

Influence of Cremophor EL on the Bioavailability of Intraperitoneal Paclitaxel¹

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ABSTRACT

It has been hypothesized that the paclitaxel vehicle Cremophor EL (CrEL) is responsible for nonlinear drug disposition by micellar entrapment. To gain further insight into the role of CrEL in taxane pharmacology, we studied the pharmacokinetics of paclitaxel in the presence and absence of CrEL after i.p. and i.v. dosing. Patients received an i.p. tracer dose of [G - 3 H]paclitaxel in ethanol without CrEL (100 μ Ci diluted further in isotonic saline) on day 1, i.p. paclitaxel formulated in CrEL (Taxol; 125 mg/m²) on day 4, an i.v. tracer of [G - 3 H]paclitaxel on day 22, and i.v. Taxol (175 mg/m²) on day 24. Four patients (age range, 54–74 years) were studied, and serial plasma samples up to 72 h were obtained and analyzed for total radioactivity, paclitaxel, and CrEL. In the presence of CrEL, i.v. paclitaxel clearance was 10.2 ± 3.76 liters/h/m² (mean \pm SD), consistent with previous findings. The terminal disposition half-life was substantially prolonged after i.p. dosing (17.0 ± 11.3 versus 28.7 ± 8.72 h), as was the mean residence time (7.28 ± 2.76 versus 40.7 ± 13.8 h). The bioavailability of paclitaxel was $31.4 \pm 5.18\%$, indicating insignificant systemic concentrations after i.p. treatment. CrEL levels were undetectable after i.p. dosing (<0.05 μ l/ml), whereas after i.v. dosing, the mean clearance was 159 ± 58.4 ml/h/m², in line with earlier observations. In the absence of CrEL, the bioavailability and systemic concentrations of i.p. paclitaxel were significantly increased. This finding is consistent with the postulated concept that CrEL is largely responsible for

the pharmacokinetic advantage for peritoneal cavity exposure to total paclitaxel compared with systemic delivery.

INTRODUCTION

The role of i.p. chemotherapy for tumors principally confined to the peritoneal cavity has been studied extensively (1). Although it has proven to be a safe procedure with encouraging results, it has not yet become a standard therapeutic procedure (1, 2). The major goal of this therapeutic strategy is to expose tumors within the peritoneal cavity to higher concentrations of antineoplastic agents for longer periods of time than can be achieved with systemic drug administration. i.p. treatment with paclitaxel is particularly attractive in patients with ovarian cancer (3–6), because i.v. paclitaxel has proven single-agent activity in ovarian cancer (7, 8), and also potentially in other tumor types confined to the abdominal cavity, such as peritoneal mesothelioma (9, 10). The antitumor effect is dependent on duration of exposure, on the drug concentration in contact with the tumor, and in the case of paclitaxel, on the unique pharmacokinetic profile of paclitaxel and its solvent vehicle CrEL,³ a nonionic castor oil derivative.

It has been demonstrated that at high local concentrations, which can be reached by i.v. and especially by i.p. administration, paclitaxel is entrapped in CrEL micelles (11). Our hypothesis is that this phenomenon accounts for the prolonged (peritoneal) activity at high concentrations as reported for intravesical treatment (12) and that, hence, paclitaxel distribution will depend on CrEL pharmacokinetics. To gain further insight into the role of CrEL in the pharmacokinetic behavior of paclitaxel, we studied paclitaxel disposition in cancer patients, with the drug formulated in the presence and absence of CrEL, after i.p. and i.v. dosing.

MATERIALS AND METHODS

Materials and Chemicals. [G - 3 H]Paclitaxel with a specific activity of 2.4 Ci/mmol was obtained from Moravek Biochemicals, Inc. (Brea, CA). The majority of the tritium is in the *m* and *p* positions of the aromatic rings, with minor amounts in the 10, 3', and 2 positions of the taxane ring system. The clinical paclitaxel formulation in CrEL and dehydrated USP-grade ethanol (1:1, v/v; Taxol) and paclitaxel powder were purchased from Bristol-Myers Squibb (Woerden, the Netherlands). The CrEL reference material was obtained from Sigma Chemical Co. (St. Louis, MO) and Coomassie brilliant blue G-250 from Bio-Rad Laboratories (Munich, Germany) as a concentrated solution in 85% (w/v) phosphoric acid-95% (v/v) ethanol (2:1, v/v). All other chemicals and reagents used were of reagent

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³ The abbreviations used are: CrEL, Cremophor EL; HPLC, high-performance liquid chromatography; AUC, area under the plasma concentration versus time curve.

