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Pergamon

European Journal of Cancer Vol. 31A, No. 5, pp. 824–826, 1995
Elsevier Science Ltd
Printed in Great Britain
0959–8049/95 $9.50+0.00

0959-8049(95)00104-2

Taxoids

S.B. Kaye

INTRODUCTION

TAXOIDS REPRESENT an important new class of cytotoxic drugs because they possess a unique mechanism of action. Their target is the cytoplasmic microtubule, and in contrast to the vinca alkaloids, they prevent rather than promote disassembly, thereby disrupting the process of cell division. Development of these drugs has been protracted for over 20 years because of the initial problems of an insufficient drug supply, as well as the concerns over hypersensitivity reactions seen in early clinical trials. Essentially, taxoids are extracts from either the Pacific or the European Yew tree. The initial extraction from the bark was grossly inefficient; more recent semi-synthetic processes using the needles as precursors have solved supply problems, allowing clinical development to accelerate.

PACLITAXEL AND DOCETAXEL

So far, there are two taxoids available for clinical evaluation; doubtless other analogues will shortly emerge. Paclitaxel (Taxol) was the first taxoid to reach the clinic, and it is now marketed in several countries for the treatment of refractory ovarian cancer [1]. Docetaxel (Taxotere) differs from paclitaxel in two separate positions on the taxane ring structure [2]; in preclinical studies, this leads to an increase in its potency over the parent compound and some increase in solubility, although both compounds are insoluble in water and require formulation in lipophilic solvent. The preclinical spectrum of activity and the animal toxicology are similar for the two compounds, although some of the data do suggest some differences in respect of schedule-dependent activity, as well as partial non-cross resistance, and the possibility of an improved therapeutic index with docetaxel [2].

The difference in preclinical potency between the compounds is of the order of 2–3 fold, and this translates fairly closely to the results of clinical Phase I trials. For paclitaxel, the maximum tolerated dose (MTD) without G-CSF support was originally reported as 200 mg/m^2 [3]. This related to a 24 h infusion given 3 weekly, and included the use of premedication comprising steroids, antihistamines and 5-HT$_2$ antagonists, all of which had been developed because of occasional severe hypersensitivity reactions in the initial trial. The dose-limiting toxicity for paclitaxel was neutropenia; alopecia was universal and peripheral neuropathy and mucositis were occasionally seen and were dose-dependent. Recent studies indicate a most interesting difference in toxicity using a shorter (3 h) infusion; myelosuppression is less pronounced, allowing higher doses to be given with no increase in hypersensitivity reactions, but the impact on antitumour efficacy is not yet clear. Indeed, current Phase I trials are exploring both shorter and longer infusion times (1–96 h); it remains to be seen whether significant differences between the schedules causing maximal myelosuppression and those giving optimal efficacy will emerge.

For docetaxel, the MTD is approximately half that of paclitaxel, i.e. 115 mg/m^2 when the drug was given over 1–5 h, and is 90 mg/m^2 when the drug is given over 24 h, in both cases 3 weekly [4, 5]. Again, neutropenia is dose-limiting, and in the early Phase I trials hypersensitivity reactions were rare. Hence, premedication was not given routinely and its toxicity profile was seen to be similar to paclitaxel. As experience with docetaxel extended, a significant difference was noted, namely a trouble-

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some syndrome of fluid retention and skin reactions occurring in approximately half the patients who received more than four courses. Although its mechanism is unclear, further studies aimed at amelioration with routine premedication are now underway and will be crucial to the further development of this analogue.

