BREAST CANCER IN FOCUS

Current Developments in the Management of Breast Cancer

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The Use of Immunotherapy in Triple-Negative Breast Cancer

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H&O Which patients with triple-negative breast cancer (TNBC) are eligible for immunotherapy?

PS We generally use immunotherapy in TNBC for 2 indications. One indication is the first-line treatment, in combination with chemotherapy, of patients with metastatic disease who test positive for programmed death ligand 1 (PD-L1). Candidates for treatment are assessed with either the Ventana PD-L1 (SP142) Assay from Roche or the PD-L1 IHC 22C3 pharmDX from Agilent; PD-L1 positivity is defined as 1% of immune cells positive on the SP142 assay or a combined positive score (CPS) of at least 10 on the 22C3 assay. Approximately 40% of patients with metastatic TNBC are eligible for immunotherapy in combination with chemotherapy.

The second indication, which received approval from the US Food and Drug Administration (FDA) in July of 2021 after the results of KEYNOTE-522, is the treatment of patients with high-risk, stage II or III TNBC. Immunotherapy is used in combination with chemotherapy as neoadjuvant treatment and then continued after surgery as a single agent. In this case, immunotherapy is beneficial for all patients, regardless of PD-L1 status. The regimen used in KEYNOTE-522 is the new standard of care for eligible patients.

H&O What makes immunotherapy a good choice for the treatment of women with TNBC?

PS As we have known for some time, TNBC tends to be more aggressive than hormone receptor–positive breast cancer, and even human epidermal growth factor receptor 2 (HER2)–positive breast cancer. As a result, researchers have been eager to find effective treatment options for these patients. Fortunately, many patients with TNBC have 2 characteristics that are important for effective immunotherapy. Firstly, TNBCs often exhibit an elevated rate of genetic instability, which makes them especially susceptible to immunotherapy. Secondly, TNBCs are more likely to be inflamed than other tumor subtypes. Inflammation is known to increase susceptibility to immunotherapy. Because TNBC is a heterogeneous subtype, these characteristics do not apply in all cases.

H&O What is the evidence for checkpoint inhibition in combination with chemotherapy in metastatic TNBC?

PS Improvements in progression-free survival (PFS) and overall survival (OS) have been demonstrated with the addition of immunotherapy to chemotherapy in patients with PD-L1–positive TNBC in 2 main phase 3 trials: IMpassion130 and KEYNOTE-355.

In IMpassion130, 902 patients with untreated metastatic TNBC who had experienced a disease-free interval of at least 12 months were randomly assigned in a 1:1 ratio to the PD-L1 inhibitor atezolizumab (Tecentriq, Genentech) plus standard nab-paclitaxel chemotherapy vs nab-paclitaxel alone as first-line treatment. KEYNOTE-355 had a similar design, but 847 patients who had experienced a disease-free interval of at least 6 months were randomly assigned in a 2:1 ratio to the PD-L1 inhibitor pembrolizumab (Keytruda, Merck) plus chemotherapy vs chemotherapy alone. The chemotherapy regimen in this trial was nab-paclitaxel, paclitaxel, or gemcitabine plus carboplatin. In addition to the differences

between the PD-L1 inhibitors and the chemotherapy regimens, a third main difference between these trials is that the PD-L1 cutoff in IMpassion130 was 1% on the SP142 assay, and in KEYNOTE-355 it was a CPS of 10 on the 22C3 assay.

The results of these trials were remarkably consistent. In both trials, the addition of a checkpoint inhibitor to treatment produced a significant, meaningful benefit in PFS, which was one of the primary endpoints. The hazard ratios (HRs) for progression or death with checkpoint inhibition among PD-L1–positive patients were very similar in the 2 trials: 0.63 in IMpassion130 and 0.65 in KEYNOTE-355. Dr Javier Cortés presented updated results from KEYNOTE-355 at the virtual European Society for Medical Oncology (ESMO) Congress 2021, reporting that the addition of pembrolizumab to treatment significantly improved OS, with an HR of 0.73 among patients with PD-L1–positive tumors. Neither trial showed a benefit in PFS or OS with checkpoint inhibition in patients who had PD-L1–negative tumors.

A third trial, IMpassion131, has made the situation a little bit difficult to interpret. This trial, which appeared in the *Annals of Oncology* in July of this year, was conducted as an FDA requirement following the accelerated approval of atezolizumab based on IMpassion130. Although it was meant to be a confirmative trial, IMpassion131 differs from IMpassion130 in several regards. Both trials examined the addition of atezolizumab to first-line therapy in patients with metastatic TNBC, and neither trial was limited to patients who tested positive for PD-L1 expression. IMpassion131 was slightly smaller than IMpassion130, at 651 patients. Patients were randomly assigned to combination treatment vs chemotherapy alone in a 2:1 ratio, which made the control group of patients with PD-L1–positive tumors relatively small. The biggest difference, however, is that the chemotherapy regimen used was conventional paclitaxel rather than nab-paclitaxel. As a result, patients required co-medication with the corticosteroid dexamethasone, which may have had an effect on the efficacy of the treatment.

