Editor-in-Chief's Note

Cancer in the Elderly

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Those readers who know about me realize that I am getting up there in age. In just a few years, I hope to cross over the threshold into the cohort known as the "old-old" – age 85.[1] I have survived the adversities common to men my age, although many friends about my age are being treated for or have died of cancer. Luckily, my only skirmish with cancer was an actinic keratosis (AK) that yielded to topical treatment. Because most AKs do not become cancerous, I do not believe it should even be counted. As a humorous aside, I can remember my mother used this same acronym, AK, to describe a few older men she did not like; these men were all about my current age (AK stood for the Yiddish/German expression *alte kacker*[2]). Curiously, she never used a comparable term to describe older women she did not like.

This month, Dr. William Hung, our Topic Editor for Geriatric Therapeutics, has assembled an update entitled "Cancer Care in Older Adults." The included articles shed light on several important topics, including screening for lung cancer, palliative care for hepatocellular carcinoma, and weighing the risks and benefits of cancer therapies.[3–6] Because some gynecologic cancers are more prevalent in elderly women, I would like to return to and expand last month's Note.[7] In the Western world, ovarian cancer (OC) leads to more deaths than any other gynecologic cancer.[8] OC is the leading cause of death in American women between the ages of 65 and 74 years (35.1%) and 75 and 84 years (23.5%).[9] I am a staunch advocate for early detection. My position has been especially reinforced by two experiences. Many years ago, I recognized signs and symptoms consistent with the need for further diagnosis and treatment in a woman who was then in her early 40s. Like many women, she was ignoring her symptoms. She described the following to me: a feeling of abdominal fullness accompanied by intermittent, one-sided abdominal pain; occasional spotting at times other than during her menses; urinary frequency; and increased fatigue. She had noted these changes for 2 months but had not mentioned them to anyone. Her OC was surgically treated; she is still doing well and is now in her mid-80s. My second experience involved a close relative who died in her late 80s. Sadly, her OC was not detected until it was too late for her to be helped.

For readers unfamiliar with OC, I want to review certain information. Although aggregated as OC, in most statistical reports there are a number of different entities that make up this diagnostic category[10]: (1) endometrioid carcinoma and clear cell carcinoma, these are sometimes associated with somatic mutations in the tumor-suppressing gene *ARID1A*; (2) mucinous carcinoma, sometimes linked to teratomas and some have *KRAS* mutations; (3) low-grade serous carcinomas, a rare type that is often indolent; and (4) high-grade serous carcinomas, the most common, highly aggressive, and associated with *P53* and *BRCA1* and *BRCA2* gene mutations. OC may also arise nearby in the fallopian tubes or peritoneum. From statistics from the United States and United Kingdom, it is clear that the incidence of OC increases with advancing age. In the United Kingdom, 28% of women diagnosed with OC were older than 75 years, with the highest incidence falling into the 75- to 79-year age bracket.[11] In the United Kingdom, the median age at time of diagnosis is 63 years, and the median age at time of death is 70 years.[12] For all types of OC in the United Kingdom, the current 5-year relative survival rate is 45%; most cases are not detected until the cancer has spread beyond the ovary.[13] When diagnosis is made and

treatment is begun before metastatic spread, survival has dramatically improved with currently available treatments; the current 5-year survival rate is estimated to be at 92%.[13,14]

As suggested in my March Note, programmed cell death protein 1 (PD-1)/programmed death ligand 1 (PD-L1) inhibitors show some benefit in ovarian tumors that show high microsatellite instability or a deficiency in DNA mismatch repair.[7] Further research is needed to elucidate the exact role of checkpoint inhibitors in OC treatment. The current standard protocol usually involves surgical removal and some combination of a platinum-based chemotherapy regimen (eg, cisplatin, carboplatin) and paclitaxel. In the past few years, three poly (ADP ribose) polymerase (PARP) inhibitors (rucaparib, olaparib, niraparib) were approved as follow-on or maintenance therapy for women who have already received this regimen.[15] PARP inhibitors are usually beneficial for tumors with somatic or germline mutations in *BRCA1* and *BRCA2* genes (ie, deletions, duplications). To enhance the likelihood of benefit, use of these PARP inhibitors is coupled with approved companion diagnostics that detect germline mutations in DNA extracted from whole blood.[15] Examples are FoundationOne CDx for rucaparib[16] and BRACAnalysis CDx for olaparib and niraparib.[17]

Cellular PARP1 is a normally occurring protein involved in repairing "nicks" (single-strand breaks) in DNA that frequently reoccur. If such breaks are not repaired before cell division, double-stranded breaks will be observed in the replicated cells. In normal cells, DNA breaks should trigger cell cycle arrest and stop cell division; their un-mutated proteins generated by the *BRCA1* and *BRCA2* genes should then repair any double-stranded DNA damage in cells. Healthy cells generally do not replicate their DNA as frequently as tumor cells and lack mutations in *BRCA* gene mutations. As such they are generally able to repair both single- and double-stranded breaks. If PARP1 is not inhibited in tumor cells, they will continue to replicate and tumor growth will ensue.[18–20] Because tumor cells that contain *BRCA* mutations already have DNA repair difficulties, the addition of a PARP inhibitor will enhance the likelihood of tumor cell death.

The three currently approved PARP inhibitors are tyrosine kinase inhibitors (TKIs). Through phosphorylation, tyrosine kinases (TKs) activate cellular proteins that promote cell division in some cells. By preventing the addition of a phosphate moiety, TKIs disrupt the viability and proliferation of tumor cells. There are many more thorough descriptions of this pathway and process; one that I found particularly useful is by Ström and Helledey.[20] As noted above, PARP inhibitors are approved for women who have had some response to platinum-based chemotherapy. For those women who do not benefit from platinum-based chemotherapy, some can benefit from combinations of gemcitabine and the antiangiogenic monoclonal antibody, bevacizumab.[21,22] In 2016, bevacizumab was additionally approved for platinum-sensitive OC.[23]

A recent letter in *The New England Journal of Medicine* offered a new perspective about immunotherapies and tumor mutational burdens.[24] Yarchoan et al[24] culled the literature to derive estimates of the median number of coding somatic mutations per DNA megabase in 27 different tumors and for their degrees of response to PD-1/PD-L1 inhibitors when given as monotherapies. In these 27 different types of tumors, they calculated a correlation coefficient of 0.74. Squaring this figure yields a variance estimate of approximately 55%. In other words, tumors with more mutations can be predicted to have a greater proportion of their treatment response attributable to anti–PD-1/PD-L1 therapy. Their data suggest that PD-1/PD-L1 checkpoint inhibitors should not have great efficacy as monotherapy of OC because the typical number of mutations in these tumors is low to intermediate.[25]

No single treatment approach has demonstrated consistent efficacy for the various forms of OC. However, given the current benefits from surgery combined with appropriately targeted monoclonal antibodies and TKIs, there is reason to believe that further research will yield even better outcomes for this and other cancers.

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