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Gemcitabine in Previously Treated Advanced or Recurrent Cervical Cancer; A Retrospective Study

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***Abstract*—Background:** Cervical cancer is the second most common female's cancer in Morocco. The objective of our study was to evaluate the efficacy and the toxicity of gemcitabin in previously treated advanced or recurrent cervical cancer.
Materials and Methods: We conducted a retrospective study in medical oncology department of University Hospital of Hassan II to evaluate the efficacy and toxicity of gemcitabine in patients with previously treated squamous cell carcinoma of cervical cancer over a period of 5 years between 2011 and 2015.
Results: Twenty one patients were included into the study. The dose of gemcitabine was 1250 mg/m2 over 30 min weekly two with a 2-weeks rest until progressive disease or adverse effects prohibited further therapy. There were two partial responses (9%) and no complete response was observed. Six patients had stable disease (28%). Gemcitabine had minimal serious adverse effects. No grade 4 adverse disease was observed. The median progression free survival was 2 months with median overall survival of 4.6 months.
Conclusion: According to our study, gemcitabine has a minimal activity in previously treated advanced cervical cancer in second line. Additional investigation is warranted to identify alternate therapy in this situation.

***Index Terms*— advanced cervical cancer, recurrent cervical cancer, chemotherapy, gemcitabine.**

I. INTRODUCTION

Cervical cancer is the second most common female's cancer in Morocco. It represents 12.8% of all female's cancers and 14.4 new cases per 100000 women per year are expected to occur in Morocco [1]. This disease is a major health issue in Morocco. More than 70% of cases are squamous cell carcinoma [1]. Cisplatin is considered the most effective agent in metastatic cervical cancer and is recommended in first line chemotherapy, reported response rates are between 20 and 30% [2]. However response is usually of short duration. Until now, there is no established second line regimen in this disease. Only few phase II studies with limited number of patients have been studied this issue. We conducted a retrospective study to evaluate the efficacy and toxicity of gemcitabine in patients with previously treated squamous cell carcinoma of cervical cancer.

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II. MATERIEL AND METHODS

We conducted a retrospective study in medical oncology department of University Hospital of Hassan II to evaluate the efficacy and toxicity of gemcitabine in patients with previously treated squamous cell carcinoma of cervical cancer over a period of 5 years between 2011 and 2015. Histologic confirmation of the primary diagnosis as squamous cell cancer of the uterine cervix was mandatory. Locally recurrent or metastatic patients were included. All patients received one prior chemotherapy regimen, based on cisplatin. Response was defined according to Response Evaluation Criteria in Solid Tumors (RECIST) guideline, version 1.1. Tolerance was evaluated according to The Common Terminology Criteria for Adverse Events (CTCAE).

III. RESULTS

Twenty one patients were included into the study. The median age of our patients was 52 years. All patients were evaluable for response. Patient's characteristics are listed in table 1. All patients had prior chemotherapy based on cisplatin, 15 with concomitant radiotherapy and 6 as first line chemotherapy. The dose of gemcitabine was 1250 mg/m2 over 30 min weekly two with a 2-weeks rest until progressive disease or adverse effects prohibited further therapy. There were two partial responses (9%) and no complete response was observed. Six patients had stable disease (28%). Table 2 resume responses and survival of the patients.

A median of three cycles was administered with a range of one to six cycles per patient. There were no treatment-related deaths. Gemcitabine had minimal serious adverse effects. No grade 4 adverse disease was observed.

The median progression free survival was 2 months with median overall survival of 4.6 months.

