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Paclitaxel Pharmacokinetics and Response to Chemotherapy in Patients with Advanced Cancer Treated with a Weekly Regimen

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Abstract. *Background: Paclitaxel pharmacokinetics were shown to be related to toxicity and survival. Patients and Methods: We evaluated the effects of time above paclitaxel concentrations of 0.05 μmol/l ($T_{>0.05}$) and systemic exposures (AUC) to total and unbound paclitaxel (tPAC, uPAC) on response in patients with advanced cancer treated with weekly 1-h or 3-h infusions. Results: After 6 weeks of therapy (WOT), 13 out of 21 assessable patients showed either partial response (PR) or stable disease (SD), while 8 had progressive disease (PD). As compared to patients with PD, those with PR or SD showed similar AUCs to uPAC and tPAC but higher ($p<0.05$) $T_{>0.05}$. Patients with $T_{>0.05}\geq 20.7$ hours had lower probability ($p<0.05$) to progress within 12 WOT. Conclusion: Taking the heterogeneity of the studied tumor types into account, we found $T_{>0.05}$ to be associated with response to treatment. This emphasizes the value of threshold models for the investigation of paclitaxel pharmacodynamics.*

Paclitaxel (PAC) is a chemotherapeutic agent with broad antitumor activity (1). PAC dosing and scheduling have been optimized during the last two decades, resulting in today's widely applied weekly regimens of 1-h or 3-h infusions (2-4). During this evolution, several investigations have emphasized the importance of pharmacokinetics for the development of administration-related toxicities (5-9). Pharmacokinetic analyses of PAC in plasma are likely to be complicated by the non-linear behavior of this drug especially at dose levels above 100 mg/m^2 PAC requiring either determination or estimation of unbound drug fractions (10-12). Times above certain PAC concentrations exceeding a particular threshold have been clearly shown to be related to both therapeutic efficacy and toxicity. The time of PAC concentrations above 0.1 μmol/l ($T_{>0.1}$) has been found to be associated with survival in patients with non-small cell lung cancer (NSCLC) and also with the extent of granulocytopenia (8, 13). The time of PAC concentrations above 0.05 mmol/l represents another threshold parameter ($T_{>0.05}$) of predictive value for the extent of neutropenia (6, 9). More recently, we described $T_{>0.05}$ to be associated with the development of peripheral neuropathy in patients with advanced cancer of different origin (14). Here, we aimed to answer the question of whether the same threshold parameter, which we found to be an independent factor for the development of peripheral neuropathy, was also associated with response to treatment in the same subset of patients.

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Patients and Methods

Study design and patients. The subset of patients investigated in this pharmacodynamic study was obtained from a pharmacokinetic analysis group (n=29) (10) from a larger prospective and randomized trial designed to investigate the effects of weekly 1-h or 3-h PAC infusions on neurotoxicity as the primary end-point in patients with advanced cancer of different origin (N=121) (15). Using this source of data, we showed recently that exposure to PAC and in particular the threshold parameter $T_{>0.05}$ is associated with the development of peripheral neuropathy (14). Based on these findings, it was the aim of the present study to analyze the influence of the obtained PAC administration's pharmacokinetic parameters including $T_{>0.05}$ on response to chemotherapy, a secondary end-point of the primary clinical trial (15).

Eligibility criteria. Patients with histologically proven, locally advanced or metastatic cancer, for whom PAC as monotherapy was a therapeutic option, were eligible candidates for this study. Exclusion criteria included age less than 18 years or more than 75 years with ECOG performance status >2, life expectancy less than 3 months, preexisting peripheral neuropathy, significant heart disease, known anaphylaxis against cremophore EL (CrEL), chemo- or radiotherapy in the previous 4 weeks, chemotherapy with taxanes in the previous year, simultaneous anticancer treatment with hormone or immunotherapy, significant renal (serum creatinine > 1.5 x upper limit of normal), hepatic (total serum bilirubin > 1.5 x upper limit of normal) or hematological insufficiency (absolute neutrophil count $<1.5x10^9$/l and platelet count $<75x10^9$/l) as well as bi-dimensionally non-measurable tumor. All patients gave informed consent according to the local ethics committee requirements.

Treatment schedule. Eligible patients were randomized between 1-h and 3-h infusion duration to receive a total of 6 weekly intravenous infusions of PAC (100 mg/m^2). After 6 weeks of therapy (defined as one cycle) response was evaluated bi-dimensionally, usually by computed tomography (CT). Patients with a stable disease, partial response or complete response after one cycle received a second cycle, provided toxic effects were not prohibitive. The exact assessment of general and neuronal toxicity and the performance of required dose reductions have been described before (15).

