

Weekly paclitaxel plus capecitabine in advanced breast cancer patients: dose-finding trial of GOIRC and GOL

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Background: Paclitaxel and capecitabine have demonstrated a synergic effect and significant antitumor activity in patients with advanced breast cancer. A weekly schedule of paclitaxel obtained a response rate of 50–68% in advanced breast cancer and less serious side-effects.

Patients and methods: Thirty-two patients with advanced breast cancer pretreated with chemotherapy were enrolled in a dose-finding trial to determine the maximum tolerated dose (MTD) and the dose-limiting toxicity (DLT) of paclitaxel given on days 1, 8 and 15 of each cycle combined with capecitabine given twice daily from day 1 through day 14, every 21 days. Three patients were recruited at one of six dose levels (paclitaxel 70–100 mg/m², capecitabine 1650–2500 mg/m²).

Results: Thirty-two patients were accrued and 31 were evaluated for toxicity. One DLT has been experienced at level VI as diarrhea grade 3. We determined dose level V as the MTD, but we recommend dose level IV for phase II studies (capecitabine 1250 mg/m² orally twice daily plus paclitaxel 80 mg/m² intravenously weekly), owing to cumulative toxicity at level V. The objective response rate was 43%.

Conclusions: Weekly paclitaxel plus capecitabine is a safety and active chemotherapy in previously treated metastatic breast cancer.

Key words: capecitabine, metastatic breast cancer, weekly paclitaxel

introduction

Systemic cytotoxic chemotherapy (CT) is the treatment of choice for patients with metastatic breast cancer (MBC) who have rapidly growing tumors and/or negative hormone receptors. The availability of new drugs with a different mechanism of action, no overlapping toxicities and no cross-resistance is the logical progression for the clinical development of new combinations [1].

The increasing use of anthracyclines earlier in the disease course means that clinicians are now more frequently faced with the challenge of treating patients with disease that is resistant to this active drug or who are not candidates to receive it because of associated cardiotoxicity.

Capecitabine is a novel, oral fluoropyrimidine carbamate that is converted to 5-fluorouracil (5-FU) through a multistep pathway concluding with thymidine phosphorylase (TP), an enzyme found in increased concentrations in tumor tissue [2, 3].

This tumor selectivity potentially reduces systemic exposure to 5-FU, improves efficacy and reduces toxicity. Capecitabine is the most extensively evaluated agent in taxane-pretreated MBC [4]. Five hundred patients were enrolled in four large multicenter trials and all these studies have demonstrated that capecitabine is highly active in this heavily pretreated population, with overall response rates (ORR) of 15–20%, with a favorable safety profile [4, 5]. Furthermore, two randomized phase II studies have shown that capecitabine may play a role as first- and second-line CT in MBC patients [6, 7].

On the other hand, paclitaxel as first-line CT in metastatic disease has shown an ORR in the range of 30–60% [8]. As a second-line or salvage single-agent therapy in metastatic patients, paclitaxel generally affords an ORR of 6–48% even in anthracycline-resistant patients [9]. Moreover, administration of weekly cycles of paclitaxel, based on the concept that reducing the interval between treatment should minimize the appearance of drug resistance and regrowth, allows us to achieve higher cumulative doses with a lack of cumulative neutropenia and manageable neurotoxicity [10–13]. Neuropathy, when present,

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is usually of mild or moderate severity. This strategy permits a better dose-dense schedule and limited data suggest that the schedule may also possess activity against tumors previously thought to be resistant to paclitaxel delivered on an every 3 weeks schedule.

Recent studies administering paclitaxel weekly by 1-h infusion at doses ranging from 80 to 100 mg/m² have reported an ORR of 50–68%.

The rationale for the development of combination CT regimens consisting of capecitabine and paclitaxel for patients with breast cancer is based on the results of preclinical studies in human tumor xenografts [14]. Sawada et al. [15] showed that both taxanes enhance the efficacy of capecitabine and (5'-dFUrd) *in vivo*, probably by modulating (dThdPase) activity in tumor tissues. Furthermore, preclinical studies demonstrated that paclitaxel up-regulates intratumoral TP, which catalyzes the final step in the conversion of oral capecitabine to 5-FU.

