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A phase II evaluation of sunitinib in the treatment of persistent or recurrent clear cell ovarian carcinoma: An NRG Oncology/Gynecologic Oncology Group Study (GOG-254)

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Author contributions

	Study conception design	Acquisition of data	Analysis and interpretation of data	Drafting of manuscript	Critical revision
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William Brady PhD	x	x	x	x	x
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Jubilee Brown MD	x	x		x	x
Mark S. Shahin MD		x	x		x
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Abstract

Objectives.—To determine the efficacy and tolerability of sunitinib in recurrent or persistent clear cell ovarian cancer patients.

Methods.—All patients had one or two prior regimens with measurable disease. Tumors were at least 50% clear cell histomorphology and negative for WT-1 antigen and estrogen receptor expression by immunohistochemistry. Sunitinib 50 mg per day for 4 weeks was administered in repeated 6-week cycles until disease progression or prohibitive toxicity. Primary end points were progression-free survival (PFS) at 6 months and clinical response. The study was designed to determine if the drug had a response rate of at least 20% or 6-month PFS of at least 25%.

Results.—Of 35 patients enrolled, 30 were treated and eligible (median age: 51, range: 27–73). Twenty-five (83%) were White, 4 (13%) Asian, and 1 (3%) unknown. The majority 28 (83%) patients, underwent 3 but 2 (7%) had 16 courses of study therapy. Five (16.7%) patients had PFS 6 months (90% CI: 6.8%–31.9%). Two (6.7%) patients had a partial or complete response (90% CI: 1.2%–19.5%). The median PFS was 2.7 months. The median overall survival was 12.8 months. The most common grade 3 adverse events were fatigue (4), hypertension (4), neutropenia (4), anemia (3), abdominal pain (3), and leukopenia (3). Grade 4–5 adverse events included: thrombocytopenia (5), anemia (2), acute kidney Injury (1), stroke (1), and allergic reaction (1).

Conclusion.—Sunitinib demonstrated minimal activity in the second- and third-line treatment of persistent or recurrent clear cell ovarian carcinoma.

Keywords

Sunitinib; Progression-free survival; Persistent or recurrent clear cell ovarian; carcinoma

1. Introduction

Accounting for 3–12% of all epithelial ovarian cancers, patients with clear cell carcinomas have a poorer prognosis compared to those with serous cancers [1–6]. Clinical and translational studies have shown that the biology and clinical behavior of clear cell carcinoma is distinct compared to other epithelial cell types [2,7–9].

Clear cell cancers of the kidney, ovary, and uterus have similar genomic profiles [10]. Renal and ovarian clear cell carcinomas have frequent mutational inactivation of the Von Hippel-Lindau (VHL) pathway [11]. Similar to renal cell cancer, angiogenesis also plays a central role in ovarian cancer progression [12,13]. Targeting angiogenesis in ovarian cancer resulted in the approval of bevacizumab for recurrent disease [14,15]. Given these similarities between renal and ovarian clear cell cancers, we hypothesized that biologic agents that are active in metastatic renal cell cancer may have activity in ovarian clear cell cancers.

Sunitinib (SU11248) is a highly potent, selective inhibitor of protein tyrosine kinases, including vascular endothelial growth factor receptor (VEGF-R) and platelet derived growth factor receptor (PDGF-R) [16–20]. In second-line treatment of metastatic renal cell cancer, a setting where no effective standard therapy, sunitinib therapy resulted in a response rate of 34% [20]. In 2006, the FDA approved sunitinib for the treatment of advanced renal cell carcinoma. Sunitinib has been shown to have modest activity in epithelial ovarian cancers based on three phase II trials from Canada, Europe and United States [21–23]. However, all of these trials included patients with various epithelial cell types with distinct molecular profiles. In fact, clear cell cancers comprised of <10% of these clinical trial patients. Furthermore, there was no defined criterion for clear cell histology with central pathology review. Since epithelial ovarian cancers are heterogeneous cancers, it is important to study clear cell ovarian cancer in a multi-center, cooperative group trial with central pathology review and standardized treatments. As such, we proposed to evaluate the anti-tumor activity and toxicity of sunitinib in persistent or recurrent clear cell ovarian cancer patients.

