Phases I Clinical and Pharmacokinetic Trial of Brequinar Sodium
(DUP 785; NSC 368390)1


ABSTRACT

Brequinar sodium is a 4-quinolincarboxylic acid analogue that inhibits dihydroorotate dehydrogenase and subsequent de novo pyrimidine biosynthesis. It has shown dose-dependent antineoplastic activity against several mouse and human tumor models. This trial evaluated Brequinar given as a single daily i.v. bolus over a 5-day period repeated every 28 days. One hundred seven courses of treatment at dosages ranging from 36 to 300 mg/m2/day x 5 were administered to 65 patients (31 male and 14 female) with refractory solid tumors; median age was 58 years (range 30–74); median Southwest Oncology Group performance status was 1 (range, 0–3). Thirty patients had prior cytotoxic chemotherapy. Dose-limiting toxicities were thrombocytopenia and a severe desquamative maculopapular dermatitis. Two of 5 good risk patients at 300 mg/m2 and 3 of 6 poor risk patients at 170 mg/m2 developed a platelet count < 25 x 104/µl. Two of 5 good risk patients at 300 mg/m2 and 1 of 6 poor risk patients at 170 mg/m2 developed a severe desquamative dermatitis. Moderate to severe mucositis was usually associated with the thrombocytopenia and/or the dermatitis. Nonhematological drug-related toxicities included nausea and vomiting, malaise, anorexia, diarrhea, phlebitis, reversible transaminase elevation, and mucositis. Other hematological toxicities were anemia, granulocytopenia, and leukopenia. There were no drug-related deaths. There were no objective tumor responses. Plasma and urine levels of Brequinar were quantified by high pressure liquid chromatography in 28 patients. Plasma levels and areas under the curve increased proportionally with increased dose. Brequinar had a harmonic mean terminal t½ of 8.1 ± 3.6 h with a model-independent determined apparent volume of distribution at steady state of 9.0 ± 2.9 liters/m2 and a total body clearance of 19.2 ± 7.7 ml/min/m2. Renal excretion was a minor route of elimination for Brequinar. The maximally tolerated dose of Brequinar on a daily x 5 i.v. schedule was 250 mg/m2 for good risk patients. For the daily x 5 i.v. schedule, the recommended dose of Brequinar for phase II evaluation is 250 mg/m2 for good risk patients and 135 mg/m2 for poor risk patients.

INTRODUCTION

Brequinar sodium or 6-fluoro-2-(2'-fluoro-1,1'-biphenyl-4-yl)-3-methyl-4-quinoline carboxylic acid sodium salt (DUP785; NSC 368390) is a quinoline carboxylic acid analogue with broad preclinical antitumor activity (Fig. 1). It has dose-dependent activity against several mouse tumors in vivo (L1210 leukemia, P 388 leukemia, colon 38 carcinoma, and B16 melanoma) as well as against several human xenografts (LX-1 lung, HCT-15 colon, MX-1 breast, BL-STX-1 stomach, and CX-1 colon) (1). Few other established or investigational agents have exhibited preclinical antitumor activity (Fig. 1). It has dose-dependent in vivo and in vitro antitumor activity against several mouse and human tumor models. This trial evaluated Brequinar given as a single daily i.v. bolus over a 5-day period repeated every 28 days. One hundred seven courses of treatment at dosages ranging from 36 to 330 mg/m2/day x 5 were administered to 65 patients (31 male and 14 female) with refractory solid tumors; median age was 58 years (range 30–74); median Southwest Oncology Group performance status was 1 (range, 0–3). Thirty patients had prior cytotoxic chemotherapy. Dose-limiting toxicities were thrombocytopenia and a severe desquamative dermatitis. Moderate to severe mucositis was usually associated with the thrombocytopenia and/or the dermatitis. Nonhematological drug-related toxicities included nausea and vomiting, malaise, anorexia, diarrhea, phlebitis, reversible transaminase elevation, and mucositis. Other hematological toxicities were anemia, granulocytopenia, and leukopenia. There were no drug-related deaths. There were no objective tumor responses. Plasma and urine levels of Brequinar were quantified by high pressure liquid chromatography in 28 patients. Plasma levels and areas under the curve increased proportionally with increased dose. Brequinar had a harmonic mean terminal t½ of 8.1 ± 3.6 h with a model-independent determined apparent volume of distribution at steady state of 9.0 ± 2.9 liters/m2 and a total body clearance of 19.2 ± 7.7 ml/min/m2. Renal excretion was a minor route of elimination for Brequinar. The maximally tolerated dose of Brequinar on a daily x 5 i.v. schedule was 250 mg/m2 for good risk patients. For the daily x 5 i.v. schedule, the recommended dose of Brequinar for phase II evaluation is 250 mg/m2 for good risk patients and 135 mg/m2 for poor risk patients.

