Evaluation of capecitabine in patients with platinum-pretreated advanced or recurrent cervical carcinoma: a retrospective study of the IRCCS National Cancer Institute of Milan

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Abstract

Background Cervical cancer is underrepresented in gynecological clinical research. The objective of this retrospective study was to evaluate the activity and safety of capecitabine in patients with platinum-pretreated recurrent cervical carcinoma.

Materials and Methods We performed a retrospective review of medical records from patients with advanced or recurrent cervical carcinoma pretreated with platinum-based therapy who received oral capecitabine at the Gynecological Units of the IRCCS National Cancer Institute of Milan (Italy). We used Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 to evaluate response to therapy and Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 to evaluate adverse events.

Results From December 2013 to April 2015, 18 patients with advanced or recurrence cervical carcinoma, already exposed to platinum, were treated with oral capecitabine 1000 or 1250 mg/m² bid continuously from day 1-14 every 21 days. All patients had received a combination of carboplatin plus paclitaxel as first-line therapy for advanced/recurrent disease. Median age at the first capecitabine administration was 56 (range 27-82) years. After three cycles of oral capecitabine the clinical benefit rate (CBR) was 55.5% with 5.5% of complete response (CR), 27.7% of partial response (PR) and 22.3% of stable disease (SD). No grade ≥3 adverse events were reported. CBR was 85.7% in adenocarcinomas versus 36.4% in squamous cell carcinomas (p=0.04). The most frequent grade 1 or 2 adverse events were fatigue (50%), hand-foot syndrome (38.9%) and diarrhea (22.2%).

Conclusions Our study suggests that oral capecitabine should be considered an active and safe treatment in patients with platinum-pretreated advanced or recurrent cervical carcinoma.

Key words: activity, cervical cancer, capecitabine, observational study

Introduction

Cervical cancer is a common female malignant tumor worldwide and it has been estimated that it will account for nearly 13,000 new diagnoses and more than 4,000 deaths in the United States in 2016 [1]. Nevertheless, it is underrepresented in the gynecological clinical research landscape, with only 58 new trials registered in ClinicalTrials.gov in 2016 [2]. The majority of International Federation of Gynecology and Obstetrics (FIGO) stage I cervical cancers are treated with surgery with or without adjuvant radiotherapy, while those presenting with locally advanced tumors undergo neoadjuvant chemotherapy or concomitant radiochemotherapy followed by surgery [3]. Even if patients receive an optimal treatment, the recurrence rates are 10-20% in early stage disease and 50-70% in locally advanced disease [4]. Unfortunately, only 15-20% of patients with recurrent tumors experienced live longer than 1 year [4]. Although cisplatin 50 mg/m² is the most active drug in this subset of patients, the overall response rate (ORR) is worse in chemotherapy and radiotherapy-pretreated recurrent cervical cancer [3]. A large phase III trial published in 2009 showed a trend in better ORR, progression-free survival (PFS), and overall survival (OS) in patients with advanced and recurrent cervical carcinoma who received cisplatin 50 mg/m² plus paclitaxel 135 mg/m² compared with other combi-
nations [5]. A more recent phase III trial demonstrated a better safety and tolerability profile of carboplatin AUC5 plus paclitaxel 175 mg/m² compared with cisplatin plus paclitaxel, especially in pretreated patients [6]. No validated standard treatment is available for platinum-resistant patients.

Capecitabine is an oral fluorouracil prodrug that is enzymatically converted to 5-fluorouracil in the tumor, where it inhibits DNA synthesis and slows tumor growth [7]. Even if the data from the literature about the use of capecitabine in patients with advanced or recurrent cervical carcinoma suggest a low antitumoral activity for capecitabine given as single agent [8-11], 5-fluorouracil is commonly used in clinical practice in patients who have failed a platinum-based first-line therapy [12]. We retrospectively collected data from patients with platinum-pretreated advanced or recurrent cervical carcinoma who received oral capecitabine. The aim of this preliminary analysis was to evaluate safety and activity after three cycles of therapy.

**Materials and methods**

We performed a retrospective review of medical records from patients with advanced or recurrent cervical carcinoma pretreated with platinum-based therapy, who received oral capecitabine at the Gynecological Units of the IRCCS National Cancer Institute of Milan (Italy). We specifically collected baseline characteristics of patients, biological features of the tumors, information regarding previous treatment, dose of capecitabine received, adverse events, and response after three cycles of therapy. Patients received a dose of oral capecitabine of 1000 or 1250 mg/m² twice a day continuously from day 1 to day 14 every 21 days. Tumor responses were evaluated with positron emission tomography (PET) in 12 (66.7%) patients and with computed tomography (CT) scan in 6 (33.3%) patients.

We used Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 to evaluate response to therapy and Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 to evaluate adverse events. We defined clinical benefit rate (CBR) as the percentage of patients with advanced or metastatic cancer who achieved complete responses (CR), partial responses (PR) or stable disease (SD) at the time of the first tumor evaluation, and overall response rate (ORR) as the percentage of patients with advanced or metastatic cancer who achieved CR and PR at the time of the first tumor evaluation. Descriptive statistics were performed using median, range, and standard deviation. Cross tabulation and the chi-square test was used to compare qualitative variables and t-test for qualitative variables. Alpha error was set at 5% (p=0.05). All analyses were carried out using the software SPSS 20.0 (IBM SPSS Statistics Inc., Chicago, Illinois, USA).