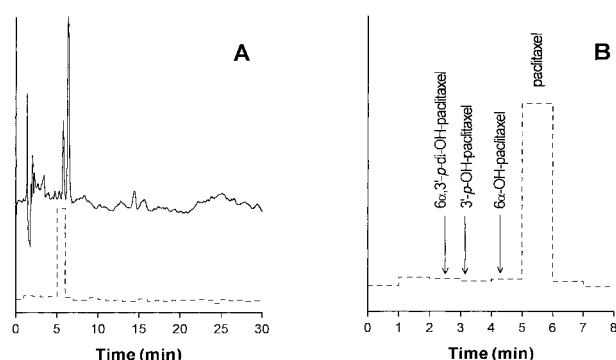


Fig. 1 Representative reversed-phase chromatographic tracings with UV detection (solid lines) and off-line liquid scintillation counting (dashed lines; 1-min fractions) of plasma extracts taken from samples collected from a patient at the end of a 3-h i.v. infusion of CrEL-free [G - 3 H]paclitaxel (100 μ Ci) on day 22, and a 3-h i.v. infusion of Taxol (175 mg/m 2) on day 25. Chromatographic peaks in the plot with UV detection correspond to unchanged paclitaxel [retention time (t_R) = 5.81 min] and the internal standard, docetaxel (t_R = 6.40 min; A). The presently identified paclitaxel metabolites 6 α ,3'- p -dihydroxypaclitaxel (t_R = 2.63 min), 3'- p -hydroxypaclitaxel (t_R = 3.09 min), and 6 α -hydroxypaclitaxel (t_R = 4.56 min) could not be detected in the plasma samples (B). Reference standards of the metabolites for determination of chromatographic retention times were obtained as described previously (16).

grade or better and originated from Rathburn (Walkerburn, United Kingdom). HPLC-grade water was obtained from a Millipore (Milford, MA) Milli-Q-UF system. Ultima Gold scintillation cocktail was purchased from Packard (Meriden, CT). The internal standard for quantitative paclitaxel analysis, docetaxel, was obtained from Aventis (Vitry-sur-Seine Cedex, France).

Patients. Eligible patients had a histologically or cytologically verified cancer with tumor morbidity attributable to localization in the abdominal cavity, for which treatment with paclitaxel was a reasonable option or for which no effective therapy was available. Other inclusion criteria included (a) age at least 18 years, (b) WHO performance status ≤ 2 , (c) no previous chemotherapy and/or radiotherapy in the past 4 weeks, (d) adequate hematopoietic function (absolute neutrophil count $\geq 1.5 \times 10^9$ /liter and platelet count $\geq 100 \times 10^9$ /liter), and (e) adequate hepatic function (total serum bilirubin level ≤ 1.25 times the upper limit of normal). Specific exclusion criteria included (a) signs of bowel obstruction and (b) peripheral neuropathy graded >1 (National Cancer Institute common toxicity criteria). The study protocol was approved by the medical ethical committee of the Rotterdam Cancer Institute, and all patients gave written informed consent before study entry.

Treatment Plan. All patients received one administration of CrEL-free i.p. [G - 3 H]paclitaxel (100 μ Ci; ~ 0.1 mg) on day 1 and one administration of i.p. (unlabeled) paclitaxel in CrEL-ethanol (Taxol) at a dose of 125 mg/m 2 (based on a previous Phase I study; Ref. 3) on day 4, followed by one administration of CrEL-free i.v. [G - 3 H]paclitaxel (100 μ Ci) on day 22 and one i.v. administration of Taxol at a dose of 175 mg/m 2 on day 25. The i.p. administrations were performed by repeated paracentesis placed under sterile conditions after sono-