2. Methods

2.1. Patient eligibility and exclusions

Patients had either recurrent or persistent clear cell ovarian cancer. They must have had one prior platinum-based chemotherapeutic regimen for management of primary disease containing carboplatin, cisplatin, or another organo platinum compound. Patients were allowed, but not required, to receive one additional cytotoxic regimen for management of recurrent or persistent disease. Patients must have had measurable disease with at least one target lesion to be used to assess response.

Patients were excluded if they have received any non-cytotoxic therapy for management of recurrent or persistent disease such as VEGF inhibitors including bevacizumab. All patients were at least 18 years old with a Gynecologic Oncology Group (GOG) performance status score of 0 (fully active) to 2 (ambulatory and capable of self-care but unable to work; up and about >50% of waking hours). All chemotherapy was discontinued at least three weeks

before registration. All patients had adequate bone marrow, renal, hepatic, and neurologic function.

2.2. Pathology screening

Primary tumors had to have at least 50% clear cell histomorphology to be eligible or have a documented recurrence with at least 50% clear cell histomorphology and negative for expression of WT-1 antigen and estrogen receptor (ER) by immunohistochemistry. The trial was designed such that if the primary tumor did not have at least 50% clear cell histomorphology, a biopsy of the recurrent or persistent tumor was required. In this study, all patients met the initial histologic criteria and did not require a subsequent biopsy of the recurrent tumor. Appropriate tissue and immune-histochemical stained slides for WT-1 antigen and ER were available for histologic evaluation for central pathology review by NRG Oncology/Gynecologic Oncology Group.

2.3. Treatment plan

Sunitinib 50 mg per day was orally administered in repeated six-week cycles of daily therapy for four weeks, followed by two weeks off. Dose reduction for grade 3 to 4 toxicity was allowed to 37.5 mg per day and then to 25 mg per day. This six-week cycle was repeated until evidence of disease progression or unacceptable toxicity.

2.4. Efficacy and toxicity assessment

Clinical examination with evaluation of tumor burden was performed at baseline and before each cycle. Disease status was also assessed radiographically at baseline, before each odd cycle, and at the end of treatment. Response and progression were evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) [24]. Using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE version 3.0), adverse events were assessed on day one of each cycle and were graded. Investigator-determined best overall response was defined by using RECIST criteria in patients with measurable tumors.

2.5. Objectives

The primary objectives were to determine the efficacy of sunitinib as estimated from the probability of surviving progression free for at least six months. Progression-free survival (PFS) was defined as the duration of time from start of treatment to time of progression or death, whichever occurs first. Response and progression were evaluated using RECIST [24]. Overall survival (OS) was defined as the duration of time from start of treatment to time of death or date of last contact.

2.6. Study oversight

The NRG Oncology/Gynecologic Oncology Group and GOG designed and conducted this study. The study was approved by the research ethics board at each participating center or by a central institutional review board and all patients provided written informed consent. With reviews by the data and safety monitoring committee, the data were collected, held, and analyzed by the statistical group. The first author (study chair) vouches for the integrity of

the data and analyses reported and for the fidelity of the trial to the protocol. Representatives from the sponsors (the Cancer Therapy Evaluation Program of the National Cancer Institute and Pfizer) had no role in the design, accrual, management or analysis of the data. The drafting and content of the manuscript and the decision to publish was undertaken by the first author with input from all the coauthors.

2.7. Statistical analysis

This was a single arm, phase II clinical trial that used a flexible, bivariate two-stage design [25]. The primary hypothesis of this study tested the proportion of patients with objective tumor response (complete or partial) and the proportion of those surviving progression-free for at least six months. The null proportions were 10% for response rate and 15% for PFS at six months. The targeted accrual for the first stage was 19 eligible and evaluable patients (range: 15 to 22) and the cumulative targeted accrual for the second stage was 31 patients. The study was designed to determine if the drug had a response rate of at least 20% or a six-month PFS of 25%.

