Making immunotherapy part of routine breast cancer treatment

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Cancer treatment is evolving rapidly, and 2015 was no exception. It was the year of immunotherapy. Following the approval by the US Food and Drug Administration in 2014 of pembrolizumab for melanoma, 2015 saw approvals of nivolumab for melanoma, lung cancer, and kidney cancer; pembrolizumab for lung cancer; and the combination of ipilimumab and nivolimab for melanoma. That's an impressive list of immunotherapy approvals for a single year.

I think that we will continue to see the greater use of immunotherapy in the management of various cancers during 2016. Numerous other immunotherapy agents are in different stages of development, and that is very good news for our patients. Ongoing and future trials will help physicians decide how we select patients for a specific immunotherapy or therapies; which patients will benefit the most from the therapy; how the therapy is sequenced with other regimens; how we manage the side effects; and what the best combinations are. In addition, we need to consider the financial impact of these very expensive agents on the patient. This is something I trust the medical community, payers, and pharmaceutical companies will continue to grapple with during the course of the year.

Breast cancer is far behind the other cancers when it comes to the use of immunotherapies. At the 2015 San Antonio Breast Cancer Symposium, investigators from the JAVELIN and KEYNOTE-028 trials reported on their phase 1b findings with avelumab and pembrolizumab, respectively. The JAVELIN study showed a 4.8% overall response rate with avelumab in heavily pretreated patients with breast cancer (p. 85), and the KEYNOTE-028 reported an ORR of 12% in women with advanced estrogen receptor-positive, HER2-negative breast cancer treated with pembrolizumab (p. 86). Those are modest results, but ongoing clinical trials will continue to help us to understand the role of immunotherapy in breast cancer.

Although the field of cancer genomics is very promising, it has not yet been shown that genomic profiling has any meaningful impact on routine patient care. Many cancer centers and companies that manufacture genomic profiling kits continue to offer and promote profiling outside of a clinical trial context. But actionable mutations from these results are low – about 11%, according to a study by Sohal and colleagues.[1] An actionable mutation means that a patient has a mutation that can be targeted therapeutically and may therefore qualify for a genomically driven clinical trial. At this point, the impact of genomic profiling in a nonclinical trial setting is very limited for routine patient care.[1]

It is therefore important for patients to have access to genomically driven clinical trials so that the potential of these tests can be demonstrated. Ongoing trials such as SIGNATURE, Mypathway, and NCI-MATCH, are addressing these questions prospectively. The strong interest in the first phase of NCI-MATCH, which seeks to determine if treating cancers on the basis of their genetic variance is effective, demonstrates the need for similar trials. However, it also raises some questions about this approach: if the chance of having an actionable mutation is about 10% – or chance of failure is 90% – is that the best way of designing the trial? How do we optimize resources if the failure rate is 90%? Are patients being exposed to unnecessary risk or is it a waste of their valuable time when they are subjected to additional new biopsies?

In addition to the aforementioned immunotherapy trial results reported at the SABCS, several other therapeutic advances in breast cancer were reported, though not all were practice changing. Two studies, BCIRG-006 and EXTnet, in HER2-positive patients were notable. Ten-year follow-up of the BCIRG-006 patients showed that overall survival was the same among patients in both intervention groups – those receiving docetaxel, carboplatin, and trastuzumab (TCH) and those receiving doxorubicin, cyclophosphamide, paclitaxel, and trastuzumab (AC-TH). A third group received doxorubicin, cyclophosphamide, and docetaxel (p. 87). But there was a substantial reduction in the risk of cardiotoxicity and leukemia among women in the TCH arm compared with the anthracycline arms. The results of the study make a very convincing argument for

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using TCH, a nonanthracycline-containing regimen, for HER2-positive patients in the adjuvant therapy.

The EXTnet results (p. 87) showed that in high-risk HER2-positive patients who completed 1 year of trastuzumab, disease-free survival remained significantly higher by adding neratinib in the extended adjuvant setting for 1 year, compared with placebo (92% vs 89.1%, respectively). Neratinib is a highly active HER2-targeted tyrosine kinase inhibitor, but diarrhea is a major side effect and all patients should be on antidiarrheal medication. Effective diarrhea management will be the key to the success of this drug. The role of neratinib in breast cancer treatment is still evolving. The ongoing phase 3 trial in the metastatic setting may give us more clarification about its use in breast cancer treatment.

Other interesting and potentially practice-changing findings were those from the ABCSG 18 trial, which showed an 18% reduction in relapse rate among postmenopausal patients with hormone-receptor-positive breast cancer who received 60 mg denosumab every 6 months. Those findings were consistent with the Oxford overview analysis of adjuvant bisphosphonates.[2] Denosumab has fewer side effects and is easier to administer than bisphosphonates, and I think the findings of this study are practice changing.

Screening update(s)

Recommendations on annual screening mammograms remain controversial. In October last year, the American Cancer Society updated its guidelines for annual mammogram screening, recommending it start at age 45 years.[3] And in January this year, the US Preventive Services Task Force recommended annual screening for women aged between 40 and 74 years, while noting that "that women aged 50 to 74 years are most likely to benefit from regular screening."[4] Hopefully, we will continue to discuss the risk and benefits of screening for patients younger than 50 or older than 75 years. At the end of the day, however, it should be a decision made by the patient and provider based on the patient's risk-benefit ratio.

Armed with the latest clinical findings from the SABCS, the revised breast screening guidelines from ACS and the US PSTF, and the prospect of more refined, practice-changing findings and new approvals this year, we look set for another exciting year in meeting the therapeutic and supportive challenges we face each day.

References

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