Coadministration of Oral Cyclosporin A Enables Oral Therapy with Paclitaxel

Jetske M. Meerum Terwogt, Mirte M. Malingré, Jos H. Beijnen, Wim W. ten Bakkel Huinink, Hilde Rosing, Franciska J. Koopman, Olaf van Tellingen, Martha Swart, and Jan H. M. Schellens

Department of Medical Oncology, The Netherlands Cancer Institute/ Antoni van Leeuwenhoek Hospital, 1066 CX Amsterdam [J. M. M. T., M. M. M., J. J. H. B., W. W. t. B. H., O. v. T., M. S., J. H. M. S.]; Department of Pharmacy and Pharmacology, The Netherlands Cancer Institute/Slotervaart Hospital, 1066 EC Amsterdam [J. M. M. T., M. M. M., J. H. B., H. R., F. J. K.]; and Department of Pharmaceutical Analysis and Toxicology, Faculty of Pharmacy, State University of Utrecht, 3584 CG Utrecht [J. H. B.], the Netherlands

ABSTRACT

i.v. paclitaxel is inconvenient and associated with significant and poorly predictable side effects largely due to the pharmaceutical vehicle Cremophor EL. Oral administration may be attractive because it may circumvent the use of Cremophor EL. However, paclitaxel, as well as many other commonly applied drugs, has poor bioavailability caused by high affinity for the mdr1 P-glycoprotein drug efflux pump, which is abundantly present in the gastrointestinal tract. Consequently, inhibition of P-glycoprotein by oral cyclosporin A (CsA) should increase systemic exposure of oral paclitaxel to therapeutic levels. A proof-of-concept study was carried out in 14 patients with solid tumors. Patients received one course of oral paclitaxel of 60 mg/m² with or without 15 mg/kg CsA and with i.v. paclitaxel in subsequent courses. The pharmacokinetics of paclitaxel and its major metabolites were determined during the first two courses. In addition, levels of CsA, Cremophor EL, and ethanol were measured. Bioavailability of oral paclitaxel in combination with CsA was 8-fold higher than after oral paclitaxel alone (P < 0.001). Therapeutic concentrations were achieved on average during 7.4 h, which is comparable with an equivalent i.v. dose. The oral combination was well tolerated and did not induce gastrointestinal toxicity or myelosuppression. Cremophor EL plasma levels after oral drug administration were undetectable. In conclusion, coadministration of oral CsA increased the systemic exposure of oral paclitaxel from negligible to therapeutic levels. The combination enables treatment with oral paclitaxel. Undetectable Cremophor EL levels after oral administration may have a very beneficial influence on the safety of the treatment with oral paclitaxel.

INTRODUCTION

Paclitaxel is an important new antitumor agent widely used in the treatment of advanced breast and ovarian cancer (1–3). However, i.v. administration of paclitaxel is inconvenient for patients and associated with significant and unpredictable side effects (4–6). The current commercially available i.v. formulation consists of a mixture of ethanol and Cremophor EL (polyoxyethylene glycerol triricinoleate 35), and it is now well established that the latter plays a major role in the hypersensitivity reactions observed after i.v. administration of paclitaxel (7, 8). Cremophor EL is also responsible for the nonlinear tissue distribution of paclitaxel (9). Oral administration of paclitaxel is to be preferred as it may circumvent the use of Cremophor EL. Paclitaxel, however, has poor bioavailability because of its high affinity for the multidrug transporter P-gp, which is abundantly present in the gastrointestinal tract (10–18). P-gp in the mucosa of the small and large intestine may limit the oral uptake of paclitaxel and mediate direct excretion of the drug in the intestinal lumen (19). This became clear when we investigated the oral uptake of paclitaxel in mdr1a (−/−) knockout mice lacking functional P-gp in the gut. In this mouse model, the systemic exposure was 6-fold higher than in wild-type mice. High systemic availability could also be achieved in wild-type mice when paclitaxel was administered p.o. in combination with SDZ PSC 833 or with CsA, both of which are efficacious P-gp inhibitors (10). On the basis of these results, we hypothesized that the systemic exposure in humans after oral administration of paclitaxel might be increased with p.o. administered CsA hopefully to therapeutic plasma drug concentrations. To investigate this, a proof-of-concept study in patients with solid tumors was initiated.

