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ORIGINAL ARTICLE

**Silwan Chedid · Edgardo Rivera · Debbie K. Frye
Nuhad Ibrahim · Francisco Esteva · Vicente Valero
Gabriel Hortobagyi · Karl L. Mettinger
Massimo Cristofanilli**

Minimal clinical benefit of single agent Orathecin (Rubitecan) in heavily pretreated metastatic breast cancer

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Abstract *Purpose*: The purpose of this phase II study was to evaluate the efficacy and tolerability of Orathecin, an oral camptothecin analog that has exhibited antitumor activity in breast cancer patients during preclinical studies. *Methods:* Sixteen patients with metastatic breast cancer previously treated with anthracycline and taxane were utilized in the study. Orathecin was administered orally at 1.5 mg/m^2 /day for the first five consecutive days of the cycle followed by 2 days of rest on a 7-day schedule. The end points of the study were efficacy and toxicity. *Results:* The median age of the patients was 51 years (range, 35–73). Eight patients (50%) had multiple disease sites, and nine patients (56%) received more than three chemotherapy regimens. All patients were evaluated for toxicity, three patients were removed from the study for toxicity or disease progression prior to 8 weeks and were thus not evaluated for efficacy. The median follow-up was 110 days (range, 15–554). There were no responses to treatment. Five of the 13 evaluable patients (38%) had stable disease, eight (61%) had progressive disease. Most adverse events were mild to moderate in intensity. The median time to progression (TTP) for evaluable patients was 109 days (range, 56–374 days) (lower 95% C.I., 57 days). The median survival time was 272 days (lower 95% C.I., 209 days). *Conclusions:* Orathecin at the dose and regimen used in this study resulted in no objective tumor responses for this heavily pretreated population. Accurate risk stratification strategies can improve patients' selection and contribute to determine the appropriate benefit of therapies in MBC.

Keywords Phase II trial · Metastatic breast cancer · Orathecin · 9-Nitro camptothecin · Rubitecan

S. Chedid · E. Rivera · D. K. Frye · N. Ibrahim · F. Esteva
V. Valero · G. Hortobagyi · K. L. Mettinger · M. Cristofanilli (✉)
Department of Breast Medical Oncology, M. D. Anderson Cancer Center, The University of Texas, 1515 Holcombe Boulevard, Unit 424, Houston, TX, 77030-4095 USA
E-mail: MCristofanilli@mdanderson.org
Tel.: +1-713-7922817
Fax: +1-713-7944385

S. Chedid · E. Rivera · D. K. Frye · N. Ibrahim · F. Esteva
V. Valero · G. Hortobagyi · K. L. Mettinger · M. Cristofanilli
SuperGen, Inc., Dublin, CA, USA

Introduction

Breast cancer is the most common female malignancy in the United States, affecting approximately 210,000 women annually. Although early detection and advances in adjuvant treatment have contributed to decreased disease-related mortality, more than 40,000 women still succumb to metastatic breast cancer each year [1]. The majority of patients with metastatic disease responds transiently to conventional treatments and develops evidence of progressive disease within 12–24 months of the initial treatment [2]. The main goals of therapy for these patients are palliation of symptoms and improvement in the quality of life [1, 3].

Anthracycline-containing and taxane-containing regimens represent the mainstay of chemotherapeutic treatments for managing metastatic breast cancer. Alternative agents for patients progressing after first-line therapy include capecitabine, vinca-alkaloids, and gemcitabine [4–6]. In a phase II trial, therapy with capecitabine—an oral fluoropyrimidine used as third-line therapy (a significant percentage of treated patients had already been exposed to anthracyclines and taxanes)—resulted in a 20% response rate, which led to FDA approval of the drug [6]. The development of additional effective, oral chemotherapy agents would be extremely advantageous for women with metastatic breast cancer.

Orathecin™ (rubitecan), an analog of camptothecin, appears to exert anticancer activity largely through the inhibition of topoisomerase I, which leads to the inhibition of DNA relegation [7]. The drug has shown activity in preclinical models of breast carcinoma [7–10]. In a dose-escalation phase I study of 29 evaluable pa-

tients with refractory cancer, six responses were noted to Orathecin given at doses of 1.0, 1.5, and 2.0 mg/m^2 . The tumors that responded were breast carcinoma, ovarian carcinoma, cholangiocarcinoma, and monomyelocytic leukemia [11, 12]. On the basis of these data, we designed a phase II single-agent study of Orathecin for patients with metastatic breast carcinoma.

Materials and methods

Study design

A prospective, open-label, phase II study was conducted at The University of Texas, M. D. Anderson Cancer Center between December 1, 1999 and August 31, 2001. The clinical trial objectives included evaluation of toxicity, objective response, time to disease progression, and overall survival (OS). Patient eligibility included measurable MBC with adequate organ function that received at least one and not more than two prior chemotherapy regimens for metastatic disease and had been exposed to an anthracycline and a taxane. Patients were excluded if they were receiving trastuzumab (Herceptin) or hormonal therapy, had brain metastasis, or if bone metastasis was the only evaluable site of the disease. The protocol was approved by the institutional review board (IRB) and all patients provided written informed consent before enrollment.