Table 1 Patient characteristics

Characteristic	Median (range)
Number of patients	4
Age (yrs)	64 (54–74)
Sex (F/M)	4/0
Weight (kg)	66 (55–72)
Height (cm)	168 (163–173)
Body-surface area (m 2)	1.70 (1.50–1.80)
Tumor type	Mesothelioma ($n = 2$); ovarian carcinoma ($n = 2$)
Toxicity	Only mild gastrointestinal and hematological

graphic localization, which is a safe and practical method for i.p. chemotherapy (13). All ascites was drained before each i.p. infusion. Paclitaxel for i.p. dosing, either unlabeled or labeled, was administered in 2 liters of isotonic sodium chloride (0.9%, w/v), preheated to 37°C. The i.p. infusion was administered in 45 min and the i.v. administrations in 3 h, also in a volume of 2 liters of isotonic sodium chloride. Polyvinyl chloride-containing infusion systems were avoided because CrEL is known to leach plasticizers from these products. Instead, cellulose acetate filters (0.22 μ m pore size) were used for infusions. Before i.v. infusion, patients were premedicated with ranitidine (50 mg), clemastine (2 mg), and dexamethasone (10 mg), all 30 min before all drug administrations.

The total dose of radioactivity delivered to the patients and the small dose of non-CrEL-bound paclitaxel were nonhazardous, and no special additional precautions were necessary (14, 15). During the first 2 h after the i.p. administration of paclitaxel was started, patients were encouraged to change positions every 15 min to maintain adequate distribution throughout the peritoneal cavity.

Clinical Assessment. Before therapy, a complete medical history was taken and a physical examination was performed. A complete blood cell count, including WBCs, differential, and serum biochemistry, was performed before treatment, as was disease evaluation. During treatment, patients were seen at least weekly by a physician, and complete blood cell counts and serum chemistries were monitored weekly.

Pharmacological Analysis. Venous blood samples of 5 ml were obtained in the two i.p. cycles at the following time points: before infusion; at 15, 30, and 40 min during instillation; and at 5, 15, and 30 min and 1, 2, 4, 8, 10, 21, 24, 48, and 72 h post instillation. For the two i.v. cycles, blood samples were collected at 0.5, 1, 1.5, 2, 2.5, and 2.55 h during infusion and at 5, 15, 30, and 45 min and 1, 2, 4, 8, 10, and 21 h post infusion. Samples were collected in tubes containing potassium EDTA as anticoagulant, and centrifuged to obtain the plasma supernatant (3000 $\times g$ for 10 min). Duplicate ascitic samples were obtained in one patient after the second i.p. administration immediately after the end of infusion and 4, 6, and 18 days after the end of infusion and in another patient after the second i.v. administration at 1.5 and 3 h after start of infusion. These samples were obtained with a Medicut 16-gauge cannula (45 \times 1.7 mm internal diameter; Sherwood Medical, Tullamore, Ireland), collected in 4.5-ml polypropylene tubes (after the first 10 ml of fluid was discarded), and processed as described above for plasma.

Table 2 Plasma pharmacokinetics of i.p. and i.v. paclitaxel

Parameter	+CrEL (Taxol)	–CrEL	P
i.p. dosing			
c_{\max}^b (μM)	0.14 ± 0.08	0.26 ± 0.07	0.12
AUC ($\mu\text{M}\cdot\text{h}$)	5.04 ± 1.92	7.55 ± 3.38	0.064
MRT (h)	40.7 ± 13.8	7.28 ± 2.76	0.003
F (%)	31.4 ± 5.18	98.8 ± 16.6	0.005
i.v. dosing			
c_{\max} (μM)	5.44 ± 1.76	3.63 ± 1.56	0.054
AUC ($\mu\text{M}\cdot\text{h}$)	22.9 ± 10.0	11.4 ± 6.50	0.011
CL (liters/h/m ²)	10.2 ± 3.76	22.8 ± 11.7	0.027

^a Wilcoxon test for matched pairs.

^b c_{\max} , peak plasma concentration; MRT, mean residence time; F, bioavailability for i.p. administration; CL, clearance.

Plasma and ascitic fluid samples were analyzed for the presence of paclitaxel and CrEL by HPLC with UV detection (16) and a colorimetric dye-binding microassay (17), respectively. The handling and measurement of [G -³H]paclitaxel was performed according to a protocol approved by the local Radiation Approval Committee of the Rotterdam Cancer Institute as described in detail elsewhere (15). Briefly, radioactivity was determined by liquid scintillation counting after the addition of Ultima Gold scintillation cocktail (Turku, Finland). All samples were counted until a preset time of 20 min was reached, with quench correction performed by external standardization.