MATERIALS AND METHODS

Patient Selection

Patients with histologically documented, advanced, solid tumors refractory to all forms of known effective therapy were candidates for this study. Other eligibility criteria included: (a) a life expectancy of at least 8 weeks; (b) a Southwest Oncology Group performance status of 3 or less; (c) age ≥18 and <75 years; (d) a minimum of 3 weeks since prior chemotherapy and/or myelosuppressive radiotherapy; (e) adequate bone marrow function (absolute granulocyte count ≥1900/µl, platelet count ≥130 x 104/µl), adequate liver function (normal bilirubin, and a serum creatinine ≤2.0 mg/dl); and (f) no other coexistent medical problems of sufficient severity to prevent full compliance with the study. Patients who had previously received a cumulative dose of ≥400 mg/m2 doxorubicin were considered ineligible. All patients gave written informed consent according to institutional and federal guidelines.

Drug Formulation and Administration

Brequinar sodium was supplied by DuPont Pharmaceuticals (Wilmington, DE) as a lyophilized powder in vials containing 100 or 500 mg of active drug. Excipients included 40 mg each of sodium cholate

Received 10/11/88; revised 5/5/89; accepted 5/16/89.

The costs of publication of this article are defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

1 Data on file at DuPont Pharmaceuticals: personal communication with Brian K. Dallaire, Pharm.D., Associate Director.

2 To whom requests for reprints should be addressed.
and glycine in the 100-mg vials and 80 mg each in the 500-mg vials. The prescribed dose was diluted in 50–100 ml of 0.9% NaCl solution and administered over 30 min through a peripheral i.v. line. The drug was administered daily for 5 days on an inpatient basis.

Study Design

Prior to initiation of treatment with Brequinar, all patients had a complete history and physical examination, hemogram, full chemistry profile, urinalysis, chest roentgenogram, electrocardiogram, and a 24-h urine collection for creatinine clearance. Measurable tumor lesions were documented with appropriate roentgenograms and computed tomographic scans.

The starting dose of Brequinar was 36 mg/m² daily x 5. This dose was escalated by 20–30% increments for each subsequent dose level. Treatment cycles were repeated every 28 days if there was no evidence of disease progression and if toxicity was acceptable. At least three patients were entered at each dose level. Dose escalation or deescalation for individual patients was allowed.

Patients were seen weekly, with a history, physical examination, and the routine laboratory studies noted above. Since myocardial necrosis had been observed in dogs, patients were evaluated for the possibility of cardiotoxicity. Starting at the 170 mg/m² dose level, a follow-up electrocardiogram was obtained on days 5 and 14 of each treatment cycle. At and above this dosage, all patients had their pretreatment left ventricular ejection fraction determined by radionuclide scanning; this measurement was repeated every two cycles of treatment. Tumor measurements were performed at least every two cycles of treatment with Southwest Oncology Group criteria used for response evaluation (10). Poor risk patients were those with: (a) prior treatment with nitrosoureas or mitomycin C; (b) prior radiotherapy to ≥30% of their bone marrow; and/or (c) prior high dose chemotherapy requiring autologous bone marrow rescue.

