a weight basis. However, BSA has been reported to correlate better with basal metabolic rate (1), blood volume (2), cardiac output (3), and pharmacokinetic drug disposition (4) than body weight. Additionally, the plasma drug concentration-time profile (area under the curve) was found to yield similar values for many chemotherapeutic agents across species lines (5). These findings led to the use of BSA as a means for dose extrapolation from laboratory animal toxicity studies to human clinical trials (6-8). The question of whether BSA provides the optimal means of dose prescription for all anticancer compounds under clinical investigation still remains unanswered.

Several problems with the use of the BSA-scaled dose prescription method have recently been reviewed (9, 10). BSA, in m², for all mammalian species is an indirect parameter, calculated from an equation.

\[
\text{BSA in m}^2 = \frac{K_w \times \text{wt}^{0.67}}{10^b}
\]

Each species has a unique constant factor (\(K_w\)) which was derived from body configuration/surface area relationships (11, 12). However, the reported \(K_w\) value for the dog represented the mean value from a limited number of specimens (mean, 10.0; range, 9.9 to 12.3). This factor has been accepted convention but may not represent the most accurate means of estimating BSA in the dog. In addition, the accuracy of the scaling factor (i.e., 0.67) within a species that exhibits wide variation in body weight and configuration (e.g., canines) has not been determined. However, the variation of this coefficient for other species has been predicted to be ±20% (13).

For many antineoplastic agents, myelosuppression is the dose-limiting normal tissue toxicity, and BSA has never been positively correlated with hematopoietic stem cell activity. In a study by Vriesendorp and Von Bekkum (14), the hematopoietic stem cell activity necessary to rescue 50% of the experimental animals (mice, rats, monkeys, dogs) following lethal, total-body irradiation was correlated better with body weight (kg) than with BSA (14).

Drugs which are metabolized and eliminated by organs with a high metabolic rate may be adequately administered if dosed according to BSA (5). The elimination half-life of drugs that have a significant proportion of their biotransformation not under the control of metabolic pathways (e.g., thermodynamic instabilities, nonenzymatic spontaneous degradation) or where organ function is immature or impaired would not be expected to correlate well with BSA. A recent study of neonates receiving chemotherapy based on BSA reports subsequent unexpected, severe hematological toxicity (15, 16).

These data suggest that a parameter which estimates normal tissue toxicity and pharmacokinetic disposition more accurately than BSA may be required for certain chemotherapeutic agents.

The purpose of this report is to describe the unexpected, weight-related, bone marrow toxicity observed in a Phase I investigation of i.v. melphalan in tumor-bearing dogs.

MATERIALS AND METHODS

This study was designed to be a Phase I dose escalation evaluation of i.v. melphalan. Criteria for entry into this protocol included histological confirmation of neoplasia; normal hematological, renal, and hepatic function assessed by complete laboratory screening; complete radiographic evaluation of the tumor; staging according to WHO classification schema; and owner-informed consent agreement.

Twenty-three dogs were entered into the study. Two dogs were unevaluable due to protocol violations. The 21 evaluable dogs had a median age of 10 yr and male:female ratio of 1.33 (12:9). The majority of tumors were malignant melanoma (18 of 21). Other histologies included lymphosarcoma (2 of 21) and mast cell tumor (1 of 21). Weight ranged from 5 kg to 55.5 kg (mean, 23.7 kg) which corresponded to a BSA range of 0.29 to 1.46 m² (mean, 0.77 m²). Prior chemotherapy, if administered greater than 30 days prior to melphalan, did not exclude a dog from the study. However, prior melphalan therapy required exclusion from this study. Only 3 dogs (OK, FD, and TR) had any prior chemotherapy.

Melphalan (Burroughs-Wellcome Co., Research Triangle Park, NC)
was dissolved in acid-ethanol, buffered to a pH of 7.4 with potassium dihydrogen phosphate, and diluted with propylene glycol. This solution was filtered through a 0.2-μm sterilizing filter into a sterile vial, kept on ice, and administered within 30 min.

Melphalan was administered as an i.v. bolus once weekly for 4 wk. Evaluation during the study included physical examination, complete blood count (including platelet count), and tumor measurements, if applicable, prior to each melphalan administration. Posttreatment laboratory evaluation was conducted at 1 wk following chemotherapy and at 3- to 4-wk intervals thereafter until bone marrow suppression resolved. Toxicity was scored as none, mild, or severe (Table 1). Criteria for discontinuation of melphalan therapy were based on development of any severe toxicity following melphalan.

