MELANOMA IN FOCUS

Current Developments in Melanoma

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The Evolving Role of Surgery in Melanoma

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H&O What has been the traditional role of surgery in melanoma?

VKS Surgery has long been the mainstay of treatment for all early-stage melanomas. We used to say early in my career that whenever surgery is possible, it is also the best treatment for advanced and metastatic melanoma. Dr Donald Morton, my mentor and the inventor of the sentinel node biopsy procedure, famously used to say that the top 3 treatments for melanoma were surgery, surgery, and surgery.

The role of surgery in the treatment of melanoma has become so ingrained that we need to take a step back and ask the question: how do we best use surgery now that we have so many treatments that are curing advanced and unresectable metastatic melanoma? Not only do current treatments have the potential to make surgery more effective, they also open the possibility of less extensive surgery with fewer side effects.

H&O What changes have been occurring when it comes to the role of surgery in melanoma?

VKS The traditional model was maximal surgery followed by adjuvant therapy. If the surgeon was able to remove all the disease, the patient was sent to the medical oncologist to see what systemic treatments could be used to prevent the disease from recurring. We originally used interferon, then we moved to the anti–cytotoxic T-lymphocyte–associated antigen 4 agent ipilimumab (Yervoy, Bristol Myers Squibb), and now we use anti–programmed death 1 (anti–PD-1) drugs such as pembrolizumab (Keytruda, Merck) and nivolumab (Opdivo, Bristol Myers Squibb).

That paradigm has evolved over time. One big change has been the use of sentinel node biopsy and adjuvant therapy to reduce the number of lymph node dissections. Another big breakthrough for advanced and metastatic disease has been the use of neoadjuvant immunotherapy and targeted therapies. The introduction of neoadjuvant therapy in melanoma has changed the question from "what do we do?" to "what do we do first?" We now need to focus on the timing and the sequencing of treatments.

In a study of patients with stage III disease, neoadjuvant immunotherapy treatment was able to better shrink tumors and induce immune responses compared with postoperative immunotherapy.[1] Although tumors were still present after systemic therapy, surgery was able to eradicate the remaining cancer. We also saw complete pathologic responses to just 1 to 3 doses of ipilimumab/nivolumab or pembrolizumab.[2]

These findings led to the transformative phase 2 S1801 clinical trial that was conducted by the Southwest Oncology Group (SWOG).[3] This trial asked a simple question: what if patients with stage III or IV melanoma were randomly assigned to either standard treatment with surgery and lymph node dissection plus 18 cycles of adjuvant pembrolizumab, or experimental treatment in which the only difference was giving the first 3 doses of pembrolizumab before surgery and the remaining 15 doses after surgery? Personally, I was hoping to see that the neoadjuvant/adjuvant approach would prove to be as effective as the all-adjuvant approach—a "draw," if

you will. Instead, we saw that event-free survival at 14.7 months was significantly longer in the neoadjuvant/adjuvant group (n=154) than in the adjuvant-alone group (n=159). Event-free survival at 2 years was 72% (95% CI, 64-80) in the neoadjuvant/adjuvant group and 49% (95% CI, 41-59) in the adjuvant-only group. The rate of grade 3 or higher treatment-related adverse events during therapy was 12% in the neoadjuvant/adjuvant group and 14% in the adjuvant-only group.

The event-free survival findings were surprising, to say the least, and showed that the way we sequence treatments matters just as much as what treatments we use. Why did neoadjuvant treatment help so much? One possible explanation is that those initial pembrolizumab treatments—given while the tumor was still present—activated the lymphocytes that were in or near the tumor, causing the immune system to fight the cancer more effectively. Surgery, by contrast, removed not only the tumor but those infiltrating lymphocytes that might be most critical to recognizing and destroying tumor cells after immunotherapy treatment.

One of the important advantages of neoadjuvant treatment is that it provides the patient and the treatment team with information about how well the tumor responded clinically and pathologically. Finding out that the tumor responded to systemic therapy is very encouraging, which can make subsequent adjuvant therapy feel more tolerable. With adjuvant-only systemic therapy, the patient is experiencing all the side effects of treatment without tangible evidence that the treatment is working. Even if the cancer never returns, we do not know whether this was just because of the surgery or whether the drugs played a role. Now, as we get more comfortable with the longer-term results of neoadjuvant therapy, it seems increasingly likely that those patients who experience a pathologic complete response to neoadjuvant therapy do not need postoperative adjuvant therapy at all. Conversely, for patients who do not respond well to neoadjuvant therapy, we may have the option of either continuing with standard postoperative adjuvant therapy or switching from immunotherapy to targeted therapy for postoperative treatment. That means that we can now begin to personalize postsurgical treatment as well as surgical treatment.

H&O Could you discuss the reduction in lymph node dissection in melanoma?

VKS We are now looking closely at when we may be able to avoid lymph node dissection in a select group of patients with clinical stage III disease, based on the results of the phase 2 PRADO trial of 99 patients with stage IIIB-D nodal melanoma.[4] What we want to do is designate the largest tumor-involved lymph node as the "index" node, mark it, and biopsy it after neoadjuvant immunotherapy. The PRADO investigators used a magnetic seed to mark the index node, whereas at our institution we use a radar-reflecting system called the Savi Scout that includes a clip. The PRADO investigators found that patients who had a major pathologic response in the index lymph node after 6 weeks of neoadjuvant ipilimumab and nivolumab were able to safely skip both lymph node dissection and adjuvant therapy, resulting in significantly lower surgical morbidity and better quality of life.

