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ORIGINAL REPORT

Activity and Safety of the Antiestrogen EM-800, the Orally Active Precursor of Acolbifene, in Tamoxifen-Resistant Breast Cancer

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

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ABSTRACT

Purpose
To determine the efficacy and safety of EM-800 (SCH-57050), the precursor of acolbifene, a new, highly potent, orally active, pure antiestrogen in the mammary gland and endometrium, for the treatment of tamoxifen-resistant breast cancer.

Patients and Methods
Forty-three post menopausal/ovariectomized women with breast cancer who had received tamoxifen, either for metastatic disease or as adjuvant to surgery for ≥ 1 year, and had relapsed were treated in a prospective, multicenter, phase II study with EM-800 (20 mg/d [n = 21] or 40 mg/d [n = 22] orally).

Results
Thirty-seven patients had estrogen receptor (ER)-positive tumors (>10 fmol/mg; mean, 146 fmol/mg cytosolic protein), three patients had ER-negative/progesterone receptor-positive tumors, and three patients had undetermined ER status. The objective response rate to EM-800 was 12%, with one complete response and four partial responses. Ten patients (23%) had stable disease for ≥ 3 months, and 7 patients (16%) had stable disease for ≥ 6 months. With a median follow-up of 29 months, median duration of response was 8 months (range, 7 to 71+ months). Treatment with EM-800 was well tolerated. No significant adverse events related to the study drug were observed clinically or biochemically.

Conclusion
EM-800 produced responses in a significant proportion of patients with tamoxifen-resistant breast cancer, thus showing that this highly potent, selective estrogen receptor modulator, which lacks estrogenic activity in the mammary gland and endometrium, has incomplete cross-resistance with tamoxifen, thus suggesting additional benefits in the treatment of breast cancer.

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INTRODUCTION

Although 30% to 40% of patients with advanced breast cancer show an initial response to tamoxifen, the duration of response is usually limited to 12 to 18 months, with subsequent development of resistance to further administration of the antiestrogen [1]. Based on many clinical observations [2-6], and demonstrated in a series of studies performed with human breast cancer cell lines in vitro as well as in vivo with xenografts, it is believed that the loss of positive response to tamoxifen in breast cancer patients is as a result, at least in part, of the intrinsic estrogenic activity of the compound or its metabolites [7-12]. It has also been shown that the inhibitory effect of tamoxifen is limited to the hormone-dependent activation function (AF) of the estrogen receptor, known as AF-2, while this compound does not inhibit the hormone-independent pathway of activation known as AF-1 [13,14]. Therefore, to test the hypothesis that a more specific and potent antiestrogen completely devoid of estrogenic

activity in human breast or endometrial carcinoma cells [14-30] would have improved clinical efficacy, we have administered the novel, orally active antiestrogen EM-800 (SCH-57050) to women who had experienced tamoxifen therapy failure.

EM-800 is the precursor of EM-652 [16]. This compound acts as a pure and highly potent antiestrogen in human breast and uterine cancer cells in vitro as well as in vivo in nude mice [15-30]. In fact, EM-800 is the most potent of the known antiestrogens and, to our knowledge, it is the only nonsteroidal antiestrogen shown to have no estrogenic activity either in human Ishikawa endometrial carcinoma cells, as assessed by changes in alkaline phosphatase activity, or in human breast carcinoma cells, as shown in cell proliferation studies [14-16,19,20,23-30]. Moreover, as mentioned above, EM-800 blocks both the AF-1 and AF-2 activities of the estrogen receptor [14], thus potentially decreasing the resistance to hormonal therapy.

