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ORIGINAL ARTICLE

A phase II study of capecitabine in the treatment of ovarian cancer resistant or refractory to platinum therapy: a multicentre Italian trial in ovarian cancer (MITO-6) trial

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Abstract
Purpose Capecitabine is an oral chemotherapeutic agent, already used in breast and colon cancer. Previous data showed encouraging results in the treatment of recurrent ovarian cancer. The aim of this study was to describe activity and toxicity of capecitabine in patients with platinum resistant or refractory ovarian cancer.
Methods Patients were eligible if they had cytologically or histologically proven epithelial ovarian cancer, refractory or resistant to prior platinum-containing chemotherapy. Capecitabine was administered at the dose of 1,250 mg/m^2 twice daily on days 1–14 of a 21-day cycle for a maximum of six cycles. The primary end point of the study was activity in terms of objective response rate in according to RECIST criteria. A two-stage minimax design for phase II studies was used: at least four objective responses had to be reached among 32 evaluable patients to define the treatment active.
Results Between March 2006 and October 2007, 36 patients were enrolled. All patients had ovarian cancer and 83.3% had previously received two or three lines of chemotherapy. Thirty-two patients were evaluable for response and included in the activity analysis. The objective response rate was 3.1% [95% exact confidence interval (CI): 0.08–16.22%], lower than the threshold required to define the treatment as active. The median progression free survival was 68 days (95% CI: 65–120). Haematological toxicity was not frequent. Nausea and fatigue were common, but never severe, and they were observed in 13 (37.1%) and 12 (34.2%) patients, respectively. Diarrhoea occurred in 11 patients (31.5%) and it was of grade 3 in 8.6% of cases. Grade 1–2 stomatitis was observed in seven

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patients (20%). Cardiovascular toxicity was reported in two cases, including a death for pulmonary embolism.
Conclusions Capecitabine is not active in platinum resistant non mucinous ovarian cancer, producing a response rate lower than that required by study design. Further trials are not warranted in these patients.

Keywords Capecitabine · Ovarian cancer · Chemotherapy

Introduction

The standard initial treatment of patients with advanced ovarian cancer is cytoreductive surgery, followed by combination chemotherapy with paclitaxel and carboplatin [1, 2]. Despite the activity of this combination chemotherapy, which gives response rates up to 80%, the majority of patients will die of recurrent disease [3]. Therefore, a large proportion of patients are candidates for further treatments. Patients who progress during or relapse within 3 months of first line therapy are defined as refractory to a platinum re-treatment [4], while patients who respond to primary treatment and relapse within 6 months are defined as platinum resistant [4]. In these patients, pegylated liposomal doxorubicin and topotecan are considered the drugs of choice, although the results are considered unsatisfactory with low response rate and short duration of response. On the contrary, patients recurring after 6 months are eligible for re-treatment with platinum, which produces a very high-response rate. However, at later progressions, due to platinum resistance, these patients are usually treated with non platinum agents, used as monotherapy, with palliative intent [5]. Agents such as epirubicin [6], etoposide [7] and more recently topotecan [8], stealth liposomal doxorubicin [9], and gemcitabine [10] show response rates ranging from 5 to 20% [5]. Although sequential treatment with different chemotherapy agents has not been proven to increase survival, palliation is often achieved.