Pharmacokinetic Study

Blood Sampling and Urine Collection. Preinfusion and end-of-infusion 8-ml blood samples were collected on days 1 through 5 of 5 patients' first cycles from an indwelling i.v. heparin lock in the arm contralateral to the infusion line. Additionally on days 1 and 5, samples were collected 15, 30, and 60 min, and 2, 4, 6, 8, 12, 14, 16, 20, and 24 h postinfusion. The samples were separated by cold centrifugation and the plasma was flash frozen in acetone-dry ice. Urine was collected prior to drug administration, from 0 to 12 h and 12 to 24 h on day 1, and every 24 h for 5 days. The total volume was recorded and a 20-ml aliquot of urine was removed. Plasma and urine samples were stored at −20°C in polyethylene tubes until further analysis.

High Pressure Liquid Chromatography Analysis. Brequinar concentrations in plasma and urine were measured by high pressure liquid chromatography. Internal standards (DuPont compounds S-6056 for plasma and DUP416 for urine) were added to each plasma/urine sample prior to extraction. Spiked urine and plasma standard curves were prepared on the day of each procedure. Tetrabutylammonium hydroxide (4 mM, 500 µl) was added to 1 ml of plasma or urine and extracted with 10 ml of methylene chloride. After shaking (Eberbach Corp., Ann Arbor, MI) of the mixture for 30 min and centrifugation at 2000 rpm for 10 min, the dichloromethane layer was removed and evaporated to dryness under a gentle stream of nitrogen. The extraction yield for both drug and internal standard averaged 89% from plasma and 100% from urine. Samples were reconstituted with 200 µl of mobile phase: CH₃CN:H₂O:0.1 M H₃PO₄, 55:25:20 (60:20:20 for urine). Ten µl of sample were then injected (WISP model 710B autosampler; Waters Associates, Milford, MA) onto a 4.6-mm x 25-cm Zorbax C₈ (urine) or a 4.6-mm x 25-cm Biophase Octyl (plasma) column, with the mobile phase pumped (model SP 8700; Spectraphysics, San Jose, CA) at a flow rate of 1 ml/min. UV absorbance (model 441; Waters, Milford, MA) was monitored at 254 nm. Chromatograms and peak height ratios were stored and analyzed on a Hewlett Packard HP9816 Computer (Hewlett Packard, Palo Alto, CA). Retention times for Brequinar and DUP416 were 8.8 and 10 min, respectively, with the lower limit of sensitivity of the assay set at 25 ng/ml. The intraday coefficient of variation ranged from 2.5% to 9.4% (five experiments) and from 0.6% to 4.2% (five experiments) for spiked urine samples. Stability of Brequinar in blind-coded spiked plasma and urine samples stored frozen at −20°C was determined at various intervals for 1 year. Brequinar was stable in frozen plasma and urine for at least 1 year.

Pharmacokinetic Analysis. Analysis of the pharmacokinetic data was performed by noncompartmental methods (12). Pharmacokinetic parameters were determined from day 1 plasma data. Total plasma clearance (CL), apparent volume of distribution (Vₐ), and volume of distribution at steady state (Vₐss) were calculated according to the following:

$$\text{CL} = \frac{\text{Dose}}{\text{AUC} \cdot \lambda}$$

$$V_{\text{ss}} = \frac{\text{Dose}}{\text{AUC} \cdot \lambda}$$

$$V_{\text{ss}} = \frac{\text{Dose} \cdot \text{AUMC}}{\text{AUC}^2} - \frac{\text{Dose} \cdot T}{2 \cdot \text{AUC}}$$

where T is the infusion time and represents the first-order elimination rate constant. The area under the plasma concentration-time curve (AUC) was estimated by the linear trapezoidal method up to the last measurable data point and extrapolated to infinity (AUCₙ₋₁). The area under the first moment curve (AUMC) was calculated according to the following equation:

$$\text{AUMC} = \text{AUMC} + \frac{t \cdot C}{\lambda} + \frac{C}{\lambda^2}$$

where C is the drug concentration at the last sampling time, t. The plasma terminal half-life (t₀½) was calculated by 0.693/λ.

