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Gemcitabine for Advanced Endometrial Cancer: A Review of the MSKCC Experience

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Abstract

Background—Gemcitabine has been used in an off-label setting for treatment of advanced endometrial cancer (EMC), but there is a lack of published data showing its efficacy in treating this disease. We performed a retrospective review to determine the progression-free survival (PFS) and response rate (RR) of EMC patients treated with gemcitabine at Memorial Sloan-Kettering Cancer Center (MSKCC).

Methods—Eligible patients had histologically confirmed advanced (stage IV or recurrent) EMC that was treated with single-agent gemcitabine at MSKCC between 1999 and 2009. Response to therapy was determined by review of CT imaging by RECIST 1.1 criteria.

Results—We identified 46 eligible patients for our review. The median age was 66 years (range, 52–87). The median dose of gemcitabine administered was 800mg/m² infused on day 1 and 8 of a 21-day cycle. The predominant histology was endometrioid (48%, n=22), followed by serous (35%, n=16), clear cell (15%, n=7), and undifferentiated (2%, n=1). The overall RR was 10.9% (95% CI, 1.9–19.9); 4 patients (9%) achieved a partial response (PR) and 1 patient (2%) achieved a PR that became a complete response after surgical removal of a site of residual disease. Thirteen patients (28%) displayed stable disease (SD) lasting at least 3 months. Of note, 5 of the 7 (71%) patients with clear cell histology displayed SD or PR (n=5). The median PFS was 3.0 months (95% CI, 2.1–3.3).

Conclusion—In a mixed population of patients with previously treated advanced EMC, gemcitabine was well tolerated and showed modest activity. Patients with clear cell histology appeared to have greater likelihood of benefit.

Introduction

Endometrial cancer is the most common cancer of the female reproductive tract and the fourth most common cancer overall in women, accounting for an estimated 43,470 new cases and 7,950 deaths in the United States in 2010 [1]. The majority of patients are diagnosed at an early stage and cured with surgery and/or radiation, leading to an overall 5-year survival of 83%. However, patients diagnosed with advanced disease continue to have a

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Disclosure Statement

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dismal prognosis with a 17% 5-year survival. In the second-line setting, cisplatin (4%), docetaxel (7.7%), ifosfamide (15%), oxaliplatin (13.5%), pegylated liposomal doxorubicin (9.5%), and ixabepilone (12%) have been shown to have response rates of 4-15% [2-7]. Based on the findings of GOG-177, the current standard of care for women presenting with advanced endometrial cancer, or relapse with metastatic disease, is triple agent combination chemotherapy with an anthracycline, taxane, and platinum agent; therefore, patients have often had prior exposure to many of the available active agents at the time of relapse [8].

Gemcitabine (Gemzar, LY188011, Eli Lilly and Company, Indianapolis, Indiana) is a cytotoxic cytidine analogue. It primarily kills cells undergoing DNA synthesis (S-phase) and also blocks the progression of cells through the G1/S-phase. Following intracellular uptake, gemcitabine is metabolized to gemcitabine diphosphate and triphosphate nucleosides, which once incorporated into DNA, result in chain termination by inhibiting DNA polymerase activity. In addition, apoptosis may be induced by recognition of incorporated gemcitabine by p53 and DNA dependent kinases [9].

Gemcitabine is widely used in the treatment of solid tumors. It is FDA approved for use in combination with carboplatin in patients with advanced ovarian cancer that have relapsed at least 6 months after prior platinum-based therapy, in patients with metastatic breast cancer after failure of prior anthracycline-containing adjuvant therapy, in combination with cisplatin for first-line treatment of inoperable stage IIIa or higher non-small cell lung cancer, and as first-line treatment for patients with stage II or higher pancreatic adenocarcinoma [10].

Gemcitabine has frequently been used off-label in the treatment of advanced endometrial cancer despite a lack of published data showing efficacy in this disease. A recently completed phase II study performed by the Gynecologic Oncology Group (GOG) was the first published study to examine the efficacy of gemcitabine in recurrent or refractory endometrial cancer [11]. Eligible patients had advanced or recurrent endometrial cancer previously treated with one chemotherapy regimen. Enrolled patients were treated with gemcitabine 800 mg/m² intravenously on day 1 and 8 of a 21-day cycle. Of the 22 patients assessed for disease response, 1 patient (4%) achieved a partial response (PR) for 11 months, 9 patients (39%) achieved stable disease (SD) for a median of 4 months, and 12 patients (52%) displayed progressive disease (PD). The most common histology seen was endometrioid (52% of patients); results were not reported for individual histologies.

