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Immunotherapy for TNBC in the Perioperative Setting: Clinical Evidence and Considerations

Announcer:
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Dr. Schmid:
Hello, and welcome to CME on ReachMD. I'm Dr. Peter Schmid, and today I'll talk about the role of immune therapy in the perioperative setting for triple-negative breast cancer.

There's a long-standing debate whether all patients with early-stage triple-negative breast cancer require systemic therapy before or after surgery. We know very clearly that patients, at least with T1C and node or higher stage disease should be considered for chemotherapy, either before or after surgery. But for patients with the smallest cancer, T1A, T1B, N0, the jury is still a little bit out. But patients with higher risk factors, I personally would consider for chemotherapy in this setting.

When we consider chemotherapy for patients with early-stage triple-negative breast cancer, we have to make a decision whether we give it before or after surgery in the form of preoperative or neoadjuvant chemotherapy or adjuvant chemotherapy. The guidelines are very clear that patients with T2 or higher or N+ disease should be considered for neoadjuvant chemotherapy, as it has a number of advantages. But even in patients with T1C and node disease, they increasingly use preoperative chemotherapy as it just allows us to better tailor treatment strategies in these patients.

What neoadjuvant chemotherapy allows us to do is not just to downstage the cancer, which facilitates less invasive surgery of the breast, but more importantly, in my opinion, also of the axilla, but it also allows us to divide patients into one of two groups. There's a group of patients with an optimal response to preoperative chemotherapy. This is called the pathological complete response, the disappearance of all invasive cancer from the breast and axilla. And those patients generally have a fantastic outlook with a very low risk of disease recurrence.

There's also a group of patients who have residual disease at the time of surgery, and those patients unfortunately still do have a higher risk of disease recurrence. What we have learned is that we can tailor the postoperative treatment strategies depending on the response to preoperative chemotherapy. And in patients who have no residual disease, we can possibly scale down our treatment options in the future. But for patients who have residual disease, we would consider further systemic therapy; for example, in the form of capecitabine as a tablet-based chemotherapy or for patients with BRCA germline mutations in the form of a PARP inhibitor.

What's the best selection of chemotherapy regimen? This may change over time. There has been an ongoing debate about whether or not patients should be considered routinely for platinum-based chemotherapy, and some of the previous studies showed a clear benefit in pathCR rates but weren't showing such a clear benefit in event-free survival.

But more recently, a large phase 3 trial has demonstrated a substantial increase in improvement in event-free survival with the addition of platinum. And also, a platinum-based regimen is the standard regimen in combination with immune therapy, and I think, therefore, the

majority of patients with early-stage triple-negative breast cancer should be considered for platinum treatment.

Now let's move to immune therapy because immune therapy has become the standard of care for patients with stage 2 or stage 3 triple-negative breast cancer, and that is very well reflected in all ongoing guidelines. This is based on the recent results of the KEYNOTE-522 trial, a phase 3 trial with 1,174 patients who were randomized 2:1 to either chemotherapy and pembrolizumab for 6 months or to chemotherapy and placebo for 6 months, then underwent surgery and continued either with immune therapy or with placebo for another 6 months.

The chemotherapy regimen chosen in this trial was 12 weeks of paclitaxel/carboplatin followed by 12 weeks of AC and EC. So an intensive chemotherapy regimen. Patients continued with the immunotherapy for a total duration of 1 year.

The trial had 2 dual endpoints: short-term endpoint with pathCR, where it demonstrated a significant improvement of pathCR rates to nearly 65%, and a long-term endpoint in terms of event-free survival, so reduction of recurrences, where we could demonstrate, with a follow-up of more than 6 years, a 35% reduction in the risk of recurrences. But most importantly and most recently, we also demonstrated a substantial and significant oral survival benefit, demonstrating that the addition of immune therapy to preoperative chemotherapy reduces the risk of death by 34%.

Of interest, the benefit of immunotherapy was seen across all relevant clinical subgroups, whether it was stage II disease or stage III disease, node-positive or node-negative disease. Even in the smallest tumors, T2 and node, we saw substantial benefit from the addition of immune therapy with an absolute delta in event-free survival rates of about 10%. We also learned that PD-L1 is not an important biomarker in the early disease setting. Patients seem to benefit similarly from the addition of immunotherapy whether they're PD-L1 positive or PD-L1 negative.

Now, in summary, the current guidelines suggest very clearly that patients with stage II or stage III triple-negative breast cancer should be considered for neoadjuvant preoperative chemotherapy in combination with the immune checkpoint inhibitor pembrolizumab, followed by surgery, and then followed by continuation of pembrolizumab for another 6 months, or possibly addition of capecitabine or olaparib if patients have residual disease.

Thank you for your attention. I hope this discussion will be useful in your practice.

Announcer:
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