RESEARCH ARTICLE

Personalized Cancer Treatment for Ovarian Cancer

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Abstract

Recently there have been numerous advances in understanding the genetic basis of cancer which have resulted in more appropriate treatments. In this paper we describe the experience of the Burzynski Clinic, involved in treatment of numerous patients based on personalized approach using novel combinations for difficult-to-treat malignancies, with gynecological cancers. This retrospective study was conducted by extracting data from Burzynski Clinic's medical records and comprehensive review. Among the advanced refractory ovarian cancers cases (N=33), an objective response (OR) was found in 42.4%. We anticipate that with improved technology and novel therapeutics this rate will increase and adverse events will be reduced.

Keywords: Ovarian cancers - Burzynski approach - personalized treatment

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Introduction

Ovarian cancer is the seventh most common cancer in women in the United States, accounting for 3% of all malignancies and 6% of deaths from cancer in women, and it almost represents one third of invasive malignancies of the female genital organs and approximately 90% are serous cystadenocarcinoma, ovarian cancer is the fifth most common cause of death from malignancy in women. Unfortunately more than two thirds of patients have advanced disease at diagnosis. By consequence ovarian cancer, it has the highest fatality-to-case ratio of all the gynecologic malignancies. The 5-year survival rate for stage III-IV is only 11-41% (Berek and Natarajan, 2007).

When recur, the (OR) ranges from 47.2-61.7% by various combination chemotherapies: [carboplatin-epidoxorubicin (Bolis et al., 2001), cyclophosphamide-doxorubicin-cisplatin (Cantu et al., 2002), carboplatin-paclitaxel (Parmar et al., 2003), and carboplatin-gemcitabine (Pfisterer et al., 2006)] for platinum sensitive diseases. Markedly lower OR of 6.1-25.7% was reported with single agent chemotherapies: [topotecan (ten Bokkel et al., 1997), pegylated liposomal doxorubicin (Gordon et al., 2001), weekly paclitaxel (Rosenberg et al., 2002), docetaxel (Berkenblit et al., 2004), gemcitabine (Mutch et al., 2007), and bevacizumab (Cannistra et al.. 2007)] for platinum resistant diseases (NCI, 2012).

Materials and Methods

Patients were educated on the regimen which they were to receive and given consent forms to complete prior to starting each medication as witnessed during the medical record review from the Burzynski Clinic (BC), Houston, Texas, on March 14, 2012. This retrospective study was done by extracting data from BC's patient records in the USA, and all patient's medical records were reviewed from March 14-21, 2012.

Our group of patients was graded according to the 2002 American Joint Committee on Cancer (AJCC) staging criteria; only patients with stage III or IV predominately epithelial ovarian cancer with variable histology were included. Patients were evaluated for tumor response after the completion of first follow up imaging which was either computed tomography (CT) or positive emission tomography (PET) or PET/CT. Patients were evaluated for measurable disease - the presence of at least one measurable lesion. The measurable disease was assumed to be neoplastic in nature as verified by prior pathology report and in line with recurrence of disease.

We analyzed 33 patients deemed evaluable and each patient was assigned one of the following categories: 1) complete response 2) partial response 3) stable disease 4) progressive disease 5) minor response 6) minor response based on PET scan.

Complete Response (CR): Disappearance of all target lesions sustained for at least four weeks. CR by PET: no metabolic activity seen on PET scan.

Partial Response (PR): More than a 50% decrease in the sum of the longest perpendicular diameters of target lesions, taking as reference the baseline sum perpendicular diameter.

Partial Response by PET: Reduction SUV uptake and no new hypermetabolic lesions.

Minor Response Based on CT: Minor response (MR) at least 25% reduction in tumor size base on sum of perpendicular diameter.

Additional criteria: Minor response based on PET scan was defined as a decrease of metabolic activity.

Stable Disease based on CT (SD): Neither sufficient shrinkage to qualify for MR nor sufficient increase to qualify for PD, taking as reference the smallest sum largest

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perpendicular diameter since the treatment started.

Stable Disease based on PET: relative stable SUV uptake and no new lesions on PET.

Progressive Disease (PD): At least a 25% increase in the sum of the perpendicular diameters, or the appearance of one or more new lesions.

