

BREAST CANCER IN FOCUS

Current Developments in the Management of Breast Cancer

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Checkpoint Inhibitors in Breast Cancer: Hype or Promise?



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H&O Could you provide a brief overview of immunotherapy?

HM The concept of immunotherapy is not a new one. In fact, back in the 1890s, a surgeon named William Coley noticed that some patients with cancer had spontaneous tumor regressions after a severe infection. After identifying the relationship between infection-related inflammation and tumor regression, Coley undertook experiments whereby he injected patients and their tumors with bacteria—and later, bacterial fragments—in order to induce a systemic immune response as a cancer treatment strategy. For this reason, Coley is considered the forefather of modern immunotherapy.

Unfortunately, interest in Coley's work diminished—in part because of the growing enthusiasm for radiation therapy as a cancer treatment strategy in that era. This history makes it all the more interesting that more than 100 years later, we are actively exploring not only those early principles of induced immune responses as a mechanism for treating cancer, but also strategies that combine immune modulation with localized therapies, such as radiation. Strategies that improve tumor-associated antigen presentation (eg, radiation, cryoablation, or radiofrequency ablation) may be needed because some tumors—including most breast cancers—are not inherently sensitive to immune modulation.

In recent years, we have seen tremendous therapeutic innovation in oncology stemming largely from the successful development of checkpoint blockade strategies. Once the immune system is activated, it is normally held in check by interactions between inhibitory receptors and their ligands. Checkpoint blockade antibodies target cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) or the programmed death 1/programmed death 1

(PD-1/PD-L1) pathway, thereby removing inhibitory signals and permitting robust immune responses. If a tumor-specific immune response can be elicited and tumor-specific immune memory can be induced, these strategies may lead to durable antitumor responses—and potentially, cure.

The first major success story with checkpoint blockade was in metastatic melanoma. Specifically, the addition of ipilimumab (Yervoy, Bristol-Myers Squibb), a fully human antibody to CTLA-4, to dacarbazine resulted in an unprecedented survival benefit in patients with advanced melanoma.¹ Further strides have since been reported with the development of the PD-1-directed antibodies pembrolizumab (Keytruda, Merck) and nivolumab (Opdivo, Bristol-Myers Squibb), as well as combination strategies, such as ipilimumab plus nivolumab. In fact, these drugs have completely transformed the natural history of metastatic melanoma such that 1-year overall survival rates improved from approximately 35% a decade ago to approximately 95% with checkpoint inhibitor strategies.²⁻⁸

Given the tremendous successes observed in advanced melanoma, investigators were keen to determine whether responses to checkpoint blockade strategies could also be elicited in other solid tumors. Within the past 5 years, responses have been reported in many tumor types, including kidney cancer, colorectal cancer, and non-small cell lung cancer. Responses in breast cancer have been more recently reported. However, we are still in the early days of learning how to administer these drugs effectively in breast cancer, and it has yet to be determined whether different strategies are required to effectively treat different breast cancer subtypes, whether predictable biomarkers of response can be identified, and whether these strategies need to be tailored to specific clinical scenarios.

H&O Is breast cancer a good candidate for immunotherapy?

HM A growing body of evidence over the past few years suggests that the presence of immune elements within the tumor or in the tumor stroma has prognostic and predictive value in breast cancer. Many studies have demonstrated that the presence of specialized white blood cells called tumor-infiltrating lymphocytes (TILs) can predict a more favorable natural history in breast cancer. For example, dense TIL populations have been observed more frequently in breast cancers that are “triple negative” or positive for human epidermal growth receptor 2 (HER2), and are associated with improved outcomes.⁹⁻¹² Furthermore, the presence of TILs may predict responses to specific therapies. In one study that randomly assigned women to receive adjuvant chemotherapy with or without a brief course of trastuzumab (Herceptin, Genentech), the presence of significant numbers of TILs predicted responses to trastuzumab.⁹ In a German study of preoperative chemotherapy with or without carboplatin, the presence of TILs predicted responses to carboplatin in both triple-negative and HER2-positive breast cancers.¹³ These findings underscore the inherent interplay between some breast cancers and the immune system, and highlight the potential for immune therapies in breast cancer.

Preliminary results from the first immune therapy clinical trials suggested that some breast cancers are indeed responsive to immunotherapy with checkpoint blockade. The use of PD-1/PD-L1 inhibitors yielded response rates of 19% in 2 studies of women with heavily pretreated, PD-L1-positive, triple-negative breast cancer. One of these studies was presented by Leisha Emens¹⁴ at the 2015 annual meeting of the American Association for Cancer Research, and the other one (KEYNOTE-012) was presented by Rita Nanda¹⁵ at the San Antonio Breast Cancer Symposium (SABCS) in 2014. These response rates are potentially better than one might expect for a population with very heavily pretreated, chemotherapy-resistant triple-negative disease. Of further note, when responses occurred, they were often durable—occasionally lasting beyond 1 year—a phenomenon that is well-described with these strategies in other settings, but would not typically be expected with chemotherapy in a heavily pretreated population.

