was 2 years [11]. Conclusions with regard to the safety of 5-HT_3 antagonist particularly to the absence of central nervous system disturbance cannot be applied to younger children so far and as for other drugs, which may possibly interact with receptors in the cerebrum, further studies in babies should be undertaken with great caution.

In conclusion, for the age group subjected to this study, ICS 205-930 proved safe, easy to use and more efficient than conventional antiemetic therapy. Presently, its most severe side-effect is inherent to its very high cost. Further evaluation of the drug should include an account of the possible shortening of hospitalisation required for chemotherapy treatment, which could compensate for the increased expenses entailed by the use of ICS 205-930.

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Phase II Study of Elliptinium Acetate Salvage Treatment of Advanced Breast Cancer

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Elliptinium acetate (Celiptium^R) is an intercalating agent belonging to the ellipticine family. This agent has demonstrated clinical activity as salvage treatment in breast cancer using a weekly regimen. However, its clinical use was hampered by important toxicities such as xerostomia and immune-mediated haemolytic reactions due to development of anti-elliptinium IgM antibodies. We have studied 83 patients previously treated for metastatic breast cancer using elliptinium acetate with a different schedule: 80 mg/m^2 daily for 3 consecutive days every 21 days. In 80 evaluable patients, an objective response (complete + partial response) was obtained in 5 of 30 patients with visceral metastases (13%), in 6 of 21 patients with soft tissue metastases (29%), and in 3 of 20 patients with mixed metastases (15%). The overall objective response rate was 14/80 (18%, 95% confidence interval = 10–26%). Moderate to severe xerostomia occurred in 10% of patients, while no anti-elliptinium antibodies or haemolytic reactions were detected using this schedule. No significant haematological toxicity, as usually reported with this drug, was observed. Elliptinium acetate has modest but definite activity as salvage treatment of breast cancer. The 3-week schedule seems as active as and less toxic than the weekly schedule.
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INTRODUCTION

ELLIPTINIUM ACETATE (Celiptium^R) is a fully synthetic derivative of ellipticine, a naturally occurring plant alkaloid with demonstrated cytotoxic activity in preclinical models [1–3]. Intercalation into DNA, demonstrated *in vitro*, has been suggested as part of the mechanism of action of drugs of this family [2]. More recently, other mechanisms of action have been put forward, such as generation of toxic free radicals and alkylating electrophilic intermediates [4], interaction with plasma membranes [5], and introduction of DNA strand breaks through an action upon topoisomerase II [3, 6, 7].

Previous phase II studies with elliptinium acetate demonstrated 19% response rate in pretreated breast cancer using a weekly schedule of 100 mg/m^2 given by 1-h infusion every 7 days [8]. However, the reporting of anti-elliptinium IgM antibody-mediated haemolytic reactions with this weekly schedule [8, 9]

prompted the exploration of other schedules in further trials. In a comparative analysis, 40% of patients treated weekly for at least 3 weeks developed antibodies as compared to none in patients treated daily for 3 consecutive days every 3 weeks [10]. Two small phase II trials using 80 mg/m^2 for 3 days every 3 weeks have confirmed clinical activity in breast cancer with absence of antibody-mediated haemolytic reactions [11, 12]. All studies confirmed a lack of significant myelosuppression associated with agents of this family. In this report we analyse antitumour activity and toxicity profile of elliptinium acetate given as salvage therapy every 3 weeks to a large group of pretreated advanced breast cancer patients in a prospective phase II study.

PATIENTS AND METHODS

Patients' characteristics

From February 1986 to May 1987, 83 patients with advanced breast cancer (52 at Institut Gustave Roussy, Villejuif and 31 at Centre René Huguenin St Cloud, France) were treated with elliptinium acetate.

Inclusion criteria of the study protocol required histologically proven advanced breast cancer patients who had measurable disease with no more than two prior chemotherapy regimens, ECOG performance status of − 2, life expectancy of > 2 months, neutrophil count > 500/ml, platelet count > 50 000/ml, and serum creatinine < 110 μmol/l. Patients were not receiving any other therapy and did not have any secondary malignancy. All patients gave their informed consent before inclusion.

