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Arzoxifene in breast cancer

S. Chan*

Nottingham City Hospital, Hucknall Road, Nottingham NG5 1PB, UK

1. Introduction

Arzoxifene is a Selective Oestrogen Receptor Modulator (SERM) which acts as a potent oestrogen antagonist in mammary and uterine tissues, while acting as an oestrogen agonist to maintain bone density and lower serum cholesterol. It is metabolised to a desmethyl metabolite. Both the parent compound and the metabolite bind to the Oestrogen Receptor (ER) with high affinity and inhibit oestrogen dependent growth of MCF-7 breast cancer cells. The potency is 3000- to 25 000-fold higher than that of tamoxifen against the MCF-7 cells. In addition, arzoxifene acts as an oestrogen antagonist on the uterus [1]. In a phase 2 trial of arzoxifene in advanced endometrial cancer (the results of the study were presented at this meeting), patients with ER progesterone receptor (PR) positive tumours received 20 mg per day of the trial medication until disease progression. The overall tumour response rate in the 60 patients enrolled was 25% (95% CI 14.7% to 37.9%) and the median duration of response was 19.3 months. The progestagen-sensitive group had a response rate of 34.4% (95% Confidence Interval (CI) = 18.5–53.2%). This is significantly higher than that achieved using medroxyprogesterone acetate in a similar set of patients (who received no prior hormone therapy) in a recent phase 2 study conducted by the Gynecological Oncology Group (GOG) [2]: Response Rate (RR) = 25% and 16% for high and low dose respectively, median duration of response = 2–3 months. The response rate in a similar phase 2 study using tamoxifen was 10% (90% CI = 5.7–17.9%) in a more recent report [3]. There is no doubt that arzoxifene has a high antitumour activity in advanced endometrial cancer. The clinical role of the drug in this setting can only be assessed in a phase 3 study in a comparison against the standard therapy of progestagen.

2. Results of studies in advanced breast cancer

In a phase 2 randomised double-blind study arzoxifene was used as a first-line treatment for advanced breast cancer. 94 subjects were randomised to one of two treatment groups: 20 or 50 mg per day of arzoxifene until disease progression. The subject characteristics in both arms were similar: there were 46 patients treated in each group, 2 patients withdrew from the trial prior to receiving treatment. All patients had good performance status; approximately 90% were postmenopausal and 75% ER- or PR-positive; 9% had prior tamoxifen. Tumour assessment was independently reviewed. RRs were similar in the two dose levels at 34–36% (95% CI 22.4 to 59). The clinical benefit rate was defined as the sum of objective tumour response (CR + PR), and stable disease (SD) lasting at least 6 months. This was the same in both groups at 64% (95% CI 32.5 to 63.3%.

In a similar phase 2 study, 119 patients with advanced breast cancer were treated with arzoxifene [4]. In the 63 tamoxifen-refractory patients, the objective response rate was 7%; 12% of patients had clinical benefit. This result suggests that there may not be complete cross-resistance between the SERMs.

3. Discussion and conclusions

Ongoing research into drug design combined with a better understanding of cellular biology has enabled more specific targeting with SERMs which in turn has increased the therapeutic ratio of the drugs. There was no doubt that arzoxifene has a high antitumour activity in advanced breast and endometrial cancer. The clinical significance of this activity in the setting of advanced breast cancer needs to be assessed against the standard treatment with tamoxifen—a phase 3 study comparing these two drugs for the treatment of advanced breast cancer is ongoing.

* Tel.: +44-163-683-0070; fax: +44-163-683-0070.
E-mail address: ytschan@innotts.co.uk (S. Chan).

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