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Review

Combination chemotherapy of the taxanes and antimetabolites: its use and limitations

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Abstract

In an effort to improve response rates of chemotherapy, taxanes have been combined with other cytotoxic agents such as antimetabolites. However, the use of some of these combinations in patients has been restricted by severe toxicity. The significance of the sequence of drug administration in combining methotrexate (MTX) and taxanes was recognised in in vitro studies, showing synergistic effects for the sequence of MTX followed by paclitaxel, and antagonism for exposure in the reverse order. A possible explanation might be an MTX-induced synchronisation of cells in the S phase of the cell cycle, after which cells are more susceptible for the cytotoxic action of taxanes. Clinical studies using this sequence were hampered by severe neutropenia and mucositis at relatively low doses of both drugs. As no pharmacokinetic interactions were observed, the excess of toxicity may have been due to sequence-dependent synergistic actions on bone marrow and mucosa. In contrast, and confusingly, in vitro studies on 5-fluorouracil (5-FU) and taxanes indicate that 5-FU preceeding or simultaneously given to paclitaxel impairs cytotoxicity as compared with paclitaxel monotherapy, while the reverse sequence results in additive or synergistic cytotoxicity. While almost all clinical studies have used the sequence of a taxane followed by 5-FU, various schedules appeared feasible and effective. The combination of a 5-FU analogue, capecitabine and taxanes was supported by in vitro data. A large phase III trial confirmed the feasibility and superior efficacy of this combination in breast cancer patients relapsing after an anthracycline. Conflicting results exist on the benefit of combining gemcitabine and taxanes in tumour cell lines. Although the accumulation of gemcitabine triphosphate (dFdCTP) in mononuclear cells was significantly higher with an increasing dose of paclitaxel, no pharmacokinetic interactions for both agents were noticed. A pharmacokinetic analysis of the gemcitabine–docetaxel combination therapy has not been published in detail. Despite numerous trials, so far no optimum schedule has been established. Regarding data on actually delivered dose intensities, a 2- or 3-weekly cycle seems favourable and feasible. However, possible severe pulmonary toxicity warrants cautious monitoring of patients treated with this combination. Different outcomes of preclinical and clinical studies reveal that combining two chemotherapeutic agents is not simply a matter of putting antitumour activities together. Drug interaction may result in synergism, not only of efficacy but also of toxic side-effects. Adding two drugs may also implicate antagonism in drug efficacy due to unwanted interference in cytotoxicity or pharmacokinetics. For agents acting at a specific phase of the cell cycle, the sequence of administration may determine the efficacy and toxicity of a combination therapy. Because of an observed discrepancy between in vitro data and clinical studies, we would like to emphasise the need for adequate dose-finding clinical trials together with pharmacokinetic data analysis before examining any new combination chemotherapy in more detail in phase II studies.

Keywords: Combination chemotherapy; Taxanes; Antimetabolites; Sequence; Pharmacokinetics

1. Introduction

Curative cancer chemotherapy nearly always consists of a combination of cytotoxic agents. Increased efficacy of combination chemotherapy may result from the increase of total exposure to a cytotoxic effect due to the addition of other agents, especially if non-overlapping toxicities allow dose intensities for the combination to be similar to those of the single agents. Other rationales for combination chemotherapy are the possibility to overcome (multi)drug resistance and synergistic effects of certain antitumour drugs [1]. Concomitant administration of anticancer agents may affect the pharmacokinetic parameters such as absorption, distribution, metabolism or excretion of a drug, or may result in pharmacodynamic interactions at the level of cellular targets or the cell cycle,

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which can have both a positive or a negative impact on the cytotoxic effects of the drugs involved.

Since the late 1980s, taxanes have proved to be effective agents in the treatment of a variety of solid tumours [2]. Paclitaxel is currently registered for the treatment of advanced breast cancer, ovarian cancer and non-small cell lung cancer and as a single agent it is usually dosed at 135–225 mg/m^2 as a 3-h intravenous (i.v.) infusion every 3 weeks [3]. Docetaxel is registered for the treatment of metastatic breast cancer and non-small cell lung cancer and is most often given at a dose of 100 mg/m^2 as a 1-h i.v. infusion in a 3-weekly schedule. Currently, weekly administration of taxanes, enabling a higher dose per time period and inducing less toxicity, is being explored in several phase I-II studies [4].

In view of the established efficacy of taxanes, numerous combinations of taxanes with other agents in various treatment schedules have been investigated in an effort to improve the response rates to palliative chemotherapy in solid tumours. Such combinations included those of taxanes with antimetabolites, but some of these yielded major problems in patients due to severe toxicity, which prevented maximum tolerable doses (MTDs) that were considered to be relevant for the single agents [5,6]. This contrasts with the feasibility of combining taxanes with other classes of cytotoxic agents almost at their respective recommended single doses. This review will summarise both preclinical and clinical studies on combinations of taxanes and the antimetabolites methotrexate (MTX), 5-fluorouracil (5-FU), capecitabine and gemcitabine, respectively, and consider possible mechanisms of interaction accounting for their efficacy and clinical feasibility. Combinations of other antimetabolites with taxanes have rarely been investigated and will therefore not be discussed.

2. Pharmacology of taxanes

Taxanes exert their cytotoxic effect by stabilising the assembly of intracellular microtubules from tubulin dimers, thereby disrupting mitosis and other vital cellular functions. In studies with hamster ovarian cell lines and human ovarian and leukaemic cell lines, paclitaxel appeared to be a phase-specific agent, being more cytotoxic to mitotic (M) cells than interphase (G_1, S, G_2) cells [7,8]. In studies with human leukaemic cell lines, paclitaxel induced a temporary accumulation of cells in G_2 and M phase [9,10]. As asynchronous human tumour cell cultures include paclitaxel-resistant interphase cells, the fraction of killed cells reaches a plateau despite an increasing concentration of paclitaxel [11]. In contrast, prolonging the exposure time of various human tumour cell lines to paclitaxel from 24 to 72 h resulted in a marked increase in cytotoxicity [11]. Even in a synchronous cell culture of mainly mitotic cells, a period of exposure of at least 4–6 h to paclitaxel at a concentration of 1.6 ug/ml was required to kill most cells, which emphasises the importance of duration of paclitaxel exposure rather than the drug concentration [8]. Besides inducing an arrest in the cell cycle in the G_2 and M phase, paclitaxel initiates apoptosis along various pathways, most of which are not yet resolved [12]. For docetaxel, a brief exposure (1 h) of a synchronous culture of HeLa cells in S phase was lethal, without a subsequent block in the cell cycle [13]. After prolonging the exposure to 24 h, both paclitaxel and docetaxel blocked the cell cycle of a human cancer cell line at the G_2–M phase [14].

The pharmacokinetics of paclitaxel and docetaxel show a large volume of distribution with extensive protein-binding, and a rapid elimination from the plasma with a short terminal half-life of 5 and 12 h, respectively, mainly due to hepatic metabolism, biliary excretion and tissue distribution [2,3]. Both paclitaxel and docetaxel are administered intravenously, using different vehicles to overcome their insolubility in water. Paclitaxel is dissolved in a 1:1 mixture of Cremophor EL (CrEL) and ethanol. CrEL has a small volume of distribution, almost similar to that of the blood compartment, and a long terminal half-life of 80 h [15]. It was recently shown that the vehicle CrEL appeared to have a major impact on the pharmacokinetics of paclitaxel, being responsible for its non-linear plasma distribution [16]. This non-linear disposition of paclitaxel implies that the total exposure to this agent increases disproportional to its dose. An increase in the concentration of CrEL causes a reduction in both the free fraction of paclitaxel and its accumulation in erythrocytes, probably due to drug trapping in the CrEL micelles, which act as the main carrier of paclitaxel in the blood compartment. Combination chemotherapy schedules with paclitaxel may carry a risk of unforeseen interactions of CrEL with other anticancer agents. Indeed, clinically significant interactions resulting in excessive toxicity have been reported when paclitaxel given as a 3-h infusion preceded a bolus infusion of doxorubicin [17].

For docetaxel, linear pharmacokinetics are observed. Docetaxel is formulated in polysorbate 80 (Tween 80), which has a rapid plasma elimination and is already undetectable in plasma after 1 h [15,18]. Due to this rapid decline from plasma, it is unlikely that this vehicle causes significant interactions in docetaxel-based combination chemotherapy [15].

3. Taxane/methotrexate combinations

3.1. Preclinical studies

MTX is one of the oldest anticancer drugs in clinical use. Antimetabolites such as MTX interfere with DNA synthesis, that is necessary for cell proliferation. Due to

their mode of action, most antimetabolites act at specific phases of the cell cycle. MTX inhibits dihydrofolate reductase, which results in the depletion of intracellular tetrahydrofolate, and thereby impedes synthesis of thymidylate and purines required for DNA synthesis. It acts as a phase-specific agent by arresting cells in the S phase. In the search for folate analogues with increased antitumour activity, new dihydrofolate reductase inhibitors such as edatrexate have been developed [19].

3.2. Paclitaxel/methotrexate

Various schedules of paclitaxel and MTX were tested *in vitro* in human breast cancer cells, using both growth inhibition and clonogenic assays to evaluate drug activity [20]. Simultaneous exposure to both agents for 3 days and exposure to paclitaxel for 6 hours after which MTX was added for 3 days resulted in antagonistic effects. However, sequential exposure to MTX for 12 h followed by the addition of paclitaxel for 12 days clearly showed synergism. The significance of the sequence in combining both drugs was confirmed by an *in vitro* study with human breast, ovarian and lung cancer cell lines, which used the isobologram method to analyse the effect of the drug combinations [21]. In this study, simultaneous exposure to both agents for 24 h and exposure to paclitaxel for 24 h followed by MTX for 24 h also exhibited antagonism, whereas the reverse sequence yielded synergistic effects. Colony forming assays in a human bladder cancer cell line demonstrated that MTX (for 24 h) prior to a low dose of paclitaxel (for 24 h) resulted in maximal synergistic cytotoxicity [22]. Chou and colleagues assessed the effect of combining edatrexate and a taxane on the inhibition of cell growth with the combination index–isobologram method [23]. In two human breast cancer cell lines, incubation with edatrexate for 3 h followed after 24 h by paclitaxel for 3 h appeared to be synergistic, while antagonism was noted with the reverse schedule.

