Neoadjuvant Therapy and the Melanoma Standard of Care: Where Does It Fit In?

Some melanoma patients benefit from cancer treatments started before surgery (neoadjuvant) instead of after (adjuvant).

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The standard of care for patients with high-risk Stage 3 melanoma with active disease, palpable lymph nodes (lymph nodes that can be felt), or in-transit metastasis (cancer cells that have started to spread but have not yet reached the lymph nodes) is surgery followed by systemic treatment. Systemic treatment that is given after surgery is called adjuvant therapy. However, in some melanoma patients given adjuvant therapy, their cancer comes back, and better treatment options are needed.

Patients with high-risk Stage 3 melanoma may benefit from a neoadjuvant approach, which is treatment given before surgery. The goals of neoadjuvant therapy include increasing the antitumor immune response and shrinking the tumor. Different types of treatments can be given before surgery, including immunotherapy, targeted therapy, and combinations of these.

Rodabe Amaria, MD, of the University of Texas MD Anderson Cancer Center in HoustonCourtesy of Melanoma Research Alliance

To learn more about neoadjuvant therapy and where it fits within the melanoma treatment

landscape, we talked to Rodabe Amaria, MD, of the University of Texas MD Anderson Cancer Center in Houston, Texas.

Immunotherapy in the Neoadjuvant Setting

Immunotherapy is treatment that aims to increase the immune system's ability to find and kill cancer cells. In melanoma, immunotherapy given as neoadjuvant treatment may lead to a stronger immune response against the tumor than if immunotherapy is given only after surgery.

When considering the comparison between adjuvant and neoadjuvant therapy, Dr. Amaria pointed to the SWOG 1801 clinical trial. In this trial, patients with advanced melanoma were randomized into either a group that received neoadjuvant treatment with 3 doses of the immunotherapy drug pembrolizumab, followed by surgery, and then 15 adjuvant doses of pembrolizumab or a group that underwent surgery first followed by 18 doses of pembrolizumab. Event-free survival (defined as melanoma that has not come back or progressed) at 2 years was 72% in the neoadjuvant group and 49% in the adjuvant group. The frequency of adverse events was similar in the two groups. This trial demonstrated the importance of the order of treatments and that neoadjuvant immunotherapy was advantageous over adjuvant immunotherapy.

Response to neoadjuvant treatment, including neoadjuvant immunotherapy, can be determined by pathologic response assessment:

- The most favorable outcome is pathologic complete response, which means "complete absence of viable tumor in the treated tumor bed." Patients who experience a pathologic complete response after neoadjuvant therapy have a lower chance of their melanoma coming back. Dr. Amaria indicated that if a patient achieves a pathologic complete response following neoadjuvant immunotherapy, then little or no adjuvant (after surgery) therapy is required. This improves quality of life for the patient.

- Patients given neoadjuvant immunotherapy who achieve any pathologic response (meaning 10-50% viable tumor remaining after neoadjuvant treatment) also do well, and adjuvant treatment may possibly be omitted, depending on the patient's individual situation.

- Patients with no pathologic response (meaning >50% viable tumor remaining after neoadjuvant treatment) require post-surgery treatment. Dr. Amaria explained that the take-home point is

that neoadjuvant therapy is a more effective approach than standard upfront surgery followed by adjuvant treatment because it provides better clinical outcomes and higher quality of life for patients.

Targeted Therapy in the Neoadjuvant Setting

Another type of neoadjuvant treatment for patients with BRAF-mutated melanoma is the combination of two targeted therapies, dabrafenib and trametinib. Dabrafenib inhibits the mutant BRAF protein, and trametinib inhibits a related protein called MEK. These drugs work together to block cancer cell growth. Clinical trials have shown that neoadjuvant treatment with these two drugs is highly effective and well tolerated.

In a randomized phase 2 clinical trial at a median follow-up of 18.6 months, median event-free survival was 19.7 months in the group given neoadjuvant dabrafenib and trametinib, followed by surgery, and then additional treatment with these drugs compared with 2.9 months in the group who received these same medications only after surgery (standard of care adjuvant treatment). Because of this large difference between the two groups, continued enrollment in the standard of care group was not advised, and the trial was stopped. Another advantage of neoadjuvant targeted therapy is that treatment may reduce the tumor size so that a patient who was originally not eligible for surgery is now able to undergo surgery.

Future Directions of Neoadjuvant Research

Dr. Amaria stated that although we have made a lot of progress in the last 8-10 years with the use of neoadjuvant treatment, several challenges and unanswered questions remain. The optimal combinations of treatments, timing of administration, and how long they should be given have not been clearly established. The small numbers of patients studied in trials and the short follow-up can also limit interpretation. According to Dr. Amaria, biomarkers that could be used to select treatment or predict response to treatment are mostly for research at this time and are not yet ready for use in everyday clinical practice.

These unanswered questions underscore the importance of clinical trials. Dr. Amaria also explained that neoadjuvant clinical trials generate a lot of data in a short amount of time, which allows the drug development process to move more quickly, identifying new drugs and combination therapies to be tested in more patients in a shorter timeframe.

“Neoadjuvant therapy can be an aggressive treatment, and patients who are considering neoadjuvant treatment should ask their doctor about expected side effects and how many doses they will receive,” stated Dr. Amaria. “However, if they respond well, neoadjuvant treatment plus surgery may be all they need.”

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