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Pharmacokinetics of Brequinar Sodium (NSC 368390) in Patients with Solid Tumors During a Phase I Study

G. SCHWARTSMANN,* W. J. F. VAN DER VIJGH,* M. B. VAN HENNIK,* I. KLEIN,* J. B. VERMORKEN,* P. DODION,‡ W. W. TEN BOKKEL HUININK,† G. JOGGI,‡ H. GALL,* N. CRESPEIGNE,‡ G. SIMONETTI,† B. WINOGRAD,* and H. M. PINEDO*

**Department of Oncology, Free University Hospital, Amsterdam, The Netherlands, †Netherlands Cancer Institute, Amsterdam, The Netherlands and ‡Institute Jules Bordet, Brussels, Belgium.*

Abstract— *The pharmacokinetics of the novel antipyrimidine agent Brequinar sodium (NSC 368390; DUP 785) was studied in 23 patients with solid tumors during the phase I study of this compound. The drug was administered by short-term (10–60 min) intravenous infusion every 3 weeks. The doses ranged from 15 to 2250 mg/m².*

At doses higher than 1500 mg/m² the areas under the plasma concentration vs. time curve (AUC) increased non-proportionally, while the total body clearance (Cl_t) dropped substantially, indicating non-linear pharmacokinetics of the drug. Brequinar sodium showed a triphasic decay of plasma concentrations with half-life ranges of 11.1–36.6 min, 1.7–6.9 h and 12.5–25.0 h, respectively. The volume of distribution (Vd_{ss}) ranged from 4.4 to 10.6 l/m². The total body clearance (Cl_t) ranged from 6.9 to 22.1 ml/min with a small contribution of the renal clearance (0.04–0.4 ml/min). Up to 7 days, the cumulative urinary excretion (CUE) and the cumulative fecal excretion (CFE) ranged from 0.4 to 8.3% and from 7.7 to 18.3% of the dose, respectively. There was evidence for the presence of drug metabolites in urine and feces. There was no drug accumulation with repeated administration of Brequinar sodium by the above mentioned drug schedule. The ratio between the plasma AUC at the maximum tolerable dose (MTD) in man and that at the mouse LD_{10} was 0.8, while the ratio beween the respective doses was 5.7. The ratios between the AUC in patients and that at the mouse LD_{10} were applied to guide dose escalation in the phase I study. The results of the above mentioned pharmacokinetic studies were useful for the choice of an optimal schedule for phase II trials of Brequinar sodium.

INTRODUCTION

BREQUINAR SODIUM [(NSC 368390; DUP 785; Fig. 1), 6-fluoro-2-(2′-fluoro-1,1′biphenyl-4-yl)-3-methyl-4-quinoline carboxylic acid sodium salt] is a novel synthetic quinoline derivative that showed significant antitumor activity in preclinical models [1–3]. This compound inhibits the mitochondrial enzyme dihydroorotate dehydrogenase (DHO-DH), blocking the conversion of dihydroorotate to orotate [2, 4]. This leads to a depletion of intracellular pyrimidine nucleotide pools which are formed by the *de novo* pathway, impairing RNA and DNA synthesis [4, 5].

In vitro studies have demonstrated that the activity of DHO-DH is inhibited shortly after the incubation of cells with Brequinar sodium. However, enzyme activity recovers after the reculture of cells in drug-free medium [4]. In WiDR human colon adenocarcinoma cells, it was shown that a prolonged exposure of cells to Brequinar sodium is necessary in order to produce a long-lasting depletion of intracellular pyrimidine nucleotide pools to cause growth-inhibitory effects [5].

The above results are in agreement with *in vivo* studies carried out in tumor-bearing mice showing that the antitumor effects of Brequinar sodium are more pronounced by frequent drug administration [1].

Brequinar sodium was recently evaluated in a phase I trial whereby the drug was administered to

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Address correspondence to: W. J. F. van der Vijgh, Ph.D., Department of Oncology, Free University Hospital, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands.
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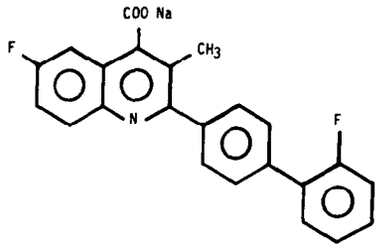

Fig. 1. Chemical structure of Brequinar sodium (NSC 368390).

patients with solid tumors by a short-term intravenous (i.v.) infusion every 3 weeks [6]. The main side-effects of this drug in that study were myelosuppression, nausea and vomiting, mucositis and skin rash. The maximum tolerable doses (MTD) were 1500 and 2250 mg/m^2, for poor- and good-risk patients, respectively. The recommended doses for phase II trials by that schedule were 1200 and 1800 mg/m^2 for these two risk categories respectively.