In a small study that was presented at the 2015 SABCS by Sylvia Adams,¹⁶ the PD-L1 inhibitor atezolizumab (Tecentriq, Roche) in combination with nab-paclitaxel (Abraxane, Celgene) showed impressive responses in triple-negative breast cancer. The response with the combination was nearly 70% in the first-line setting and approximately 25% to 30% in the second-line and third-line settings. And again, when responses occurred, they tended to be durable.

I think that we have consistent data to indicate that there is a role for immunotherapy in the treatment of breast cancer. As with other therapies, we are working to identify correlates or biomarkers to help select patients who are most likely to respond.

For those patients who may not respond to immunotherapy alone, investigators at our institution and other sites are exploring the application of immunotherapy in combination with local treatments, such as radiation or cryoablation. The goal with these combination strategies is to optimize the presentation of tumor antigens to generate a more potent and tumor-specific immune response.

H&O Why has the emphasis been on triple-negative breast cancer?

HM Triple-negative breast cancers appear to be more likely than hormone-sensitive tumors to be associated with immune elements such as TILs, indicating an inherent interaction with the immune system. This inherent immune sensitivity may reflect, in part, the higher mutational load in this subtype and the associated increase in novel antigens for immune presentation. Given the reported response rates of 19% with PD-1/PD-L1-targeted antibodies in women with heavily pretreated triple-negative breast cancer, much of the research has focused on this subtype.

However, studies in other subtypes are underway and 2 studies have been reported in the estrogen receptor (ER)-positive setting, albeit with more modest responses than were reported in the triple-negative setting. Studies are also ongoing in women with HER2-positive disease. Here at Memorial Sloan Kettering Cancer Center (MSKCC), for example, we are studying the use of tremelimumab, a CTLA-4-directed antibody, in women who are undergoing standard-of-care brain irradiation for breast cancer brain metastases. The general idea is for the radiation to break down the tumor into smaller pieces that are more easily digested by immune cells, and then to boost the immune system to those tumor-associated antigens by administering tremelimumab. This study is open to women with both HER2-positive and HER2-negative breast cancer, with concurrent HER2-directed therapy permitted for women with HER2-positive disease. As another example, the PANACEA study (NCT02129556) is an active phase 1b/2 trial investigating pembrolizumab together with trastuzumab in patients with trastuzumab-resistant HER2-positive metastatic breast cancer.

Thus, although initial studies of checkpoint blockade focused on triple-negative breast cancer, these strategies are actively being explored in all subtypes. It is an exciting time for innovation in oncology, and it is anticipated that the results of these and other immunotherapy studies will be reported over the next several years.

H&O What other studies have looked at immunotherapy for breast cancer?

HM At the 2015 SABCS, Hope Rugo presented the results of KEYNOTE-028, a phase 1b study of pembrolizumab alone in 25 women with ER-positive, HER2-negative, PD-L1 overexpressing advanced breast cancer who previously had received chemotherapy.¹⁷ A response rate of 12% was reported, which was encouraging in light of the number of prior therapies (11/25 had ≥ 5 lines of therapy). It also confirmed that some hormone-sensitive tumors are sensitive to immune modulation, and thus supports further research in this subset.

In the JAVELIN study (Avelumab in Metastatic or Locally Advanced Solid Tumors), presented at the 2015 SABCS by Luc Dirix, the PD-L1-directed antibody avelumab was administered to women with breast cancer of any subtype.¹⁸ The reported responses were relatively modest, at 8.6% in the triple-negative breast cancer group and 2.8% in the ER-positive, HER2-negative group. It is difficult to know why the responses in the JAVELIN study were more modest than the other reports to date. However, it is important to note that these have all been small studies, with different criteria to define PD-L1 expression and different assays applied to measure PD-L1 expression. Larger studies across all tumor subtypes are underway and are likely to further inform this field.

Although most of the data for checkpoint blockade in breast cancer pertain to PD-1/PD-L1 blockade, a study of the CTLA-4 antibody tremelimumab also has been reported. In this study, the combination of tremelimumab and exemestane was explored in women with hormone receptor-positive disease that had progressed on endocrine therapy.¹⁹ The combination did not produce any partial or complete responses but led to a 42% rate of stable disease, which is notable because a significant proportion of these women had previously progressed on exemestane alone. I think that the results of this study, along with the results from KEYNOTE-028—and to a lesser degree, JAVELIN—signal that immunotherapy may play a role in hormone receptor-positive breast cancer.

