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Ovarian Cancer Update

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BRIEF CLINICAL UPDATE

Ovarian Cancer Update

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Women diagnosed with ovarian cancer are living longer today than ever before. The national Surveillance, Epidemiology, and End Results (SEER) Program tracks the incidence of cancers each year and collects follow up information on all previously diagnosed patients until their death. Women diagnosed with ovarian cancer are now more likely to live to at least five years than not, with estimated 5-year survival of 54% as of 2020. This was not the case as recently as fifteen years ago, when women with ovarian cancer had <50% 5-year survival.[1] This trend reflects many advances in this challenging, often devastating disease. Here, I will focus on recent advances in ovarian cancer over the past year. Progress has been seen in both detection of ovarian cancer, non-chemotherapy treatment approaches, and even technological advances that enhance women's experience, surviving with this disease.

Women's survival greatly depends on the extent of disease at the time of diagnosis. Currently, more than half of women have advanced stage disease at diagnosis. Only one in five women have disease detected while confined to the ovary. If found at this early stage, we anticipate a cure rate of over 90%.[1] Therefore, research continues to focus on early detection. Screening women with a routine blood test can significantly reduce late-stage diagnoses. The 21-year update of the Normal Risk Ovarian Screening Study (NROSS) showed that screening postmenopausal women with CA 125, followed by a risk-adapted approach with transvaginal sonography and surgery, reduced the diagnosis of stage III and stage IV ovarian cancer by 30%.[2] This study was not adequately powered to provide outcomes for population level screening, but supports incorporating serum analyses for disease detection. Promising detection data was presented at the 2024 SGO Annual Meeting on Women's Cancer. Circulating tumor DNA was analyzed in women with ovarian cancer, after receiving both chemotherapy and surgery. These women underwent laparoscopy, or minimally invasive surgery, to look for residual disease to help correlate the accuracy of the ctDNA testing. Blood samples were able to accurately identify women with persistent microscopic amounts of disease, at high risk for clinical recurrence.[3] Thus, helping to identify women at high risk for relapse, and validating ctDNA as a detection tool. Researchers also evaluated a blood-based machine learning assay that combines cell-free DNA fragmentomes with protein biomarkers to detect ovarian cancer in plasma of women with known ovarian cancer, without cancer, and with benign adnexal masses. The analysis detected ovarian cancer with a specificity of over 99% and sensitivity ranging from 69%, 76%, 85%, and

100% for stage I to IV disease.[4] Multiple multi-gene assays are already available for use. This data demonstrates the progress made in detection with optimism for future progress in early detection. As cost effectiveness improves, screening may be expanded to the population level, with potential for reduced mortality.

Treatment advances in ovarian cancer in the past year include many exciting novel approaches. The FDA approved mirvetuximab soravtansine-gynx, or Elahere, based on promising results seen in the MIRASOL trial on 3/22/2024.[5] This antibody drug conjugate includes a folate receptor alpha directed antibody combined with a microtubule inhibitor conjugate. It targets and kills ovarian cancer cells which express a folate receptor alpha protein on the surface of the tumor while sparing healthy cells. Women whose disease expressed folate receptor alpha who received mirvetuximab soravtansine-gynx experienced more than double the response rate (ORR 42% v 16%) and lived 30% longer than women treated with chemotherapy alone (median OS 16.4 months v 12.7 months).[6] This year, also released updated data on the promising effects of hyperthermic intraperitoneal chemotherapy (HIPEC). The final survival analysis of the Dutch-Belgian phase III OVHIPEC-1 trial showed that women treated with hyperthermic intraperitoneal chemotherapy during cytoreduction, commonly known as debulking surgery, were 1.5 times more likely to be alive ten years later than women treated with conventional surgical approaches. While the positive effects of intraperitoneal chemotherapy at the time of surgery has been known, this confirms the long term survival benefit.[7] For women with known BRCA gene mutations, two studies show promising outcomes with novel approaches to the use of poly (ADP-ribose) polymerase (PARP) inhibitors. Currently, patients with BRCA mutations are encouraged to take PARP inhibitors as maintenance therapy following completion of chemotherapy and surgery. This year's DUO-O trial reported the addition of durvalumab immunotherapy to PARP maintenance lengthened the median time until disease relapse by 14.3 mo, or a 51% reduction in the risk of disease progression in women with both BRCA gene mutations and homologous recombination deficiency (HRD)-positive tumors.[8] The second study, the NOW trial, examined the use of PARP inhibitors in place of chemotherapy prior to surgical debulking. Just two months of PARP inhibitor therapy increased optimal surgical outcomes. This should lead to more research on whether PARP inhibitors can be given in lieu of chemotherapy in the neoadjuvant setting.