Of note a negative PET at baseline, with a positive PET at follow-up is PD based on a new lesion. No PET at baseline and a positive PET at follow-up: If the positive PET at follow-up corresponds to a new site of disease on CT, this is PD. If the positive PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Treated patients underwent routine blood tests such as a comprehensive metabolic panel, complete blood count, urinalysis and tumor markers such as CA-125. Additional testing of serum included analysis of Vascular Endothelial Growth Factor (VEGF range 40-92 pg/mL), Epidermal Growth Factor Receptor (EGFR range 67-87 ng/mL), Human Epidermal Growth Her2/Neu Extracellular Domain (HER2/Neu range 0-12 ng/mL), and c-kit mutation status in serum.

Since 2010 patients began to be tested with more extensive molecular profiling of the tumor tissue which was embedded in paraffin or present in unstained slides. Testing which was performed by Caris Life Sciences included mutational analysis, immunohistochemistry (IHC) to determine the level of protein expression, fluorescence in situ hybridization (FISH) to detect gene deletions, amplifications, translocations and fusions, and a microarray analysis which is able to measure the level of RNA expression in twenty four thousand genes. Afterwards the treatment plan was formulated with this information and searching through the literature for further support.

Results

All 33 patients were summarized and shown in Table 1. All responses were analyzed and shown in Table 2. Objective Response Rate (OR) was found to be 42.4%.

Table 1. Summary of Treatment History of All 33 Ovarian Cancer Patients

Age	Diagnosis Date	Diagnosis Detail	Prior Treatment	Our Treatment	Response to Treatment
73	11/15/95	Poorly-Differentiated, Infiltrating Carcinoma of the Ovary with metastases to lymph nodes	Carbo/Taxol Avastin, Cytoxan	PB, Tarceva,	PR w/o confirmation
50	7/15/86	Low grade serous carcinoma with metastases to the anterior mediastinum and right hilum	Adjuvant Cytoxan, Cisplatin	PB, Tarceva, Avastin, Nexavar, Cytoxan	CR
54	2/15/01	Ovarian carcinoma, serous type, with metastases to the colon	Yes but NA	PB, Tarceva, Sutent	CR based on PET
73	11/4/04	Poorly differentiated papillary serous carcinoma of the ovary with metastases to the liver	1)Carbo/Taxol, then single Carbo 2)Topotecan 3)Doxil/Gemzar then single Gemzar	PB, Herceptin, Tarceva, Cytoxan, Tykerb	MR based on CT
65	11/2/07	Adenocarcinoma of the ovary, with multiple metastases	Yes but NA	PB, Arimidex, Herceptin, Xeloda, Avastin, Tykerb, Nexavar, Zolinza, Tarceva, Rapamune	PD
61	9/15/05	Ovarian carcinoma with diffuse metastases to the pelvic region	1)Carbo/Taxol, Carbo/Docetaxel 2)Arimidex 3)XRT	PB, Tarceva, Avastin	MR based on CT
57	2/12/08	Papillary serous adenocarcinoma of the ovaries and metastatic papillary serous adenocarcinoma to uterus and cervix, omental and left adnexa	Carbo/Taxol	PB, Tarceva, Avastin, Tamoxifen, Cytoxan	SD
49	11/3/00	Papillary serous carcinoma of the bilateral ovaries with metastases to the omentum, multiple lymph nodes, and left breast	1)Carbo/taxol 2)IP Taxol/Cisplatin 3)Doxil 4)Carbo	PB, Avastin, Nexavar, Arimidex, Zolinza	SD
55	3/25/09	High-grade malignancy of the fallopian tube with metastases to the ovary, appendix and peritoneal lymph nodes	No	PB, Arimidex, Carboplatin, Taxol, Avastin	SD
66	2/7/05	Adenocarcinoma of the right ovary, papillary serous metastases to mesentery and abdomen	Carbo/Taxol	PB, Avastin, Nexavar	SD based on PET
51	6/16/08	Adenocarcinoma of the ovaries with metastases to liver and omentum	Carbo/Taxol	PB, Tykerb, Avastin, Herceptin, Nexavar	CR based on PET
46	12/19/07	Serous adenocarcinoma, well differentiated, of ovaries with metastases to left fallopian tube, appendix, uterus, cul-de-sac, lymph nodes, omentum, diaphragm, terminal ileum, peritoneum, and rectosigmoid colon	1)Carbo/Taxol 2)Patupilone 3)Topotecan+DSI-201 4)Topotecan 5)Femara 6)Cisplatin/Gemzar	PB, Nexavar, Zolinza, Avastin, Herceptin, Tykerb, Pazopanib	CR
60	1/25/10	Adenocarcinoma of the ovary, serous papillary	No	PB, Trastuzumab, Bevacizumab, Carboplatin, Paclitaxel, Lapatinib, Sorafenib	CR w/o confirmation
76	12/17/01	Poorly differentiated papillary serous adenocarcinoma of the ovaries with invasive implants involving ovarian serosa and fallopian tube, parametrial soft tissue, fibrous tissue, omentum, adipose tissue with metastasis to liver and lung	1)Taxotere/Carboplatin, then single Taxotere 2)Doxil 3)IMC-1121B	PB, Rapamune, Nexavar, Avastin, Tamoxifen	SD
70	7/19/08	Right ovarian and right fallopian serous cystadeno-carcinoma, high-grade, with invasion to right ascending colon and metastases to peritoneum, retroperitoneal , right common iliac and right intracaval aortic lymph nodes	1)Carbo/Taxol	PB, Avastin, Nexavar, Abraxane	CR based on PET
63	3/31/10	Papillary serous cystadenocarcinoma, high-grade of the bilateral ovaries, Stage IIIC	No	PB, Lapatinib,Carboplatin, Paclitaxel, Bevacizumab, Tamoxifen, Doxil, Cyclophosphamide, Topotecan	CR w/o confirmation