The results of the primary PFS analysis showed that adding atezolizumab to paclitaxel did not improve investigator-assessed PFS in the PD-L1–positive population. The HR was 0.82 and was not statistically significant. What is interesting is that the Kaplan-Meier curves began to diverge within the first 6 months in IMpassion130 and KEYNOTE-355, but they did not diverge in IMpassion131 until after the first 6 months. Something seems to have happened in the first 6 months that caused a delay in the separation of the curves.

A preplanned analysis of PFS based on a central review of imaging data showed slightly better results with pembrolizumab in the PD-L1–positive population, with an HR of 0.73. The results just missed statistical significance, with a 95% confidence interval of 0.54 to 1.0, but they were very similar to the results of the other 2 studies. These results also revealed a late separation of the Kaplan-Meier curves. It is difficult to interpret what was going on in IMpassion131, but we know that it was the smallest of the 3 trials, that it was largely performed after the results of IMpassion130 were already available, and that the control arm was very small, especially the PD-L1–positive subgroup. These imbalances may have contributed to the results we saw. We also know that TNBC is a highly heterogeneous disease, which may have affected the results. For example, the median OS of patients in the control group of IMpassion131 was 28 months. We have never seen a result like this with paclitaxel alone, which suggests the possibility of some form of inadvertent patient selection.

H&O What is the evidence for single-agent checkpoint inhibition in metastatic TNBC?

PS When we first developed immunotherapy for TNBC, we started with single-agent trials. We ran 2 nonrandomized single-agent studies, one with pembrolizumab and one with atezolizumab. We learned 3 interesting facts from these early trials. Firstly, we learned that single-agent immunotherapy works—we clearly saw activity of the agents. Secondly, we learned that the earlier immunotherapy is given, the better it seems to work. The response rates in these nonselective cohorts were approximately 25% in the first-line setting and dropped to below 5% in second-line and later settings. Thirdly, we learned that when patients do respond to immunotherapy, the benefit can be transformative. In the atezolizumab study, for example, in the small number of patients who did respond, the median duration of response was approximately 22 months. At the time that this study was conducted, 22 months was longer than the median OS of patients with metastatic TNBC.

We subsequently embarked on the phase 3 KEYNOTE-119 trial, in which patients who had metastatic TNBC were randomly assigned to single-agent immunotherapy with pembrolizumab vs physician's choice of chemotherapy as second- or third-line treatment. The results were very interesting. If you look at the Kaplan-Meier curves for OS, we see little difference between pembrolizumab and chemotherapy in the intention-to-treat population (HR, 0.97). However, when we look at the patients with a low level of PD-L1 expression (CPS ≥1), we see that the curves are beginning to separate, and this separation increases in the patients with higher PD-L1 scores. The HR is 0.78 in the patients with a CPS of at least 10, approaching statistical significance.

In an exploratory analysis, we looked at patients with even higher levels of PD-L1 expression (CPS ≥20) and saw a statistically significant improvement in OS (HR, 0.58)—the median OS was 14.9 months with pembrolizumab and 12.5 months with chemotherapy. Only approximately 17% of patients with TNBC had a CPS of 20 or higher in this trial, but the response rate in this small subgroup was significantly better than that in the other groups, at 26%.

So, the simple answer is that we have positive phase 3 data for immunotherapy only in combination with chemotherapy; the single-agent trial was negative. But if you look at the data in more detail, you can see that a small subgroup of patients with highly immunogenic, inflamed tumors are potential candidates for single-agent therapy, even in later lines of treatment. This finding is something that warrants further investigation.

H&O Could you talk about the evidence for immunotherapy in the setting of early-stage TNBC?

PS The 2 randomized phase 3 trials in early TNBC that have reported data so far are KEYNOTE-522, which I briefly mentioned earlier, and IMpassion031. Whereas KEYNOTE-522 used pathologic complete response (CR) and event-free-survival (EFS) as primary endpoints, IMpassion031 was powered to look only at pathologic CR. Pathologic CR is generally defined as the absence of residual invasive cancer in the breast or lymph nodes at the time of surgery. This is an important endpoint because previous chemotherapy trials established that long-term outcomes are substantially improved in patients who have a pathologic CR. The association between pathologic CR and EFS is clear, and the relationship between pathologic CR and OS is even stronger.

