Eur J Cancer, Vol. 29A, No. 9, pp. 1228–1231, 1993.
Printed in Great Britain

0964–1947/93 $6.00 + 0.00

Taxol and Taxotere—Current Status and Future Prospects

SOME WOULD claim that after 20 years of development the taxanes represent a major breakthrough in cancer chemotherapy. Over the next few years the true extent to which this enthusiasm is warranted will become apparent. Here we review the current standing of the prototype drug, taxol, and its semi-synthetic analogue, taxotere, and outline the ongoing studies which are likely to determine the place of these drugs in clinical practice.

During the 1960s the National Cancer Institute (NCI) screened more than 35 000 plant species for anticancer activity. Bark extracts of the Pacific yew tree (*Taxus brevifolia*) demonstrated activity in several murine tumours, but the active constituent of these extracts, taxol, was not identified until 1971 [1]. Further preclinical studies with the drug demonstrated only modest cytotoxicity and, because of the problems of its limited availability and aqueous insolubility, taxol was regarded as a spindle poison of little clinical promise. However, following the discovery in 1979 of its unique mechanism of action, namely the promotion of tubulin polymerisation [2], interest was rekindled and the first clinical trials of taxol began in 1983. Preparation of taxol from the yew tree bark necessarily requires felling of the tree, which regrows slowly from its stump, and adequate stocks of the drug have been difficult to maintain. The phase I trials with taxol ran far from smoothly, and the early observation of life-threatening anaphylactoid delayed studies for a considerable time. Because of its poor aqueous solubility taxol is formulated in 50% ethanol and 50% Cremophor EL, and the latter may be responsible for these reactions [3]. An empirically derived premedication regimen, consisting of dexamethasone and both H_1 and H_2-histamine blockers, has reduced the incidence of serious hypersensitivity reactions to less than 5%, although mild reactions such as facial flushing still occur in about a third of patients [3]. With similar premedication it has also been possible to repeat treatment in patients who have had severe reactions. The hypersensitivity reactions influenced the scheduling of taxol so that almost all the early clinical experience was with 24 h infusions. Concern then arose following the observation of ventricular tachycardia and heart block in a few patients receiving taxol and cisplatin [4]. Large numbers of patients have now been treated with cardiac monitoring and while taxol certainly does cause a transient asymptomatic bradycardia it rarely if ever causes serious dysrhythmias, and routine cardiac monitoring is not required. It remains to be seen whether the drug can safely be used in the presence of cardiac disease, and at present it is still recommended that patients do not receive taxol within 6 months of myocardial infarction, or if they have angina, cardiac failure, or pre-existing arrhythmias, or if they are taking β-blockers, calcium antagonists, or digoxin.

The predominant dose-limiting toxicity in phase I studies has been neutropenia [5]. Although the initial clinical experience suggested that myelotoxicity was not schedule dependent, more recently a large randomised trial has clearly shown that a 24 h infusion of taxol causes a significantly higher frequency of grade 4 neutropenia than a 3 h infusion at the same dose [6]. The maximum tolerated dose (MTD) of taxol given by 24 h infusion is between 175 and 250 mg/m^2, depending on the extent of previous treatment [5]. Although at these doses up to 80% of patients have grade 3 or 4 neutropenia, in the great majority this is short-lived and not associated with sepsis. An important factor in this is the infrequency of severe mucositis, which provides a common portal of entry for pathogens in patients rendered neutropenic by other cytotoxics. Thus, contrary to conventional practice, it has been recommended that no dose reduction is made for grade 4 neutropenia which lasts less than 7 days and is not associated with fever [7]. Through the addition of cytokines such as G-CSF it is possible to make minor increases in the dose of taxol up to a maximum of 300 mg/m^2, but at these doses oral mucositis and peripheral neuropathy become dose-limiting [8, 9]. Other toxicities which have been regularly observed but are not dose-limiting include myalgias, alopecia, and phlebitis; nausea and vomiting has rarely required anti-emetic therapy.

