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Case report

Tumor grade and chemotherapy response in endometrioid endometrial cancer

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ABSTRACT

The objective of this study is to evaluate the association between tumor grade and response to chemotherapy in patients with endometrioid endometrial adenocarcinoma.

Patients with advanced or recurrent endometrioid endometrial adenocarcinoma of known tumor grade who received at least 3 cycles of chemotherapy were retrospectively identified at three institutions. RECIST 1.1 criteria were used to assess response to neoadjuvant, postoperative or salvage chemotherapy. Chi-square testing was used to evaluate the association between tumor grade and chemotherapy response.

Ninety-one patients met inclusion criteria: 13 with grade 1, 29 with grade 2 and 49 with grade 3 tumors. Eighty-four percent of patients received chemotherapy for recurrence, 12% for postoperative residual disease, and 4% in the neoadjuvant setting. The majority (85%) received carboplatin and paclitaxel. Forty-six percent (6/13) of grade 1, 72% (21/29) of grade 2 and 43% (21/49) of grade 3 tumors achieved an objective response. Grade 2 tumors were more likely to respond to chemotherapy compared to grade 3 tumors (72% vs. 43%, $p = 0.02$; Table 2), and specifically more likely to respond to carboplatin/paclitaxel (72% vs. 41%, $p = 0.016$). Median progression-free survival for patients receiving chemotherapy for recurrence or progression was 9 months for grade 1, 8 months for grade 2, and 5 months for grade 3 tumors. Similar results between grade and treatment response were apparent in the subset of 37 patients with a recently re-assigned tumor grade (G2 88% vs. G3 44%, $p = 0.032$).

In this series of endometrioid endometrial cancers, grade 2 tumors had the best measurable response to chemotherapy.

1. Introduction

Endometrial cancer (EC) is the most common gynecologic malignancy, frequently presenting in early stages. For women with localized disease at diagnosis, 5-year survival rates exceed 90% (Siegel et al., 2014). For those with distant disease at diagnosis, 5-year survival is below 20% (Siegel et al., 2014). While early disease is often cured by primary surgery, adjuvant therapy is often administered for more advanced cases (Network NCC, 2014). According to the most recent National Comprehensive Cancer Network (NCCN) guidelines for EC, chemotherapy with or without the addition of radiation is considered to be the cornerstone of treatment for patients with surgically staged advanced disease. Certain risk features in women with early stage disease—advanced age, lymphovascular space invasion, large tumor size, lower uterine segment or surface cervical glandular involvement—may also receive adjuvant chemotherapy (Network NCC, 2014).

Chemoresistance remains an important factor in the management of EC. In GOG-177, a trial evaluating doxorubicin and cisplatin +/− paclitaxel in women with advanced or recurrent endometrial cancer, 25% of regimens were discontinued due to progressive disease (Fleming et al., 2004). Response durations in EC tend to be shorter than those for ovarian cancer (McMeekin et al., 2007). Over half of patients don't respond to NCCN-recommended regimens at all (Network NCC, 2014; McMeekin et al., 2007) and may suffer from treatment-related toxicities without benefit. Ideally, chemotherapy would be used only in those likely to respond, while the predicted non-responders would receive other treatment modalities. With some data suggesting that genetic aggressiveness generally trends with grade, the objective of our study was to ascertain the association of tumor grade with chemotherapy response in patients with EEC.

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2. Materials and methods

We conducted a multi-institutional IRB-approved retrospective study of EC at Duke University, the University of North Carolina-Chapel Hill (UNC) or the Medical University of South Carolina (MUSC). Inclusion criteria were advanced or recurrent EEC, documented tumor grade, treatment with chemotherapy between 1994 and 2013, and measurable disease using RECIST 1.1 criteria (RECIST, 2014). Patients must have received a minimum of 3 cycles of chemotherapy and have pre-and post-chemotherapy imaging available for review. Patients with recurrent disease were included for their response to salvage chemotherapy for measurable disease. Exclusion criteria were non-endometrioid histology, non-measurable disease, lack of assigned grade at diagnosis, synchronous primaries, or prior malignancy within 5 years of diagnosis. Pathology specimens were reviewed and tumor grades assigned at each respective institution. At UNC and MUSC there were 4 and 5 pathologists, respectively, who received pathology At Duke, the majority of specimens were reviewed by 3 senior pathologists at Duke. A single observer assessed RECIST responses retrospectively.

Statistical comparisons were performed using ANOVA tests for continuous variables. Chi-square tests were used to test associations of categorical variables. Due to the small number of subjects with grade 1 tumors, statistical analysis of tumor response among all grades was not conducted; grade 1 patients are presented with descriptive statistics only. Inferential statistical analyses were performed comparing grade 2 and grade 3 tumors. Our null hypothesis was that there is no difference in tumor response to chemotherapy based on tumor grade. Our experimental hypothesis was that tumor grade is associated with response; lower grade tumors exhibit lower response rates. Using the two-sample binomial arcsin approximation method (assuming a one-sided alpha of 0.05), we obtain 71% power to detect a 25% difference in response rates between grade 2 and grade 3 tumors. Statistical analyses were conducted using SAS v. 9.3 software (SAS Institute, Inc., Cary, NC).