3. Results

From 2010 to 2014, 35 patients were enrolled and 30 were treated and eligible (median age: 51, range: 27–73). Five patients were not included: two never treated, and three ineligible. Twenty-five (83%) were White, 4 (13%) Asian, and 1 (3%) unknown. Performance status of 0,1, and 2 comprised of 18 (60%), 10 (33.3%), and 2 (6.7%) patients. Twenty (67%), 9 (30%) and 1 (3%) patients had 1, 2, and 3 cycles of prior chemotherapy. (Table 1) Two (6.7%) patients had a partial or complete response (90% CI: 1.2%–19.5%). The median PFS was 2.7 months. Eight (27%), 16 (53%), 1 (3%), 1 (3%), 1 (3%), 1 (3%), and 2 (7%) patients had 1, 2, 3, 4, 9, 11 and 16 courses of study therapy, respectively. The median OS was 12.8 months. Five (16.7%) patients had PFS   6 months (90% CI: 6.8%–31.9%). (Table 2 and Fig. 1).

The most common grade 3 adverse events were fatigue ($n = 4$), hypertension ($n = 4$), neutropenia ($n = 4$), anemia ($n = 3$), abdominal pain ($n = 3$), and leukopenia ($n = 3$). Grade 4–5 adverse events included: thrombocytopenia ($n = 5$), anemia ($n = 2$), acute kidney Injury ($n = 1$), stroke ($n = 1$), and allergic reaction ($n = 1$). Three grade 5 events were reported. One patient died from a stroke which was attributed as possibly related to treatment. Two patients died due to disease. (Table 3).

4. Discussion

Compared to other epithelial cell types, clear cell ovarian carcinomas have a poorer prognosis [1–6]. Given that the molecular characteristic of clear cell ovarian cancers is similar to that of clear cell renal carcinoma, we hypothesized that effective and approved novel targeting agents for renal clear cell cancers may also be active in ovarian clear cell cancers. VHL-associated tumors, including most renal and clear cell ovarian cancers, produce high levels of vascular endothelial growth factor (VEGF) and platelet-derived growth factor receptor (PDGFR) alpha expression [26–31]. These investigations resulted in the development of biologic agents targeting the VHL-HIF pathway and angiogenesis in

renal cell cancer, including tyrosine kinase and mTOR inhibitors such as sunitinib, sorafenib, and temsirolimus [32]. Sunitinib is a highly potent, selective inhibitor of protein tyrosine kinases, including VEGF-R and PDGF-R [16–20].

Sunitinib is an active FDA-approved agent against solid tumors including renal cell cancer and gastrointestinal stromal tumors. The safety and efficacy of sunitinib has been evaluated in three phase II trials in ovarian cancers. The National Cancer Institute of Canada Clinical Trials Group treated 30 recurrent platinum-sensitive ovarian cancer patients with sunitinib; of which 20 (67%) had serous and 3 (6%) had clear cell cancers. The response rate was approximately 3% with a median PFS of four months [21]. These authors concluded that sunitinib has modest activity in recurrent platinum sensitive disease. In a European study, the AGO investigators performed a randomized multicenter phase II trial in 73 platinum-resistant ovarian cancer patients and showed a 16.7% response with a median PFS and OS of 4.8 and 13.6 months, respectively [22]. In another phase II study from United States, Campos et al. treated 36 recurrent and refractory epithelial ovarian cancer patients, of which five cases were clear cell, and found a response rate of 8.3% with a 6-month PFS of 36% [23].

Given the molecular similarities between renal and ovarian clear cell cancers and the activity of sunitinib in epithelial ovarian and renal cell cancers in prior clinical trials, we anticipated that sunitinib may have significant activity in clear cell ovarian cancer. The FDA approved sunitinib for renal cell cancer based on a randomized trial of treatment-naïve metastatic renal cell cancer patients and showed an objective response rate of 27.5% in the sunitinib arm compared to only 5.3% in the interferon-α arm [33]. In addition to the molecular similarities to renal cell cancers, clear cell ovarian tumors have frequent mutational inactivation of the Von Hippel-Lindau (VHL) pathway associated angiogenesis and disease progression, we anticipated that the anti-VEGF activity of sunitinib would be effective in the treatment of clear cell ovarian cancers patients [11,12,13]. However, we found minimal activity with a response rate of only 6.7% in recurrent clear cell ovarian cancer patients in this current study. These unanticipated findings may be explained by the differences in the biology of clear cell cancers and selection of patients.

