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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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HIGHLIGHTS

- Efficacy of sunitinib in recurrent or persistent clear cell ovarian cancer
- 16.7% of patients had PFS >6 months 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.

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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.
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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%.

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