OVARIAN CANCER

The considerable attention which the taxoids have attracted derives from the initial data on antitumour efficacy, originally in patients with refractory ovarian cancer. In the initial three Phase II studies with paclitaxel in ovarian cancer in which the overall response rate for 110 evaluable cases was 30%, a total of 68 cases were clearly platinum-refractory, i.e. were progressing during platinum therapy, and of these 13, 19% responded to paclitaxel [6–8]. Since this is a clinical situation in which a response to any therapy is most unusual, interest was heightened, and the studies were extended in ovarian cancer and other disease types. For advanced ovarian cancer, an interesting audit of the activity of paclitaxel among the first 1000 heavily-pretreated patients treated in multiple centres revealed a response rate of 22% in 652 evaluable cases with a median response duration of only 5 months, and median survival of only 9 months [9]. Clearly, the drug is likely to make a more substantial impact in ovarian cancer as part of first-line combination therapy, and a recent GOG study in the U.S.A. has compared paclitaxel/cisplatin with cyclophosphamide/cisplatin as initial treatment for a total of six courses [10]. A significant survival benefit was found in the paclitaxel/cisplatin arm, and the drug is now widely used as part of first-line therapy in the U.S.A. for this disease.

This and other studies used the 24 h infusion schedule for paclitaxel. As mentioned previously, a 3 h infusion schedule causes less myelosuppression, allowing higher doses to be given, and the majority of Phase II and III studies which have been planned recently have reverted to a 3 h schedule. These include studies of paclitaxel in combination with other drugs, including carboplatin, doxorubicin and cyclophosphamide. In one study with doxorubicin, toxicity was unexpectedly severe [11], and further studies to define the optimal sequence of drugs remain to be done.

For docetaxel, all Phase II studies have been conducted with a 1 h infusion of 100 mg/m^2. These are now also employing premedication schedules, similar in nature to those used with paclitaxel, and preliminary data do suggest a reduction in the degree of fluid retention [12]. As regards the activity of docetaxel in ovarian cancer, pooled data from three Phase II studies (two in the EORTC and one in the U.S.A.) indicate a level of activity at least equivalent to that of paclitaxel, with an overall response rate of 34% in a total of 200 evaluable cases, with a 27% response rate in 30 patients with apparently platinum-refractory disease [13].

BREAST CANCER

In breast cancer, both taxoids exhibit significant degrees of activity. Paclitaxel has been tested in Phase II studies both as first- and second-line therapy, and the initial trials (at the higher dose of 250 mg/m^2 with or without G-CSF) yielded response rates of 47–56% in a total of 76 cases [14]. Interestingly, so far docetaxel has proved at least as active at the MTD of 100 mg/m^2, with response rates of 62–71% as second- or first-line therapy in 31 and 95 cases, respectively [14]. Moreover, paclitaxel studies were conducted in single institutes, while docetaxel was studied on a multicentre basis. As expected, response rates (for paclitaxel) have fallen in the context of multicentre randomised trials, to 16–24% as second-line therapy at the lower doses of 135–175 mg/m^2 [15]; randomised studies for docetaxel have not yet been conducted.

WHAT ABOUT ACTIVITY IN OTHER TUMOUR TYPES?

Both drugs have interesting activity (in Phase II trials) in patients with previously untreated non-small cell lung cancer, with response rates of 22% and 28%, respectively, for paclitaxel (49 cases) and docetaxel (76 cases). Similarly, in small cell lung cancer, response rates of 34% have been reported for 32 previously untreated cases given paclitaxel, and 28% for 18 previously treated cases given docetaxel. Activity with both drugs has also been seen in head and neck cancer (response rates of 43% for paclitaxel (28 cases), 37% for docetaxel (38 cases) and in melanoma, 14% (87 cases) and 25% (28 cases), respectively). Trials in colon cancer and renal cancer have been negative for both drugs, while in pancreatic cancer, some responses have been seen (13% with paclitaxel (28 cases) and 21% for docetaxel (24 cases)). Paclitaxel also has activity in refractory testicular cancer (24% response rate in 25 refractory cases) [16], while docetaxel has demonstrated some activity in patients with refractory soft tissue sarcoma (21% response in 28 cases). One difference seen so far has been in gastric cancer, where paclitaxel proved to be inactive in 27 cases, whereas docetaxel had a response rate of 26% among 34 evaluable cases.

