Phase I study of Brequinar sodium (NSC 368390) in patients with solid malignancies

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Summary. Brequinar sodium (DUP 785, NSC 368390) is a novel quinoline-carboxylic acid derivative that has been selected for clinical evaluation because of its broad spectrum of antitumor activity in animal models and its novel chemical structure. This compound inhibits the mitochondrial enzyme dihydroorotate dehydrogenase (DHO-DH), which catalyzes the conversion of dihydroorotate to orotate, leading to a blockage in the pyrimidine de novo biosynthesis. A total of 43 patients received 110 courses of Brequinar sodium by short-term intravenous (i. v.) infusion, which was repeated every 3 weeks. Dose escalation was initially based on a modified Fibonacci scheme. After pharmacokinetic data from mice and man became available, a pharmacologically guided dose escalation was used; at toxic levels, dose escalation was applied on the basis of clinical judgement. The dose-limiting toxicities were myelosuppression, mucositis, skin rash, nausea and vomiting. The maximum tolerable doses for poor- and good-risk patients were 1,500 and 2,250 mg/m², respectively. One mixed response was observed in a patient with papillary carcinoma of the thyroid. The recommended doses for phase II studies are 1,200 and 1,800 mg/m² Brequinar sodium, given by a 1-h i. v. infusion every 3 weeks to poor- and good-risk patients, respectively.

Introduction

Brequinar sodium (DUP 785, NSC 368390; Fig. 1), 6-fluoro-2(2'-fluoro-1,1'-biphenyl-4-yl)-3-methyl-4-quinoline carboxylic acid sodium salt, was selected for clinical evaluation by the Early Clinical Trials Group (ECTG) of the European Organization for Research and Treatment of

Cancer (EORTC) because of its broad spectrum of antitumor activity in preclinical models and its novel chemical structure [4].

Brequinar sodium inhibits the mitochondrial enzyme dihydroorotate dehydrogenase (DHO-DH), which catalyzes the conversion of dihydroorotate to orotate, thereby blocking pyrimidine de novo biosynthesis [2, 7]. In L1210 leukemia, exposure of cells to Brequinar sodium leads to a strong inhibition of DHO-DH activity. However, enzyme activity rapidly recovers after reculture of cells in drug-free medium. Prolonged drug exposure is required for the achievement of sustained DHO-DH inhibition and long-lasting depletion of pyrimidine nucleotide pools, impairing cell growth [2, 7, 10]. In vitro studies indicated that Brequinar sodium was among the most active drugs in a series of 11 new compounds tested in human colon-cancer cell lines [8].

In vivo studies in murine models have shown that Brequinar sodium is active against L1210 leukemia, cytosine arabinoside-resistant L1210 leukemia, and colon 38 adenocarcinoma. It is moderately active against P388 leukemia and marginally active against B16 melanoma [4]. Experiments using human tumor xenografts implanted in the subrenal capsule of nude mice revealed that Brequinar sodium is active against MX-1 breast, LX-1 lung, BL/STX-1 stomach, and CX-1 colon carcinomas. It shows antitumor activity against HTC-15, Clone A, and DLD-2 human colon adenocarcinomas growing subcutaneously in nude mice, tumors which are resistant to cytosine arabinoside and doxorubicin and moderately sensitive to 5-fluorouracil. The antitumor effects of Brequinar sodium are schedule-dependent and similar by the i. v., i. p., s. c., or p. o. routes [4, 10].

Preclinical toxicity studies of Brequinar sodium were carried out in mice, rats, dogs, and monkeys. At toxic doses, Brequinar sodium induced a state of decreased spontaneous motor activity and toxicity to the gastrointestinal tract, bone marrow, and lymphoid system. Histopathological evaluation of these tissues in dogs revealed the presence of erosions and hemorrhages in the gastrointestinal mucosa, erythroid and myeloid hypoplasia, and lymphoid depletion of the thymus and spleen.

In the ECTG, three different schedules for the i. v. administration of Brequinar sodium have been selected for phase I studies: (a) a single, short-term infusion every 3 weeks; (b) a single, weekly short-term infusion; and (c) a daily-times-five short-term infusion every 4 weeks.

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Fig. 1. Structural formula of Brequinar sodium (NSC 368390)

In this paper, we describe the results of the first phase I trial of Brequinar sodium, in which the drug was given i.v. as a short-term (10–60 min) infusion that was repeated every 3 weeks in patients with solid tumors. In CD_2F_1 mice, the LD_{10} (dose lethal to 10% of mice) for the single-dose i.v. schedule was 396 mg/m^2 . Because $1/10$ of the LD_{10} was still toxic in dogs, the starting dose in the present study was based on $1/3$ of the TDL (toxic dose low) in dogs (15 mg/m^2).

