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Platinum-Gemcitabine-Avastin (PGA) for platinum-resistant/refractory ovarian cancer

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Summary

Objectives: Synergism between gemcitabine and platinum is known clinically. Bevacizumab in combination with single-agent chemotherapy has demonstrated significant clinical activity in platinum-resistant recurrent ovarian cancer in AURELIA study. However, the efficacy of platinum-gemcitabine-bevacizumab (PGA) has not been investigated in the platinum-resistant population. *Materials and Methods:* A retrospective chart review was conducted in all patients with platinum-resistant/refractory ovarian cancer treated with triplet combination therapy containing a platinum agent, gemcitabine, and bevacizumab between July 2011 and December 2013. *Results:* In total, 13 patients met the selection criteria, including ten patients with resistant disease (10/13, 77%) and three patients with refractory disease (3/13, 23%). Most of the patients were heavily pre-treated, having received over three lines of prior chemotherapy regimens on average (range 1-11). All patients had previously received taxane therapy; four patients received gemcitabine, seven patients failed combination regimens including bevacizumab, and three patients progressed on chemotherapy including both gemcitabine and bevacizumab. Ten patients responded biochemically to the therapy (defined by CA-125 declined by at least 50%). Of ten responders, one patient achieved CR for 24 months (8%), six patients achieved PR for 6.8 months (46%), three had stable disease for 6.7 months (23%), and three patients had PD (23%) by RECIST 1.1 criteria. The regimen was well-tolerated. One patient (8%) developed grade 3 neutropenia and neutropenic fever, requiring hospitalization, two patients developed grade 3 thrombocytopenia, two patients (15%) developed thrombosis in internal jugular vein, requiring discontinuation of bevacizumab, one patient (8%) experienced skin ulcer, and two patients developed thrombosis in internal jugular vein, requiring discontinuation of bevacizumab. *Conclusions:* Combination of PGA appears to be safe and very active against platinum-resistant/refractory ovarian cancer and merits further evaluation prospectively. A randomized phase II study (NCT01936974) is currently under way to confirm this important finding.

Key words: Ovarian cancer; Resistant; Refractory; Chemotherapy; Platinum; Gemcitabine; Bevacizumab.

Introduction

Ovarian cancer is the fifth leading cause of cancer death in women in the United States. An estimated 21,290 women would be diagnosed with ovarian cancer in 2015, approximately 80% women with ovarian cancer present with advanced Stage (III or IV) disease [1]. After cytoreductive surgery and systemic chemotherapy, unfortunately, majority of the patients will relapse and require further systemic therapy. Irrespective of treatment selected, recurrent ovarian cancer remains incurable at present; 14,180 patients were projected to die from ovarian cancer in 2015, highlighting the great need for effective therapy [1].

Platinum-paclitaxel combination is regarded as the gold standard to treat women with advanced ovarian cancer in the frontline setting. The platinum-free interval (PFI) after the initial therapy is widely used to predict the response and duration of response to re-treatment with platinum-based therapy as well as other agents such as taxanes or anthracyclines. Therefore, the recurrent ovarian cancer has been dichotomized to either platinum-sensitive (PFI > six months) or platinum-resistant (PFI ≤ six months) disease [2].

Platinum-sensitive recurrent ovarian cancer is generally treated with platinum alone or in combination. Unfortunately, most of platinum-sensitive ovarian cancer will develop resistance to platinum as well as non-platinum agents over time. By contrast, platinum-resistant recurrent ovarian cancer is a totally different scenario. Within this category, those patients which progress on platinum-based therapy are defined as platinum-refractory disease. Platinum-resistant/refractory recurrent ovarian cancer is generally treated with non-platinum-based chemotherapy [3]. In this setting, the most active agents have shown an overall response rate of 10-15%, with a progression-free survival (PFS) of less than four months and overall survival (OS) of approximately one year [3-6]. There is definitely an unmet medical need for this population of patients.

Recently, bevacizumab, an anti-angiogenesis agent, in

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combination with chemotherapy (weekly paclitaxel, liposomal doxorubicin or topotecan) was demonstrated to have a significant activity across all the treatment groups in platinum-resistant recurrent ovarian cancer in AURELIA study; median PFS was 6.7 months for bevacizumab plus chemotherapy versus 3.4 months for chemotherapy alone [7]. Chemotherapy with bevacizumab now represents a new standard of care for platinum-resistant recurrent ovarian cancer. Previously, carboplatin/gemcitabine/bevacizumab (PGA) combination was shown to prolong PFS in platinum-sensitive, recurrent ovarian cancer patients [8]. However, platinum/gemcitabine with bevacizumab has not been studied in platinum-resistant/refractory patients to the best of our knowledge.