A major impetus to pursue clinical studies of taxol came from the observation of objective responses in phase II trials in patients with advanced and refractory ovarian cancer, reported from the Johns Hopkins Oncology Centre, the Gynaecologic Oncologic Group (GOG), and the Albert Einstein Cancer Centre. When their results are combined the overall response rate was 33/111 (30%) [10–12]. All patients in these studies had previously received platinum-based chemotherapy, and in the Hopkins study the majority of patients had received at least two prior chemotherapeutic regimens. Attention has focussed in particular on the group of "platinum-resistant" patients, defined as those in whom there was disease progression either during or within 6 months of completion of platinum-based chemotherapy. Pooling the data, the response rate in platinum-resistant ovarian cancer was 38/111 (34%) and in platinum-sensitive disease 12/36 (33%) (Dr Benjamin Winograd, personal communication). This degree of activity in previously treated ovarian cancer compares favourably with other second-line therapies in this tumour type. Second exposure to platinum complexes has been shown to produce overall response rates of about 35% [13], and although better response rates have been reported in patients who have a treatment-free interval of more than 2 years [14], few patients with platinum-resistant tumours respond.

Because of difficulties with drug supply and the hypersensitivity reactions observed in phase I trials, phase II studies with taxol were limited initially to tumour types in which antitumour activity had been observed in the phase I studies, namely ovarian cancer and melanoma. Broad phase II studies have more recently shown responses in small cell and non-small cell lung cancer, and squamous cancer of the head and neck, but it is the results in breast cancer which have attracted most attention. A response rate of 14/25 (56%) in metastatic breast cancer was reported by the M.D. Anderson group, using doses of 200–250 mg/m^2, albeit at the cost of considerable myelosuppression [15]. Infection occurred in 5% of courses, and in the absence of sepsis taxol

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Received 15 Feb. 1993; accepted 18 Feb. 1993.

doses were not reduced if the neutrophil nadir was greater than 250/mm^3, so that dose reductions were only required in 14% of course. Similar antitumour activity has been observed with taxol in combination with G-CSF in 26 patients with stage IV breast cancer at the Memorial Sloan Kettering Hospital (response rate 61%) [9]: In the M.D. Anderson study responses occurred in 2/6 patients with doxorubicin-resistant tumour; this was defined as disease relapsing within 6 months of adjuvant doxorubicin-containing chemotherapy or progressing during treatment with doxorubicin. Given the limited clinical experience with taxol in breast cancer, we must be cautious in the interpretation of these results, but clearly further evaluation of taxol is warranted in this disease.

A major question which remains unanswered is the optimum dose and schedule of taxol. The extent of previous chemotherapy limited the dose of taxol which could be administered in the published ovarian and breast cancer studies, so that these patients received doses ranging between 135 and 250 mg/m^2 of taxol, and many responses followed treatment at considerably less than the MTD [16]. At present there is no evidence that there is any improvement in the response rate with doses above 200 mg/m^2, and these high doses are associated with a different spectrum of toxicity including mucositis and neuropathy [6]. It is possible that the duration of drug exposure above a threshold concentration is the major determinant of cytotoxicity rather than the absolute dose. There are indeed preclinical data to suggest that the antitumour effects of taxol are dependent on the schedule of administration with an advantage to prolonged infusions [5], but there is still no clinical evidence to support this, and objective responses have been reported in a phase I study with 6 h infusions of taxol [17]. A European–Canadian study in ovarian cancer may help to answer some of these questions. Its bifactorial design compares 3 and 24-h infusions, at doses of 135 and 175 mg/m^2, in the total of 407 patients with refractory ovarian cancer, and already there is evidence that the 3 h schedule causes less myelotoxicity [5]. Interestingly this study has also shown that hypersensitivity reactions are not schedule dependent, and out-patient taxol therapy with shorter infusions may thus be feasible.

Throughout its development taxol has been greatly hampered by the limited availability of its source material, and its complex chemical structure has made synthesis of the complete molecule extremely difficult. However, it is not possible through a semi-synthetic process to produce taxol from an extract prepared from other biomass sources. Large scale semisynthetic production is now under way and it appears that the drug supply problem may have been solved.

The next step in the development of taxol will logically be its combination with other cytotoxics, and the activity of the drug in ovarian cancer has stimulated combination studies with cisplatin. *In vitro* data suggest that the sequencing of taxol and cisplatin may be important [18]; there are theoretical disadvantages to giving cisplatin, which induces G_2M block, prior to a phase specific drug like taxol. In fact, the clinical trial of alternating sequences of taxol and cisplatin showed that the administration of cisplatin before taxol produced more severe myelotoxicity, and pharmacokinetic data suggest that this is due to a cisplatin-related fall in taxol clearance [19]. Neutropenia and peripheral neuropathy are dose limiting when taxol and cisplatin are combined, but toxicity is acceptable using a combination of taxol 135–170 mg/m^2 and cisplatin 75 mg/m^2, doses which are clearly active when either drug is given as a single agent [19]. The GOG have recently completed accrual within their phase III study comparing cisplatin and cyclophosphamide with cisplatin and taxol. Other drugs being tested in phase I combination studies with taxol include cyclophosphamide, doxorubicin, carboplatin, ifosfamide, etoposide, and topotecan. Experience with taxol and doxorubicin indicates indicates that such studies require to be undertaken cautiously. Significant synergistic toxicity, namely dose-limiting mucositis, was observed when the combination of taxol 125 mg/m^2 and doxorubicin 60 mg/m^2 was given [20].

