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Translational research in the Gynecologic Oncology Group: Evaluation of ovarian cancer markers, profiles, and novel therapies ☆

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ABSTRACT

Objectives. To review the translational research (TR) performed in the Gynecologic Oncology Group (GOG) to evaluate ovarian cancer markers, profiles and novel therapies.

Methods. Prospective trials with stand alone or embedded TR objectives involving patient and specimen accrual as well as retrospective studies using banked specimens and resources were and continue to be performed in the GOG. Appropriate statistical methods are employed to evaluate associations with clinical characteristics and outcomes including tumor response, adverse events, progression free survival and overall survival.

Results. Highlights are presented for some of the collaborative and multidisciplinary TR conducted with the GOG to evaluate markers, pathway and novel therapeutics in epithelial ovarian, primary peritoneal and/or fallopian tube cancer. For example, in GOG 111, high immunohistochemical (IHC) expression of cyclin E was associated with a shorter median survival (29 versus 35 months) and an increased risk of death (hazard ratio [HR]=1.4, 95% confidence interval [CI]=1.0–2.1, p=0.05). In GOG 114/132, non-detectable immunoblot expression of maspin was associated with debulking status (p=0.034) and an increased risk of disease progression (HR=1.89, 95% CI=1.04–3.45, p=0.038) and death (HR=1.99, 95% CI=1.07–3.69, p=0.030) while high CD105-microvessel density (MVD), but not CD31-MVD in tumor was associated with increased risk of disease progression (HR=1.873, 95% CI=1.102-3.184, p=0.020) but not death. In GOG 172, low IHC expression of BRCA1 was associated with advanced stage (p<0.001), serous histology (p<0.001) and a reduced risk of disease progression (HR=0.64, 95% CI=0.42–0.96) and death (HR=0.51, 95% CI=0.32–0.83) while the CA/AA versus CC genotypes in C8092A in ERCC1 were associated with an increased risk of disease progression (HR=1.44, 95% CI=1.06–1.94, p=0.018) and death (HR=1.50, 95% CI=1.07–2.09, p=0.018).

Conclusions. The GOG has an extensive TR program that provides clues regarding the molecular and biochemical mechanisms of disease, treatments and outcomes in women with or at risk for a gynecologic malignancy.

Introduction

Translational research (TR) is the bridge between clinical research and basic science that provides clues regarding the molecular and biochemical mechanisms of disease, treatments, and outcomes in clinical trials and the rationale for integrating advances in oncology, science, technologies, and drug development into clinical trials and practice. Given the plethora of agents and modalities available for testing in clinical trials, coordinated and collaborative approaches are needed to move the most promising regimens through the drug development process as rapidly and efficiently as possible. Issues such as costs, reimbursements, and access must also be considered during the drug development process because it is not sufficient to define new standards of care if the more effective treatments cannot be adopted into the continuum of clinical practices in the community.

The Gynecologic Oncology Group (GOG) is a multidisciplinary and international Cooperative Trial Group with a TR program that evaluates markers and profiles with potential diagnostic, prognostic, and predictive values in prospective trials involving patient and specimen accrual as well as retrospective studies using banked specimens and resources. The GOG recognizes that TR is a critical element of cooperative group clinical trials in the 21st century and the success of these studies requires the integration of objectives that are scientifically sound and hypothesis-based; standard operating

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procedures and training that permit member institutions to submit high-quality data and specimens; experienced and funded laboratories with appropriate expertise and validated conventional and high throughput assays; and an infrastructure with well-annotated specimens and resources for cutting-edge TR that improves clinical management, outcomes, and quality of life. This review starts with overviews about cancer biology, signal transduction, and cancer therapeutics and then provides highlights of some of the collaborative and multidisciplinary TR conducted with the GOG to evaluate markers, pathway, and novel therapeutics in ovarian, primary peritoneal, and/or fallopian tube cancer. Ultimately, GOG phase II and III trials will selectively treat and manage patients based on markers and profiles, and personalized medicine will become the new standard of care for women with gynecologic malignancies.

Cancer biology

The Cancer Genome Atlas (TCGA) project in ovarian cancer is beginning to release data that is confirming that epithelial ovarian cancers (EOCs) exhibit extensive molecular heterogeneity with alterations in numerous pathways including oncogenes, tumor suppressors, cell cycle regulation, and DNA repair. EOCs exhibit aneuploidy, chromosomal alterations, genomic instability, mutations, amplifications, overepxression, amplifications, silencing, modifications, splicing, and epigenetic mechanisms as well as natural and induced sequence variations. Genomic and epigenetic alterations not only drive tumorigenesis, invasion, metastasis, and disease progression but also affect which patients will or won't respond to specific treatments or experience adverse events. Among the hundreds of defects and alterations observed within the tumors in individual patients with EOC, most are likely passengers while only a fraction are species-specific operators (drivers). Identification of the casual drivers in individual EOC patients will enable us to design more effective marker-driven clinical trials that select the right drugs for the right patients.

