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Phase IB study of doxorubicin in combination with the multidrug resistance reversing agent S9788 in advanced colorectal and renal cell cancer

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Summary S9788 is a new triazineaminopiperidine derivate capable of reversing multidrug resistance (MDR) in cells resistant to chemotherapeutic agents such as doxorubicin. It does not belong to a known class of MDR revertants, but its action involves the binding of P-glycoprotein. Thirty-eight evaluable patients with advanced colorectal or renal cell cancer were treated with doxorubicin alone (16 patients) or in combination with S9788, obtaining disease progression in the group of patients treated with doxorubicin alone at suprapharmacological doses. The addition of S9788 to doxorubicin resulted in a significant survival benefit.

Inherent or acquired multidrug resistance (MDR) is an important cause of failure of cancer chemotherapy. Several mechanisms responsible for MDR have been described, and the most extensively investigated is the expression of the product of the MDR1 gene, P-glycoprotein (P-gp) or P-170 (Roninson, 1992). This protein acts as an efflux pump for a number of commonly used cytotoxic agents, e.g. doxorubicin, vincristine, vinblastine and actinomycin D. Different compounds have been shown to reverse P-gp-mediated MDR, including calcium channel antagonists (verapamil), calmodulin inhibitors (quinine, quinidine), oestrogen receptor antagonists (tamoxifen), steroids and immunomodulators (cytosporin A). The mechanisms by which these drugs influence MDR have not always been identified. The clinical use of these MDR modulators is hampered by the toxic side-effects that occur when the suprapharmacological doses required to achieve significant reversal of MDR are used. Therefore, the search for novel and more potent MDR modulators is of major importance.

S9788 is a triazineaminopiperidine derivate capable of reversing MDR in vitro and in vivo in a dose-dependent way. It increases the intracellular accumulation and retention of doxorubicin, vincristine and vinblastine in resistant cell lines displaying the P-gp-mediated MDR phenotype. S9788 has been shown to modulate the expression of MDR1, the latter being infused over 30 min or 6 h, have shown cardiac arhythmias (mainly AV blocks, bradycardia, tachycardia), hypotension and prolongation of the QT interval on electrocardiograms in some patients. S9788 has been shown not to interfere with doxorubicin plasma pharmacokinetics. Preliminary results of phase I studies of doxorubicin plus S9788, the latter being infused over 30 min or 6 h, have shown cardiac arhythmias (mainly AV blocks, bradycardia, tachycardia), hypotension and prolongation of the QT interval on electrocardiograms in some patients.
advanced colorectal and renal cell cancer were included in the study as these types of cancer are resistant to anthracyclins, with response rates of 7% (95% CI 1.9–17.1%) and 2.9% (95% CI 1.8–4.2%) respectively (Frytak et al, 1975; Yagoda et al, 1995). Although other mechanisms may play a role in their resistance to chemotherapy (Redmond et al, 1991; Chapman and Goldstein, 1995), tumour cells of both these types of cancer are known to express the MDR1 gene and contain high levels of P-gp activity (Goldstein et al, 1989; Kanamaru et al, 1989; Lai et al, 1991; Kramer et al, 1993), and this may therefore play a key role in their resistance to anthracyclins. The aims of the present study were to investigate the toxicity, anti-tumour activity and pharmacokinetics of S9788 administered before and after infusion of doxorubicin in patients with advanced colorectal and renal cell cancer. A suboptimal dose of doxorubicin was chosen for this study (50 mg m⁻² once every 3 weeks) because of the possible potentiation of its side-effects by S9788.