Concentration-time profiles for paclitaxel and total radioactivity were analyzed by noncompartmental modeling using Siphar V4 (InnaPhase, Philadelphia, PA). The AUC was calculated by the linear trapezoidal rule with extrapolation to infinity, and the apparent plasma clearance was calculated as the ratio of dose delivered (in mg/m²) and AUC. On the basis of the known pharmacological properties of paclitaxel after i.v. administration (15), we anticipated that circulating paclitaxel metabolite concentrations would be very low. Indeed, analysis of extracted patient samples indicated that none of the paclitaxel metabolites identified at present (6 α ,3'-*p*-dihydroxypaclitaxel, 3'-*p*-hydroxypaclitaxel, and 6 α -hydroxypaclitaxel) was detected at any time point in any patient after i.v. or i.p. drug administration of paclitaxel when formulated in CrEL (Fig. 1). This suggests that concentrations were always lower than the lower limit of quantitation of our HPLC assay (*i.e.*, 10 ng/ml). Thus, because the paclitaxel metabolites are not contributing significantly to total circulating drug, the total radioactivity was equated with the (unchanged) parent drug concentration. In the pharmacokinetic data analysis, we also assumed that partitioning of paclitaxel out of CrEL micelles occurs rapidly (*i.e.*, much faster than the partitioning into tissues/cells), which establishes this process as an unimportant kinetic process, and assumed that the two entities were interchangeable. This assumption is based on previous observations that *in vitro* equilibrium between paclitaxel in CrEL micelles and free paclitaxel (outside micelles) was reached within 1 min (18). This can be considered instantaneous on the time scale of paclitaxel pharmacokinetics both after i.v. and especially after i.p. drug administration.

The bioavailability (*F*) for i.p. paclitaxel was calculated as: $F = (\text{AUC}_{\text{i.p.}}/\text{AUC}_{\text{i.v.}}) \times (\text{dose}_{\text{i.v.}}/\text{dose}_{\text{i.p.}}) \times 100\%$. All pharmacokinetic parameters were determined from the data obtained

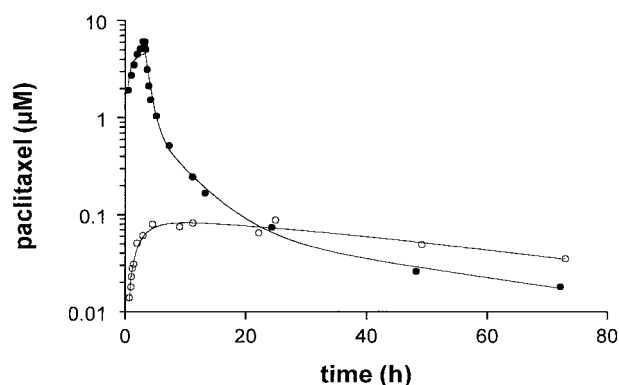


Fig. 2 Representative plasma concentration-time profiles of total paclitaxel after i.p. (○) and i.v. (●) delivery of paclitaxel formulated in a mixture of CrEL and USP-grade ethanol (1:1, v/v).

with the full nonradioactive dose and represent dose-normalized mean values (to 125 mg/m² for i.p. and to 175 mg/m² for i.v.) with SDs. Statistical evaluation was performed with the NCSS package V5.X (J. Hintze, East Kaysville, UT), using the nonparametric Wilcoxon test for matched pairs. The level of significance was set at $P < 0.05$.

RESULTS

Patient Characteristics and Toxicity. Of six eligible patients, two withdrew consent before the second i.p. infusion of paclitaxel because of rapid progressive disease (one patient) or unrelated and unexpected occurrence of psychiatric illness (one patient). Four patients received the four planned administrations of paclitaxel, and all were pharmacologically evaluable. The patient characteristics are summarized in Table 1. Overall, the treatment was very well tolerated, with no infusion-related complications and no grade 3–4 hematological and nonhematological toxicity. Disease stabilization was initially obtained in all four patients.