Based on these data, treatment of patients with recurrent ovarian cancer remains a challenge and there is a need for new and more effective drugs. 5-fluorouracil has shown response rates in ovarian cancer ranging between 10 and 23% with different doses and schedules [11, 12], also demonstrating activity in patients with resistant disease. Capecitabine is a prodrug, that is enzymatically converted to 5-fluorouracil in the tumor, where it inhibits DNA synthesis [13]. The activation of capecitabine follows a pathway with three enzymatic steps and two intermediary metabolites, 5′-deoxy-5-fluorocytidine (5′-DFCR) and 5′-deoxy-5-fluorouridine (5′-DFUR), to form 5-fluorouracil. Activity of capecitabine has been shown in several cancers [14–16]. The oral administration of the drug and the safe toxicity profile could make it a convenient treatment option in the setting of recurrent ovarian cancer patients. Conflicting results on activity of capecitabine in patients with recurrent ovarian cancer have been published. In a phase II study, Vasey et al. [17] have shown that capecitabine was active in a population of patients with ovarian cancer, who progressed or recurred within 12 months, with a 28% response rate. The toxicity profile of capecitabine was favourable, with hand-foot syndrome and gastrointestinal toxicity as the most frequent side effects. On the contrary, two studies showed minimal activity in patients with platinum resistant ovarian cancer [18, 19]. The aim of this phase 2 study was to confirm the activity of capecitibine in patients with ovarian cancer resistant or refractory to platinum therapy, in order to plan a possible phase three trial within the MITO group.

Patients and methods

Patient eligibility

Patients were eligible if they had cytologically or histologically proven epithelial ovarian cancer refractory (i.e. progressed during platinum-based treatment or relapsed within 3 months from completion of platinum based treatment) or resistant (i.e.: relapsed within 6 months from completion of platinum based treatment) to prior platinum containing chemotherapy. Other eligibility criteria included age ≤ 75 years, presence of at least one target lesion, white blood count $\geq 4{,}000/mm^3$, platelet counts $\geq 100{,}000/mm^3$, serum creatinine < 1.25 mg/dl, SGOT and SGPT $< 1.25 \times$ upper normal value, performance status < 3 according to the ECOG classification, and a life expectancy of at least 3 months. Patients were excluded if they were treated with more than three lines of chemotherapy, or received previous treatment with capecitabine, or had heart disease (heart failure, myocardial infarction in the 6 months before enrollment in the study, arrhythmias, atrioventricular block), or previous or concomitant malignancy (except adequately treated non-melanoma skin cancer or in situ carcinoma of the uterine cervix). Patients unable to follow the protocol study because of family, psychological, geographical or social reasons were also excluded. The study was performed in accordance with good clinical practices and complied with requirements established by the Declaration of Helsinki. The study protocol was approved by local Ethics Committees. All subjects gave written informed consent.

Treatment plan

Patients received oral capecitabine 1,250 mg/m^2 twice daily, on days 1–14, every 3 weeks. First restaging was

planned after three cycles. In the absence of unacceptable toxicity, patients with stable disease, or who achieved an objective response continued treatment for up to a total of six cycles. Conditions required for retreatment were leukocytes > 3,000/mm^3, platelets ≥ 100,000/mm^3, and absence of organ toxicity (excluding alopecia). Treatment was discontinued due to unacceptable prolonged toxicity in patients requiring a treatment delay of more than 2 weeks. A 20% dose reduction for capecitabine was planned in patients with neutrophils < 500/mm^3 or platelets < 50,000/mm^3 for more than 5 days or in case of palmar–plantar erythrodysesthesia. A 50% dose reduction was allowed in case of a second episode of the same toxicity after the first dose-reduction.

No prophylactic use of G-CSF was recommended. In case of grade 4 neutropenia, even without fever, therapeutic and prophylactic use of G-CSF was allowed. Haematological support with recombinant human erythropoietin was used according to standard guidelines.

Patient evaluation

Pre-treatment staging was performed within 14 days before starting therapy and included a complete medical history and physical examination, blood cell counts and serum chemistries, urine exams, serum Ca125, ECG, chest X-ray, computerized axial tomography or nuclear magnetic resonance of the abdomen and pelvis. All the instrumental and laboratory tests described above were repeated after the third and sixth cycles.

Response evaluation was in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) [20]. Toxicity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 [21].

Statistical considerations

The primary end point of the study was the activity of capecitabine in terms of objective response rate (complete and partial response). A two-stage minimax design for phase II studies was used, with the following parameters: power 90%, alpha error 0.10, minimum acceptable response rate (p0): 5%, favourable response rate (p1): 20%. At first step, a sample size of 18 evaluable patients was needed. If at least one response was observed, treatment was considered for the next stage, enrolling 32 patients. At the end of the study, the treatment could have been considered active if at least four objective responses had been reached. The response rate was assessed after the third and sixth cycles.