3. Results

Ninety-one subjects met eligibility criteria: thirteen with grade 1, 29 with grade 2, and 49 with grade 3 tumors. Clinical characteristics are listed in Table 1. Most patients were Caucasian; neither age (mean 63) nor BMI (mean 33) differed substantially across tumor grade. Neoadjuvant chemotherapy was administered due to tumor burden in 5 patients (5.5%), as postoperative therapy for residual disease in 10 (11%), and for recurrence in 76 (84%) cases. All patients receiving neoadjuvant or postoperative chemotherapy received carboplatin and paclitaxel.

Table 2 summarizes objective responses stratified by most recently assigned grade. The overall response rate was 6/13 (46%) for grade 1, 21/29 (72%) for grade 2, and 21/49 (43%) for grade 3 tumors. Seventy two percent of grade 2 tumors exhibited a response (CR or PR) compared to 43% of grade 3 tumors ($p = 0.02$). Seventy-seven patients received carboplatin/paclitaxel during the course of their treatment. Eighteen of 25 (72%) grade 2 tumors treated with this regimen achieved a response (CR or PR) compared to 17/41 (41%) of grade 3 tumors ($p = 0.016$).

Of the 15 patients receiving chemotherapy in the neoadjuvant or adjuvant setting, 6/6 (100%) grade 1/2 and 4/9 (44%) grade 3 tumors responded. Of the 48 patients treated for biopsy-proven progression or recurrence, 23 patients (48%) had a tumor grade re-assignment. Of these, 5 (22%) were upgraded compared to that assigned at diagnosis, while 78% retained their original grade. Among 37 patients with a recently assigned grade prior to starting chemotherapy (either in the neoadjuvant/post-operative setting or with a grade re-assigned at time of recurrence), 3 of 4 (75%) of grade 1 tumors achieved a response to treatment. Seven out of 8 patients (88%) with grade 2 tumors achieved a response compared to 11/25 (44%) of grade 3 tumors ($p = 0.032$). [Table 3].

Table 1
Patient characteristics by tumor grade on most recent biopsy.

	Grade 1 n = 13(%)	Grade 2 n = 29(%)	Grade 3 n = 49(%)	Total n = 91
Age at diagnosis, mean	62.4	63.4	62.6	63.0
Race/ethnicity				
Caucasian/non-Hispanic	10 (77)	24 (83)	32 (65)	66
Caucasian/Hispanic	0	0	2 (4)	2
African-American	1 (8)	4 (14)	14 (29)	19
Other	2 (15)	1 (3)	1 (2)	4
BMI at diagnosis, mean	29.6	33.9	33.5	33.1
Chemotherapy setting				
Neoadjuvant	2 (15)	0	3 (6)	5
Post-operative	1 (7)	3 (10)	6 (12)	10
Recurrence	10 (77)	26 (90)	40 (82)	76
Stage at presentation				
I	5 (38)	18 (62)	21 (43)	44
II	0	2 (7)	4 (8)	6
III	2 (15)	4 (14)	13 (27)	19
IV	6 (46)	5 (17)	11 (22)	22
Lymph nodes removed, mean (range)				
Pelvic	4 (0–12)	14 (0–45)	13 (0–53)	12
Para-aortic	2 (0–7)	3 (0–17)	5 (0–29)	4
Received prior chemotherapy	5 (38)	4 (14)	9 (18)	18 (20)
Target in prior irradiated field (n)	2	8	9	19
Chemotherapy regimen				
Carboplatin/paclitaxel	9 (68)	25 (87)	34 (69)	68 (75)
Cisplatin/doxorubicin/paclitaxel	1 (8)	1 (3)	2 (4)	4 (4)
Cisplatin/pegylated liposomal doxorubicin	1 (8)	1 (3)	1 (2)	3 (3)
Gemcitabine/docetaxel	1 (8)	0	0	1 (1)
Other	1 (8)	2 (7)	13 (25)	16 (17)

BMI: Body mass index.

Table 2
Response to chemotherapy based on most recent tumor grade.

	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)
Complete response	3 (23)	7 (24)	6 (12)
Partial response	3 (23)	14 (48)	15 (31)
Stable disease	5 (39)	7 (24)	7 (14)
Progressive disease	2 (15)	1 (4)	21 (43)

The majority (10/13) of grade 1 tumors were treated for recurrent disease; two received neoadjuvant therapy, while one received post-operative chemotherapy. Both grade 1 subjects receiving neoadjuvant chemotherapy achieved a CR. The first was a patient with para-aortic lymphadenopathy, who received 4 cycles of neoadjuvant chemotherapy, and achieved a CR on follow-up imaging. At time of surgery, the only site of disease was focal residual tumor within the uterus. The second patient had biopsy-proven liver metastases and received 8 cycles of neoadjuvant chemotherapy with a CR on pre-operative imaging (Fig. 1). At the time of surgery, there was no gross residual disease and no residual intra-uterine tumor on final pathology. The one subject with a grade 1 tumor who received post-operative chemotherapy achieved a partial response. The remaining grade 1 responses were seen in the group of 10 receiving treatment at recurrence (1 CR, 2 PR). At last follow-up, 4/10 patients had died of disease, 1 was without evidence of disease, 4

Table 3
Response to chemotherapy in only patients with recently assigned tumor grade.

	Grade 1 (%) N = 4	Grade 2 (%) N = 8	Grade 3 (%) N = 25
Complete response	2 (50)	2 (25)	2 (8)
Partial response	1 (25)	5 (63)	9 (36)
Stable disease	1 (25)	1 (12)	3 (12)
Progressive disease	0	0	11 (44)