3.3. Docetaxel/Methotrexate

Similar schedule-dependent synergistic or antagonistic effects were observed for the combination of edatrexate and docetaxel [23].

Thus, preclinical data suggest that for efficacy it may be best to administer MTX prior to the taxane. A possible explanation for the sequence-dependent synergism observed *in vitro* might be an MTX-induced synchronisation of the cells in the S phase, after which cells are more susceptible to the cytotoxic action of the taxanes [23]. Indeed, another compound which arrests cells at the S phase, such as gallium nitrate, also shows sequence-dependent synergism when given at least 12 h prior to paclitaxel [24]. These studies indicate that MTX should preceed taxane administration by at least 12 h, the time necessary for cells to enter the M phase [20,24]. In the reverse sequence, paclitaxel might reduce the cytotoxicity of MTX by arresting the cell cycle and preventing cells from entering the S phase, in which they are most susceptible to MTX.

3.4. Clinical studies

Nearly all studies combining taxanes and MTX used a 3-weekly cycle. Dosing schedules and response rates of these trials are depicted in Tables 1 and 2.

3.5. Paclitaxel/Methotrexate

Two trials in urothelial carcinoma investigated paclitaxel and MTX administered both on day 1, in combination with carboplatin or cisplatin, respectively [25,26]. Paclitaxel and MTX were administered i.v. immediately after each other. Toxicity mainly consisted of grade 3–4 neutropenia and grade 1–2 neurotoxicity and appeared tolerable. In contrast, the regimen of Huber and colleagues administering MTX as a bolus 24 h prior to paclitaxel as a 24 h infusion was found to be fairly toxic, with febrile neutropenia preventing further dose escalation of paclitaxel beyond 135 mg/m^2 despite G-CSF support [6]. As paclitaxel plasma levels during the paclitaxel infusion were not altered by prior MTX infusion in this study, the observed excessive toxicity in this regimen is unlikely to be related to pharmacokinetic interactions [6]. Unfortunately, further pharmacokinetic data on the paclitaxel–MTX combination in humans are lacking, which is a major drawback of the reported studies. Taking into account the *in vitro* data on the synergism for the sequential administration of MTX preceding paclitaxel, the severe myelosuppression in the latter trial might be due to similar synergistic activity on normal bone marrow cells [21]. Another explanation for the observed toxicity may be the long duration of the paclitaxel infusion of 24 h. Indeed, a similar sequence of another folate analogue, edatrexate, followed after 24 h by paclitaxel given as a short 3-h infusion was well tolerated in two studies and did not require the support of growth factors [27,29].

3.6. Docetaxel/Methotrexate

Only two trials have investigated the combination treatment of docetaxel and MTX, both involving patients with solid tumours (Table 2) [5,30]. Administration of both drugs on the same day appeared to be feasible, and did not require the support of haematopoietic growth factors [30]. A bolus infusion of MTX followed after 24 h by docetaxel given as a 1-h infusion was complicated by dose-limiting neutropenia and mucositis at relatively low doses of the drugs, even despite the additional use of haematopoietic growth

Table 1
Clinical studies combining methotrexate and paclitaxel

Reference	q (weeks)	Paclitaxel regimen	MTX regimen	G-CSF	Tolerable dose of paclitaxel–MTX (mg/m^2) per cycle	Tumour type	Prior chemotherapy	No. of evaluable patients	RR (%)
[25]	3	d 1 3 h	d 1 + carboplatn	+	200–60	Bladder	–	32	56
[26]	3	d 1 3 h	d 1 0.5 h + cddp	+	200–30	Bladder	+	25	40
[6]	3	d 2 24 h	d 1	–	85–23	Solid	+	41	10
				+	135–40				
[27][a]	3	d 2 3 h	d 1 1 h	–	175–350[a]	Breast	±	35	31
[28][a]	3	d 2 24 h	d 1, 15	+	170–250[a]	Solid	+	40	33
[29][a]	4	d 2,16 3 h	d 1, 15	–	350–240[a]	Solid	+	34	24

q, every; , G-CSF, granulocyte-colony stimulating factor; MTX, methotrexate; RR, response rate; d, day; h, hour; cddp, cisplatin. All studies administered MTX as a bolus infusion, unless stated otherwise

[a] Study using edatrexate instead of MTX.

Table 2
Clinical studies combining methotrexate and docetaxel

Reference	Docetaxel regimen	MTX regimen	G-CSF	Tolerable dose of docetaxel–MTX per cycle (mg/m^2)	Tumour type	Prior chemotherapy	No. of evaluable patients	RR (%)
[5]	d 2 1 h	d 1, 15	+	75–80	Solid	+	18	22
[30]	d 8	d 1, 8	–	90–80	Solid	ng	28	14

d, day; h, hour; G-CSF, granulocyte-colony stimulating factor; MTX, methotrexate; RR, response rate; ng, data not given in publication. All studies used a 3-weekly cycle.

factors [5]. Extensive pharmacokinetic analyses revealed no pharmacokinetic interactions for this sequence [5]. A study on the effect on MTX pharmacokinetics by the administration of docetaxel immediately or 24 h afterwards found a non-significant rise in the area under the concentration curve (AUC) and a somewhat lower plasma clearance of MTX [31]. Another pharmacokinetic study confirmed a lack of interaction of the concomitant administration of docetaxel and MTX [30].

The combination schedules of MTX followed by a taxane after an interval of 24 h show a striking excess of toxicity at relatively low doses of both agents, with no apparent benefit on tumour responses. As no pharmacokinetic interactions were observed, severe toxicity may be due to sequence-dependent synergistic cytotoxicity on normal tissue such as bone marrow and mucosa. Some of the preclinical studies as mentioned above support this explanation.

4. Taxane/5-FU combinations

4.1. Preclinical studies

5-FU is a pyrimidine antimetabolite, which is phosphorylated to 5-fluorouridine triphosphate (5-FUTP). Subsequent incorporation into RNA interferes with cellular RNA processes. Another activated 5-FU metabolite, 5-fluorodeoxyuridine monophosphate (5-FdUMP), inhibits thymidylate synthase, which is required for DNA synthesis. *In vitro* treatment of mouse T-lymphocytes and human breast cancer cell lines with 5-FU resulted in an interruption at the G_1–S phase of the cell cycle [32,33].

4.2. Paclitaxel/5-FU

Kano and colleages investigated various schedules of paclitaxel and 5-FU *in vitro* in four human cancer cell lines, evaluating dose–response effects with isobolograms [34]. Synchronous exposure to both agents for 24 h, or sequential exposure to 5-FU for 24 h followed by paclitaxel for 24 h showed an antagonistic interaction, while reversal of the sequence of exposure had an additive effect. Interestingly, prolongation of the interval of simultaneous exposure to 5 days resulted in an additive interaction. *In vitro* studies with human breast and epidermoid cancer cell lines indicated that pretreatment with 5-FU for 6 h or simultaneous treatment with 5-FU and paclitaxel for 24–72 h impaired overall cell killing activity compared with paclitaxel monotherapy [33]. The antagonistic effect of 5-FU on paclitaxel cytotoxicity was no longer apparent if tumour cells were pretreated with paclitaxel at least 24 h prior to 5-FU. A similar schedule-dependency with antagonism for 5-FU followed by paclitaxel and synergism for the reverse sequence was

noticed in a clonogenic assay of human breast cancer cells [35]. The authors suggested that 5-FU appeared to interfere with paclitaxel cytotoxicity by preventing tumour cells from accumulating in the G_2–M phase of the cell cycle, in which paclitaxel exerts its cytotoxic effect. It is confusing that a similar reasoning was used to explain the synergistic effect of MTX followed by taxanes. Apparently, we lack an appropriate mechanism. Other *in vitro* studies using DNA fragmentation techniques revealed that pretreatment or simultaneous exposure with 5-FU together with paclitaxel reduced the induction of apoptosis by paclitaxel, whereas it blocked paclitaxel-induced bcl-2 phosphorylation, c-raf-1 phosphorylation and $p21^{WAF/CIP1}$ expression [36].

All preclinical data on the combination of 5-FU and paclitaxel favour the sequence of paclitaxel prior to 5-FU.

4.3. Docetaxel/5-FU

Preclinical studies investigating the simultanous treatment of docetaxel and 5-FU in xenografts of colon carcinoma in mice resulted in a synergistic cell kill [37]. To our knowledge, preclinical studies with cell lines on the influence of sequence in using 5-FU and docetaxel have not been performed.

4.4. Clinical studies

Tables 3 and 4 summarise data of clinical trials evaluating the addition of 5-FU to paclitaxel and docetaxel, respectively. A large variety of chemotherapy schedules has been studied. For the ease of survey, studies using the combination of 5-FU and taxanes with other cytotoxic agents were excluded. As a sequence-dependent synergism for the administration of taxanes followed by 5-FU was observed in the preclinical studies, all clinical studies except one [50] used this preferred sequence. In contrast to the *in vitro* studies, many clinical trials added leucovorin to the 5-FU-paclitaxel chemotherapy regimen.

4.5. Paclitaxel/5-FU

Five studies investigating paclitaxel and 5-FU in a 3-weekly cycle noticed tolerable side-effects of mainly leucocytopenia and mild neurotoxicity [39–43]. Nicholson and colleagues investigated a 4-weekly cycle of paclitaxel and 5-FU in 52 evaluable patients with metastatic breast cancer, of whom 47 had been pretreated with chemotherapy [44]. Toxicity was acceptable with mucositis ($n=3$) and neutropenic fever (5% of cycles). In a study applying continuous infusion of 5-FU, apart from neutropenia and mucositis, neurotoxicity grade 2 was also observed in 43% of these patients [45]. A regimen of 6 weeks of treatment with both agents followed by 2 weeks of rest administered as second-line therapy to 34 evaluable breast cancer patients was found feasible with grade 3–4 leucopenia in 36% of cycles [46]. Unfortunately, and in line with the studies combining paclitaxel and MTX, possible pharmacokinetic interactions have not been analysed in any of these studies and data on delivered dose intensities are lacking.