PATIENTS AND METHODS

Patients with a histological proof of cancer for whom no standard therapy of proven benefit existed were eligible for the study. Previous radiotherapy or chemotherapy other than taxoid therapy was allowed as long as the last treatment was at least 4 weeks before study entry, and any resulting toxicities were resolved. Patients had to have acceptable bone marrow (WBC, >3.0 × 10⁹/liter; platelets, >100 × 10⁹/liter), liver (serum bilirubin, ≤25 μmol/liter; serum albumin, ≥25 g/liter) and kidney (serum creatinine, ≤160 μmol/liter or clearance, ≥50

Received 2/11/99; revised 5/25/99; accepted 5/25/99.

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

1 To whom requests for reprints should be addressed, at The Netherlands Cancer Institute/Slotervaart Hospital, Department of Pharmacy and Pharmacology, Louwesweg 6, 1066 EC Amsterdam, the Netherlands. Phone: 31-20-512-4657; Fax: 31-20-512-4753; E-mail: apjmt@slz.nl.

2 The abbreviations used are: P-gp, P-glycoprotein; CsA, cyclosporin A; AUC, area(s) under the (concentration-time) curve.
ml/min) functions and a WHO performance status ≤2. Patients were excluded if they suffered from uncontrolled infectious disease, neurological disease, bowel obstruction, or brain metastases. Additional exclusion criteria were concomitant use of known P-gp inhibitors, CYP3A-substrates, H2-receptor antagonists, or proton pump inhibitors. The trial was approved by the ethics committee of the institute, and all of the patients gave written informed consent.

In the first part of the study, it was planned that a small cohort of four evaluable patients would receive paclitaxel p.o. as a single agent at a dose of 60 mg/m² during course 1 and paclitaxel i.v. at a dose of 175 mg/m² administered as a 3-h infusion during course 2. In the second part of the study, it was planned that eight evaluable patients would receive paclitaxel on two randomized occasions. On one occasion, they would receive paclitaxel p.o. at a dose of 60 mg/m² combined with a single oral dose of CsA of 15 mg/kg. This low oral dose was selected for safety reasons because the results in mice indicated increased systemic exposure to paclitaxel after oral administration combined with CsA as compared with i.v. administration of paclitaxel alone. Paclitaxel (Paxene) and CsA (Neoral) were ingested as oral solutions with 100 ml of tap water. Paclitaxel was taken 10 min after CsA. On the other occasion, paclitaxel would be administered as a 3-h infusion at a dose of 175 mg/m² without CsA. The oral and i.v. dosages were administered at 9:00 a.m. after an overnight fast. A standard breakfast was served at 2 h after paclitaxel administration. The i.v. formulation of paclitaxel [Paxene, i.e., paclitaxel (6 mg/ml), dissolved in Cremophor EL and ethanol 1:1 v/v, Baker Norton, Miami, FL] was used for both i.v. and oral administration. On all occasions, patients were premedicated with dexamethasone (20 mg) p.o. 12 and 6 h before, clemastine (1 mg) i.v. 30 min before, and ranitidine (50 mg) i.v. shortly before paclitaxel administration. If it was in their best interest, all of the patients continued on a 3-weekly schedule of i.v. paclitaxel at a dose of 175 mg/m².

Pharmacokinetic monitoring of paclitaxel and its major metabolites (6α-hydroxypaclitaxel, 3′p-hydroxypaclitaxel and 6α,3′p-dihydroxypaclitaxel) was performed during the first two courses. Whole blood samples of 5 ml each were collected at 15 time points up to 48 h after paclitaxel administration. After centrifugation plasma was stored at −20°C and analyzed within 4 weeks using a validated high-performance liquid chromatographic assay (20, 21). Noncompartmental pharmacokinetic methods were applied to interpret the results (22). The AUC of paclitaxel was calculated, using the trapezoidal rule without extrapolation to infinity. To compare the systemic exposure after oral and i.v. administration of paclitaxel, the ratio of the median value of the AUC after oral and i.v. administration was calculated and corrected for the difference in dose, using the following formula:

\[ F = \frac{\text{AUC oral paclitaxel}}{\text{AUC i.v. paclitaxel}} \times \frac{175}{60} \]

Other parameters to be assessed were the maximal plasma concentration of paclitaxel (C_{max}), the time to maximal plasma concentration (T_{max}), total plasma clearance after i.v. administration (CL), terminal half-life (t_{1/2}), and volume of distribution at steady state (V_{ss}). The terminal t_{1/2} was calculated as ln 2/k, where k is the rate constant of the terminal phase (h⁻¹) of the plasma concentration-time curve. C_{max} and T_{max} were determined graphically. Statistical analysis of the data were performed using SPSS/PC+ (SPSS/PC+ Advanced Statistics, version 6.1, 1994; Chicago, IL). Nonparametric tests (Mann-Whitney U-test) were used for comparison of the oral and i.v. results.