In light of the recent discoveries on the pathogenesis of clear cell cancers since the conception of this current study, our results were not completely unexpected. While we utilized histology to select patients who may benefit from sunitinib, the current data indicate that directing targeted therapy based on molecular tumor aberrations may be a more rational approach for identifying promising agents in a target group of patients. Recent studies have shown that clear cell ovarian cancers may arise from malignant transformation of endometriosis with a shared genetic lineage [34–35]. AR1D1A, a tumor suppressor gene that encodes BAF250a chromatin remodeling protein, is mutated in nearly half of endometriosis-associated clear cell cancers [36]. Colony stimulating factor-1 receptor is a lethal target of AR1D1A-deficient endometriosis associated clear cell ovarian carcinoma [37]. In vitro inhibition of CSF1 selectively inhibited the proliferation of AR1D1A-deficient endometriosis associated clear cell ovarian cancer cell lines. Given these findings, the NRG (GOG283) is currently evaluating dasatinib (NSC #732517 IND #120636) in women with

clear cell ovarian cancer with retention or loss BAF250a tumor expression to enhance the selection of patients and clinical activity of these targeted therapies.

Clinical trials evaluating single-agent biologics in clear cell ovarian cancer have shown minimal to modest activity [39–41]. (Table 4) In a recent trial of platinum-resistant ovarian cancer patients, AUREL1A investigators showed that the combination of chemotherapy with biologic agents was superior to chemotherapy alone [14]. In a subsequent retrospective study from our research group, we also found that patients who had chemotherapy combined with bevacizumab had better outcomes compared those with bevacizumab alone [38]. Therefore, it is possible that combination treatment rather than single-agent biologic or chemotherapy alone may be required to obtain sufficient activity in recurrent and resistant clear cell ovarian cancer.

This current study included only clear cell ovarian cancer patients with recurrent, persistent, and most with platinum-resistant disease. We selected for all primary tumors with at least 50% clear cell histomorphology and negative for expression ofWT-1 antigen and estrogen receptor based on immunohistochemistry. All patients entered on trial had a primary tumor with at least 50% clear cell histomorphology and thus did not require a biopsy of recurrent tumor. Nevertheless, it may be more informative to obtain biopsies of recurrent disease to assure the selection of recurrent clear cell cancers based on histomorphologic criteria and genomic characteristics. Unlike renal cell cancers, recurrent ovarian clear cell cancers may be more heterogeneous and require molecular characterization of relapsed tumors to individualize effective treatments.

In clear cell ovarian cancer, numerous trials have evaluated chemotherapeutic and biologic agents with modest results [39]. 1mmune modulators targeting the microenvironment of clear cell cancers may have promise. In the CheckMate 025 trial with advanced recurrent renal cell cancer, nivolumab, a programmed cell death receptor 1 inhibitor, improved the median overall survival by 5.4 months compared to everolimus [40]. Further, the combination of nivolumab plus ipilimumab, a cytotoxic T lymphocyte-associated antigen 4 inhibitor, improved the overall survival compared with sunitinib, resulting in an update of the European Association of Urology Guidelines Recommendations [41]. In recurrent platinum-resistant ovarian cancer, Hamanishi et al. treated twenty patients with nivolumab and found an overall response rate of 15%. Of the two patients with a durable complete response, one had clear cell carcinoma [42]. Pembrolizumab, a programmed cell death receptor 1 inhibitor, was recently approved for the treatment of unresectable or metastatic, microsatellite instability high or mismatch repair deficient solid tumors, regardless of tumor site or histology [43]. In a case report of chemotherapy and radiation-resistant ovarian cancer, pembrolizumab led to an exceptional response with tumor harboring a PD-L1 gene structural variations causing aberrant PD-L1 expression [44].