Time to progression and overall survival were described by the Kaplan–Meier product limit method [22].

Results

Patient characteristics

Thirty-six patients were enrolled in the study at six Institutions, between March 2006 and October 2007. One patient withdrew consent before starting treatment and was excluded from all the analyses. The characteristics of the 35 analyzed patients are reported in Table 1. All patients had been treated with platinum-based combination chemotherapy, and 85.7% of patients had previously received two or three lines of chemotherapy.

Activity

Thirty-two patients were included in the activity analysis: three patients were not eligible for the following reasons: age > 75 years (two patients) and absence of target lesions (one patient) (Table 2). Response was not actually assessed in four patients (12.5%), due to refusal (one case), death (one case), progression before the third cycle (one case) and toxicity (one case); all these patients were considered as non-responsive. In the first stage of the study, 1 partial response was observed in 18 patients, meeting the criteria for proceeding to the next stage. No other objective responses were observed in the second step of the study. Thus, the objective response rate was 3.1% (95% exact CI: 0.08–16.22%), lower than the threshold required to define the treatment as active. A 50% reduction in Ca 125 was observed in two patients. In the spirit of an intention to treat analysis, considering also the two patients excluded due to age > 75 years, the overall response rate for capecitabine was 2.9%. As of May 2008, 34 patients progressed and 22 died. The median progression free survival was 68 days (95% CI: 65–120). The estimated 6-month progression-free survival rates was 6.4%. Kaplan–Meier curve of progression-free survival is reported in Fig. 1. The median overall survival was 322 days (95% CI: 222–432). The estimated 6 months and 1-year survival rates were 82.5 and 48.9%, respectively. Kaplan–Meier curve of overall survival is reported in Fig. 2.

Compliance to treatment and safety

A total of 123 chemotherapy courses were administered to 35 evaluable patients; 8 patients received all the planned 6 cycles of treatment while 27 discontinued treatment earlier because of progression (21 patients), toxicity (3 patients, 1 of whom died), refusal (2 patients) or medical decision (1 patient).

Haematological and non-haematological toxicities are summarized in Table 3.

Table 1 Baseline characteristics of patients

Variable	*N* = 35
Age, median (range)	60 (42–76)
Line of treatment, *n* (%)	
Second	5 (14.3)
Third	14 (40)
Fourth	16 (45.7)
Stage at diagnosis, *n* (%)	
Ic	2 (5.7)
II	–
III	24 (68.6)
IV	9 (25.7)
Residual disease at diagnosis, *n* (%)	
Absent	7 (20.0)
≤1 cm	9 (25.7)
>1 cm	17 (48.6)
No surgery	2 (5.7)
Grading at diagnosis, *n* (%)	
1	–
2	3 (8.6)
3	28 (80.0)
Unknown	4 (11.4)
Sensitivity to platinum, *n* (%)	
Resistant	26 (74.3)
Refractory	9 (25.7)
Previous chemotherapy, *n* (%)	
Carboplatin	35 (100)
Paclitaxel	33 (94.3)
PLD	21 (60)
Gemcitabine	8 (22.8)
Topotecan	7 (20)
Cisplatin	6 (17.1)
Cyclophosphamide	3 (8.6)
Doxorubicin/Epirubicin	2 (5.7)
Histotype, *n* (%)	
Sierous	22 (62.9%)
Mucinous	–
Endometrioid	5 (14.3)
Undifferentiated	6 (17.1)
Clear cells	1 (2.9)
Other	1 (2.9)

PLD pegylated liposomal doxorubicin, *N* number of patients

Table 2 Outcomes (35 patients)