In the present study, the pharmacokinetics of Brequinar sodium was evaluated in plasma, urine and faeces of patients included in the phase I trial [6]. In addition, comparative pharmacokinetic studies between mice and man were performed in order to evaluate prospectively the use of preclinical data for the dose escalation procedure [7–9]. Pharmacokinetics was an important component of the phase I trial [10], and biochemical pharmacology data were decisive for the choice of an optimal drug schedule for future clinical trials of Brequinar sodium.

PATIENTS AND METHODS

Patients

Forty-three patients participated in the phase I trial of Brequinar sodium. Pharmacokinetic studies were performed in 23 patients (21 males and two females) who received the drug for the first time. Three patients were also sampled during a second course. The dose ranged from 15 to 2250 mg/m^2. The median age was 56 years (range 35–69). The median performance status (WHO) was 1 (range 1–3). Thirteen patients had prior chemotherapy, two patients had radiation therapy, 10 patients had both; and one patient had prior immunotherapy. All patients had a normal liver and renal function prior to admission to the trial. Table 1 shows the main characteristics of the patients included in the study.

Materials

Brequinar sodium was supplied by Du Pont Pharmaceuticals (Geneva, Switzerland) to the New Drug Development Office (NDDO) of the EORTC

Table 1. Characteristics of patients included in the pharmacokinetic study of Brequinar sodium

Patient No.	Dose (mg/m^2)	Age (years)	PS (WHO)	Tumor type	Prior therapy CT	Prior therapy RT
1	15	58	0	Melanoma	+	−
2	15	62	2	Head and neck	+	−
3	30	50	1	Melanoma	+	−
1*	30	58	1	Melanoma	+	−
4	45	60	1	Colorectal	+	−
5†	45	46	1	Head and neck	+	+
6	67.5	43	1	Pancreatic	+	−
7	90	35	3	Melanoma	+	−
8	90	56	1	Kidney	+	−
9	135	55	1	Colorectal	+	−
10	200	60	1	Melanoma	+	−
11	200	63	0	Esophagus	+	−
12	300	66	1	AUP	+	−
13	300	47	1	Head and neck	+	+
14	300	59	1	Colorectal	+	+
15	600	42	1	Pancreatic	+	−
16†	1200	57	2	Head and neck	+	+
17	1200	46	1	Lung	−	+
18	1500	69	3	Prostate	+	−
19	1500	73	1	Lung	+	−
20	1800	42	2	Colorectal	+	+
21	1800	66	2	Lung	−	+
22	2250	71	1	Head and neck	+	+
23	2250	37	0	Kidney	−	−

*Intrapatient dose escalation.
†Pharmacokinetics done in courses 1 and 2.
PS = performance status; CT = chemotherapy; RT = radiotherapy; AUP = adenocarcinoma of unknown primary origin.

(Amsterdam, The Netherlands) as a freeze-dried powder in 10 ml vials containing 100 mg DUP 785, 40 mg of sodium cholate and 40 mg of glycine. The powder was dissolved in 0.9% NaCl solution (10 mg/ml) immediately before administration to the patient.

Drug administration

Brequinar sodium was given every 3 weeks i.v. with an infusion time (T) of 10–60 min. The starting dose was 1/3 of the toxic dose low (TDL) in the dog (TDL = 46 mg/m^2) being 15 mg/m^2.

Intra-patient dose escalation was only allowed at the non-toxic dose levels (patient 1). Details of dose escalation are shown in Table 1.

Patient sampling

Samples for pharmacokinetic purposes were collected during the first course of Brequinar sodium, except for patients 5 and 16 who were sampled during courses 1 and 2.