The high potency of EM-800 derives in part from the high affinity of its active metabolite (EM-652 [SCH-57068]) for the estrogen receptor (ER) [24,26]. In fact, EM-652 has the highest affinity for ER of any known compound to date, with a low dissociation constant of 0.05 nmol/L. In fact, EM-652 is 1.5- to 3.0-fold more potent than 17 beta-estradiol and diethylstibestrol in displacing [^{3}H]estradiol from the ER in human breast cancer and normal uterine tissue. EM-652 is 200-fold more potent than tamoxifen, and is five-fold more potent than hydroxytamoxifen (the active metabolite of tamoxifen). In comparison to other antiestrogens. EM-800 has also demonstrated high potency in vivo. In a murine model, EM-800 was at least 30-fold more potent than tamoxifen in inhibiting estrogen-stimulated uterine growth. In addition, the maximal inhibitory effect on uterine weight achieved with EM-800 is 2.5-fold greater than the maximum effect achieved with tamoxifen [18].

The clinical potential of an antiestrogen more potent and more specific than tamoxifen is supported by the finding that tamoxifen-resistant human breast cancer cell lines remain sensitive to compounds showing pure antiestrogenic activity on cell proliferation in the mammary gland, under in vitro conditions [10,31-33] and when grown as xenografts in nude mice [12,15,34,35]. This compound has been shown to inhibit human breast cancer tumor growth in nude mice below the inhibition achieved with tamoxifen [15,27,28]. The current phase II study was conducted to assess the activity and safety of EM-800 in patients with tamoxifen-resistant breast carcinoma.

PATIENTS AND METHODS

Patients

Forty-two post menopausal or ovariectomized women and one premenopausal woman with tamoxifen-resistant breast cancer were enrolled between March 21, 1996, and June 13, 1997. The study was approved by the institutional review board of each hospital or university, and all patients gave informed consent. Eligible patients had progressive metastatic or locally advanced biopsy-proven or fine needle aspiration-proven inoperable breast cancer that had responded to tamoxifen (complete response [CR] or partial response [PR]) or had remained stable for at least 6 months before progression. Thus, 21 patients had acquired tamoxifen resistance while being treated with tamoxifen for advanced disease. Patients originally treated with adjuvant tamoxifen for at least 1 year after surgery who subsequently progressed either while on tamoxifen (18 patients) or after its discontinuation (four patients) were also eligible. For these 22 patients, differentiation between acquired and de novo tamoxifen resistance could not be made since a possible response before progression cannot be detected. In fact, this tamoxifen resistance could be acquired or existing (de novo) before the start of treatment. Tamoxifen therapy must have been discontinued at least 1 month before initiating treatment with EM-800, unless the investigator judged that the disease was rapidly progressing. Eligible patients could not have received previous treatment for metastatic disease (including systemic cytostatic or hormonal treatment) other than tamoxifen. Adjuvant chemotherapy was allowed but must have been completed $\geq$ 1 year before study entry. Eligible patients had Eastern Cooperative Oncology Group performance status of $\leq$ 2, a life expectancy $\geq$ 6 months, and measurable lesion(s) according to WHO criteria [36]. Tumors had to be ER-positive, progesterone receptor-positive (>10 fmol/mg cytosolic protein or positive by immunocytochemistry), or of unknown status. All patients underwent a baseline staging evaluation. Baseline hematology, clinical chemistry, and urinalysis had to be normal according to the accepted values of each hospital.

Exclusion criteria included cancer other than breast carcinoma (except successfully treated in situ carcinoma of the cervix or skin carcinoma other than melanoma), CNS involvement by cancer, lymphangitic pulmonary metastases, severe infection, and severe liver or kidney disease. Patients with neutropenia or thrombocytopenia unrelated to chemotherapy were also excluded.

Treatment

Patients were treated with a daily oral dose (20 or 40 mg) of EM-800. The drug was administered with 240 mL of tap water in the evening (at bedtime, at least 2 hours after the last meal) for 6 months or until progression or unacceptable toxicity. The first eight patients were treated with 20 mg/d EM-800. Following confirmation by an independent review board of the tolerance and safety of the 20-mg dose in at least four patients treated for at least 1 month, a second group of eight patients were treated with 40 mg/d EM-800. Thereafter, patients were randomly allocated to receive either 20 mg or 40 mg EM-800. Patients and investigators were blinded to the dose level. Patients were to be removed from the study for any of the following: development of serious drug-related adverse event, poor compliance (ie, treatment interruption for 7 consecutive days), or disease progression confirmed on two observations at least 1 month apart.

