Resistance to chemotherapy agents is a major obstacle to successful treatment of malignancies. Multidrug resistance, which shows, regardless of its different mechanisms of action, cross-resistance to the major anticancer agents, including anthracyclines, alkaloids, podophyllotoxins, and taxanes, is one of the significant obstacles to cancer chemotherapy. Such a resistance can be observed in cancer cells after repeated chemotherapy (acquired resistance), or in cancer cells which may have already been resistant (refractory) before initiation of chemotherapy (intrinsic resistance), typically described in refractory cancer such as pancreatic cancer (1). The effectiveness of natural product–derived anticancer drugs is limited by the ability of many cancer cells to display an intrinsic or acquired multidrug resistance phenotype. Multidrug resistance is often associated with the expression of transmembrane efflux proteins resulting in a decreased drug accumulation (2). Among the family of ATP-binding cassette proteins, the Pgp170 is the most extensively characterized. Expression of this protein is sufficient to confer multidrug resistance in cell culture and in animal models of human cancers (3). Attempts to improve anticancer therapy by coadministration of P-glycoprotein inhibitors to date have been disappointing (4). However, many of the earliest P-glycoprotein inhibitors were compounds developed for other clinical uses and lacked sufficient potency and/or specificity to adequately test a clinical hypothesis. Many exhibited nontargeted related toxicities that compromised the achievement of therapeutic exposures (5).

MS209 was developed specifically as a selective P-glycoprotein inhibitor (Fig. 1; ref. 6). MS209 alone had no antitumor activity. The metabolites of MS209 showed marginal enhancement of efficacy of antitumor agents and no significant cellular toxicity. In preclinical models, MS209 enhanced antitumor effects of anticancer agents including Adriamycin, vincristine, paclitaxel, and docetaxel multidrug resistant tumor cell lines (7). It also enhanced the efficacy of anticancer agents against cancer cells sensitive to anticancer agents. MS209 in combination with Adriamycin was more effective than Adriamycin alone against transplanted murine tumors, multidrug-resistant murine tumors, and human tumors transplanted to nude mouse (8). The efficacy is considered to be due to an increase of Adriamycin concentration in tumor tissue.
When taken together, these characteristics indicate that MS209 warrants investigation in reversing clinical drug resistance mediated by P-glycoprotein. For docetaxel, the 170-kDa P-glycoprotein, encoded by the MDR-1 gene, is one of the mechanisms conferring resistance (9, 10). Therefore, we initiated a phase I trial designed to determine the safety and tolerability of MS209 when given in combination with docetaxel. The study was also designed to evaluate whether biologically effective plasma concentrations of MS209 could be achieved in cancer patients who received the drug orally and the effects of MS209 on docetaxel pharmacokinetics and toxicity.

**Patients and Methods**

**Patient selection.** Patients who were at least 18 years of age and met all the following criteria were eligible for the study: (a) histologically confirmed diagnosis of any malignant solid tumor (except gastric carcinoma), (b) no previous treatment with docetaxel, (c) absence of any digestive disease that hampers the absorption, (d) prior radiation therapy and chemotherapy completed at least 4 weeks before study enrollment (6 weeks if prior treatment was nitrosourea or mitomycin C), (d) performance status of 0 to 2 on the Eastern Cooperative Oncology Group Scale, (e) estimated life expectancy of at least 16 weeks, (f) performance status of 0 to 2 on the Eastern Cooperative Oncology Group Scale, (g) absence of all the following criteria were eligible for the study: (a) adequate bone marrow and major organ function (neutrophils ≥1.5 × 10^9 cells/L; platelets ≥100 × 10^9 cells/L; hemoglobin ≥9.5 g/L; bilirubin ≤1.5 upper limit of normal alanine transaminase and aspartate transaminase ≤2.5 upper limit of normal, serum creatinine ≤1.4 mg/dL). All patients must use effective contraception if of reproductive potential. Females must not be pregnant or lactating. This study was done in two French centers (Institut Curie and Centre Oscar Lambret) and was approved by the Institutional Review Board and Ethics Committee. Written informed consent was obtained from all patients. This study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice ICH guidelines and French regulatory requirements.