RESULTS

Forty-five patients were entered in this trial. Patient characteristics are shown in Table 1. The median performance status was 1, with only 8 of 45 patients having a performance status of ≥2. Thirty patients had received prior chemotherapy. Patients with non-small cell lung or colorectal cancer represented 69% of the patients treated. A total of 107 courses of Brequinar were administered. Two patients received an incomplete course because of cancer-related complications during treatment. Two additional courses were ineligible because of dosage errors. Patients received a median of 2 cycles of treatment (range, 1–10), with only 5 patients receiving 5 or more cycles. There were a total of 3 deaths in the study, all disease related: one patient with Staphylococcus aureus sepsis complicating metastatic squamous cell carcinoma of the lung, one patient with small bowel obstruction and Gram-negative sepsis secondary to intraabdominal metastases from a non-small cell lung cancer, and...
cases, skin biopsies revealed a nonspecific mononuclear infil-
trate. On empiric systemic steroids, the rash subsided within
7–10 days in both instances. In one poor risk patient treated
with 170 mg/m², a desquamative rash of slightly less severity
involving the inguinoperineal and scrotal areas was observed.
In other instances the rash was mild and asymptomatic, ap-
pearing mostly in areas of skin contact (i.e., cardiac monitor
patches, waist bands, etc.). In the only patient with dermatitis
that was rechallenged with drug, this mild rash did not worsen.
In another patient is persisted for 3 months after discontinua-
tion of drug treatment.

Nausea and vomiting were easily controlled with conven-
tional doses of phenothiazines. Reversible elevation of liver
enzymes (serum glutamic-oxalacetic transaminase and serum
glutamic-pyruvic transaminase) occurred in a total of 6 courses
by day 7 (median) and returned to normal by day 21 (median).
In only 1 patient was this elevation associated with liver dys-
function, as evidenced by a marked rise and rapid decline in
serum bilirubin. Phlebitis, characterized by burning at the in-
jection site, was easily controlled by increasing the volume of
the infusate from 50 to 100 ml. Diarrhea was mild to moderate
and reversible, with only 1 patient requiring i.v. hydration.
Mucositis was clearly dose related and was worse in patients
with extensive prior therapy. The two episodes of grade 3
mucositis, all at 170 mg/m², occurred in poor risk patients.
In good risk patients, mucositis was grade 2 or less. Although not
dose-limiting, diarrhea and phlebitis were also dose related
(Table 3).

No cardiotoxicity was observed in this trial.

Hematological toxicities are summarized in Table 4. Throm-
bocytopenia was the dose-limiting myelosuppressive toxicity
developing at median day 8 (range, days 4–18) and consistently
resolving by day 28 (>130 × 10³/µl). In 2 patients a bone
marrow aspirate and biopsy at the time of hematological nadir
showed decreased cellularity and reduced number of megakar-
yocytes, confirming the myelosuppressive effect of Brequinar.
No bleeding complications occurred. Although 10 of 21 courses
at 250 mg/m² were associated with thrombocytopenia, none of
these was associated with a nadir platelet count <50 × 10³/µl.
Two patients have each received 7 and 9 courses of treatment
at this dose level. Mild thrombocytopenia (grade 1) was ob-
served in 6 of 7 cycles in the first patient, suggesting no
cumulative myelosuppression. The second patient has not ex-
hibited any toxicity.

The few episodes of anemia were associated with a low
reticulocyte count and resolved by day 21. No patient required
blood transfusions. Granulocytopenia and leukocytopenia were
clearly dose related but not dose limiting. When present, they
were always associated with thrombocytopenia.

As shown in Table 3, the majority of the toxic courses at 170

Table 1 Patient characteristics

<table>
<thead>
<tr>
<th>Total</th>
<th>45 (107 courses)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>31/14</td>
</tr>
<tr>
<td>Median age (range)</td>
<td>58 (30–74)</td>
</tr>
<tr>
<td>Median Southwestern Oncology Group performance status (range)</td>
<td>1 (0–3)</td>
</tr>
</tbody>
</table>

Prior treatment

None | 6
Radiation only | 7
Immunotherapy only | 2
Chemotherapy only | 18
Radiation + chemotherapy | 12

Tumor types

Lung (non-small cell) | 16
Colorectal | 15
Renal cell | 5
Prostate | 3
Breast | 2
Stomach | 1
Melanoma | 1
Adenocarcinoma unknown primary | 1
Lymphoma | 1