Evaluation of Response

Tumor response was evaluated according to the WHO criteria [36]. Chest radiography, computed tomography scan of lung for lesions less than 2 cm in diameter, abdominal ultrasound and computed tomography scan of liver (in cases having a positive ultrasound), bone radiography, and isotopic bone scan were performed at start of treatment. In patients with locally advanced

Table 1. Patient Characteristics at Study Entry

Baseline Characteristics	
Age, years	
Mean	66
Range	43-86
ER status, No. of patients	
ER positive*	37
ER negative/PR positive*	3
Not determined	3
ER level, fmol/mg†	
Mean	146
Range	7-686
Time to relapse from start of tamoxifen, weeks	
Median	34
Range	5-159
Setting of prior tamoxifen therapy, No. of patients	
Adjuvant therapy	22
Advanced metastatic disease	16
Adjuvant and metastatic disease	5

Abbreviations: ER, estrogen receptor; PR, progesterone receptor.
*>10 fmol/mg cytosolic protein or positive by immunocytochemistry.
†Based on 34 patients for whom a quantitative measurement of ER level was made.

disease with no evidence of metastases, these tests were repeated after 6 months of treatment unless the patient developed particular signs or symptoms of progression during the study. If exams were positive for metastases at the start of treatment, the exams were repeated at 1, 3, and 6 months for evaluation of response. Superficial or palpable lesions (cutaneous metastases, lymph nodes) were measured in two dimensions at monthly intervals. Hematology and blood chemistry analysis, as well as urinalysis, were performed at start of treatment, at 1, 2, and 4 weeks, and at monthly intervals thereafter. Vital signs were measured and a tolerability questionnaire was filled out at the same time intervals.

RESULTS

Patient and Treatment Characteristics

Forty-three patients were enrolled; 21 patients received 20 mg/d EM-800, and 22 patients received 40 mg/d EM-800. The demographic and baseline clinical characteristics of the patients are shown in Table 1. The median age was 66 years (range, 43 to 86 years). Thirty-seven patients had ER-positive tumors (> 10 fmol/mg cytosolic protein), three patients had ER-negative/progesterone receptor-positive tumors, and three patients were of unknown ER status. The mean ER level was 146 fmol/mg (range, 7 to 686 fmol/mg) in 34 patients for whom a quantitative determination was available. Twenty-two patients had been treated with tamoxifen in the adjuvant setting only, 16 patients had been treated with tamoxifen for advanced metastatic disease only, and five patients had received the antiestrogen both as adjuvant therapy and then for advanced metastatic disease. The median time to relapse from the start of tamoxifen therapy was 34 weeks (range, 5 to 159 weeks).

Response to Therapy

In the total study population, objective tumor responses were observed in five of 43 (12%) patients (Table 2), including one CR and four PRs; 10 patients (23%) had stable disease (SD) for at least 3 months, and seven patients (16%) had SD for at least 6 months. With a median follow-up of 29 months, the median duration of response for the five responders was 8 months (range, 7 to 71+ months); one of the five responders (20%) continues to respond after 71 months. Among the patients treated with 20 mg EM-800, two patients (10%) had a PR, with a response duration of 8 to 71+ months, and three patients (14%) had SD for a duration of 8 to 10 months. Among patients treated with 40 mg EM-800, one patient had a CR and responded for 57 months; two patients (9%) had a PR, with a response duration of 7 and 8 months, while seven patients (32%) had SD, with a duration of 3 to 77+ months. Two patients continue to respond at 71 and 77 months, respectively. No significant dose effect was observed.