**MATERIALS AND METHODS**

**Inclusion criteria**

Eligibility criteria included histological proof of advanced colorectal or renal cell cancer with documented progression within the last 2 months before entry into the study, measurable disease parameters, age between 18 and 75 years, Karnofsky performance status ≥80%, no radiotherapy, hormone therapy or immunotherapy during the last 2 weeks and no chemotherapy during the last 4 weeks before study entry. Normal values for Hb, platelets, WBC and serum electrolytes were required. Liver transaminases were allowed to be ≤2.5 times and bilirubin, amylase, creatinine and urea ≤1.25 times the upper normal values, and creatinine clearance ≥60 ml min⁻¹. Any history of significant cardiac arrhythmias, cardiac failure or recent myocardial infarction was not allowed, and patients were required to have normal cardiac ventricular ejection fraction (≥40%), no clinical signs of central nervous system metastasis, no concurrent use of other investigational or anti-neoplastic agents and no second malignancy. Written informed consent was obtained from all patients. Before initiation of this trial, institutional review board approval was obtained at each of the participating centres.

**Study design and drug administration**

Patients were either initially treated with the combination of doxorubicin and S9788, or after documented progression of disease on treatment with doxorubicin alone. This decision was left to the investigators of the various institutions, as some centres considered treatment of patients with colorectal and renal cell cancer with single-agent doxorubicin not acceptable. S9788 (6-4-[2,3-di(4-fluoro­phenyl) ethylamino]-1-piperidinyl] N,N-di-2-propenyl 1,3,5-triazine 2,4-diamine) was provided by IRIS (Courbevoie, France) in 10-ml vials at a concentration of 10 mg ml⁻¹ formulated in a bismethane sulphonate salt solution. The drug was diluted in either 250 ml (loading dose) or 1000 ml (2-h infusion) of dextrose 5% in water. A fixed loading dose of S9788 at 56 mg m⁻² administered over 30 min i.v. was followed by a 2-h infusion at different dose levels starting at 24 mg m⁻². Doxorubicin 50 mg m⁻² was administered over 5 min i.v. either alone or directly after the loading dose. A minimum of three patients were entered at each 2-h infusion dose level of S9788. No intra-patient dose escalation was allowed. Cycles were repeated every 3 weeks. All patients received antiemetic prophylaxis before doxorubicin infusion. Dose-limiting toxicity (DLT) was defined as any of the following events: (1) decrease ≥ 15% of ventricular ejection fraction; or (2) mucositis, cardiac, renal, hepatic, neurological or any major unexpected toxicity ≥ WHO grade 3. DLT occurring in two or more patients treated at the same dose level was considered as the clinical end point for this study.

**Study monitoring**

A complete history, physical examination, performance status and laboratory studies (complete blood count with leucocyte differential (weekly), prothrombin and partial thromboplastin times, blood urea nitrogen, serum electrolytes, creatinine, calcium, phosphorus, liver transaminases, total bilirubin, amylase, alkaline phosphatase and urinalysis) were obtained at baseline and before each cycle. Ventricular ejection fraction, determined by either ultrasound or nuclear scanning, was planned for each patient at baseline and after completion of every two cycles. It was intended that all patients should have continuous cardiac telemetry and/or Holter recording for 24 h starting a minimum of 30 min before S9788 infusion or doxorubicin alone. Determination of the maximum corrected QT intervals (QTc max) was performed according to the method described by Bazett (1920). QTc values of ≤440 ms were considered as normal. Twelve-lead electrocardiograms were performed before and directly after each cycle. Patients were evaluated weekly for toxicity and every two cycles for response. Toxicity and response were scored according to WHO criteria. Cycles could only be repeated if granulocyte cell counts were ≥2 000 × 10⁹ l⁻¹ and in the absence of grade ≥2 mucositis, renal, hepatic, neurological or other haematological toxicity at the time of retreatment.