We mark the index node so we can later confirm that this was a tumor-containing node. What is interesting is that most of the time, the pathologist can tell whether a noncancerous node was once cancerous or whether it was always normal. For example, the pathologist may be able to find microscopic evidence of fibrosis and scarring in the node and say, "I see a lymph node that had a 2-cm area of tumor that is now gone." Further research is looking at whether patients who experience a partial response can also have a degree of reduction in treatment, such as having a lymph node dissection but skipping adjuvant therapy.

H&O Does the use of neoadjuvant and adjuvant therapy have other effects on surgery, such as the excision margins?

VKS We often see patients who present with a thick melanoma and a palpable lymph node at the time of presentation. We used to begin by resecting the primary tumor with a 2-cm margin, but now we go straight to neoadjuvant therapy. We usually see an excellent pathologic response to neoadjuvant therapy at the primary site, which tends to respond even better than the lymph node. We still need to do a lot more research to validate this, but our initial experience has been that if the pathologic response is good, the wide excision can have a 1-cm margin instead of a 2-cm margin.

H&O Does the use of neoadjuvant and adjuvant therapy affect the use of radiation therapy in melanoma?

VKS The use of neoadjuvant and adjuvant therapy absolutely can affect the use of radiation therapy. The need for radiation therapy is a big factor in morbidity, because the rate of lymphedema is much higher with the combination of lymph node dissection and radiation to the lymph node basin than with either one alone. A patient who has a large burden of disease in their lymph nodes who goes straight to surgery will often need not only adjuvant immunotherapy, but adjuvant radiation therapy as well. Not everybody uses radiation therapy in this instance, but at our institution we carry out adjuvant radiation to the nodal basin in these patients, especially if extranodal extension is found in a patient with multiple positive lymph nodes. If we take

that same patient and get an excellent tumor response to preoperative treatment, we can often skip the radiation without affecting the risk of regional recurrence.

On the flip side, if a patient still has a lot of tumor with extranodal extension after preoperative immunotherapy, we know that the risk for both regional and distant recurrence is extraordinarily high. We also know that the patient is resistant to the first-line treatment, so we typically want to use radiation to do everything we can to control the disease. The use of neoadjuvant treatment has been transformative in the ability to personalize postoperative radiation therapy.

H&O What other studies are looking at the evolving role of surgery in melanoma?

VKS We are looking forward the results of the international, phase 3 NADINA trial (NCT04949113), which has some similarities to the S1801 study from SWOG. In S1801, the treatment was the same in the 2 groups except that the order of a few doses was different. Today, treatment for melanoma is more personalized. In NADINA, an estimated 420 patients will be randomized in a 1:1 ratio to receive either 2 cycles of neoadjuvant ipilimumab/nivolumab every 3 weeks followed by lymph node dissection (arm A) or standard upfront lymph node dissection followed by 12 cycles of adjuvant nivolumab every 4 weeks (arm B). Patients with a pathologic partial response or nonresponse in arm A will receive 11 cycles of adjuvant nivolumab, or adjuvant dabrafenib plus trametinib in cases of *BRAF* V600E/K mutation positivity, whereas those with a pathologic complete response will receive no further treatment. If the results of NADINA mirror those of S1801, that will represent further evidence in favor of neoadjuvant therapy, although this particular trial will not address the question of whether omission of lymph node dissection can be safely employed in good responders.

We all want to know the answer to the question: when do we need the big-gun approach of combination immunotherapy and when can we use less-toxic, single-agent anti–PD-1 treatment? Also, how do we perform surgery most safely in someone who has had all this immunotherapy preoperatively? The side effects of immunotherapy can have important consequences in the perioperative period. For example, immunotherapy patients are often on corticosteroids and may have adrenal insufficiency or other endocrine issues. Surgeons need to be very alert to the substantial consequences that can arise from these derangements. Finally, we ought to begin asking the question: can we skip surgery entirely in some people after upfront systemic therapy? If we skip surgery, we lose the ability to have a pathologist examine the tumor and tell us how much of it is cancerous; in other words, how much of a pathologic response was achieved. Although no computed tomography scan, positron emission tomography scan, or magnetic resonance imaging scan is able to give us the equivalent information at this time, we may be able to come up with new biomarkers, imaging approaches, or other ways to tell which patients had excellent responses and hence can avoid overtreatment.

Another important surgical study, which is being led by researchers at the University of Pennsylvania, is examining whether the use of pembrolizumab before sentinel node biopsy can improve outcomes in early-stage melanoma (NCT03757689). A nonpalpable sentinel node is not going to contain much tumor, if any, which makes this approach more difficult than examining an enlarged lymph node. The basic concept is the same, however—namely, that earlier use of pembrolizumab might eliminate cancer in the sentinel node and work better than postoperative administration of the same drug.

H&O Is there anything you would like to add?

VKS It is very important that surgeons embrace the idea of stepping back and letting our medical oncology colleagues treat some of our resectable melanoma patients. We have been taught for so long that upfront surgery is the preferred way: "spare the knife and lose the life." Now we are learning that there are huge advantages to holding off on surgery and making use of neoadjuvant therapy. All surgeons who take care of patients with melanoma, wherever it occurs, need to learn about neoadjuvant therapy. We also need to routinely use percutaneous biopsy, preferably with a localizing clip, instead of excisional biopsy of palpable nodes, so that more patients are eligible for neoadjuvant therapy. This is an exciting time in melanoma treatment, and our patients are seeing the benefits of surgeons, pathologists, medical oncologists, and radiation oncologists all working together.

Disclosures

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