GYNECOLOGIC CANCER IN FOCUS

Current Developments in the Management of Gynecologic Cancer

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Advances in Uterine Serous Carcinoma and Uterine Carcinosarcoma

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H&O Uterine serous carcinoma and uterine carcinosarcoma have distinct molecular and histologic profiles. How do these differences affect prognosis?

GF Uterine serous carcinoma and uterine carcinosarcoma are both aggressive endometrial cancers with incidence rates that are rising in the United States. In addition, both occur disproportionately in Black women. The outcomes are even worse with carcinosarcoma than with serous carcinoma and other aggressive endometrial cancers.

Uterine carcinosarcoma is more histologically and clinically heterogeneous than uterine serous carcinoma. It is biphasic, with a sarcoma component and a carcinoma component. Sarcoma-dominant tumors (in which more than half of the tumor has sarcoma histology) have a worse prognosis than carcinoma-dominant tumors.[1] Almost 40% of cases were noted to be sarcoma-dominant in one landmark series.[1] The carcinoma elements of carcinosarcoma have been reported to be more likely to metastasize and spread distantly, whereas the sarcoma elements are more likely to spread locally.[2] As a result, some experts have hypothesized that radiation therapy might be more important in the treatment of sarcoma-dominant carcinosarcoma.[3] Some retrospective data suggest that in general, outcomes in women with carcinosarcoma are better with adjuvant chemoradiotherapy than with adjuvant chemotherapy alone or adjuvant radiotherapy alone.[4,5]

The histology of the carcinoma portion of carcinosarcoma can also vary. In the United states, the carcinoma component is usually serous or undifferentiated, but in one Japanese cohort, 85% of the carcinoma components of carcinosarcomas were endometrioid.[6] These differences can be associated with different genomic profiles and lead to potentially different treatments and outcomes; however, we do not have much in the way of guidelines regarding adjusting the treatment of carcinosarcoma according to histologic differences, in part because carcinosarcoma is rare. Carcinosarcomas were lumped together with sarcomas in earlier clinical trials and today remain excluded from many clinical trials for uterine carcinoma.

H&O How do the differences between serous carcinoma and carcinosarcoma affect treatment?

GF Although serous carcinoma is usually aggressive, with more than half of cases having spread beyond the uterus at the time of diagnosis (stage III or stage IV disease),[7] it is usually sensitive to chemotherapy initially.

A study from the Gynecologic Oncology Group in the pre-NRG Oncology days looked at multiple trials of chemotherapy in endometrial cancer—including serous carcinoma and carcinoma with other endometrial histologies, but not carcinosarcoma—and found that chemotherapy was as effective at shrinking tumors and improving progression-free survival for serous carcinomas as for the more common endometrioid carcinomas.[8] Because carcinosarcoma was omitted from these trials, it is unclear how effective chemotherapy is in patients with these tumors. There is some hint that carcinosarcoma may

be more resistant than serous carcinoma to at least some therapies, although we do not have prospective, head-to-head comparisons. In a retrospective series of women whose endometrial cancer was treated with bevacizumab, the rate of stable disease was far lower in patients with carcinosarcoma than in those with serous carcinoma.[10]

H&O With the growing role of molecular classification in endometrial cancer, how are genomic and biomarker-driven approaches influencing risk stratification and treatment selection?

GF For uterine serous carcinoma, almost all categories in The Cancer Genome Atlas (TCGA) are copy number–high (the highest-risk category) and have *P53* mutations. Almost all are mismatch repair–proficient, but it is still recommended to test serous tumors for mismatch repair deficiency because of the important clinical implications of mismatch repair deficiency. Most carcinosarcomas in the United States are also copy number–high and have *P53* mutations. Carcinosarcomas, however, particularly those with endometrioid histology in the carcinomatous component may be *POLE*-mutated or mismatch repair–deficient, with prognostic and treatment implications.[11] As a result, it is important to test carcinosarcomas for *POLE* mutations and mismatch repair deficiency.

Overall, the tumor next-generation sequencing (NGS) profiles for carcinosarcoma and uterine serous cancer are fairly similar in the United States. Mutations are usually seen in *P53*, and the *CCNE1* gene is frequently amplified.

H&O What is the standard frontline treatment for patients with serous carcinoma and carcinosarcoma?