(*a*) *Blood.* Five ml heparinized blood for plasma preparation were obtained immediately before infusion, at the end of infusion and at 15, 30, 60 and 120 min after infusion as well as at 4, 8, 12, 24, 48, 72, 96 and 120 h after drug administration. The samples were immediately centrifuged at 3000 rpm for 10 min. The plasma was stored frozen at −20°C until analysis.

(*b*) *Urine.* Urine samples were collected 24 h prior to drug infusion and from 0–6, 6–12, 12–18 and 18–24 h on the first day; and every 24 h for the following days (until day 7, when possible). The volumes were accurately measured and portions of 10 ml were stored frozen at −20°C until analysis.

(*c*) *Feces.* Feces were collected immediately prior to infusion and daily thereafter (until day 7). The total amount of feces produced during each day was weighed and homogenized in water. Portions of 10 ml were stored frozen at −20°C until analysis.

Animal studies

CD_2F_1 mice received brequinar sodium at the LD_{10} (132 mg/kg) by i.v. bolus injection in the tail vein. The drug was diluted in normal saline immediately before administration. Plasma samples were collected prior to administration, at the end of injection and at 15, 30, 60 and 120 min after injection, as well as 4, 8, 12, 48 and 72 h after drug administration. At each time-point, three mice were sacrificed to collect blood for preparing plasma. The samples were processed as described for patients.

Extraction procedure

Two hundred µl plasma samples from patients (or spiked plasma standards) in extraction tubes coated with internal standard (Dup 416) and provided with an aqueous solution of 200 µl 4mM tetrabutylammonium hydroxide were extracted with 10 ml CH_2Cl_2 by shaking at low speed (Heto shaker) for 30 min. After centrifuging at 3000 rpm for 10 min, 8 ml of the CH_2Cl_2 layer was transferred to a clean tube and evaporated to dryness. The residues were reconstituted with 200 µl mobile phase. Ten µl was injected into the HPLC system.

Urine and feces samples were diluted with water to such an extent that the concentration of Brequinar sodium was within the range of the calibration line. Diluted samples were processed as described for plasma.

HPLC procedure

The HPLC column (4.6 mm × 25 cm) was filled with Zorbax TMS 6 µm (Dupont Instruments, U.S.A.). The mobile phase consisted of CH_3CN: 0.046 M H_3PO_4 (55:45, v/v). The flow rate was 1 ml/min. An UV detector (LDC UV III monitor Model 1203) with a fixed wavelength of 254 nm was used. At the end of a series of injections, the column was regenerated with CH_3CN:H_2O (55:45, v/v).

Calculation of drug concentrations

The peak heights of Brequinar sodium and IS were corrected for possible blank plasma constituents at the corresponding retention times. Unknown concentrations in patient and mice samples were calculated by interpolation on calibration lines calculated by means of the least squares method. Only correlation coefficients >0.99 were accepted for further calculations. Besides, quality control samples (10 and 50 µg/ml) should not deviate more than 10% from their known concentration. Concentrations used for the calculation of pharmacokinetic parameters are means of independent duplicate measurements.

Calculation of pharmacokinetic parameters

Only the concentration–time (C–t) curves determined over at least 2 days (Fig. 2) were used to calculate the main pharmacokinetic parameters. The ln$C$–t curves were fitted by NONLIN and additionally over selected time intervals by using the linear least squares method. The areas under the concentration versus time curve (AUC) were calculated by the trapezoidal rule down to 1 µg/ml (AUC_1), to the limit of detection (AUC_{LD}) or to infinity (AUC^∞). The cumulative urinary excretion (CUE) and the cumulative fecal excretion (CFE) were expressed as a percentage of the administered dose. The following non-compartmental pharmacokinetic parameters were calculated: mean residence time MRT = $AUMC^\infty/AUC^\infty$, total body clearance $Cl_t = D/AUC^\infty$, renal clearance $Cl_r = CUE_t/AUC_t$