It provides encouragement in effort to either enhance or reduce the need for chemotherapy in this disease.[9]

Advances in AI allow for improved education regarding ovarian cancer. A study of the AI system chatGPT found that chatGPT accurately and comprehensively responded to questions about topics such as genetic testing, and genetic syndromes associated with ovarian cancer over 80% of the time.[10] Social media misinformation about ovarian cancer, however, remains widespread. An analysis of gynecologic cancer content on Tik Tok showed that over 73% of content was inaccurate and of low educational quality. Alarmingly, the top five hashtags for ovarian cancer had more than 466 million views.[11] This shows the power of social media to feed misinformation, and harm the health, of patients and families affected by ovarian cancer. It highlights the need to respond to patients' questions when navigating this challenging diagnosis.

Women who face a serious diagnosis, such as ovarian cancer, are at increased mental health risk. This is a challenging journey, both physically and psychologically. Mental health research reports magic mushrooms show as a positive option. Psilocybin, the active ingredient in magic mushrooms, is thought to be as effective as antidepressants with few or no side effects. Pooled data from 10 clinical trials reported one or two doses of psilocybin rapidly improved depression, with the effect lasting up to six months. Additional trials are exploring explore the impact of psilocybin, to improve psychological distress including depression, anxiety, PTSD, and end-of-life distress.[12]

Investigators share excitement over several novel agents based on encouraging small trial results. Nemvaleukin alfa binds to IL-2 receptors, activating and expanding antitumor CD8-positive-, natural killer-, and T regulatory cells. This adds to therapies meant to activate and enhance the immune system to fight and kill cancer. This agent will be combined with the checkpoint inhibitor pembrolizumab, for patients with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer in the phase III ARTISTRY-7 trial.[13] The second agent is relacorilant. Relacorilant is a selective glucocorticoid receptor modulator which binds the glucocorticoid receptor, to block cortisol and enhance the ability of chemotherapy to induce cell death by apoptosis. It aims to restore chemosensitivity and enhance chemotherapy effects. This will be combined with standard chemotherapy for patients with recurrent, platinum-resistant ovarian cancer in the phase III Rosella trial.[14] Third is a combination of novel immunotherapeutics botensilimab with balstilimab, an anti-CTLA-4 antibody and PD-1 antibody respectively. Phase Ib data recently presented at the Society of Gynecologic Oncology (SGO) 2023 Annual Meeting on Women's Cancer showed substantial improvement in both response rates and tolerability when compared to standard chemotherapy.[15] Lastly, an anticancer vaccine is being studied. Patients treated with a modified oncolytic vaccinia virus olvimulogene nanivacirepvec, in combination with platinum-based chemotherapy experienced promising overall response rates and progression free survival with

manageable safety profiles.[16] We can look forward to additional results from these exciting treatment studies.

This brief clinical update presents the past year's advances in ovarian cancer. Happily, ovarian cancer patients are now living longer than ever. This is a direct result of scientific discovery and increased treatment options. This year has included promising data on ovarian cancer detection, non-chemotherapy treatment options, and anti-cancer vaccine development. We learned that magic mushrooms may be helpful for mental health, to stay off Tik Tok for ovarian cancer advice, and that chatGPT AI may be a valuable educational resource for many ovarian cancer topics. There is significant optimism as women live longer than ever while being offered treatment options that either enhance the effect of chemotherapy or replace it altogether. We look forward to this coming year of scientific advances.

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