The use of comparative pharmacokinetics between mice and man was prospectively studied to guide dose escalation in this phase I trial. It has been shown for several cytotoxic agents that the ratio between the plasma AUC (area under the concentration-time curve) at the LD_{10} in mice and at the maximum tolerable dose (MTD) in man is closer to 1 than the ratio between the respective doses [3, 5, 11]. This means that by knowing the plasma AUC in patients at the initial dose levels and the AUC at the LD_{10} in mice, this ratio may give an indication of the expected AUC at the MTD in man, provided that linear pharmacokinetics apply [3, 5].

This study had several objectives: (a) to determine the MTD of Brequinar sodium for this drug schedule; (b) to describe the spectrum of toxicities of Brequinar sodium and quantify them; (c) to seek initial evidence of the therapeutic activity of Brequinar sodium in patients with advanced solid tumors; and (d) to compare the pharmacokinetics of this drug in man with that at the mouse LD_{10} and prospectively use the information as a guide to dose escalation.

Materials and methods

Patient selection. Patients who entered the study were required to have a microscopically confirmed diagnosis of a solid tumor no longer amenable to established forms of treatment. Informed consent was required to enter the study, in addition to a life expectancy of at least 9 weeks and a performance status of <3 (ECOG). Moreover, eligibility criteria included an adequate bone marrow function (leukocytes, $>4.0 \times 10^9/\text{l}$; thrombocytes, $>100 \times 10^9/\text{l}$), a normal hepatic function (bilirubin levels of $<25 \text{ } \mu\text{mol/l}$ and other liver function tests within 2 times the upper limit of normal), and a normal renal function (serum creatinine values $<120 \text{ } \mu\text{mol/l}$). None of the patients had pleural effusions or ascites.

Patients were not eligible if they had received prior chemotherapy, hormonal therapy, immunotherapy, or radiotherapy during the preceding 4 weeks (6 weeks for

nitrosoureas, mitomycin C, and extensive radiotherapy). Patients with active bacterial infections, bleeding, and cardiac or pulmonary disease requiring medication were not eligible for the study.

Treatment plan. Brequinar sodium was obtained from Du Pont Pharmaceuticals (Geneva, Switzerland) as a freeze-dried powder containing 100 mg Brequinar sodium, 40 mg sodium cholate, and 40 mg glycine. The starting dose was 15 mg/m^2 every 3 weeks. Up to a dose of 200 mg/m^2 , the drug was reconstituted in 10 ml normal saline and given via a peripheral vein over 10 min. However, due to pain at the infusion site, the volume of the drug solution was increased to 500 ml and given as a 1-h infusion to all patients receiving a dose of $>200 \text{ mg/m}^2$.

Prior to drug administration, patients underwent a physical examination and complete blood cell counts and urinalysis, whereby serum chemistry included electrolytes (Na, K, Ca, P), total protein, albumin, glucose, bilirubin, alkaline phosphatase, γGT , SGOT, SGPT, lactic dehydrogenase, creatinine, and uric acid. Furthermore, an ECG and a chest X-ray were done. Complete blood counts were repeated at least twice weekly; serum chemistry, every week; and ECG and chest X-ray, every 3 weeks. Performance status and toxicity (WHO) were evaluated at weekly intervals. Patients were considered to be poor risk in case of a performance status of >2 , pretreatment with mitomycin C or nitrosourea, or extensive prior radiation therapy. In patients who had measurable or evaluable disease, tumor response was assessed every 3 weeks. Objective responses were classified according to WHO guidelines.

Dose escalation procedure. At least three patients were included per dose level. Dose escalation in individual patients was allowed only in patients receiving Brequinar sodium at the initial non-toxic dose levels. The dose was initially escalated according to a modified Fibonacci scheme (Table 2). In most instances, patients were retreated at the same dose level at the completion of each 3-week interval if no severe toxicity (grade 3–4) or progression of disease was observed. When dose-limiting toxicity was observed at a given dose level, the patient was retreated at the preceding dose level. Five patients were evaluated at the level of dose-limiting toxicity to establish the MTD for both poor- and good-risk patients.