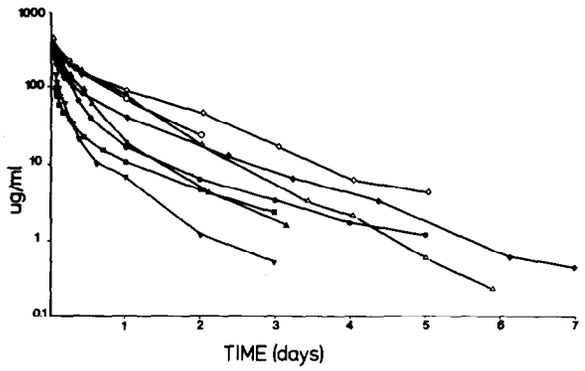

Fig. 2. Semilogarithmic concentration vs. time plot of Brequinar sodium in plasma of eight patients receiving the drug at various dose levels: (■) 300, (▼) 600, (●) 1200, (▲) 1200, (♦) 1500, (△) 1800, (◊) 1800 *and* (○) 2250 mg/m², *respectively.*

and the apparent volume of distribution at steady state

$$Vd_{ss} = \frac{\text{D. AUMC}^{\infty}}{(\text{AUC}^{\infty})^2} - \frac{D.T}{2.\text{AUC}^{\infty}}$$

in which T = infusion time.

RESULTS

The detection limit of the Brequinar sodium HPLC assay was sometimes influenced by the presence of small peaks at the retention time of the drug, as determined by extracting the plasma sample obtained just before drug administration. The detection limit ranged from 0.02 to 0.15 μg/ml.

Plasma half-lives of Brequinar sodium calculated by NONLIN are shown in Table 2. A best fit with three exponential terms was obtained for the majority of the *C–t* curves. For two patients (Nos. 17 and 20), however, only two exponential terms could be found by the computer. Visual inspection of these two curves revealed that although the curves were best fitted by two exponential terms, two weakly pronounced initial phases were nevertheless present. Therefore, all curves were also analyzed by the curve stripping procedure, which allowed the analysis of the *C–t* curves over many preset time intervals. Comparing all individual best fits, it appeared that a very good compromise could be obtained by calculating the three half-lives of all patients over the same time intervals, i.e. 0–30 min, 30–1440 min and day 1–final time point. The goodness of fit obtained by this approach (as shown by the residual standard deviations) was only slightly less than that obtained by NONLIN, but has the advantage that consistent half-lives were obtained for all patients. The advantage of this population-based optimal fit is that, because of the homogeneous population of pharmacokinetic parameters, mean values of all three half-lives could be calculated, which strict handling might not for the NONLIN values. This is clearly indicated by the smaller standard deviations of the mean half-lives obtained by CSTRIP compared to those obtained by NONLIN. $t_{\frac{1}{2}\alpha}$ ranged from 11.1 to 36.6 min, $t_{\frac{1}{2}\beta}$ ranged from 1.7 to 6.9 h and $t_{\frac{1}{2}\gamma}$ ranged from 12.5 to 25.0 h, respectively.

Non-compartmental pharmacokinetic parameters of Brequinar sodium are shown in Table 3. MRT ranged from 11.7 to 35.2 h; Vd_{ss} ranged from 4.4 to 10.6 l/m²; Cl_t ranged from 7.7 to 22.1 ml/min, with lower Cl_t values in the higher dose range. Cl_r calculated over 0–24 h ranged from 0.04 to 0.4 ml/min. AUC_1 and $AUC_{1.D}$ could be calculated for the *C–t* plots of all patients. The AUCs did not increase linearly with the dose (Fig. 3) as statistically confirmed by a significant ($P = 0.002$) second order effect obtained by polynomial regression. For the dose vs. AUC plot, AUC_1 was chosen to allow the inclusion of data from all patients in the study. This decision was also taken to avoid the inaccuracy or the impossibility of estimating the final half-life in patients sampled only over a short time interval due to the low dose administered.

Table 2. Half-lives of Brequinar sodium calculated by NONLIN and CSTRIP

Patient No.	Dose (mg/m²)	Sampling period (days)	NONLIN $t_{\frac{1}{2}\alpha}$ (min)	NONLIN $t_{\frac{1}{2}\beta}$ (h)	NONLIN $t_{\frac{1}{2}\gamma}$ (h)	NONLIN Res. St.Dev.	CSTRIP* $t_{\frac{1}{2}\alpha}$ (min)	CSTRIP* $t_{\frac{1}{2}\beta}$ (h)	CSTRIP* $t_{\frac{1}{2}\gamma}$ (h)	CSTRIP* Res. St.Dev
13	300	3	40.7	2.7	20.6	1.2	35.3	2.3	19.8	2.1
15	600	3	8.7	2.2	13.9	2.0	11.1	2.4	12.5	2.7
16	1200	5	27.9	4.1	29.3	5.9	11.6	3.1	25.0	14.1
17	1200	3	26.4	7.2	—	14.3	17.1	4.8	13.8	18.0
18	1500	7	17.0	1.6	18.0	2.3	19.4	2.9	22.3	4.7
20	1800	6	33.7	14.4	—	10.0	36.6	6.9	13.6	18.9
21	1800	5	18.0	3.6	21.4	7.9	15.6	5.3	20.1	10.5
22	2250	2	12.7	1.0	14.6	2.5	15.3	1.7	15.4	3.8
		Mean	23.1	4.6	19.6		20.3	3.7	17.8	
		S.D.	10.9	4.4	5.6		10.1	1.8	4.6	