Table 2 Dose escalations of Brequinar

<table>
<thead>
<tr>
<th>Dose (mg/m²)</th>
<th>No. of patients</th>
<th>No. of evaluable courses</th>
</tr>
</thead>
<tbody>
<tr>
<td>36</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>48</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>64</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>85</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>110</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>135</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>170</td>
<td>11</td>
<td>17</td>
</tr>
<tr>
<td>210</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>250</td>
<td>6</td>
<td>21</td>
</tr>
<tr>
<td>300</td>
<td>5</td>
<td>7</td>
</tr>
</tbody>
</table>

* Patients stratified into good and poor risk groups.

Table 3 Courses of Brequinar associated with nonhematological toxicity

<table>
<thead>
<tr>
<th>Dose (mg/m²)</th>
<th>Total no. of courses</th>
<th>Nausea and vomiting</th>
<th>Malaise and anorexia</th>
<th>Hepatotoxicity</th>
<th>Phlebitis</th>
<th>Diarrhea</th>
<th>Mucositis</th>
<th>Dermatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>48</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>64</td>
<td>10</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>85</td>
<td>8</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>110</td>
<td>10</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>135</td>
<td>11</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>170</td>
<td>17</td>
<td>7</td>
<td>3</td>
<td>4</td>
<td>7</td>
<td>1</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>210</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>250</td>
<td>21</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>300</td>
<td>7</td>
<td>4</td>
<td>3</td>
<td>0</td>
<td>5</td>
<td>3</td>
<td>4</td>
<td>6</td>
</tr>
</tbody>
</table>

* 4 of 7 poor risk.
+ 3 of 4 poor risk.
* 3 of 5 poor risk.
* 1 of 1 poor risk.

4650

Downloaded from cancerres.aacrjournals.org on April 20, 2017. © 1989 American Association for Cancer Research.
mg/m² were observed in poor risk patients. At this same dosage, 5 of 6 courses associated with grade 3 or 4 myelosuppression occurred in poor risk patients (Table 4), suggesting an adverse effect of extensive prior therapy on patient tolerance to Brequinar.

Table 5 summarizes the dose-limiting toxicities in this study. Two of 5 good risk patients at 300 mg/m² and 3 of 6 poor risk patients at 170 mg/m² developed a severe desquamative dermatitis.

Antitumor Activity. There were no objective tumor responses to Brequinar when it was given as a daily i.v. bolus over a 5-day period.

Pharmacokinetics. Plasma and urine concentrations of Brequinar were quantified by high pressure liquid chromatography. Median peak plasma levels did not change appreciably from day 1 to day 5. However, median trough levels increased from 0.68 µg/ml on day 1 to 1.43 µg/ml on day 5 (data not shown). A typical plasma concentration-time curve for days 1 and 5 is shown in Fig. 2.

The pharmacokinetic parameters derived from the data obtained on day 1 in all 28 patients are presented in Table 7. Although large interpatient variability was observed, AUCs increased proportionally with increasing doses of Brequinar (r = 0.85). Brequinar had a harmonic mean terminal t½, of 8.1 ± 3.6 h with an apparent volume of distribution of 15.5 ± 6.0 liters/m². The apparent steady state volume of distribution was 9.0 ± 2.9 liters/m². The mean plasma clearance was 19.2 ± 7.7 ml/min/m². The percentage of the total dose that was excreted unchanged in the urine in a 24-h period varied between 0.13% and 5.5%. To assess pharmacokinetic linearity during the 5-day treatment, day 1 AUC was then compared with day 5 AUC. AUCs increased from day 1 to day 5 by only a mean of 23% (range, −1 to 42%). Interestingly, the percentage of change in the pretreatment platelet count induced by Brequinar treatment correlated well with the day 1 AUC (R < 0.002; Spearman rank test) (Fig. 3). The observed decrease in platelet count did not correlate with peak plasma drug levels (data not shown).