Treatment administration. Vials containing 30 mg of PAC formulated in a mixture of CrEL and ethanol USP (1:1, volume/volume) were purchased from Bristol Myers Squibb (Munich, Germany). PAC was diluted in 500 ml of 5% (weight/volume) dextrose in water and given to the patient *via* peripheral or central venous catheter using a motor-driven programmable infusion pump over a 1-h or 3-h period.

Assessment of response. Response criteria were as follows: complete response (CR) was defined as disappearance of all clinical and radiographic evidence of disease; partial response (PR) was defined as a ≥50% decrease in the sum of products of bi-perpendicular diameters of measurable lesions or a ≥50% reduction in the size of assessable lesions and no increase in or appearance of new lesions; stable disease (SD) was defined as a less than 50% decrease in the sum of products of the bi-perpendicular diameters of measurable lesions or in the size of assessable lesions and no increase in or appearance of new lesions; and progressive disease (PD) was defined as a ≥25% increase in lesion size or the appearance of new lesions.

Pharmacokinetics of paclitaxel. The methodologies and results of the pharmacokinetic study used for this analysis have been reported individually (10). Briefly, plasma samples were obtained during the first Paclitaxel administration at the University of Freiburg, Department of Hematology and Oncology or at the Tumor Biology Center of Freiburg, Germany. Concentrations of total Paclitaxel (tPAC) were determined by reversed-phase high performance liquid chromatography and unbound Paclitaxel (uPAC) plasma concentrations by equilibrium dialysis using a [*G*-^{3}H]Paclitaxel tracer.

Statistical analysis. For the statistical evaluation of the impact of the pharmacokinetic parameters AUC and $T_{>0.05}$ on response, which were obtained at the first drug application, the assumption was made that these parameters remained constant during the whole course of therapy. Thus, all patients with dose reductions within the first 6 weeks of therapy had to be excluded from this study. As there were no complete responses in this subset of patients, we defined response either as partial response (PR) or stable disease (SD) after 6 weeks of therapy. PK parameters were then compared between patients with PR/SD and PD. *P*-values ≤0.05 were considered significant. Graphs and statistical analyses presented in this publication have been plotted respectively performed with the use of Prism 4.00 for Windows software (Graph Pad Software, San Diego, CA, USA).

Results

Patients and treatment delivery. Pharmacokinetic data were available for 29 patients. Eight of them were not assessable for this analysis due to incorrect infusion durations (N=2), dose reductions within the first 6 weeks of therapy (N=3) or missing remission controls after the first 6 weeks of therapy (N=3). Thus, all of these eligible 21 patients received at least one remission control after and no dose reductions within the first 6 weeks of therapy. Four patients experienced a single event of treatment interruption exceeding the allowed limit of 14 days (15, 17, 19 and 21 days) between the first and the second cycle but were still considered assessable for this analysis. Based upon their response to therapy after 6 weeks, patients were split into two groups: one patient group with partial remissions or stable diseases (N=13) and one group with progressive diseases (N=8). No complete responses were observed in these patients. The patients' characteristics are displayed in Table I.

Pharmacodynamics of unbound and total Paclitaxel. Patients with partial responses or stable diseases (PR/SD) after 6 weeks of therapy showed similar systemic exposures (AUC) to both total (Figure 1A) and unbound PAC (Figure 1B). Patients of the PR/SD-group showed significantly (p=0.039) higher times of PAC concentrations above 0.05 μmol/l ($T_{>0.05}$) than those with PD (Figure 1C). To further investigate the therapeutic efficacy in a time-dependent manner, we performed a Kaplan-Meier analysis after subdividing the patients into one group with $T_{>0.05}$≥20.7 h (N=5) and into a second group with $T_{>0.05}$<20.7 h (N=16). The cut off-point was chosen as all patients reaching or exceeding the threshold of 20.7 h showed a response after 6 weeks of therapy. Four of these 21 patients received dose reductions due to peripheral neuropathy (weeks 7, 7, 11 and 12) and 3 further patients did not have a second remission control due to refusal of therapy (N=1) or toxicity-related study exclusions (N=2). Thus, these 7 patients had to be censored after 6 weeks of therapy but kept being assessable for the first cycle. Applying the log-rank test, patients with

Table I. *Patient characteristics. A total of 21 patients were assessable for both pharmacokinetics and response evaluation after 6 weeks of therapy and had received no dose reductions in this period.*