**Pharmacokinetic analysis**

Heparinized venous blood samples were collected before and at the end of the 30-min infusion of the loading dose of S9788 as well as before and 1, 2, 2.5 and 24 h after the start of the 2-h maintenance infusion of S9788. Samples were quickly centrifuged and plasma was stored at −20°C until analysis. S9788 was quantitated by a specific high-performance liquid chromatographic method (HPLC) as described previously (Bakes et al, 1993) using a solid-phase extraction procedure and a reversed-phase HPLC (Hypersil ODS) with ultraviolet detection (230 nm). The mean precision and accuracy were 5.0% and 7.9%, respectively, over a range of 1–500 ng ml⁻¹ with a quantification limit of 1 ng ml⁻¹. S9788 plasma concentrations were modelled over time, using extended least squares regression on the computer program Micropharm (S. Vrien, LOGINSERM) version 4.0. The two-compartment model was chosen using Akaike’s information criterion (Yamaoka et al, 1978). The total body clearance (Cl, h⁻¹), distribution volume at steady state (Vus, l), distribution half-life (t½α, min) and elimination half-life (t½β, h) were estimated by the model.

**Statistical methods**

The correlation between dose of S9788 and QTc max was analysed using general linear models with the dose of S9788 as the main effect and the patient as the nested effect. The data from 63 cycles in 26 patients were analysed. The difference in non-cardiac toxicities between treatment with doxorubicin and doxorubicin plus S9788 was analysed (t = 0.05) using the two-sided chi-square and the Fisher’s exact tests.
Patients characteristics

A total of 39 patients were entered into the study in eight participating institutions. One patient was considered ineligible because of pretreatment with doxorubicin at a cumulative dose of 490 mg m⁻² and a previous second malignancy. The number of assessable patients was therefore 38: 27 patients with colorectal cancer and 11 with renal cell cancer. The median age was 61 years (range 34–74) and median Karnofsky performance score was 90% (range 80–100%). The 28 patients pretreated with chemotherapy had received a median of two (1–3) regimens. The majority of these patients had received a 5-fluorouracil-containing regimen for colorectal cancer. Six of eleven patients with renal cell cancer had received prior immunotherapy.

Treatment

Sixteen patients started treatment with doxorubicin alone at 50 mg m⁻² and received a median of two (1–5) cycles. Of these, 12 patients later received combined treatment with S9788 plus doxorubicin. The reasons that four patients did not receive the combined treatment were death due to progressive disease (1), multiple ventricular extrasystoles during doxorubicin treatment (1), patient refusal (1) and loss to follow-up (1). The remaining 22 patients started treatment with the combination of S9788 with doxorubicin.

The number of patients treated at the different dose levels of the 2-h infusion of S9788 is shown in Table 1. A total of 34 patients received a median of two cycles (1–8) of S9788. The planned dose for both drugs was respected in all patients but one, in whom the doxorubicin dose was reduced because of grade 3 stomatitis and grade 4 leucocytopenia. Although the clinical end point of the study was not reached, the study was terminated because of the occurrence of a torsade de pointe with syncope in a patient treated in another French phase I study at a 59788 dose that was lower than the doses that were used in our study (Terret et al, 1996).

Cardiac toxicity

No major haemodynamic changes occurred in any patient during the study. No variation > 10% in the ventricular ejection fraction value was observed within individual patients. A total of 87 Holter registrations (73 of 24-h and 14 of 48-h) were obtained from 26 patients. On 19 Holter recordings of seven patients during administration of doxorubicin alone, no arrhythmias or prolongation of QTc max > 440 ms were observed. Asymptomatic arrhythmias, occurring after the start of S9788 infusion and disappearing within 18 h, were demonstrated on 21 out of 68 Holter recordings of 13 out of 34 patients receiving doxorubicin plus S9788. The following arrhythmias (frequency of occurrence) were seen: Mobitz type I (1), Mobitz type II (1), third-degree atrioventricular block (2), non-sustained ventricular tachycardia (3), supraventricular (8) and ventricular (4) extrasystoles, supraventricular tachycardias of less than 30 s duration (6). These arrhythmias occurred at all dose levels of S9788 and were not consistently present during every cycle in individual patients. In patients receiving doxorubicin plus S9788, the QTc max was ≤ 440 ms in one patient, > 440 and ≤ 600 ms in 20 patients, and > 600 ms in five patients, with a median value of 541 ms (range 404–685). QTc max occurred within 3 h after the start of S9788 infusion in 7 out of 26 patients, between 3 and 6 h in 16 out of 26 patients, and after 6 h in 3 out of 26 patients. There was a statistically significant correlation between the QTc max and the dose level of S9788 and the QTc max of S9788 (r = 0.38, P = 0.001, Figure 1). An increase in the dose of S9788 of 24 mg m⁻² increased the QTc max with an average of 21.5 ms. There was no correlation between the QTc max and the occurrence of arrhythmias. No cumulative effect of S9788 on the QTc max was seen, but a cumulative effect on the occurrence of arrhythmias could not be excluded.

