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The clinical rationale for developing docetaxel (Taxotere®)

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Clinical empiricism has recognized resistant breast cancer as a privileged target for docetaxel (Taxotere®). This worldwide registration will offer medical oncologists the opportunity to develop new indications for docetaxel. Pharmacokinetics, preclinical optimal combination and clinical practice will constitute the rationale for the future development of docetaxel.

Keywords: Docetaxel (Taxotere®), phase I, pharmacokinetics, pharmacodynamics.

Introduction

Empirical clinical studies are still used to establish the optimal dose and schedule for new anticancer agents. The therapeutic potential of new drugs is approached in phase I studies and the clinical response in specific disease areas is established in phase II studies. The optimal dose and schedule for anticancer drugs is often established years after their initial introduction into the clinic. When 5-fluorouracil (5-FU) was first introduced, it was not anticipated that it would be used as a continuous infusion and modulated with folinic acid, nor that it would be used as an adjuvant treatment for colorectal cancer [1]. Similarly, the schedule of administration for etoposide has changed substantially since its introduction, and its use with platinum drugs to modulate the action of cisplatin, leading to cure in otherwise cisplatin-resistant testicular cancers, was not anticipated [2]. Clinical empiricism is still the major tool in the establishment of the optimal schedules of treatment and combinations for anticancer drugs. However, a rationale, supported by preclinical and early clinical evidence, must be presented in order to justify further development of an agent. The study of a drug during combined phase I trials presents an opportunity for the clinical researcher to investigate the potential of the drug and to develop its optimal use.

Clinical studies with docetaxel

The recommended dose and schedule for phase II trials of docetaxel (Taxotere®) were derived from phase I studies which are summarized in Table 1. Phase I studies, conducted in patients suffering from a variety of solid tumours, used several different infusion times and schedules for docetaxel administration. The establishment of a recommended dose and schedule was straightforward for docetaxel. The dose-limiting toxicity, neutropenia, was the same in all phase I studies, and the amount of drug required to be given to reach the recommended dosage was established to be 100 mg/m². The only remaining issue was the schedule of administration. All extended-infusion and multiple-dose schedules were limited by mucositis, resulting in the recommended schedule consisting of a 1-h infusion every 3 weeks.

Table 1. Summary of phase I results

Infusion	No. of patients	MTD (mg/m²)	Schedule	DLT	Ref
1–2 h	65	110	q 3 weeks	Neutropenia	[3]
1 h	10	–	q 3 weeks	Neutropenia	[4]
24 h	30	90	q 3 weeks	Neutropenia, mucositis	[5]
1 h	30		16 x 5 days 1–5	Neutropenia, mucositis	[6]
2 h	18	115	q 3 weeks	Neutropenia, skin reaction	[7]
6 h	40	100	q 3 weeks	Neutropenia, mucositis	[7]
1 h	33	55 x 2	days 1 + 8	Neutropenia	[8]

MTD, maximum tolerated dose; DLT, dose-limiting toxicity.

Significant antitumour activity was seen in phase I trials, as had been expected from the preclinical studies, and phase II trials were initiated with the great advantage of having a straightforward, established effective dose and schedule, which was, and is, unlikely to require any alteration to optimize antitumour activity, and a simple single dose-limiting toxicity which could be anticipated and monitored.

A prospective study of population pharmacokinetics and pharmacodynamics was conducted during phase

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II trials [9,10], using a sparse sampling strategy amongst 577 patients. This study represented the first instance of the collection of pharmacodynamic data at such an early stage in the development of an anticancer drug. The area under the plasma concentration–time curve (AUC) for docetaxel was found to be very closely related to the dose given, indicating that effects related to plasma concentration could be predicted from the dose given. The clearance of docetaxel follows a linear three-compartment model [3]. Interpatient variability in docetaxel plasma clearance (mean 36.7 l/h) was found to be moderate and to be related to body surface area, plasma α_1-acid glycoprotein levels (to which docetaxel is bound) and hepatic enzyme levels, but not to be affected by the age or sex of patients [10]. Clearance variability was found to be a strong predictor of the odds of grade 4 neutropenia. Since docetaxel is metabolized by the liver, impaired liver function is likely to reduce docetaxel clearance. It has been shown that the presence of liver metastases, without the presence of impaired liver function, does not adversely affect docetaxel clearance or increase toxicity [11], but care must be taken to assess liver function and to reduce the dose when liver function is compromized.

The most important findings of the pharmacokinetic studies are that docetaxel pharmacokinetics are independent of dose and schedule. Docetaxel is highly bound to plasma protein, is metabolized by the liver, forming four metabolites for which the activity and toxicity is yet to be established, and is excreted mainly in the faeces [10]. The straightforward pharmacokinetic profile of docetaxel means that this is a predictable drug, with a strong correlation between the dose given, the AUC, and the neutrophil nadir (Figure 1), allowing it to be used with confidence in the clinic.

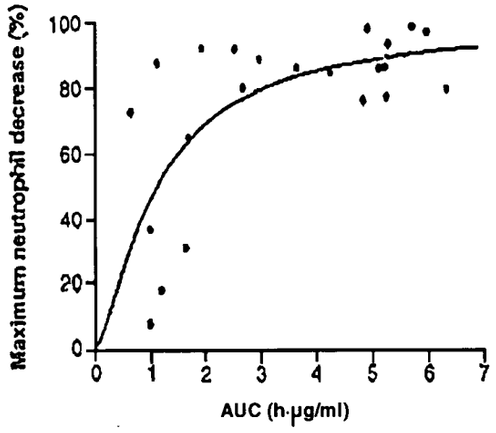

Figure 1. Correlation between area under the curve (AUC) and neutropenia.

Docetaxel in combination

Dose-finding studies for combinations of docetaxel with other established agents are being carried out in patients with solid tumours, with some studies being directed at specific disease areas. Studies of the combination of docetaxel with other active agents are ongoing with doxorubicin, vinorelbine, cyclophosphamide, 5-FU, cisplatin and CPT-11. Combination studies will lead to the development of treatment schedules for patients with a wide variety of cancers. Epidermoid cancers, from the lips to the anal canal, may represent the most appropriate clinical arena for investigating the use of docetaxel in association with 5-FU, CPT-11 and vinorelbine.

One frequent disadvantage of drug combinations over single agent treatments is increased toxicity. Mucositis, for instance, is seen more often in combination studies, and neuropathy has proved to be a problem with some combinations when it is not a significant problem with either drug alone. Neuropathy has not yet proved to be a problem with docetaxel combination studies, even when docetaxel is combined with navelbine, another spindle poison [12]. Combinations of docetaxel and doxorubicin [13] have no added cardiotoxicity which could be a limitation for the paclitaxel–doxorubicin combination. The Taxotere®–CPT11 combination has significant activity in second-line therapy after platinum combination with 5-FU, navelbine or VP16 (C Couteau, JF Dufour, D Oulid-Aissa, *et al.*, presentation for European Society of Medical Oncologists Congress, Vienna, November 1996). These phase I–II combined modalities offer a new opportunity to rediscover the role of docetaxel in orphan diseases.

Conclusion

Phase I and II studies have shown docetaxel to be a manageable drug with only one dose-limiting toxicity. The consistent use of one dosage regimen throughout phase II studies has allowed the pharmacokinetics and toxicity profile of docetaxel to be well defined. Further studies of docetaxel in combination, and in other disease areas, will extend the use of this promising new therapy.

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