In KEYNOTE-522, we randomly assigned 1174 patients with stage II or III early TNBC in a 2:1 ratio to receive either intensive chemotherapy plus pembrolizumab or intensive chemotherapy plus placebo. Patients in the pembrolizumab group received neoadjuvant treatment with pembrolizumab plus paclitaxel and carboplatin for 4 cycles, followed by pembrolizumab plus cyclophosphamide and either doxorubicin or epirubicin for 4 cycles, before surgery. This regimen was followed by adjuvant treatment with 9 cycles of pembrolizumab. Patients in the placebo group received the same regimen, except that placebo was used in place of pembrolizumab.

In the somewhat smaller IMpassion031 study, researchers randomly assigned 333 patients with stage II or III TNBC in a 1:1 ratio to either chemotherapy plus atezolizumab or chemotherapy plus placebo as neoadjuvant treatment. The chemotherapy regimen used in this study was less intensive and less effective than that used in KEYNOTE-522, consisting of nab-paclitaxel, doxorubicin, and cyclophosphamide. Patients were unblinded after surgery, and those in the atezolizumab group could continue with atezolizumab.

The findings of the 2 trials were remarkably consistent. KEYNOTE-522 showed a substantial, meaningful, and significant increase in the pathologic CR rate among the first 602 patients who underwent randomization, from 51.2% to 64.8%—an absolute difference of 13.6% with a significant *P* value. IMpassion031 showed an improvement in the pathologic CR rate from 41.1% with chemotherapy alone to 57.6% with chemotherapy plus atezolizumab—an absolute increase of 16.5%.

Why is PD-L1 status a clear predictor of response in the metastatic setting, but not in the early-stage setting?

Another interesting finding of these trials relates to patients with lymph node involvement, in whom a pathologic CR is usually less likely than in those without nodal involvement after neoadjuvant chemotherapy. The patients who had lymph node involvement did especially well with the addition of immunotherapy in both of these studies, however. With chemotherapy alone, patients who have node-positive disease are normally 15% to 20% less likely to have a pathologic CR. In KEYNOTE-522, the pathologic CR rate with chemotherapy alone was 44% in the patients with node-positive disease and 59% in those with node-negative disease. In IMpassion031, the pathologic CR rate with chemotherapy alone was 31% in node-positive disease and 49% in node-negative disease. What was interesting was that when immunotherapy was added, the pathologic CR rates no longer differed between the patients with node-positive and those with node-negative disease. In KEYNOTE-522, the pathologic CR rate with chemotherapy plus immunotherapy was 64.9% in node-positive disease and 64.8% in node-negative disease—identical results. We saw a substantial improvement in the pathologic CR rates in the node-negative patients who received immunotherapy. We saw exactly the same phenomenon in IMpassion031, in which the pathologic CR rate was

57.1% in node-positive disease and 57.8% in node-negative disease—again, identical results.

We also saw that when it comes to pathologic CR, the relative benefit from immunotherapy does not differ between PD-L1–positive and PD-L1–negative patients. In KEYNOTE-522, the added benefit from immunotherapy was 14% in PD-1–positive patients and 18% in PD-L1–negative patients. Similarly, in IMpassion031, immunotherapy added a 19% benefit in PD-L1–positive patients and a 13% benefit in PD-L1–negative patients.

Why is PD-L1 status a clear predictor of response in the metastatic setting, but not in the early-stage setting? Our current understanding is that early-stage tumors are still highly dynamic, so that a tumor that is PD-L1–negative on day 1 may be PD-L1–positive 2 weeks later; the reason is that the start of chemotherapy can cause an influx of immune cells and upregulation of these checkpoints.

Regarding the endpoint of EFS, I just presented our most recent results from KEYNOTE-522 at the virtual ESMO Congress 2021. After a median follow-up of 39.1 months, we saw a statistically significant, highly meaningful improvement in EFS with pembrolizumab. The event rate was 15.7% in the pembrolizumab group and 23.8% in the chemotherapy-alone group, for an HR of 0.63 with the addition of pembrolizumab. Regarding 3-year EFS, the rate was 84.5% in the pembrolizumab group vs 76.8% in the chemotherapy-alone group, an absolute difference of 7.7%.

The rate of distant recurrences was 12.8% with pembrolizumab and chemotherapy vs 20.3% with placebo and chemotherapy, a decrease of 7.5% (HR, 0.61). The fact that we are preventing distant recurrences means that we will eventually improve OS. Although OS follow-up is still a bit short, at just 3 years, we are already seeing a separation of the curves, with an HR of 0.72 that is not statistically significant. We will continue to follow these patients for OS.

Disclosure

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Suggested Readings

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