Antiestrogen therapy in recurrent ovarian cancer resulting in 28 months of stable disease: a case report and review of the literature

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SUMMARY

Hormonal therapy for adjuvant treatment of ovarian cancer may provide a low toxicity option in some patients with refractory disease. A 53 year-old patient with stage IIIC papillary serous ovarian cancer previously treated with multiple chemotherapy regimens with platinum-resistant disease was treated with antiestrogen therapy for 28 months before requiring reinstitution of cytotoxic chemotherapy. Hormonal therapy may be effective in a subset of epithelial ovarian cancer patients with endocrine sensitivity and should be considered in the treatment of platinum-resistant patients.

KEY WORDS: *Ovarian Neoplasms; Antineoplastic Agents, Hormonal; Selective Estrogen Receptor Modulators; Tamoxifen; Aromatase*

INTRODUCTION

There has been a modest improvement in the five-year overall survival rate of epithelial ovarian cancer (EOC) from about 37% in 1975 to 45% in 2002 (1). Factors contributing to this improvement include aggressive debulking and the introduction of platinum compounds and taxanes (2,3).

Despite these improvements, most patients will relapse and develop refractory disease. Thus, the goal of second-line chemotherapy is palliation. Considerations in the choice of second-line therapy should include response to therapy and treatment related toxicity. Hormonal therapies are an attractive option owing to their limited toxicity profile and ease of administration (4). We present a patient with advanced ovarian cancer who had stable disease on hormonal therapy for 28 months.

CASE

A 53-year-old woman presented with a two-week history of abdominal bloating. Pelvic examination revealed a 2-3 cm right adnexal mass. A CT scan confirmed the mass and showed abdominal and pelvic ascites. Serum CA-125 was elevated at 3050 U/ml (normal 0-35 U/ml). The patient underwent optimal debulking including total abdominal hysterectomy, bilateral salpingoophorectomy, omentectomy and lymph node sampling. Pathology demonstrated stage IIIC grade 2 papillary serous adenocarcinoma involving the omentum and peritoneal surfaces.

Following surgery, the patient was treated with seven cycles of postoperative intravenous (IV) carboplatin and paclitaxel. CA-125 decreased but did not normalize (nadir = 66) in the setting of a negative physical exam. A peritoneal catheter was placed for purposes of intraperitoneal (IP) chemotherapy at which time persistent disease was documented histologically during the second-look surgery. She was given one cycle of IV cisplatin 65 mg/m^2 on day 1 and IV etoposide 90 mg/m^2 on days 1 through 3, while healing from the second-look surgery. Subsequently, she received five cycles of IP carboplatin 300 mg/m^2 on day 1 and IV etoposide 90 mg/m^2 on days 1 through 3 as second-line, took two months off from chemotherapy, and then received one cycle of IP carboplatin and two cycles of IP carboplatin and IV etoposide at the above doses. CA-125 increased from 27 to 54, so she received five cycles of single agent IV paclitaxel 185 mg/m^2 as third-line therapy. CA-125 decreased to 24 at the completion of paclitaxel. CT scans and pelvic exam always remained negative, and she had no symptoms of her disease. Because hormone receptors on her original tumor were determined to be positive for both estrogen and progesterone, she started with tamoxifen 20 mg per day.

After one month of being on tamoxifen, her CA-125 had fallen to 14. Three months later, it rose to 27. Tamoxifen dose was doubled to 40 mg per day. Her CA-125 remained stable for eight months, when it rose to 45. Tamoxifen was discontinued, and anastrozole 1 mg per day was prescribed. Five months later, CA-125 had decreased to 19.

While on anastrozole, her CA-125 gradually rose to 96 over the course of six months. Anastrozole was discontinued, and a monthly dose of fulvestrant 250 mg intramuscularly was initiated. CA-125 fell to 68 and stayed in that range for about 5 months, when it rose to 106, and CT scan showed new development of enlarged retroperitoneal nodes. After 28 months of stable disease on hormonal measures, she required reinstitution of platinum-based chemotherapy. The patient had either a transient or no response to single agent carboplatin, carboplatin and taxol, carboplatin and etoposide, doxorubucin, gemcitabine, avastin, and finally cytoxan and avastin. She died of complications secondary to bowel obstruction.

DISCUSSION

In platinum-resistant patients, there are a number of cytotoxic agents that have activity based on retrospective studies and phase II trials with objective response rates varying from 5 to 25%, and the duration of these responses lasting less than 8 months. An additional 35 to 50% of patients may maintain stable disease. The main advantage of using hormonal therapy among second-line therapy options is its limited toxicity profile and ease of administration, making it a suitable option for patients who are unable to tolerate or do not desire to continue cytotoxic chemotherapy due to side effects or comorbidities contraindicating the use of cytotoxic agents (4).

In this patient, despite rising CA-125 levels after ultimately developing resistance to tamoxifen, the subsequent use of anastrozole and fulvestrant still resulted in stable disease. Thus, resistance to one hormonal therapy does not preclude trial of another. One explanation is the differing mechanisms of actions of each of these agents. Tamoxifen and fulvestrant bind to estrogen receptors.