4.6. Docetaxel/5-FU

Most of the clinical studies examining the feasibility of combining docetaxel with 5-FU used a cycle of 3 weeks, and noticed tolerable toxicities of mainly neutropenia, stomatitis and diarrhoea [48,49,52]. The only study that administered a taxane (docetaxel) after the start of 5-FU did not show any apparent lack of efficacy [50]. In a dose-finding study in pretreated solid tumours, the MTD of both drugs in a 3-weekly cycle was almost similar to those of the drugs used as single agent, grade 4 neutropenia being the dose-limiting toxicity (DLT)

Table 3
Clinical studies combining 5-FU and paclitaxel

Reference	q (weeks)	Paclitaxel regimen	5-FU regimen	LV	Tolerable dose of paclitaxel–5-FU per cycle (mg/m^2)	Tumour type	Prior chemotherapy	No. of evaluable patients	RR (%)
[38]	2	d 1 1 h	d 1–5, 8–12 ci[a]	–	135–3500	Breast	–	16	38
[39]	3	d 1 3 h	d 2 3 h	–	175–1500	Gastric	–	29	66
[40]	3	d 1 3 h	d 1, 8, 15 b[b]	–	225–1500	Gastric	+	15	13
[41]	3	d 1 3 h	d 1–5 2 h	+	175–3000	Nasopharyngeal	+	24	13
[42]	3	d 1 3 h	d 2–5 b	+	175–1480	Solid	±	17	35
[43]	3	d 1–4 ci	d 5 23 h	+	140–1000	Solid	+	10	70
[44]	4	d 1 3 h	d 1–3 b	+	175–1050	Breast	+	52	52
[45]	6	d 1, 22 3 h	d 1–42 ci	–	350–10500	Breast	+	42	50
[46]	8	d 1, 22 3 h	d 1, 8, 15, 22, 2, 9, 36, 24 h	+	350–12000	Breast	+	34	53
[47]	8	d 1, 22 3 h	d 1, 8, 15, 22, 29, 36, 24 h	+	350–12000	Gastric	–	22	32

q, every; d, day; h, hour; RR, response rate; LV, leucovorin; 5-FU, 5-fluorouracil.
[a] ci, continuous infusion.
[b] b, bolus infusion.

Table 4
Clinical studies combining 5-FU and docetaxel

Reference	q (weeks)	Docetaxel regimen	5-FU regimen	LV	Tolerable dose of docetaxel–5-FU per cycle (mg/m^2)	Tumour type	Prior chemotherapy	No. of evaluable patients	RR (%)
[48]	3	d 1 1 h	d 1–5[a] ci	–	85–3750	Solid	+	39	13
[49]	3	d 1 1 h	d 1–5 ci	–	85–3750	Breast	+	32	56
[50]	3	d 2 1 h	d 1–4 2 h	+	80–2400	Gastric	–	26	31
[51]	3	d 1, 8, 15	d 1–14 ci	–	75–2100	Gastric	–	10	100
[52]	3–4	d 1 1 h	d 1–5 ci	–	50–2500	Breast	+	18	50
[53]	4	d 1 1 h	d 1–5 ci	–	60–1500	Solid	+	37	8

q, every; 5-FU, 5-fluorouracil; d, day; h, hour; LV, leucovorin; RR, response rate.
[a] ci, continuous infusion.

[48]. Another phase I study using a similar schedule found similar MTDs in pretreated breast cancer patients [49]. This study was the only one to mention that the doses were administered on time and without dose reductions in 97 and 95% of the cycles, respectively. Of note, two other studies found a lower MTD especially for docetaxel, despite an even longer schedule of 3–4 or 4 weeks instead of 3 weeks [52,53]. The Japanese study of Ando and colleagues did not administer corticosteroid premedication and was the only one to report grade 3–4 diarrhoea as a DLT in 2 out of 6 patients at their highest dose level [52]. Petit and colleagues did not continue dose escalation because of grade 4 neutropenia lasting for more than 7 days and neutropenic fever in their heavily pretreated patients [53]. Pharmacokinetic analyses noticed no apparent relationship between the clearance and AUC of both docetaxel and 5-FU [48]. In general, the combination of 5-FU and a taxane seems feasible and the observed response rates at least do not suggest an antagonistic effect. Randomised phase II/III studies will be required to adequately assess efficacy.

5. Taxane/capecitabine combinations

5.1. Preclinical studies

Capecitabine is an oral prodrug of 5-FU that is converted along a pathway with three enzymes to the active compound 5-FU. The final step of conversion into 5-FU is catalysed by thymidine phosphorylase (TP), an enzyme that is more abundantly expressed in tumour tissue than in healthy cells. In studies with human colon and breast cancer xenografts in nude mice, both paclitaxel and docetaxel enhanced the level of TP in tumour cells [54]. These *in vitro* data support the use of the combination of capecitabine and taxanes. Indeed, simultaneous treatment of paclitaxel or docetaxel with orally administered capecitabine showed synergistic antitumour activity in the xenograft models, while only additive activity was noted with a taxane–5-FU combination.

5.2. Clinical studies

Six trials explored the clinical feasibility of oral capecitabine in combination with a taxane in a 3-weekly schedule (Table 5) [55–60]. The encountered DLT in the combination with paclitaxel was neutropenia, while other side-effects were similar to those following administration of the single agents [56]. Of notice, asthenia was the DLT for the combination with docetaxel [60]. Extensive pharmacokinetic analyses revealed no significant effects of paclitaxel or docetaxel on the AUC of capecitabine and its metabolites, and *vice versa* [56,60].

Combining capecitabine with a taxane therefore seems attractive, with acceptable toxicity and a promising efficacy. Data from a large randomised phase III trial in 511 metastatic breast cancer patients relapsing after anthracycline-based therapy showed superior activity with the combination of docetaxel and capecitabine versus docetaxel single agent therapy [59]. The combination resulted in a RR of 42% and a median survival of 13.7 months (95% CI: 12.3–16.1), versus a RR of 30% and a median survival of 11.1 months (95% CI: 9.8–12.4) for docetaxel alone.

6. Taxane/gemcitabine combinations

6.1. Preclinical studies

Gemcitabine is a nucleoside analogue that impairs DNA synthesis. It is phosphorylated intracellularly to active triphosphate metabolites, the intracellular concentrations are increased and prolonged by several self-potentiating mechanisms [62]. After *in vitro* exposure to gemcitabine, human lung cancer cells accumulated in the G_0–G_1 and S phases [63,64].

6.2. Paclitaxel/Gemcitabine

Clonogenic survival assays of human tumour cell lines have shown less than additive cytotoxicity for any sequential exposure to gemcitabine and paclitaxel, and

Table 5
Clinical studies combining capecitabine and a taxane

Reference	Taxane regimen	Capecitabine regimen	Tolerable dose of taxane–capecitabine per administration (mg/m2)	Tumour type	Prior chemotherapy	No. of evaluable patients	RR (%)
[55]	d 1 3 h	d 1–14	P 175–1650	Breast	+	19	56
[56]	d 1 3 h	d 3–21	P 175–1331	Solid	+	17	0
[57]	d 1	d 1–14	P 175–2000	Breast	+	64	63
[58]	d 1	d 1–14	P 175–1650	Breast	+	37	49
[59]	d 1 1 h	d 1–14	D 75–2500	Breast	+	255	42
[60]	d 1 1 h	d 1–14	D 100–1650	Solid	+	33	15
[61]	d 1, 8 , 15	d 5–18	D 36–1250	Solid	±	15	27

RR, response rate; d, day; h, hour; P, paclitaxel; D, docetaxel. All studies used a 3-weekly cycle, except Ref. [61].

antagonism for concomitant exposure to both drugs [65]. Kroep and colleagues investigated various combinations of both simultaneous and sequential administration of gemcitabine and paclitaxel in 4- and 24-h intervals in non-small cell lung cancer cell lines [66]. Multiple drug effect analysis from non-clonogenic assays in this study showed that any sequence resulted in not more than additive cytotoxicity [66]. However, as the administration of paclitaxel prior to gemcitabine was found to increase both the accumulation of gemcitabine triphosphate in the tumour cells, the incorporation of gemcitabine into RNA as well as the apoptotic index, this sequence might be favourable. Studies of various schedules of combined treatment of paclitaxel and gemcitabine in xenograft models of adenocarcinoma in mice resulted in an enhanced delay of tumour growth compared with monotherapy with either agent [67]. Although the efficacy was dependent on schedule and sequence, lethal toxicity was frequently encountered. So far, no conclusive preclinical data support the use of a specific sequence of gemcitabine and a taxane. One could even state that the available preclinical data do not really support the use of such combinations in man.

6.3. Clinical studies

Nevertheless, in view of the relevant single agent activity of these agents, numerous studies have explored a large variety of dosing schedules of the combination regimen, especially in the treatment of metastatic breast cancer and non-small cell lung cancer (Tables 6 and 7). Although not all trials reported the sequence of administration, most used a schedule of a taxane followed by gemcitabine. A possible correlation of the dosing schedule and the MTDs of the multidrug regimen is obscured by the large variety of investigated schedules, in various tumour types with different extents of pretreatment. The fact that almost all of these studies were investigator initiated explains the apparent lack of a systematic approach.

