Toremifene and tamoxifen in advanced breast cancer – a double-blind cross-over trial

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Summary

Toremifene (TOR) is a triphenylethylene derivative related to tamoxifen (TAM). TOR has antitumor activity, not dependent on estrogen receptors, and responses with TOR have been observed in patients with progressive disease during TAM-treatment. To elucidate possible cross-resistance between these two antiestrogens, we compared their anti-tumor activity in a randomized, double-blind, cross-over study.

66 postmenopausal women with advanced estrogen receptor positive or unknown breast cancer and a median age of 63 years (range 38–82) were included. Patients were randomized to TAM 40mg/day or TOR 240mg/day. Treatment continued until progressive disease, when cross-over to the alternative treatment was done. The response rate with first line TOR was 29% (95% confidence limits 10–41%) and with TAM 42% (95% confidence limits 25–61%). Response rates and response durations, survival and toxicity were not significantly different between the two treatments. 44 patients progressing on first line TAM or TOR were evaluable for second line TOR or TAM treatment. As no responses were observed, the possibility of overlooking a response rate of 20% or more is less than 1%.

In conclusion, this study strongly indicates that TOR and TAM are clinically cross-resistant in patients with advanced breast cancer.

Introduction

Toremifene (TOR) is a triphenylethylene derivative related to tamoxifen (TAM). TOR has a high affinity for the estrogen receptor (ER) in breast cancer tissue and is active against the MCF-7 breast cancer cell line [1]. Furthermore, TOR inhibits the growth of rat mammary carcinomas induced by dimethylbenzanthracene and causes regression of such tumors [2]. TOR appears to have less estrogenic effect than TAM at equivalent antiestrogenic doses [1]. In ER-negative murine uterine sarcomas, high doses of TOR (100 and 200mg/kg) had cytotoxic activity, an effect not observed with high doses of TAM [2]. It has been proposed that this is independent of ERs and mediated by specific antiestrogen binding sites [2] or by stimulation of transforming growth factor beta-1 [3].

In phase I studies, TOR has been well tolerated in doses up to 460mg/day [1, 4]. In phase II trials in-
cluding previously untreated patients with ER-positive advanced breast cancer, response rates between 48 and 68% have been observed [5–8]. These results are comparable to those obtained with TAM.

Anti-tumor activity of TOR has been described in patients previously treated with TAM. Ebbs et al. [3] treated 16 patients with locally advanced breast cancer who had progressed on TAM treatment with TOR 200 mg daily. Partial responses were observed in 4 patients with a median duration of 10 months (range 4–11). In another small study, activity of TOR was also observed after progression on TAM-treatment [9].

The dose of TAM has been prospectively tested over a range of 2–100 mg/m² body surface area twice daily. No clear benefit of using doses higher than 20–40 mg a day was shown [10]. As a few cases of remission have been reported after escalating the daily dose of TAM from 20 to 40 mg [11], we used the 40 mg daily dose. Based on the proposed different mechanisms of action, when TOR is given in high doses compared with low doses, and on the unexpected responses obtained with high-dose TOR in patients previously treated with TAM, we designed a double-blind crossover study to further elucidate whether TOR and TAM are clinically cross-resistant.

Methods

Patients

Patient inclusion criteria were: histologically verified inoperable primary, metastatic, or recurrent breast cancer, measurable or evaluable disease according to WHO criteria [12], ER-positive (>10 fmol/mg protein) or unknown tumors, at least 6 months since termination of any adjuvant endocrine therapy, a performance status of ≤2 (WHO), and postmenopausal stage defined as: 1) more than one year since last menstruation or 2) surgical or radiation castration or 3) ≥55 years if a hysterectomy had been performed. Patients previously treated with TAM for advanced breast cancer or patients receiving corticosteroids were not eligible.

Patients were randomized to TAM (40 mg orally o.d.) or TOR (120 mg orally b.i.d.). To ensure blinding of the trial, patients receiving TOR were given identical placebo tablets of TAM (and vice versa). Treatment was continued until progressive disease (PD) when patients were crossed over to the alternative treatment.

Clinical examination, tumor measurements, and blood tests (hemoglobin, leukocytes, thrombocytes, sodium, potassium, creatinine, calcium, LDH, alkaline phosphatase, bilirubin, albumin, and ASAT) were done before inclusion and then every 4 weeks. Chest X-rays and X-ray and/or ultrasound of suspicious areas were performed before inclusion and then every 8 weeks or when clinically indicated.

Response criteria

WHO response criteria were applied [12]. Complete response (CR) was defined as disappearance of all evidence of disease for at least 4 weeks. In patients with bone metastases, complete disappearance of all lesions on X-ray was required. The duration of CR was defined as lasting from the day CR was first recorded until the day of PD.

Partial response (PR) was determined by 2 observations not less than 4 weeks apart and required a decrease of 50% or more in total measured tumor size; additionally, no new lesions or increase of ≥25% of any lesion should be observed. In case of bone metastases, decrease in size of lytic lesions or recalcification were considered PR. The duration of PR was defined as lasting from the first day of treatment until PD. No change (NC) was only applied after at least 4 weeks (in case of bone metastases after at least 8 weeks) from start of treatment. PD was defined as appearance of any new lesion or an increase of ≥25% in any existing lesion.

Estrogen receptor analysis

Estrogen receptors were measured biochemically or on paraffin-embedded, formalin-fixed specimens as previously described [13, 14]. In the bio-