Characteristics	All	PR/SD after 6 WOT	PD after 6 WOT
Assessable patients:	21	13	8
Male/female	9/12	5/8	4/4
Age, years:			
Median	58	60	55.5
Range	42-72	50-72	42-70
Infusion duration (randomized):			
1-h infusion	12	8	4
3-h infusion	9	5	4
Performance status (ECOG):			
ECOG 0	5	2	3
ECOG 1	13	9	4
ECOG 2	2	2	0
ECOG ≤2	1	0	1
Site of primary tumor:			
Breast	6	4	2
Lung	5	3	2
Ovary	3	2	1
Bladder or ureter	2	2	0
Esophagus	2	2	0
Head/neck	1	0	1
Penis	1	0	1
Kidney	1	0	1
Prior therapy	19	11	8

PR: Partial response, SD: Stable disease, PD: Progressive disease, WOT: Weeks of therapy.

$T_{>0.05} \geq 20.7$ h showed significantly lower probability ($p=0.0499$) to progress with their disease within 12 weeks of therapy (Figure 1D).

Discussion

We obtained pharmacokinetic parameters during the first PAC application and made the assumption that the same parameters can be applied to future PAC administrations. For this reason, we excluded all patients requiring dose reductions within the first cycle from this analysis. Nevertheless, there is a possibility that drug interactions or changing elimination conditions have altered these parameters. Performing an explorative analysis, we found no association between the systemic exposure to total or unbound PAC and response, but patients with progressive disease showed significantly lower times of PAC concentrations above 0.05 μmol/l. As this exploration was limited by the heterogeneity of the tumors and by the small numbers in the individual cancer sub-groups, we did not perform a further subset analysis.

Patients in this study were randomized to receiving either 1-h or 3-h infusions, with the purpose of investigating differences in the development of peripheral neuropathy between these groups (15). It was a concern that a reduction of infusion time from 1 to 3 h, which is associated with a reduced systemic exposure to PAC (10, 16), could have an unfavorable effect on response rates. However, taking the heterogeneity of tumor types into account and analyzing the response and survival data of the patients that have been enclosed in the primary multicenter trial, we could not find significant differences between these two infusion groups (15, 17). These results coincide with the findings of the present pharmacodynamic sub-study, where the systemic exposure (AUC) to PAC was not associated with response to therapy. Furthermore, times of PAC concentrations above 0.05 μmol/l, that we describe here to contribute to response, are not significantly different between 1-h and 3-h infusions (10).

Studying neurotoxicity as the primary end-point of our trial and its association with pharmacokinetics systematically, we could describe, for the first time, the pharmacodynamic effects of $T_{>0.05}$ on the development of peripheral neuropathy, which also included the independent predictive value of this threshold (14). The association of $T_{>0.05}$ with response to treatment in this analysis is clearly in line with previous observations that the threshold parameter $T_{>0.1}$ was related to survival in a single cancer type (13). Our study represents a preliminary observation. Further trials will be needed to investigate the effect of $T_{>0.05}$ on response and survival in patients with a single cancer subtype and comparable risks factors.

As it is an aim of modern oncology to separate toxicity from the desired inhibitory effects on tumor growth, the understanding of pharmacodynamics is critical for further improvement of both therapeutic efficacy and patients' quality of life. Our results emphasize the value of threshold models for the investigation of PAC pharmacodynamics and support previously published investigations (6, 8, 9, 13, 14).

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References

1 Rowinsky EK and Donehower RC: Paclitaxel (taxol). N Engl J Med *332*: 1004-1014, 1995.

2 Akerley W, Glantz M, Choy H, Rege V, Sambandam S, Joseph P, Yee L, Rodrigues B, Wingate P and Leone L: Phase I trial of weekly paclitaxel in advanced lung cancer. J Clin Oncol *16*: 153-158, 1998.