The AUCs of the metabolic products were determined using the trapezoidal rule without extrapolation to infinity. The C_{max} and the T_{max} are the highest measured values and the T_{det} represents the duration that the metabolites could be detected in plasma. Additionally, relationships between metabolite concentrations and paclitaxel concentrations were evaluated by calculation of the ratios of the mean AUC of the metabolites and the mean AUC of paclitaxel.

Concentrations of CsA (in whole blood), Cremophor EL (in plasma), and ethanol (in plasma) at different time points were measured according to validated methods. Concentrations of CsA and Cremophor EL were measured at the time points corresponding with the time points of the paclitaxel sampling, and ethanol concentrations were measured at three separate time points: 15 min, 30 min, and 1 h after oral administration of paclitaxel with CsA. Cremophor EL was quantified using a high-performance liquid chromatographic assay, as described previously (24) with minor modifications. CsA was measured with a fluorescence polarization immuno assay (Ref. 25, Abbott TDx-FLx, Amstelveen, the Netherlands), and ethanol was quantitatively determined by gas chromatography.

**RESULTS**

In total, 14 patients were enrolled in the study. Patient characteristics are outlined in Table 1. Three patients went off-study before they had received paclitaxel i.v. in a second course because of rapid disease progression. Five patients received oral paclitaxel at a dose of 60 mg/m² without CsA during the first course, and three of them received i.v. paclitaxel during course 2 and subsequent courses. Five other patients received oral paclitaxel at a dose of 60 mg/m² in combination with CsA.
at a dose of 15 mg/kg at the first course, and, in four patients, this was followed by i.v. administration of paclitaxel during course 2 and subsequent courses. The remaining four patients started with i.v. paclitaxel during the first course, followed by oral paclitaxel and CsA during the second course. During all of the subsequent courses, paclitaxel was administered i.v. Table 2 summarizes the main pharmacokinetic parameters. The mean AUC in patients who received oral paclitaxel in combination with CsA was 1.7 µM.h (± 0.9), which is approximately 8-fold higher than the mean AUC of 0.2 µM.h (± 0.1) in patients who received oral paclitaxel without CsA (P < 0.001; Fig. 1). The mean AUC in the five patients who started with oral paclitaxel + CsA was not significantly different from the mean AUC in the four patients who received oral paclitaxel + CsA at the second course. The dose-corrected ratio of mean AUC values of oral paclitaxel and i.v. paclitaxel was 0.036 and of oral paclitaxel + CsA and i.v. paclitaxel 0.282, respectively. However, because of the nonlinear pharmacokinetics of paclitaxel caused by Cremophor EL effects, this calculation results in an underestimation of the true bioavailability (9, 26). In a dose-finding study performed by Huizing et al., a mean AUC of i.v. paclitaxel at a dose of 100 mg/m² of 5.8 h.µM was reported (23). Recalculation of the above ratios applying the dose-adjusted AUC found by Huizing et al. provided values of 0.059 for the ratio of oral paclitaxel:i.v. paclitaxel and 0.474 for the ratio of oral paclitaxel + CsA:i.v. paclitaxel. The mean time of the paclitaxel plasma concentration above a previously defined level of 0.05 µM was 1.2 (± 0.9) h after oral paclitaxel and 7.4 (± 4.4) h after oral paclitaxel plus CsA (P < 0.001). The mean duration of plasma levels above 0.1 µM was 3.7 (± 2.2) h after oral paclitaxel with CsA, and this threshold was not reached after oral paclitaxel alone. CL after i.v. paclitaxel was 13 (± 3) liter/m²/h in three patients who had received oral paclitaxel without CsA at the first course and 12 (± 2) liter/m²/h in the eight other patients [not statistically significant (NS)]. The terminal t₁/₂ of i.v. paclitaxel in the two groups of patients was 17.7 (± 2.7) h (n = 3) and 16.3 (± 10.5) h [n = 8 (NS)]. The difference in Vₚ was also not statistically significant in the two groups of patients and was 69 (± 27) liter/m² (n = 3) and 86 (± 62) liter/m² (n = 8). The i.v. pharmacokinetic data are in good agreement with earlier observations (1, 23).

