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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Keeping Pace in Women's Cancer: Targeting Advanced Endometrial Cancer

Announcer:
Welcome to CME on ReachMD. This activity, entitled "Keeping Pace in Women's Cancer: Targeting Advanced Endometrial Cancer" is provided by AGILE and Prova Education.

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Dr. Penson:
We're all too aware that women facing a diagnosis of advanced endometrial cancer have endured a grim survival prognosis. However, with the emergence of immunotherapy into our therapeutic approaches, this dire prognosis is changing.

This is CME on ReachMD, and I'm Dr. Richard Penson. Today, I'm talking with Dr. Nicoletta Colombo about the recent emergence of immunotherapy agents in the management of advanced endometrial cancer and how we might select which patients receive which interventional strategy. We will also be speaking with Ms. Christine Ghione to get a better perspective from the patient's side.

Dr. Colombo and Ms. Ghione, welcome to the show.

Dr. Colombo:
Thank you, Dr. Penson.

Ms. Ghione:
Thank you, Dr. Penson. It's very nice to be here.

Dr. Penson:
Dr. Colombo, what are the immunotherapeutic agents that have emerged for the treatment of advanced endometrial cancer, and how might they best be approached in clinical practice? Moreover, in what ways might they impact the current standard of care, especially related to the use of molecular risk classification, when managing advanced endometrial cancer?

Dr. Colombo:
Endometrial cancer has been recognized as one of the solid tumors with the highest percentage of mismatch repair deficiency, or microsatellite instability-high. Therefore, it is an ideal candidate for immunotherapy. The study KEYNOTE-158 demonstrated a 57% response rate among 49 patients with MSI-high endometrial cancer treated with pembrolizumab. And subsequently, the GARNET study showed a 44.7% response rate for dostarlimab in 103 patients with mismatch repair-deficient endometrial cancer. And interestingly, these responses were very long lasting.

So if this is true for a biomarker-selected population, the data are less encouraging for the mismatch repair-proficient tumors. However, in this setting, we just heard at the SGO meeting the impressive results of study 309, KEYNOTE-775 which was a randomized, phase 3 study comparing the combination of pembrolizumab/lenvatinib with standard of care in patients with endometrial cancer previously treated with platinum. And the study demonstrated a significant improvement for the experimental arm in all the endpoints, namely progression-free survival, overall survival, and response rate for both of the intention-to-treat population and the mismatch repair-

proficient tumors. So this data opened new hope for the use of immunotherapy in the majority of patients with endometrial cancer, which do not have MSI-high or mismatch repair deficiency.

Dr. Penson:
There's a lot of excitement about immunotherapy, but I think there was some early disappointment because the tumors that are microsatellite instable are relatively rarer. And for example, in KEYNOTE-158, the response rate in ovarian cancer was 33%, and we really haven't seen that with other immunotherapeutic trials, so it's the patient population that is key. Now we have, as you say, this really exciting addition of lenvatinib which makes tumors that were cold, hot, and gives more patients the opportunity of benefiting from immunotherapy.

Thank you for providing us with such a clear explanation of how emerging immunotherapeutic agents can offer benefits to a subset of women with advanced endometrial cancer. That said, very few therapies have come without adverse side effects, some of which are serious. While toxicity and adverse effects are well known with the use of chemotherapy and endometrial cancer, what adverse events are we seeing with these immunotherapeutic agents, and how do they compare with chemotherapy-associated adverse events? How often would you say these events interfere with the completion of therapy?

Dr. Colombo:
Chemotherapy has very well-recognized side effects that sometimes make it difficult, the administration, particularly in the old patients with several comorbidities, which is the case for the majority of endometrial cancer patients. So in this respect, immunotherapy may represent a more attractive option. In fact, in the GARNET study, which I mentioned before, only 4% of patients had to discontinue treatment because of side effects. And most of these events were mild, namely fatigue, diarrhea, liver enzymes increased, and hypothyroidism, and the grade III toxicity were extremely rare. We do not have specific data for endometrial cancer patients on the comparison between chemotherapy and immunotherapy. However, a recent metanalysis of 22 trials involving more than 12,000 patients with advanced solid tumors demonstrated that patients receiving immunotherapy experienced fewer adverse events, 65%, compared to patients receiving chemotherapy, 85%. Also, the likelihood of side effects grade III and higher was lower in patients receiving immunotherapy versus chemotherapy, 16.5% versus 41%. And additionally, termination of therapy was less likely in patients receiving immunotherapy, 6% versus chemotherapy, 10%. So decreased risk for both adverse events and treatment cessation are, I think, are important benefits of immunotherapy that should be discussed with patients.

Dr. Penson:
This is CME on ReachMD, and I'm Dr. Richard Penson. Today, I'm talking with Dr. Nicoletta Colombo about the recent emergence of immunotherapy agents in the management of advanced endometrial cancer and how we might select which patients receive which interventional strategy. We will also be speaking with Ms. Christine Ghione to get a better perspective from the patient's side.

Let's look a bit deeper into the knowledge and experience base of oncologists with regard to anticipating, responding to, and even preventing immune-related adverse events. There are frequent regional differences in how clinicians approach these adverse events, in part because of a lack of familiarity with the immunotherapeutic agents themselves. How do we bring all oncology personnel to the same starting point regarding immune-related AEs? We need everyone to be able to use these agents effectively in advanced endometrial cancer, but how do we get there?