Treatment

Elliptinium acetate (2-*N*-methyl 9-hydroxy ellipticinium acetate, NSC-264137) was provided by Sanofi Recherche, France. Treatment was given at the dose of 80 mg/m^2 intravenously/ day for 3 days. The daily dose was diluted in 500 ml of 5% dextrose in water and infused over 1 h. Treatment courses were repeated every 3 weeks.

Evaluation

Prior to each treatment course a complete history and clinical examination including weight, ECOG performance status and clinical measurement of target lesions were performed. Chest X-ray, laboratory safety tests including complete blood count, blood electrolytes, serum creatinine, hepatic enzymes and anti-elliptinium antibodies, were also performed before each course, together with any other special examination needed for evaluation of target lesions. WHO criteria were used for evalution of tumour response and toxicity grading.

The initial number of patients was determined at 14 in each group (visceral – soft tissue – mixed) and then increased accordingly to the number of responders [15].

RESULTS

Patient characteristics are shown in Table 1. All patients received prior chemotherapy with a mean number of five prior drugs (range three to eight). 8 patients had received only adjuvant chemotherapy, while 75 patients had prior chemotherapy for metastatic or recurrent disease (one regimen : 22 patients, two regimens : 53 patients). Patients were classified into three groups according to the site(s) of their metastatic lesions : only visceral metastases, only soft tissue metastases, and mixed. Bone lesions were not considered in this subclassification.

Patients received a total number of 222 courses. Mean number

Table 1. Patients' characteristics

Number of patients	83
Age (years)	
Range	27–73
Mean	55
ECOG Performance status	
0	35 patients
1	30 patients
2	18 patients
Hormone receptors	
E+	27 patients
E−	20 patients
P+	26 patients
P−	21 patients
Unknown	36 patients
Prior chemotherapy	83 patients
Only adjuvant 1 regimen	8 patients
Chemotherapy for metastic disease	
One regimen	22 patients
Two regimen	53 patients
Prior anthracycline treatment	79 patients
Number of prior cytotoxic drugs	
Range	3–8
Mean	5
Prior hormonal treatment	64 patients
Types of metastases	
Only visceral	40 patients
Only soft tissue	22 patients
Mixed	21 patients

E = Oestrogen; P = Progesterone.

Table 2. Clinical tolerability

	Number of patients WHO Grade II	III	Total (%)
Xerostomia	5	3	8 (1.0%)
Fatigue	2	5	7 (8%)
Anorexia	1	3	4 (5%)
Vomiting	2	1	3 (4%)
Muscular cramps	0	3	3 (4%)
Phlebitis	1	0	1 (1%)
Drug fever	1	0	1 (1%)

In the absence of a WHO grading, moderate and severe toxicity were graded as grade II and III, respectively.

Table 3. Tumour response

Type of metastases	No. of patients	CR	PR	Total (%)	SD	PD
Visceral	39	0	5	5 (13%)	8	26
Soft tissue	21	1	5	6 (29%)	2	13
Mixed	20	0	3	3 (15%)	7	10
Total	80	1	13	14 (18%)	17	49

CR: Complete response; PR: partial response; SD: stable disease; PD: progressive disease.

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Table 4. Responders' characteristics

Patient no.	Age	Hormonal receptors	Prior hormonal therapy	Prior hormonal-chemotherapy and response				Elliptinium acetate and response				Reason for treatment cessation
				Adjuvant chemotherapy	Chemotherapy for metastases	Target lesions	Response	Target lesions	No. of treatment courses to induce response	Response	Total no. of treatment courses	
1	64	E+ P−	+	AVCM	CVF	Skin	+	Skin	1	CR	6	Patient refusal
2	73	?	+	0	FAC	Lungs	−	Lungs	2	PR	7	Hepatic toxicity
3	58	?	+	CMF	0	0	0	Lungs	5	PR	11	End of protocol
4	49	?	+	CVF	A.Mito	Nodes, Pleural	−	Nodes, Pleural	4	PR	8	Lost to follow-up
5	54	?	+	0	AVCF	Hepatic, Nodes	+	Hepatic	2	PR	4	Lost to follow-up
6	?	E+ P+	?	CVF	AVCMF	Hepatic	+	Hepatic	2	PR	5	Lost to follow-up
7	54	E+ P+	+	CMF	0	0	0	Skin	4	PR	5	Progression
8	71	?	+	0	FAC	Local relapse, Hepatic	Stable	Nodes, Hepatic	4	PR	6	Progression
9	51	?	+	0	FAC	Nodes	−	Abdominal, Metastases	4	PR	6	Progression
10	58	?	+	0	AVCMF FAC	Hepatic, Bone	−	Hepatic	2	PR	11	Progression
11	42	E+ P+	+	AVM	0	0	0	Hepatic	5	PR	8	Progression
12	64	?	+	0	FACOM	Nodes	−	Skin, Nodes	2	PR	3	Toxicity
13	73	E+ P+	+	CVMF	0	0	0	Skin, Nodes	2	PR	5	Patient refusal
14	57	E+ P+	+	FAC	CMF	Nodes	Stable	Nodes	1	PR	4	Toxicity