Melphalan dose group determinations were based on previously established guidelines for Phase I trials (17). The initial dose, 20 mg/m², was estimated from preclinical toxicity studies in normal dogs (18, 19). Subsequent doses evaluated were 7.5, 10, 11.25, and 12.5 mg/m². Melphalan dose in mg/m² was also expressed as dose in mg/kg. The relationship between toxicity score and dose, for mg/m² and mg/kg, was evaluated using a continuous logistic regression procedure (20). Regression equations in the form ln(P/1−P) = α + β(x), where P is probability of severe toxicity, 1−P is probability of no or mild toxicity, α and β are regression constants, and x is dose were also calculated.

RESULTS

Table 2 lists patient weight, surface area, dose determined by surface area and weight as well as toxicity (if any), and the number of melphalan treatments associated with toxicity.

Severe leukopenia and/or thrombocytopenia (defined in Table 1) was observed in 10 dogs (Table 2). The mean weight of dogs with severe toxicity was 15.6 ± 10.9 kg which was significantly less (P = 0.008) than the mean weight of dogs that did not develop severe toxicity (30.3 ± 11.4 kg). For purposes of comparison, and based on the finding of more toxicity in small dogs, dogs less than 14 kg (30 lb) were arbitrarily classified as “small dogs.” Although this study was not prospectively designed to stratify dose groups according to weight, there was an equal distribution of small dogs (<14 kg) and large dogs (>14 kg) in the 20-mg/m² and 10-mg/m² dose groups. The 7.5- and 12.5-mg/m² had 1 of 4 and 1 of 3 small dogs per group, respectively. The 11.25-mg/m² group consisted of only 2 dogs, both large. Therefore the enhanced toxicity seen in dogs weighing less than 14 kg cannot be attributed to small dogs receiving higher doses than large dogs. Seven of eight (87.5%) dogs weighing <14 kg experienced severe toxicity compared to only 3 of 13 (23%) weighing >14 kg (χ² analysis, P = 0.016).

In all dose groups evaluated, only small dogs became severely toxic, while only one large dog showed severe toxicity except for the highest dose group (20 mg/m²). All dogs entered at 20 mg/m² experienced severe toxicity 1 wk after the initial treatment.

Based on continuous logistic regression (20), mg/kg dose and mg/m² dose were both significantly correlated with toxicity score. However, mg/kg dose correlated better with severe toxicity than mg/m² dose, P = 0.008 versus P = 0.022, respectively. Furthermore, with backward regression, no further improvement in prediction of severe toxicity was observed when mg/m² dose was considered beyond that accomplished by evaluation based on mg/kg dose alone. Logistic regression equations were used to generate dose-response curves relating probability of a severe toxicity as a function of mg/kg and mg/m² doses. In order to display these curves on the same coordinates, mg/kg and mg/m² doses were normalized to the dose calculated to be associated with 97.5% probability of severe toxicity (Fig. 1).

DISCUSSION

The lack of correlation of the hematological toxicity of melphalan with BSA may potentially relate to the mechanism of elimination of melphalan in addition to the inability of basal metabolic rate to adequately predict hematopoietic sensitivity. In humans the plasma half-life of melphalan is approximately 1.4 h and is nearly equivalent to the in vitro half-life in human plasma (21). This suggests that the rate-limiting process involved in melphalan elimination is independent of organ function. The elimination half-life of melphalan in dogs is similar (1.1 h) (19). The in vitro elimination constant is not known in dogs. However, in dogs, melphalan is nonenzymatically degraded to two hydrolysis products and at least three metabolites (19). This information suggests similar disposition of melphalan in the dog as in humans. If melphalan dosage is based on BSA, a disproportionately greater dose would be given to smaller dogs on the assumption that metabolic rate was greater in these smaller dogs and, therefore, metabolism or elimination of drug would also be greater. If the elimination of melphalan is independent of metabolic rate, as it appears, overdose of small dogs would occur.

Failure of BSA as a uniform basis for dose adjustments in this Phase I trial suggests that melphalan toxicity is not adequately estimated by basal metabolic rate. Seemingly, patient weight relates more closely to the hematological toxicity of melphalan than BSA. This is supported by logistic regression analysis. Furthermore, the slope of the dose-response curve based on weight is steeper than the BSA dose-response curve, which suggests that the response of a group of patients to i.v. melphalan will be more homogeneous if melphalan is dosed based on body weight than on surface area. In addition, the mg/m² dose-response curve is shifted to the left of the mg/kg dose-response curve. This suggests that any given level of toxicity