This is the first study designed to treat patients with clear cell ovarian cancer. All tumors underwent central path review with histomorphologic validation, standardized treatment, and surgical staging by gynecologic oncologists. There are limitations that may have contributed to the minimal activity demonstrated with this agent during this trial. It is possible that the immune and microenvironment of tumors may be different and thus the same agent may not

be as effective across organs. Moreover, the intra-tumoral heterogeneity of clear cell ovarian cancers may require personalized molecular therapy. Further, adaptive clinical trials may be necessary to validate tumor and serum biomarkers to advance novel treatments for clear cell ovarian cancer patients.

Acknowledgements

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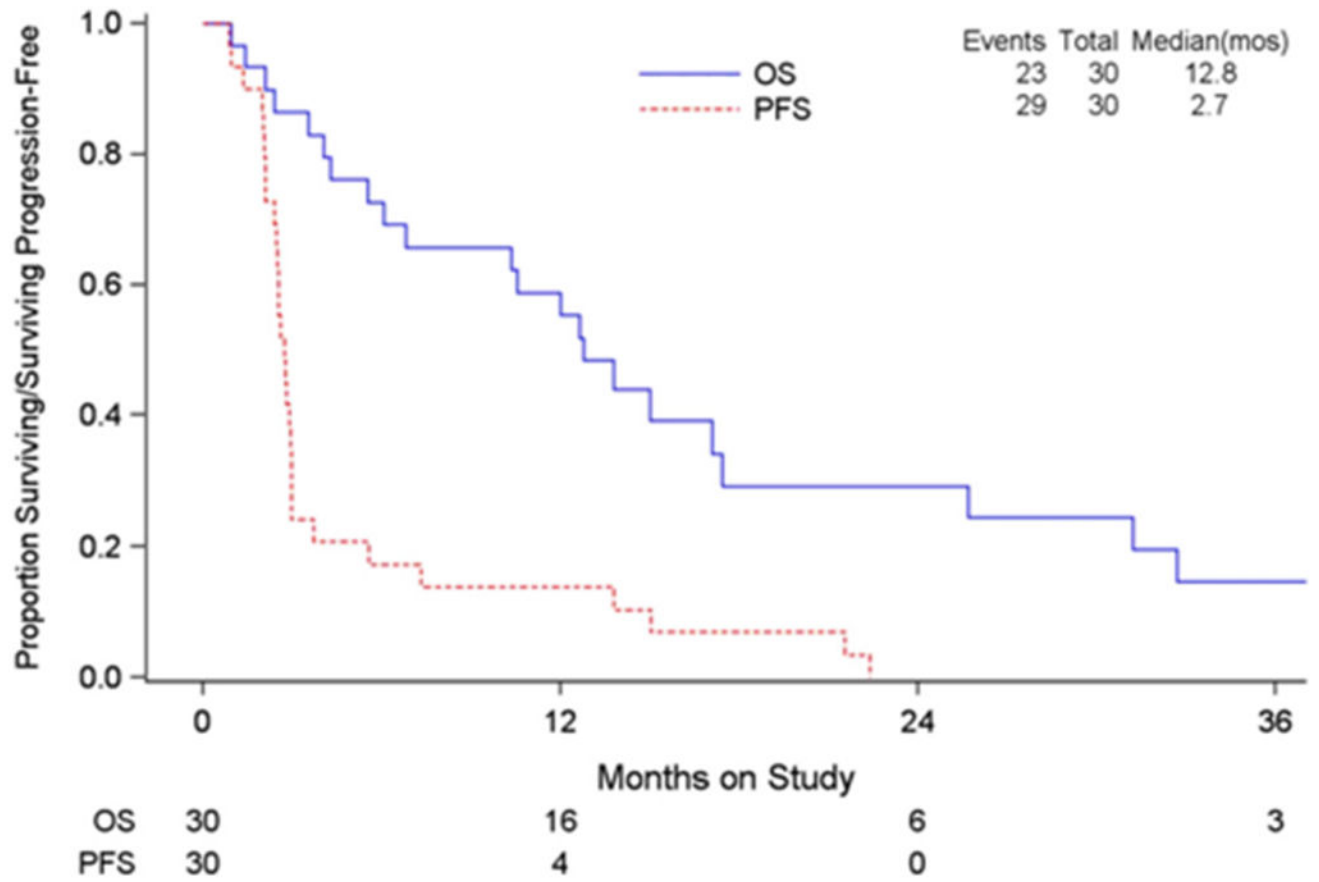
HIGHLIGHTS

- Efficacy of sunitinib in recurrent or persistent clear cell ovarian cancer

- 16.7% of patients had PFS N6months and 6.7% had responses with PFS of 2.7 months.