Combination regimens of paclitaxel and 5-FU have demonstrated clinical antitumor activity and have shown cytotoxicity in MCF-7 breast cancer cell cultures *in vitro* when 5-FU follows paclitaxel exposure [16]. Paclitaxel plus 5-FU trials in previously treated MBC gave an ORR of 52–55% with a good safety profile [17, 18].

Based on these data, we designed a dose-finding study in pretreated patients with MBC to determine the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of capecitabine when administered twice daily according to the standard, intermittent schedule in combination with paclitaxel.

materials and methods

eligibility criteria

Thirty-two patients with histologically or cytologically proven progressive MBC entered into this dose finding trial. Eligibility criteria included: treatment with one or more lines of CT, treatment with taxanes in adjuvant setting stopped at least 12 months before, Eastern Cooperative Oncology Group performance status ≤2, life expectancy >3 months, normal hepatic and renal function, normal cardiac function and written informed consent.

Patients were ineligible if they were pregnant or lactating, had received prior treatment with taxanes and/or continuous infusion of 5-FU and/or capecitabine as advanced disease, had experienced previous or concurrent second malignant disease (except superficial squamous or basal-cell carcinoma of the skin or *in situ* carcinoma of the cervix) or non-malignant systemic disease such as congestive heart failure, angina pectoris, previous history of myocardial infarction, history of significant neurological or psychiatric disorders including dementia or seizures, active infection, peptic ulcer, or unstable diabetes mellitus precluding administration of CT. An history of prior allergic reactions to drugs containing Cremophor EL (teniposide, K vitamin, cyclosporine) was an exclusion criteria. Patients with neutrophil count <2 × 10⁹/l and/or platelet count <100 000/ml were not included.

All investigators were required to notify the trial office by telephone of any serious unexpected adverse event.

study design

This trial was a prospective, open label, dose-finding study in which three to six patients at each dose level were recruited. Before escalating to the next dose level, at least three patients had to have received at least one cycle and were observed for acute toxicity for a minimum of 2 weeks. If

none of three patients experienced a DLT, an additional three patients were accrued at the next dose level. If one of the three had a DLT, then three additional patients were treated at the same dose level, and further escalation was permitted if one of six had a DLT. The MTD was defined as dose level below which at least two of three or six patients had a DLT.

DLT was defined as the occurrence of one or more of the following toxicities during the first cycle of CT: absolute neutrophil count (ANC) <500 mm³ for ≥5 days, neutropenic fever defined as ANC <500 mm³ with fever ≥38.5°C (single evaluation) or temperature >38°C in two evaluations lasting 12 h each, platelets <25 000/mm³ for more 5 days or with bleeding requiring transfusions, any grade 3 or 4 non-hematological toxicity, except: grade 3–4 alopecia, grade 3–4 vomiting and neuropathy grade ≥2. Toxicities were graded using the National Cancer Institute (NCI) common toxicity criteria.

After informed consent was given by the patient, screening was completed and eligibility was verified, patients were registered by GOIRC Data Centre (Italy) with assignment of the patient's number.

treatment

Escalating dose levels of capecitabine and paclitaxel were used according to the schedule listed in Table 1. Paclitaxel was given weekly as a 1 h infusion, combined with capecitabine given twice daily from day 1 through day 14 (2 weeks' treatment, 1 week rest). Paclitaxel required pre-medications of dexamethasone (20 mg intravenously half an hour before the paclitaxel infusion), orphenadrine (40 mg intramuscularly half an hour before infusion) and ranitidine (50 mg intravenously half an hour before infusion) for prophylaxis of hypersensitivity reactions.

Any adverse events that were considered serious were reported within one working day to the Data Centre, and their intensity and relationship to trial drug was presented as summary tables.

Capecitabine is foreseen as a self-administered outpatient treatment, therefore it was critical that patients were informed regarding the need to interrupt treatment if moderate or severe toxicity occurred. In order to ensure that the patient was complying adequately with their medication regime, at each visit by a patient, the returned medication was checked and counted and the amount returned logged in the drug dispensing log. If a patient stopped treatment for more than a week, then that patient was withdrawn from the trial for non-compliance (unless the treatment interruption was due to toxicity). Minimum treatment duration for patient evaluation in the standard activity analysis was 3 weeks, from the start of first cycle to the second. Conditions for withdrawal were defined by failure of the patient to attend (two consecutive) scheduled visits, adverse events (including intercurrent illnesses), violations and deviations from the protocol, patients withdrawing consent, administrative/other or death.