*Calculation over selected time-intervals: 0–30 min, 30–1440 min, day 1–final time point.

Table 3. Non-compartmental pharmacokinetic parameters of Brequinar sodium

Patient No.	Dose (mg/m²)	AUC$^{\infty}$ (μg.h/ml)	MRT (h)	Vd_{ss} (l/m²)	Cl_t(ml/min)	Cl_r(ml/min)
13	300	998.5	35.2	10.6	10.5	0.3
15	600	770.4	11.7	9.1	22.1	0.3
16	1200	2531.1	19.7	9.1	15.8	0.4
17	1200	2850.7	12.3	5.0	15.2	0.2
18	1500	3574.0	23.4	9.6	14.5	0.04
20	1800	6693.7	16.8	4.4	7.7	0.1
21	1800	7444.7	29.1	7.0	8.5	0.3
22	2250	6660.7	19.9	6.5	9.3	—

AUC$^{\infty}$ = area under the plasma concentration–time curve calculated to infinity; MRT = mean residence time; VD_{ss} = apparent volume of distribution; Cl_t = total body clearance; Cl_r = renal clearance.

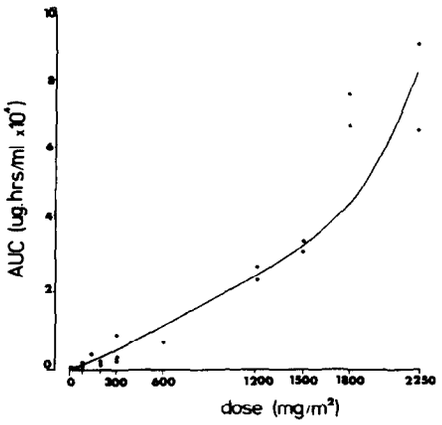

Fig. 3. Dose vs. AUC_1 plot in patients receiving Brequinar sodium at various levels (range 15–2250 mg/m²).

The ratio between plasma AUCs in patients sampled at the starting dose and in mice at the LD_{10} was 0.0003. The ratio between the mean plasma AUC$^{\infty}$ in patients who received the drug at the MTD (2250 mg/m²) and the AUC$^{\infty}$ at the LD_{10} in mice (132 mg/kg) was 0.8, while the ratio between the respective doses was 5.7.

The CUE ranged from 0.5 to 8.3% of the administered dose, with most of the drug being excreted during the first 1–3 days. At the highest dose levels, Brequinar sodium was still detectable in the urine up to days 4–5 in some patients.

The CFE measured in four patients over 7 days ranged from 7.7 to 18.3% of the administered dose. The total urinary and fecal excretion of Brequinar sodium in these four patients ranged from 10.9 to 19.6% of the dose.

Three patients were sampled during the first two courses of Brequinar sodium. There was no evidence of changes in pharmacokinetic data or drug accumulation by repetitive administration of the drug as established by undetectable drug levels at the start of the second dose and by comparable peak levels obtained after the two subsequent administrations.

In patients receiving the drug at the highest dose levels, there was clear evidence for the presence of drug metabolites in urine and feces. The proper identification of these metabolites as well as the evaluation of their cytotoxic properties should be studied separately. No antitumor effect could be observed in patients with plasma levels of the drug higher than 10 μg/ml for at least 3 days.