Tamoxifen has some agonist activity whereas fulvestrant does not. Anastrozole is an aromatase inhibitor that blocks the peripheral conversion of androgens to estrogen, thereby decreasing the total amount of estrogen in the body.

Tamoxifen is the most studied of the three agents. In a large prospective study, patients with recurrent or persistent disease (platinum-sensitive and resistant) given tamoxifen 20 mg per day after first-line chemotherapy, a 17% objective response was observed (5). Analysis limited to platinum-resistant patients showed an overall response rate (of 13%) (6). Tamoxifen does not appear to improve responses in combination with cytotoxic agents (7,8). Clinical studies using letrozole have shown conflicting results. One study showed an objective response of 15%; the other showed no objective responses (9,10). Fulvestrant 500 mg IM on day 1, 15, and 250 mg IM on day 28 and monthly thereafter has been studied in patients with recurrent EOC. Objective response rates were 8% with another 35% achieving stable disease (11). Other options for hormonal therapy include gonadotropin analogs, progesterones, and androgens. A review of published papers on the use of tamoxifen alone or in combination with other agents, aromatase inhibitors, and fulvestrant in recurrent EOC is shown in Tables 1-5. Of published studies that likely had overlapping patients, the study with a higher number of patients or analysis of the overall data (versus a subpopulation) were included.

Other factors thought to affect response to therapy include dosage and receptor status. Higher doses of tamoxifen in breast cancer have not been shown to be more effective and may even be more toxic (12-14). Dose escalation in uterine cancer has shown similar results (15). There are no data comparing dose responses of tamoxifen or other antiestrogen therapy in ovarian cancer. Varying doses (20 mg to 160 mg) and regimens of tamoxifen have been used. Estrogen and progesterone receptors are thought to play a role in the development of EOC and their presence would be expected to correlate with response to hormonal therapy in ovarian cancer as in breast cancer. However, the role that receptor status plays in the response to hormonal therapy in ovarian cancer remains unclear and should not necessarily influence treatment choices. A few trials suggest that response to tamoxifen may be related to hormone receptor status (5,16,17), but no studies have been specifically designed to examine this effect.

Our patient had one of the longest remissions reported to hormonal therapy. Hormonal therapy may have some activity in a subset of EOC patients with endocrine sensitivity. It should be considered in patients unable to tolerate cytotoxic chemotherapy or in the palliative setting as most of the literature focuses on patients with refractory or progressive disease. Further studies are needed to better characterize the role of hormonal therapy in ovarian cancer.

Table 1. Review of published literature on the use of tamoxifen alone in epithelial ovarian cancer

Study and Year	Type of study	N	Median number of prior regimens	Tamoxifen dose	CR (%)	PR (%)	SD (%)	PD (%)	Median PFS mos (range)	Median OS mos (range)	
Schwartz 1982 (18)	Phase II	13	2(1-4)	10 mg BID to 40 mg QID	0	1 (7.6)	4 (30.7)	8 (61.5)	NA	NA	
Shirey1985 (19)	Phase II	23	NA	10 mg to 20 mg BID	0	0	19 (82.6)	4 (17.4)	4.3 (2-11.8)	not reached	
Slevin 1986 (20)	Phase II	22	2(1-5)	10 mg to 20 mg BID	0	1 (4.5)	0	21 (9.5)	1.4 (0.75-3)	3.5 (0.75-12)	
Weiner 1987 (16)	Phase II	31	3	40 mg QD for 7 days f/b 10 mg BID	1 (3.2)	2 (6.4)	6 (19.3)	22 (70.9)	14 (3-23)	responders 16, nonresponders 7	
Osborne 1988 (21)	Phase II	51	NA	100 mg/m^2 in 4 divided doses over 24 h and then 20 mg BID	0	1 (1.9)	0	50 (98.0)	2	4 (1-16)	
Hatch 1991 (5)	Phase II	105	1	20 mg PO BID	10 (9.5)	8 (7.6)	40 (38.0)	47 (44.7)	NA	NA	
Ahlgren 1993 (22)	Phase II	29	NA	40 mg PO BID for 30 days then 20 mg BID	2 (6.8)	3 (10.3)	NA	NA	1.9	6.1	
Jager 1995 (23)	Phase II	37	1-2	30 mg QD	0	0	2 (5.4)	31 (83.7)	NA	6.5	
Van der Vange 1995 (24)	Phase II	10	NA	20 mg PO BID	0	1 (10.0)	1 (10.0)	4 (40.0)	NA	4.8 (0.4-17)	2 early deaths and 2 NA
Van der Velden 1995 (25)	Phase II	30	1-3	20 mg PO BID	2 (6.6)	0	10 (33.3)	18 (60.0)	NA	NA	
Marth 1997 (26)	Phase II	65	Majority 1-2	30 mg or 40 mg QD	2 (3.0)	2 (3.0)	50 (75.7)	11 (16.6)	11.5 (mean) (4-30) in patients with stable disease	3.8	
Markman 2004 (27)	Retrospective	56	NA	20 mg or 40 mg PO QD	NA	NA	NA	NA	3 (1-30)	NA	
Karagol 2007 (28)	Retrospective	29	NA	20 mg BID	1 (3.4)	2 (6.9)	6 (20.6)	20 (68.9)	4	15	

CR: complete response; PR: partial response; SD: stable disease; PD: progressive isease; PFS: progression free survival; OS: overall survival; ER: estrogen receptor; NA: data not available in this study; f/b: followed by.