Here, the authors report their institutional experience with treating platinum-resistant/refractory, recurrent ovarian cancer patients with this three-drug regimen. This regimen shows excellent tolerability and activity in this difficult-to-treat group.

Materials and Methods

Study population

This retrospective analysis was approved by the Institutional Review Board at Cancer Treatment Centers of America (CTCA). A retrospective chart review was conducted in all patients with platinum-resistant/refractory ovarian cancer treated with at least one dose of triplet combination therapy containing a platinum agent, gemcitabine and bevacizumab (PGA) at Western Regional Medical Center, CTCA between July 2011 and December 2013. All patients had histologically confirmed recurrent epithelial ovarian cancer. Other demographic characteristics were documented including age, sex, ethnicity, performance status, and prior therapies.

All patients had disease progression during or within six months of previous platinum-based chemotherapy including the following four categories: 1) primary platinum-refractory: previously untreated patients who do not achieve at least a partial response to platinum-based chemotherapy; 2) primary platinum-resistant: previously untreated patients who have achieved at least a partial response to platinum-based chemotherapy but experience a relapse within a period of six months of its conclusion; 3) secondary platinum-refractory: previously treated patients have a relapse six months after the conclusion of chemotherapy, but fail to achieve at least a partial response; 4) secondary platinum-resistant: previously treated patients have a relapse six months after the conclusion of chemotherapy, achieve at least a partial response with platinum-based therapy as second-line therapy, but experience relapse within six months. Recurrence was confirmed by clinical examination, imaging studies, and an increase of CA 125, a tumor marker if secreted by the ovarian cancer.

Assessment of response, PFS

Tumor response. Patients were assigned to one of the following categories based on the response criteria outlined in RECIST 1.1: 1) complete response (CR); 2) partial response (PR); 3) stable disease (SD); 4) progressive disease (PD). An objective response was defined as either a CR or a PR. *Biochemical response* was defined as reduction of CA 125 levels to ≤ 50% of pretreatment levels. *Duration of response* was determined for subjects with an objective response only and was defined as the period of time from the date of first objective response to the date of progression. PFS was defined as the period of time from the date of administration of the first dose to the date that the subject was determined to have PD or death due to any cause.

Table 1. — *Patient demographics (n=13).*

Patient demographics	No. of patients (%)
Age, years	
Median	56
Range	25 − 65
ECOG performance status	
0	3 (23)
1	9 (69)
2	1 (8)
Tumor histology	
Serous	12 (92)
Endometrioid	1 (8)
Mucinous	0
Tumor differentiation grade	
1	0
2	0
3	13 (100)
Number of prior chemo regimens	
1	3 (23)
2	3 (23)
3	3 (23)
≥ 4	4 (31)
Platinum sensitivity	
1° Platinum-resistant	7 (54)
1° Platinum-refractory	1 (8)
2° Platinum-resistant	3 (23)
2° Platinum-refractory	2 (15)
Previous exposure	
Taxane	13 (100)
Gemcitabine	4 (31)
Bevacizumab	7 (54)
Gemcitabine + bevacizumab	3 (23)

Assessment of toxicity

Toxicity related to the treatment regimen was evaluated and reported in all the patients who received any amount of a platinum agent, gemcitabine, or bevacizumab. Severity of toxicity was graded according to the CTCAE version 4.03.

Results

Patients

A total of 13 patients met the selection criteria, including seven patients with primary resistant disease (7/13, 54%), three patients with secondary resistant disease (23%), one patient with primary refractory disease (8%), and two patients with secondary refractory disease (15%). Patient characteristics are summarized in Table 1. The median age of the evaluable patients was 56 years. All patients but one had histologically proven, grade 3 serous carcinoma including two patients with papillary serous carcinoma. The majority of patients had a performance status of ECOG 1 (69%). Most of the patients were heavily pre-

Table 2. — *Toxicity of platinum/gemcitabine/bevacizumab.*

Toxicity (grade)	No. of patients (%)
Neutropenia (G3)	1 (8)
Neutropenia (G4)	0
Neutropenic fever	1 (8)
Thrombocytopenia (G3)	2 (15)
Thrombocytopenia (G4)	0
Skin ulceration (G3)	1 (8)
Venous thrombosis (G2)	2 (15)
Allergic reaction (G2)	3 (23)

Table 3. — *Response to platinum/gemcitabine/bevacizumab.*

Response type	No. of patients (%)	Duration of response (months)
Complete response	1 (8)	24
Partial response	6 (46)	6.8
Stable disease	3 (23)	6.7
Progressive disease	3 (23)	
Biochemical response	10 (77)	

treated, having received over three lines of prior chemotherapy regimens on average (range 1-11). All patients had previously received taxane therapy; four patients received gemcitabine, seven patients failed combination regimens including bevacizumab, and three patients progressed on chemotherapy including both gemcitabine and bevacizumab.

