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Achievements, Investigations in Gynecologic Oncology Explored

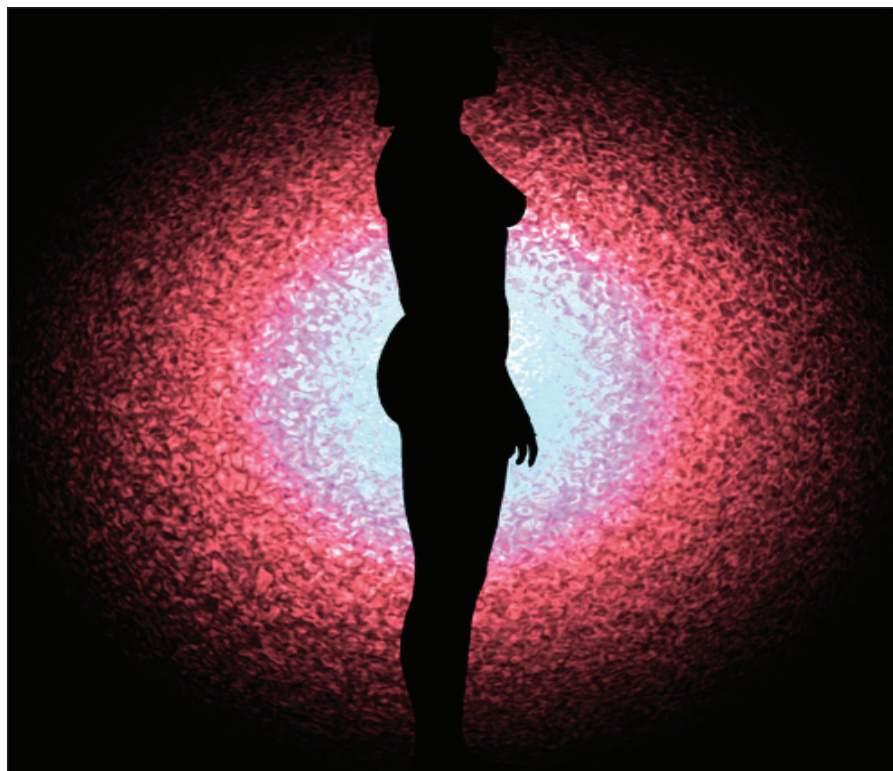
BY JENNIFER LEAH MCNALLY, MD, & JONATHAN S. BEREK, MD, MMS

According to the American Cancer Society's most recent data, each year approximately 105,890 women are diagnosed with gynecologic cancer and 30,890 women die from it (*CA Cancer J Clin* 2016;66:7-30). These data can be further broken down by age and stage of disease. In recent years, there have been many exciting developments in the field of gynecologic oncology. The following summary of these advances celebrates these achievements and highlights areas for future investigation.

Ovarian Cancer

Ovarian cancer is the fifth leading cause of cancer death among women. It is generally diagnosed at an advanced stage because the presenting symptoms are non-specific and screening modalities such as pelvic ultrasonography and CA-125 testing have proved ineffective.

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Benefits of Panobinostat for Multiple Myeloma

BY MEERI KIM, PHD

Throughout the past decade, dramatic advancements in treatment have improved overall survival for patients with multiple myeloma and particularly for those in older populations. Specifically, developments of new drugs that fall into two classes—proteasome inhibitors and immunomodulatory drugs (IMiDs)—contributed to better outcomes through lowered toxicity and a more rapid control of disease at the outset.

Despite the success of these agents in initial therapy, a number of patients still progress following treatment. A new subgroup analysis using data from the PANORAMA 1 clinical trial has found panobinostat, a potent pan-deacetylase inhibitor, in combination with bortezomib and dexamethasone, has the greatest benefit for patients who have received two or more prior regimens.

Progression-Free Survival Benefit

PANORAMA 1 consisted of a randomized, double-blind, phase III study of 768 patients with relapsed or relapsed and refractory multiple myeloma. The combination of panobinostat plus bortezomib and dexamethasone led to an increase in progression-free survival as compared to placebo plus bortezomib and dexamethasone.

This subgroup analysis compared patient outcomes in the trial according to prior treatment, either an IMiD, bortezomib plus an IMiD, or two or more regimens including bortezomib and an IMiD. When compared to the treatment with placebo in place of panobinostat, results indicated a clear

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Physicians Experience Cost and Time Burdens of Tracking Quality

BY PEGGY EASTMAN

The evolving U.S. health care system is requiring physician practices to spend increasing amounts of money and time

to track, document, and report quality measures, according to a news briefing here sponsored by *Health Affairs* at the National Press Club, Washington, DC.