Table 1. Dose escalation scheme

Dose level	Paclitaxel (mg/m ²)	Capecitabine (mg/m ²)	Total no. of patients	Median courses	DLT (No. patients/toxicity)
I	70	1650	3	3	–
II	70	2000	3	3	–
III	80	2000	4	6	–
IV ^a	80	2500	4	4	–
V ^b	90	2500	9	3	–
VI ^c	100	2500	9	4	1 (diarrhea)

^aRecommended dose level: IV.

^bMaximum tolerated dose level: V.

^cOne DLT at dose level VI.

DLT, dose-limiting toxicity.

follow-up

Forms were sent to the Data Centre for the study for each patient after the first cycle of CT and at the end of treatment. Before each course of therapy, patients had to undergo a physical examination, including neurological examination, hematological studies, renal and hepatic function studies, and serum carcinoembryonic antigen and CA 15-3 were performed. No specific neurometric testing that required any instrumentation beyond a reflex hammer had to be performed. Neurological examination consisted of gross evaluation of cranial nerve function, patellar reflexes, light touch sensation in the trunk and extremities, fine and gross-motor function assessment (flexion, extension, abduction and adduction) and cerebellar function (point-to-point testing and rapid rhythmic alternating movements).

Efficacy was not the aim of the study but ORR was evaluated. Response to treatment was assessed every 9 weeks (three cycles) and after the end of the treatment. At that time, if clinically indicated, a chest-X-ray, abdominal computed tomography scan or ultrasound and bone scan were performed, and any other instrumental investigations found to be abnormal at any evaluation. ORR was recorded according to standard WHO response criteria.

study end points and statistical methods

The primary objective of this study was the safety of a combination regimen with escalating regimen doses of paclitaxel and capecitabine.

Patients who did not receive at least one course (14 days) of capecitabine and paclitaxel (2 weeks) were excluded from the analysis of the toxicity results. All remaining patients were included in the intention-to-treat analysis and classified according to the achievement of a documented ORR. Drop-outs, early progression and early deaths were classified as failures. Patients withdrawn from treatment because of toxicity or other causes were classified as failures, unless an ORR was documented. The SPSS 9.0 statistical package was used for the statistical procedures.

results

patient characteristics

Thirty-two patients were enrolled in this trial, 31 (97%) were evaluable for toxicity, 23 (72%) were evaluable for tumor response, one (3.1%) was classed as a drop-out because she received only 1 day of CT and refused to continue the treatment. The median age of the patients was 61 years (range 33–76), with performance status of 0 in 29 (90.6%). The median number of previous lines of CT for advanced disease was one (range one to two), 11 (34.4%) patients were pretreated with antracyclines and the median number of previous hormonal therapy was two (range one to five).

The dominant site of metastatic disease was visceral disease in 20 (62.5%) patients, skin/soft tissue in seven (21.9%) patients and bone in five (15.6%) patients. Twenty-two (68.9%) patients had measurable disease. The other patient characteristics are listed in Table 2.

toxicity

Six dose levels were completed and the number of events in all cycles are listed in Tables 3 and 4. One DLT was experienced in dose level VI (capecitabine 2500 mg/m² and paclitaxel 100 mg/m²), characterized by diarrhea grade 3 associated with vomiting grade 2 and skin (hand-foot syndrome) grade 2. Three additional patients were accrued at this dose level, but no patient experienced DLT according to protocol. Dose level V was nevertheless the MTD, because of the incidence of

Table 2. Characteristics

Characteristics	n (%)
Number of evaluable patients	32 (100)
Median number of courses/patient (range)	3 (1–10)
Age, years [median (range)]	61 (33–76)
ECOG performance status (%)	
0	29 (90.6)
1	3 (9.4)
Histology	
Duttal	23 (74.2)
Lobular	4 (12.9)
NOS	4 (12.9)
Primary surgery	
Mastectomy	19 (59.4)
Quadrantectomy	11 (34.4)
Previous therapy	
Adjuvant hormoneotherapy	16 (50)
Advanced disease hormoneotherapy	19 (59.4)
Neo-adjuvant CT	2 (6.3)
Adjuvant CT	15 (46.9)
Metastatic disease CT	11 (34.4)
Antracycline based	
No. of CT lines [median (range)]	1 (1–2)
No. of hormonal lines [median (range)]	2 (1–5)

ECOG, Eastern Cooperative Oncology Group; NOS, not otherwise specified; CT, chemotherapy.

cumulative toxic events at level V such as neurotoxicity and skin (neurotoxicity grade 1–2, 36 events and grade 3–4, one event; cutaneous toxicity grade 1–2, two events and grade 4, one event); the recommended dose of paclitaxel was 80 mg/mq (dose level IV). Myelosuppression was mild at all dose levels. No patients died due to toxicity. Four (12.9%) patients were hospitalized during treatment (after one cycle) for toxicity: three patients were hospitalized for anemia and grade 3 fatigue and one patient for grade 4 skin rash and grade 3 neurotoxicity.