Toxicity

One patient received carboplatin (AUC 5)/gemcitabine (1,000 mg/m^2 on days 1 and 8)/bevacizumab (15 mg/kg) every three weeks. Two patients received carboplatin (AUC 3)/gemcitabine (1,000 mg/m^2)/bevacizumab (ten mg/kg) every two weeks. Due to history of allergic reaction to carboplatin, one patient received cisplatin (75 mg/m^2)/gemcitabine (1,000 mg/m^2)/bevacizumab (15 mg/kg) every three weeks, two patients received cisplatin (40 mg/m^2)/gemcitabine (1,000 mg/m^2)/bevacizumab (ten mg/kg) every two weeks, and two patients (including one patient who received cisplatin initially and developed allergic reaction to cisplatin) received oxaliplatin (85 mg/m^2)/gemcitabine (1,000 mg/m^2)/bevacizumab (ten mg/kg) every two weeks. The majority of the patients (6/13, 46%) received carboplatin (AUC 5)/gemcitabine (1,000 mg/m^2)/bevacizumab (15 mg/kg) every three weeks. In general, the regimens were well tolerated (Table 2). An average of seven (range: 1-14) cycles (defined as either every two or three weeks depending on the regimen) of chemotherapy were delivered to each patient. Hair loss was not assessed; nausea was uncommon with standard prophylactic antiemetics. Eleven of 13 (85%) patients received growth factor support at some point. As a result, only one patient (8%) developed grade 3 neutropenia and neutropenic fever, requiring hospitalization. There was no grade 4 neutropenia. Two patients developed grade 3 thrombocytopenia and no grade 4 thrombocytopenia was documented. Two patients (15%) developed thrombosis in internal jugular vein, requiring discontinuation of bevacizumab. One patient (8%) experienced skin ulcer likely secondary to bevacizumab use. Two patients (15%) developed three episodes of allergic reaction (G2); as a consequence platinum was discontinued in both patients. No GI perforation was observed.

Treatment efficacy

All 13 patients were assessed for biochemical and radiographic responses. Ten of 13 (77%) patients had biochemical response to the therapy. Of ten responders, one (8%) patient achieved CR after six cycles of chemotherapy with carboplatin (AUC 3)/gemcitabine (1,000 mg/m^2)/bevacizumab (ten mg/kg) every two weeks followed by bevacizumab maintenance for 24 months, six (46%) patients achieved PR for 6.8 months, three (23%) had stable disease for 6.7 months (23%), and three (23%) patients had PD by RECIST 1.1 criteria (Table 3).

Discussion

Platinum-resistant/refractory ovarian cancer poses a tremendous therapeutic challenge for clinicians. Cytotoxic chemotherapy remains the mainstay to treat this entity of disease. Re-treatment with platinum agents is highly debatable [9]. Platinum monotherapy has a response rate of less than 10% in this setting [10, 11]. Conversely, as a single agent, gemcitabine has one of the lowest response rates in platinum-resistant ovarian cancer, as demonstrated in a phase III randomized controlled trial [12]. Gemcitabine is a deoxycytidine analogue, which disrupts DNA polymerization during DNA synthesis; it has also been shown to inhibit ribonucleotide reductase, thereby disrupting DNA repair mechanisms [13]. Enhanced DNA repair is one of the mechanisms involved in platinum resistance commonly observed in recurrent tumors previously exposed to platinum therapy. In preclinical studies, the combination of gemcitabine with cisplatin has been shown to have synergistic activity with regard to platinum-DNA adduct formation [14, 15]. Oxaliplatin or cisplatin combined with gemcitabine showed much greater activity with response rate of approximately 30% in phase II studies [16, 17]. Thus, platinum-gemcitabine combination seems to represent a rational approach to treat platinum-resistant/refractory ovarian cancer.