Patients received eight weeks (one cycle) of Orathecin capsules (obtained from SuperGen, Inc., Dublin CA), administered on a 7-day schedule given orally for the first five consecutive days of the cycle followed by 2 days rest. The initial daily dose of Orathecin was 1.5 mg/m^2 . Patients with tumor regression or stabilization after eight weeks were to continue treatment. It was recommended that patients increase their oral hydration to at least 3 l/day during Orathecin treatment to reduce the possible occurrence of cystitis. In cases of toxicity, the dose schedule could be changed to four days treatment each week (level −1) or further decreased to 1.0 mg/m^2 / day for four days each week.

Evaluation of clinical activity

The primary objective was to determine the efficacy of the treatment by assessing the objective response rate. Patients were considered evaluable for efficacy if they had completed at least 8 weeks of treatment. An intent-to treat (ITT) analysis was not planned for this study. Measurable disease was evaluated by bi-dimensional criteria and was assessed at baseline and every 8 weeks. An objective response required confirmation at 4 weeks. Time to progression (TTP) and OS time were estimated by the Kaplan–Meier method.

Objective response, the primary endpoint of the study, was evaluated and defined as follows: complete response, the complete disappearance of clinically detectable disease; partial response, a $>50\%$ decrease in tumor area (sum of the products of the longest perpendicular diameters) for at least 4 weeks with no lesion progressing $>25\%$ and no new lesions appearing; stable disease, a change in measurable disease too small to meet the requirement for complete response, partial response, or progression; and progressive disease, an increase $>25\%$ in the size of the lesion present at baseline or after the initial response or the appearance of new lesions. The TTP was measured from the first day of dosing to objective progression or death. The OS was measured from the first day of dosing to death from any cause.

Statistical considerations

The primary objectives for this phase II study were efficacy and safety. We evaluated tumor response (complete response + partial response), TTP, toxicity, and OS time. We used Simon's optimal design with types I and II error rates of 0.05 and 0.20, targeting a clinical activity of between 20 (p_0) and 40% (p_1) [13]. The maximum accrual objective was 35 patients. The interim analysis was to take place after 11 evaluable patients were treated. If no responses were observed in this first cohort of patients, then the study would not be recommended for continuation. If at least one patient showed a response, the accrual would continue up to a total of 35 patients. If fewer than 11 of the 35 patients showed a response to the treatment, the drug would be rejected. The trial allowed for false-positive and false-negative error rates of 10%. Duration of response, TTP, and OS time were also analyzed.

Results

Patient characteristics are summarized in Table 1. A total of 16 women were enrolled in the trial between December 1, 1999 and June 30, 2000. One patient died within 30 days of study enrollment presumably (but not documented) because of progressive disease and was excluded from the final analysis. About 13 patients received at least 8 weeks of treatment and were evaluated for treatment efficacy, two were discontinued before eight weeks for the following reasons: one developed severe thrombocytopenia 6 days after starting treatment (platelet count, 33,000; 11,000 on confirmation); another patient had symptomatic progression less than 8 weeks from the start of treatment and was switched to a different salvage regimen. The median age of the evaluable patients was 51 years (range, 35–73); all had a Karnofsky performance status of >70 (Table 2). All patients had already undergone surgery; 12 (75%) had had radiotherapy; 10 (63%) had had hormone therapy; and 100% had had adjuvant chemotherapy. All patients had been treated with anthracyclines and taxanes as adjuvant therapy, as therapy for metastatic disease, or both.

Table 1 Most common grade 3-4 toxicities

Toxicity	Grade 3–4 (WHO)
General	
Allergy	4 (25)
Pain	3 (19)
Dehydration	2 (13)
Hematologic	
Granulocytopenia	1 (6)
Anemia	1 (6)
Thrombocytopenia	2 (13)
Gastrointestinal	
Diarrhea	6 (38)
Constipation	2 (13)
Nausea	2 (13)
Vomiting	2 (13)
Dyspepsia	1 (6)
Urogenital	
Dysuria	2 (13)
Cystitis	1 (6)
Hemorrhagic cystitis	1 (6)
Musculoskeletal	
Myalgia	4 (25)
Nervous	
Paresthesia	1 (6)
Respiratory	
Dyspnea	1 (6)

WHO World health organization classification system

Nine patients (56%) of the original 16 patients had already been treated with three or more regimens (including adjuvant therapy), among them was one patient who had had high-dose chemotherapy with peripheral stem-cell rescue.

The toxicity profiles consisted mainly of hematologic, gastrointestinal and urogenital toxicities (Table 1). Most adverse events were mild to moderate in intensity. The events requiring dose reduction included nausea and vomiting, diarrhea with dehydration, dysuria, and thrombocytopenia.

There were no objective responses to the treatment. Five (38%) of the 13 evaluable patients had stable disease, and eight patients of 13 (61%) had progressive disease. The mean number of days on the study was 163 ± 170.4 (range, 18–554). Eight patients (61%) were on study for >91 days. A total of nine patients died, all of known or presumed progressive disease. The median time on the study for patients with stable disease was 185 days (range, 105–374, 95% C.I.). For patients who received a minimum of 8 weeks of treatment (evaluable), the median TTP was 109 days (range, 56–374 days, lower 95% C.I., 57 days) (Fig. 1); the median survival time was 272 days (lower 95% C.I., 209 days) (Fig. 2).