Plasma metabolite concentrations after i.v. paclitaxel as well as after oral paclitaxel with CsA showed large interpatient variability. After oral administration of paclitaxel alone, metabolites could not be detected. The mean pharmacokinetic parameters of the metabolites after oral administration of paclitaxel with CsA and after i.v. administration are represented in Table 3. After oral administration with CsA, the mean peak plasma concentration ratios of 6α-hydroxypaclitaxel, 3’p-hydroxypaclitaxel, and 6α,3’p-dihydroxypaclitaxel to paclitaxel were 0.78,
Coadministration of CsA with Oral Paclitaxel
per patient was four (range, one to eight). Flushing grade 2 in another patient. Mild nausea grade 1 (4 of 0.06, and 0.26, respectively. After i.v. administration, these values were 0.08, 0.03, and 0.04. For the AUCs, these ratios were 0.87, 0.16, and 0.44 after oral administration with CsA and 0.06, 0.03, and 0.04 after i.v. administration. Significant increases in metabolite:paclitaxel ratios were observed after oral administration compared with i.v. administration (P < 0.001). All three of the metabolites could be detected in plasma for only a limited period of time.

Whole blood CsA concentrations were measured in seven patients. Maximum CsA concentrations ranged from 2.1 mg/liter to 4.7 mg/liter (mean, 3.0 mg/liter) and were reached at 3–4 h after intake. The concentrations 10 h after intake ranged from 0.3–1.3 mg/liter (mean, 0.7 mg/liter). Cremophor EL levels in plasma after oral administration of paclitaxel with or without CsA were lower than the lower limit of quantitation of the assay of 0.05 µM (24). Ethanol concentrations were measured in seven patients, and the highest detected ethanol concentration in plasma was 0.11‰, which was found in three patients 13 min after paclitaxel intake. Paclitaxel in the oral formulation with or without CsA had a bitter taste but was very well tolerated. No significant side effects were seen after one course of oral paclitaxel with or without CsA. A pattern of toxicity common to paclitaxel developed after two to three i.v. courses. CTC grade 2 myalgia was observed in 7 (50%) patients, and grade 1 neurotoxicity occurred after two to three i.v. courses. CTC grade 2 myalgia was also seen in another patient. Mild nausea grade 1 (4 patients) and vomiting grade 1 (3 patients) were observed but only after i.v. paclitaxel. At present, 5 of the 14 patients are still on study. A total of 61 courses of paclitaxel have been administered, 14 of which were oral. The median number of courses per patient was four (range, one to eight).