Two events of grade 3–4 hepatic toxicity, such as abnormalities of bilirubin value, were observed at dose level VI. One (3.3%) patient experienced total body hyperpigmentation and one (3.3%) allergic reaction to paclitaxel. Although one episode of DLT was observed at dose level VI, further escalation of both drugs was not planned.

dose intensity and response rate

Dose intensity (DI) was defined in the first cycle according to dose level. Thirty-one patients (97%) were evaluable for DI; one patient was excluded from analysis because she received only 1 day of treatment.

The median DI of capecitabine administered was 72% (range 41–89%) at dose level I, 89% (89–94%) at level II, 92% (41–95%) at level III, 95% (41–95%) at level IV, 89% (36–95%) at level V and 94% (41–111%) at level VI. The median DI of paclitaxel administered was 51% (51–94%) at dose level I, 93% (70–96%) at level II, 92% (90–96%) at level III, 96% (27–97%) at level IV, 79% (58–96%) at level V and 74% (3–95%) at level VI. The patients received a median of four cycles of therapy (range one to 10). Among 31 evaluable patients there were 10 responses [ORR 43.5%; 95% confidence interval (CI) 23% to

Table 3. Toxicity of capecitabine and paclitaxel

Toxicity	Number of events in all cycles					
	Level I	Level II	Level III	Level IV	Level V	Level VI
Hematological						
Neutropenia						
Grade 1–2	7	–	6	–	16	22
Grade 3–4	1	–	3	–	5	6
Anemia						
Grade 1–2	16	4	49	20	38	45
Grade 3–4	–	1	0	–	–	1
Thrombocytopenia						
Grade 1–2	–	–	–	–	–	–
Grade 3–4	–	–	–	–	–	–
Leukopenia						
Grade 1–2	13	10	15	–	24	32
Grade 3–4	1	–	–	–	1	5
Non-hematologic						
Nausea						
Grade 1–2	3	3	–	4	6	12
Grade 3–4	–	–	–	–	–	3
Diarrhea						
Grade 1–2	2	1	4	2	8	2
Grade 3–4	–	–	2	–	1	1
Vomiting						
Grade 1–2	1	2	1	1	3	5
Grade 3–4	–	–	–	–	1	–
Hyperbilirubinemia						
Grade 1–2	2	–	2	1	8	7
Grade 3–4	2	–	–	–	–	–
Mucositis						
Grade 1–2	5	1	–	–	4	8
Grade 3–4	–	–	–	–	1	–
Neurotoxicity						
Grade 1–2	8	–	9	8	36	23
Grade 3–4	–	–	2	–	1	–

Table 4. Cutaneous toxicity in all cycles

Toxicity	Number of events													
	Skin grade 1–2							Onycholysis grade 1–2						
	Cycle							Cycle						
	1	2	3	4	5	6	7	1	2	3	4	5	6	7
Dose level I	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Dose level II	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Dose level III	–	1	1	–	–	–	–	–	–	–	–	–	2	2
Dose level IV	–	–	1	–	–	–	–	–	–	–	–	–	–	1
Dose level V	–	2	1 ^a	–	–	–	–	–	–	–	–	–	–	1
Dose level VI	1	1	1	–	1	–	–	–	–	–	–	1	–	3 ^b

^aGrade 4; ^bgrade 2.