Non-cardiac toxicity

These consisted of alopecia, nausea, vomiting, stomatitis, and myelosuppression, as might be expected from treatment with doxorubicin. Compared with treatment with doxorubicin alone, treatment with the combination of doxorubicin plus S9788 caused a significant increase in the number of patients experiencing WHO grade 3–4 granulocytopenia (Table 2). No episode of febrile neutropenia occurred in any patient. A cumulative effect of doxorubicin as a cause for this toxicity was unlikely, as the first appearance of grade 3–4 granulocytopenia occurred during the

<table>
<thead>
<tr>
<th>Dose level of 2-h infusion of S9788 (mg m⁻²)</th>
<th>Patients (n)</th>
<th>Total number of cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>48</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>72</td>
<td>9</td>
<td>29</td>
</tr>
<tr>
<td>96</td>
<td>10</td>
<td>26</td>
</tr>
<tr>
<td>120</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td>34</td>
<td>89</td>
</tr>
</tbody>
</table>

All patients received a loading dose of S9788 at 56 mg m⁻² i.v. in 30 min and doxorubicin at 50 mg m⁻² i.v. in 5 min prior to the 2-h infusion of S9788.
Table 2  Non-cardiac toxicities

<table>
<thead>
<tr>
<th>Toxicities</th>
<th>WHO grade</th>
<th>Doxorubicin</th>
<th>Doxorubicin plus S9788</th>
<th>P-value overall/grade 3–4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>0</td>
<td>10 (62%)</td>
<td>10 (29%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1/2</td>
<td>6 (38%)</td>
<td>24 (71%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3/4</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>12 (80%)</td>
<td>17 (50%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1/2</td>
<td>2 (13%)</td>
<td>14 (41%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3/4</td>
<td>1 (7%)</td>
<td>3 (9%)</td>
<td></td>
</tr>
<tr>
<td>Stomatitis</td>
<td>0</td>
<td>16 (100%)</td>
<td>28 (82%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1/2</td>
<td>0</td>
<td>3 (9%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3/4</td>
<td>0</td>
<td>3 (9%)</td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>0</td>
<td>12 (75%)</td>
<td>14 (47%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1/2</td>
<td>4 (25%)</td>
<td>13 (45%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3/4</td>
<td>0</td>
<td>3 (10%)</td>
<td></td>
</tr>
<tr>
<td>Leucopenia</td>
<td>0</td>
<td>4 (25%)</td>
<td>4 (14%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1/2</td>
<td>10 (62%)</td>
<td>13 (45%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3/4</td>
<td>2 (13%)</td>
<td>12 (41%)</td>
<td></td>
</tr>
<tr>
<td>Granulocytopenia</td>
<td>0</td>
<td>5 (31%)</td>
<td>6 (22%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1/2</td>
<td>8 (50%)</td>
<td>6 (22%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3/4</td>
<td>3 (19%)</td>
<td>15 (56%)</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0</td>
<td>15 (94%)</td>
<td>33 (97%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1/2</td>
<td>1 (6%)</td>
<td>1 (3%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3/4</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The incidence of overall toxicity (three categories: grade 0, grade 1–2, grade 3–4) and of grade 3–4 toxicity in patients treated with doxorubicin vs doxorubicin plus S9788 was analysed two-sided (α = 0.05) with the chi-square test (overall toxicity) and the exact test (grade 3–4 toxicity). A significant difference was noted in the incidence of grade 3–4 leucocytopenia and granulocytopenia. Numbers are patients.