DISCUSSION

Pharmacokinetic studies performed in animals have demonstrated that the plasma elimination half-life of Brequinar sodium is faster in mice (4.8–6.6 h) than in rats (15–19 h) or dogs (21–27 h). This interspecies difference might explain in part the increased sensitivity of dogs to the toxic effects of Brequinar sodium when compared to mice or rats during toxicological studies. Therefore, the starting dose in this phase I study was based on 1/3 of the toxic dose low (TDL) in dogs because 1/10 of the mouse LD_{10} (lethal dose of 10%) was still toxic to those animals. Final half-lives in humans were comparable to those in rats and dogs.

Up to now, indications for non-linear pharmacokinetics of Brequinar sodium have only been obtained in humans. It was strongly suggested in patients who received the drug at dose levels higher than 1500 mg/m². Non-linear pharmacokinetics was not observed in mice, most probably due to the short dose range (10–50 mg/kg) at levels amply lower than the LD_{10} (132 mg/kg). The non-linear pharmacokinetics of Brequinar sodium in patients might probably be explained by the saturation of enzyme systems involved in drug metabolism, especially because Brequinar sodium seems to be metabolized to a great extent, because consistently the same unidentified peaks were observed in urine, as well as in feces, of patients at the higher dose range.

During this phase I trial, the ratio between the AUCs in plasma of patients and that in mice at the

LD_{10} was evaluated at each dose escalation step. The reason for this approach was to evaluate prospectively the use of comparative pharmacokinetics in the dose escalation procedure during the phase I trial, because it has been shown previously for several anticancer drugs that the ratio of the AUCs at LD_{10} in mice and at the MTD in man is closer to unity that the respective ratio between doses [7, 8].

Due to the lack of clinical toxicity as well as the observation of very low AUC ratios during the initial part of our trial, large increments of dose could be safely applied, which avoided several unnecessary dose escalation steps. Although it was previously said that this approach was not applicable to drugs exhibiting schedule dependance like antimetabolites or non-linear pharmacokinetics [7, 8], it was useful for Brequinar sodium by the determination of the AUC at each dose level. Ultimately, the ratio between the plasma AUC at the MTD in patients and that at the LD_{10} in mice was 0.8, while the ratio between the respective doses was 5.7.

The distribution of radiolabelled [^{14}C]Brequinar sodium was studied in mice implanted subcutaneously with human colon carcinoma xenografts [11]. After 1 h of an i.v. injection, the drug was detectable in all tissues studied including the tumor. The tumor-to-plasma drug concentration ratio ranged from 0.2 to 0.4 and the elimination half-life of the intact drug in tissues was almost equal to the elimination from plasma. At 24 h, the plasma drug concentration was still >10 μg/ml and the tumor to plasma concentration ratio was 0.4. In our study, patients who received Brequinar sodium at the highest dose levels showed plasma levels >10 μg/ml up to 3–5 days.

Although no antitumor effect was observed in these heavily pretreated patients, these plasma drug concentrations were sufficient to cause antitumor effects *in vitro* and in animal models [1–4]. However, tumor cells can circumvent the blockage in the *de novo* pyrimidine nucleotide biosynthesis by the use of salvage pathways [12, 13].

In vivo, pyrimidine nucleosides which are released by cellular breakdown in necrotic areas of the tumor or which are available from the plasma may be utilized to maintain intracellular nucleotide pools during drug exposure [12–14]. Therefore, it is important that Brequinar sodium is given to patients by frequent drug administrations, in order to be present in the tissues by the time salvage pathways are exhausted. In addition, studies done in peripheral lymphocytes of patients who entered our study have shown that DHO-DH activity is inhibited shortly after drug administration, but recovers within hours to days. The length of enzyme inhibition correlated with the degree of myelosuppression [15].

There are several reasons to advocate a frequent drug schedule of Brequinar sodium during clinical evaluation studies: (a) the drug has shown exposure dependence for its antitumor effect both *in vitro* and in animal experiments; (b) the administration of Brequinar sodium at the toxic doses by the 3-weekly shedule leads to the inhibition of DHO-DH activity for not longer than a few days, as shown by our studies performed in peripheral lymphocytes; (c) the recovery from acute side-effects when the drug is given to patients by the 3-weekly schedule is rapid [6]. In another ongoing trial, Brequinar sodium is being administered to patients once-weekly with comparable clinical toxicity to that observed in our trial (H. Hansen, personal communication). Furthermore, our study showed no evidence for drug accumulation in the body after repeated i.v. administration, which is an extra reason to support the choice for a more frequent drug schedule in future clinical trials.

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