Although the molecular classification of EOC clearly represents a landmark advance for women with a diagnosis of EOC or increased risk of this disease, the more challenging work lies before us. Effective treatments with long-term clinical benefit will not only require sustained inactivation or recontrol of the critical drivers of tumorigenesis operating in a particular cancer patient but must also anticipate and counteract natural feedback loops, redundant, and divergent genes and pathways as well as innate and acquired resistance mechanisms that are differentially induced in select EOC patients. This includes drug efflux, metabolism, detoxification, clearance along with DNA repair pathways, expression, posttranslational modifications, silencing, alternative splicing, isoform-switching, and epithelial–mesenchymal transitioning, for example. It is also becoming clear that a number of the molecular defects and mechanisms operative in EOC vary more by cell type and grade than by disease site. A number of clinical trials are already focusing eligibility criteria on select histologies within or across disease sites.

Signal transduction

Tumorigenesis, invasion, metastasis, and disease progression can be controlled of membrane-bound, cytoplasmic, and nuclear receptors that can be activated by ligands. After activation, receptors dimerize or oligomerize and undergo conformational changes, autophosphorylation, and phosphorylation of signaling molecules that ultimately regulate transcription, translation, and posttranslational modifications as well as processes affecting cell proliferation, maturation, contact, adhesion, migration, invasion, survival, resistance, and the production and secretion of growth factors, cytokines, chemokines, and soluble receptors (Figs. 1A and B). These autocrine, paracrine, and systemic factors then affect different cells in the tumor microenvironment and distant sites, thus further regulating cancer progression, angiogenesis, vasculogenesis, permeability, immune function, as well as the efficacy and toxicities associated with cancer treatments.

Inappropriate receptor activation promotes tumorigenesis and can be induced by a number of mechanisms including overexpression of autocrine and paracrine factors. Receptors can also be mutated causing constitutive activation in the absence of ligand binding or be overexpressed via gene amplification, transcriptional activation, or posttranscriptional mechanisms that typically require ligand availability and binding for activation. Cross talk between different receptor super families can also activate receptors by a ligand-independent mechanism. Cancer progression, invasion, and metastasis are promoted by the amplification, mutation, or overexpression of signaling molecules downstream from receptors. Various cell types within the tumor microenvironment can be induced to secrete proinflammatory factors that stimulate the vasculature to recruit leukocytes to the tumor. After activation, these tumor-associated leukocytes can release factors that recruit more inflammatory cells and stimulate angiogenesis and neovasculogenesis to sustain tumor growth, promote disease progression, and facilitate tumor invasion and metastasis. Schematics are provided for p53 (Fig. 1C), cell cycle regulation (Fig. 2A), effects of genotoxic stress (Fig. 2B), nucleotide excision repair (Fig. 2C), and BRCA1 (Fig. 2D) because these pathways are the subject of a number of TR studies conducted by the GOG.

Cancer therapeutics

Insights into the molecular and biochemical mechanisms operative in cancer development, progression, and metastasis have uncovered a wide array of molecules in tumor cells and/or the tumor microenvironment including stromal cells, endothelial cells, endothelial precursor cells, pericytes, and immune cells that can be targeted therapeutically. Among these agents are the molecular targeting therapies that inhibit receptor tyrosine kinases, nonreceptor tyrosine kinases, serine/threonine kinases, transferases, proteases, as well as other enzymes, processes, and/or pathways. Some of the molecular targeting therapies are selective inhibitors, while others are dual inhibitors or multiple inhibitors (Table 1). Figs. 1A and B provide a few examples of molecular targeting agents that can inhibit epidermal growth factor (EGF), EGF receptor (EGFR)$^{ErbB1/Her1}$, ErbB2^{Her2}, vascular endothelial growth factor-A (VEGF-A), VEGF receptor (VEGFR), or downstream signaling molecules. A number of these agents are being evaluated in human EOC and specifically in GOG clinical trials as illustrated in Figs. 1A and B. In addition to the molecular targeting agents, there is an arsenal of traditional cytotoxic anticancer drugs (Table 2). Alkylating agents and microtubule inhibitors have been particularly effective in EOC. Despite high initial response rates to first-line treatment and rechallenge with platinum agents and taxanes, about 30% of women with advanced-stage EOC fail to respond to initial platinum–taxane-based chemotherapy, and 5-year survival remains below 40% for women with advanced-stage EOC who underwent surgical staging and cytoreduction.

TR in phase III protocols

See below for highlights of some of the retrospective and prospective TR conducted in GOG phase III ovarian, primary peritoneal, and/or fallopian tube protocols that have completed accrual.

GOG 111 protocol

GOG 111 was a Cancer Therapy Evaluation Program (CTEP)-sponsored, randomized phase III protocol by McGuire et al. [1] that showed improvements in response rate ($p = 0.01$), progression-free