The favorable outcome demonstrated by AURELIA trial has made chemotherapy (weekly paclitaxel, liposomal doxorubicin or topotecan) plus bevacizumab increasingly accepted as the front-line therapy for recurrent platinum-resistant ovarian cancer. Like many other great trials, it brings more questions than answers. There were three chemotherapy regimens used in AURELIA: weekly pacli-

taxel, liposomal doxorubicin or topotecan. The trial was not powered to answer which regimen is the best when combined with bevacizumab. Nonetheless, subgroup analysis seems to suggest weekly paclitaxel plus bevacizumab represent the most active combination among them, which prolonged PFS from 3.9 months to 10.4 months, much longer than liposomal doxorubicin or topotecan combination with bevacizumab [18]. It is worth noting that weekly paclitaxel, as a single agent, appeared to be more active than liposomal doxorubicin or topotecan, which is consistent with the present authors' clinical experience as well. This observation suggests that the foundation for chemotherapy-bevacizumab regimens is grounded on the inherent value of chemotherapy backbone and that optimizing chemotherapy regimens might yield even better treatment outcomes. Indeed in the present study, the platinum-gemcitabine-bevacizumab was used to treat this heavily pretreated population of patients. Ten of 13 (77%) patients achieved biochemical response and clinical benefit. Of five patients who met the criteria of AURELIA study (platinum-resistant ovarian cancer receiving no more than two lines of therapy), one patient achieved CR and four patients achieved PR, highly suggestive of the great activity of the triplet regimen against platinum-resistant disease.

Ninety-three percent of the patients in AURELIA received no prior antiangiogenic therapy, and thus no conclusions could be drawn on the efficacy of bevacizumab in bevacizumab-pretreated patients [7]. In colorectal cancer, continuation of antiangiogenesis with second-line chemotherapy significantly improved OS in patients who had received first-line bevacizumab-containing regimens [19, 20]. Studies in ovarian cancer addressing this issue are currently ongoing. In this retrospective series, seven (54%) patients had prior bevacizumab, three patients achieved PR, and one patient had stable disease. It suggests that PGA could also be effective in platinum-resistant ovarian cancer with previous bevacizumab exposure. The present study also included three patients who previously progressed on both gemcitabine and bevacizumab. One patient experienced PR, one patient had stable disease, and one patient had symptomatic improvement with decreased tumor marker after one cycle, but unfortunately developed internal jugular vein thrombosis and progressed shortly after bevacizumab discontinuation. These results suggest the pivotal role of platinum in this three-drug combination. In the present series, one patient developed allergic reaction to carboplatin, the other patients experienced allergic reaction to cisplatin first and subsequently to oxaliplatin as well. In both patients, platinum had to be discontinued. Both patients resulted in progression of disease to continuation of gemcitabine + bevacizumab. These results also seem to support the notion that platinum is essential for PGA to overcome platinum-resistance/refractoriness. Gemcitabine is usually administrated weekly and routinely used in combination with either biweekly or on a two weeks on, one week off schedule [8, 16]. However, gemcitabine is quite myelosuppressive when used in combination with carboplatin to treat heavily pretreated patients, often requiring dose reduction and treatment interruption. In the present study, 7/13 (54%) patients received PGA with gemcitabine 1,000 mg/m^2 every three weeks. Two patients had PD and five patients achieved PR. It appears that when used as PGA triplet, gemcitabine every three weeks might be sufficient to function as a sensitizer. Based on this experience, gemcitabine is administered every three weeks in the present authors' current ongoing prospective study.

Platinum-refractory ovarian cancer presents the utmost challenge to the treating physicians. It was excluded from AURELIA and no standard therapy exists at the current time. In the present study, one patient with primary refractory disease did not respond to PGA and two patients with secondary refractory disease experienced stable disease, suggestive of clinical benefit of PGA in this challenging group of patients.

In conclusion, combination of PGA appears to be safe and very active against platinum-resistant/refractory ovarian cancer and merits further evaluation prospectively. A randomized phase II study (NCT01936974) is currently under way to confirm this important finding.

References

[1] Siegel R.L., Miller K.D., Jemal A.: "Cancer statistics, 2015". *CA Cancer J. Clin*., 2015, *65*, 5.

[2] Pinato D.J., Graham J., Gabra H., Sharma R.: "Evolving concepts in the management of drug resistant ovarian cancer: dose dense chemotherapy and the reversal of clinical platinum resistance". *Cancer Treat. Rev.*, 2013, *39*, 153.

[3] Gore M.E., Fryatt I., Wiltshaw E., Dawson T.: "Treatment of relapsed carcinoma of the ovary with cisplatin or carboplatin following initial treatment with these compounds". *Gynecol. Oncol.*, 1990, *36*, 207.

[4] Naumann R.W., Coleman R.L.: "Management strategies for recurrent platinum-resistant ovarian cancer". *Drugs*, 2011, *71*, 1397.

[5] Markman M., Blessing J., Rubin S.C., Connor J., Hanjani P., Waggoner S.: "Phase II trial of weekly paclitaxel (80 mg/m2) in platinum and paclitaxel-resistant ovarian and primary peritoneal cancers: a Gynecologic Oncology Group study". *Gynecol. Oncol.*, 2006, *101*, 436.