Objective tumor response analysis (%)	*N* (%)
Not eligible	3
Age > 75 years	2 (66.7%)
No target lesions	1 (33.3%)
Eligible	32
Complete response	–
Partial response	1 (3.1%)
Stable disease	8 (25%)
Progressive disease	19 (59.4%)
Not assessable (non-responsive)	4 (12.5%)
Objective response rate, *n* (%)	1 (3.1%)
(95% exact CI)	(0.08–16.22)
Progression free survival (PFS)	
Events, *n* (%)	34 (97.1%)
Median PFS (days)	68
(95% confidence interval)	(65–120)
Overall survival	
Events, *n* (%)	22 (62.9%)
Median OS (days)	322
(95% confidence interval)	(222–432)

N number of patients

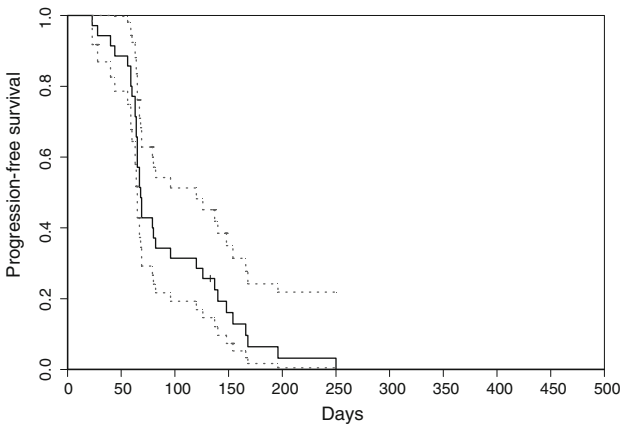

Fig. 1 Kaplan–Meier's estimated curve of progression-free survival

Haematological toxicity was not frequent: nine patients experienced neutropenia, that was severe (grade 4) in 1 case. Grade 3 anemia occurred in 1 patient, but red blood cells transfusion were not required. Ten patients had grade 1 thrombocytopenia.

Among non haematological toxicity, nausea and fatigue were common, but never severe (grade 3–4), and they were observed in 13 (37.1%) and 12 (34.2%) patients, respectively. Diarrhoea occurred in 11 patients (31.5%) and it was of grade 3 in 3 patients (8.6%). Grade 1–2 stomatitis was observed in seven patients (20%). Cardiovascular toxicity was reported in two cases: one patient, who had a pleural and pericardial effusion at baseline, developed cardiac tamponade after the first cycle of chemotherapy (relationship with treatment was judged to be not probable); the other patient suffered a grade 3 diarrhoea after the completion of the first cycle of chemotherapy and died for pulmonary embolism during hospitalization (relationship with treatment judged probable).

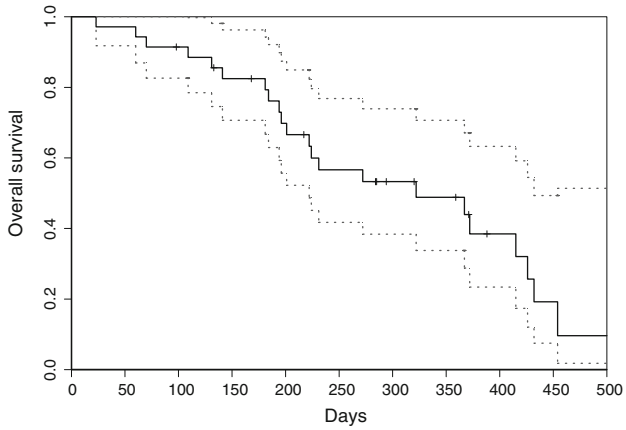

Fig. 2 Kaplan–Meier's estimated curve of overall survival

Table 3 Toxicity ($n = 35$)