6.4. Paclitaxel/Gemcitabine

A pharmacokinetic analysis of the combination of paclitaxel and gemcitabine was performed in patients with non-small cell lung cancer [93]. The accumulation of gemcitabine triphosphate (dFdCTP) in mononuclear cells was significantly higher with a C_{max} of 106 pmol/10^6 cells with paclitaxel at a dose of 200 mg/m^2, compared with 88 pmol/10^6 cells with paclitaxel at a dose of 150 mg/m^2. Moreover, the C_{max} of dFdCTP shifted from 2 h after the administration of gemcitabine as a single agent or with paclitaxel 150 mg/m^2 to 4 h after gemcitabine and paclitaxel 200 mg/m^2. Although the pharmacokinetics of either drug were not affected by the other agent, paclitaxel seems to increase the accumulation of the active metabolite of gemcitabine [91,93]. Combining gemcitabine and paclitaxel in a 2- or 3-weekly cycle appeared feasible and mainly resulted in neutropenia and mild neurotoxicity (Table 6). The addition of granulocyte-colony stimulating factor (G-CSF) does not seem to increase the MTDs of both paclitaxel and gemcitabine [75,83,87]. Two trials using a 3-weekly cycle reported difficulty in administering gemcitabine at day 15 due to myelotoxicity [84,85]. In schedules administering paclitaxel at day 8, the MTDs of paclitaxel were relatively low due to observed grade 4 neutropenia [86,87,92]. De Pas and colleagues reported a higher delivered dose intensity for both agents at one dose level below the one of MTD (paclitaxel 100 mg/m^2 and gemcitabine 1500 mg/m^2) and subsequently recommended this dose level for further testing [91]. Unfortunately, only few other studies reported the actually delivered dose intensities [74,77,83,87]. Regarding the planned monthly doses in Table 6, a 2-weekly administration of both drugs seems to achieve the highest dose per unit of time. Full papers of this schedule confirm its good tolerability [69,72,74].

Only recently, dose-limiting severe pulmonary toxicity has been described in detail as a side-effect of the

Table 6
Clinical studies combining gemcitabine and paclitaxel

Reference	q (weeks)	Fixed dose	Paclitaxel regimen	Gemcitabine regimen	Tolerable dose of paclitaxel–gemcitabine per administration (mg/m^2)	Tolerable dose of paclitaxel–gemcitabine per month (mg/m^2)	Tumour type	Prior chemotherapy	No. of evaluable patients	RR (%)
[68]	1	+	d 1 1 h	d 1	85–1000	267–3240	Lung	−	28	14
[69]	2	+	d 1 3 h	d 1 1 h	150–2500	300–5000	Breast	−	38	68
[70]	2		d 1 1 h	d 1	175–3000	350–6000	Lung	−	26	35
[71]	2	+	d 1 3 h	d 1	150–3000	300–6000	Lung	−	10	20
[72]	2	+	d 1 3 h	d 1	150–2000	300–4000	Lung	−	89	32
[73]	2	+	d 1 3 h	d 1	135–2500	270–5000	Breast	+	44	45
[74]	2		d 1 3 h	d 1	150–3000	300–6000	Solid	+	37	5
[75]	2	+	d 1 3 h	d 1 + G-CSF	150–2500	300–5000	Bladder	+	15	53
[76]	3	+	d 1 3 h	d 1, 8	200–1000	267–2667	Lung	−	49	24
[77]	3	+	d 1 3 h	d 1, 8	200–1000	267–2667	Lung	−	64	38
[78]	3	+	d 1 3 h	d 1, 8	175–1000	233–2667	Lung	−	10	50
[79]	3	+	d 1 3 h	d 1 , 8	175–1250	233–3333	Lung	+	20	50
[80]	3		d 1 3 h	d 1 ,8	200–1300	267–3467	Solid	+	25	16
[81]	3		d 1 3 h	d 1, 8	150–900	200–2400	Solid	+	18	22
[82]	3		d 1 1 h	d 1, 8	225–1200	300–3200	Bladder	−	12	67
[83]	3		d 1 1 h	d 1, 8 + G-CSF	240–1000	320–2667	Breast	+	30	53
							Ovarian	+	13	46
[84]	3	+	d 1 1 h	d 1, 8, (15)	200–1000	267–2667	Bladder	−	35	57
								+	15	47
[85]	3	+	d 1 3 h	d 1,8, (15)	175–1000	233–2667	Breast	+	29	55
[86]	3		d 8	d 1, 8	175–1000	233–2667	Ovarian	+	10	40
[87]	3	+	d 8 3 h	d 1, 8 + G-CSF	175–900	233–2400	Lung	+	49	18
[88]	3	+	d 1, 8, 15	d 1, 8	80–1000	320–2000	Lung	+	16	19
[89]	4		d 1, 8, 15 3 h	d 1, 8, 15	130–1000	390–3000	Solid	±	24	17
[90]	4		d 1, 8, 15 1 h	d 1, 8, 15	40–1000	120–3000	Lung	−	8	38
[91]	4		d 1, 8,15 1 h	d 1, 8, 15	100–1500	300–4500	Lung	−	30	43
[92]	4		d 8	d 1, 8, (15)	100–800	100–2400	Ovarian	+	8	50

q, every; d, day; h, hour; RR, response rate; G-CSF; granulocyte-colony stimulating factor. All studies administered gemcitabine as a 30-min infusion, unless stated otherwise.

combination of gemcitabine and paclitaxel [90]. Despite standard corticosteroid premedication, other studies have occasionally reported patients with severe lung oedema [69,71,72].

6.5. Docetaxel/Gemcitabine

Even more studies have explored numerous schedules combining docetaxel and gemcitabine (Table 6). To our knowledge, pharmacokinetic parameters of the gemcitabine-docetaxel combination therapy have not been published in detail [118]. No full papers have yet been published on a weekly or 2-weekly schedule. Most studies administering docetaxel at day 1 of a 3-weekly cycle used a fixed dose, despite the lack of a full paper of a dose finding trial on such a regimen [99,100,102–104]. As docetaxel induces neutropenia after 5–8 days, more recent studies investigated a 3-weekly cycle administering docetaxel at day 8 in order to enable the repeated infusion of gemcitabine at the same day [105–116]. Rischin and colleagues noticed in their dose finding study a good tolerability, with neutropenic fever and prolonged grade 4 neutropenia as the DLTs [112]. Other commonly noticed side-effects were alopecia and asthenia. Data on the achieved dose intensities of the 3-weekly regimens ranged from 75 to 90% and from 73 to 94%, for docetaxel and gemcitabine, respectively [103,104,109, 112–114,116]. Regarding Table 7, the support of G-CSF does not seem to enable a relevant higher dose of both agents. Although no direct comparisons have been made, most of the 3-weekly schedules administering docetaxel at day 8 seemed to give a somewhat higher dose of docetaxel, as compared with those administering docetaxel at day 1. A 4-weekly cycle even using a very low dose of docetaxel at day 15 appeared not to be feasible because of thrombocytopenia and elevated liver enzymes [125,127]. Likewise, two studies using a cycle of 4 weeks with docetaxel on day 1 reported a delivered dose intensity of only 64 and 74% for gemcitabine, due to required dose reductions at day 8 or 15 because of myelotoxicity [123,125]. As a consequence, 4-weekly schedules do not result in an adequate dose intensity of both agents.

While some studies with the docetaxel-gemcitabine combination have also occasionally reported pulmonary toxicity [108,112,113,119,121,124,131,132], Dunsford and colleagues described a high incidence of severe lung toxicity in 4 out of 7 patients with metastatic urothelial cancer, despite the use of dexamethasone starting 24 h prior to treatment [100]. Another study was prematurely

Table 7
Clinical studies combining gemcitabine and docetaxel

Reference	q (weeks)	fixed dose	Docetaxel regimen	Gemcitabine regimen	Tolerable dose of docetaxel–gemcitabine per administration (mg/m^2)	Tolerable dose of docetaxel—gemcitabine per month (mg/m^2)	Tumour type	Prior chemotherapy	No. of evaluable patients	RR (%)
[94]	1		d 1	d 1	40–800	160–3200	Pancreas	–	20	?
[95]	2		d 1	d 1	75–3000	150–6000	Solid	ng	16	19
[96]	2		d 1	d 1 0.5 h	55–3500	110–7000	Solid	±	23	13
				d 1 10 mg/min	50–1600	100–3200				
[97]	2	+	d 1	d 1 + G-CSF	50–1500	100–3000	Breast	–	34	59
[98]	3		d 1	d 1, 5	75–900	100–2400	Lung	–	22	27
[99]	3	+	d 1	d 1, 15	65–1000	87–2667	Lung	–	19	47
[100]	3	+	d 1	d 1, 15	60–1000	80–2667	Bladder	–	5	0
[101]	3		d 1	d 1, 8	80–900	107–2400	Lung	+	23	39
[102]	3	+	d 1 1 h	d 1, 8	80–1000	106–2667	Breast	+	30	60
[103]	3	+	d 1	d 1, 8 + G-CSF	75–1000	100–2667	Breast	+	39	36
[104]	3	+	d 1 1.5 h	d 1, 10 + G-CSF	80–1000	107–2667	Lung	–	34	50
[105]	3		d 8	d 1	85–900	113–2400	Lung	–	9	22
[106]	3	+	d 8	d 1, 8	75–1000	100–2667	Lung	–	8	25
[107]	3	–	d 8	d 1, 8	60–800	80–2133	Lung	±	30	15
[108]	3		d 8	d 1, 8	85–1000	113–2667	Lung	±	16	38
[109]	3	+	d 8	d 1, 8	75–1000	100–2667	Lung	ng	37	46
[110]	3		d 8	d 1, 8	90–1000	120–2667	Solid	+	25	?
[111]	3	+	d 8	d 1, 8	85–1000	113–2667	Solid	+	5	40
[112]	3		d 8	d 1, 8	85–1200	113–3200	Solid	±	28	29
[113]	3	+	d 8	d 1, 8 + G-CSF	100–900	133–2400	Lung	–	51	37
[114]	3	+	d 8	d 1, 8 + G-CSF	100–900	133–2400	Breast	+	52	54
[115]	3	+	d 8	d 1, 8 + G-CSF	75–1000	100–2667	Bladder	–	16	50
[116]	3	+	d 8	d 1, 8 + G-CSF	100–1000	133–2667	Pancreas	–	54	13
[117]	3		d 1, 8	d 1, 8	40–1000	107–2667	Breast	+	19	16
[118]	3		d 1, 8	d 1, 8	40–800	106–2133	Solid	–	23	30
[119]	3	+	d 1, 8	d 1, 8	30–800	80–2133	Lung	+	40	33
[120]	3	+	d 2, 9	d 1, 8	40–1000	106–2667	Lung	+	15	60
[121]	4		d 1	d 1, 8, 15	60–600	60–1800	Solid	+	21	29
[122]	4		d 1	d 1, 8, 15	70–800	70–2400	Solid	±	24	0
[123]	4	+	d 1	d 1, 8, 15	100–800	100–2400	Breast	+	32	59
[124]	4		d 1	d 1, 8, 15, 10 mg/min	80–1000	80–3000	Lung	–	8	25
				idem	80–800		Lung	+	10	20
[125]	4		d 1 1 h	d 1, 8, 15	100–800	100–2400	Solid	+	40	35
			d 15 1 h	d 1, 8, 15	<45–800	<45–2400				
[126]	4	+	d 1 1 h	d 1, 8	100–800	100–2400	Lung	+	40	33
[127]	4	+	d 15 1 h	d 1, 8, 15	<85–800	<85–2400	Solid	+	11	9
[128]	4		d 1, 8, 15	d 1, 8, 15	40–1000	120–3000	Lung	–	16	25
[129]	4	+	d 1, 8, (15)	d 1, 8, (15)	30–800	90–2400	Lung	–	41	29
[130]	ng	+	d 1	d 1, 8, 15	75–800	75–2400	Pancreas	ng	9	33
[131]	3 or 4	+	d 8	d 1, 8	75–1000	150–2000	Lung	–	13	31