H&O Can PD-L1 expression be used to predict response to checkpoint inhibitors in breast cancer?

HM We do not have the answer to that question yet. We have some evidence that PD-L1 expression is associated with enriched responses to immunotherapy in melanoma, but some patients with PD-L1 overexpression do not respond and other patients without PD-L1 expression do respond. Furthermore, unlike ER or HER2, tumor PD-L1 expression is dynamic, with levels of expression that change in response to specific exposures. For example, tumor T-cell infiltration

results in release of interferon- γ , which in turn upregulates tumor expression of PD-L1. In other words, the tissue tested, the circumstances of the tissue collection, and other parameters can all influence PD-L1 expression results. Thus, the presence of PD-L1 expression may enrich for response, but it does not appear to tell the complete story.

H&O Could you further discuss the use of checkpoint inhibitors in combination with other agents for breast cancer?

HM Immunotherapy can be combined with conventional cytotoxic chemotherapy. The chemotherapeutic agent cyclophosphamide, for example, seems to have a priming effect on the immune system. Numerous studies are looking at combinations of various checkpoint blockade drugs with conventional cytotoxic chemotherapy agents in breast cancer. For example, one study is examining a combination of pembrolizumab and eribulin (Halaven, Eisai) as first-line treatment in breast cancer. Another study is comparing physician's-choice chemotherapy with pembrolizumab as second- or third-line treatment of triple-negative breast cancer (NCT02555657). Our institution is also planning to enroll patients in a study of pembrolizumab with chemotherapy in the first-line setting.

Another approach that we have investigated at MSKCC is the use of neoadjuvant checkpoint blockade with ipilimumab, the CTLA-4-directed antibody, in combination with cryoablation in women with early-stage breast cancer.^{20,21} The idea with this strategy is to apply cryoablation to create tumor fragments before definitive surgery occurs, and concurrently “boost” the immune system with ipilimumab in order to generate a robust tumor-specific immune response. If successful, long-term tumor-specific immune memory could be generated, which could translate into improved recurrence rates—and ultimately, cure. A randomized study comparing preoperative checkpoint blockade plus cryoablation vs standard preoperative care is planned.

H&O What other immunotherapeutic agents besides checkpoint inhibitors might be used in breast cancer?

HM Numerous other immunotherapeutic agents are currently being tested. T-cell agonists, including antibodies that target OX40 and 4-1BB, are under investigation. Unlike antibodies that inhibit immune suppressive targets such as CTLA-4 and PD-1/PD-L1, these agonists work by augmenting T-cell activation. Antibodies to other immune targets, including colony stimulating factor 1 receptor (CSF1R), are under investigation. CSF1R antibodies inhibit downstream signaling and thus, the proliferation, differentiation, and chemotaxis of mononuclear phagocytes. This

may in turn limit cancer progression. Another approach is to inject tumors with an adenoviral vector that has been engineered to overproduce specific cytokines, such as interleukin 12, with the aim of attracting immune elements into the individual's tumor and thus inducing a tumor-specific immune response. At MSKCC, we have an ongoing study exploring that strategy in women with disease that is stable or responsive to first- or second-line chemotherapy. The goal is to see if we can induce a durable break from chemotherapy (NCT02423902).

Another interesting area under investigation in breast cancer is adoptive T-cell therapy with engineered T cells, or chimeric antigen receptor (CAR) T cells. With this approach, an individual's T cells are isolated via leukapheresis and engineered to recognize a specific tumor antigen prior to reinfusion. For example, colleagues at MSKCC have developed CAR T cells that target mesothelin, an antigen that is overexpressed in approximately one-third of triple-negative breast cancers. These research efforts are underway and results are highly anticipated.

H&O Would you say that the use of checkpoint inhibitors in breast cancer is truly promising, or is it being overhyped?

HM I think that checkpoint inhibitors are extremely promising in breast cancer. First, these agents have relatively few significant side effects compared with cytotoxic chemotherapy, which is important from a quality-of-life perspective. Second, for patients with breast cancer who do respond, the responses seem to be durable. This is completely unlike conventional chemotherapy, whereby drug resistance occurs in a relatively predictable way over time. To see durable responses in patients with chemotherapy-resistant triple-negative breast cancer, for example, is a tremendous innovation. Women with chemotherapy-refractory triple-negative breast cancer typically have a poor prognosis, and so the observation of responses in this setting that are durable—potentially beyond the 1-year mark—is remarkable.

We are still learning how to apply and refine immunotherapy strategies for the treatment of breast cancer, and the successful identification of biomarkers of response is needed. However, the data reported to date are certainly encouraging. The possibility of durable, tumor-specific response—and thus, cure—now appears to be within reach.

Suggested Readings

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