

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-

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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-

Table 1. Patient demographic and clinical characteristics at baseline.

| Characteristics | Patients (n=18) |
|---|-----------------|
| Median age, years | 50.5 |
| FIGO stage, n (%) | |
| I | 2 (11.2) |
| II | 4 (22.3) |
| III | 8 (44.5) |
| IV | 3 (16.5) |
| Unknown | 1 (5.5) |
| Histology, n (%) | |
| Squamous cell carcinoma | 12 (61.2) |
| Adenocarcinoma | 6 (38.8) |
| Previous radical treatment, n (%) | |
| Surgery | 11 (61.1) |
| Concomitant chemoradiotherapy | 6 (33.3) |
| Previous chemotherapy, n (%) | |
| Neoadjuvant | 4 (22.3) |
| Adjuvant | 9 (50.0) |
| Response to platinum-based therapy | |
| CR | 2 (11.2) |
| PR | 3 (16.5) |
| SD | 4 (22.3) |
| PD | 9 (50.0) |

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

vant chemotherapy (3 patients with FIGO stage IIB and 1 with IIIB), 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

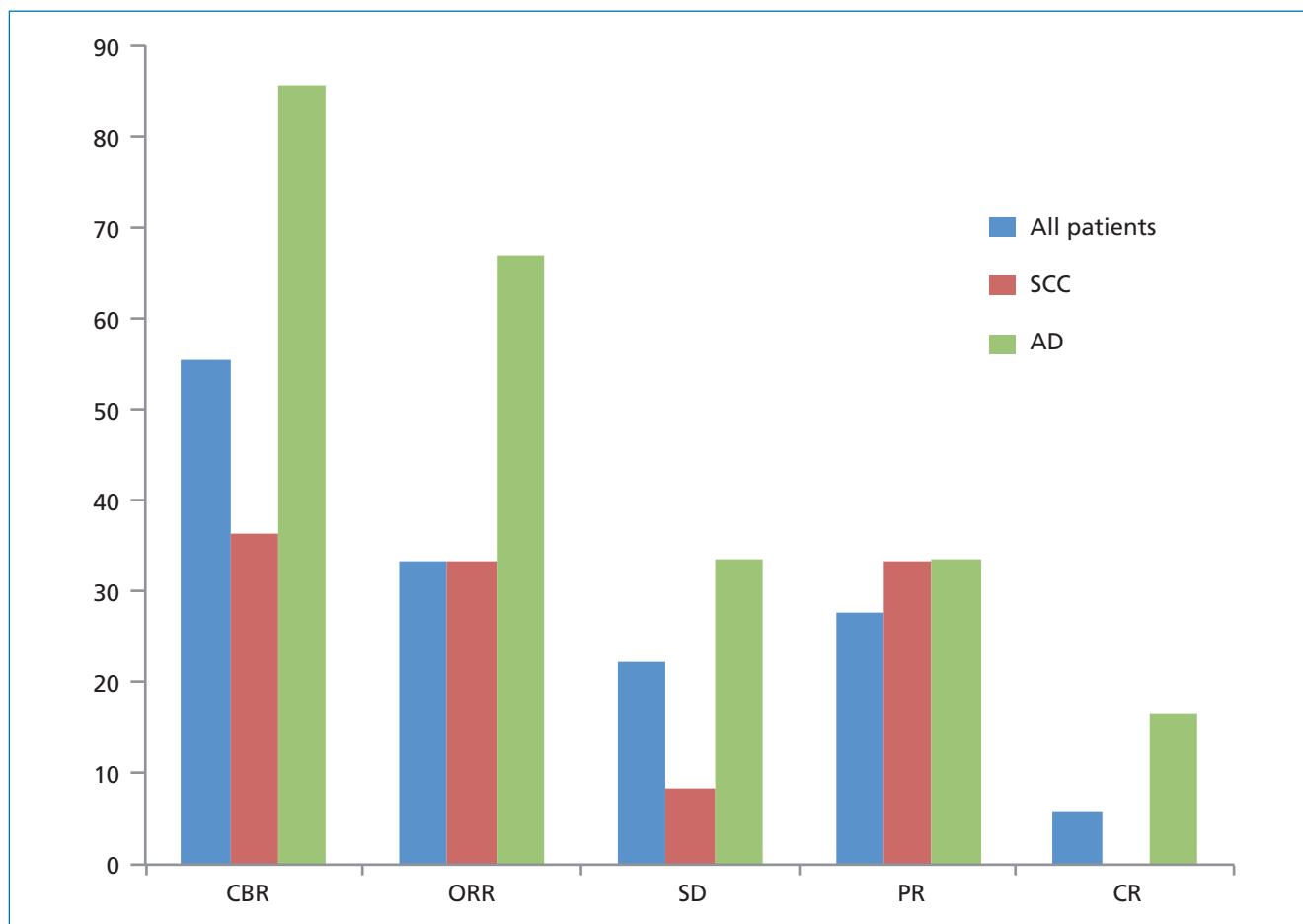


Fig. 1. Clinical response in 18 patients with pretreated cervical carcinoma, after 3 cycles of oral capecitabine. AD: adenocarcinoma; CBR: clinical benefit rate; CR: complete response; ORR: overall response rate; PR: partial response; SD: stable disease; SCC: squamous cell carcinoma.