G-CSF, granulocyte-colony stimulating factor; d, day; h, hour; RR, response rate; q, every; idem, the same; ng, data not given in publication. All studies administered docetaxel as a 1 h infusion and gemcitabine as a 30-min infusion, unless stated otherwise.

terminated because of severe lung toxicity in 5 out of 26 lung cancer patients [128]. The discrepancy in observed pulmonary toxicity cannot be explained by a difference in sequence, as Rizvi and colleagues found no difference in clinical toxicity for either regimen [118].

When looking at the planned dose intensities of the various schedules in Table 7, a cycle of 2 or 3 weeks might be favoured in terms of a maximal dose intensity and good tolerability. For 3-weekly schedules, docetaxel may be preferentially administered at day 8. However, side-effects still render the combination of these two agents not very interesting and, in view of the lack of preclinical evidence to combine these agents, it may be worthwhile to consider halting further clinical development.

7. Conclusions

Table 8 summarises preclinical, clinical and pharmacokinetic data on the combination treatment of taxanes and antimetabolites.

Table 8
Summary of taxanes and antimetabolites

Drug combination	Sequence	*In vitro* studies	Pharmacokinetic studies	Clinical studies
Paclitaxel and				
MTX	**MTX-P**	**Synergism**	Scarce	**Toxic**
	P-MTX	Antagonism	?	?
	Concomitant	Antagonism	?	Feasible
5-FU	5-FU-P	Antagonism	?	?
	P-5-FU	**Synergism**	?	**Effective and feasible**
	Concomitant	Antagonism	?	?
Capecitabine	C-P	?	?	?
	P-C	?	No change	Feasible
	Concomitant	**Synergism**	No change	**Effective and feasible**
Gemcitabine	G-P	No synergism	?	Feasible
	P-G	No synergism	No change	**Feasible**
	Concomitant	No synergism	No change	?
Docetaxel and				
MTX	**MTX-D**	? (edatx: synergism)	No change	**Toxic**
	D-MTX	? (edatx: antagonism)	?	?
	Concomitant	? (edatx: mixed results)	No change	Feasible
5-FU	5-FU-D	?	?	?
	D-5-FU	?	Scarce	**Effective and feasible**
	Concomitant	Synergism	?	?
Capecitabine	C-D	?	?	?
	D-C	?	No change	?
	Concomitant	**Synergism**	No change	**Effective and feasible**
Gemcitabine	G-D	?	**?**	Feasible
	D-G	?	**?**	**Feasible**
	Concomitant	?	?	?

MTX, methotrexate; D, docetaxel, 5-FU, 5-fluorouracil; P, paclitaxel; C, capecitabine; G, gemcitabine; edatx, edatrexate.

Preclinically observed synergism for the sequence of MTX prior to a taxane might explain excessive bone marrow toxicity found in some clinical studies. However, despite *in vitro* observed antagonism, simultaneous exposure resulted in high response rates and good tolerance in patients with breast cancer and urothelial cancer, although the results do not look strikingly different from the reported single agent activities. Thus, MTX/taxane combinations may not be ideal for pursuing further studies. As the antagonistic effect of 5-FU prior to paclitaxel was evident from the *in vitro* studies, all clinical studies used the reverse sequence. Various schedules appeared feasible and effective in both gastric and breast cancer patients. Again, activity data are not very different from the single agent data, with the clear exception for the combination of capecitabine with docetaxel in breast cancer. Despite a lack of preclinical data suggesting synergism for any combination schedule of gemcitabine and a taxane, many studies using multiple schedules have noted efficacy, especially in metastatic breast cancer and non-small cell lung cancer, although not strikingly dissimilar from the single agent activity. An optimal schedule has, however, not yet been established. Regarding data on actually delivered dose intensities, a 2- or 3-weekly cycle might be favoured and most feasible. Possible severe pulmonary toxicity warrants cautious monitoring of patients treated with this combination.

Combining two chemotherapeutic agents is not simply a matter of putting antitumour activities together. Drug interactions may result in synergism, not only of efficacy, but also of toxic side-effects. Adding two drugs may also cause antagonism in drug efficacy due to unwanted interference in cytotoxicity or pharmacokinetics. It is therefore disappointing that, in the vast majority of reviewed clinical studies, the preclinical evidence of schedule dependency was simply ignored and the sequence of drug administration was not made part of the clinical protocol. Besides interference with the pharmacokinetics of an antimetabolite by a taxane, or *vice versa*, the vehicle CrEL might also have a major impact on the pharmacokinetics of drugs other than paclitaxel itself. If one compares the number of studies done on antimetabolites plus taxanes as summarised in Tables 1–7 with the number of studies that include an adequate assessment of pharmacokinetics, the lack of such assessments becomes striking. This suggests that investigators are not adequately aware of the possible pharmacokinetic interactions and the necessity at least to exclude negative interactions. Clearly, trial design issues are not appropriately considered. This is a major concern since, in the case of these combinations, the increase and duplication of likely unnecessary trials may not have benefited our patients. A better use of registries of trials seems warranted to avoid such duplications.

For agents acting at a specific phase of the cell cycle, the sequence of administration may determine the efficacy and toxicity of a combination. Because of observed discrepancy between the *in vitro* data and clinical studies, we would like to stress the urge for adequate dose finding clinical trials together with pharmacokinetic data analysis before examining any new combination chemotherapy in more detail in phase II studies. With the exception of the combination of capecitabine with docetaxel, other combinations of antimetabolites with taxanes were either not very promising or very toxic. Further studies should only be started after careful consideration of the data available.