63%], including two CRs. Eight (26.7%) patients had SD. Eight out of 10 responses were obtained at dose level ≥IV (Table 5).

discussion

Oral capecitabine is activated to 5-FU by a TP-dependent process that generates 5-FU preferentially in tumor tissue,

Table 5. Tumor response

Response	Level						Total (%)
	1	2	3	4	5	6	
PR	1	–	1	–	2	4	8 (26.7)
CR	–	–	–	1	1	–	2 (20)
SD	–	–	3	1	2	2	8 (26.7)
PD	1	1	–	–	2	1	6 (20)
NE	1	2	–	1	2	2	6 (20)
OR (PR + CR)	1	–	1	1	3	4	10 (43.5)
95% CI							23–63

PR, partial response; CR, complete response; SD, stable disease; PD, progressive disease; NE, not evaluable; OR, overall response; CI, confidence interval.

reducing systemic exposure to 5-FU and potentially improving efficacy. Furthermore, oral capecitabine mimics continuous infusion 5-FU and avoids the inconvenience, complications and additional costs associated with intravenous CT and with central venous catheters. Oral administration enables convenient, patient-oriented, home-based therapy, which most patients prefer to intravenous treatment [19, 20]. Phase II studies have demonstrated the activity of capecitabine in heavily pretreated patients who are refractory to or have failed anthracyclines and taxanes with a response rate (RR) of 20–25%, with an impressive 29% RR in patients refractory to both paclitaxel and doxorubicin [5]. The benefit of capecitabine is not restricted to the treatment of heavily pretreated patients, but also as first-line treatment for MBC.

O’Shaughnessy et al. [6] published the results of a randomized trial in 511 women with MBC treated with docetaxel with or without capecitabine 1250 mg/m². The overall median survival was longer in patients randomized to the combination than to docetaxel alone (14.5 versus 11.5 months; *P* = 0.006); the RR was also higher in the combination arm (42% versus 30%; *P* = 0.006). Although many of the adverse effects were similar, grade 3 hand–foot syndrome occurred in 24% of patients in the combination arm, but in only 1% of patients in the docetaxel-only arm. Approximately 65% of patients in the combination arm required dose reductions compared with 36% in the single-agent arm. This study provided important evidence of a superior survival duration in patients with MBC with the addition of capecitabine. Although, it should be emphasized that the question of whether combination treatment (sequentially or in combination) in MBC is preferable remains controversial.

Paclitaxel is active in the treatment of MBC as first-line therapy as well as in heavily pretreated patients [8]. As mentioned in the Introduction, weekly administration of paclitaxel has several merits compared with even 3-week administration in terms of both toxicity and efficacy [10–13]. With weekly administration of moderate doses of paclitaxel, higher cumulative doses can be achieved than with an every 3 weeks schedule, yet myelosuppression is generally modest. In an effort to minimize bone marrow suppression and other toxicities of the weekly paclitaxel schedule, both the dose and infusion time have been reduced compared with the every 3 weeks schedule. This dose-dense approach may inhibit tumor

regrowth between cycles and limit the emergence of malignant cells resistant to CT. More frequent exposure to paclitaxel may also enhance its apoptotic and angiogenic effects [21].

This dose-finding study demonstrated that this regimen has a favorable toxicity profile and is feasible on an out-patient basis. Only one DLT was observed at dose level VI (diarrhea grade 3), but the cumulative toxicity shown at dose levels V and VI obliges us to recommend dose level IV for a phase II study: capecitabine 2500 mg/m² orally twice daily on days 1–14 plus paclitaxel 80 mg/m² intravenously weekly, with cycles repeated every 21 days.

Neurotoxicity, which can be cumulative with paclitaxel treatment, was mild with weekly paclitaxel doses up to 80 mg/m². The principal cumulative toxicity at dose levels V and VI was sensory-motor neuropathy, onycholysis and nail mycosis. These side-effects were registered within a weekly administration schedule of taxanes in particular these drugs usually cause hyponychium hyperpigmentation, most likely due to matrix melanocyte stimulation, and reduce nail growth. Although this trial was designed to define the best dose of paclitaxel and capecitabine, the combination also demonstrated high antitumor activity. An objective response was observed in 43% of evaluable patients, with 26.7% SD. The DI of both drugs was high in all dose levels.