A : Doxorubicin; V : vincristine; C : cyclophosphamide; M : methotrexate; F : 5-fluorouracil; Mito : mitomycin; O : orthophosphate; CR : complete response; PR : partial response.

Table 5. Cumulated response rate using the 21-day schedule

Study	No. of evaluable patients	CR	PR	Total (%)
Treat, *et al.* (11)	18	0	2	2 (11%)
Budzar, *et al.* (12)	33	1	4	5 (15%)
This report	80	1	13	14 (18%)
Total	131	2	19	21 (16%)

CR : Complete remission; PR : partial remission.

of courses/patient was three (range one to 12). 3 patients were non-evaluable for response : 1 patient had no measurable lesions, 1 patient received concomitant tamoxifen therapy while on study, and 1 patient did not receive the study drug treatment after being included.

Of 83 patients enrolled in the study, 82 patients were evaluable for toxicity. Several clinical manifestations were associated with treatment by elliptinium acetate. Table 2 shows commonly observed side-effects. The lack of alopecia and mucositis is noteworthy. WHO grading of laboratory tests showed only minimal drug-related toxicity with 4 patients having grade 2 leukopenia and 2 grade 1 serum creatinine elevation. There was no thrombocytopenia and no drug-related liver toxicity. With elliptinium antibody screening on day 21 of each cycle, no patients had detectable antibodies. There was no haemolysis and no drug-related deaths.

Of 83 patients, 80 patients were evaluable for the response. Patients with early progression or early disease-related death after one cycle were all considered as progressive disease. Table 3 shows the objective response rate (complete + partial response) according to the patients' subgroup. Table 4 shows the responders' characteristics.

The highest response rate was observed in patients with soft tissue lesions. Overall response rate was 18% (95% confidence interval = 10–26%) with a mean response duration of 17 ± 6 weeks.

DISCUSSION

This report deals with a large prospective phase II study of elliptinium acetate as salvage treatment in metastatic breast cancer using a treatment schedule every 3 weeks. Two smaller studies using the same treatment schedule in the same patient population have already been reported [11, 12].

Table 5 shows the cumulated number of treated patients and the overall objective response in the three studies. This confirms a modest but a definite clinical activity of elliptinium acetate as second-line treatment in patients with metastatic breast cancer (cumulated response rate of 16%, 95% confidence interval = 10–22%). Responses were observed in all types of metastases with the highest response rate being observed in soft tissue lesions. Previous reports described favourable responses in bone lesions as well [13].

Although there is no comparative study, the use of the present treatment schedule at the dose of 80 mg/m^2 daily for 3 days every 3 weeks seems to improve clinical tolerability. Fewer patients were reported to have xerostomia, fatigue, vomiting, phlebitis, muscular cramps and fever as compared to toxicity results using the 100 mg/m^2 weekly schedule [8]. Screening for antibodies has eliminated immune-mediated haemolytic reactions as patients who developed these antibodies were withdrawn from treatment [11, 12]. In the two previous reports using the same schedule, a total of 5 patients (9%) developed antibodies. However, it was not clear at what time during the cycle these antibodies were detected and when they disappeared. In our study, screening for antibodies was only performed on day 21 of each cycle just prior to the new treatment course and no patients had detectable antibodies at that time.

Finally, this report confirms the minimal haematological toxicity of elliptinium acetate which makes drugs of this family interesting candidates for combination therapy. Few data are available on the use of elliptinium acetate in combination. However, a very interesting 55% response rate in previously treated breast cancer patients was observed with the combination of elliptinium acetate, mitomycin-C, and etoposide [14].

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