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Review Article

Moving forward with actionable therapeutic targets and opportunities in endometrial cancer: A NCI clinical trials planning meeting report

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HIGHLIGHTS

- Consolidation of current molecular uterine cancer knowledge and optimization of molecular subgrouping
- Dissection of molecular subgroups for actionable molecular and/or clinicopathologic findings
- Identify and select agents for actionable molecular targets for phase II/III evaluation
- Consideration of novel and alternative trial designs to advance molecular diagnostic grouping

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ABSTRACT

The incidence of endometrial cancer (EC) in the U.S. has been rising, from an estimated annual incidence of 49,560 in 2013 to 61,380 in 2017. Meanwhile, the SEER-based relative survival of women with EC in the U.S. has remained flat [82.3% from 1987 to 1989, 82.8% from 2007 to 2013] and our recent increased understanding of EC biology and subtypes has not been translated into therapeutic advances. The U.S. National Cancer Institute (NCI) therefore convened a Uterine Clinical Trials Planning Meeting in January 2016 to initiate and accelerate design of molecularly-targeted EC trials. Prior to the meeting a group of experts in this field summarized available data, emphasizing data on human samples, to identify potentially actionable alterations in EC, and the results of their work has been separately published. The Clinical Trials Meeting planners focused on discussion of (1) novel trial designs, including window-of opportunity trials and appropriate control groups for randomized trials, (2) targets specific to serous carcinoma and promises and pitfalls of separate trials for women with tumors of this histology (3) specific recommendations for future randomized trials.

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1. Introduction

The Cancer Therapy Evaluation Program of the National Cancer Institute held a clinical trials planning meeting (CTPM) in 2016, *Designing Targeted Trials for Targeted Endometrial Cancer Populations Using Targeted Agents*, through which to advance clinical trial development to address unmet needs for women with endometrial cancer (EC). The goals of the meeting were to address diagnostic strategies for molecular subtypes of EC, to evaluate biomarkers to facilitate targeted therapies,

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and to develop a research agenda across all phases of clinical study for evaluation of agents that target molecularly defined pathways, alone or in combination with standard chemotherapy in EC, and for translational directions to further advance knowledge of –omics characterization of endometrial cancers.

2. Considerations on trial design: the window of opportunity (WoO) trial

WoO trials have emerged as a study design for focused drug evaluation [1]. The most common objective of WoO trials is to assess pharmacodynamic or surrogate endpoints to justify further study of the agent in question [2]. Endometrial cancers are prime candidates for WoO trials as surgery remains a mainstay of primary treatment. A short exposure to a promising agent that may accelerate understanding of the targeted agent on the tumor and its molecular targets can be accomplished as part of standard of care surgical intervention planning. For example, this type of proof of concept study could be built into the pre-surgical waiting time occurring between office diagnosis and definitive surgery for EC patients. The overall patient exposure to drug is limited in WoO studies and should neither cause toxicity nor compromise standard of care surgical and medical therapeutic interventions [4].

Several WoO trials have been performed in EC, including one through the NCI National Clinical Trials Network (NCTN) [3]. A number of surgical WoO trials have examined the effects of metformin on the endometrium, based upon the scientific rationale that metformin reduces cellular proliferation by inhibition of the PI3K-AKT-mTOR pathway [5–8], commonly dysregulated in EC. Those studies focused on measurements of cellular proliferation in metformin-exposed endometrioid EC, and showed that short-term pre-surgical metformin exposure caused a reduction in the Ki-67 proliferation index. This finding led to an ongoing randomized clinical trial of metformin in the advanced disease setting (NCT02065687). GOG-0211 was a WoO study of medroxyprogesterone acetate for endometrioid EC patients and demonstrated downregulation of progesterone receptor (PR), KI67, and bcl-2 [9]. Thus, WoO trials offer a novel opportunity to accelerate drug development in EC, an area of major unmet need [10], while improving our understanding of the biology driving this disease.