Table 1 Classification scheme of hematological toxicity in tumor-bearing dogs

<table>
<thead>
<tr>
<th>Normal range</th>
<th>Mild toxicity</th>
<th>Severe toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-17 x 10⁹</td>
<td>&lt;2 x 10⁹</td>
<td>&gt;2 x 10⁹</td>
</tr>
<tr>
<td>4-10 x 10⁹</td>
<td>1.5-4 x 10⁹</td>
<td>&gt;1.5 x 10⁹</td>
</tr>
<tr>
<td>150-900 x 10⁹</td>
<td>80-150 x 10⁹</td>
<td>&gt;80 x 10⁹</td>
</tr>
</tbody>
</table>

Table 2 Patient characteristics, dose, and toxicity score

<table>
<thead>
<tr>
<th>Patient</th>
<th>Wt (kg)</th>
<th>BSA (m²)</th>
<th>mg/kg</th>
<th>mg/m²</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>SI</td>
<td>27.3</td>
<td>0.91</td>
<td>0.25</td>
<td>7.5</td>
<td>Mild (3)</td>
</tr>
<tr>
<td>DG</td>
<td>29.5</td>
<td>0.95</td>
<td>0.24</td>
<td>7.5</td>
<td>Mild (4)</td>
</tr>
<tr>
<td>KA</td>
<td>55.5</td>
<td>1.46</td>
<td>0.20</td>
<td>7.5</td>
<td>None</td>
</tr>
<tr>
<td>RS</td>
<td>5.0</td>
<td>0.29</td>
<td>0.44</td>
<td>7.5</td>
<td>Severe (1)</td>
</tr>
<tr>
<td>BG</td>
<td>9.1</td>
<td>0.43</td>
<td>0.47</td>
<td>10.0</td>
<td>Severe (2)</td>
</tr>
<tr>
<td>JD</td>
<td>27.3</td>
<td>0.91</td>
<td>0.33</td>
<td>10.0</td>
<td>None</td>
</tr>
<tr>
<td>SM</td>
<td>21.8</td>
<td>0.77</td>
<td>0.35</td>
<td>10.0</td>
<td>None</td>
</tr>
<tr>
<td>LT</td>
<td>11.4</td>
<td>0.59</td>
<td>0.44</td>
<td>10.0</td>
<td>Mild (1)</td>
</tr>
<tr>
<td>TL</td>
<td>31.0</td>
<td>0.99</td>
<td>0.32</td>
<td>10.0</td>
<td>None</td>
</tr>
<tr>
<td>TM</td>
<td>7.7</td>
<td>0.38</td>
<td>0.49</td>
<td>10.0</td>
<td>Severe (4)</td>
</tr>
<tr>
<td>PB</td>
<td>35.0</td>
<td>1.07</td>
<td>0.31</td>
<td>10.0</td>
<td>None</td>
</tr>
<tr>
<td>TB</td>
<td>14.0</td>
<td>0.58</td>
<td>0.41</td>
<td>10.0</td>
<td>Severe (4)</td>
</tr>
<tr>
<td>OK</td>
<td>25.0</td>
<td>0.85</td>
<td>0.38</td>
<td>11.25</td>
<td>None</td>
</tr>
<tr>
<td>FD</td>
<td>42.7</td>
<td>1.22</td>
<td>0.32</td>
<td>11.25</td>
<td>None</td>
</tr>
<tr>
<td>TR</td>
<td>26.4</td>
<td>0.89</td>
<td>0.42</td>
<td>12.5</td>
<td>Mild (3)</td>
</tr>
<tr>
<td>BH</td>
<td>7.7</td>
<td>0.38</td>
<td>0.62</td>
<td>12.5</td>
<td>Severe (3)</td>
</tr>
<tr>
<td>CR</td>
<td>27.3</td>
<td>0.91</td>
<td>0.41</td>
<td>12.5</td>
<td>Severe (2)</td>
</tr>
<tr>
<td>SB</td>
<td>40.0</td>
<td>1.17</td>
<td>0.59</td>
<td>20.0</td>
<td>Severe (1)</td>
</tr>
<tr>
<td>MS</td>
<td>10.5</td>
<td>0.47</td>
<td>0.36</td>
<td>20.0</td>
<td>Severe (1)</td>
</tr>
<tr>
<td>GT</td>
<td>13.6</td>
<td>0.57</td>
<td>0.84</td>
<td>20.0</td>
<td>Severe (1)</td>
</tr>
<tr>
<td>CC</td>
<td>21.4</td>
<td>0.77</td>
<td>0.72</td>
<td>20.0</td>
<td>Severe (1)</td>
</tr>
</tbody>
</table>

*a Numbers in parentheses, number of treatments.*
implications for future clinical drug trials. It seems prudent to consider administering chemotherapeutic agents whose rate of elimination is not primarily determined by organ function or whose limiting normal tissue sensitivity may not correlate to metabolic rate on a more appropriate parameter than BSA (e.g., weight).

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REFERENCES

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