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 capecitabine 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-fluorouracil in uterine and cervical cancer and the prodrug capecitabine is frequently used in clinical practice [12].

Garcia A and colleagues conducted a phase II study investigating first-line therapy with capecitabine 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 capecitabine in 23 patients with advanced squamous cell cervical cancer [14]. Capecitabine was given at a dosage of 2000 mg/m² twice a day continuously from day 1 to day 14 every 21 days. Although capecitabine was well tolerated, only 5 patients achieved SD, with a median duration of response of 3.5 (range 3-6.5) months. Of note, the study enrolled both squamous and nonsquamous cell cervical cancers. In our analysis, a large difference in CBR was observed between adenocarcinoma and squamous cell carcinomas (85.7% vs 36.4%; p=0.04). Thus,

we speculated that the lack of response documented by Jenkins AD may be due to heterogeneity in histology. However, a multi-institutional study that investigated the safety and the activity of capecitabine in 20 patients with refractory nonsquamous cell carcinoma of the cervix showed no objective response [9]. In this study patients received a median of 2.5 (range 1-11) cycles and showed an unexpected toxicity, with 5% grade 4 neutropenia and one septic death. By contrast, no grade 4 toxicities were documented in our analysis.

Capecitabine is not the only oral fluoropyrimidine tested in cervical cancer. In a Japanese phase II study, 36 patients with cervical cancer received S-1 35 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 capecitabine 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 capecitabine 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.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin* 2016;66(1):7-30.
2. <https://clinicaltrials.gov/ct2/results?term=cervical+cancer+%2B+2016&Search=Search> Accessed on October 27th, 2016.
3. Colombo N, Carinelli S, Colombo A et al. Cervical cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2012;23 Suppl 7:vii27-32.
4. Lorusso D, Ferrandina G, Pignata S et al. Evaluation of pemetrexed (Alimta, LY231514) as second-line chemotherapy in persistent or recurrent carcinoma of the cervix: the CERVIX 1 study of the MITO (Multicentre Italian Trials in Ovarian Cancer and Gynecologic Malignancies) Group. *Ann Oncol* 2010;21(1):61-6.
5. Monk BJ, Sill MW, McMeekin DS et al. Phase III trial of four cisplatin-containing doublet combinations in stage IVB, recurrent, or persistent cervical carcinoma: a Gynecologic Oncology Group study. *J Clin Oncol* 2009;27(28):4649-55.
6. Nishio S, Kitagawa R, Shibata T et al. Prognostic factors

- from a randomized phase III trial of paclitaxel and carboplatin versus paclitaxel and cisplatin in metastatic or recurrent cervical cancer: Japan Clinical Oncology Group (JCOG) trial: JCOG0505-S1. *Cancer Chemother Pharmacol* 2016 Oct;78(4):785-90.
7. Desmoulin F, Gilard V, Malet-Martino M et al. Metabolism of capecitabine, an oral fluorouracil prodrug: (19)F NMR studies in animal models and human urine. *Drug Metab Dispos* 2002;30(11):1221-9.
 8. Garcia AA, Blessing JA, Darcy KM et al. Phase II clinical trial of capecitabine in the treatment of advanced, persistent or recurrent squamous cell carcinoma of the cervix with translational research: a gynecologic oncology group study. *Gynecol Oncol* 2007;104(3):572-9.
 9. Look KY, Blessing JA, Michener CM et al. Phase II evaluation of capecitabine in refractory nonsquamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. *Int J Gynecol Cancer* 2008;18(4):773-8.
 10. Mountzios G, Soultati A, Pectasides D et al. Novel approaches for concurrent irradiation in locally advanced cervical cancer: platinum combinations, non-platinum-containing regimens, and molecular targeted agents. *Obstet Gynecol Int* 2013;2013:536765.
 11. Domingo E, Lorvidhaya V, de Los Reyes R et al. Capecitabine-based chemoradiotherapy with adjuvant capecitabine for locally advanced squamous carcinoma of the uterine cervix: phase II results. *Oncologist* 2009;14(8):828-34.
 12. Farmaci con uso consolidato nel trattamento dei tumori solidi nell'adulto per indicazioni anche differenti da quelle previste dal provvedimento di autorizzazione all'immissione in commercio. Available from: http://www.agenziafarmaco.gov.it/allegati/all_1_oncologia_adulti_160109.pdf. Accessed on October 27th, 2016.
 13. Tsuda N, Watari H, Ushijima K. Chemotherapy and molecular targeting therapy for recurrent cervical cancer. *Chin J Cancer Res* 2016;28(2):241-53.
 14. Jenkins AD, Ramondetta LM, Sun C et al. Phase II trial of capecitabine in recurrent squamous cell carcinoma of the cervix. *Gynecol Oncol* 2005;97(3):840-4.
 15. Katsumata N, Hirai Y, Kamiura S et al. Phase II study of S-1, an oral fluoropyrimidine, in patients with advanced or recurrent cervical cancer. *Ann Oncol* 2011;22(6):1353-7.