Pharmacokinetics. Blood samples were collected at various dose levels (15 – $2,250 \text{ mg/m}^2$). Brequinar sodium was extracted from 200 μl plasma by 10 ml dichloromethane after the addition of 200 μl 4 mM tetrabutylammonium chloride as an ion-pairing agent in tubes containing DUP 416 as an internal standard. Thereafter, 8 ml extract was evaporated to dryness. The residue was dissolved in 200 μl mobile phase and analyzed by high-performance liquid chromatography (HPLC). The HPLC column (4.6 mm $\times$ 25 cm) was filled with 6 μm Zorbax TMS (DuPont Instruments, USA); the mobile phase consisted of $\text{CH}_3\text{CN}:0.046 \text{ M H}_3\text{PO}_4$ (55:45, v/v). The flow rate was 1 ml/min. A 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 $\text{CH}_3\text{CN}:\text{H}_2\text{O}$ (55:45, v/v). The plasma AUC was calculated using the trapezoidal rule.

Table 1. Patient characteristics

Total number of patients	43
Men	33
Women	10
Age: median (range)	58 years (35–75 years)
Performance status (ECOG):	
0	3
1	27
2	10
3	3
Prior therapy:	
Chemotherapy	20
Radiotherapy	4
Immunotherapy	2
Chemotherapy and radiotherapy	17
Tumor types:	
Head and neck	8
Breast	5
Colon-rectum	5
Kidney	5
Melanoma	5
Lung	4
Pancreas	2
Soft-tissue sarcoma	2
Unknown primary	2
Other	5

Table 2. Number of patients and courses per dose level

Patients (n)	Dose level (mg/m ²)	Initial courses (n)	Subsequent courses (n)	Total courses (n)
3	15	3	1	4
3 ^a	30	2	1	3
4 ^a	45	3	6	9
3	67.5	3	2	5
3	90	3	2	5
3	135	3	7	10
3	200	3	9	12
3	300	3	3	6
3 ^a	600	2	6	8
1 ^b	900	–	2	2
3	1,200	3	3	5
1 ^b	1,200	–	1	1
5	1,500	5	1	6
5	1,800	5	12	17
4 ^b	1,800	–	10	10
5	2,250	5	2	7
Totals		43	67	110

^a One patient was previously treated at a lower dose level

^b Patients retreated at a reduced dose level (from 1,200 to 900 mg/m², from 1,800 to 1,200 mg/m², and 2,250 to 1,800 mg/m², respectively)

To determine the plasma AUC at the LD₁₀ in mice, series of three CD₂F₁ mice were injected i.v. with Brequinar sodium at a dose of 396 mg/m² (132 mg/kg) and bled by cardiac puncture at various intervals (0–72 h). The ratio between the patient plasma AUC at the various dose levels and that at the mouse LD₁₀ was then calculated as a guide for dose escalation.

Results

A total of 43 patients were entered into this phase I study; their characteristics are shown in Table 1. A total of 110 courses were given. The number of patients and courses per dose level is depicted in Table 2.

Up to a dose of 300 mg/m², the only toxicities observed were pain at the site of drug administration in four patients, grade 1 leukopenia in four cases and grades 1–2 thrombocytopenia in two patients. By that time, preliminary results on the pharmacokinetics of the drug in mice and in the first patients became available [9, 12]. The plasma AUC at the mouse LD₁₀ was about 20 times higher than the AUC in patients treated with 300 mg/m². Considering the latter findings and the lack of significant toxicity, the dose was doubled for the next two steps, up to 1,200 mg/m². Only minor toxicity was observed, except in one patient who developed grade 3 thrombocytopenia at the 1,200 mg/m² dose level (Tables 3–5).

This patient was a 64-year-old woman with breast cancer and widespread bone metastases, who had previously been treated with combination chemotherapy including cyclophosphamide, doxorubicin, methotrexate, and 5-fluorouracil. After the dose had been reduced to 900 mg/m², grade 3 thrombocytopenia was again observed (Tables 4 and 5). Although no pharmacokinetic data were obtained in the latter patient, the ratio between the plasma