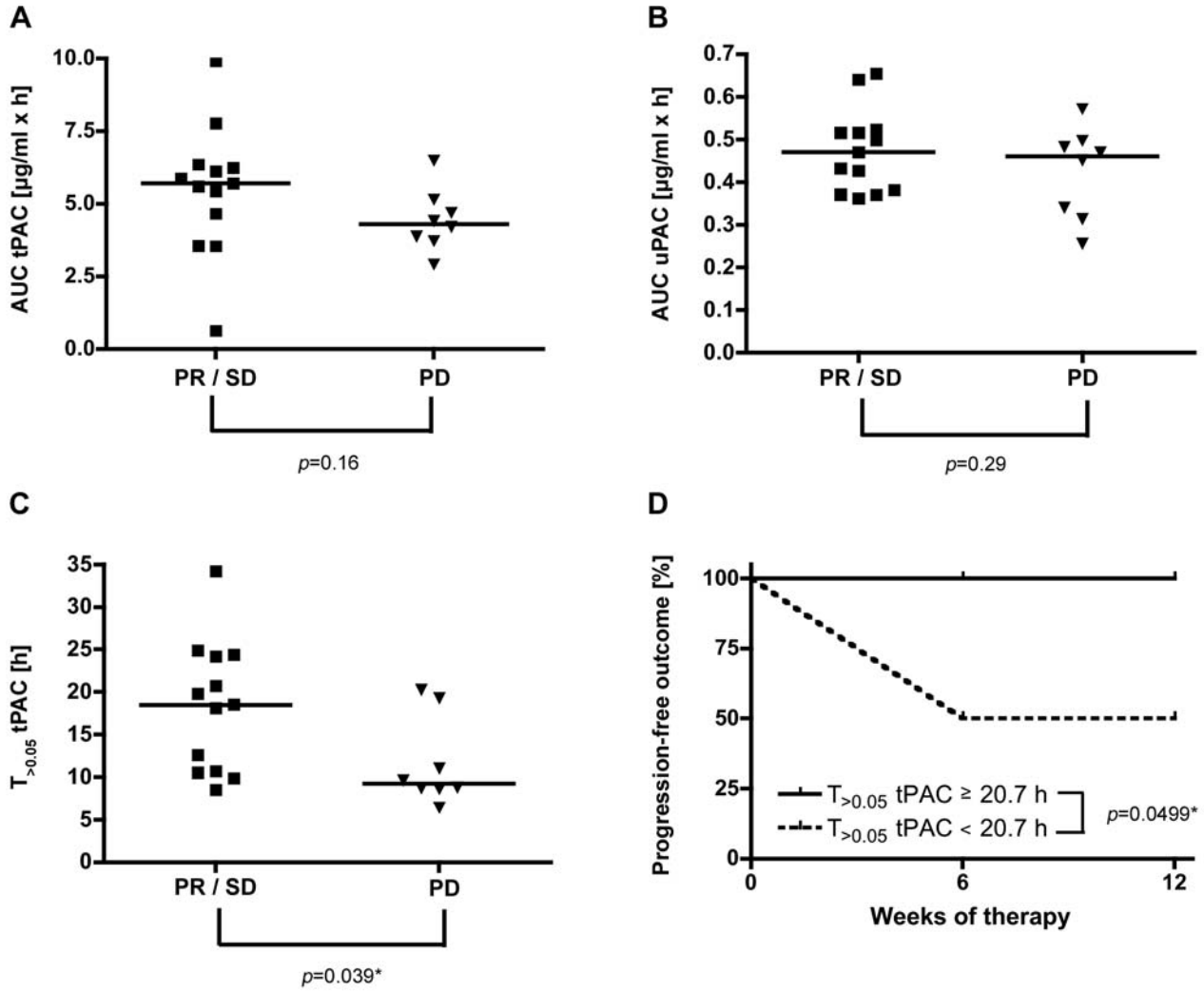

Figure 1 A-C. *Scatter plots of pharmacokinetic parameters as obtained during the first drug application in 13 patients with (■) and 8 patients without (▼) response to chemotherapy. The horizontal bars indicate the median of each group. A two-tailed, nonparametric Mann-Whitney test was applied to examine for differences between these two groups. D: Kaplan-Meier analysis of progression-free outcome during the first 12 weeks of therapy in 5 patients with $T_{>0.05} \geq 20.7$ h (breast cancer (N=3), ovarian cancer (N=1), lung cancer (N=1)) and 16 patients with $T_{>0.05} < 20.7$ h (breast cancer (N=3), ovarian cancer (N=2), lung cancer (N=4), other tumors (N=7)). An unadjusted two-tailed log-rank test was applied to compare between these two groups and approached statistical significance (p=0.0499). AUC: systemic drug exposure, tPAC: total paclitaxel, uPAC: unbound paclitaxel, $T_{>0.05}$: time of total paclitaxel concentrations above 0.05 µmol/l, PR: partial response, SD: stable disease, PD: progressive disease.*

3 Perez EA, Vogel CL, Irwin DH, Kirshner JJ and Patel R: Multicenter phase II trial of weekly paclitaxel in women with metastatic breast cancer. J Clin Oncol *19*: 4216-4223, 2001.