Close attention should be paid to a number of factors in design of these trials. WoO studies are opportunistic trials with no therapeutic intent [2,11]. Thus, the patient risk-benefit ratio must be considered and very little toxicity can be tolerated. Moreover, insurance coverage in the U.S. is limited when there is no therapeutic intent, and funding for the research interventions is needed. The translational design of these studies is based upon early detection of a signal of activity or preclinical science to support the investigation and requires pharmacodynamic assays to prove target and/or tumor modulation. The biomarkers and assays used need be well qualified, robust, accurate within the tested dynamic range, precise, reproducible, and sensitive [2]. The amount and type of tissue available from an initial biopsy and the preanalytical quality control of pre-and on/post-treatment specimens must be considered. Moreover, a convenience sample of ECs will likely include a high percentage of low grade, early stage tumors that are unlikely to metastasize, and may be of less interest for anti-cancer drug development. Endometrial sampling is the most common means of pre-surgical diagnosis for EC, although core or laparascopic biopsies may be obtained in more advanced cases. These will be compared with a surgical specimen in most gynecologic cancer WoO studies, which may affect analysis of some biomarkers. Completion of a WoO trial needs to be timely to remain of interest for drug development, and may require considerable multidisciplinary collaboration and logistical coordination to recruit patients, and process and analyze tissue in real time [12].

2.1. Recommended directions for high-priority WoO trials in EC

Hormonal intervention was the only FDA-approved targeted treatment for EC until after the CTPM when immune checkpoint inhibition for metastatic/recurrent microsatellite unstable (MSI) tumors, including a percentage of ECs, was approved. Sex hormones are implicated in endometrial carcinogenesis directly or via influencing other hormones and metabolic pathways [13]. There remains a significant gap in understanding the relationship between expression of PR or estrogen receptors (ER), the response rate to hormonal therapy, and the mechanisms involved in treatment resistance. Responses to progestins remain low, ~20–25% with few durable remissions [14]. This may be due to low PR expression at baseline or loss of PR as a response to progestin therapy, as seen in the GOG-0211 study [9].

Histone deacetylases (HDACs) are involved in the maintenance and function of chromatin structure [15]. Acetylation of ER and PR is emerging as a mechanism to regulate their expression. HDAC overexpression is seen frequently in EC and may lead to epigenetic silencing of hormone receptors [16]. Epigenetic modulators, such as HDAC inhibitors, may restore expression of down-regulated hormone receptors [17]. This information led to the development of NRG GY011, a WoO study randomizing women to the combination of the HDAC inhibitor, entinostat, with medroxyprogesterone acetate (MPA), or MPA alone (NCT03018249). The primary endpoint will be assessment of PR based upon the hypothesis that concomitant administration of entinostat will either maintain or reactivate PR expression. Secondary objectives include modulation of Ki67 proliferation index. Further WoO studies evaluating the unique biology of endometrioid EC are under development.

Serous EC has a distinct biology characterized by deleterious somatic *TP53* mutation, early dissemination, poor clinical outcome, and both histologic and genomic changes similar to those seen in high grade serous ovarian cancers [18]. WoO and early phase trial exploration were endorsed for this moderately rare EC subtype. The role of genomic instability and DNA repair dysfunction is unknown in serous EC, and both are likely important due to the similarity in copy number variability to high grade serous ovarian cancer [19]. Triapine is a small molecule ribonucleotide reductase inhibitor that exerts its antineoplastic activity by inhibiting DNA synthesis and repair through blocking production of necessary deoxyribonucleotides [20]. It has been shown to phenocopy homologous recombination dysfunction caused by loss of BRCA1/2 function [21]. Triapine arrests cells at the G1/S checkpoint in the presence of abnormal p53, disrupting DNA replication and cell duplication. A WoO trial was proposed to assess the effect of triapine on serous EC carcinomas prior to definitive debulking surgery (NRG GY0013). Novel biomarkers assessing cell cycle arrest using immunohistochemistry will be evaluated. The CTPM endorsed WoO studies in EC as methods through which to enhance scientific and clinical knowledge of EC and from which to spur clinical development of promising directions.

3. Defining the appropriate control regimen for metastatic, recurrent endometrial cancer

Doublet therapy with carboplatin and paclitaxel is currently the international standard of care for first recurrence or primary metastatic EC [22]. This was established following a series of studies investigating regimens with a doxorubicin backbone in patients with chemotherapy-naïve recurrent or metastatic EC (Table 1). The addition of either cyclophosphamide or cisplatin resulted in a significant prolongation in progression-free survival (PFS), without improving OS [23,24]. Paclitaxel as a single agent demonstrated an overall response rate (ORR) of 35%. It was then examined in a triplet regimen with doxorubicin and cisplatin (TAP; GOG-0177), and then as a doublet in GOG-0209, comparing TAP to carboplatin and paclitaxel (TC). The latter trial included non-measurable disease and was designed as a non-inferiority phase 3 trial. The doublet yielded similar median OS of over 36 months in the

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