DISCUSSION
The results presented above prove that the coadministration of a P-gp inhibitor significantly increases the systemic exposure of p.o. administered paclitaxel. Paclitaxel administered p.o. as a single agent without CsA exhibits poor apparent bioavailability of only 4% of the exposure after i.v. administration. Coadministration of CsA increased the systemic exposure of paclitaxel up to 28%. However, the true oral bioavailability may be significantly underestimated because paclitaxel clearly shows pronounced nonlinear pharmacokinetics due to the presence of Cremophor EL (9, 26). Recalculation of these figures using the AUC of i.v. paclitaxel at a lower dose (23), which is more realistic for comparison purposes, resulted in an apparent bioavailability of 47% after administration of oral paclitaxel with CsA. An important pharmacokinetic parameter is the time-period of exposure above a certain paclitaxel threshold concentration. Earlier data indicate a strong positive relationship between the duration of the paclitaxel plasma concentration above 0.05 µM or 0.1 µM and pharmacological activity (23, 26). The frequently applied i.v. dose of paclitaxel of 175 mg/m² resulted in a time-period above 0.05 µM of 28.1 (± 8.9) h. Even at the low oral dose of 60 mg/m² applied in our study, plasma concentrations higher than 0.05 µM were achieved during 7.4 (± 4.4) h. Our preclinical data obtained in wild-type and P-gp-negative mdr1a knockout mice, combined with these first clinical results, reveal that CsA increases the absorption of paclitaxel by effectively blocking P-gp in the gut. A second mechanism that may contribute to the increased systemic exposure is an inhibition of paclitaxel metabolism by CsA, because paclitaxel and CsA are both substrates for the cytochrome F₄₅₀ (CYP) 3A4-isozymes (27, 28). The three main metabolites of paclitaxel are 6α-hydroxypaclitaxel, 3’p-hydroxypaclitaxel, and 6α,3’p-dihydroxypaclitaxel and are formed via CYP 2C8, CYP 3A4, and both CYP 2C8 and 3A4, respectively (Fig. 2; Ref. 29). All of the metabolites showed reduced in vitro cytotoxicity as compared with paclitaxel (30). Competition for CYP 3A4 by CsA may result in altered ratios between the metabolite levels. This hypothesis was supported by our data. Oral administration of paclitaxel with CsA resulted in an increase in the AUC ratio metabolite:paclitaxel for all three of the metabolites. However, a relative larger increase (15-fold) in the AUC ratio 6α-hydroxypaclitaxel:paclitaxel and 6α,3’p-dihydroxypaclitaxel:paclitaxel is observed in comparison with the AUC ratios of 3’p-hydroxypaclitaxel:paclitaxel and 6α,3’p-dihydroxypaclitaxel:paclitaxel (a 5- and 11-fold increase, respectively). Increased metabolism of paclitaxel after oral administration can be explained by the relatively higher amount of paclitaxel passing the liver (first-pass effect). Additionally, metabolism of paclitaxel in the intestinal wall may contribute to the increased metabolite levels. Increased metabolism after oral administration may indeed result in diminished levels of the active drug and, possibly, reduced efficacy. However, in our

| Table 3 | Pharmacokinetics of paclitaxel metabolites: main pharmacokinetic parameters of 6α-hydroxypaclitaxel, 3’p-hydroxypaclitaxel, and 6α,3’p-dihydroxypaclitaxel in plasma, represented as means (±SD) |
|----------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
|          | n   | Tₜₜₜ (h) | Tₘₘₘ (h) | Cₘₘₘ (µM) | AUC (µM ⋅ h) | Ratio AUC metabolite: AUC paclitaxel |
| 6α-hydroxypaclitaxel |          |          |          |          |          |          |
| oral paclitaxel + CsA | 9   | 11.7 (±7.9) | 4.2 (±1.8) | 0.18 (±0.11) | 1.25 (±1.23) | 0.87 |
| i.v. paclitaxel | 8   | 7.4 (±9.0) | 3.2 (±0.2) | 0.37 (±0.34) | 1.05 (±1.29) | 0.06 |
| 3’p-hydroxypaclitaxel |          |          |          |          |          |          |
| oral paclitaxel + CsA | 9   | 6.8 (±6.8) | 4.1 (±1.3) | 0.03 (±0.02) | 0.22 (±0.02) | 0.16 |
| i.v. paclitaxel | 8   | 7.6 (±8.8) | 3.3 (±0.2) | 0.14 (±0.11) | 0.56 (±0.71) | 0.03 |
| 6α,3’p-dihydroxypaclitaxel |          |          |          |          |          |          |
| oral paclitaxel + CsA | 9   | 10.7 (±8.3) | 6.4 (±2.0) | 0.06 (±0.04) | 0.62 (±0.59) | 0.44 |
| i.v. paclitaxel | 8   | 5.7 (±9.5) | 3.7 (±0.5) | 0.18 (±0.31) | 0.67 (±1.38) | 0.04 |
opinion, the achieved gain in increased uptake outweighs the possible loss by the increased metabolism.

A plausible explanation for the relative larger increase in 6α-hydroxypaclitaxel levels may be that competitive inhibition of CYP 3A4 by CsA results in relatively less formation of 3′-p-hydroxypaclitaxel and 6α,3′-p-dihydroxypaclitaxel. Consequently, metabolism of paclitaxel by CYP 2C8 is favored, resulting in increased formation of 6α-hydroxypaclitaxel. Thus, as CsA interferes with CYP-mediated metabolism of paclitaxel, decreased elimination by inhibition of the metabolic enzymes may contribute to the observed increase in systemic exposure. In addition, Sparreboom et al. (19) showed that direct intestinal excretion of paclitaxel, another important route of drug elimination, is significantly diminished in the absence of P-gp. At present, it is unknown whether involvement of other factors, including drug release from the pharmaceutical formulation (dissolution), modification of biliary excretion, and drug degradation in gastrointestinal fluids, may contribute to the extent of the systemic exposure of p.o. administered paclitaxel.