This increasing cost and time burden, which also has been highlighted by the Association of Community Cancer Centers, draws time away from patient care and is a key factor driving physicians to sell their practices, according to speakers at the briefing. U.S. physician practices now spend more than \$15.4 billion annually to report quality measures, according to a national survey from a team led by Lawrence P. Casalino, MD, PhD,

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Understanding the pathogenesis of ovarian cancer has shifted considerably. It is now believed that up to 50 percent of ovarian cancers arise from a genetic predisposition. Studying the BRCA population who undergo risk-reducing removal of their ovaries and fallopian tubes has led to the discovery of pre-invasive lesions in the fallopian tubes, called serous tubal intraepithelial cancer (STIC). These STIC lesions are most often found in the fimbriae, suggesting novel strategies and targets for ovarian cancer prevention and screening.

Regarding prevention, it has been suggested women who desire permanent sterilization have a bilateral salpingectomy (removal of the fallopian tubes), rather than simple tubal ligation or Essure (*Obstet Gynecol* 2015;125:338-45). It is becoming more common to remove the fallopian tubes for cancer prevention, even in women undergoing hysterectomy for benign reasons. The presence of these precursor lesions yields new targets for cancer screening. In trying to figure out how to interrogate the fallopian tubes, one of the first attempted techniques was the use of cervical and endometrial cytology to capture sloughed tubal cells. Researchers went further, looking at the cells themselves and at the genetic expression of these cells to screen for a set of 12 genes that can be found in ovarian cancer. Although promising, this has been studied only in women with a known cancer.

The genetic pathways involved in ovarian cancer are becoming clearer. For example, high-grade ovarian cancers almost always have a mutation in TP53, while borderline and low-grade ovarian cancers often have a mutation in BRAF or KRAS. Knowing which pathways are involved makes targeted therapies attractive. Mutations in BRAF/KRAS make the Ras/MEK/ERK pathway a potential target. The Mek inhibitor trametinib was designed to inhibit this pathway and clinical trials are currently studying its efficacy. Targeting the VEGF pathway with bevacizumab has led to improved progression-free survival in patients receiving up-front treatment. Data presented as an ASCO abstract from GOG 213 show a trend toward improvement in overall survival when bevacizumab is used to treat platinum-sensitive recurrences.

Certainly one of the most exciting targeted drugs are the PARP inhibitors that exploit mutations in BRCA. The BRCA genes are a key component of homologous recombination. PARP proteins are crucial for DNA repair. PARP inhibitors act, in part, by providing a second hit to cells that are BRCA-deficient, blocking DNA repair via homologous recombination, thereby causing cell death. By targeting cells deficient in the BRCA gene, this treatment can more specifically target cancer cells, decreasing toxicity to the patient. There are a number of PARP inhibitor drugs under development, including olaparib, which received expedited approval by the U.S. Food and Drug Administration (FDA) in 2014 for the treatment of ovarian cancer in BRCA patients. The PARP inhibitors show promise beyond patients with germline BRCA mutations, because up to 50 percent of high-grade serous ovarian cancers have a spontaneous mutation in BRCA. As a result, there are ongoing clinical trials to assess the efficacy of these drugs in patients without germline BRCA mutations.

There have been advances in the treatment of ovarian cancer with the development of techniques such as intraperitoneal (IP) and dose-dense chemotherapy. The traditional way to dose first-line chemotherapy for ovarian cancer is carboplatin at an AUC of 6 and paclitaxel at 175 mg/m² every three weeks for six cycles.

The trial (JGOG 3016) that showed a benefit to the dose-dense regimen dosed carboplatin at an AUC of 6 every three weeks followed by paclitaxel at 80 mg/m² on a weekly basis. The trial (GOG 172) showing an

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Learning Objectives for This Month's CME Activity: After participating in this CME activity, readers should be better able to identify advances in the field of gynecologic oncology and areas for future investigation.

overall survival benefit to IP treatment used cisplatin instead of carboplatin and was dosed as follows: the IV arm was paclitaxel 135 mg/m² on day 1 and cisplatin 75 mg/m² on day 2 with every three week cycles; while the IP arm was paclitaxel IV 135 mg/m² on day 1, cisplatin IP 100 mg/m² on day 2, and paclitaxel 60 mg/m² on day 8, also with every three week cycles.