Plasma Pharmacokinetics. The pharmacokinetic data for i.p.- and i.v.-delivered paclitaxel in the presence and absence of CrEL are shown in Table 2. In the presence of CrEL, the terminal disposition half-life of paclitaxel was substantially prolonged after i.p. dosing compared with i.v. dosing (28.7 ± 8.72 versus 17.0 ± 11.3 h; $P = 0.006$), as was the mean residence time (40.7 ± 13.8 versus 7.28 ± 2.76 h; $P = 0.005$; Fig. 2), which may be advantageous for local antitumor effects. The bioavailability of i.p.-delivered paclitaxel formulated in CrEL was only $31.4 \pm 5.18\%$, indicating low concentrations within the systemic compartment. However, in the absence of CrEL, the bioavailability (98.8 ± 16.6 versus $31.4 \pm 5.18\%$; $P = 0.005$) and systemic exposure (7.55 ± 3.38 versus 5.04 ± 1.92 $\mu\text{M}\cdot\text{h}$; $P = 0.064$) of i.p.-delivered paclitaxel were significantly increased, which may eventually lead to increases in systemic (hematological) toxicity.

The systemic CrEL levels were undetectable after i.p. dosing of paclitaxel (<0.05 $\mu\text{g/ml}$), whereas after i.v. dosing, the mean clearance of CrEL was 159 ± 58.4 ml/h/m², in line with previous observations (19, 20).

Ascitic Fluid Penetration. Given the relatively high total protein content in the ascites of the patients (range, 38–45 mg/ml), no correction for protein binding was performed. After i.p. administration in the presence of CrEL, the paclitaxel concentration peaked immediately after the end of instillation at levels >1600-fold higher than concomitant plasma concentrations. Paclitaxel elimination from ascites was extremely slow, with detectable levels (~ 10.2 ng/ml) even at 18 days after dosing and an apparent disappearance half-life of ~ 140 h. In contrast, measurement of paclitaxel in ascites after i.v. administration with CrEL indicated that <1.3% of systemic concentrations were present in ascites, indicating lack of a sink effect.

DISCUSSION

The results of the present study show that the use of CrEL as a formulation vehicle results in a drastic alteration in the pharmacokinetics of paclitaxel after i.p. or i.v. administration. Indeed, the presence of CrEL in the pharmaceutical formulation (Taxol) leads to a substantial decrease in the bioavailability after i.p. drug administration (31.4 *versus* 98.8%). The overall result is a 50% decrease in the paclitaxel plasma AUC after i.p. administration and a 100% increase after i.v. administration.

The human pharmacokinetics of paclitaxel after i.v. administration have been studied extensively using sensitive and selective HPLC methods (18, 21, 22). Because the normal pharmaceutical formulation already contains significant amounts of CrEL, we used an i.v. formulation that does not contain this vehicle substance to allow determination of comparative pharmacokinetic profiles. Because paclitaxel without its solvent CrEL is not registered for human use, we were required to use a nonhazardous radiolabeled tracer dose. Thus, we compared therapeutic doses of paclitaxel with CrEL to very small doses of paclitaxel without CrEL and dose-normalized the pharmacokinetic data. Theoretically, this might introduce a methodological flaw, as has been described previously for some agents (23). However, the altered disposition of drugs when tracer doses are used compared with pharmacological doses has been shown to be caused by the variable degree in saturation of enzymes involved in (hepatic) biotransformation. It has been shown previously, for example, that tracer doses of erythromycin produce aberrant metabolic profiles and therefore altered drug clearance, and administration of therapeutic doses along with the radiolabeled tracer in those cases has been advocated (24). However, it is highly unlikely that this also accounts for the observed differences in paclitaxel pharmacokinetics, because: (a) The apparent Michaelis-Menten constant (*i.e.*, K_m) and the maximum reaction velocity (*i.e.*, V_{max}) values for the principal metabolic route, *i.e.*, paclitaxel 6 α -hydroxylation, were 5.4 ± 1.0 μ M and 30 ± 1.5 nmol/min/nmol of cytochrome P-450, respectively, for cDNA-expressed cytochrome P-450 isoform 2C8; the values were 4.0 ± 1.0 μ M and 0.87 ± 0.06 nmol/min/mg of protein, respectively, for human hepatic microsomes (25). These values are ~ 50 – 100 -fold higher than peak concentrations of unbound paclitaxel after therapeutic doses (135–225 mg/m²) in patients receiving 1-, 3-, or 24-h i.v. infusions (22). (b) The binding of paclitaxel by plasma proteins (26, 27) and the erythrocyte partitioning of paclitaxel in human samples (11) have previously