Figure 2. S9788 plasma concentration profile of a patient receiving S9788 at a 30 min loading dose of 56 mg m⁻² followed by a 5-min bolus infusion of doxorubicin and a S9788 2-h maintenance dose of 72 mg m⁻². x-axis, time from start infusion of loading dose of S9788; y-axis, S9788 concentration (μM).

first cycle of doxorubicin plus S9788 in 76% of patients, and 5 out of 12 patients with grade 3–4 leucocytopenia and 8 out of 15 patients with grade 3–4 granulocytopenia were not initially treated with cycles of doxorubicin alone. No statistically significant differences were found between treatment with doxorubicin and with doxorubicin plus S9788 when overall toxicity was observed (Table 2). When the incidence of toxicity was compared with the number of cycles with and without S9788, a statistically significant increase was also found in the incidence of nausea (grade 1–2) and vomiting (grade 1–3) in cycles with doxorubicin plus S9788. Nausea increased from an incidence of 6 out of 38 of cycles with doxorubicin alone (16%) to 43 out of 89 of cycles with doxorubicin plus S9788 (48%) (P = 0.001), and vomiting from 3 out of 38 cycles (8%) to 30 out of 89 cycles (34%) (P = 0.005). No significant differences occurred in the incidence or grade of diarrhoea, hepatic or renal toxicity (data not shown).

**S9788 pharmacokinetics**

A total of eight patients were included in the pharmacokinetic study. All these patients received a loading dose of S9788 of 56 mg m⁻² followed by doxorubicin infusion. Thereafter, three patients received a 2-h infusion of S9788 at 24 mg m⁻², one patient at 48 mg m⁻², two patients at 72 mg m⁻² and two patients at 96 mg m⁻². A typical plasma concentration profile of S9788 over time is presented in Figure 2. The mean ± standard deviation (s.d.) of the maximum plasma concentration reached at the end of the 56 mg m⁻² loading dose was 1.31 ± 0.41 μM (range 0.73–2.00). The maximum values for S9788 concentration during the 2-h maintenance infusion increased with the administration dose from 0.38 ± 0.11 μM up to 1.05 ± 0.50 μM for 24 and 96 mg m⁻² respectively. The mean ± s.d. pharmacokinetic parameters were as follows: CI = 47 ± 18 l h⁻¹, Vdss = 669 ± 247 l, t₁/₂α = 7 ± 5 min, t₁/₂β 14 ± 10 h.

**Clinical response**

Of the 34 patients who received doxorubicin plus S9788, 29 were evaluable for response. Of these, one patient with colorectal cancer had a partial response of 6 months’ duration after disease progression on two cycles of doxorubicin alone. Three patients (one colorectal and two renal cell cancer) treated with doxorubicin plus S9788 had stable disease for 3, 4 and 7 months respectively. The remaining 25 patients had progressive disease.
DISCUSSION

Clinical studies with MDR-modulating agents have shown disappointing results so far, mainly because of toxicities occurring at doses that were needed to achieve relevant plasma concentrations of the MDR modulator. Effective MDR reversal by S9788 in vitro has been observed, beginning at concentrations of 0.25 μM (Soudon et al, 1995). Therefore, this study shows that, using this schedule, effective concentrations of S9788 can be reached at nontoxic doses in patients. The high total body clearance and short initial half-life of S9788 that we found support the rationale for a prolonged infusion over bolus infusion of S9788, as was suggested by others (Perez et al, 1993; Julia et al, 1994; Soudon et al, 1995).