Toxicity	CTCAE worst grade (%)				
	1	2	3	4	5
Allergy	–	–	–	–	–
Anemia	10 (28.6)	7 (20.0)	1 (2.8)	–	–
Leukopenia	7 (20.0)	2 (5.7)	2 (5.7)	–	–
Neutropenia	4 (11.4)	4 (11.4)	–	1 (2.8)	–
Febrile Neutropenia			–	–	–
Platelets	10 (28.6)	–	–	–	–
Heart	–	–	–	1 (2.8)	1 (2.8)
Pulmonary	–	1 (2.8)	–	–	–
Kidney	1 (2.8)	–	–	–	–
Fatigue	8 (22.8)	4 (11.4)	–	–	–
Fever	3 (8.6)	1 (2.8)	–	–	–
Hair loss	–	–	–	–	–
Skin	6 (17.1)	3 (8.6)	–	–	–
Anorexia	1 (2.8)	–	–	–	–
Constipation	3 (8.6)	3 (8.6)	–	–	–
Diarrhoea	5 (14.3)	3 (8.6)	3 (8.6)	–	–
Nausea	8 (22.8)	5 (14.3)	–	–	–
Stomatitis	4 (11.4)	3 (8.6)	–	–	–
Vomiting	2 (5.7)	5 (14.3)	–	–	–
Liver	3 (8.6)	–	–	–	–
Neurologic	2 (5.7)	–	1 (2.8)	–	–

N number of patients, *CTCAE* common terminology criteria for adverse events

Discussion

In this phase 2 study we have shown that capecitabine, although having an acceptable toxicity profile even in heavily pre-treated patients, has minimal activity in recurrent ovarian cancer.

Treatment of recurrent ovarian cancer, refractory or resistant to platinum-taxane chemotherapy, is a frequent and challenging problem for patients and physicians. Although pegylated liposomal doxorubicin and topotecan are the first choices of treatment [5, 8, 9], many patients maintain a good performance status over time and have the need of further palliative treatments. Therefore, the research of active drugs with a safe tolerability profile is of value in this setting.

The negative results of our study are in contrast with those published by Boehmer et al. [23] and Vasey et al. [17]. In the first study, a 25% response rate was observed in a phase 1–2 trial that enrolled 14 patients: however, only 12 patients were eligible for response evaluation, and early cessation of chemotherapy was necessary in two patients due to toxicity. In the second study, a 28% response rate was reported, using serum Ca 125 to evaluate tumor response: however, among 14 patients who had measurable disease at baseline, a radiological response was observed only in one patient, giving a clinical overall response rate of 7%.

Subsequently, three other phase 2 studies have been conducted and all reported minimal activity or negative results. Rischin et al. [18] treated with capecitabine 35 patients with heavily pretreated ovarian cancer and observed only a 9% response rate, combining RECIST and Ca 125 criteria, and a 5% response rate, in the cases evaluable only by RECIST. The GOG evaluated capecitabine in the same setting: the study was prematurely closed, due to the low activity found in the first stage (8% response rate) [19]. Moreover, a treatment related death was reported. More recently, Wolf et al. [24] reported a response rate of 8.3% with capecitabine and significant toxicities (grade 3 gastrointestinal, fatigue, and hand-foot syndrome) in 42 patients with recurrent ovarian cancer (92% of which treated with more than 2 previous lines of chemotherapy). The difference in outcome between the first two published studies and all the other more recent trials, including our study, could be explained with a difference in selection criteria: in our study, all patients were refractory or resistant to prior platinum containing chemotherapy, while in the Vasey study 70% of patients had a platinum-free interval > 6 months. Moreover, in our series there was no case of mucinous ovarian cancer, while the histotypes were not reported in the Vasey study [17]. This might represent an important difference: in fact it is well known that mucinous ovarian cancer have a poor response to standard chemotherapy, while the potential of activity of capecitabine in this population could be significant, based on the data available in gastrointestinal cancer. A trial with capecitabine possibly combined with oxaliplatin or irinotecan could be of interest in this setting.

In conclusion, our study confirms that capecitabine has minimal activity for the treatment of platinum resistant ovarian cancer with non mucinous histotype and further trials are not warranted in this setting of patients.

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Conflict of interest statement No conflict of interest declared by the authors.

Appendix

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