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Review Article

Randomized phase IIB evaluation of weekly paclitaxel versus weekly paclitaxel with oncolytic reovirus (Reolysin®) in recurrent ovarian, tubal, or peritoneal cancer: An NRG Oncology/Gynecologic Oncology Group study☆

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HIGHLIGHTS

- Reovirus when added to paclitaxel is not active in unselected patients with recurrent ovarian cancer.
- Severe neutropenia and respiratory toxicity is more common with reovirus exposure.
- The activity of weekly paclitaxel in recurrent ovarian cancer is confirmed.

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ABSTRACT

Objective. To assess whether the addition of oncolytic reovirus (Reolysin®) to weekly paclitaxel prolonged progression-free survival (PFS) in the treatment of women with recurrent or persistent ovarian, tubal or primary peritoneal cancer.

Patients and methods. Patients with recurrent or persistent epithelial ovarian, tubal, or peritoneal carcinoma, measurable or detectable disease, and three or fewer prior regimens were randomly assigned to paclitaxel (80 mg/m^2 intravenously days 1, 8, and 15 every 4 weeks) or the combination of paclitaxel (80 mg/m^2 intravenously days 1, 8, and 15) plus reovirus 3×10^{10} $TCID_{50}$/day intravenously on days 1–5, both every 4 weeks until disease progression or toxicity. The primary end point was PFS. The study was designed with 80% power for a one-sided alternative at a 10% level of significance to detect a reduction in the hazard by 37.5%.

Results. The study accrued 108 patients, 100 of whom were evaluable for toxicity. Median PFS was 4.3 months for paclitaxel and 4.4 months for paclitaxel plus reovirus (hazard ratio, 1.11; 90% two-sided CI, 0.78 to 1.59; one-sided $P = 0.687$). The proportion responding (overall response rate) to paclitaxel was 20% among 45 patients with measurable disease receiving paclitaxel alone, and 17.4% among the 46 patients treated with the combination. The asymptotic relative probability of responding was 0.87 (90% CI, 0.42 to 1.79). Severe adverse events were more common in the combination regimen than in paclitaxel arm for severe neutropenia (grade ≥ 4, 12%

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versus 0%), and severe respiratory adverse events (grade ≥ 3, 25% versus 2%). No deaths were considered treatment related.

Conclusion. The addition of reovirus to weekly paclitaxel in the treatment of women with recurrent or persistent ovarian, tubal or peritoneal cancer did not sufficiently reduce the hazard of progression or death to warrant further investigation.

Contents

1. Introduction

Few FDA approved options exist for the treatment of recurrent ovarian cancer. In patients with recurrent disease, re-treatment with paclitaxel using a weekly schedule has demonstrated activity, possibly through anti-angiogenic as well as direct cytotoxic mechanisms [1]. Gynecologic Oncology Group (GOG)-0126N demonstrated a 21% objective response rate (and a 46% rate of stable disease) in this population [2].

Reovirus serotype 3-dearing strain (Reolysin®) is a naturally occurring, ubiquitous, non-enveloped human reovirus with a genome that consists of 10 segments of double-stranded RNA. While community-acquired reovirus infection in humans is generally mild and limited to the upper respiratory and gastrointestinal tract, reovirus has been shown to replicate specifically in, and be cytopathic to, transformed cells possessing an activated Ras signaling pathway. The specificity of the reovirus for Ras-transformed cells, coupled with its relatively nonpathogenic nature in humans, makes it an attractive anti-cancer therapy candidate. In transformed cells with mutations of the Ras proto-oncogene (approximately 30–40% of all human tumors), reovirus has been shown to possess cytopathic activity [3]. Activated Ras is present in greater than 20% of ovarian cancers, and appears to be dependent on histology [4]. Importantly, activating Ras mutations are not requisite for reovirus efficacy, since activation or over-expression of regulatory elements in Ras signaling pathways can also lead to antitumor effects from reovirus [3]. In ovarian cancer, it has been shown that increased Ras signaling contributes to pathogenesis seen with reovirus [4].

Given the susceptibility of ovarian cancer cells to reovirus and the safety of IV reovirus in patients with advanced malignancies, reovirus has been investigated using IV and intraperitoneal (IP) administration in patients with recurrent ovarian cancer [5], demonstrating viral replication in peritoneal tumors when reovirus is delivered systemically [6].

Recent preclinical data suggests that reovirus has a synergistic effect when administered with taxanes [7]. In an in vitro model, exposure of cells to reovirus in combination with docetaxel or paclitaxel demonstrated enhanced apoptotic cell death when compared to either agent alone. Furthermore, in a murine model, reovirus monotherapy slowed tumor growth and prolonged median overall survival time compared to control treatment, whereas docetaxel alone had no effect. When administered in conjunction with reovirus, the combined therapy significantly suppressed tumor growth and replicating virus was identified within tumors [8]. Thus, we set out to assess whether weekly paclitaxel, when combined with intravenous reovirus, reduces the risk of disease progression when compared with paclitaxel alone.

2. Methods

This was an open-label prospective randomized phase IIB trial of single-agent weekly paclitaxel compared with weekly paclitaxel plus reovirus (GOG-186-H; ClinicalTrials.gov. Identifier: NCT01166542). Eligible patients included women with measurable (per RECIST 1.1) or detectable persistent or recurrent epithelial ovarian, fallopian tube, or primary peritoneal carcinoma with documented disease progression. Detectable disease required at least one of the following conditions: cancer antigen (CA)-125 at least 2× upper limit of normal (ULN), ascites and/or pleural effusion attributed to tumor, or solid and/or cystic abnormalities on radiographic imaging that did not meet RECIST 1.1 definitions for target lesions. Patients must have had one prior platinum-based chemotherapeutic regimen for management of primary disease containing carboplatin, cisplatin, or another organoplatinum compound. This initial treatment may have included intraperitoneal therapy, consolidation, non-cytotoxic agents or extended therapy administered after surgical or non-surgical assessment. If patients were treated with paclitaxel for their primary disease, this could have been given weekly or every 3 weeks. Patients were allowed to have received two additional cytotoxic regimens for management of recurrent or persistent cancer, with no more than one non-platinum, non-taxane regimen. Treatment with weekly paclitaxel for recurrent or persistent disease was not allowed. Patients were also allowed to have received non-cytotoxic (biologic and/or targeted agents such as bevacizumab) therapy as part of their primary treatment regimen but were not allowed to have received any non-cytotoxic therapy for management of recurrent or persistent disease. Patients with either platinum-sensitive (platinum-free interval [PFI] > 182 days) or platinum-resistant (PFI < = 182 days) disease were eligible. Importantly, patients who had received only one prior cytotoxic regimen (platinum-based regimen for management of primary disease), must have had a PFI of less than 12 months, or had progressed during platinum-based therapy, or had persistent disease after a platinum-based therapy.

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