**Trial design.** This trial was a prospective phase I, with escalated multiple dose levels following the modified Fibonacci model. Patients were entered in the study in cohorts of three and received treatment during multiple cycles of 21 days. In vitro preclinical studies, 300 mg per body was the minimal dose where the plasma concentration reached the level over 3 μmol/L at which the multidrug resistance-reversal effect was observed. This dose was also used in former phase I and early phase II trials done in Japan. Thus, starting dose of MS209 was fixed at 300 mg. Starting dose of docetaxel (single agent) was 60 mg/m² instead of the standard dose of 100 mg/m², to reduce possible toxicity at the start. Once the maximum dose of MS209 was proven to cause no dose limiting toxicities the dose of docetaxel was raised to its standard level.

Dose escalation of both MS209 and docetaxel was done with docetaxel dose ranging from 60 to 80 mg/m² and MS209 dose ranging from 300 to 1,200 mg per body (Table 1), based on assessment of toxicity observed at cycle 2 when MS209 is introduced. Evaluation done during treatment included weekly physical examinations, complete blood counts, and serum biochemistry analyses. Dose-limiting toxicities for the combination of MS209 and docetaxel (determined during cycle 2) was defined as grade ≥3 nonhematologic toxicity (according to the National Cancer Institute Common Toxicity Criteria version 2.3, excluding alopecia, nausea or vomiting) or grade 4 neutropenia lasting ≥7 days, grade 4 thrombocytopenia, and febrile neutropenia defined as grade 4 neutropenia for 3 days and fever ≥38.5°C for 1 day. If dose-limiting toxicity occurred in one of the first three patients treated at a given dose level, three additional patients were to be treated at that dose level. If none of these additional patients experienced a dose-limiting toxicity, dose escalation was to continue. If dose-limiting toxicity occurred in two of six patients, dose escalation was stopped. The maximum tolerated dose and the recommended dose for further development was defined as one dose level lower than the dose level at which at least two of six patients experienced dose-limiting toxicity. Both maximum tolerated dose and dose-limiting toxicity were documented in patients who received at least two cycles of protocol treatment.

**Treatment and clinical evaluation.** At cycle 1, docetaxel alone was given as 1-hour infusion. From cycle 2, patients received MS209 by oral administration 30 minutes before the infusion of docetaxel. The following docetaxel premedication was given to all patients: dexamethasone 8 mg oral – 13. – 7, and 1 hour before docetaxel then every 6 hours for 2 days after docetaxel infusion. Cycles were done every 3 weeks. Treatment could be extended up to nine cycles in case of clinical benefit.

Tumor response was evaluated after the second cycle of therapy and then every two cycles. Responses were quantified by either physical examination or appropriate imaging according to the Response Evaluation Criteria in Solid Tumors.

**Table 1. Hematologic toxicity at cycle 1 (docetaxel alone)**

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Hematologic toxicity grade 3 (n)</th>
<th>Hematologic toxicity grade 4 (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DL1, 4 patients, MS209 300 mg, docetaxel 60 mg/m²</td>
<td>Neutropenia (2)</td>
<td>Leukopenia (1), neutropenia (1)</td>
</tr>
<tr>
<td>DL2, 3 patients, MS209 300 mg, docetaxel 80 mg/m²</td>
<td>Neutropenia (1), anemia (1)</td>
<td></td>
</tr>
<tr>
<td>DL3, 7 patients, MS209 600 mg, docetaxel 80 mg/m²</td>
<td>Leukopenia (3), neutropenia (2)</td>
<td>Leukopenia (1), neutropenia (2)</td>
</tr>
<tr>
<td>DL4, 10 patients, MS209 900 mg, docetaxel 80 mg/m²</td>
<td>Leukopenia (4), neutropenia (2)</td>
<td>Leukopenia (1), neutropenia (5)</td>
</tr>
<tr>
<td>DL5, 6 patients, MS209 1,200 mg, docetaxel 80 mg/m²</td>
<td>Leukopenia (2), neutropenia (2)</td>
<td>Neutropenia (1)</td>
</tr>
</tbody>
</table>

Abbreviation: DL, dose level.
Pharmacokinetic sampling and assays. Plasma samples were drawn from all patients at cycle 1 (10 samples) and at cycle 2 (11 samples for docetaxel and MS209). Plasma concentrations of both docetaxel and MS209 were determined by the validated high-performance liquid chromatography, and their pharmacokinetic variables were evaluated.