Seidman et al. [22] administered paclitaxel (100 mg/m²) weekly to patients with previously treated MBC and observed a 53% ORR, with 10% CRs. In the subgroup with anthracycline-resistant disease, the RR was 50%. Therapy was well-tolerated, with a lack of cumulative neutropenia and manageable neurotoxicity. A multicenter study reported a lower RR of 25%. In a large CALGB trial (9840), Seidman et al. [23] evaluated weekly paclitaxel versus standard 3-h infusion every third week in the treatment of MBC in combination with trastuzumab for HER2-positive patients and randomized for trastuzumab in patients with HER2 normal. This trial enrolled 585 patients with advanced breast cancer and showed that weekly paclitaxel was superior to standard schedule of paclitaxel with respect to RR (40% versus 28%; $P = 0.017$) and time to progression (9 versus 5 months; $P = 0.0008$). Overall survival was 24 months for weekly versus 16 months (hazard ratio 1.19; $P = 0.17$) with standard schedule. Recently, 258 patients with clinical stage I–IIIA breast cancer were randomized between weekly paclitaxel (for a total of 12 doses) or every 3 weeks (four cycles) followed by four cycles of FAC (5-FU, adriamycin, cyclophosphamide) as neo-adjuvant treatment [24]. Weekly schedule improved the pathological CR rate (28.2% versus 15.7%; $P = 0.02$), with an improved breast conservation rate ($P = 0.05$).

Del Mastro et al. [25] reported an ORR with weekly paclitaxel of 53.7% in 41 elderly patients with MBC, with a median progression-free survival of 9.7 months and a median survival of 35.8 months; however, in this trial there was an increased risk of cardiotoxicity (five out of 46) ranging from grade 2 to 5. No cases of cardiotoxicity were reported in previous studies with weekly paclitaxel in MBC. The principal reason for this toxicity may be related to the median age of patients (74 years; range 70–87) and other cardiotoxicity risk factors. In our trial, with patients receiving weekly paclitaxel plus capecitabine, no patients developed clinical cardiotoxicity. In our trial patients received echocardiographic evaluation only if they developed symptoms.

Batista et al. [26] evaluated in a multicenter trial the efficacy and safety of capecitabine (2000 mg/m² days 1–14) and paclitaxel (175 mg/m²) in 73 anthracycline-pretreated advanced or MBC. The ORR was 52% (95% CI 40% to 63%) with 11% CR. Median time to progression was 8.1 months and overall survival was 16.5 months. The most common toxicities grade 3/4 were hand–foot syndrome (11%), alopecia (22%), diarrhea (26%) and neutropenia (12%).

Gradishar et al. [27] treated, in multicenter phase II trial, 46 women with the combination of capecitabine plus 3-week paclitaxel (175 mg/m²). The ORR was 51% with seven (15%) CRs. Forty-four (94%) patients received this combination therapy as first-line treatment for metastatic disease. Median duration of response was 12.6 months, median time to progression and overall survival were 10.6 and 29.9 months, respectively. Neutropenia (15%), alopecia (13%) and hand–foot syndrome (11%) were the only grade 3–4 treatment-related adverse events that occurred in more than 10% of patients. In this trial the dose of capecitabine (825mg/m² twice daily) was significantly lower than other phase II trials. The lower dose reduced the frequency and severity of gastrointestinal toxicity (4%) compared with 14–64% higher dose.

Recently, two retrospective analyses evaluating the delivered dose of capecitabine in patients with advanced breast cancer suggested that a lower dose of capecitabine (2000 mg/m²) was better tolerated, without compromising efficacy [28, 29].

A recent phase II trial using capecitabine plus paclitaxel every 3 weeks at a dose of 135–175 mg/m² as a 3-h infusion found myelosuppression during 18 of 66 courses (27%) [7]. This toxicity was higher than our study and might be explained by the use of 3-weekly schedule of paclitaxel, although the theoretic DI in the weekly paclitaxel schedule (80 mg/m²) was 79.9 mg/m²/week, while in 3-week paclitaxel (175 mg/m²) it was 58 mg/m²/week. The low toxicity may reflect the observation that paclitaxel's induction of neutropenia relates neither to peak plasma concentration nor to the area under the concentration–time curve, but to the period during which the drug concentration exceeds a threshold level. This critical concentration has been estimated to be 0.05–0.10 mmol/l. Data from studies of weekly paclitaxel demonstrate that the majority of patients were in the 'safe' zone of ≤ 0.1 mmol/l only 6 h after infusion, and no patient examined 25 h after infusion was above this threshold [30].

In conclusion, we suggest that capecitabine (1250 mg/m² orally twice daily on days 1–14) plus weekly paclitaxel (80 mg/m²) is a safe and active combination that may offer patients with advanced cancer an optimized palliative CT treatment. Further trials in phase II–III are warranted.

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