Patterns of Failure

At the start of EM-800 administration, the predominant sites of metastasis following tamoxifen failure were (in decreasing order of occurrence): bone (29 patients), lymph nodes (15 patients), liver (11 patients), lung (10 patients), skin (five patients) and breast (two patients; Table 3). Metastases were present at other sites in six patients. Progression was present at only one site in 19 patients, at two sites in 17 patients, and at three sites or more in seven patients at the start of EM-800 treatment. Most responses were observed

Table 2. Best Response to EM-800 and Response Durations by Dose

	20 mg (n = 21)			40 mg (n = 22)		
Best Response	No.	%	Response Duration (months)	No.	%	Response Duration (months)
CR	0	0	—	1	5	57
PR	2	10	8, 71+	2	9	7, 8
SD	3	14	8, 9, 10	7	32	3, 4, 5, 16, 16, 17, 77+
PD	16	76	—	12	54	—

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; +, response still ongoing.

Table 3. Disease Site(s) at Start and at Failure to EM-800 Therapy and Best Response by Disease Site

Site(s) of Disease	No. of Patients					
		Best Response				
	At Start of Treatment	CR	PR	SD	PD (any site)	At Failure to EM-800
Bone(s)	29	—	1	7	21	17
Node(s)	15	1	3	1	10	5
Liver	11	—	—	2	9	9
Lung	10	—	1	1	8	5
Skin	5	—	1	2	2	2
Breast	2	—	1	—	1	—
Others	6	—	—	2	2	3
One organ site	19	1	2	6	10	—
Two organ sites	17	—	1	3	13	—
Three organ sites	7	—	1	1	5	—

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.
NOTE. Eighteen patients had progressed while receiving tamoxifen while four progressed following cessation of tamoxifen.

in patients with bone, skin, breast, and/or nodal metastases (Table 3). No CRs or PRs were observed in patients with liver metastases. Nine of 11 (82%) patients with liver metastases and eight of 10 (80%) patients with lung metastases at start of treatment progressed at those initial sites of disease. Seventeen of 29 (59%) patients with progression in the bones at start of study progressed at the same site during the study. In the majority of cases, patients who failed EM-800 therapy progressed at the same site(s) where they were progressing at the start of EM-800 treatment.

Response Based on Previous Tamoxifen Therapy

No correlation was observed between response to EM-800 therapy and duration of prior tamoxifen therapy. The single CR occurred after 2 months of treatment with 40 mg EM-800 in a patient who had progressed in a right axillary lymph node while receiving tamoxifen after 42 months of adjuvant tamoxifen therapy. Among the four PRs, three patients had received adjuvant tamoxifen therapy for 5, 61, and 64 months, respectively, while one patient had received tamoxifen for advanced disease for 8 months. Among the five patients who responded to EM-800, three progressed while receiving tamoxifen (one CR and two PR) while two progressed 3 and 3.5 years after having received tamoxifen for 5 years, 4 years, and 3 months, respectively. Among patients with SD, two patients had received adjuvant tamoxifen therapy for 70 and 73 months, six patients had received tamoxifen for advanced disease for periods ranging from 10 to 92 months, and two patients had received tamoxifen both as adjuvant therapy and for advanced disease.

With respect to any association between response to EM-800 and the disease stage before tamoxifen therapy, four of five (80%) objective tumor responses to EM-800 were observed in patients who had received adjuvant tamoxifen therapy (Table 4). However, when SD is included in the comparison, the proportion of responding patients (improvement or stabilization of disease following EM-800 treatment) was similar between subgroups: six of 22 (27%) patients who had received tamoxifen as adjuvant therapy, and seven of 16 (44%) patients who had received tamoxifen for advanced disease. Both of these subgroups were well balanced with respect to sites of metastases, with 43% of patients in each group having liver or lung metastases.

Table 4. Best Response Based on Disease Stage of Previous Tamoxifen Therapy

Previous Treatment Setting	No. of Patients	Best Response			
		CR	PR	SD	PD
Adjuvant	22*	1†	3‡	2	16
Advanced disease	16	—	1	6	9
Adjuvant + advanced disease	5	—	—	2	3

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.
*Eighteen patients had progressed while receiving tamoxifen while four progressed following cessation of tamoxifen.
†was progressing under tamoxifen.
‡One patient was progressing under tamoxifen, while one progressed 3 years and 5 months after having received tamoxifen for 4 years and 3 months, while the other patient had progressed 3 years after having received tamoxifen for 5 years.