Table 1. Summary of Treatment History of All 33 Ovarian Cancer Patients (continued)

Age	Diagnosis Date	Diagnosis Detail	Prior Treatment	Our Treatment	Response to Treatment
63	3/2/05	Bilateral ovarian papillary serous cyst adenocarcinoma, moderate and poorly differentiated, with metastases to lymph nodes, rectosigmoid, and omentum	1)Carbo/Taxol 2)Taxol 3)Gemzar/Carbo	PB, Nexavar, Avastin, Tykerb	CR based on PET
71	4/21/10	Papillary serous carcinoma of the ovaries with metastases to the fallopian tubes, omentum, left and right pelvic lymph nodes	No	PB, Tykerb, Avastin, Abraxane, Votrient, Everolimus, Gemcitabine, Rapamune	SD based on PET
54	5/19/07	Ovarian serous carcinoma, high-grade, with metastases to left gutter, cul-de-sac, uterus, diaphragm, omentum, sigmoid colon, spleen, liver and lungs	1)Carbo/Taxol 2)Cisplatin/Taxol 3)IP Cisplatin/Taxol 4)Topotecan/Avastin	PB, Afinitor, Votrient, Avastin, Topotecan	CR based on PET
70	7/19/10	High grade ovarian carcinoma with metastases to retroperitoneal lymph node	No	PB, Abraxane, Avastin, Arimidex, Femara	PR w/o confirmation
82	10/7/10	Adenocarcinoma, ovarian primary with omental and peritoneal carcinomatosis, and ascites	No	PB, Carboplatin, Taxol, Avastin, Votrient, Afinitor, Etoposide, Rapamune, Nexavar, Xeloda	SD
51	2/13/06	Clear cell carcinoma of the right ovary, Stage IV, with metastases to the uterine fundus, bladder serosa, right pelvic sidewall, and omentum	1)Carbo/Taxol 2)Doxil	PB, Pasopanib, Lapatinib, Avastin	CR
78	6/17/04	Moderately to poorly differentiated serous carcinoma with metastasis to omentum and fallopian tubes	Tamoxifen, and Weekly Taxol	PB, Tarceva, Gemzar	PD
75	xx/xx/79	Invasive, poorly differentiated high grade mixed serous adenocarcinoma and transitional cell carcinoma of ovary with metastasis to diaphragm, retroperitoneal pelvic wall, liver, lymph nodes, and lungs	1)Cisplatin/Taxol 2)Topotecan	PB, Tamoxifen, Doxil, Avastin	PD
69	7/20/04	Endometroid adenocarcinoma of ovaries with metastasis to liver, bones, and peritoneum	1)Carbo/Taxol then Taxol/Avastin 2)Gemzar/Cisplatin then Gemzar 3)Topotecan	PB, Tarceva, Sutent, Nexavar, Zolinza	PD
65	12/8/08	Poorly differentiated serous carcinoma of ovary, involving omentum, uterus and positive peritoneal washings	1)Cisplatin/Taxol 2)HIPEC 3)Chemoembolization with Doxil 4)Doxil/Avastin 5)Topotecan	PB, Tarceva, Nexavar, Rapamune, Cytoxan	PD
53	9/10/09	Papillary serous carcinoma of ovary with metastasis to liver	1)IP Carbo/IV Taxol 2)Carbo/Taxol	PB, Votrient, Afinitor, Vorinostat, Tamoxifen	PD
16	3/29/10	Ovarian neoplasm with epithelial neuroendocrine and rhabdoid features with metastasis to lungs, and retroperitoneal adenopathy	1)Cisplatin/Etoposide 2)VAC alternating with Carbo/Taxol	PB, Afinitor, Gemzar, Avastin	PD
47	4/25/05	Ovarian carcinoma with brain metastasis	Yes but NA	PB, tykerb, herceptin, nexavar, avastin	PD
74	10/8/09	Serous papillary ovarian carcinoma with metastasis to liver and bowel	1)Carbo/Taxol 2)Doxil 3)Topotecan 4)Gemzar/Cisplatin	PB, Nexavar, Avastin, Tamoxifen, Afinitor, Herceptin	PD
59	11/18/08	Poorly differentiated adenocarcinoma of ovary, metastasis to rectum	1)Neoadjuvant Carbo/Taxol 2)IP Cisplatin/IV Taxol 3)Doxil 4)Tamoxifen	PB, Herceptin, Avastin, Tykerb, Nexavar, Gemzar, Cisplatin	PD
74	11/29/05	Serous adenocarcinoma of ovary with metastasis to liver and lungs	1)Carbo/Taxol 2)Cisplatin 3)Doxil 4)Topotecan 5)Gemzar	PB, Tarceva, Avastin, Rapamune, Topotecan, Votrient	PD
64	5/23/05	Adenocarcinoma of ovary with metastasis to omentum, liver, and bladder	1)Carbo/Taxol 2)Taxol 3)Topotecan 4)Gemzar	PB, Tarceva, Sutent, Tykerb, Avastin	PD