been shown to be independent of the paclitaxel concentration within the therapeutic range associated with 3-h i.v. infusions. (c) No signs of nonlinearity in paclitaxel distribution [unbound (28), whole blood (21), and tissue concentrations (29, 30)] and elimination [urinary and fecal concentrations (21)] have been noted previously.

After i.p. administration, paclitaxel concentrations in plasma were initially less than those after i.v. administration, and several hours were required for equilibrium to be attained between the peritoneal cavity and the systemic circulation. The limited surface area for paclitaxel diffusion relative to the volumes of fluid and the fact that the peritoneal fluids are not well stirred likely contributed to the slow equilibrium kinetics. Nevertheless, concentrations in plasma equivalent to those after i.v. administration were achieved after ~ 20 h in all patients, and paclitaxel appeared to be more slowly eliminated from the peritoneal cavity than from plasma. This is in keeping with earlier findings, which we now confirm, indicating slow peritoneal clearance of paclitaxel and high peritonea-plasma concentration ratios of >1000 after i.p. drug administration (3). These authors also documented the persistence of significant peritoneal paclitaxel levels even at 1 week after initial i.p. drug administration, already suggesting very slow peritoneal clearance and continuous exposure of the peritoneal cavity to active concentrations of paclitaxel (4). Thus, although the described data on paclitaxel accumulation are limited to only four patients, our results are fully in agreement with previous findings and suggest that i.p. administration of paclitaxel can produce significant drug distribution in the peritoneal cavity. In this context, it is of particular interest that the cytotoxicity of paclitaxel is a function of the time to drug exposure above a certain threshold concentration (20, 31). The paclitaxel penetration and subsequent accumulation in the peritoneal cavity thus might offer a potential therapeutic advantage in that tumor cells are exposed to high local drug levels for prolonged time periods. In contrast, there appears to be rapid clearance after i.p. paclitaxel administration without CrEL, with bioavailability approaching unity. This suggests a reduced ability of paclitaxel to interact with tubulin or other essential targets as well as an increased risk of severe (hematological) toxicity in cancer patients treated with paclitaxel in the absence of CrEL.

We expect that the results presented here for paclitaxel are representative of other poorly water-soluble drugs formulated in this vehicle. This is supported by recent observations that several commonly used anticancer agents, including anthracyclines and epipodophyllotoxins, can be readily incorporated into CrEL micelles (32), thereby strongly affecting the plasma pharmacokinetics (33). This implies that reformulation of hydrophobic anticancer agents with a vehicle containing CrEL for i.p. treatment might achieve improvement of their therapeutic index.

In conclusion, we have shown that CrEL is mainly responsible for the pharmacokinetic advantage for peritoneal cavity exposure to total paclitaxel compared with systemic delivery and compared with a CrEL-free paclitaxel formulation. These findings provide a rationale for attempts to improve local drug distribution after i.p. administration of other hydrophobic anticancer agents by concomitant administration of CrEL.

