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Introduction: moving beyond chemotherapy

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Preface

Introduction: moving beyond chemotherapy

Epithelial ovarian cancer and related cancers arising in extrauterine Mullerian epithelium are generally chemosensitive—particularly to the platinum drugs, cisplatin and carboplatin, that form the backbone of first-line treatments upon diagnosis even at early stages. Doublets of platinums with paclitaxel have represented the standard-of-care since the late 1990s, with further notable advances taking place by intraperitoneal administration (in Gynecologic Oncology Group studies) after optimal surgical cytoreduction is achieved, and by divided doses of paclitaxel (in a Japanese GOG study). Adding another agent to improve on these results has otherwise proven to be quite challenging. Nevertheless, continued forays into introducing 'targeted therapies' are beginning to bear fruit, and form part of this *Translational Cancer Research* (*TCR*) supplement. The purpose of this supplement is to provide a summary of the advances in tumor biology and a glimpse into where targeted therapeutics are moving, and their successes to date.

In overcoming the challenges faced during the past decades, awareness of the heterogeneity encompassed by the diagnosis of ovarian cancer represents the first step. Dubeau describes how current understanding of the pathogenesis, molecular alterations and features, and clinical behavior of extrauterine Mullerian tumors has helped to guide the treatment of this disease beyond standard chemotherapy. The development of ovarian cancer mouse models and xenograft models summarized by Hasan, Ohman and Dinulescu has further offered insight into tumorigenesis and therapeutic options. In fact, clinicopathologic studies of low grade serous and mucinous cancers described by Gershenson have focused on targeted therapies and are already starting to replace chemotherapy, which historically has had limited activity in these histologic subtypes. In high-grade serous cancer, The Cancer Genome Atlas (TCGA) findings and its clinical implications analyzed by Verschraegen and her basic science team have not only helped to better understand the biology of most common ovarian cancers but also, have reinforced the vast heterogeneity of genome mutations—a feature that accounts both for the chemosensitivity of the disease and for many of the difficulties encountered in targeting a narrow set of signaling pathways.

Fortunately, these greater insights into tumor biology are already refining our therapeutic options. Kwa and Jandial describe how one might further capitalize on the successes of intraperitoneal chemotherapy's superiority to standard intravenous chemotherapy following primary optimal debulking surgery for high grade serous cancers—targeted therapies may assist in achieving greater drug penetration and drug delivery into peritoneal nodules. Anti-angiogenesis with bevacizumab has impacted on platinum-resistance and the United States Food and Drug Administration (FDA) recently approved it as one of two targeted agents for patients with recurrent ovarian cancer: bevacizumab, and is joined by olaparib, a poly (ADP ribose) polymerase (PARP) inhibitor in heavily pretreated BRCA mutated patients. Multiple other trials targeting angiogenesis are summarized by Coleman's group, and trials of PARP inhibitors are discussed by Frey and Pothuri and will undoubtedly lead to further insight into the role of these pathways in ovarian cancer proliferation and resistance to chemotherapy.

Preclinical studies have demonstrated derangements in several other pathways, which are currently being investigated in clinical trials: Musa and Schneider have summarized the phosphoinositidyl-3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathway in ovarian cancer, which may prove to be of benefit in this disease. We provide an overview of studies targeting the human epidermal growth factor receptor 2 (HER2/*neu*) and the epidermal growth factor receptor (EGFR) pathways that unfortunately, have proven to be disappointing to date. Identifying mechanisms of resistance to target inhibition may help guide us in a second generation of trials. Other approaches for improving outcomes include targeting the folate receptor, which is summarized by Lutz, and improving on the standard taxane/platinum doublet by adding targeted agents, including tyrosine kinase inhibitors, Src kinase inhibitors, and histone deacytelase (HDAC) inhibitors, as described by Kudlowitz.

Ultimately, ovarian cancer still remains the leading cause of gynecological cancer related death and we must continue to work to improve outcomes for our patients. The articles included in this supplement are written by some of the key leaders in this field and address the developments and challenges described above. We have started to move beyond chemotherapy and it is our hope that future research will move us into a new 'era' of treating ovarian cancer with improved and novel therapeutic agents.

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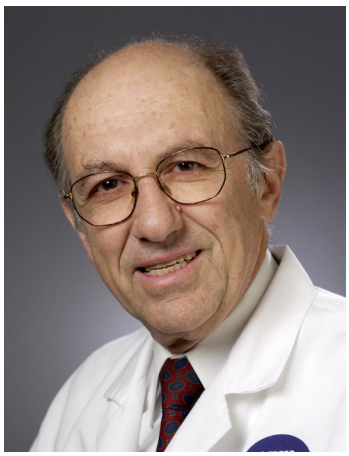

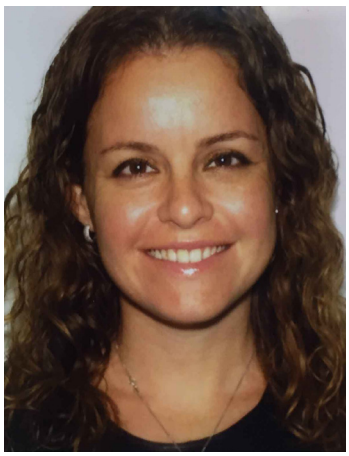

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