While progress in the phase I trials of taxol was being hampered by the problems of drug supply and hypersensitivity reactions, work was proceeding on a semisynthetic analogue, taxotere, prepared from an extract of the needles of the European yew tree (*Taxus baccata*) [21]. This drug inhibits microtubule depolymerisation in a similar manner to taxol and was shown to have a broad spectrum of activity in preclinical studies [22, 23]. The potential advantages of this agent over taxol were seen to include the renewable source of its natural precursor and its formulation in polysorbate 80 instead of Cremophor EL. The spectra of activity of taxol and taxotere are similar in transplantable leukaemias and solid tumours in mice, but taxotere is approximately twice as potent [22], and one *in vivo* study has claimed a superior therapeutic index when compared with taxol [23]. Another potentially important difference is that in preclinical testing, the antitumour effects of taxotere appeared to be enhanced by the intermittent administration of bolus doses compared with schedules which mimicked a continuous infusion [23].

Taxotere entered phase I studies in 1990 and broad phase II studies are already nearing completion, underlining the rapidity with which this drug has been developed. As with taxol, neutropenia has proved to be the dose-limiting toxicity [24–28], and following the experience with taxol grade 4 neutropenia has been deemed tolerable when it is short-lived and not associated with sepsis. Hypersensitivity reactions have been reported in the phase I studies but have rarely been severe, and premedication with steroids were not used in the initial phase II trials. The other observed toxicities are similar to taxol: alopecia is universal, emesis is rarely worse than grade 1–2, and peripheral neuropathy occurs sporadically with doses close to the MTD. Additional toxicities including a pruritic skin eruption, peripheral oedema, and pleural thickening have been observed with taxotere [29]. It is quite conceivable that they have not occurred with taxol because of the concomitant steroid premedication, and studies of taxotere given with routine premedication are now planned.

Mucositis as well as neutropaenia is dose-limiting with a 24 h infusion of taxotere [24], but less frequent with the schedule chosen for initial phase II studies, a 1 h infusion. The MTD for this schedule of taxotere is 110 mg/m^2, just below half the MTD for taxol, and this ratio of doses is remarkably similar to that seen in *in vitro* studies of tubulin polymerisation with the two drugs [22]. In the phase I studies taxotere demonstrated unequivocal clinical activity in heavily pretreated patients with ovarian and breast cancer. A broad phase II programme, using a dose of 100 mg/m^2, is underway in Europe and the U.S.A. and the results are eagerly awaited. Until these are available comparisons between taxol and taxotere cannot be made, but eventually direct comparative trials may be appropriate.

The clinical pharmacology of taxol and taxotere has been studied in some detail and overall the drugs are very similar with regard to their disposition and elimination in man. The plasma drug concentration profile of each is best characterised by a bi-

exponential model, with a $t_{1/2}\alpha$ of less than 1 h and a terminal half life of up to 8 h [6, 27]. There are large interindividual differences in the disposition of both drugs but no evidence of non-linear pharmacokinetics. The peak plasma concentration achieved at the MTD with a 6 h infusion of taxol is up to 8 μmol/l and with taxotere administered in the same way is 1 μg/ml. Both drugs are extensively protein bound but are readily cleared from plasma, and while less than 10% of the parent compound can be recovered in the urine a greater percentage is metabolised in the liver and excreted in the bile. At present the metabolites have not been completely characterised and their antitumour activity has not been assessed. It is clear however that taxotere is not simply a prodrug of taxol. Given their similar pharmacological profiles it is hard to explain why different schedules have essentially opposite effects on the activity of the two drugs in the murine tumours.