References

1. Verweij J, Stoter G. Principles of systemic therapy of cancer. In Cavalli F, Kaye S, Hansen HH, eds. *Textbook of Medical Oncology*. New York, Dunitz Martin Ltd, 1966, 23–40.
2. Verweij J, Clavel M, Chevalier B. Paclitaxel and docetaxel: not simply two of a kind. *Ann Oncol* 1994, **5**, 495–505.
3. Rowinsky EK, Donehower RC. Paclitaxel (taxol). *NEJM* 1995, **332**, 1004–1014.
4. Löffler TM. Is there a place for "dose-dense" weekly schedules of the taxoids? *Semin Oncol* 1998, **25**(Suppl. 12), 32–34.
5. Louwerens M, Smorenburg CH, Sparreboom A, Loos W, Verweij J, de Wit R. Phase I and pharmacokinetic study of the combination of docetaxel and methotrexate in patients with solid tumors. In press.
6. Huber MH, Lee JS, Newman RA, *et al*. A phase I investigation of the sequential use of methotrexate and paclitaxel with and without G-CSF for the treatment of solid tumors. *Ann Oncology* 1996, **7**, 59–63.
7. Donaldson KL, Goolsby GL, Wahl AF. Cytotoxicity of the anticancer agents cisplatin and taxol during cell proliferation and the cell cycle. *Int J Cancer* 1994, **57**, 847–855.
8. Lopes NM, Adams EG, Pitts TW, Bhuyan BK. Cell kill kinetics and cell cycle effects of taxol on human and hamster ovarian cell lines. *Cancer Chemother Pharmacol* 1993, **32**, 235–242.
9. Rowinsky EK, Donehower RC, Jones RJ, Tucker RW. Microtubule changes and cytotoxicity in leukemic cell lines treated with taxol. *Cancer Res* 1988, **48**, 4093–4100.
10. Roberts JR, Allison DC, Donehower RC, Rowinsky EK. Development of polyploidization in taxol-resistant human leukemia cells in vitro. *Cancer Res* 1990, **50**, 710–716.
11. Liebmann JE, Cook JA, Lipschultz C, Teague D, Fisher J, Mitchell JB. Cytotoxic studies of paclitaxel in human tumour cell lines. *Br J Cancer* 1993, **68**, 1104–1109.
12. Wang TH, Wang HS, Soong YK. Paclitaxel-induced cell death. Where the cell cycle and apoptosis come together. *Cancer* 2000, **88**, 2619–2628.
13. Hennequin C, Giocanti N, Favaudon V. S-phase specificity of cell killing by docetaxel in synchronised HeLa cells. *Br J Cancer* 1995, **71**, 1194–1198.
14. Ferlini C, Distefano M, Pignatelli F, *et al*. Antitumour activity of novel taxanes that act at the same time as cytotoxic agents and P-glycoprotein inhibitors. *Br J Cancer* 2000, **83**, 1762–1768.
15. Van Zuijlen L, Verweij J, Sparreboom A. Role of formulation vehicles in taxane pharmacology. *Invest New Drugs* 2001, **19**, 179–196.
16. Sparreboom A, van Zuijlen L, Brouwer E, *et al*. Cremophor EL-mediated alteration of paclitaxel distribution in human blood: clinical pharmacokinetic implications. *Cancer Res* 1999, **59**, 1454–1457.
17. Gianni L, Vigano J, Locatelli A, *et al*. Human pharmacokinetic characterization and in vitro study of the interaction between doxorubicin and paclitaxel in patients with breast cancer. *J Clin Oncol* 1997, **15**, 1906–1915.
18. Van Tellingen O, Beijnen JH, Verweij J, Scherrenberg EJ, Nooijen WJ, Sparreboom A. Rapid esterase-sensitive breakdown of polysorbate 80 and its impact on the plasma pharmacokinetics of docetaxel and metabolites in mice. *Clin Cancer Res* 1999, **5**, 2918–2924.
19. Sirotnak FM, DeGraw JI, Schmid FA, Goutas LJ, Moccio DM. New folate analogs of the 10-deaza-aminopterin series. *Cancer Chemother Pharmacol* 1984, **12**, 26–30.
20. Yeh YA, Olah E, Wendel JJ, Sledge GW, Weber G. Synergistic action of taxol with tiazofurin and methotrexate in human breast cancer cells: schedule-dependence. *Life Sci* 1994, **54**, 431–435.
21. Kano Y, Akutsu M, Tsunoda S, Furuta M, Yazawa Y, Ando J. Schedule-dependent synergism and antagonism between paclitaxel and methotrexate in human carcinoma cell lines. *Oncology Res* 1998, **10**, 347–354.
22. Cos J, Bellmunt J, Soler C, *et al*. Comparative study of sequential combinations of paclitaxel and methotrexate on a human bladder cancer cell line. *Cancer Invest* 2000, **18**, 29–435.
23. Chou TC, Otter GM, Sirotnak FM. Schedule-dependent synergism of taxol or taxotere with edatrexate against human breast cancer cells in vitro. *Cancer Chemother Pharmacol* 1996, **37**, 222–228.
24. Hata Y, Sandler A, Loehrer PJ, Sledge GW, Weber G. Synergism of taxol and gallium nitrate in human breast carcinoma cells: schedule dependency. *Oncol Res* 1994, **6**, 19–24.
25. Edelman MJ, Meyers FJ, Miller TR, Williams SG, Gandour-Edwards R, deVere White RW. Phase I/II study of paclitaxel, carboplatin and methotrexate in advanced transitional cell carcinoma: a well-tolerated regimen with activity independent of p53 mutation. *Urology* 2000, **55**, 521–525.
26. Tu SM, Hossan E, Amato R, Kilbourn R, Logothetis CJ. Paclitaxel, cisplatin and methotrexate combination chemotherapy is active in the treatment of refractory urothelial malignancies. *J Urol* 1995, **154**, 1719–1722.
27. D'Andrea G, Fennelly D, Norton L, *et al*. Phase I study of escalating doses of edatrexate in combination with paclitaxel in patients with metastatic breast cancer. *Clin Cancer Res* 1999, **5**, 275–279.
28. Diamandidis DT, Lee JS, Shin DM, *et al*. Phase I study of taxol and edatrexate combination with G-CSF support in solid tumors. Proc Am Soc Clin Oncol 1995, **14**, 470 (abstr 1523).
29. Rigas JR, Kris MG, Miller VA. Phase I study of the sequential administration of edatrexate and paclitaxel in patients with advanced solid tumors. *Ann Oncol* 1999, **10**, 601–603.
30. Zanetta S, Guillot A, Ardiet C, *et al*. A dose finding and pharmacokinetic study of docetaxel and methotrexate in patients with epithelial cancer. *Eur J Cancer* 1999, **35**(Suppl. 4), 288 (abstr 1158).
31. Sparreboom A, Loos WJ, Nooter K, Stoter G, Verweij J. Liquid chromatographic analysis and preliminary pharmacokinetics of methotrexate in cancer patients co-treated with docetaxel. *J Chromatogr B* 1999, **735**, 111–119.
32. Maybaum J, Ullman B, Mandel HG, Day JL, Sadee W. Regulation of RNA- and DNA-directed actions of 5-fluoropyrimidines in mouse T-lymphoma (S-49) cells. *Cancer Res* 1980, **40**, 4209–4215.
33. Johnson KR, Wang L, Miller MC, Willingham MC, Fan W. 5-Fluorouracil interferes with paclitaxel cytotoxicity against human solid tumor cells. *Clin Cancer Res* 1997, **3**, 1739–1745.
34. Kano Y, Akutsu M, Tsunoda S, *et al*. Schedule-dependent interaction between paclitaxel and 5-fluorouracil in human carcinoma cell lines in vitro. *Br J Cancer* 1996, **74**, 704–710.
35. Grem JL, Nguyen D, Monahan BP, Kao V, Geoffroy FJ. Sequence-dependent antagonism between fluorouracil and

paclitaxel in human breast cancer cells. *Biochem Pharmacol* 1999, **58**, 477–486.
36. Johnson KR, Young KK, Fan W. Antagonistic interplay between antimitotic and G_1-S arresting agents observed in experimental combination therapy. *Clin Cancer Res* 1999, **9**, 2559–2565.
37. Bissery MC, Vrignaud P, Bayssas M, Lavelle F. Taxotere synergistic combination with cyclophosphamide, etoposide and 5-fluorouracil in mouse tumor models. *Proc Am Assoc Cancer Res* 1993, **34**, 299 (abstr 1782).
38. Collichio FA, Fogleman J, Griggs J, Amamoo M, Graham M. A phase II study of first-line low dose weekly infusional 5-fluorouracil and every two weeks paclitaxel in metastatic breast cancer. *Proc Am Soc Clin Oncol* 2001, **20**, 71b (abstr).
39. Murad AM, Petroianu A, Guimaraes RC, Aragao BC, Cabral LOM, Scalabrini-Neto AO. Phase II trial of the combination of paclitaxel and 5-fluourouracil in the treatment of advanced gastric cancer. *Am J Clin Oncol* 1999, **22**, 580–586.
40. Cascinu S, Ficarelli R, Safi MAA, Graziano F, Catalano G, Cellerino R. A phase I study of paclitaxel and 5-fluorouracil in advanced gastric cancer. *Eur J Cancer* 1999, **33**, 1699–1702.
41. Ciuleanu TE, Ciuleanu E, Todor N, Todor N, Ghilezan N. Taxol, 5-fluorouracil and leucovorin 2nd line chemotherapy in refractory/relapsed nasopharyngeal carcinoma patients. *Ann Oncol* **11**(Suppl. 4), 93 (abstr 417).
42. Takimoto CH, Morrison GB, Frame JN, *et al*. A phase I and pharmacologic trial of paclitaxel and 5-fluorouracil plus leucovorin in patients with solid tumors. *Proc Am Soc Clin Oncol* 1995, **14**, 471 (abstr 1526).
43. Madajewicz S, LiPera W, Pendyala L, *et al*. Phase I study of 96 hours continuous intravenous infusion (CI) of taxol followed by 24 hours CI of 5-fluorouracil and folinic acid. *Proc Am Soc Clin Oncol* 1995, **14**, 487 (abstr 1589).
44. Nicholson B, Paul D, Shyr Y, Garrett M, Hande KR, Johnson DH. Paclitaxel/5-fluorouracil/leucovorin in metastatic breast cancer: a Vanderbilt Cancer Center phase II trial. *Semin Oncol* 1997, **24**(Suppl. 11), 20–23.
45. Vredenburgh J, Fishman R, Coniglio D, *et al*. The addition of paclitaxel to continuous infusion 5-fluorouracil is an active regimen for metastatic breast cancer. *Am J Clin Oncol* 1998, **21**, 543–547.
46. Klaassen U, Harstrick A, Wilke H, Seeber S. Preclinical and clinical study results of the combination of paclitaxel and 5-fluorouracil/folinic acid in the treatment of metastatic breast cancer. *Semin Oncol* 1996, **23**(Suppl. 1), 44–47.
47. Bokemeyer C, Hartmann JT, Lampe CS, *et al*. Paclitaxel and weekly 24-infusion of 5-fluorouracil/folinic acid in advanced gastric cancer. *Semin Oncol* 1997, **24**(Suppl. 19), 96–100.
48. Van den Neste E, de Valeriola D, Kerger J, *et al*. A phase I and pharmacokinetic study of docetaxel administered in combination with continuous infusion of 5-fluorouracil in patients with advanced solid tumors. *Clin Cancer Res* 2000, **6**, 64–71.
49. Lortholary A, Maillard P, Delva R, *et al*. Docetaxel in combination with 5-fluorouracil in patients with metastatic breast cancer previously treated with anthracycline-based chemotherapy: a phase I, dose-finding study. *Eur J Cancer* 2000, **36**, 1773–1780.
50. Eniu A, Ciuleanu TE, Todor N, Ghilezan N. Docetaxel, 5-fluorouracil and leucovorin: an outpatient first line palliative regimen for advanced/metastatic gastric cancer. *Ann Oncol* 2000, **11**(Suppl. 4), 65 (abstr 283).
51. Chun H, Puccio C, Mittelman A. A combination of continuous infusion 5-fluorouracil and weekly docetaxel: an active regimen for elderly patients with advanced or metastatic cancer of the stomach and distal esophagus. *Ann Oncol* 2000, **11**(Suppl. 4), 66 (abstr 291).
52. Ando M, Watanabe T, Sasaki Y, *et al*. A phase I trial of docetaxel and 5-day continuous infusion of 5-fluorouracil in patients with advanced or recurrent breast cancer. *Br J Cancer* 1998, **77**, 1937–1943.
53. Petit T, Aylesworth C, Burris H, *et al*. A phase I study of docetaxel and 5-fluorouracil in patients with advanced solid malignancies. *Ann Oncol* 1999, **10**, 223–229.
54. Sawada N, Ishikawa T, Fukase Y, Nishida M, Yoshikubo T, Ishitsuka H. Induction of thymidine phosphorylase activity and enhancement of capecitabine efficacy by taxol/taxotere in human cancer xenografts. *Clin Cancer Res* 1998, **4**, 1013–1019.
55. Villalona-Calero M, Blum J, Diab S, *et al*. Phase I study of capecitabine in combination with paclitaxel in patients with previously treated metastatic breast cancer. *Ann Oncol* 2001, **12**, 605–614.
56. Villalona-Calero MA, Weiss GR, Burris HA, *et al*. Phase I and pharmacokinetic study of the oral fluoropyrimidine capecitabine in combination with paclitaxel in patients with advanced solid malignancies. *J Clin Oncol* 1999, **17**, 1915–1925.
57. Batista N, Perez Manga G, Constenla M, *et al*. Phase II study of capecitabine in combination with paclitaxel in the treatment of patients with locally advanced or metastatic breast cancer: preliminary results. *Ann Oncol* 2000, **11**(Suppl. 4), 32 (abstr. 130).
58. Meza LA, Amin B, Horsey M, Petralia A, Szatrowski TP, Gradishar WJ. A phase II study of capecitabine in combination with paclitaxel as first or second line therapy in patients with metastatic breast cancer. *Proc Am Soc Clin Oncol* 2001, **20**, 70b (abstr 2029).
59. O'Shaughnessy J. Results of a large phase III trial of Xeloda/Taxotere combination therapy vs taxotere monotherapy in metastatic breast cancer patients. San Antonio Breast Cancer Symposium 2000, In press.
60. Pronk LC, Vasey P, Sparreboom A, *et al*. A phase I and pharmacokinetic study of the combination of capecitabine and docetaxel in patients with advanced solid tumours. *Br J Cancer* 2000, **83**, 22–29.
61. Villalona-Calero MA, Nadella P, Shapiro C, *et al*. Phase I study of capecitabine in combination with weekly docetaxel in patients with solid malignancies. *Breast Cancer Res Treatment* 2000, **64**, 125 (abstr 537).
62. Plunkett W, Huang P, Xu YZ, Heinemann V, Grunewald R, Gandhi V. Gemcitabine: metabolism, mechanisms of action, and self-potentiation. *Semin Oncol* 1995, **22**(Suppl. 11), 3–10.
63. Hertel LW, Boder GB, Kroin JS, *et al*. Evaluation of the antitumor activity of gemcitabine (2′,2′-difluoro-2′-deoxycytidine). *Cancer Res* 1990, **50**, 4417–4422.
64. Tolis C, Peters GJ, Ferreira CG, Pinedo HM, Giaccone G. Cell cycle disturbances and apoptosis induced by topotecan and gemcitabine on human lung cancer cell lines. *Eur J Cancer* 1999, **35**, 796–807.
65. Theodossiou C, Cook JA, Fisher J, *et al*. Interaction of gemcitabine with paclitaxel and cisplatin in human tumor cell lines. *Int J Oncol* 1998, **12**, 825–832.
66. Kroep JR, Giaccone G, Tolis C, *et al*. Sequence dependent effect of paclitaxel on gemcitabine metabolism in relation to cell cycle and cytotoxicity in non-small-cell lung cancer cell lines. *Br J Cancer* 2000, **83**, 1069–1076.
67. Cividalli A, Mauro F, Livdi E, *et al*. Schedule dependent toxicity and efficacy of combined gemcitabine/paclitaxel treatment in mouse adenocarcinoma. *J Cancer Res Clin Oncol* 2000, **126**, 461–467.
68. Ives C, Akerley W, Safran H, *et al*. Weekly gemcitabine and paclitaxel for advanced non-small cell lung cancer: a multi-institutional, phase II trial by the Brown Oncology Group. *Proc Am Soc Clin Oncol* 2001, **20**, 280b (abstr 2870).
69. Colomer R, Llombart A, Lluch A, *et al*. Paclitaxel/gemcitabine administered every two weeks in advanced breast cancer: preliminary results of a phase II trial. *Semin Oncol* 2000, **27**(Suppl. 2), 20–24.
70. Athanassiadis A, Roussos G, Zahou K, Papakostulis T, Athanassiadou D. Biweekly paclitaxel and gemcitabine in non-resectable non-small cell lung cancer. *Ann Oncol* 2000, **11**(Suppl. 4), 111 (abstr 507).

