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Review

Contemporary phase III clinical trial endpoints in advanced ovarian cancer: assessing the pros and cons of objective response rate, progression-free survival, and overall survival

J. Tate Thigpen *

Division of Hematology and Oncology, University of Mississippi Medical Center, Jackson, MS, USA

HIGHLIGHTS

- A low 10-year ovarian cancer survival rate suggests an unmet medical need.
- Overall survival clinical endpoints are confounded by post-progression therapies.
- Progression-free survival is a useful endpoint for phase III ovarian cancer trials.

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ABSTRACT

Among gynecologic cancers, ovarian cancer provides the greatest challenge because 75% to 80% of patients present with stage III/IV disease. Over the last 40 years, a series of large trials conducted by the Gynecologic Oncology Group and other cooperative groups has produced striking improvements in patient outcome; but the majority still dies of their disease. Further research in both the laboratory and the clinic is essential to continued improvement in patient management. Clinical trials, however, have become a major challenge because of issues with trial endpoints. Historically, overall survival (OS) has been regarded as the "gold standard" of endpoints. Lack of effective treatment for patients who progressed on or recurred after front-line therapy allowed trials to avoid obfuscation of OS by post-progression therapy. More recently, studies have identified over 20 agents active against ovarian cancer. Reasonable evidence shows that effective post-progression therapy with multiple lines of active agents can render the survival endpoint uninterpretable. Two other endpoints avoid this problem. The objective response rate, assessed by the Response Evaluation Criteria in Solid Tumors (RECIST), is an accepted endpoint for accelerated approval in ovarian cancer. More importantly, progression-free survival (PFS), measured from study entry to progression of disease, avoids post-progression therapy completely. Without effective post-progression therapy (prior to 1990), data show that PFS is a surrogate for OS. Recent experience with 4 large trials of bevacizumab shows that PFS can be accurately assessed if progression is clearly defined and if timing of assessments is consistent in all study arms. Acceptance of PFS as the optimal endpoint for ovarian cancer trials by investigators and regulatory agencies is crucial to further advances in management because effective post-progression therapy has rendered differences in OS virtually impossible to assess reliably.

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* Division of Hematology and Oncology, University of Mississippi Medical Center, 2500 N State St, Jackson, MS 39216. Fax: +1 601 984 5599.
E-mail address: jtthigpen@att.net.

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Introduction

Ovarian cancer constitutes a unique challenge among cancers of the female genital tract. Of the 3 cancer types that account for more than 90% of gynecologic cancers, only ovarian cancer lacks an effective means of early detection [1]. Over 90% of women with endometrial carcinomas present early with abnormal vaginal bleeding [2] and have International Federation of Gynecology and Obstetrics (FIGO) stage I or II disease. Neoplastic processes of the uterine cervix are generally diagnosed as preinvasive disease by cervical cytology in the asymptomatic woman. In contrast, the most common presenting stage for ovarian cancers is FIGO stage III, and stage III and IV cases together account for 75% to 80% of these malignancies [3].

By far the most common type of ovarian cancer (90%) is epithelial ovarian carcinoma [4], which is thought to arise from celomic epithelium that lines the peritoneal cavity and invests the ovary during development. Because it usually presents as advanced disease, treatment for epithelial ovarian carcinoma is surgical staging and cytoreduction followed by systemic cytotoxic therapy [4]. Research over the last 40 years has significantly altered the picture for patients with epithelial ovarian carcinoma. Landmarks include: (1) showing that surgical bulk reduction can improve outcome [5,6]; (2) identifying activity of cisplatin and carboplatin [7–9]; (3) expanding the therapeutic armamentarium to include over 20 additional active agents [4,10–16]; (4) demonstrating the efficacy of intravenous paclitaxel or docetaxel plus carboplatin, which now constitutes the international standard for initial treatment of ovarian carcinoma [4,8,9]; (5) pinpointing potentially enhanced activity of the intraperitoneal route of administration of chemotherapy in patients with minimal residual disease [17]; and (6) developing targeted therapy for the tumor microenvironment, particularly the antiangiogenic agent bevacizumab [18–21]. These advances, achieved through well-designed clinical trials, have resulted in far fewer patients with massive and uncontrolled ascites and in markedly improved 5- and 10-year survival rates. With an estimated 36% or more of patients alive at 10 years, clear progress has been made, but much work remains to help the up to 64% of patients who recur and require further therapy [3].

Progress in the management of epithelial ovarian carcinoma depends on the demonstration of the efficacy and tolerability of therapeutic approaches in well-designed clinical trials addressing specific questions with a sufficient number of patients to answer those questions. Essential to success is a clear definition of appropriate study endpoints that fall into 3 categories: observational endpoints, patient-reported endpoints, and toxicity endpoints. Most cancer clinical trials have a primary observational endpoint, as well as secondary endpoints from all 3 categories. The most common primary observational endpoints are objective response, progression-free survival (PFS), and overall survival (OS). The ensuing discussion will evaluate the relative merits of each.

Objective response

Assessing objective response requires widely accepted criteria so that the report is clear and understandable. The first attempt at standardization of response assessment, the World Health Organization (WHO) tumor response criteria [22], fell short because criteria for neither the bidimensional method of measurement nor the selection of target lesions were clear. Tumor response rates were poorly reproducible because of inter- and intra-observer variability [23]; modifications of WHO criteria by individual groups resulted in loss of comparability between different studies [24].

These problems led to new criteria: Response Evaluation Criteria in Solid Tumors (RECIST) 1.0 [24]. Important differences from WHO criteria included: unidimensional instead of bidimensional measurements of lesions; a new partial response definition of at least a 30% decrease in the sum of longest dimensions from baseline with confirmation at 4 weeks; complex definitions for measureable and non-measurable disease including small lesions with a longest diameter of <10 mm, ascites, pleural effusions, and cystic or necrotic lesions; selection of up to 5 target lesions per organ and 10 total based on size and suitability for accurate repeated measurements; mandatory noting of non-target lesions (all other lesions or sites of disease) at baseline and on follow-up scans; and new definitions of response.

Support for RECIST came from reported similarities between WHO and RECIST response rates [25–28] and correlation between unidimensional measurements of RECIST and volume measurements by helical CT [29]; but many investigators found RECIST too cumbersome for daily practice [30]. Modifications in 2009 (RECIST 1.1) [31] addressed these issues: assessed target lesions reduced from 5 to 2 per organ; detailed instructions about lymph node assessment; progression of disease based on substantial worsening in non-target disease; and inclusion of [^{18}F]-fluorodeoxyglucose positron emission tomography (FDG-PET) to detect new lesions defining progression.

Criticisms of response as an endpoint

Criticisms of RECIST fall into 4 categories: problems with complexity and consistency of the RECIST criteria, issues related to the arbitrariness of the criteria, questions about appropriateness and reliability of RECIST, and problems in specific circumstances.

Problems with complexity and consistency of the RECIST criteria

The first category of criticism of the RECIST criteria focuses on complexity and consistency. As noted above, RECIST 1.1 addressed complexity concerns [25–33] by enhancing clarity of the response definition, limiting measurement to one dimension, reducing the number of required target lesions, and providing detailed criteria for lymph node assessment. The detailed descriptions of how to apply the criteria in RECIST 1.1 have