Plasma concentrations of docetaxel and MS209 were determined with an high-performance liquid chromatography analysis system equipped with UV detector with a lowest limit of quantization of 0.02 and 0.005 μg/mL, respectively. Plasma concentrations of MS209 are represented as the free base of MS209.

Pharmacokinetic analysis. Individual plasma concentration-time profiles of both docetaxel and MS209 were analyzed using the software package WinNonlin (Pharasisht Corp., Cary, NC) by determining the slopes of the terminal elimination curves fitted to noncompartmental model, and the terminal elimination rate constant ($\lambda_2$) was determined. $C_{\text{max}}$ (maximum plasma concentration) and $T_{\text{max}}$ (time to reach maximum plasma concentration) were determined by inspection of the observed concentrations. $T_{1/2}$ (terminal half-life), $\text{AUC}_{0\text{-}\text{inf}}$ (area under the plasma concentration-time curve regarded as 0 value. $T_{\text{min}}$ (time to reach minimum plasma concentration) was determined by inspection of the observed concentrations. $T_{1/2}$ (terminal half-life), $\text{AUC}_{0\text{-}\text{inf}}$ (area under the plasma concentration-time curve regarded as 0 value.

Results

Patient characteristics. Thirty patients were enrolled in the trial. Median age was 55.5 years (range, 18-68 years). The patients had a variety of tumor types: breast cancer ($n = 9$ patients), colorectal ($n = 5$), head and neck ($n = 5$), lung ($n = 3$), osteosarcoma ($n = 2$), cervix ($n = 2$), ovary ($n = 1$), pancreatic ($n = 1$), and unknown ($n = 2$). Metastatic disease was present in all patients. All patients had received chemotherapy previously (25 for advanced disease) and 26 patients had received prior radiation therapy.

Toxicity. Dose escalation was dependent on toxicities attributable to MS209 and docetaxel combination. A total number of 131 cycles was given (median, 4; range, 1-9).

Docetaxel dosing began at 60 mg/m$^2$ and was escalated to 80 mg/m$^2$. There were few significant hematologic toxicities attributable to docetaxel alone (cycle 1) or to the combination of docetaxel with MS209 (cycles 2 and higher; Tables 1 and 2). One patient enrolled in cohort 1 (docetaxel, 60 mg/m$^2$ and MS209, 300 mg) experienced grade 4 neutropenia in cycle 1 lasting >7 days. Thus, this patient was replaced. However, as the patient had recovered from toxicity at day 21, it was decided to treat her with the combination at cycle 2. Interestingly this patient did not present grade 4 neutropenia in the subsequent eight cycles and experienced complete clinical response of her breast metastasis. Analysis of mean nadir counts for neutrophils and platelets during cycles 1 and 2 suggests that concurrent oral administration of MS209 does not alter the hematologic toxicity associated with docetaxel.

Significant nonhematologic toxicities associated with docetaxel or the combination docetaxel and MS209 were also uncommon (Table 2). At dose level 5, two patients experienced a dose-limiting toxicity (grade 3 anorexia, grade 3 fatigue, and grade 3 stomatitis in one patient; grade 4 stomatitis, grade 4 dysphagia, and dehydration in the other

### Table 2. Toxicity at cycle 2 (MS 209 + docetaxel)

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Biological toxicity (n)</th>
<th>Nonbiological toxicity (n)</th>
<th>Dose-limiting toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3</td>
<td>Grade 4</td>
<td>Grade 3</td>
</tr>
<tr>
<td>DL1, 4 patients, MS209 300 mg, docetaxel 60 mg/m$^2$</td>
<td>Neutropenia (1), leukopenia (2)</td>
<td>Neutropenia (1)</td>
<td>—</td>
</tr>
<tr>
<td>DL2, 3 patients, MS209 300 mg, docetaxel 80 mg/m$^2$</td>
<td>Anemia (1), GT (1)</td>
<td>—</td>
<td>Fatigue (1)</td>
</tr>
<tr>
<td>DL3, 7 patients, MS209 600 mg, docetaxel 80 mg/m$^2$</td>
<td>Neutropenia (3), leukopenia (4)</td>
<td>Neutropenia (4), leukopenia (2)</td>
<td>Fatigue (1), stomatitis (1), infection (1)</td>
</tr>
<tr>
<td>DL4, 10 patients, MS209 900 mg, docetaxel 80 mg/m$^2$</td>
<td>Neutropenia (2), leukopenia (2), anemia (1), hyponatremia (1)</td>
<td>Neutropenia (3), leukopenia (2)</td>
<td>Stomatitis (1), dysphagia (1), fatigue (1)</td>
</tr>
<tr>
<td>DL5, 6 patients, MS209 1,200 mg, docetaxel 80 mg/m$^2$</td>
<td>Neutropenia (1), leukopenia (4), GT (1)</td>
<td>Neutropenia (4), leukopenia (2)</td>
<td>Fatigue (2), odynophagia (1), dehydration (1)</td>
</tr>
</tbody>
</table>