Table 5. Summary of Adverse Events Occurring in ≥10% of Patients at Either Dose Level by WHO Grade

	20 mg (n = 21)		40 mg (n = 22)			
	Grade I/II		Grade I/II		Grade III/IV	
Adverse Event	No. of Patients	%	No. of Patients	%	No. of Patients	%
Bone/muscle pain	14	67	15	68	2	9
Nausea	7	33	9	41	2	9
Fatigue	5	24	10	45	—	—
Asthenia	4	19	7	32	—	—
Vomiting	5	24	3	14	3	14
Hot flashes	4	19	3	14	—	—
Heartburn	2	10	5	23	—	—
Abdominal pain	2	10	3	14	1	5
Flu-like symptoms	2	10	4	18	—	—
Decreased appetite	3	14	3	14	—	—
Constipation	2	10	3	18	1	5
Depression	2	10	4	18	—	—
Diarrhea	3	14	1	5	—	—
Headache	5	24	5	23	—	—
Soft stools	2	10	—	—	—	—
Urinary tract infection	2	10	—	—	—	—
Decreased hemoglobin	2	10	—	—	—	—
Paresthesias	2	10	—	—	—	—

Safety

No clinically significant adverse event (AE) related to the study drug was observed at either dose level. Commonly reported AEs are shown in Table 5. At the 20-mg dose level, no WHO grade 3/4 AE was observed. Bone and muscle pain was the most common grade 1/2 AE, occurring in 14 patients (67%). Headache, vomiting, and fatigue each occurred in five patients (24%). At the 40-mg dose level, grade 3/4 vomiting occurred in three patients (14%), while severe nausea and bone/muscle pain each occurred in two patients (9%). The most common grade 1/2 AE was also bone/muscle pain reported in 15 patients (68%) in the 40-mg dose group. The next most frequent mild to moderate AEs were fatigue, nausea, and asthenia that occurred in 10 (45%), nine (41%), and seven (32%) patients, respectively. No patient complained of vaginal dryness or altered libido. In long-term follow-up of patients who remained on EM 800 therapy for at least 2 years, 10 various AEs were reported by eight patients, including nausea and vomiting (two patients), pleural effusion (two patients), bone pain, dyspnea, melena, chest pain, back pain, abdominal pain, and constipation (one patient each). One death from breast cancer occurred in the 40-mg dose group within 30 days of treatment interruption.

DISCUSSION

The present data show that EM-800, a novel selective estrogen receptor modulator (SERM) having pure antiestrogenic activity in the mammary gland, was well tolerated and induced clinical responses in a significant proportion of patients with advanced-stage, tamoxifen-resistant breast cancer. A 12% objective response rate (CRs + PRs) was observed, with a median response duration of 8 months at 29 months of median follow-up, with one of these five patients continuing to respond at 71 months. In addition, 23% of patients had SD for a median duration of 9 months, one of these seven patients still responding at 77 months. Similar results were observed in a series of 19 tamoxifen-resistant patients treated with monthly intramuscular injections of the pure steroidal antiestrogen fulvestrant [37]. In that small preliminary study, seven patients (36%) had a PR, and six patients (31%) had SD for a median duration of 25 months. In two large-scale studies performed in a comparable population of patients who had failed tamoxifen and received the pure steroidal antiestrogen fulvestrant, 44.6% and 42.2% had clinical benefit rates (CR + PR + SD ≥ 24 weeks), respectively. [38,39].

These results appear superior to those obtained with other antiestrogens or SERMs that have been investigated as salvage therapy in tamoxifen-resistant patients. For example, two large phase II studies of high-dose toremifene in patients with tamoxifen-refractory advanced breast cancer demonstrated objective response rates of only 4% and 5%, thus leading the authors to conclude that there is significant cross-resistance between toremifene and tamoxifen [40,41]. Salvage therapy with raloxifene in 14 patients produced no CR or PR, although five patients (36%) had SD [42].

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