AUC in the other two patients treated with 1,200 mg/m² to that at the mouse LD₁₀ had reached a level of 0.2, which supported the clinical judgement to slow down the subsequent dose escalation to 25% in poor risk patients and to 50% in good-risk patients. Five poor-risk patients received 1,500 mg/m² Brequinar sodium; grade 4 thrombocytopenia occurred in two patients, in one of whom grade 4 leukopenia was observed (Tables 4 and 5). Grade 4 gastrointestinal toxicity was observed in two patients (Table 3). One 69-year-old man had widespread bone metastases of prostatic cancer, a performance status of grade 3, and had received prior chemotherapy including mitomycin C. The patient developed severe nausea and vomiting that started about 6 h after the administration of Brequinar sodium and lasted for 7 days. He failed to respond to antiemetics and required i.v. fluids. Endoscopy revealed severe esophagitis, diffuse hemorrhagic gastritis, and duodenitis. The leukocyte count dropped to a nadir of $2.7 \times 10^9/l$ on day 8 and the thrombocyte count, to $22 \times 10^9/l$ on day 12. Hematuria was observed on days 10–12. Blood counts returned to normal on day 18. The second patient was a 67-year-old woman with widespread bone metastases of a breast cancer and a performance status of grade 1. She had received extensive prior radiation therapy and a combination chemotherapy regimen without mitomycin C. This patient developed thrombocytopenia and grade 4 leukopenia, leading to septicemia, which was successfully treated with i.v. antibiotics.

Skin rash was observed in two other patients; it was characterized by widespread papulo-erythematous lesions that started on days 4–5 and disappeared spontaneously in 1 week. Due to this severe toxicity, the 1,500 mg/m² dose level was considered to be the MTD for poor-risk patients. In the good-risk group, the dose was further escalated from 1,200 to 1,800 mg/m², at which level five

Table 3. Grades of non-hematological toxicities (WHO) of Brequinar sodium

Dose level (mg/m ²)	Evaluable courses (n)	Pain at i.v. site:	Stomatitis: mucositis:	Skin rash:	Fatigue/ malaise:	Nausea/ vomiting:	Diarrhea:
		1 2	1 2 3 4	1 2 3	1 2 3	1 2 3 4	1 2 3
600	8	1 –	– – – –	– – –	– – –	– – – –	– – –
900 ^a	2	– –	1 1 – –	– – –	– – –	– 1 – –	– – –
1,200	6	– –	– 3 – –	– – –	1 – –	– 1 – –	– – –
1,500	6	1 1	1 2 – 1	2 1 –	3 1 1	1 1 – 1	– – –
1,800	17	3 –	3 7 1 –	1 – 1	1 – –	4 3 4 –	1 1 –
1,800 ^a	10	– –	3 1 – –	4 1 –	5 – –	2 2 – –	– – –
2,250	7	2 –	4 1 2 –	1 1 –	2 – 1	– 3 1 –	– – 2

^a Patients retreated at a reduced dose level**Table 4.** Grades of hematological toxicities (WHO) of Brequinar sodium

Dose level (mg/m ²)	Evaluable courses (n)	Leukopenia:	Thrombocytopenia:	Anemia:
		1 2 3 4	1 2 3 4	1 2 3
600	8	1 1 – –	– – – –	3 – –
900 ^a	2	2 – – –	– – 1 –	2 – –
1,200	6	1 – – –	– – 1 –	1 1 –
1,500	6	– 1 – 1	1 – – 2	1 1 1
1,800	17	2 – – –	2 1 – –	6 1 –
2,250	7	3 1 – –	– 1 – 2	3 – 1

^a Patients retreated at a reduced dose level**Table 5.** Median (range) nadir values of leukocytes and thrombocytes observed after different doses of Brequinar sodium

Dose level (mg/m ²)	Evaluable courses (n)	Leukocytes ($\times 10^9/l$)	Thrombocytes ($\times 10^9/l$)
900 ^a	2	3.5 (3.4–3.6)	84 (45–122)
1,200	6	4.4 (3.6–6.0)	156 (36–177)
1,500	6	4.7 (1.0–7.6)	102 (20–194)
1,800	17	4.6 (3.2–7.1)	120 (56–195)
1,800 ^a	10	4.6 (3.0–7.9)	165 (80–195)
2,250	7	3.9 (2.8–8.0)	104 (16–420)

^a Patients retreated at a reduced dose level

patients with a total of 17 evaluable courses were studied. In one patient, a widespread papulo-erythematous skin rash (grade 3) was observed (Fig. 2). The patient was treated symptomatically with topical steroids, and the lesions disappeared in about 10 days. Grades 1–3 gastrointestinal toxicity and grades 1–2 bone marrow toxicity were observed as well. The ratio between the AUC in two patients treated at the 1,800 mg/m² dose level and that at the LD₁₀ in mice was 0.7.