71. Fontaine C, Neyns B, Grauwels D, *et al*. Phase I/II study of paclitaxel and gemcitabine in patients with advanced non small cell lung cancer. *Proc Am Soc Clin Oncol* 1999, **18**, 503a (abstr 940).
72. Isla D, Rosell R, Sanchez JJ, *et al*. Phase II trial of paclitaxel plus gemcitabine in patients .with locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol* 2001, **19**, 1071–1077.
73. Sanchez P, Medina MB, Mohedano N, *et al*. Results from a phase II study of gemcitabine in combination with paclitaxel in metastatic breast cancer. *Ann Oncol* 1998, **9**(Suppl. 4), 16 (abstr 77).
74. Rothenberg ML, Sharma A, Weiss GR, *et al*. Phase I trial of paclitaxel and gemcitabine administered every two weeks in patients with refractory solid tumors. *Ann Oncol* 1998, **9**, 733–738.
75. Marini L, Sternberg CN, Sella A, Calabro F, van Rijn A. A new regimen of gemcitabine and paclitaxel in previously treated patients with advanced transitional cell carcinoma. *Proc Am Soc Clin Oncol* 1999, **18**, 346a (abstr 1335).
76. Giaccone G, Smit EF, van Meerbeeck JP, *et al*. A phase I-II study of gemcitabine and paclitaxel in advanced non-small-cell lung cancer patients. *Ann Oncol* 2000, **11**, 109–112.
77. Kosmidis P. Paclitaxel/carboplatin vs paclitaxel/gemcitabine in advanced non-small-cell lung cancer. *Oncology* 2000, **14**(Suppl. 4), 41–48.
78. Lazaro M, Jorge M, Castellanos J. Phase II study of paclitaxel and gemcitabine in advanced non-small cell lung cancer. *Ann Oncol* 2000, **11**(Suppl. 4), 109 (abstr 493).
79. Domine M, Gonzalez Larriba J, Morales S, *et al*. Gemcitabine and paclitaxel as second line treatment in small celllung cancer. A multicenter phase II study. *Proc Am Soc Clin Oncol* 2001, **20**, 317b (abstr 1263).
80. Rinaldi DA, Lormand N, Brierre JE, *et al*. A phase I trial of gemcitabine and paclitaxel in patients with advanced solid tumors, administered every 21 days. *Proc Am Soc Clin Oncol* 2000, **19**, 217a (abstr 848).
81. Fleming DR, Glisson SD, Bhupalam L, Michelson GD, Goldsmith GH, LaRocca RV. Phase I study of palitaxel and day 1/day 8 gemcitabine in patients with solid malignancies. *Am J Clin Oncol* 2000, **23**, 349–352.
82. Garcia-Arroyo FR, Constenla M, Lorenzo I, *et al*. Phase I study of gemcitabine & paclitaxel in patients with advanced urothelial cancer. *Ann Oncol* 2000, **11**(Suppl. 4), 79 (abstr 351).
83. Iaffaioli RV, Tortoriello A, Santangelo M, *et al*. Phase I dose escalation study of gemcitabine and paclitaxel plus colony-stimulating factors in previously treated patients with advanced breast and ovarian cancer. *Clin Oncol* 2000, **12**, 251–255.
84. Meluch AA, Greco FA, Burris HA, *et al*. Paclitaxel and gemcitabine chemotherapy for advanced transitional-cell carcinoma of the urothelial tract: a phase II trial of the Minnie Pearl Cancer Research Network. *J Clin Oncol* 2001, **19**, 3018–3024.
85. Murad AM, Guimaraes RC, Aragao BC, Scalabrini-Neto AO, Rodrigues VH, Garcia R. Gemcitabine and paclitaxel as salvage therapy in metastatic breast cancer. *Oncology* 2001, **15**(Suppl.), 25–27.
86. Poole CJ, Perren T, Hogberg T, *et al*. Phase I study to investigate alternate sequencing of the combination of gemcitabine and paclitaxel in ovarian carcinoma. *Eur J Cancer* 1997, **3**(Suppl. 8), 121 (abstr 543).
87. Androulakis N, Kouroussis C, Kakolyris S, *et al*. Salvage treatment with paclitaxel and gemcitabine for patients with non-small-cell lung cancer after cisplatin- or docetaxel-based chemotherapy: a multicenter phase II study. *Ann Oncol* 1998, **9**, 1127–1130.
88. Dongiovanni V, Buffoni L, Occelli M, *et al*. Weekly paclitaxel and gemcitabine as second line chemotherapy in non small cell lung cancer. *Proc Am Soc Clin Oncol* 2001, **20**, 261b (abstr 2794).
89. Einhorn LH, Raghavan D, Kindler H, *et al*. A phase I trial of gemcitabine plus paclitaxel combination therapy in patients with refractory solid tumors. *Proc Am Soc Clin Oncol* 1998, **17**, 207a (abstr 796).
90. Thomas AL, Cox G, Sharma RA, *et al*. Gemcitabine and paclitaxel associated pneumonitis in non-small cell lung cancer: report of a phase I/II dose-escalating study. *Eur J Cancer* 2000, **36**, 2329–2334.
91. De Pas T, de Braud F, Danesi R, *et al*. Phase I and pharmacologic study of weekly gemcitabine and paclitaxel in chemo-naïve patients with advanced non-small-cell lung cancer. *Ann Oncol* 2000, **11**, 821–827.
92. Poole CJ, Cook J, Hogberg T, Jungnelius U, Anderson K, Russell L. A phase I clinical trial of gemcitabine and paclitaxel in patients with recurrent epithelial ovarian cancer. *Ann Oncol* 1996, **7**(Suppl. 5), 72 (abstr 341).
93. Kroep JR, Giaccone G, Voorn DA, *et al*. Gemcitabine and paclitaxel: pharmacokinetic and pharmacodynamic interactions in patients with non-small-cell lung cancer. *J Clin Oncol* 1999, **17**, 2190–2197.
94. Lueck A, Ridwelski K, Lippert H. Phase I study of a treatment with gemcitabine and docetaxel weekly in advanced pancreatic cancer. *Ann Oncol* 1998, **9**(Suppl. 4), 52 (abstr 249).
95. Eckardt JR, Schmidt AM, Needles BM, Greco AO, White LA, Denes AE. A phase I study of the combination of docetaxel and gemcitabine. *Proc Am Soc Clin Oncol* 1998, **17**, 240a (abstr 920).
96. Obrocea M, Davis TH, Lewis LD, *et al*. Phase I clinical and pharmacologic study of docetaxel and gemcitabine in patients with advanced solid tumors; a novel two week schedule. *Ann Oncol* 1998, **9**(Suppl. 2), 95 (abstr 363).
97. Kornek G, Raderer M, Fiebiger W, *et al*. Treatment of advanced breast cancer with docetaxel and gemcitabine + human granulocyte colony-stimulating factor. *Proc Am Soc Clin Oncol* 2001, **20**, 57b (abstr 1978).
98. Bildat S, Harstrick A, Gatzemeier U, *et al*. Phase I study of docetaxel in combination with gemcitabine as first line chemotherapy in patients with metastatic non small cell lung cancer. *Proc Am Soc Clin Oncol* 1999, **18**, 497a (abstr 1917).
99. Ventriglia M, Estevez R, Alume H, Bondulich G. Docetaxel plus gemcitabine. A new combination in the treatment of patients with advanced NSCL. A preliminary analysis. *Ann Oncol* 1998, **9**(Suppl. 2), 96 (abstr 365).
100. Dunsford ML, Mead GM, Bateman AC, Cook T, Tung K. Severe pulmonary toxicity in patients treated with a combination of docetaxel and gemcitabine for metastatic transitional cell carcinoma. *Ann Oncol* 1999, **10**, 943–947.
101. Jensen NV, Hansen O, Rose C. Combination of docetaxel and gemcitabine in the treatment of advanced non-small cell lung cancer. *Eur J Cancer* 1999, **35**, 258 (abstr 1026).
102. Brandi M, Giotta F, Vici P, *et al*. Salvage chemotherapy with docetaxel and gemcitabine in metastatic breast cancer: preliminary results of a multicenter phase II trial of GOIM. *Proc Am Soc Clin Oncol* 2001, **20**, 52b (abstr 1956).
103. Fountzilas G, Nicolaides C, Bafaloukos D, *et al*. Docetaxel and gemcitabine in anthracycline-resistant advanced breast cancer: a Hellenic Cooperative Oncology Group phase II study. *Cancer Invest* 2000, **18**, 503–509.
104. Hejna M, Kornek GV, Raderer M, *et al*. Treatment of patients with advanced non small cell lung carcinoma using docetaxel and gemcitabine plus granulocyte-colony stimulating factor. *Cancer* 2000, **89**, 516–522.
105. Schlösser NJJ, Richel DJ, Van Zandwijk N, *et al*. Phase I study of docetaxel and gemcitabine combination chemotherapy in chemotherapy naive patients with advanced or metastatic non small cell lung cancer. Proc Am Soc Clin Oncol 1998, **17**, 499a (abstr 1924).
106. Lizon J, Feliu J, Morales S, Dorta J, Belon J. A phase II study of gemcitabine plus docetaxel as first line treatment in non-small cell lung cancer. *Am Soc Clin Clin Oncol* 2001, **20**, 270b (abstr 2833).