REFERENCES

- Markman, M. Intraperitoneal antineoplastic agents for tumors principally confined to the peritoneal cavity. *Cancer Treat. Rev.*, 13: 219–242, 1986.
- Markman, M. Intraperitoneal therapy of ovarian cancer. *Semin. Oncol.*, 5: 356–360, 1998.
- Markman, M., Rowinsky, E. K., Hakes, T., Reichman, B., Jones, W., Lewis, J. L., Rubin, S., Curtin, J., Barakat, R., Philips, M., Hurwitz, L., Almadrones, L., and Hoskins, W. Phase I trial of intraperitoneal Taxol: a Gynaecologic Oncology Group Study. *J. Clin. Oncol.*, 10: 1485–1491, 1992.
- Francis, P., Rowinsky, E., Schneider, J., Hakes, T., Hoskins, W., and Markman, M. Phase I feasibility and pharmacologic study of weekly intraperitoneal paclitaxel: a Gynaecologic Oncology Group Pilot Study. *J. Clin. Oncol.*, 13: 2961–2967, 1995.
- Markman, M., Brady, M. F., Spirtos, N. M., Hanjani, P., and Rubin, S. C. Phase II trial of intraperitoneal paclitaxel in carcinoma of the ovary, tube, and peritoneum: a Gynaecologic Oncology Group Study. *J. Clin. Oncol.*, 16: 2620–2624, 1998.
- Markman, M., Rowinsky, E., Hakes, T., Reichman, B., Jones, W., Lewis, J. L., Rubin, S., Curtin, J., Barakat, R., Almadrones, L., and Hoskins, W. Intraperitoneal administration of Taxol in the management of ovarian cancer. *J. Natl. Cancer Inst. (Bethesda)*, 15: 103–106, 1993.
- Dunton, C. J. New options for the treatment of advanced ovarian cancer. *Semin. Oncol.*, 24: 2–11, 1997.
- McGuire, W. P., and Ozols, R. F. Chemotherapy of advanced ovarian cancer. *Semin. Oncol.*, 25: 340–348, 1998.
- Garcia Moore, M. L., Savaraj, N., Feun, L. G., and Donnelly, E. Successful therapy of peritoneal mesothelioma with intraperitoneal chemotherapy alone: a case report. *Am. J. Clin. Oncol.*, 15: 528–530, 1992.
- Eltabbakh, G. H., Piver, M. S., Hempling, R. E., Recio, F. O., and Intengen, M. E. Clinical picture, response to therapy, and survival of women with diffuse malignant peritoneal mesothelioma. *J. Surg. Oncol.*, 70: 6–12, 1999.
- Sparreboom, A., Van Zuylen, L., Brouwer, E., Loos, W. J., De Bruijn, P., Gelderblom, H., Pillay, M., Nooter, K., Stoter, G., and Verweij, J. Cremophor EL-mediated alteration of paclitaxel distribution in human blood: clinical pharmacokinetic implications. *Cancer Res.*, 59: 1454–1457, 1999.
- Knemeyer, I., Wientjes, M. G., and Au, J. L.-S. Cremophor reduces paclitaxel penetration into bladder wall during intravesical treatment. *Cancer Chemother. Pharmacol.*, 44: 241–248, 1999.
- Vidal-Jove, J., Pessagno, A. M., Esquivel, J., Buck, D. R., Steves, M. A., and Sugarbaker, P. H. Technical aspects and morbidity assessment of intraperitoneal chemotherapy administered by repeated paracentesis. *Reg. Cancer Treat.*, 4: 294, 1992.
- Walle, T., Walle, U. K., Kumar, G. N., and Bhalla, K. N. Taxol metabolism and disposition in cancer patients. *Drug Metab. Dispos.*, 23: 506–512, 1995.
- Gelderblom, H., Verweij, J., Brouwer, E., Pillay, M., De Bruijn, P., Nooter, K., Stoter, G., and Sparreboom, A. Disposition of [^3H]paclitaxel and Cremophor EL in a patient with severely impaired renal function. *Drug Metab. Dispos.*, 27: 1300–1305, 1999.
- Sparreboom, A., De Bruijn, P., Nooter, K., Loos, W. J., Stoter, G., and Verweij, J. Determination of paclitaxel in human plasma using single solvent extraction before isocratic reversed-phase high-performance liquid chromatography with ultraviolet detection. *J. Chromatogr. B*, 705: 159–164, 1998.
- Sparreboom, A., Loos, W. J., Verweij, J., De Vos, A. I., Van der Burg, M. E. L., Stoter, G., and Nooter, K. Quantification of Cremophor EL in human plasma samples using a calorimetric dye-binding microassay. *Anal. Biochem.*, 255: 171–175, 1998.