Because dose-limiting toxicities were not observed at that dose level, the dose was further escalated to 2,250 mg/m². Five patients received Brequinar sodium at this dose, and a total of seven courses were evaluable. Two patients developed grade 4 thrombocytopenia during the first course; the thrombocytes decreased to 20 and 16 $\times 10^9/l$ on days 10 and 11, respectively. Mild to moderate leukopenia was observed in four courses (Tables

4, 5). Severe mucositis, fatigue, nausea and vomiting, diarrhea, and skin rash were observed as well (Table 3). Grade 2 skin toxicity was considered to be dose-limiting in one patient with papillary carcinoma of the thyroid who developed widespread papulo-erythematous lesions in the perineum and inguinal region that caused marked discomfort. The patient was treated symptomatically with topical steroids, and the skin recovered after 14 days. This patient had significant relief of pain and tumor regression in a metastatic lymph node over a period of 4 weeks. Therefore, two additional courses were given at the previous dose level of 1,800 mg/m², with tolerable toxicity. However, disease progression was documented in the contralateral lymph nodes during this period (mixed response). The 2,250 mg/m² dose level was considered to be the MTD for the good-risk patient category. The ratio between the mean plasma AUC in two patients receiving

Fig. 2. Papulo-erythematous skin in a patient receiving Brequinar sodium at a dose of $1,800 \text{ mg/m}^2$

Brequinar sodium at the MTD and that at the LD_{10} in mice was 0.78.

Thrombocytopenia was more severe than leukopenia at the highest dose levels. The thrombocyte nadir occurred between days 10 and 12, with a rapid recovery to normal values in the following 3–7 days. Leukocytes reached a nadir between days 7 and 10 and usually recovered within 3–6 days (Fig. 3). Nausea and vomiting most often started 3–8 h after drug administration and usually resolved on day 2. Diarrhea was observed in some patients starting on days 2–4 and persisted no longer than 3–5 days. Mucositis usually started on days 4–8 and recovered by the completion of the 2nd week (Table 3).

Less common side effects observed in individual patients included the development of angioneurotic edema of the eyelid and lip, hot flushes shortly after drug administration, hyperpigmentation of the skin at the site of

previous plaster bandages, mild bilateral conjunctivitis, and transient elevations of lactic dehydrogenase and bilirubin during the first 3 days after therapy. All of these side effects were reversible.

Brequinar sodium showed non-linear pharmacokinetics in man, as shown in Table 6, in which the AUCs and the total body clearances (Cl_t) are presented over the dose range of $200\text{--}2,250 \text{ mg/m}^2$. Although there was a large variation in the calculated parameters at the same dose, it seemed to indicate that non-linearity occurred in two steps, i.e., from 600 to $1,200 \text{ mg/m}^2$ and from 1,500 to $1,800 \text{ mg/m}^2$. The ratio between the mean AUC_∞ at the MTD in patients (2250 mg/m^2) and the AUC_∞ at the LD_{10} in mice (132 mg/kg) was 0.8, whereas the ratio between the respective doses was 5.7. Representative pharmacokinetic data obtained from four patients who received Brequinar sodium at the highest dose levels ($1,500\text{--}2,250 \text{ mg/m}^2$) are presented in Table 7. Non-linear pharmacokinetics was not reflected in the half-lives. The concentration-time curves of Brequinar sodium in the above mentioned patients are shown in Fig. 4. The pharmacokinetics of this drug will be extensively described elsewhere (Schwartzmann et al., submitted).

Discussion

Brequinar sodium was selected for clinical studies mainly on the basis of its broad spectrum of antitumor activity in murine tumors as well as human tumor xenografts and its novel chemical structure. Other quinoline carboxylic acid analogs showed similar antitumor activity, but Brequinar sodium was the most active compound in the series and was also readily soluble in water.

In the present phase I study, the principal toxicities of Brequinar sodium were myelosuppression, nausea and vomiting, mucositis, diarrhea, and skin rash, resembling the toxicity spectrum of *N*-(phosphonacetyl)-L-aspartic acid (PALA) [1, 6]. Both myelosuppression and gastrointestinal toxicity were predicted by animal toxicology studies. The choice of $1/3$ of the TDL in dogs as the starting dose in this study was based on the observation of severe bone marrow and gastrointestinal toxicity after these

Fig. 3. Leukocyte and thrombocyte counts following the administration of Brequinar sodium at various dose levels ($1,500\text{--}2,250 \text{ mg/m}^2$) in four patients

Fig. 4. Semilogarithmic plots of concentration vs time of Brequinar sodium in four patients treated at dose levels of (◆) 1,500, (▲, ●), 1,800 and (■) 2,250 mg/m², respectively