The IP arm had significant side effects, such that only 42 percent of patients were able to complete all six planned cycles of chemotherapy. The Katsumoto and Armstrong trials inspired further studies in this area and the data from two of these—GOG 262 and GOG 252—recently became available. GOG 252 compared IP carboplatin/paclitaxel to IP cisplatin/paclitaxel to dose-dense carboplatin/paclitaxel and found no difference in progression-free survival among the three arms. This suggests dose-dense may provide a similar benefit to IP chemotherapy with less toxicity, but the final data from this study has not yet matured.

It should further be noted bevacizumab was used in all three arms, and it is unclear what effect this had. GOG 262 compared the dose-dense carboplatin/paclitaxel regimen to standard q3 week carboplatin/paclitaxel regimen (*New Engl J Med* 2016;374:738-48). There was no difference in survival seen between the two groups, but these conclusions need to be interpreted in light of the fact that providers were given the option to add bevacizumab to the participants' treatment.

In a subset analysis of participants who did not get bevacizumab, there appeared to be a benefit to the dose-dense regimen. The conclusion was that the use of bevacizumab with more standard every three week chemotherapy may provide a similar benefit to the dose-dense regimen. Therefore, the optimal regimen has still not been determined.

Uterine Cancer

Uterine cancer is the most common gynecologic cancer, with the most common histology being endometrioid. Unlike ovarian cancer, endometrial cancer presents with distinct symptoms such as irregular bleeding in premenopausal women or vaginal bleeding/spotting in postmenopausal women. This is why more than 70 percent of women are diagnosed at stage 1. It should be noted all postmenopausal bleeding or spotting should be evaluated, and women should be counseled to report it.

Because early stage disease has the potential to be cured with surgery alone, one of the biggest advances in uterine cancer has been in the operative approach. The LAP2 trial enrolled 1,696 women and showed that open and laparoscopic approaches were equivalent in terms of overall survival. This, and other studies, showed additional benefits of the laparoscopic approach, including decreased hospital stay, shorter recovery time, and fewer postoperative complications. The laparoscopic approach can be completed using either straight-stick laparoscopy or the robotic system. This latter system was FDA-approved in 2000.

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MOONSHOT INITIATIVE

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But, the proposed increase in the NCI appropriation would be considerable and could really help.”

What would you say are the other biggest barriers facing the Moonshot Initiative besides the financial ones?

“The two big barriers are first that we don’t understand enough about cancer. We need to do more research to understand basic mechanisms more, as well as increase our understanding of how the new treatments work, because the long-term goal is to do multi-drug treatments. So to understand how new combination treatments will work and to minimize side effects, we need to do a tremendous amount of research.

“That’s one big bottleneck and it can only be solved by lots of people doing lots of research. That’s one of the problems.

“Another problem is that we already have a lot of good drugs against the targets that we know exist—the druggable genome. There are a set number of proteins that have become favorite targets for targeted treatments. Similarly, there are parts of the immune system that have been targeted, but there are many others that could be enormously helpful.

“That’s the other big issue—really developing additional effective interventions against other targets beyond the ones that are already successful in the ones that we are targeting.”

Last time we spoke—nearly a year ago (OT 6/25/15 issue)—you mentioned you were still involved in research in the lab yourself. Is that still the case?

“I am still involved in research in my laboratory, but my number one, two, and three priorities are being Acting Director of NCI, being Acting Director of NCI and being Acting Director of NCI.” **OT**

Sarah DiGiulio is a contributing writer.

GYNECOLOGIC CANCER

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In GOG 99, researchers identified a group of high-intermediate risk women who would benefit from adjuvant radiation after surgery for uterine cancer. This was initially done using pelvic external beam radiation (EBRT). However, the PORTEC-2 trial showed brachytherapy was equivalent to EBRT in terms of decreasing local recurrence with the benefit of fewer gastrointestinal side effects.

Another potential area of development is in immunotherapy. The PD-1 inhibitors, which have been FDA-approved to treat melanoma, may work on gynecologic cancers. It appears the presence of microsatellite instability (MSI) predicts a subset of patients that will respond to this treatment (*New Engl J Med* 2015;372:2509-20). Uterine cancer can exhibit MSI either spontaneously or, more commonly, when associated with Lynch syndrome. Clinical trials of PD-1 inhibitors including this patient population are under way. Whether this class of drugs will be effective in treating uterine cancers remains to be seen, but certainly holds promise.

