Combination of hormonal-based therapy in endometrial cancer: ready for prime time

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Endometrial cancer is currently the only gynecologic malignancy with increasing incidence (approximately 1% per year since the mid-2000s).[1] Although the majority of patients are diagnosed in early stage and are surgical candidates, approximately 3–13% of patients will experience disease recurrence, and this accounts for the vast majority of endometrial cancer-related deaths.[1] For this reason, there is a need for novel therapies. In this month's Lead Article, Mahdi[2] and colleagues review the treatments of metastatic or recurrent low-grade endometrioid adenocarcinoma of the uterus. The authors are to be commended for their review and update on novel therapeutic options in patients with advanced or recurrent endometrial cancer. Here they focus on an often low-priority option in this patient population: hormonal therapy.

First, the authors highlight that patients with low-grade disease are often poor responders to chemotherapy.[3] The majority of low-grade uterine endometrioid tumors are molecularly classified as non-specific molecular profile and often express estrogen and/or progesterone receptor. As a result, clinical guidelines highlight hormone therapy as a treatment that appears to have the greatest benefit for recurrent, low-grade, slowly progressive, hormone receptor-positive tumors.[1] However, in advanced stage or recurrent endometrial carcinoma, response rates to hormonal therapy monotherapy range from 8–58%.[4] To that end, in their article, the authors advocate for combination hormonal therapy and targeted therapies in the future management of low-grade advanced and recurrent endometrial cancer.

Approximately 93% of endometrioid tumors harbor mutations that suggest there is potential for targeted therapy.[5] There is a correlation between the PI3K/AKT/mTOR pathway and estrogen receptor, and deregulation of this pathway is one mechanism of hormonal therapy resistance. In a single-arm, phase II trial, Slomovitz *et al* demonstrated that the mTOR inhibitor everolimus in combination with letrozole in patients with recurrent endometrial cancer results in a clinical benefit rate of 40% (14 of 35 patients) and an objective response rate of 32% (11 of 35 patients; 9 complete responses and 2 partial responses).[6] GOG 3007 evaluated everolimus in combination with letrozole compared with the alternating regimen of medroxyprogesterone acetate/tamoxifen. The everolimus/letrozole combination was associated with prolonged progression-free survival, particularly in chemo-naïve patients.[7] The PALEO trial is the first randomized trial to evaluate the efficacy of a CDK4/6 inhibitor (palbociclib) in combination with an aromatase inhibitor (letrozole) in patients with advanced or recurrent estrogen receptor-positive endometrial cancer. The combination treatment resulted in significantly improved progression-free survival with a median of 8.3 versus 3.0 months, respectively (HR 0.56, 95% CI 0.32 to 0.98; p=0.041).[8] Additional phase II trials have suggested synergy for the addition of CDK4/6 inhibitors in combination with letrozole.[9 10]

Lastly, the authors highlight that research strategies used to improve the effectiveness of hormonal treatments in metastatic breast cancer may be a valuable approach when treating endometrial cancer.[2] Work is also underway on hormone therapy studies in low-grade ovarian cancer which is often hormone receptor-positive and responds poorly to chemotherapy.[2] In their article, the authors highlight that hormonal therapies are a strategy for low-grade advanced and recurrent endometrial cancer, since these have a good safety profile and knowing that these are tumors that respond poorly to chemotherapy. Nevertheless, most studies are still in phase II and more trials are needed to establish hormonal treatments and targeted therapies for patients with metastatic or recurrent low-grade endometrioid cancer as a standard of care.

Although all these data on combined treatments in recurrent or metastatic endometrial cancer are promising, one must understand that these are phase II studies, and therefore tested in a very small number of patients. There are also no studies that compare which of these combinations of targeted therapies could be better in combination with hormonal therapy as a standard treatment.

Knowing that endometrial cancer is a disease that is increasing in prevalence, in tandem with the fact that recurrence represents the vast majority of deaths related to endometrial cancer, these are very promising therapeutic alternatives. However, further refinement of molecular subgroups could help select those patients most likely to benefit from these therapies as

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these subgroups are incorporated into molecularly targeted trials and treatment recommendations.

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