[6] Fracasso P.M., Blessing J.A., Morgan M.A., Sood A.K., Hoffman J.S.: "Phase II study of oxaliplatin in platinum-resistant and refractory ovarian cancer: a gynecologic group study". *J. Clin. Oncol.*, 2003, *21*, 2856.

[7] Pujade-Lauraine E., Hilpert F., Weber B., Reuss A., Poveda A., Kristensen G., *et al.*: "Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial". *J. Clin. Oncol.*, 2014, *32*, 1302.

[8] Aghajanian C., Blank S.V., Goff B.A., Judson P.L., Teneriello M.G., Husain A., *et al.*: "OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer". *J. Clin. Oncol.*, 2012, *30*, 2039.

[9] Matsuo K., Lin Y.G., Roman L.D., Sood A.K.: "Overcoming platinum resistance in ovarian carcinoma". *Expert Opin. Investig. Drugs*, 2010, *19*, 1339.

[10] See H.T., Freedman R.S., Kudelka A.P., Burke T.W., Gershenson D.M., Tangjitgamol S., *et al.*: "Retrospective review: re-treatment of patients with ovarian cancer with carboplatin after platinum resistance". *Int. J. Gynecol. Cancer*, 2005, *15*, 209.

[11] Piccart M.J., Green J.A., Lacave A.J., Reed N., Vergote I., Benedetti-Panici P., *et al.*: "Oxaliplatin or paclitaxel in patients with platinum-pretreated advanced ovarian cancer: A randomized phase II study of the European Organization for Research and Treatment of Cancer Gynecology Group". *J. Clin. Oncol.*, 2000, *18*, 1193.

[12] Mutch D.G., Orlando M., Goss T., Teneriello M.G., Gordon A.N., McMeekin S.D., *et al.*: "Randomized phase III trial of gemcitabine compared with pegylated liposomal doxorubicin in patients with platinum-resistant ovarian cancer". *J. Clin. Oncol.*, 2007, *25*, 2811.

[13] Peters G.J., Van Moorsel C.J., Lakerveld B., Smid K., Noordhuis P., Comijn E.C., *et al.*: "Effects of gemcitabine on cis-platinum-DNA adduct formation and repair in a panel of gemcitabine and cisplatin-sensitive or -resistant human ovarian cancer cell lines". *Int. J. Oncol.*, 2006, *28*, 237.

[14] Wynne P., Newton C., Ledermann J.A., Olaitan A., Mould T.A., Hartley J.A.: "Enhanced repair of DNA interstrand crosslinking in ovarian cancer cells from patients following treatment with platinum-based chemotherapy". *Br. J Cancer*, 2007, *97*, 927.

[15] van Moorsel C.J., Pinedo H.M., Veerman G., Bergman A.M., Kuiper C.M., Vermorken J.B., *et al.*: "Mechanisms of synergism between cisplatin and gemcitabine in ovarian and non-small-cell lung cancer cell lines". *Br J. Cancer*, 1999, *80*, 981.

[16] Bozas G., Bamias A., Koutsoukou V., Efstathiou E., Gika D., Papadimitriou C.A., *et al.*: "Biweekly gemcitabine and cisplatin in platinum-resistant/refractory, paclitaxel-pretreated, ovarian and peritoneal carcinoma". *Gynecol. Oncol.*, 2007, *104*, 580.

[17] Kalykaki A., Papakotoulas P., Tsousis S., Boukovinas I., Kalbakis K., Vamvakas L., *et al.*: "Gemcitabine plus oxaliplatin (GEMOX) in pretreated patients with advanced ovarian cancer: a multicenter phase II study of the Hellenic Oncology Research Group (HORG)". *Anticancer Res.*, 2008, *28*, 495.

[18] Pujade-Lauraine E., Hilpert F., Weber B., Reuss A., Poveda A., Kristensen G., *et al.*: "AURELIA: A randomized phase III trial evaluating bevacizumab (BEV) plus chemotherapy (CT) for platinum (PT)-resistant recurrent ovarian cancer (OC)". *J. Clin. Oncol.*. 2012, *30*, abstr LBA5002.

[19] Tabernero J., Yoshino T., Cohn A.L., Obermannova R., Bodoky G., Garcia-Carbonero R., *et al.*: "Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study". *Lancet Oncol.*, 2015, *16*, 499.

[20] Bennouna J., Sastre J., Arnold D., Osterlund P., Greil R., Van Cutsem E., *et al.*: "Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial". *Lancet Oncol.*, 2013, *14*, 29.

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