This review examines the efficacy of gemcitabine in patients treated at Memorial Sloan-Kettering Kettering Cancer Center (MSKCC) for advanced endometrial cancer between 2000 and 2009.

Methods

Following Institutional Review Board approval, all patients treated at MSKCC by the Gynecologic Medical Oncology Service with gemcitabine from 1999-2009 were reviewed. Out of these patients, 67 were identified who were treated with single-agent gemcitabine for advanced or recurrent endometrial cancer. All patients were required to have received at least 1 prior cytotoxic treatment for endometrial cancer and histological confirmation of diagnosis by MSKCC pathology.

All included patients were required to have measurable disease, with at least 1 “target lesion” as defined by Response Evaluation Criteria in Solid Tumors (RECIST 1.1) [12]. Both baseline and interval imaging while on treatment with gemcitabine was required to be performed at MSKCC. Twenty-two patients were excluded due to lack of available imaging. All radiology imaging was reviewed and all responses [partial response (PR), stable disease

(SD), or progression of disease (PD)] were confirmed by RECIST 1.1 criteria by independent radiology review.

Toxicity was determined by review of clinical notes and Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 graded review of systems performed at each MD visit during treatment.

Statistical Design

This was a single institutional retrospective analysis with the primary objective of determining the response rate (RR) and progression-free survival (PFS) of patients treated with gemcitabine for recurrent or refractory endometrial cancer. The PFS time was calculated from the therapy starting date to the date of progression of disease, death, or last follow-up for patients who did not progress or die and were censored. Progression date was defined as date of radiographic progression by RECIST 1.1 criteria. The PFS rate was estimated using Kaplan-Meier method. Two-sided confidence intervals at $P=0.05$ were calculated for RR and PFS.

Results

The median age of evaluable patients was 66 years (range, 52-87) and the median number of prior therapies was 2 (range, 1-8). Twenty-six (57%) patients had received prior abdominal or pelvic radiation. The most common dosing schedule of gemcitabine was 800mg/m² given on days 1 and 8 of a 21-day cycle (Table 1). Most non-hematologic toxicities were grade 1 or 2, the most common being fatigue and constipation (Table 2). There was one death related to small bowel obstruction and one hospitalization due to small bowel obstruction while on treatment with gemcitabine; both of these were felt to be related to progression of disease. Ten patients (22%) required treatment with granulocyte-colony stimulating factor.

Of 46 evaluable patients, 13 (28%), displayed stable disease (SD) 3 months, and 5 patients (11%) experienced a partial response (PR) by RECIST 1.1 criteria. One patient who achieved a PR went on to have an isolated site of residual disease resected; she remains disease-free 83 months later. The overall response rate (RR) of the group was 10.9% (95% CI, 1.9-19.9), with a median progression-free survival (PFS) of 3.0 months (95% CI, 2.1-3.3). The 5 patients with a PR had a mean of 2.6 (range, 1-7) prior lines of treatment before initiating therapy with gemcitabine. Of note, out of 7 evaluable patients with clear cell histology, 4 displayed SD and 1 achieved a PR, producing a clinical benefit rate (CBR) of 71% within that group. The mean number of prior lines of therapy within the clear cell group was 3.3 (range, 1-6).

Discussion

This retrospective review found that in a heavily pre-treated population gemcitabine is well tolerated and has modest activity as a single agent treatment for recurrent or refractory endometrial cancer. It is interesting to note that within the clear cell population a clinical benefit rate (CBR) of 71% (5/7 patients) was seen.

Clear cell endometrial cancer is rare, accounting for 3-6% of all endometrial cancers, but is the third most prevalent type of endometrial cancer following endometrioid and serous histology [13-16]. Clear cell carcinoma was first described in the English literature in 1957 [17]. Since that time it has been identified as an independent risk factor for poor prognosis and extrauterine spread of disease [18, 19]. The 5-year overall survival for clear cell endometrial cancer is reported to be 62.5%, in contrast to 83.2% for those with endometrioid endometrial cancer [20]. A review of 4180 women treated for endometrial cancer found that

clear cell carcinoma of the uterus was associated with a significantly poorer prognosis compared to grade 3 endometrioid endometrial cancer [18]. Amongst 1203 patients treated on 4 GOG trials for advanced or recurrent endometrial cancer, clear cell histology was associated with poorer PFS and OS [21].