In summary, it seems very likely that the taxoids will have an established role in the treatment of a number of solid tumours. Outstanding issues include the optimal schedule particularly for paclitaxel, and the feasibility of combination regimens with a range of other active drugs. On the question as to which of the currently available two agents proves to be the most valuable, at present the jury is still out.

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Pergamon

European Journal of Cancer Vol. 31A, No. 5, pp. 826–827, 1995
Elsevier Science Ltd
Printed in Great Britain
0959–8049/95 $9.50+0.00

0959-8049(95)00105-0

New Endocrine Agents in the Treatment of Breast Cancer

H.T. Mouridsen

INTRODUCTION

THE HORMONE responsive tumours include breast cancer, endometrial cancer and prostate cancer, all common cancers and in Denmark five-year survival for these are approximately 60, 70 and 25%, respectively. Quantitatively and qualitatively, therefore, these tumours represent a significant challenge to the treatment of solid tumours. This review will relate to the treatment of breast cancer. It will briefly mention the available endocrine therapies and then present new groups of drugs recently developed.

AVAILABLE ENDOCRINE THERAPIES

The available endocrine therapies aim at reducing the level of circulating oestrogens or their binding to the oestrogen receptor which is present in approximately two-thirds of primary breast cancer cases. The clinical rationale for this approach is the early demonstration of tumour response following the surgical removal of endocrine glands such as the ovaries, the adrenals and the pituitary [1].

Oestrogens are produced by aromatisation of androgens (androstenedione) by the enzyme aromatase. Pre- and postmenopausal women have distinct sites of oestrogen production [2], the former in the ovary under luteinising hormone (LH) and follicle-stimulating hormone (FSH) control, and the latter in the extra glandular tissue (e.g. fat tissue or liver) under the influence of various agents including ACTH, glucocorticoids and several growth factors [3].

The available endocrine treatment modalities include ablative therapy, additive therapy, competitive therapy and inhibitive therapy.

Ablative therapy with oophorectomy significantly reduces the levels of circulating oestrogens.

The mechanism of action of additive therapy with progestins remains controversial, but part of its effect is probably mediated via inhibition of the synthesis of pituitary hormones, thus leading to suppression of the synthesis of sex steroids in the ovary and in the adrenals. They may also act as "physiological" antiproliferative agents through progesterone or androgen receptors or they may act by decreasing synthesis of oestrogens or androgens [4].

Competitive therapy with antioestrogens seems to exert its action by antagonism of oestrogen action at the oestrogen receptor level [5]. Binding of oestrogen to its specific receptor stimulates the secretion of growth factors exerting autocrine or paracrine control of growth, and it has been argued that tamoxifen may exert part of its action by increasing the secretion of transforming growth factor-beta [6]. However, the antioestrogen also binds to other sites, but the potential role of these additional bindings sites in the mediation of the antiproliferative effect is largely unknown [1].

Inhibitive therapies include aromatase inhibitors and analogues of gonadotrophin-releasing hormone (GnRH). The aromatase inhibitors act through the inhibition of the conversion of androgen, primarily androstenedione, to oestrogen. Aminoglutethimide in addition inhibits cortisol biosynthesis [2]. The GnRH analogues work indirectly by inhibition of the secretion of the pituitary hormones [7].

With the endocrine therapies available today, approximately one-third of unselected patients, and one-half of women with oestrogen-receptor positive tumours will respond [1, 8], with no major advantage as regards efficacy associated with any of the modalities.

NEW ENDOCRINE AGENTS

Recent years have seen the development of new drugs, especially aimed at achieving an enhanced suppression of circulating levels of oestrogens (new aromatase inhibitors), and enhanced interaction at the oestrogen receptor level (new antioestrogens) or an action on the progesterone receptor (antiprogesterones).

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