Compared with treatment with doxorubicin alone, patients treated with doxorubicin plus S9788 experienced a significant increase in the occurrence of WHO grade 3–4 granulocytopenia, but not in the occurrence or severity of other toxicities. When toxicities were compared on a per cycle basis, there was also an increase in the occurrence of nausea and vomiting. A cumulative effect of doxorubicin is unlikely as these toxicities mainly occurred during the first cycle of doxorubicin plus S9788, and occurred equally in patients initially treated with and without cycles of doxorubicin without S9788. A pharmacokinetic interaction between S9788 and doxorubicin, as has been shown for instance for verapamil and epirubicin (Scheithauer et al, 1993) and cyclosporine and doxorubicin (Bartlett et al, 1994), can be excluded as the interference of S9788 with the pharmacokinetics of doxorubicin has been investigated by the intra-individual comparisons of the pharmacokinetics parameters of doxorubicin obtained during two different cycles of doxorubicin treatment without or with S9788 administration (de Valeriola et al, 1997). In this study, S9788 was not shown to interfere with doxorubicin pharmacokinetics.

The most common doxorubicin-induced cardiotoxicity is a cumulative dose-related myocardial cell damage that may result in congestive heart failure. Acute electrocardiographical changes and/or arrhythmias during and shortly after administration have also been described and consist primarily of reversible non-specific ST–T segment changes, sinus tachycardia, premature atrial and ventricular contractions, and decrease in voltage (Tokaz and Von Hoff, 1984). The incidence of these abnormalities ranges from 0 to 41%. Prolongation of the QTc interval associated with arrhythmias has been described during anthracycline therapy in children and occurred more frequently in patients who received high cumulative doses (Bender et al, 1984; Schwartz et al, 1993). In this study, we found no electrocardiographical changes or arrhythmias in patients treated with doxorubicin alone, except for one patient who experienced multiple ventricular extrasystoles. However, in the 26 patients of whom Holter recordings were available during treatment with the combination of doxorubicin and S9788, a prolongation of QTc max and cardiac arrhythmias occurred in 25 out of 26 and 13 out of 26 patients respectively. Although it has been demonstrated that Holter recordings of healthy subjects show arrhythmias in a significant percentage (Stinson et al, 1995), a causal relationship between S9788 and these arrhythmias seemed probable as they occurred after the start of S9788 infusion and disappeared within 18 h. A correlation was established between the dose of S9788 and the prolongation of QTc max, although there was a high variation between individuals. There was no correlation between the dose of S9788 and the occurrence of arrhythmias. However, it should be noted that this study did not have the appropriate design to establish these correlations for the following reasons: QTc max is known to vary between and within individuals, and the QTc dispersion (i.e. the distribution of repolarization on the heart) rather than the absolute value of QTc max may be considered as a risk factor for the occurrence of arrhythmias (Surawicz and Knoebel, 1984).

Moreover, in our study patients were not randomized for the different S9788 dose levels. In contrast, Terret et al (1996) found no correlation between QTc lengthening and dose of S9788 in other phase I studies. This might be explained by the above-mentioned reasons, and/or by the fact that other doses and schedules of S9788 were used. Although a predictive value of QTc lengthening for the occurrence of severe arrhythmias has never been established for values < 600 ms (Surawicz and Knoebel, 1984), the study was terminated after the occurrence of severe cardiac arrhythmias (torsade de pointe with syncope) in another ongoing study with S9788 given over 6 h (Terret et al, 1996). Such a risk would preclude the routine use of S9788.

The clinical activity of treatment with doxorubicin plus S9788 was limited to one partial response in a patient with colorectal cancer, but a causative role of S9788 was obvious as this patient had disease progression during prior treatment with doxorubicin alone. It should be noted that a suboptimal dose of doxorubicin was chosen for safety reasons.

In conclusion, we have safely administered a combination treatment of doxorubicin and S9788 to 39 patients, and with the doses used relevant concentrations of S9788 were achieved. However, because of the unpredictable occurrence of cardiac arrhythmias, the company has decided to withdraw the drug S9788 from further clinical development.

ACKNOWLEDGEMENTS

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