Table 2. Review of published literature on the use of tamoxifen in combination with other hormonal agents in epithelial ovarian cancer

Study and year		N	Median number of previous regimens	Tamoxifen dose	Other Agent Dose	CR (%)	PR (%)	SD (%)	PD (%)	Median PFS mos (range)	Median OS mos (range)
Belinson 1987 (29)	Phase II	19	1-2	20 mg QD	160 mg MPA	0	0	10 (52.6)	9 (47.3)	NA	NA
Jakobsen 1987 (30)	Phase II	26	NA	10 mg TID for 14 days	400 mg MPA BID for 14 days after tamoxifen	0	0	7 (26.9)	19 (73.0)	NA	NA
Hasan 2005 (31)	Phase II	26	3 (1-8)	20 mg PO QD	Goserelin 3.6 mg SC monthly	1 (3.8)	2 (7.7)	10 (38.5)	NA	4	36

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; PFS: progression free survival; OS: overall survival; ER: estrogen receptor; NA: data not available in this study.

Table 3. Review of published literature on the use of tamoxifen in combination with cytotoxic chemotherapy in epithelial ovarian cancer

Paper and year		N	Median number of previous regimens (range)	Tamoxifen dose	Cytotoxic chemo dose	CR (%)	PR (%)	SD (%)	PD (%)	Median PFS mos (range)	Median OS mos (range)
Schwartz 1989 (8)	Prospective Randomized	49	0	10 mg BID only to ER positive patients	Cisplatin 50 mg/m^2 and doxorubicin 50mgm^2	NA	NA	NA	NA	NA	30.6
Millward 1992 (32)	Phase II	11	NA	160 mg BID for 6 days	Etoposide (dose NA) on days 4,5,6.	0	1 (9.0)	3 (27.2)	7 (63.6)	NA	NA
Benedetti Panici 2001 (33)	Phase II	50	Majority 1 prior, but 2 or more also included	80 mg QD for 30 days f/b 40mg QD	100 mg/m^2 cisplatin or 400 mg/m^2 carboplatin q21 days	15 (30.0)	10 (20.0)	12 (24.0)	13 (26.0)	8.5 (3-42)	23 (3-48) measurable disease 19 platinum resistant 20
Markman 2004 (7)	Retrospective	14		80 mg QD for first cycle then reduced to 40 mg QD	Carboplatin AUC 5 q21 days	0	0	NA	NA	2 (1-5)	NA
Wagner 2007 (34)	Phase II	49	2 (2-8)	40 mg QD	Gefitinib 500 mg PO QD	0	0	16 (28.6)	33 (58.9)	2	8.4

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; PFS: progression free survival; OS: overall survival; ER: estrogen receptor; NA: data not available in this study; f/b: followed by.

Table 4. Review of the published literature on the use of aromatase inhibitors in epithelial ovarian cancer

Paper and year		N	Median number of previous regimens	Letrozole or anastrozole dose	CR (%)	PR (%)	SD (%)	PD (%)	Median PFS mos (range)	Median OS mos (range)	Comments
Bowman 2002 (9)	Phase II	50	Majority 1, but 2, 3-5 also included	Letrozole 2.5 mg QD	0	0	10 (20.0)	40 (80.0)	8.8	14 (1-35)	
Papadimitriou 2004 (10)	Phase II	27	Majority 1, but 2, and 3 or more also included	Letrozole 2.5 mg QD	1 (4)	3 (11.1)	5 (18.5)	18 (66.6)	2.6 (1.2-33.6)	26.7 (2.4-44.2)	
Smyth 2007 (35)	Phase II	42	Majority 1, but 2 and 3 or more also included	Letrozole 2.5 mg QD	0	3 (7.1)	14 (42)	NA	NA	NA	ER positive patients only
del Carmen 2003 (36)	Phase II	53	NA	Anastrozole 1mg QD	0	1	42	NA	2.8	NA	

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; PFS: progression free survival; OS: overall survival; ER: estrogen receptor; NA: data not available in this study.

Table 5. Review of the use of fulvestrant in epithelial ovarian cancer

FULVESTRANT		N	Median number of previous regimens (range)	Fulvestrant dose	CR (%)	PR (%)	SD (%)	PD (%)	Median PFS mos (range)	Median OS mos (range)	Notes
Argenta 2009 (11)	Phase II	26	5(2-13)	500 mg IM on Day 1, 250 mg IM on Day 15, and 250 mg IM on Day 29 repeated every 28 days	1 (3.8)	1 (3.8)	9 (34.6)	15 (57.7)	2.1	not reached	modified Rustin criteria
Argenta 2009 (11)					0	0	13 (50%)	13 (50%)			RECIST criteria

Conflict of interest

We declare no conflicts of interest.

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