Table 1. Patient characteristics

Characteristic	Number
Age (year) Median Range	 52 38-76
Performans status 0 1 2	 0 7 14
Disease Locally recurrent Metastatic	 8 13
Prior pelvic radiotherapy	15
Prior cisplatin chemotherapy Concomitant with radiotherapy First line in metastatic disease	21 15 6

Table 2. Response of patients

Characteristic	Number
Cycles Median Range	 3 1-6
Response Partial Stable Progression	 2 (9%) 6 (28%) 13 (63%)
Progression-free interval (months) Median Range	 2 1-8
Survival (months) Median Range	 4.6 2.5-11

IV. DISCUSSION

Gemcitabine is an antimetabolite originally developed as an antiviral agent [2]. It is an effective agent in pancreatic, breast, ovarian and non small cell lung cancer. Recurrent and advanced cervical cancers are associated with high mortality and a lack of effective treatment options, especially for women who are poor candidates for surgery or radiation therapy. The low toxicity of gemcitabine in other human malignancies suggests that it might be useful in treating cervical tumors. In cervical cancer, gemcitabine was evaluated in two phase II studies of the Gynecologic Oncology Group in both squamous and non squamous subtypes [3,4]. Results were that gemcitabine as a single agent had minimal activity in previously treated patients with non-squamous cell carcinoma of the uterine cervix. Gemcitabine as a single agent had minimal activity in previously treated patients with squamous and non-squamous cell carcinoma of the uterine cervix. For squamous cervical cancer, twenty-seven patients were entered into the trial. The overall response rate was 8% with 21% of patients having stable disease. The median progression-free interval was 1.9 months (range: 0.5–9.0) and overall survival was 4.9 months (range: 1.5–16.3) [3]. The association of docetaxel and gemcitabin was evaluated in a phase II trial as second-line chemotherapy in cervical cancer in twenty six patients, this combination has activity against platinum resistant metastatic cervical cancer [5]. The overall response rate was 26%, although the ability to deliver d8 Gemcitabine is compromised because of hematological toxicity.

Our results are consistent with literature; gemcitabine appears to have minimal activity in previously treated metastatic cervical cancer.

Other agents that have shown reponses or prolongation of progression free survival may be useful as second line chemotherapy include: bevacizumab [6], docetaxel[7], irinotecan[8], 5 fluorouracil[9], ifosfamide [10], nab paclitaxel [11], pemetrexed [12], topotecan [13], and vinorelbin [14]. Table 3 summarizes the rate responses of these agents.

There have been significant advances in the past several years with regard to immunotherapy for cancer. A promising agent in development is live attenuated Listeria monocytogenes-based immunotherapy (ADXs11-01). ADXS11-001 is a drug that is designed to create a Th-1 type immunologic response, generating CD8+ T cells that target HPV-E7-transformed cells while simultaneously suppressing the immunologic tolerance within the lesions [15]. In a recent phase 2 study of ADXS11-001 in the treatment of persistent or recurrent cervical cancer, patients previously treated with chemotherapy, radiotherapy, or both were randomized to either 3 or 4 dosages of ADXS11-001 with cisplatin [16]. In the study, 18-month survival was 28% and 12-month survival was 36%. There was an 11% ORR, with an average duration of 10.5 months after 1 cycle of ADXS11-001. Prior therapy, baseline performance status, and the addition of cisplatin had no effect on survival or response. Current studies are needed to optimize the dosage and inclusion of multiple cycles with other agents to determine whether ADX11-001 can be used as an active agent against recurrent cervical cancer.

Based on these results, other immunotherapies such as nivolumab and ipilimumab are currently being evaluated in phase 2 trials [17, 18].

Table 3. Main studies of drugs in previously treated advanced cervical cancer

Drug	Study/ number of patients	Response rate
bevacizumab	Phase II/46	ORR : 10.9%
Docetaxel	Phase II/27	PR: 8.7%
5-fluorouracil and high-dose leucovorin	Phase II/55	ORR: 8.8%
irinotecan	Phase II/42	ORR: 21%
nab-paclitaxel	Phase II/37	ORR: 28.6%
Topotecan	Phase II/45	ORR: 12.5%
pemetrexed	Phase II/29	ORR: 15%
vinorelbine	Phase II/44	ORR: 13.7%
ifosfamide	Phase II/41	ORR: 31%

V. CONCLUSION

According to our study, gemcitabine has a minimal activity in previously treated advanced cervical cancer in second line. Additional investigation is warranted to identify alternate therapy in this situation.

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