**Results**

From December 2013 to April 2015, we treated with oral capecitabine 18 patients with advanced or recurrent cervical carcinoma, pretreated with platinum and recurring as platinum-resistant. Baseline characteristics are displayed in Table 1. Median age at diagnosis of cervical carcinoma was 50.5 (range 27-81) years. Overall, 11.2% of patients presented with FIGO I at the first diagnosis, 22.3% with FIGO II, 44.5% with FIGO III, and 16.5% with FIGO IV (for 1 patient FIGO stage at diagnosis was not known). The majority of cancers were squamous cell carcinomas (61.2% CR 38.8% adenocarcinomas). In their clinical history, only 4 patients received neoadju-
vant chemotherapy (3 patients with FIGO stage IIB and 1 with IIIIB), 6 patients received a combination of chemo and radiotherapy with radical intent, 11 patients underwent primary surgery and 9 patients received adjuvant chemotherapy. The median time to disease recurrence was 13.8 (range 3-128) months. All patients received a combination of platinum (16 carboplatin and 2 cisplatin) plus paclitaxel as first-line therapy for advanced/recurrent disease. Notably, 11.2% of patients experienced CR as best response to first-line chemotherapy, 16.5% PR, 22.3% SD, and 50% progressive disease (PD). Only 3 patients received a second-line platinum-based therapy before oral capecitabine. Median age at the first capecitabine administration was 56 (range 27-82) years. Overall, 12 (66.7%) patients started capecitabine at the full dose of 1250 mg/m² twice a day continuously from day 1 to day 14 every 21 days, 6 (33.3%) patients started with a reduced dose (1000 mg/m² twice a day continuously from day 1 to day 14 every 21 days); due to diarrhea, 2 patients received a reduced dose starting from the second cycle and 1 patient starting from the third cycle. In these 18 patients, after three cycles of oral capecitabine, the CBR was 55.5% and the ORR was 33.2% (5.5% of CR, 27.7% of PR and 22.3% of SD) (Figure 1). Of note, 3 patients who experienced disease progression as best response from platinum-based therapy given as first-line therapy achieved a SD (1 patient) or a PR (2 patients) with oral capecitabine. Furthermore, 85.7% of patients with adenocarcinoma achieved a clinical benefit (CR, PR or SD) after three cycles of oral capecitabine, compared with only 36.4% of patients with squamous cell carcinomas (p=0.04). No differences were observed in terms of CBR between patients who received 1250 mg/m² twice a day continuously from day 1 to day 14 every 21 days and patients who received a reduced dose (p=0.343).

No grade 3 or worse adverse events were reported. Overall, 50% of patients experienced grade 1-2 fatigue, 38.9% grade 1-2 hand-foot syndrome, and 22.2% grade 1-2 diarrhea.

**Discussion**

In this retrospective study we observed an ORR of 33.3% with oral capecitabine in advanced or recurrent cervical carcinoma.

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Fig. 1. Clinical response in 18 patients with pretreated cervical carcinoma, after 3 cycles of oral capecitabine. AD: adenocarcinoma; CBR: clinical benefit rate; CR: complete response; ORR: overall response rate; PR: partial response; SD: stable disease; SCC: squamous cell carcinoma.
cancer, which is close to the ORR reported in the literature with cisplatin and higher than any other drug tested in this setting [13]. Moreover, the safety profile in our preliminary analysis is very intriguing, with no grade 3 or worse adverse events.

As mentioned above, randomized clinical trials focused on cervical cancer are rare and this disease may be considered neglected. Phase II studies investigating the role of capcitabine as a single agent in advanced or recurrent cervical cancer are very heterogeneous in terms of the baseline characteristics of enrolled patients, and a meta-analysis is not feasible. However, the Italian Medicines Agency (AIFA) allows the use of 5-fluouracil in uterine and cervical cancer and the prodrug capcitabine is frequently used in clinical practice [12].

Garcia A and colleagues conducted a phase II study investigating first-line therapy with capcitabine single agent [8]. The study employed a two-stage accrual design. If at least 7 responses were observed in the 28 patients enrolled, a second phase of accrual would be initiated. The first stage of the study demonstrated a PR of 15.4% (4 patients out of 26 enrolled) and a SD rate of 34.6% (9 out of 26); no CR was observed, thus the study was stopped. However, we considered the trial still interesting because it showed an ORR of 15.4% and a CBR of 50%. Moreover, it is important to note that response could not be assessed in 2 patients (7.7%).

Another phase II was published in 2005 by Jenkins AD and colleagues investigating the efficacy and the safety of capcitabine in 23 patients with advanced squamous cell cervical cancer [14]. Capcitabine was given at a dosage of 2000 mg/m² twice a day continuously for 28 days, repeated every 6 weeks [15]. Eligible patients were women who had stage IVB or recurrent uterine cervical cancer, and who had received no more than one platinum-containing chemotherapy regimen. After a median follow-up duration of 25 months, the ORR was 30.6%, the median time to progression was 5.2 months, and median survival was 15.4 months. The most frequent grade 3-4 adverse events were anemia (16%), anorexia (16%), and diarrhea (22%).

In conclusion, in our retrospective analysis capcitabine in patients with advanced carcinoma of the cervix led to a CBR of 55.5% and an ORR of 33.2%. On the basis of these results, we have planned a phase II study with the aim of investigating the activity and safety of single agent capcitabine in patients with platinum-pretreated advanced or recurrent cervical carcinoma.

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Conflict of Interest
The Authors declare there are no conflicts of interest in relation to this article.

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