Abbreviation: DL, dose level.
one). At dose level 4, initially six patients were treated. Following the two dose-limiting toxicities observed at dose level 5, dose level 4 was defined as the recommended dose and four more patients had been included at this dose.

**Antitumor responses.** Among the 28 patients evaluable for antitumor responses, one patient experienced a complete response to therapy. This patient had recurrent and metastatic breast cancer with skin, lymph node, and lung involvement. She had previously received neoadjuvant chemotherapy (paclitaxel-doxorubicin) as well chemotherapy for metastatic disease (5-fluorouracil-vinorelbine, FEC regimen), cytotoxic agents known to induce multidrug resistance. Two patients experienced a partial response (larynx and breast carcinoma). Fourteen patients had stable disease as best response to treatment including seven patients who received 6 cycles of therapy.

**Pharmacokinetics.** Plasma concentrations of both docetaxel and MS209 were measured using validated high-performance liquid chromatography method.

From dose level 3, the systemic exposure of docetaxel increased after combined treatment with MS209. At cycle 1, the mean maximum concentration was measured at the end of infusion at one hour. At cycle 2, the mean C_{max} was nearly identical with the mean C_{max} at C1 and was reached 1 hour after the start of infusion. From dose level 3 onwards, 1.5-fold higher AUC data of docetaxel were observed after combined treatment with MS209 (Table 3; Fig. 2).

Plasma levels of MS209 increased proportionally with increased doses (Table 4). At dose levels 4 and 5, mean C_{max} data of MS209 were reached ~2 hours after dosing. Subsequently, plasma levels declined with a mean terminal half-life of 2.8 hours (dose level 4) or 3.52 hours (dose level 5).

**Discussion**

Recently, second- or third-generation multidrug resistance–modulating agents have entered clinical trials. These agents, such as valsapodar (PSC-833) and biricodar (VX-710) are characterized by enhanced potency against P-glycoprotein with less nontargeted related toxicities. Valspodar is perhaps the most extensively studied P-glycoprotein modulator in the clinic to date. With administration of valsapodar, plasma concentrations able of inhibiting P-glycoprotein in vivo can be attained consistently (11, 12). However, significant alterations of the clearance of cogiven chemotherapeutic agents with consequent

