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Review Article

Clinical trials in gynecologic oncology: Past, present, and future

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HIGHLIGHTS

- Groundbreaking clinical trials have historically been run through cooperative groups.
- Recent trial design accelerates approval of new agents from phase 1 or 2 settings.
- Biomarkers are essential to move research forward expeditiously.
- Our clinician scientists are well positioned to drive new discoveries to patients.

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ABSTRACT

The Gynecologic Oncology Group has historically performed ground-breaking, practice-changing clinical trials in women's cancers. The current standard of care for initial treatment of ovarian, endometrial, cervical, and trophoblastic cancers was determined by clinical trials completed within this cooperative group structure. For example, trial GOG-0111 set the standard for combining platinum and taxane chemotherapy in ovarian cancer, and more recently GOG-0240 provided evidence for adding bevacizumab to chemotherapy for women with advanced cervical cancer. The landscape of clinical trial design has markedly changed in recent decades, with a clear emphasis on streamlining drug development towards specific patient populations and indications for investigational agents. Translational science in gynecologic cancers can set the stage for rapid and efficient introduction of new therapies for our patients. The gynecologic oncology community of researchers and clinicians is well positioned to enter into the new era of drug development, with breakthrough discoveries increasing each year. It is clear that we must incorporate smarter clinical trial design to get the right drugs to the right patients expeditiously, so we can continue to improve outcome for women with gynecologic cancers.

Contents

1. Introduction

The Gynecologic Oncology Group has historically performed ground-breaking, practice-changing clinical trials in women's cancers.

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2. Current FDA guidance in clinical trials

The FDA has implemented four programs to improve efficiency of the drug development process. These designations include Fast Track, Breakthrough Therapy, Priority Review, and Accelerated Approval (https://www.fda.gov/forpatients/approvals/fast/ucm20041766.htm). The purpose of these expedited programs is to facilitate development and expedite review of drugs that treat serious conditions and fill an unmet medical need, with the goal of getting important new drugs to patients earlier. The seriousness of a condition is difficult to define, but is based on whether a drug can have an impact on measures of clinical benefit, such as survival, physical function, or progression of a disease to a more serious condition.

The Fast Track designation is given to products that have the potential to address an unmet clinical need, provide therapy where none exists or that is potentially better than available therapy. A sponsor may request Fast Track designation at any time during drug development, and the Agency must provide a response to the request within 60 days. This designation is based on preliminary measures of efficacy in the serious condition, and must have a well-delineated development plan that addresses an unmet medical need. The plan should evaluate whether the agent has an ability to provide benefit while reducing toxicity, for example, or an ability to provide benefit in patients unresponsive to alternative treatment. Successful Fast Track designation allows early and frequent communication with FDA throughout the drug development process such as for discussion of endpoints, biomarker development, or other aspects of trial design to support drug approval. Additionally, Fast Track designation permits a sponsor to request "rolling review," whereby completed sections of its biologics license application (BLA) or new drug application (NDA) may be submitted instead of submitting an entire completed application.

For a product to qualify for Breakthrough Therapy, it must hold the promise of demonstrating a substantial improvement over available therapy. This is based on the magnitude of the treatment effect in preliminary clinical studies, which must show an advantage compared to a historical control. For example, rucaparib was granted Breakthrough Therapy designation in April 2015, when clinical data from the ARIEL2 study showed that 65% of patients achieved a RECIST response. This is better than historical control with chemotherapy where response rates are <50% in the third line treatment of women with platinum-sensitive ovarian cancer. The Breakthrough designation allowed the FDA to expedite the review of this drug, and to closely guide the generation of evidence needed to support final approval, which was granted in December 2016. The endpoint must measure an effect on irreversible morbidity or mortality, or on symptoms that represent a serious consequence of the disease process. The FDA defines the most clinically significant endpoint for a cancer indication as overall survival. Endpoints could also include a validated surrogate endpoint, or even a pharmacodynamic biomarker, though these endpoints may not be sufficient in and of themselves for later marketing approval. For example, overall response rate and duration of response may be acceptable surrogates if they are closely linked to improving overall survival with an improvement in quality of life. The Breakthrough Therapy designation permits increased FDA guidance, and is thus more efficient if the drug development program starts in the phase 1 setting. Generally, the FDA recommends a preliminary discussion prior to submission of a Breakthrough Designation Request. Once submitted, a response is provided within 60 days.

Priority Review Designation shortens the review period before FDA takes action on an application to 6 months, from the 10 months under standard review. These applications are chosen on the basis of providing significant improvement to treatment safety or efficacy. Applicants may request priority review, but all applications get assigned a review designation by the Agency. Designation of "priority" does not alter the scientific or medical standard for approval, but does allocate more resources for the review of the benefit: risk assessment in order to shorten the review clock, with the goal of getting safe and effective drugs to patients faster. The Prescription Drug User Fee Act (PDUFA) was first enacted in 1992 in order to collect fees from drug companies applying for approval (http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee). If the data in the application meet the criteria for Priority Review Designation, then the 6-month review period date is set from the time that the initial New Drug Application was completed (www.fda.gov/Drugs/DevelopmentApprovalProcess).

The Accelerated Approval mechanism, enacted in 1992 and modified in 2012, focuses on surrogate endpoints that may be demonstrated earlier than the clinical benefit endpoints used for regular approval. These endpoints could be biomarkers, radiographic images, or other measures that are considered reasonably likely to predict clinical benefit based on supportive scientific evidence. In this setting, reduction of tumor burden is considered reasonably likely to predict a clinical benefit, but can be measured well before learning whether a treatment allows patients to live longer. If considering accelerated approval, post-marketing clinical trials should be underway at the time of approval. These confirmatory trials must have a primary endpoint, such as overall survival, that clearly shows clinical benefit.

3. Implementing these strategies

The FDA approved 80 new drug indications for non-hematologic malignancies between 2011 and 2016 (Table 1). Five of these were for gynecologic cancers. The bevacizumab approval was expanded to include three indications in gynecologic cancers: in combination with chemotherapy for cervical cancer, in combination with chemotherapy for platinum-resistant recurrent ovarian cancer, and combined with platinum-based chemotherapy for platinum-sensitive recurrent ovarian cancer. Two indications were based on clinical trials implemented by the Gynecologic Oncology Group/NRG Oncology. These include GOG-240, for the use of bevacizumab with chemotherapy in advanced cervical cancer; and GOG-213, for the use of bevacizumab with chemotherapy in platinum-sensitive recurrent ovarian cancer [2,3]. Olaparib and rucaparib were initially approved for treatment of women with BRCA-mutated ovarian cancer. The first FDA indication for each of these drugs was based on biomarker-positive cancer: olaparib received its first approval for the treatment of women with germline BRCA mutation, with recurrent ovarian cancer after 3 or more lines of therapy; rucaparib was approved for the treatment of women with deleterious BRCA mutation (germline or somatic) associated advanced ovarian cancer who have been treated with 2 or more prior regimens.

4. Recently completed gynecologic oncology clinical trials

During the time period 2011–2016, the Gynecologic Oncology Group/NRG Oncology published 58 peer reviewed articles reporting

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