- Common adverse events were fatigue, hypertension, neutropenia, and anemia.

- Sunitinib was tolerable but had minimal activity.

Fig. 1.
Progression-free and Overall Survival.

Table 1

Patient characteristics.

	Number of patients	**Percent of patients**
Age (y)		
20–29	2	6.7
30–39	1	3.3
40–49	10	33.3
50–59	9	30.0
60–69	7	23.3
70–79	1	3.3
Race		
White	25	83.3
Asian	4	13.3
Unknown	1	3.3
Performance status		
0	18	60.0
1	10	33.3
2	2	6.7
Number of prior chemotherapies		
1	20	67
2	9	30
3	1	3

Table 2

Clinical response to treatment.

Endpoint		Number of patients	Percent of cases
PFS > 6 months	Yes	5	17%
	No	24	80%
	Indeterminate	1	3%
Clinical response	Partial response	2	7%
	Stable disease	4	13%
	Progressive disease	20	67%
	Indeterminate	4	13%

Table 3

Adverse events.

	Grade				
	1	**2**	**3**	**4**	**5**
Blood/Lymphatics					
Anemia	6	12	3	2	0
White Blood Cell Decreased	6	9	3	0	0
Lymphocyte count decreased	2	1	2	0	0
Neutrophil count decreased	8	4	4	0	0
Platelet count decreased	8	3	1	5	0
Cardiovascular					
Hypertension	1	5	4	0	0
Hypotension	0	1	1	0	0
Thromboembolic Event	0	1	2	0	0
Gastrointestinal					
Nausea	15	1	2	0	0
Vomiting	7	2	2	0	0
Abdominal pain	5	4	3	0	0
Rectal hemorrhage					
Nervous system					
Headache	6	2	2	0	0
Stroke	0	0	0	0	1
Renal					
Creatinine increased	0	0	1	2	0
Urinary tract infection	1	0	1	0	0
Acute kidney injury	0	0	1	1	0
Respiratory					
Dyspnea	0	3	2	0	0
Pleural Effusion	0	0	1	0	0
Metabolism/nutrition					
Hypokalemia	1	0	2	0	0
Hypoalbuminemia	1	2	2	0	0
General/Skin					
Fatigue	9	7	4	0	0
Pain	1	2	2	0	0
Palmar-Plantar Erythrodysesthesia Syndrome	2	0	1	0	0

Table 4

Clinical trials for clear cell ovarian cancer.

Agent	Year open	Author, organization	Number of patients	Results/status
Chemotherapy				
Docetaxel-irinotecan [45]	2013	Ueda, Osaka University	62	RR = 53% Disease control rate = 67%
Paclitaxel + carboplatin vs. irinotecan + cisplatin [46]	2010	Takakura, JGOG	99	PFS tended to be longer with irinotecan + cisplatin in small volume disease
Paclitaxel + carboplatin vs. Irinotecan + Cisplatin 47]	2016	Sugiyama, JGOG/GCIG	667	No significant survival benefit was found for Irinotecan + Cisplatin
Biologic				
Sunitinib	2010	Chan, NRG	35	RR = 20%, 6 mo PFS17%
Paclitaxel-carboplatin-temsirolimus	2010	Farley, NRG	90	Completed
Dasatinib	2014	Hyman, NRG	62	Suspended
Nintedanib	2015	Glasspool, NHS	120	Recruiting
Cabozantanib (XL184)	2015	Farley, NRG	NA	Closed after first stage
ENMD-2076	2013	Oza, University Health	36	Recruiting
Everolimus or temsirolimus	NA	Vicus, NRG	NA	Under development
Pazopanib	NA	Glen, NRG	NA	Under development

RR = response rate; PFS = progression-free survival.