Treating Melanoma Patients Before Surgery

Can new therapies benefit patients with early stage melanoma, where spread of disease has yet to be observed?

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With the advent of targeted and immunotherapies, the past decade has seen tremendous advances for patients facing late stage melanoma. But can these new therapies benefit patients with early stage melanoma, where spread of disease has yet to be observed? Typically, such patients have their tumors surgically removed, and then watch and wait. Over 90% will never see their tumors come back or spread to other sites, but is there a way to prevent recurrence in those patients that will eventually go on to relapse?

One approach currently being tested in clinical trials, termed neoadjuvant therapy, is to treat early stage patients with targeted or immunotherapy before surgical removal of their tumor. In theory, such a treatment could rid the body of any microscopic tumors or circulating tumor cells that cannot be detected by our scans, but can cause the melanoma to recur and become metastatic given sufficient time. Advantages of this approach are that patients with early stage disease tend to respond better to cancer therapies than those with metastatic disease, and treating patients with other anti-cancer drugs like chemotherapy or anti-hormonal therapy before surgery has been shown to shrink tumors in other malignancies, although not necessarily to improve survival. Moreover, for immunotherapy, there are reasons to suspect that treatment before surgery might be particularly effective by virtue of there being more tumor cells present to help prime the immune cells to recognize and attack the target.

Over 40 thought leaders came together for this discussion at the 2019 MRA Scientific Retreat to explore and discuss key issues central to developing and safely applying neoadjuvant therapies for melanoma. Participants included representatives from academia, FDA, industry, National Cancer Institute, and MRA. The session was moderated by MRA Board Member Suzanne Topalian of Johns Hopkins University and MRA Chief Science Officer Marc Hurlbert. Among the topics discussed were how best to test neoadjuvant therapy, how to determine which patients would benefit most from such treatment, and whether such treatment might even preclude the need for surgery.

Topalian noted that “it’s the right time to talk about neoadjuvant therapy in melanoma” given that it has been the focus of nearly 40 clinical trials. Most of these trials are ongoing, and a few have recently reported favorable results. But Marc Theoret and Patricia Keegan of the FDA cautioned

that most of these studies were done in academic settings on small numbers of patients. They stressed the need for larger, industry-supported trials, or for greater harmonization of the types of data collected in small studies so they can be combined to provide a more robust assessment of neoadjuvant therapy in melanoma. Both Keith Flaherty of Massachusetts General Hospital and Gregory Friberg of Amgen suggested NIH fund larger, more robust trials, and provide a means to combine such data across trials

But the harmonization across studies required to pool data is more difficult than it seems. For example, how do you best measure immunotherapy response? Typically, tumor regression is measured – but this may not be appropriate given that tumors treated with immunotherapy frequently expand before shrinking, presumably due to the influx of immune cells. Topalian and others suggested devising new indicators of response. One such correlate could include pathological tumor response, which has been used as a clinical correlate of response for neoadjuvant trials in breast cancer. Tumor samples with 10% or fewer viable tumor cells may serve as an early indicator that patients are responding to neoadjuvant therapy. Dermatopathologist Janis Taube of Johns Hopkins University noted that she and her colleagues have developed a new scoring system for evaluating pathological responses to immunotherapies and stressed that full cross-sections of tumors are needed to evaluate those responses and should be collected during clinical trials.

Ashley Ward of FDA emphasized the need to validate the utility of using pathological response as a surrogate for endpoints like overall survival or progression-free survival. Such validation would likely be necessary for approving any drugs in the neoadjuvant setting. Kellie Malloy of OncoSec Medical indicated that carrying out such trials would be a challenge for industry due to the needed length of trials, numbers of patients needed to enroll, and the high costs since the vast majority of early stage patients never relapse and for those that do, the tumors may not rebound for many years.

One advantage of treating patients prior to surgery is that the degree of response seen in their tumor samples may suggest their risk of relapse after surgery. If the tumor did not respond to neoadjuvant therapy at the time of surgery, they can be given another treatment after surgery, Tara Mitchell of University of Pennsylvania noted.

Other participants stressed the need to strike an appropriate risk/benefit balance with neoadjuvant treatment. Many non- metastatic melanoma patients are cured by surgery alone, so additional treatment may not be warranted, especially when additional treatment carries risk of adverse reactions that in the case of immunotherapy can be lifelong. There is also the risk that while patients are on neoadjuvant therapy, their tumors may not respond and instead continue to grow, becoming too large to be surgically removed. The few studies that have been done show that most melanoma patients who receive neoadjuvant combination immunotherapy will experience immune-related adverse events, including severe autoimmune reactions, such as diabetes or an inflamed colon. “Maybe we need to back away from such aggressive treatment in the neoadjuvant setting,” Topalian said, suggesting treatment with just one immunotherapy, or having a good means for predicting which patients are at greater risk for recurrence and likely to respond to such

immunotherapies.

Current risk prediction models, which are based on how deep the tumor is and whether tumor cells have spread to the lymph nodes, “is refined for melanoma but not perfect,” Topalian said. She stressed the need to select “the most likely patients for relapse.”

Another question neoadjuvant treatment raises is whether its use might allow some patients, whose tumors shrink substantially, to avoid surgery altogether because their tumors will likely go on to completely disappear. “Why not just skip surgery in those cases?” Michael Atkins of Georgetown University and Chair of MRA’s Medical Advisory Panel posited, especially since increasingly, except for its very early stages, melanoma is being viewed as a systemic rather than localized disease that should be treated with a systemic therapy such as immunotherapy, he said. Paul Chapman of Memorial Sloan Kettering Cancer Center agreed and added that, “We could avoid surgery if we see a major response at three weeks.”

All agreed more studies need to be done, and Chapman cautioned “we don’t want to speed neoadjuvant therapy approval when we haven’t established that it works, because it has a lot of financial and toxicity costs.” But he added the robust data about the high relapse rate for Stage 3 melanoma patients “should make us pay attention.” Christian Blank of Netherlands Cancer Institute responded by pointing out that neoadjuvant therapy is less expensive than treatment given after surgery, and may be less expensive than surgery itself, since the drugs are only given for a short period of time. MRA Chief Science Officer Emerita Louise Perkins added that neoadjuvant therapy may also be preferred by patients who prefer to avoid surgery.

The discussion revealed that while neoadjuvant therapy does show great promise for early melanoma patients, many questions remain and given the potential risks involved, proceeding with caution is warranted. “This is a hot topic that is critical to MRA and to the melanoma field,” Hurlbert stressed. Stay tuned.

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