Dr. Colombo:
Yeah, you're right. While the adverse events related to chemotherapy may significantly impact quality of life, these adverse events are at least well known and recognized and understood by oncologists after decades of use in the field. On the other hand, the immunotherapy may be associated with a spectrum of unknown, unrecognized, and poorly understood adverse events. So the so-called immune-related adverse events can affect any organ system. So the most typical are endocrine disorder such as hypothyroidism and diabetes, or inflammatory disorders such as colitis, hepatitis, pneumonitis, myositis, and even skin reactions. So they can have delayed onset and also prolonged duration, making diagnosis challenging for clinicians.

A recent study underscored a poor agreement on immune-related adverse events, occurrence, and grade. So because oncologists are less familiar with immune-related adverse events than with the side effects from some treatments, they may be more likely to misdiagnose them. So these challenges in recognition, diagnosis, and treatment of immune-related adverse events underscore the need for further clinician education.

Dr. Penson:
I think what's happened is that oncologists have made friends, as they did with anti-angiogenics, you know, a favorite cardiologist, to help them navigate hypertension management, for example. Many clinicians now have connected with endocrinologists, gastroenterologists, other clinicians to manage immunotherapeutic toxicities.

Ms. Ghione, shared decision-making is the collaboration between the clinician and the patient regarding all things associated with the interventional strategy. The efficacy versus toxicity and adverse side effects of any regimen, and the patient's preferences must be included in the final choices. Many oncologists may not be well trained in this form of counseling. What has been your personal experience with the shared decision-making process? And moving forward, from your point of view, what about this process can be improved?

Ms. Ghione:
Thank you, Dr. Penson. My initial experience with the choice of cancer care was really difficult in Spain. Some of you may know, but traditionally in Spain, the doctor is the decision maker. More often now, patients are becoming empowered and gathering information to be better informed and equipped to make decisions about their treatment options. Many first-time cancer patients and their family members are in shock upon receiving a cancer diagnosis, and they are often trusting their doctor's opinions and recommendations without questioning them.

In my personal experience, I was referred immediately to a surgeon who had programmed me for surgery the following week – on day 2 after my diagnosis. I was still getting over the shock of the news and trying to gather information about the proper recommended testing. When I questioned the surgeon as to why I couldn't receive additional testing prior to surgery, including genetic testing, I was told that my family history, without testing, clearly indicated I was a high-risk patient.

Fortunately, I was a more informed patient than the average patient as I was attending medical conferences and hearing about the latest findings and treatment plans, including personalized medicine and genetic screening. I challenged the surgeon and looked for an oncologist who was willing to perform additional testing prior to surgery. I then changed surgeons for someone who was willing to listen to my concerns, answer questions, and not rush the operation.

In terms of my treatment plan, I was fortunate that the oncologist that I chose was very sensitive to my well-being and my quality of life. I struggled with impairing side effects for months, and together, we decided to stop and restart treatment three times in one year to attempt to reduce the side effects. After a year, we looked at the risk/benefit of my treatment and decided to suspend treatment as my quality of life was being greatly affected by the side effects and my recurrence [rate] was [estimated at] 5%.

Culturally, in many countries, it's not well accepted that patients question their medial team. I think it's important to train physicians and better communicate with patients about their treatment preferences.

Dr. Penson:
You are a marvelous example of somebody who's empowered and engaged in these important decisions. Well done.

Dr. Colombo:
I fully agree because, you know, Italy is very similar to Spain, but also the patients in Italy are not really willing to discuss. Sometimes they prefer not to be involved. So I do believe that this is the role of the advocacy groups, to try to really teach the patients and empower the patients and telling them that they have to be part of the decision.

Dr. Penson:
Well, this has certainly been a fascinating conversation, but before we wrap up, Dr. Colombo and Ms. Ghione, can you each share your one take-home message with our audience? Let's start with you, Dr. Colombo.

Dr. Colombo:
I do believe that the recent data on endometrial cancer are very encouraging, and we have now effective immunotherapy treatment for mismatch repair-deficient endometrial cancer and an extremely effective combination regimen, including immunotherapy, in not mismatch repair-deficient tumors. So immunotherapy has changed the face of many cancers during the last years and, finally, this is happening also for endometrial cancer.

Ms. Ghione:
I believe an open dialogue must be had between the cancer patient and the medical team. There are a lot of groups out there, there are patient organizations, but many first-time diagnosed patients may not be aware of them, so I think it would be great if physicians can help provide additional support by recommending these organizations to patients.

Dr. Penson:
I think my take-home message is the scientific understanding of cancer biology really has identified biomarkers. So special stains and gene tests are what we have to do to understand the right treatment for each patient.

Unfortunately, that's all the time we have, today. So I want to thank our audience for listening in and thank you, Dr. Nicoletta Colombo and Ms. Christine Ghione, for joining me and for sharing all of your valuable insights. It was great speaking with you both today.

Dr. Colombo:
Thank you very much. It was a great pleasure for me.

Ms. Ghione:
Thank you. It was a pleasure speaking with you.

Announcer:
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