DISCUSSION

We have evaluated Brequinar sodium, an inhibitor of de novo pyrimidine biosynthesis, in a phase I clinical and pharmacokinetic trial of a daily i.v. bolus injection over a 5-day period. Preclinical studies have shown a maximum tolerated dose of 6 mg/m² i.v. daily × 5 in dogs. According to current practice in phase I clinical trials with anticancer drugs, the starting dose in humans should have been one third of that (13) or 2 mg/m². However, at the time of initiation of this trial, doses of 100 mg/m² i.v. daily × 5 had been safely administered to patients with advanced cancer and minimal prior treatment (14). Based on this preliminary information, an initial dose of 36 mg/m² i.v. daily × 5 was chosen.

The dose-limiting toxicities in this trial were thrombocytopenia and a severe maculopapular desquamative dermatitis, usually associated with moderate to severe mucositis. These findings are consistent with the preclinical toxicology studies, which showed that the major target organs of toxicity in all species tested were the gastrointestinal epithelium and the bone marrow. Accordingly, diarrhea, leukopenia, and granulocytopenia were also observed in this trial and, although not dose limiting, they were clearly related to dose (Tables 3 and 4). Similar to other inhibitors of de novo pyrimidine biosynthesis such as N-(phosphonacetyl)-L-aspartic acid (PALA) and pyra-
Table 7 Pharmacokinetic parameters of Brequinar

<table>
<thead>
<tr>
<th>Dose (mg/m²)</th>
<th>No. of patients</th>
<th>Day 1 AUC_{0→t}* (µg·h/ml)</th>
<th>Day 5 AUC_{0→t}* (µg·h/ml)</th>
<th>t½ (h)</th>
<th>CL (ml/min/m²)</th>
<th>V_{ss} (liters/m²)</th>
<th>V_{app} (liters/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>36</td>
<td>3</td>
<td>25.38</td>
<td>26.81</td>
<td>8.2</td>
<td>23.92</td>
<td>18.22</td>
<td>9.43</td>
</tr>
<tr>
<td>48</td>
<td>3</td>
<td>39.71</td>
<td>41.46</td>
<td>8.6</td>
<td>24.60</td>
<td>19.66</td>
<td>11.46</td>
</tr>
<tr>
<td>64</td>
<td>4</td>
<td>114.81</td>
<td>98.92</td>
<td>7.9</td>
<td>15.42</td>
<td>10.94</td>
<td>7.34</td>
</tr>
<tr>
<td>85</td>
<td>3</td>
<td>95.56</td>
<td>130.80</td>
<td>7.8</td>
<td>17.35</td>
<td>13.53</td>
<td>8.59</td>
</tr>
<tr>
<td>110</td>
<td>3</td>
<td>88.11</td>
<td>114.00</td>
<td>5.7</td>
<td>22.25</td>
<td>12.48</td>
<td>7.48</td>
</tr>
<tr>
<td>135</td>
<td>3</td>
<td>103.53</td>
<td>143.23</td>
<td>7.3</td>
<td>22.40</td>
<td>14.27</td>
<td>8.06</td>
</tr>
<tr>
<td>170</td>
<td>2</td>
<td>123.83</td>
<td>151.19</td>
<td>8.1</td>
<td>24.57</td>
<td>22.15</td>
<td>12.96</td>
</tr>
<tr>
<td>210</td>
<td>3</td>
<td>258.82</td>
<td>309.85</td>
<td>8.3</td>
<td>14.66</td>
<td>12.30</td>
<td>8.38</td>
</tr>
<tr>
<td>250</td>
<td>2</td>
<td>230.00</td>
<td>301.60</td>
<td>9.5</td>
<td>19.32</td>
<td>15.98</td>
<td>8.78</td>
</tr>
<tr>
<td>300</td>
<td>2</td>
<td>714.37</td>
<td>919.02</td>
<td>19.5</td>
<td>7.70</td>
<td>12.79</td>
<td>9.08</td>
</tr>
</tbody>
</table>

Mean (28 patients)  
SD  
8.09*  
3.6  
19.19  
7.7  
15.54  
6.0  
8.97  
2.9  
8.28  
1.79

* AUC, area under the plasma concentration-time curve; t½, plasma terminal half-life; CL, total plasma clearance; V_{ss}, apparent volume of distribution; V_{app}, volume of distribution at steady state.

