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BRIEFINGS FROM WOMEN'S HEALTH EXPERTS

DEAR COLLEAGUE,

The year 2019 brought what many of us have been waiting for – exciting and promising advances in the treatment for ovarian cancer (OvCa). For decades, with standard treatment options, progressive disease developed within 3 years in 75% of our patients. Now, with a better understanding of the role of surgery and several new medications the prognosis for OvCa may become less dire. However, the number of options now available makes counseling our patients especially difficult. In this newsletter are highlights of articles published in high-impact journals in the last 12 months, which can provide some guidance.

Sincerely,

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Advances in Ovarian Cancer Treatment 2020: Many Options!

by Ernst Lengyel, MD, PhD

Surgery

The outlook on the surgical debulking of advanced OvCa is evolving as we are trying to refine the scope and timing of the procedure, and the overall philosophy surrounding it. One factor however, has remained unchanged: The volume of residual disease after debulking surgery is the strongest prognostic factor for progression free survival (PFS) and overall survival (OS). The importance and relevance of surgical effort for the survival of the patient is clear.

The **Lymphadenectomy in Ovarian Neoplasm (LION)** phase III trial showed no difference in PFS or OS between a systematic pelvic and para-aortic lymph node (LN) dissection and no LN dissection. However, there was a higher incidence of complications with a systematic lymph node dissection [1]. Going forward, only enlarged, diseased LN should be removed.

Hyperthermic intraperitoneal chemotherapy (HIPEC). In a recent phase III trial, patients who had responded to neo-adjuvant chemotherapy (3x carboplatin/paclitaxel) were randomized to undergo interval debulking surgery alone or HIPEC with heated (40°C) cisplatin to the peritoneal cavity [2]. The authors found that HIPEC leads to improved recurrence free survival (14 *versus* 11 months) and OS (46 *versus* 34 months) compared to the standard treatment arm. Complication rates were similar and both groups received 3 cycles of carboplatin/paclitaxel postoperatively.

Primary debulking surgery is generally preferred, but neoadjuvant chemotherapy, followed by interval debulking surgery, is an acceptable alternative for patients with large disease burden or multiple co-morbidities [3].

Secondary debulking surgery offered no treatment benefit to women with platinum-sensitive, recurrent ovarian cancer, deemed amenable to complete tumor resection by the treating physician (GOG-213) [4].

PARP-inhibitors as Maintenance Treatment After Primary Chemotherapy

Four phase III trials reported on the role of PARP inhibitors (PARPi) as maintenance in the first-line treatment of high-grade serous/endometrioid OvCa: niraparib (PRIMA) [5], veliparib (VELIA) [6], olaparib (PAOLA-1) [7], and olaparib (SOLO1) [8]. As a representative example, the PRIMA trial [5] showed that in homologous-recombination deficient cancers, including those with BRCA1/2 mutations, PFS was longer with niraparib maintenance (22 *versus* 10 months). In homologous-recombination proficient tumors, the PFS was 8.1 *versus* 5.4 months.

All four trials [5-8] showed a similar clinical benefit for PARP inhibitors as maintenance in the first-line treatment of high-grade serous OvCa, but none of the trials have mature OS results. The benefits of PARP inhibitors are most significant in BRCA-1/2 mutated tumors followed by homologous recombination deficient tumors. Quality of life was not adversely affected by PARPi. Common side effects of PARPi include hematologic (anemia, thrombocytopenia, neutropenia); GI (nausea, diarrhea, vomiting), and fatigue. Most complications are within the first months of treatment. Adverse effects may be managed by dose interruption or dose reduction.

(Continued)

Chemotherapy / Anti-angiogenic Therapy

Bevacizumab as maintenance therapy. After almost 9 years of follow-up [9], updated results from GOG 218 published this year showed that there was no overall survival (OS) benefit with concurrent and maintenance bevacizumab added to carboplatin/paclitaxel chemotherapy. Still in patients with stage IV tumors, concomitant and maintenance bevacizumab treatment may be beneficial (there was a 10-month improvement in OS in the treatment group when compared to controls).

Weekly *versus* q3 week chemotherapy. Both the American GOG 262 study [10] and the British ICON 8 phase III trial [11] showed that carboplatin/paclitaxel administered every 3 weeks was as efficient as the weekly, dose-intense Japanese GOG 3016 regimen published in 2013 [12].

Intraperitoneal chemotherapy was not more effective than chemotherapy with iv carboplatin/paclitaxel combined with bevacizumab, but had higher toxicity (GOG 252) [13].