---

**Table 3. Pharmacokinetic variables of docetaxel**

<table>
<thead>
<tr>
<th>Dose level</th>
<th>DL1, MS209</th>
<th>DL2, MS209</th>
<th>DL3, MS209</th>
<th>DL4, MS209</th>
<th>DL5, MS209</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients</td>
<td>4</td>
<td>3</td>
<td>7</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>AUC_{0-24h} (µg h/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C1</td>
<td>2.53 (0.91-4.12)</td>
<td>3.32 (2.21-5.52)</td>
<td>2.75 (2.33-3.73)</td>
<td>2.82 (1.26-4.86)</td>
<td>2.89 (1.51-5.02)</td>
</tr>
<tr>
<td>C2</td>
<td>1.69 (1.25-2.16)</td>
<td>2.42 (1.27-3.70)</td>
<td>3.81 (2.20-5.92)</td>
<td>5.53 (2.51-11.7)</td>
<td>4.46 (2.57-11.03)</td>
</tr>
<tr>
<td>C_{max} (µg/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C1</td>
<td>2.31 (1.30-2.96)</td>
<td>2.64 (1.85-4.15)</td>
<td>2.78 (2.07-3.5)</td>
<td>2.77 (1.40-4.14)</td>
<td>2.71 (1.44-4.26)</td>
</tr>
<tr>
<td>C2</td>
<td>2.04 (1.47-2.52)</td>
<td>2.16 (1.07-3.29)</td>
<td>3.87 (1.98-3.42)</td>
<td>3.82 (1.87-3.72)</td>
<td>2.76 (1.74-4.67)</td>
</tr>
<tr>
<td>Cl (L/h/m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C1</td>
<td>15.2</td>
<td>15</td>
<td></td>
<td>25.7 (23.7-29)</td>
<td>NC</td>
</tr>
<tr>
<td>C2</td>
<td>—</td>
<td>—</td>
<td>18.2 (14.6-18.2)</td>
<td>15.5 (8.64-31.6)</td>
<td>NC</td>
</tr>
<tr>
<td>T_{1/2} (h)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C1</td>
<td>3.37</td>
<td>2.35</td>
<td>—</td>
<td>0.60</td>
<td>0.21 (0.18-0.24)</td>
</tr>
<tr>
<td>C2</td>
<td>—</td>
<td>—</td>
<td>1.63 (0.60-2.21)</td>
<td>1.63 (0.98-2.29)</td>
<td>NC</td>
</tr>
</tbody>
</table>

NOTE: C1: docetaxel alone; C2: docetaxel + MS209.
Abbreviations: NC, not calculated (due to lack of sufficient data points), DL, dose level.

* Data available in six of seven patients.
† Data available in one patient.
‡ Data available in three of seven patients.
increases in overall exposure required dose reductions of the cytotoxic agent given concurrently. In a study of valsapar given with doxorubicin, valsapar administration resulted in an ~30% decrease in doxorubicin clearance, significant increases in the AUC of doxorubicin (13). The extent to which the pharmacokinetic interactions observed are related to P-glycoprotein interactions versus inhibition of other ATP-binding drug transporters (such as MRPs) or metabolic pathways (such as CYP3A) is not fully understood. Randomized clinical trials in which valsapar was combined with dose-reduced cytotoxic agents have yielded disappointing results to date (14, 15).

For MS209, pharmacokinetic interactions were not detectable in preclinical studies done. This trial was designed to assess whether MS209 enhanced the known toxicities of docetaxel. No significant differences were observed in docetaxel-induced nadir neutrophil and platelet counts in the absence or presence of MS209. However, pharmacokinetic data showed an increased docetaxel AUC with higher dosages of MS209.

Recently, some data suggested that the efficacy of systemic treatment with docetaxel may be limited against tumor or metastasis in the brain (16, 17). Probably, the major cause of this lack of efficiency is the blood-brain barrier that restricts the penetration of drugs into the brain. An important component of the brain barrier is P-glycoprotein. Inhibition of P-glycoprotein may, therefore, be an attractive strategy for increasing the penetration of docetaxel into the brain (18). However, tumor cell resistance to docetaxel may also result from several mechanisms, including insufficient cellular accumulation, mutations of the β-tubulin binding site, altered β-tubulin isotype expression, or defective apoptotic signaling (19).

In summary, this study showed that MS209 can be given safely in combination with docetaxel. The results of this study support for further investigation of the combination of oral MS209 with docetaxel.

Acknowledgments

We thank W. Sato and C. Zurch (Nihon Schering) for sponsoring the trial and supplying MS209 and N. Blanchard (Institut Curie, France), Y. Vendel (Centre Oscar. Lambret, France), B. Baron, S. Mali, and P. Nguyen (European Organization for Research and Treatment of Cancer Data Center) for their help in data management.

References

Phase I Combining a P-Glycoprotein Inhibitor, MS209, in Combination with Docetaxel in Patients with Advanced Malignancies

Véronique Diéras, Jacques Bonneterre, Valérie Laurence, et al.


Updated version
Access the most recent version of this article at:
http://clincancerres.aacrjournals.org/content/11/17/6256

Cited articles
This article cites 15 articles, 7 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/11/17/6256.full.html#ref-list-1

Citing articles
This article has been cited by 3 HighWire-hosted articles. Access the articles at:
/content/11/17/6256.full.html#related-urls

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.