Extensive prior treatment decreased the tolerance to the higher doses of Brequinar. At 170 mg/m², we prospectively divided our patient population into good and poor risk groups. Four of 6 poor risk patients at this dose level developed unacceptable toxicity: grade 4 thrombocytopenia with moderate to severe mucositis (3 patients) and a severe rash (1 patient). Other nonhematological toxicities were also more evident in the poor risk group. The majority of courses associated with nausea and vomiting, hepatotoxicity, and mucositis occurred in poor risk patients (Table 3), further indicating a biological impact of extensive prior therapy on subsequent patient tolerance to Brequinar.

Since few patients received multiple courses of treatment at the maximum tolerated dose, cumulative toxicity with Brequinar cannot be addressed by this trial. Furthermore, all the instances of dose-limiting toxicity occurred during the first cycle of treatment and, therefore, cannot be considered to be due to cumulative drug effects. Only 2 patients received 7 and 9 courses of treatment each (250 mg/m²) with minimal myelosuppression occurring in only the first one.

No objective responses were observed in this trial. However, the limited number of patients and tumor types entered at the higher doses precludes any conclusion as to the antitumor efficacy of Brequinar. Since recent preclinical data indicate that a continuous presence of the drug is more effective in depleting pyrimidine pools (8), and given the pharmacokinetic profile of...
Brequinar (see below), it is conceivable that a continuous infusion of this agent might be more effective in achieving an antitumor effect. Furthermore, since depletion of pyrimidine pools enhances the metabolism of 5-fluorouracil (18), Brequinar may enhance the antitumor activity of other antimetabolites. Further studies are necessary to address these possibilities.

The pharmacokinetic data showed that the plasma disposition of Brequinar followed a biexponential pattern, with a harmonic mean terminal half-life of 8.1 h. Large interpatient variability was observed, but AUCs correlated well with the dose of Brequinar and with the observed percentage of change in the pretreatment platelet count. There was a mean 23% increase in day 5 AUC compared to day 1 AUC, suggesting a small decrease of drug clearance over the 5-day treatment period. In agreement with animal pharmacokinetic data,3 renal excretion of Brequinar was minimal. At dosages up to 250 mg/m²/day × 5, our recommended dose for phase II clinical trials, the pharmacokinetic parameters were clearly independent of dose (Table 7). The mean plasma clearance and terminal half-life at 300 mg/m² (2 patients) suggest that pharmacokinetics might become nonlinear at higher doses. Due to the limited number of patients with severe toxicity and concurrent pharmacokinetic determinations, we cannot correlate further the severity of the side effects with any potentially predictive pharmacokinetic parameter.

Based on the results of this study, the recommended phase II dose of Brequinar given i.v. daily × 5 is 250 mg/m² for good risk patients and 135 mg/m² for poor risk patients. It is possible that, in the absence of toxicity at 250 mg/m², some patients may tolerate higher doses of Brequinar. However, because of: (a) the lack of cumulative toxicity data; (b) the pharmacokinetic data suggesting nonlinearity at doses higher than >250 mg/m²; and (c) the unpredictable and severe toxicity we observed at 300 mg/m² in patients with good performance status and no significant prior treatment, escalating Brequinar above 250 mg/m² daily × 5 cannot be recommended.

ACKNOWLEDGMENTS

The nursing and dietetic care provided by the staff at the Audie Murphy Veterans Hospital Special Diagnostic and Treatment Unit is appreciated. We wish to thank Heidi Herndon, R.N., Robbie Fuqua, Nancy Pullin, and Shirley McVea, R.N., for their assistance in data management.

REFERENCES


Phase I Clinical and Pharmacokinetic Trial of Brequinar Sodium (DUP 785; NSC 368390)

Carlos L. Arteaga, Thomas D. Brown, John G. Kuhn, et al.


Updated version  Access the most recent version of this article at: http://cancerres.aacrjournals.org/content/49/16/4648

E-mail alerts  Sign up to receive free email-alerts related to this article or journal.
Reprints and Subscriptions  To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.
Permissions  To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.