The single oral dose of 15 mg/kg of CsA resulted in C\textsubscript{max} and trough values that are in the therapeutic range for immunosuppression and may be associated with toxicity, in particular renal dysfunction. However, the available studies of CsA, pharmaceutically formulated in Neoral, are limited (31) and, more importantly, this side effect is mainly associated with CsA when given on a chronic treatment basis. No renal toxicity, or any other side effect clearly associated with the single CsA administration, was observed. The CsA concentrations found in our study were higher than we expected, possibly because of competition for CYP-mediated metabolism by paclitaxel.

Cremophor EL levels could not be detected after oral administration of paclitaxel (dissolved in Cremophor EL-ethanol) as a single agent nor when coadministered with CsA (formulated in alcohol and α-tocoferol). This may be very beneficial for the safety profile of oral paclitaxel because Cremophor EL plays a pivotal role in the hypersensitivity reactions associated with i.v. paclitaxel administration (4–8). The maximum measured ethanol levels of 0.1% are not clinically relevant. Besides a bitter taste, paclitaxel in the oral formulation at a dose of 60 mg/m\textsuperscript{2} was very well tolerated without induction of gastrointestinal or bone marrow toxicity. The main side effects were alopecia and myalgia CTC grade 1 or 2, which developed after 2–3 courses of i.v. paclitaxel. Regarding the nearly uneventful oral administration of the dose of 60 mg/m\textsuperscript{2}, oral doses can be escalated or given b.i.d. to prolong exposure at therapeutic levels. The ultimate goal is to test whether at least equal activity of oral paclitaxel can be obtained, as compared with i.v. paclitaxel, but with better safety. However, coadministration of a P-gp inhibitor may increase paclitaxel levels in brain and heart tissue and may, therefore, enhance the risk of central neurotoxicity or cardiac toxicity (32). Neither in our clinical study nor in animal studies did we observe signs of central neurotoxicity or cardiac toxicity, at least not at the dosages that were used. Furthermore, oral administration opens the opportunity to explore therapeutic activity and safety on a chronic daily treatment schedule. Finally, the concept of modulation of P-gp may well be applied to other drugs, including noncytotoxic agents, which have a high affinity for P-gp and are associated with poor oral bioavailability, e.g., HIV protease inhibitors (33). The knowledge presently gained by the extensive analysis of mdr1a knockout mice has proven to be extremely valuable to the development of new strategies to further optimize drug treatment (34, 35). The improvement of systemic exposure of oral paclitaxel and other drugs as well as the development of an optimal pharmaceutical formulation for oral administration are presently investigated in our institute. On the basis of these early results, oral administration of paclitaxel in combination with CsA may be a realistic alternative to the current treatment modalities. In summary, we have demonstrated for the first time in cancer patients the proof of the concept of efficient oral uptake of paclitaxel, made possible by concomitant administration of the P-gp blocker CsA.

ACKNOWLEDGMENTS

We thank the nurses of the clinical ward for their dedicated contribution to the study and our clinical colleagues for their active support. Paclitaxel (Paxene) was kindly supplied by Baker Norton Pharmaceutical Inc., Miami, FL.

REFERENCES


3 J. van Asperen, A. Sparreboom, O. van Tellingen, and J. H. Beijnen. Cremophor EL masks the effect of mdr1a P-gp on the plasma pharmacokinetics of paclitaxel in mice, submitted for publication.
Coadministration of CsA with Oral Paclitaxel


Coadministration of Oral Cyclosporin A Enables Oral Therapy with Paclitaxel

Jetske M. Meerum Terwogt, Mirte M. Malingré, Jos H. Beijnen, et al.


Updated version
Access the most recent version of this article at:
http://clincancerres.aacrjournals.org/content/5/11/3379

Cited articles
This article cites 29 articles, 7 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/5/11/3379.full.html#ref-list-1

Citing articles
This article has been cited by 27 HighWire-hosted articles. Access the articles at:
/content/5/11/3379.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.