Table 2. Summary of Treatment Responses of All 33 Ovarian Cancer Patients

CR	CR PET	CR w/o conf	PR	PR w/o conf	MR based on CT	SD	SD based on PET	PD	ORR	Total Patients
4	5	2	0	1	2	5	2	12	14	33
0.12121	0.15152	0.060606		0.030303	0.0606	0.15152	0.0606061	0.3636364	0.424242	1
12.1212	15.1515	6.060606		3.030303	6.0606	15.1515	6.0606061	36.363636	42.4242	100

Discussion

Given that the platinum-sensitive recurrent ovarian cancers responses to 2nd line chemotherapy in 47.2-61.7% (Bolis et al., 2001; Cantu et al., 2002; Parmar et al., 2003; Pfisterer et al., 2006) and platinum-refractory responses

in only 6.1-25.7% (ten Bokkel et al., 1997; Gordon et al., 2001; Rosenberg et al., 2002; Berkenblit et al., 2004 Cannistra et al. 2007; Mutch et al., 2007), this group of patients treated at Burzynski's Clinic should response in 6.1-25.7%, similar to platinum-refractory cases. Surprisingly, they responded in 42.42%. This is twice the maximum response rate in the literature mentioned above.

The response rates found in other groups of ovarian cancer with heavily pretreated by chemotherapies and radiotherapies were also surprising as these patients should not have response rates as close to 40%. (NCI, 2012) However, response rates from personalized-targeted therapy are as high as at least 42.42% could be yielded. (Table 2).

Strength of this study is that there has never been any report of this kind of treatment before in the medical literature, as it is the innovative approach in treating cancers by Dr Burzynski SR. The weakness of this study may be that it was a retrospective study in which the data might be incomplete, and filled with some biases. With more patients in the future, a better report of this kind of treatment may be accomplished.

In conclusion, the goal of this paper is to present the various changing diagnostic and therapeutic possibilities in treating metastatic ovarian cancer to prevent resistance, give an improved quality of life and in essence a better outcome for patients. The original histological diagnostic techniques are limited and it is evident that the diversity in these tumors is intertwined with genomic instability, over expression of oncogenes, loss of tumor suppressor genes, up regulated signaling pathways fueling growth factors, angiogenesis and other features of tenacity of resistant ovarian cancer. Ideally eliminating neoplastic cells and neoplastic stem cells can be theoretically done with the proper pharmaceuticals which are aimed at each cancers genetic signature. The gynecological community is coming to agreement that the standard surgical debulking and front line chemotherapy needs to have additional agents included to focus on this heterogeneity of ovarian cancer. As the era of personalized cancer care has arrived, we can be optimistic that future treatments will be more effective due to improved molecular analysis and new therapeutics.

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