Do the taxanes genuinely offer clinical superiority compared with other cytotoxics which act on tubulin? Although the mechanism by which they interfere with tubulin is unique, the effects, on normal tissues at least, of the taxanes are somewhat similar to those of the vinca alkaloids. Both groups of drugs are also substrates for the multi-drug resistance P-glycoprotein. Recently interest has focussed on the use of prolonged infusion of drugs such as the vincas to overcome drug resistance, and there is now some clinical evidence that this approach is successful in haematological malignancies [30, 31]. However, although prolonged infusions of vinblastine have also shown some activity in refractory breast cancer [32], no responses have been observed in refractory ovarian cancer [33], suggesting that the the novel mechanism of action of taxanes does convey specific advantages. These comparisons with vinca alkaloids assume that taxanes operate solely as anti-mitotic poisons, but there is evidence that they do exert cytotoxic effects which are not phase specific, and these may include disruption of cell membrane structure, intracellular transport, or signal transduction [5].

Much remains to be learnt about taxol and taxotere, their spectra of activity and relative clinical usefulness in comparison with existing cytotoxics, and the extent to which their use in combination chemotherapy will alter the outcome of treatment. After several years of disappointment in new drug development a number of exciting new compounds are now emerging through phase I and II trials. As well as the taxanes these include the antimetabolite, gemcitabine [34], the anthrapyrazole, biantrazole [35] and the topoisomerase I inhibitors, CPT-11 and topotecan [36, 37]. Activity in a range of diseases has been seen with these drugs, some of which compare favourably with the taxanes at least in terms of toxicity. Thus the taxanes still have to prove themselves in terms of efficacy and toxicity against these new agents as well as those conventional drugs whose limitations are well known. Nonetheless it does seem likely that their future development will lead to significant progress. This makes it all the more important that we continue the process of rational and scientific evaluation of these drugs in the setting of closely monitored clinical trials, in order that their appropriate place in cancer therapy can be defined quickly and efficiently.

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Acknowledgements—The authors are grateful to Benjamin Winograd, Bristol-Myers Squibb, and Martine Bayssas, Rhone Poulenc Rorer, for their assistance in the preparation of this review.

Eur J Cancer, Vol. 29A, No. 9, pp. 1231–1236, 1993.
Printed in Great Britain

0964–1947/93 $6.00 + 0.00

Papers

Carcinoma of the Cervical Stump: A Review of 213 Cases

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From 1970 to 1987, 213 cases of carcinoma of the cervical stump were accrued in a multi-institutional prospective cooperative study. This group accounted for 5.5% of cervical carcinoma diagnosed during the same period. 13 had *in situ* carcinoma and 200 had invasive carcinoma (96% squamous cell carcinoma, 4% adenocarcinoma). Radiotherapy alone (external and brachytherapy) was given to 77%, brachytherapy and surgery to 15% and surgery alone to 8%). FIGO stage distribution was: I (31%), IIa (15%), IIb (27%), IIIa (5%), IIIb (17%) and IV (5%). Five-year locoregional control per stage was 100% in Ia, 85% in Ib, 82% in IIa, 71% in IIb, 45% in IIIa, 54% in IIIb and 30% in IV. Corrected 5-year survival per stage was 82% in Ib, 78% in IIa, 73% in IIb, 69% in IIIa, 38% in IIIb and 0% in IV. The diameter of disease in stage II strongly influenced the 5-year locoregional control (81% for tumours of less than 3 cm vs. 68% for tumours more than 3 cm). Lymphangiogram was associated with a 44.5% 5-year locoregional control when positive vs. 74% when non-positive. Brachytherapy was advantageous in obtaining locoregional control in patients receiving external irradiation and brachytherapy: 81.5% vs. 38.5% in patients treated with external radiotherapy alone. Surgery was performed only for *in situ* carcinoma and for part of stages Ia, Ib and IIa. There is no significant difference in locoregional control at equal stage between radiotherapy alone and treatment schemes including surgery. However, lethal complications were observed in 6% of the patients of the surgical group as compared to 0.6% of the patients treated with radiotherapy alone. Radical radiotherapy seems to provide similar results of locoregional control and survival at equal stages in carcinoma of the cervical stump compared to carcinoma developed on an intact uterus. The rate of severe complications reported with the French–Italian glossary is 13% for G3 and 3% for G4, which is close to the observed rate during the same period in our series of radical radiotherapy to the intact uterus.
Eur J Cancer, Vol. 29A, No. 9, pp. 1231–1236, 1993.

INTRODUCTION

TWO MAJOR controversies still remain linked with the prevention and treatment of carcinoma arising on the cervical stump: should subtotal hysterectomies be banished from the treatment modalities of benign gynaecological conditions? Are there new arguments favouring either radiotherapy alone or combined radiotherapy and surgery in carcinoma of the stump?

This paper reports on the outcome of treatment of 213 patients with cervical stump carcinoma treated in a prospective non-randomised study over nearly two decades. The technical and