Table 2 Patients characteristics ($n = 16$)

Characteristic	No of patients (%)
Evaluable	
Yes	13 (81)
No	3 (19)
Age (years)	
Median	51
Range	(35-73)
Estrogen receptors	
Positive	2 (75)
Negative	4 (25)
Site of metastases	
Bone/soft tissue	6 (37.5)
Visceral	2 (12.5)
Both	8 (50)
Prior chemotherapy regimens (including adjuvant)	
≥ 2	7 (44%)
≥ 3*	9 (56%)
Prior hormonal treatment	
Yes	12 (75)
No	4 (25)

Discussion

The use of the plant alkaloid camptothecin, a topoisomerase I inhibitor, has been limited as an antitumor therapy mostly because of severe side effects (hematologic toxicities are dose limiting) [14]. The development of camptothecin derivatives, which have less severe side effects and better water solubility than the parent compound [15, 17], has stimulated the investigation of this agent in solid tumors, including breast cancer. Irinotecan (CPT-11 [Camptosar]) and DX-8951f are among the agents of this class that have shown some activity in the management of metastatic breast cancer [18–20]. The development of resistance to the drugs in this class has been related to the inducible expression of the breast cancer resistance protein (BCRP), a newly identified member of the family of ATP-dependent drug efflux proteins [21].

9-Nitro camptothecin (Orathecin) is an analog of camptothecin. The antitumor activity of Orathecin has been seen in a wide variety of human tumor xenografts, including human melanoma, human breast carcinoma, human ovarian carcinoma, and human pancreatic carcinoma [11]. As expected, more activity was seen when treatment started soon after tumor transplantation. However, Orathecin‘ was able to induce tumor regressions even in mice bearing large, well-established tumors. These very impressive results were obtained in BRO human melanoma, in MDA-MB-231 human

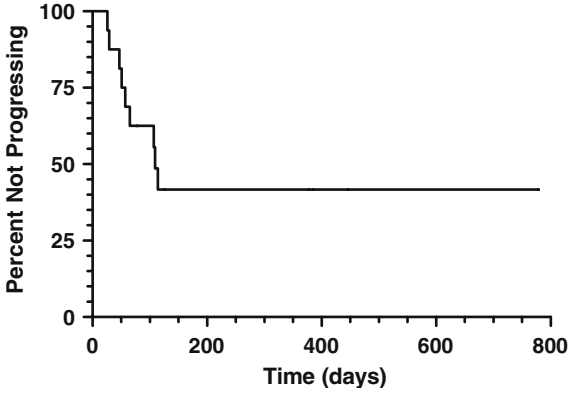

Fig. 1 Kaplan–Meier representation of Time of Disease Progression in days

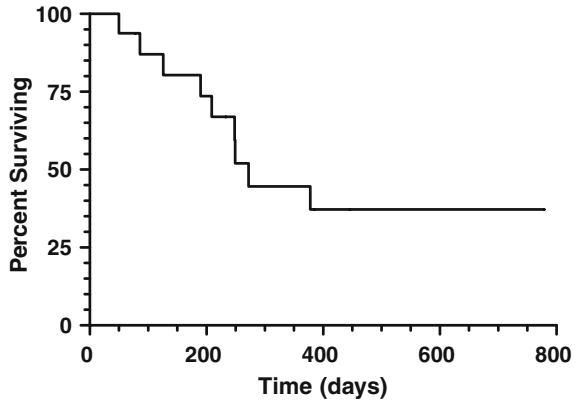

Fig. 2 Kaplan–Meier representation of OS in days

breast carcinoma xenografts, and in human ovarian carcinoma 2774.

The results of this study demonstrate that Orathecin at the dose and schedule used in this study has limited activity as a single agent in heavily pretreated metastatic breast cancer, as indicated by the lack of objective response. Although there were no objective tumor responses, it is interesting to report that, in spite of the adverse prognostic features of this cohort of patients (>50% had multiple sites of metastasis and had received three or more regimens of chemotherapy) encouraging durable stable disease was present in 38% of the evaluable patients who could be maintained for a median of 6 months on oral medication with adequate symptoms control. The sustained clinical benefit in a fraction of patients may indicate that a better selection of the patients' population could have provided a better chance to obtain prolonged benefit.

In fact, it is widely accepted that the management of MBC remains for the most part palliative with a median survival of approximately 18 months [2]. In refractory MBC the probability of objective response to additional therapy is reported to be 20% or less with very few agents demonstrating any meaningful activity [6, 22, 23]. Our possibilities to impact the prognosis of women with metastatic disease is related to the capacity to best select patients based on their biological profile and prognostic features [24, 25]. We believe that this approach would increase the chance to demonstrate any meaningful clinical benefit with drugs that would have otherwise been considered ineffective. Moreover, it will indicate the clinical setting where any additional therapeutic intervention is highly unlikely to even provide symptomatic improvement.

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