107. Miyazaki M, Takeda K, Ichimaru Y, *et al*. A phase I/II study of docetaxel and gemcitabine combination chemotherapy for advanced non-small cell lung cancer. *Proc Am Soc Clin Oncol* 2001, **20**, 265b (abstr 2812).
108. Quantin X, Tranchand B, Pujol JL, *et al*. Phase I and pharmacokinetic study of docetaxel and gemcitabine in patients with non small cell lung cancer. *Proc Am Soc Clin Oncol* 1999, **18**, 187a (abstr 720).
109. Garcia C, Milla A, Feliu J, *et al*. Phase II study of gemcitabine in combination with docetaxel in advanced non-small cell lung cancer patients. *Ann Oncol* 2000, **11**(Suppl. 4), 113 (abstr 516).
110. Jaremtchuk AV, Zarba JJ, Ferro A, Aman EF, Alvarez R. Gemcitabine and docetaxel in patients with advanced solid tumors. A Getics phase I trial. *Proc Am Soc Clin Oncol* 1999, **18**, 215a (abstr 828).
111. Pawinski A, Louwerens M, Tonelli D, van Oosterom AT, Verweij J. A phase I study of taxotere and gemzar in patients with advanced solid tumors. *Ann Oncol* 1998, **9**(Suppl. 4), 139 (abstr 665).
112. Rischin D, Boyer M, Smith J, *et al*. A phase I trial of docetaxel and gemcitabine in patients with advanced cancer. *Ann Oncol* 2000, **11**, 421–426.
113. Georgoulias V, Kouroussis C, Androulakis N, *et al*. Front-line treatment of advanced non-small-cell lung cancer with docetaxel and gemcitabine: a multicenter phase II trial. *J Clin Oncol* 1999, **17**, 914–920.
114. Mavroudis D, Malamos N, Alexopoulos A, *et al*. Salvage chemotherapy in anthracycline-pretreated metastatic breast cancer patients with docetaxel and gemcitabine: a multicenter phase II trial. *Ann Oncol* 1999, **10**, 211–215.
115. Dimopoulos MA, Anagnostopoulos A, Pantazopoulos D, *et al*. Primary treatment of muscle-invasive bladder cancer in elderly patients and in patients with impaired heart or lung function with gemcitabine and docetaxel. *Proc Am Soc Clin Oncol* 1999, **18**, 337a (abstr 1297).
116. Stathopoulos GP, Mavroudis D, Tsavaris N, *et al*. Treatment of pancreatic cancer with a combination of docetaxel, gemcitabine and granulocyte colony-stimulating factor: a phase II study of the Greek Cooperative Group for Pancreatic Cancer. *Ann Oncol* 2001, **12**, 101–103.
117. Frasci G, Comella P, D'Aiuto G, *et al*. Weekly docetaxel plus gemcitabine or vinorelbine in refractory advanced breast cancer patients: a parallel dose-finding study. *Ann Oncol* 2000, **11**, 367–371.
118. Rizvi NA, Marshall J, Dahut W, Hawkins MJ. Phase I dose escalation and sequencing study of gemcitabine and docetaxel in advanced cancers. *Ann Oncol* 1998, **9**(Suppl. 4), 131 (abstr 629).
119. Chen YM, Perng RP, Whang-Peng J, *et al*. Phase II study of docetaxel plus gemcitabine in patients with non-small cell lung cancer that failed previous chemotherapy. *Ann Oncol* 2000, **11**(Suppl. 4), 115 (abstr 522).
120. Carreca IU, Mangiameli A, Dispenza J, Agueli R, Cucciare S . Gemcitabine and docetaxel as second line therapy of non-small cell lung cancer. A pilot study. *Ann Oncol* 2000, **11**(Suppl. 4), 114 (abstr 519).
121. Ryan DP, Lynch TJ, Grossbard ML, *et al*. A phase I study of gemcitabine and docetaxel in patients with metastatic solid tumors. *Cancer* 2000, **88**, 180–185.
122. Poole ME, Churchel MA, Bernard SA. Phase I study of gemcitabine and docetaxel for locally advanced and/or metastatic cancer of the head and neck, non-colorectal gastrointestinal cancer, hepatoma, and soft tissue sarcoma. *Proc Am Soc Clin Oncol* 2000, **19**, 222a (abstr 866).
123. Laufman LR, Spiridonidis CH, Carman L, *et al*. Second-line chemotherapy with weekly gemcitabine and monthly docetaxel in patients with metastatic breast cancer: a phase II study. *Proc Am Soc Clin Oncol* 2000, **19**, 106a (abstr 408).
124. Garland LL, Wagner H, Shaw GS, *et al*. Phase I study of constant dose rate infusion gemcitabine with taxotere in advanced non-small cell lung cancer. *Proc Am Soc Clin Oncol* 1999, **18**, 504a (abstr 1946).
125. Spiridonidis CH, Laufman LR, Jones J, Rhodes VA, Wallace K, Nicol S. Phase I study of docetaxel dose escalation in combination with fixed weekly gemcitabine in patients with advanced malignancies. *J Clin Oncol* 1998, **16**, 3866–3873.
126. Spiridonidis CH, Laufman LR, Carman L, *et al*. Second-line chemotherapy for non-small-cell lung cancer with monthly docetaxel and weekly gemcitabine: a phase II trial. *Ann Oncol* 2001, **12**, 89–94.
127. Pawinski A, Louwerens M, Tonelli D, van Oosterom AT, Verweoj J. A phase I study of taxotere and gemzar in patients with advanced solid tumors. Proc Am Soc Clin Oncol 1998, **17**, 249a (abstr 957).
128. Kouroussis C, Kakolyris S, Mavroudis D, *et al*. A phase I study of weekly docetaxel and gemcitabine in advanced non-small cell lung cancer. *Proc Am Soc Clin Oncol* 2001, **20**, 273b (abstr. 2844).
129. Hainsworth JD, Burris HA, Greco FA. Weekly docetaxel as a single agent and in combination with gemcitabine in elderly and poor performance status patients with advanced non-small cell lung cancer. *Sem Oncol* 2001, **3**(Suppl. 9), 21–25.
130. Jacobs AD, Otero H, Picozzi V, Aboulafia D, Rudolph R, Weiden P. Gemcitabine and taxotere in patients with unresectable pancreatic carcinoma. *Proc Am Soc Clin Oncol* 1999, **18**, 288a (abstr 1103).
131. Rubio G, Blajman C, Capó A, *et al*. Docetaxel and gemcitabine in metastatic non-small-cell lung cancer. A phase II study. Preliminary feasibility report. *Proc Am Soc Clin Oncol* 1999, **18**, 522a (abstr 2012).
132. Briasoulis E, Froudarakis M, Milionis H, Peponis I, Constantopoulos S, Pavlidis N. Chemotherapy-induced non-cardiogenic pulmonary edema related to gemcitabine plus docetaxel combination with granulocyte colony-stimulating factor support. *Respiration* 2000, **67**, 680–683.