Ovarian cancer in 2010

"This issue of Therapy *reviews ongoing studies on numerous fronts that have the potential to further improve outcomes related to the prevention, diagnosis and treatment of patients with ovarian cancer."*

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Ovarian cancer remains responsible for the most gynecologic cancer-related deaths in women worldwide, and is the fifth leading cause of death overall [1]. The careful development of a series of randomized trials involving numerous patients, investigators and clinical trial groups encompassing many countries have led to an improvement in median overall survival from 1 year in 1975 to approximately 5 years in 2009 for optimally debulked patients with stage III disease [2–4]. This issue of *Therapy* reviews ongoing studies on numerous fronts that have the potential to further improve outcomes related to the prevention, diagnosis and treatment of patients with ovarian cancer.

Improved cancer outcomes are associated with the need to further improve fertility preservation techniques for women with ovarian cancer. However, a recent study suggested that only 47% of oncologists refer cancer patients of childbearing age to a reproductive endocrinologist [5]. This important issue is reviewed by Herzog and colleagues [6]. They review data supporting the appropriate setting to consider fertility preservation for patients with low malignant potential, germ cell tumors and early-stage epithelial ovarian cancer. The lack of large randomized studies to direct choices in an evidence-based fashion is acknowledged, but the careful interpretation of smaller studies has allowed the development of consensus-based recommendations. In addition to the technical aspects of fertility-sparing surgery, the lack of an apparent negative effect of modern adjuvant therapy on subsequent fertility is also discussed [7]. The second part of the review addresses the emerging technology with regard to fertility preservation options. Embryo, oocyte and ovarian tissue cryopreservation allow for a wide variety of options not heretofore possible. The retrieval of oocytes also no longer requires surges in estrogen, which is important in patients with potentially estrogen-sensitive malignancies [8]. In addition, *in vitro* maturation techniques are further improving the viability of oocyte and embryo cryopreservation specimens [9]. The challenges presented here are how to integrate these technologies in a way that does not compromise cancer outcome, and this requires a careful collaboration of medical and gynecologic oncology with reproductive endocrinologists and maternal–fetal specialists.

The association with improved survival and optimal primary surgical cytoreduction remains well established and recent data support the goal of complete surgical cytoreduction as having the best outcome [10]. As with many important questions in oncology, the role of secondary surgical cytoreduction is not as well defined due to a variety of factors, including patient heterogeneity, physician and patient biases, and the lack of multiple randomized prospective trials. Chi and colleagues summarize the available data supporting this approach [11]. Theoretical support is derived from older mathematical models suggesting that there is an increased rate of growth (hence chemotherapy sensitivity) in small-volume tumors, and decreasing the number of tumor cells lessens the chance for resistance-inducing mutations. The case is made that the goal of secondary surgical cytoreduction must be a complete resection if a benefit is to be achieved. The article goes on to examine selection criteria proposed to predict a successful surgical outcome (utilizing the DESKTOP I and II trials), estimates the frequency with which this can be accomplished and, finally, identifies the prognostic factors to predict prolonged survival after secondary surgical cytoreduction [12]. Most importantly, both the AGO and GOG are conducting large randomized trials addressing the value of secondary cytoreduction followed by chemotherapy versus chemotherapy only, and participation in these trials is essential to define the role of this potentially important approach for patients.

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Many investigators in cancer medicine have recognized that we cannot continue the serendipitous combination of numerous novel agents in large randomized clinical trials in a stepwise fashion and make necessary progress. Birrer and colleagues provide a thorough review of techniques allowing the evaluation of personalized therapy for patients with ovarian cancer [13]. The heterogeneity of ovarian tumors beyond grade and histology is becoming increasingly clear. Genomic analysis of low malignant-potential tumors and invasive low-grade tumors show them to be distinct from high-grade serous tumors. Initiating molecular events are also being characterized, such as the necessity of activation of the RAF/RAS/MEK pathway in low-grade tumors, which is relevant as inhibitors of these pathways are now available for testing [14]. In parallel, they review the data identifying which patients harboring EGF mutations with lung cancer respond to EGF-targeted therapy, and how gene profiling can predict the behavior of patients with breast cancer [15–17]. The need to apply similar approaches to patients with ovarian cancer as a way to direct future research efforts is obvious. Finally, they review genomic characterizations showing the similarity of gene expression in ovarian, endometrial and renal clear cell carcinomas as one example that targeting a specific molecular pathway may be more rational than directing therapy based on the site of origin [18]. This will serve to build needed bridges across diseases and promote collaborations with colleagues in other disciplines.