Traditionally, endometrial cancer is characterized as developing through two possible pathways. The classic, or type I pathway, is associated with endometrioid histopathology and is characterized by atypical hyperplasia as a precursor, earlier age of onset, and development in the setting of estrogen excess. In contrast, the type II pathway is not associated with estrogen excess, involves atrophic endometrium, proceeds through the precursor lesion endometrial intraepithelial carcinoma, and presents in older patients with higher stage and grade [22]. Type I tumors tend to have frequent PTEN and ras mutations, be estrogen receptor (ER) and progesterone receptor (PR) positive and express E-cadherin; type II tumors generally display p53 mutations, are ER/PR negative, and less commonly express E-cadherin [22, 23]. Although clear cell endometrial cancer is generally grouped as a type II tumor, it generally displays lower p53 expression and may arise from atypical hyperplasia or endometrial intraepithelial carcinoma [14, 24]. It is therefore unclear if clear cell endometrial cancer is properly characterized by the two pathway paradigm of ovarian cancer pathogenesis.

Zorn et al evaluated gene expression profiles of endometrioid, serous, and clear cell tumors of both ovary and endometrial origin. They found that while the endometrioid and serous tumor expression profiles were organ specific, clear cell cancers showed a marked similarity in gene expression profiles across organs [22]. Gemcitabine is an active agent for treatment of recurrent or refractory ovarian cancer, and has been reported in case studies to show particular efficacy in clear cell histology [25-28].

Our findings suggest that gemcitabine shows modest activity in endometrial cancer with a CBR of 39%. The subgroup of patients with clear cell histology treated with gemcitabine displayed a CBR of 71% (5/7 patients) despite having received an average of 3.3 (range, 1-6) prior lines of therapy. Although this retrospective analysis is limited by evaluation of a small number of patients, these findings warrant further investigation into the efficacy of gemcitabine in clear cell endometrial cancer.

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FIGURE 1.
Progression free-survival

Table 1**Patient Characteristics**

Median Age	66 (range, 52-87)
# of Non-Hispanic White Women	39 (85%)
# of Patients with Prior Radiation	26 (57%)
Histology:	
Endometrioid	22
Serous	16
Clear Cell	7
Undifferentiated	1
Stage at Diagnosis:	
I	10 (22%)
II	2 (4%)
III	18 (39%)
IV	16 (35%)
Gemcitabine Regimen:	
800 mg/m ² ; Days 1,8 of 21 Day Cycle	28 (61%)
675-1000 mg/m ² ; Days 1,8,15 of 28 Day Cycle	8(17%)
675-1000 mg/m ² ; Days 1,8 of 21 Day Cycle	8 (17%)
800 mg/m ² ; Days 1,8,15 of 21 Day Cycle	1 (2%)
1000mg/m ² ; Day 1 of 21 Day Cycle	1 (2%)
Median # of Prior Lines of Chemotherapy	2 (range, 1-8)

Table 2

Non-Hematologic Toxicities

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Bleeding	4	0	1	0	0	5 (11%)
Constipation/Obstruction	19	6	1	2	1	29 (63%)
Diarrhea	4	0	0	0	0	4 (9%)
Edema	1	4	0	0	0	5 (11%)
Fatigue	25	13	1	0	0	39 (85%)
Fever	8	1	0	0	0	9 (20%)
Mucositis	3	1	0	0	0	4 (9%)
Myalgias	9	1	0	0	0	10 (22%)
Nausea	10	1	0	0	0	11 (24%)
Neuropathy	11	6	1	0	0	18 (39%)
Pulmonary	10	7	1	0	0	18 (39%)
Rash	1	1	1	0	0	3 (7%)

Table 3

Response by Histology

Histology	Partial Response (PR)	Stable Disease (SD)	Progressive Disease (PD)	Response Rate (RR)	Clinical Benefit Rate (CBR)
Endometrioid	3	5	14	14%	36%
Serous	1	4	11	6%	31%
Clear Cell	1	4	2	14%	71%
Undifferentiated	0	0	1	0%	0%
All	5	13	28	11%	39%