GF The standard frontline treatment is chemotherapy—typically carboplatin plus paclitaxel. The addition of immune checkpoint inhibitor therapy with either dostarlimab (Jemperli, GSK)[12] or pembrolizumab (Keytruda, Merck)[13] has improved progression-free survival for mismatch repair–proficient endometrial cancer in general. A total of 44 patients with carcinosarcoma were included in the study using dostarlimab, so the addition of dostarlimab to frontline chemotherapy may be considered for women with carcinosarcoma.[12]

H&O What are the most promising approaches to systemic treatment for these conditions beyond traditional chemotherapy?

GF The most exciting advance we have seen recently is anti-HER2 therapy. Initially, a phase 2 study of 61 patients with advanced or recurrent HER2-positive uterine serous carcinoma showed a benefit from the addition of intravenous trastuzumab to carboplatin/paclitaxel chemotherapy.[14] This study defined HER2 positivity traditionally: 3+ on immunohistochemical staining or 2+ on immunohistochemical staining with gene amplification confirmed by fluorescence in situ hybridization. This was a very small study that did not include carcinosarcoma.

> I expect more ADCs to be available in the near future for use in both uterine serous cancer and uterine carcinosarcoma.

An ongoing follow-up study that is much larger and does include carcinosarcoma is the phase 3 NRG-GY026 study, which is looking at a combination of paclitaxel or carboplatin either (a) alone or combined with either (b) injectable trastuzumab (Herceptin Hylecta, Genentech) or (c) an injectable combination of pertuzumab and trastuzumab (Phesgo, Genentech), in an effort to confirm the benefit of naked anti-HER2 antibody therapy in the frontline setting for women with traditionally HER2-positive disease.

Even more exciting is the use of anti-HER2 antibody-drug conjugates (ADCs) in endometrial cancer. Trastuzumab deruxtecan (T-DXd; Enhertu, Daiichi-Sankyo/AstraZeneca) was first approved in 2019 for use in patients with pretreated unresectable or metastatic HER2-positive breast cancer. It has since been approved by the US Food and Drug Administration (FDA) for use in any pretreated unresectable or metastatic HER2-positive (expressing HER2 at the 3+ level by immunohistochemistry) solid tumors. We know that among endometrial cancers, the levels of HER2 expression and amplification are highest in uterine serous carcinoma. In one series, 49% of serous carcinomas stained 3+ for HER2 by immunohistochemistry.[15] The frequency of HER2 expression in carcinosarcomas is also fairly high (23% stained 3+ in the Krakstad series), although the frequency of expression tends to be higher in the carcinoma component.[16]

The DESTINY-Breast04 trial showed that T-DXd is effective even in breast cancers with lower levels of HER2.[17] Similarly, the STATICE trial from Japan showed that T-DXd was efficacious in patients with uterine carcinosarcoma

whether their tumors were HER2-high (defined in this trial as 2+ or 3+ by immunohistochemistry) or HER2-low (defined in this trial as 1+ by immunohistochemistry).[18] The overall response rate was 55% in the HER2-high group and 70.0% in the HER2-low group, which is overwhelmingly impressive. Attempts are underway to confirm the efficacy of T-DXd in endometrial cancers that stain less strongly (1+ or 2+) for HER2, and to test its use earlier in the treatment of endometrial cancer.

Although no other ADCs have yet been approved for use in endometrial cancer, the folate receptor alpha (FRα)–directed ADC mirvetuximab soravtansine (Elahere, AbbVie) has been approved for use in women with ovarian cancers that express high levels of FRα. The levels of FRα expression in many endometrial cancers, including uterine serous carcinoma and the carcinoma component of uterine carcinosarcoma, are often high.[19] A small study has looked at mirvetuximab soravtansine in combination with pembrolizumab in women with endometrial cancer, with promising preliminary response rates.[20] A phase 2 trial testing single-agent mirvetuximab soravtansine in endometrial cancer is underway (NCT03832361).

Another ADC that is being studied for use in endometrial cancer is the TROP2-directed agent sacituzumab govitecan (Trodelvy, Gilead), which is already approved for use in breast cancer. A phase 2 trial in patients with endometrial cancers, including a substantial percentage of uterine serous cancers, showed a meaningful response rate,[21] and a phase 3 trial is underway (NCT06486441). Datopotamab deruxtecan (Dato-DXd; Datroway, Daiichi Sankyo/AstraZeneca), a different TROP2-targeting antibody that is also FDA-approved for use in breast cancer, has also shown promising preliminary efficacy in the treatment of endometrial cancer.[22] I expect more ADCs to be available in the near future for use in both uterine serous cancer and uterine carcinosarcoma.

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