Table 6. AUC and total body clearance in relation to the dose of DUP 785

Patient number	Dose (mg/m ²)	AUC (µg · h/ml)	Cl _t (ml/min)
10	200	233.4	30.1
11	200	183.8	38.2
12	300	275.3	29.1
13	300	998.5	10.5
14	300	311.0	28.9
15	600	770.4	22.1
16	1,200	2,531.1	15.8
17	1,200	2,850.7	15.2
18	1,500	3,574.6	14.5
19	1,500	3,266.6	14.5
20	1,800	6,693.7	7.7
21	1,800	7,444.7	8.5
22	2,250	6,660.7	9.3
23	2,250	9,049.1	8.3

animals received $1/10$ of the mouse LD₅₀. In contrast, skin toxicity was not observed in preclinical toxicology studies; nevertheless, it was dose-limiting in one of the present patients. Skin toxicity was dose-dependent and was

characterized by the appearance of widespread papulo-erythematous lesions on days 4–6. The acute phase resolved in 5–7 days and was followed by recovery after 7–10 days. A similar clinical picture has previously been described in patients receiving PALA, another inhibitor of the pyrimidine de novo pathway [1, 6]. Although there is no structural relationship between PALA and Brequinar sodium, it is possible that both agents lead to skin toxicity through a common mechanism [6, 7].

One provocative aspect of this study concerns the methodology of dose escalation. Initially, it was based on a modified Fibonacci scheme. When pharmacokinetic data for Brequinar sodium in mice and patients became available, a pharmacologically guided dose-escalation procedure was used, which saved at least three unnecessary dose-escalation steps (from 200 to 1,200 mg/m²). Later, when significant clinical toxicity was documented, dose escalation was guided by clinical judgement as well as by careful pharmacokinetic monitoring, by which non-linear pharmacokinetics was observed. This observation clearly underlines the necessity of monitoring pharmacokinetics at each dose level.

Although the use of comparative pharmacokinetics between mice and man is said to be nonapplicable for compounds that exhibit marked schedule dependency (e.g.,

Table 7. Pharmacokinetic parameters of brequinar sodium in four patients at the highest dose levels

Dose level (mg/m ²)	C _{peak} (µg/ml)	Half-life			MRT (h)	Vd _{ss} (l/m ²)
		t _{1/2 α}	t _{1/2 β}	t _{1/2 γ}		
1,500	522.2	15.8	112.0	18.7	23.4	9.6
1,800	609.0	33.4	145.5	13.6	16.8	4.4
1,800	625.5	15.6	318.3	20.1	29.1	7.0
2,250	495.1	15.3	99.2	15.4	19.9	6.5

C_{peak}, peak level corrected for infusion time; MRT, mean residence time; Vd_{ss}, apparent volume of distribution

antimetabolites) [3], it seemed to be useful for Brequinar sodium given by the present schedule. For this compound, the ratio between the AUCs was 0.78 vs a ratio of 5.7 between the mouse LD₁₀ and the MTD in man.

Non-linear pharmacokinetics could not be observed in mice treated with Brequinar sodium, which might be explained by the small dose range (10–50 mg/kg) used during preclinical studies. Preclinical studies have indicated that prolonged exposure of cells to Brequinar sodium is necessary for the attainment to its optimal cytotoxic effects [2, 4, 7, 10]. This suggests that, as with other antimetabolites, in clinical trials Brequinar sodium may show better antitumor activity if given more frequently. The rapid recovery from myelosuppression and/or mucocutaneous toxicity, as well as a lack of drug accumulation after repeated drug administrations (data not shown), also lend support to this hypothesis.

In conclusion, the results of this phase I study on patients with solid tumors show that the dose-limiting toxicities of Brequinar sodium given by a short-term i.v. infusion every 3 weeks included thrombocytopenia, leukopenia, nausea and vomiting, and skin rash. The MTD for poor- and good-risk patients were 1,500 and 2,250 mg/m², respectively. The recommended doses for phase II trials are 1,200 and 1,800 mg/m² Brequinar sodium, given by a short-term i.v. infusion every 3 weeks to poor and good-risk patients, respectively. This study also illustrates the potential usefulness of preclinical and (early) clinical pharmacology for the guidance of dose escalation in phase I studies. Further studies on the mechanism of action of Brequinar sodium as well as the results of other clinical trials should be awaited before the optimal drug schedule for this compound can be recommended.

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