No area continues to grow more steadily than our understanding of genetic mutations and the clinical implications of such findings in patients. Daly reviews the current status of using laparoscopic prophylactic oophorectomy as a way to reduce the risk of ovarian carcinoma in patients who harbor the BRCA1 and -2 mutations [19]. They discuss a number of case–control, retrospective and prospective studies, including a recent meta-analysis including 2480 patients with a pooled estimate risk-reduction ratio of 0.21 (95% CI: 0.12–10.38) [20]. More information is needed in order to understand if there is a differential in the risk reduction for patients with one mutation over another [21]. Data are presented regarding the timing and type of surgery, as well as the need to remove and carefully section the fallopian tubes along with the ovaries [22]. The latter recommendation has sparked a new area of research implicating the fallopian tube as the possible nidus for ovarian cancer development, which has potential implications both for screening, with its p53 mutation signature, and treatment [23]. Finally, the lack of definitive data regarding the long-term physiologic consequences of surgical menopause is discussed. This story is far from complete as large population-based studies examine the rates of cardiovascular disease, osteoporosis, metabolic syndrome and cognitive decline in patients across various ages having bilateral salpingo-oophorectomy. The notion that ovaries in postmenopausal patients are nonfunctional is not straightforward and additional study is required to clearly articulate long-term benefits and risks.

On the treatment front, Oza and colleagues summarize the emerging data with bevacizumab and other antiangiogenic approaches for patients with ovarian cancer [24]. This class of agents continues to produce response rates and disease stability durations that set them apart from others [25–27]. On the other hand, side effects that include hypertension and bowel perforation require ongoing analysis to define patients who may be at higher risk [28,29]. Oza emphasizes the large randomized trials in both the primary and recurrent setting, all of whom will have preliminary data available shortly. There will also be many questions to consider that will require additional studies; will there be an overall survival benefit? If not, is a strategy that prolongs progression-free survival only sufficient? How long should bevacizumab be given for? Should it be continued longer than 15 months, or to disease progression, or for life? Is the phenotype of relapsed disease more virulent when bevacizumab is discontinued? Finally, is the 'cure' proportion improved with prolonged bevacizumab use? One logical question that is being addressed in upcoming cooperative group trials is how to combine intraperitoneal therapy safely with bevacizumab-containing treatment.

Editorials in this issue provide insights into two interesting areas. Freuhauf addresses the current status of utilizing *in vitro* assays in determining optimal chemotherapy agents based on tumor-specific biology [30]. This is a longstanding goal that has not been fully realized. He raises the interesting point that if *in vitro* assays are to be accurate, the next generation of them must take into account the microenvironment surrounding the tumor cells and address disparate issues, including tumor hypoxia and the crosstalk with other cellular elements, such as vascular endothelial cells [31,32]. Scholler looks into the possibilities now at hand of screening large libraries of recombinant antibodies to isolate and optimize targeting reagents for the *in vitro* and *in vivo* diagnosis and treatment of ovarian cancer [33]. She reviews the

characteristics that these antibodies have that may confer advantages over those derived in mouse models or their humanized counterparts [34].

Finally, an opinion article by Markman offers a unique perspective on the randomized data suggesting that platinum-based combination retreatment is superior to single-agent therapy for patients with platinum-sensitive relapse [35]. A recent study further suggests that liposomal doxorubicin with carboplatin is superior to its combination with paclitaxel [36–38]. By analyzing the reported treatment histories of patients in these studies, Markman offers the opinion that while the data suggest that combination platinum-based chemotherapy is superior to single-agent platinum retreatment, it is unknown if the planned sequential administration of a platinum agent followed by another active agent may be as effective with less adverse effects. He proposes this as a reasonable trial end point for future study.

The articles in this themed issue of *Therapy* focus on numerous important areas affecting patients at risk for or diagnosed with ovarian cancer. It is the incremental progress in each area that will continue to forge collaborations and drive subsequent clinical trial development, and that will continue to improve the outcome for women with ovarian cancer in a meaningful way.

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