- Van Zuylen, L., Karlsson, M. O., Verweij, J., Brouwer, E., De Bruijn, P., Nooter, K., Stoter, G., and Sparreboom, A. Pharmacokinetic modeling of paclitaxel encapsulation in Cremophor EL micelles. *Cancer Chemother. Pharmacol.*, 47: 309–318, 2001.
- Sparreboom, A., Verweij, J., Van der Burg, M. E. L., Loos, W. J., Brouwer, E., Vigano, L., Locatelli, A., De Vos, A. I., Nooter, K., Stoter, G., and Gianni, L. Disposition of Cremophor EL in human limits the potential for modulation of the multidrug resistance phenotype *in vivo*. *Clin. Cancer Res.*, 4: 1937–1942, 1998.
- Brouwer, E., Verweij, J., Hauns, B., Loos, W. J., Nooter, K., Mross, K., Stoter, G., and Sparreboom, A. Linearized colorimetric assay for Cremophor EL: application to pharmacokinetics after 1-hour paclitaxel infusions. *Anal. Biochem.*, 261: 198–202, 1998.
- Gianni, L., Kearns, C. M., Giani, A., Capri, G., Vigano, L., Locatelli, A., Bonadonna, G., and Egorin, M. J. Nonlinear pharmacokinetics and metabolism of paclitaxel and its pharmacokinetic/pharmacodynamic relationships in humans. *J. Clin. Oncol.*, 13: 80–190, 1995.
- Van Zuylen, L., Gianni, L., Verweij, J., Mross, K., Brouwer, E., Loos, W. J., and Sparreboom, A. Interrelationships of paclitaxel disposition, infusion duration and Cremophor EL kinetics in cancer patients. *Anticancer Drugs*, 11: 331–337, 2000.
- Watkins, P. B., Murray, S. A., Winkelman, L. G., Heuman, D. M., Wrighton, S. A., and Guzelian, P. S. Erythromycin breath test as an assay of glucocorticoid-inducible liver cytochromes P-450. Studies in rats and patients. *J. Clin. Invest.*, 83: 688–697, 1989.
- Watkins, P. B., Hamilton, T. A., Annesley, T. M., Ellis, C. N., Kolars, J. C., and Voorhees, J. J. The erythromycin breath test as a predictor of cyclosporine blood levels. *Clin. Pharmacol. Ther.*, 48: 120–129, 1990.
- Rahman, A., Korzekwa, K. R., Grogan, J., Gonzalez, F. J., and Harris, J. W. Selective biotransformation of Taxol to 6 α -hydroxytaxol by human cytochrome P450 2C8. *Cancer Res.*, 54: 543–5546, 1994.
- Kumar, G. N., Walle, U. K., Bhalla, K. N., and Walle, T. Binding of Taxol to human plasma, albumin and α 1-acid glycoprotein. *Res. Commun. Chem. Pathol. Pharmacol.*, 80: 337–344, 1993.
- Brouwer, E., Verweij, J., De Bruijn, P., Loos, W. J., Pillay, M., Buijs, D., and Sparreboom, A. Measurement of fraction unbound paclitaxel in human plasma. *Drug Metab. Dispos.*, 28: 1141–1145, 2000.
- Eskilsson, A., Karlsson, M. O., Vigano, L., Gianni, L., Verweij, J., and Sparreboom, A. Mechanism based pharmacokinetic model for paclitaxel. *J. Clin. Oncol.*, 19: 4065–4073, 2001.
- Sparreboom, A., Van Tellingen, O., Nooijen, W. J., and Beijnen, J. H. Nonlinear pharmacokinetics of paclitaxel in mice results from the pharmaceutical vehicle Cremophor EL. *Cancer Res.*, 56: 2112–2115, 1996.
- Sparreboom, A., Van Tellingen, O., Nooijen, W. J., and Beijnen, J. H. Tissue distribution, metabolism and excretion of paclitaxel in mice. *Anticancer Drugs*, 7: 78–86, 1996.
- Helson, L., Helson, C., Malik, S., Ainsworth, S., and Mangiardi, J. A saturation threshold for Taxol cytotoxicity in human glial and neuroblastoma cells. *Anticancer Drugs*, 4: 487–490, 1993.
- Kessel, D. Properties of Cremophor EL micelles probed by fluorescence. *Photochem. Photobiol.*, 56: 447–451, 1992.
- Van Zuylen, L., Verweij, J., and Sparreboom, A. Role of formulation vehicles in taxane pharmacology. *Investig. New Drugs*, 19: 125–141, 2001.