4 Wist EA, Sommer HH, Ostenstad B, Risberg T and Fjaestad K: Weekly one-hour paclitaxel as first-line chemotherapy for metastatic breast cancer. Acta Oncol *43*: 11-14, 2004.

5 Eisenhauer EA, ten Bokkel Huinink WW, Swenerton KD, Gianni L, Myles J, van der Burg ME, Kerr I, Vermorken JB, Buser K, Colombo N *et al*: European-Canadian randomized trial of paclitaxel in relapsed ovarian cancer: high-dose *versus* low-dose and long *versus* short infusion. J Clin Oncol *12*: 2654-2666, 1994.

6 Gianni L, Kearns CM, Giani A, Capri G, Vigano L, Lacatelli A, Bonadonna G and Egorin MJ: Nonlinear pharmacokinetics and metabolism of paclitaxel and its pharmacokinetic/pharmacodynamic relationships in humans. J Clin Oncol *13*: 180-190, 1995.

7 Henningsson A, Karlsson MO, Vigano L, Gianni L, Verweij J and Sparreboom A: Mechanism-based pharmacokinetic model for paclitaxel. J Clin Oncol *19*: 4065-4073, 2001.

8 Huizing MT, Keung AC, Rosing H, van dK, V, ten Bokkel Huinink WW, Mandjes IM, Dubbelman AC, Pinedo HM and Beijnen JH: Pharmacokinetics of paclitaxel and metabolites in a randomized comparative study in platinum-pretreated ovarian cancer patients. J Clin Oncol *11*: 2127-2135, 1993.
9 Ohtsu T, Sasaki Y, Tamura T, Miyata Y, Nakanomyo H, Nishiwaki Y and Saijo N: Clinical pharmacokinetics and pharmacodynamics of paclitaxel: a 3-hour infusion *versus* a 24-hour infusion. Clin Cancer Res *1*: 599-606, 1995.
10 Gelderblom H, Mross K, ten Tije AJ, Behringer D, Mielke S, van Zomeren DM, Verweij J and Sparreboom A: Comparative pharmacokinetics of unbound paclitaxel during 1- and 3-hour infusions. J Clin Oncol *20*: 574-581, 2002.
11 Mross K, Hollander N, Hauns B, Schumacher M and Maier-Lenz H: The pharmacokinetics of a 1-h paclitaxel infusion. Cancer Chemother Pharmacol *45*: 463-470, 2000.
12 Sparreboom A, van TO, Nooijen WJ and Beijnen JH: Nonlinear pharmacokinetics of paclitaxel in mice results from the pharmaceutical vehicle Cremophor EL. Cancer Res *56*: 2112-2115, 1996.
13 Huizing MT, Giaccone G, van Warmerdam LJ, Rosing H, Bakker PJ, Vermorken JB, Postmus PE, van ZN, Koolen MG, ten Bokkel Huinink WW, van d, V, Bierhorst FJ, Lai A, Dalesio O, Pinedo HM, Veenhof CH and Beijnen JH: Pharmacokinetics of paclitaxel and carboplatin in a dose-escalating and dose-sequencing study in patients with non-small-cell lung cancer. The European Cancer Centre. J Clin Oncol *15*: 317-329, 1997.
14 Mielke S, Sparreboom A, Steinberg SM, Gelderblom H, Unger C, Behringer D and Mross K: Association of Paclitaxel pharmacokinetics with the development of peripheral neuropathy in patients with advanced cancer. Clin Cancer Res *11*: 4843-4850, 2005.
15 Mielke S, Mross K, Gerds TA, Schmidt A, Wasch R, Berger DP, Lange W and Behringer D: Comparative neurotoxicity of weekly non-break paclitaxel infusions over 1 *versus* 3 h. Anticancer Drugs *14*: 785-792, 2003.
16 Mross K, Haring B, Hollander N, Mielke S, Behringer D, Massing U and Unger C: Comparison of 1-hour and 3-hours paclitaxel infusion pharmacokinetics: results from a randomized trial. Onkologie *25*: 503-508, 2002.
17 Mielke S, Mross K, Gerds T A, Schmidt A, Lange W and Behringer D: A multicenter, randomized phase III study on neurotoxicity, safety and efficacy of weekly Paclitaxel infused over 1-h *vs.* 3-h in patients with advanced solid tumors. [Abstract] Eur J Cancer *Suppl 1*: 164, 2003.

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