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CLINICAL TRIAL REPORT

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Phase II study of a new vinca alkaloid derivative, S12363, in advanced breast cancer

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Abstract Vinca alkaloids are widely used in the medical treatment of breast cancer. Our study aimed to evaluate the therapeutic activity of a new vinca alkaloid derivative, S12363 (vinfosiltine), which is 36 and 72 times more cytotoxic in vitro than vincristine and vinblastine, respectively. Because phase I studies did not allow a choice of the best treatment schedule, a randomization was performed between two schedules with the same dose intensity, that is, 0.3 mg/m^2 given weekly or 0.6 mg/m^2 given every 2 weeks. A total of 16 patients with advanced breast cancer who had failed a first-line treatment without any vinca alkaloid were entered in the study. Additionally, 6 women received the bimonthly regimen as first-line treatment of advanced breast cancer. Altogether, 17 patients received, prior to vinfosiltine, an anthracycline-based regimen given either as adjuvant (n = 4) or as first-line palliative treatment (n = 13). All 22 patients were evaluable for both toxicity and response. Neutropenia was the main toxic event (maximal toxicity per patient) with grade 3 (WHO) toxicity developing in 7/22 patients and grade 4, in 8/22. Other severe toxicities included leukopenia (n = 9), anemia (n = 1), diarrhea (n = 1), constipation (n = 1), and fatigue (n = 1). No patient achieved a complete or partial response. Vinfosiltine does not appear to have significant single-agent activity in advanced breast cancer at the doses and the schedules used in our study.

Key words Breast cancer · Chemotherapy · Vinca alkaloid

Introduction

Despite the important contribution of anthracyclines in the first-line treatment of advanced breast cancer (ABC), most patients require second-line or salvage chemotherapy. The overall rate of response to salvage chemotherapy in patients who have failed to respond to anthracyclines is about 20% [1]. Despite the observation that vincristine has a limited place in the treatment of advanced breast cancer, other vinca alkaloids such as vindesine or vinorelbine may play a role in this context [2, 7–9], as they do in the first-line treatment of ABC [3, 4]. S12363 (vinfosiltine) is a new vinca alkaloid derivative that is 36 and 72 times more cytotoxic than vincristine and vinblastine, respectively, when tested on a panel of murine and human cell lines using the methyltetrazolium assay [6]. Four phase I studies have been completed using various dosing regimens of vinfosiltine [5]; regardless of the regimen, the only acute dose-limiting toxicity was leukopenia [5]. With the aim of testing the activity of this molecule in breast cancer, 16 patients with ABC who had failed first-line treatment without any vinca alkaloid (group A) were entered in the present study. Additionally, 6 women received the bimonthly regimen as first-line treatment of ABC (group B). Because phase I studies did not allow a choice of the best treatment schedule, a randomization was performed between two schedules with the same dose intensity.

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Patients and methods

Vinfosiltine was infused intravenously over 30 min in 5% dextrose as a weekly regimen (0.3 mg/m^2, n = 7) or as a bimonthly regimen (0.6 mg/m^2, n = 9). Overall, 22 patients received vinfosiltine for ABC; their median age was 55 (range, 38–68) years and their median Karnofsky index was 90% (range 80%–100%). All but 3 patients from group A received, prior to vinfosiltine, an anthracycline-based regimen [fluorouracil, adriamycin, cyclophosphamide (FAC) fluorouracil, epirubicin, cyclophosphamide (FEC)] given as first-line palliative treatment; 2 patients received the cyclophosphamide, methotrexate, fluorouracil (CMF) regimen, and 1 received a combination of cyclophosphamide,

fluorouracil, and mitoxantrone. In group B, 4 of 6 patients received, prior to vinfosiltine, the FEC regimen given as adjuvant treatment. Sites of measurable malignant disease included: breast primary (n = 5), nodes (n = 9), liver (n = 6), lung (n = 3), cutaneous (n = 9), and bones (n = 4). In all, 11 patients had 1 metastatic site, 8 had 2 sites, and 3 had 3 sites. Response and toxicity were defined according to WHO criteria.

Results and discussion

All 22 patients were evaluable for both toxicity and response. A median of 4 (range, 2–8) and 3 (range, 3–8), cycles were given in the weekly and the bimonthly regimen, respectively. There was no toxic death. As anticipated with phase I studies, neutropenia was the main toxic event (maximal toxicity per patient), with grade 3 toxicity developing in 7/22 patients and grade 4, in 8/22. Additionally, grade 3 leukopenia occurred in 9/22 patients. Of the 22 patients, 11 (5/7 and 6/15 in the weekly and the bimonthly regimen, respectively) had their treatment delayed at least once (up to 4 times) due to inadequate neutrophil or leukocyte counts. Other severe toxicities included anemia (n = 1), diarrhea (n = 1), constipation (n = 1), and fatigue (n = 1). No patient achieved a complete or partial response. In all, 9 patients had progressive disease and 13 had stable disease. Therefore, we could exclude at the risk level of $\beta = 5\%$ a response rate higher than 10%. Other vinca alkaloids have been shown to exert some clinical activity in refractory ABC [2, 7–9]. For vindesine or vincristine given as single agents, overall response rates ranging from 10% to 20% were reported about 10 years ago [7–9]. More recently, using vinorelbine, Degardin et al. [2] showed a 16% response rate and a 5-month median response duration in 100 patients who had been refractory to anthracyclines and heavily pretreated. In our study, the new vinca alkaloid vinfosiltine did not appear to have significant single-agent activity in ABC at the doses and the schedules used.

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