A **bevacizumab biosimilar**, (bevacizumab-bvzr - Zirabev), which is less expensive, was FDA approved in 2019.

Genetic Testing for Families with OvCa

Low rates of genetic testing. Only 30% of all at-risk first-degree family members of individuals who carry a mutation in a cancer gene, such as BRCA, undergo genetic testing [14]. Moreover, a cost-effectiveness analysis showed that, genetic testing for BRCA1/2 and PALB2 for all patients with breast cancer is very cost-effective and could prevent more deaths in family members than BRCA1/2 testing given only to those with breast cancer who meet family history or clinical criteria [15]. It is very clear that, currently, genetic testing is underutilized.

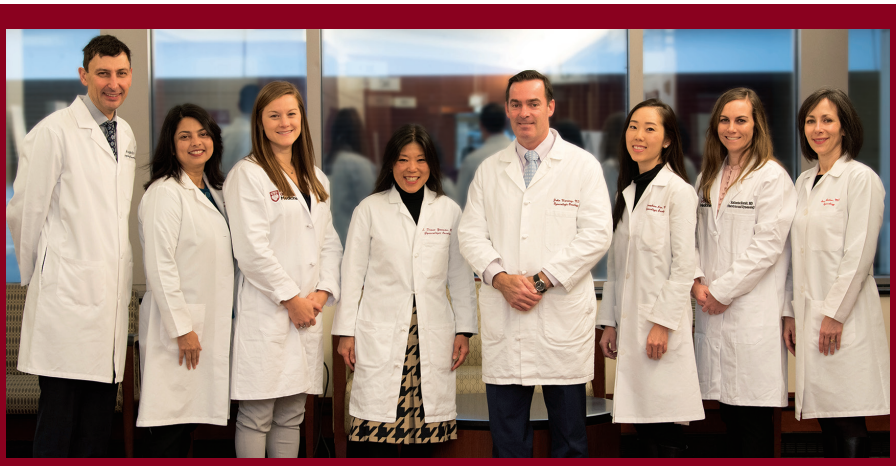
Imaging

Ultrasound. A prospective study [16] with 4567 patients showed that if an adnexal mass has benign ultrasound morphology it may be managed without surgery, since the risk of malignancy is low (invasive cancer 0.4%, borderline tumor 0.3%, torsion (0.4%) and a small risk of cyst rupture (0.2%). Clinical/ultrasound follow-up at 3, 6, and 12 months was recommended.

Summary

Genomic testing and new drugs have expanded options for OvCa patients in 2020, but have made decision making more complicated for physicians. Patients treated at centers with high surgical volume, frequent clinical study participation, and high rates of macroscopically complete resection have a median OS of more than 5 years. Given that OvCa is rare a patient with OvCa should be co-managed by medical and gynecologic oncologists experienced in genetic testing and the surgical and medical management of this aggressive disease.

[1] P. Harter, et al., *N. Engl. J. Med.*, **2019**, 380, 822. [2] W. J. van Driel, et al., *N. Engl. J. Med.*, **2018**, 378, 230. [3] J. A. Rauh-Hain, et al., *JAMA oncology*, **2017**, 3, 76. [4] R. L. Coleman, et al., *N. Engl. J. Med.*, **2019**, 381, 1929. [5] A. Gonzalez-Martin, et al., *N. Engl. J. Med.*, **2019**, 381, 2391. [6] R. L. Coleman, et al., *N. Engl. J. Med.*, **2019**, 381, 2403. [7] I. Ray-Coquard et al., *N. Engl. J. Med.*, **2019**, 381, 2416. [8] K. Moore, et al., *N. Engl. J. Med.*, **2018**, 379, 2495. [9] K. S. Tewari, et al., *J. Clin. Oncol.*, **2019**, 37, 2317. [10] J. K. Chan, et al., *N. Engl. J. Med.*, **2016,** 374, 738. [11] A. R. Clamp, et al., *Lancet*, **2019**, 394, 2084. [12] N. Katsumata, et al., *Lancet Oncol.*, **2013**, 14, 1020. [13] J. L. Walker, et al., *J. Clin. Oncol.*, **2019**, 16, 1380. [14] N. E. Griffin, et al., *Gynecol. Oncol.*, **2019** *in press*. [15] L. Sun, et al., *JAMA oncology*, **2019**, 5, 1718. [16] W. Froyman, et al., *Lancet Oncol.*, **2019**, 20, 448.



Gynecologic Oncology Team at The University of Chicago. From left to right: Drs. Lengyel, Lee, Mills, Yamada (Section Chief), Moroney, Kim, Kurnit, Lindau.

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