Cervical Cancer

Cervical cancer was once the most common gynecologic cancer in the U.S., but this is no longer true following widespread use of Pap smear screening and human papillomavirus (HPV) vaccination. Since the 1980s when persistent HPV infection was first identified as the cause of cervical dysplasia and cancer, the subtypes involved have been increasingly characterized. Although a large percentage of women will be exposed to HPV during their lifetime, the majority will clear it spontaneously within 12-24 months. On average the time from initial HPV infection to development of high-grade dysplasia or cancer is 15 years, which allows time for screening, prevention, and treatment of precancerous lesions. Knowing this timeline has allowed physicians to follow women who are HPV carriers or who have early precancerous lesions without having to perform cervical procedures such as LEEPs or cone excisions that lead to infertility or obstetric complications. This improved understanding of the HPV virus has allowed detection of HPV infection to become part of the screening process.

Prevention of HPV infection through vaccination appears to be effective in preventing the development of cervical dysplasia and cancer. There are several forms of this vaccine, some that are bivalent and cover just the high-risk types 16 and 18, and another that is quadrivalent, covering 16 and 18, and 6 and 11, which are low risk and associated with genital warts. In one study, the quadrivalent vaccine was shown to be 98 percent effective at preventing the development of cervical dysplasia or cancer. Educating parents about the importance of vaccinating children of both sexes at an age before exposure to the virus (currently recommended for ages 11-12) is critical for this vaccine to be effective.

It is important to highlight some of the advances in treatment of cervical cancer. In early stage cancer—up to stage IB1—treatment generally involves surgery in the form of radical hysterectomy. Advances in laparoscopy

have improved patient recovery time, just as with uterine cancer. In later stage cancers—up to stage IIIB—combined chemotherapy and radiation therapy is preferred. Improvements in radiation technology have allowed for more precise targeting of tumor and for adjusting the treatment plan as the tumor shrinks. This allows the dose of the radiation to be focused on the tumor, thereby increasing treatment efficacy and decreasing side effects from spread to adjacent organs. In patients with advanced or recurrent cervical cancer, the addition of bevacizumab has been shown to increase both progression-free survival (PFS) and overall survival. In a disease that has proven to be largely chemo-resistant, this is an important development.

Vulvar Cancer

Vulvar cancer is the rarest of the gynecologic cancers. The most common type is squamous cell carcinoma of the vulva. Risk factors include infection with high-risk HPV subtypes, smoking, and lichen sclerosus. Whenever feasible, the preferred method of treatment is radical local excision or modified radical vulvectomy. However, in some cases based on the size or location of the lesion, this has meant a morbid exenterative procedure.

To decrease the morbidity of surgery, it was shown that performing combined chemotherapy and radiation to shrink the tumor before surgery was an effective approach. Based on the size and depth of the tumor, groin node excision may be indicated. Traditionally this has meant a full inguinofemoral lymphadenectomy with long-term complications including lymphedema in up to 69 percent of patients. It has subsequently been shown that, in appropriately selected women, sentinel node excision using a combination of lymphoscintigraphy and blue dye has a high sensitivity with a false negative rate of 2 percent. This has greatly reduced the surgical morbidity. It is crucial to select the proper candidate for this approach. Although it may be acceptable to perform sentinel nodes when the tumor is less than 2 cm, it is important to counsel patients that the bigger the tumor, the higher the risk of a groin node recurrence. One study showed that when sentinel node dissection was performed, groin recurrence rate was 14.3 percent in tumors 2-4 cm, 3.3 percent in tumors 10-20mm, and 0 percent for tumors <10mm. In studies interviewing patients about the trade-offs of surgical morbidity versus mortality from recurrence, it was found women would rather accept side effects like lymphedema than death from a recurrence. This emphasizes the point that appropriate patient counseling is critical.

Expanding on this topic of sentinel lymph nodes, there is active research into the role of this procedure for cervical and endometrial cancer. This can be done using technetium and blue dye (as described above), and development of dye and camera technology allows this to be done using a minimally-invasive approach. As is this case with other cancers where sentinel nodes are used, the goal is to optimize the diagnosis and treatment of patients while minimizing surgical side effects.

In summary, there have been exciting advances across the spectrum of gynecologic malignancy. As more of the genetics and pathways driving these cancers are uncovered, treatments will become ever more targeted and effective. By highlighting some of these developments, attention can be focused on this important field, thereby encouraging new discovery. **OT**