MELANOMA IN FOCUS

Current Developments in the Management of Melanoma

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Neoadjuvant Therapy in Melanoma: The Fast Track to Critical New Answers

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H&O What are the potential advantages of neoadjuvant therapy in melanoma?

AT Outcomes are poor for patients with melanoma who are candidates for neoadjuvant therapy; that is, those who have locally or regionally advanced melanoma that is surgically operable. The 5-year tumor recurrence rate for these patients has been reported at approximately 68% to 89% after prior surgical management. The use of newer immunotherapies, targeted agents, and combinations has the potential to make a major impact in the management of these patients.

We hope that neoadjuvant therapy can lead to improvements in outcomes in melanoma just as it has for other solid tumors, including cancers of the head and neck, breast, bladder, esophagus, and rectum. The benefits seen in these patients include improvements in survival, surgical resectability, local control, and organ preservation.

The biggest advantage of neoadjuvant therapy is the ability to test tumor and blood samples both before and after the initiation of systemic therapy. This allows for a complete investigation of antitumor mechanisms of action, along with the conduct of biomarker studies. This may enable more selective application of therapeutic agents to these patients who are more likely to benefit. Such findings would improve the therapeutic index and cost effectiveness of these therapeutic agents.

Secondly, neoadjuvant therapy allows us to avoid any delay in systemic therapy. This is a potential problem in the adjuvant setting because patients need to recover from surgery prior to initiation of therapy. Earlier systemic therapy means earlier targeting of distant micrometastases that could become the source of future disease relapse.

H&O Can studies using neoadjuvant therapy provide meaningful answers based on a smaller sample size?

AT Yes; studies of neoadjuvant therapy can provide urgently needed preliminary data that might not be possible otherwise. Significant findings that may only be possible through small studies of neoadjuvant therapy (given the access to tumor biospecimens before and during systemic therapy) can be further investigated and validated in larger trials, including trials in the adjuvant setting and the advanced-disease setting.

H&O Which agents have been studied for use in neoadjuvant therapy in melanoma?

AT Neoadjuvant studies in melanoma have tested chemotherapy with temozolomide, and immunotherapy with high-dose interferon alfa (IFN-α) and ipilimumab (Yervoy, Bristol-Myers Squibb). Studies found that neoadjuvant chemotherapy with temozolomide had limited activity, and this regimen was not developed further. Two phase 2 biochemotherapy studies (the first by Buzaid and colleagues; the second by Gibbs and colleagues) looked at the combination of the chemotherapeutic agents cisplatin, vinblastine, and dacarbazine in combination with either IFN-α

or interleukin 2; both of these studies demonstrated tumor response rates approaching 50%. However, later randomized clinical trials in metastatic melanoma failed to deliver any survival benefits when biochemotherapy was compared with chemotherapy alone, so both of these regimens were abandoned as neoadjuvant treatment.

Neoadjuvant IFN-α-2b was, however, shown to have important immune-modulating and mechanistic effects in a study from the University of Pittsburgh that was published in the *Journal of Clinical Oncology* in 2006. In this study, 20 patients with melanoma who had palpable regional lymph node metastases underwent surgical biopsy followed by intravenous IFN-α-2b for 4 weeks, complete lymphadenectomy, and subcutaneous maintenance IFN-α-2b for 48 weeks. Biopsy samples were obtained before and after the intravenous regimen of IFN-α-2b. No evidence of recurrent disease was found in 10 of the patients at a median follow-up of 18.5 months. The researchers found that patients whose tumors responded had significantly greater increases in endotumoral CD11c+ and CD3+ cells and significantly greater decreases in endotumoral CD83+ cells compared with those whose tumors did not respond.

Another study, published in *PloS One* in 2014, found immune-modulating and mechanistic effects with neoadjuvant ipilimumab. In this study, 35 patients received ipilimumab given at 10 mg/kg intravenously every 3 weeks for 2 doses, before and after surgery. Tumor and blood biospecimens were obtained at baseline and at surgery. After a median follow-up of 18 months, median progression-free survival was 11 months among the 33 patients available for evaluation. Improved PFS was associated with reductions in circulating myeloid-derived suppressor cells (MDSC) and increases in circulating regulatory T cells.

These findings support further investigations of neoadjuvant IFN-α-2b and also neoadjuvant ipilimumab, possibly in combinations. The biomarker findings warrant further investigations in both the adjuvant and metastatic disease settings, specifically as predictors of therapeutic benefit or disease risk. These studies are ongoing at this time.

H&O And are there any ongoing or planned studies that are looking at neoadjuvant therapy in melanoma?

AT Yes, there are several neoadjuvant studies that are investigating both immunotherapy and targeted therapy. These include 2 major studies at the University of Pittsburgh. This first study, which is nearing completion of accrual, is testing a combination of ipilimumab and high-dose IFN-α-2b (NCT01608594). The second study is testing a combination of the programmed death 1 (PD-1) inhibitor pembrolizumab (Keytruda, Merck) with high-dose IFN-α-2b (NCT02339324). This also is being led at the University of Pittsburgh, in collaboration with a regional consortium of sites in Pennsylvania, Ohio, and New York.

Another study that is being launched is a neoadjuvant study of a combination of ipilimumab and nivolumab (Opdivo, Bristol-Myers Squibb), which has shown promise as treatment for metastatic melanoma. This is a national study that will be taking place across a consortium of 5 or 6 sites.

Other groups are testing neoadjuvant targeted therapy in patients with *BRAF*-mutant melanoma, including dabrafenib (Tafinlar, GlaxoSmithKline) plus trametinib (Mekinist, GlaxoSmithKline), and vemurafenib (Zelboraf, Genentech/Daiichi Sankyo) plus the investigational agent cobimetinib.

H&O How do you see neoadjuvant therapy for melanoma being developed in the future?

AT I think these 4 studies will allow us to identify the optimal neoadjuvant backbone—from both a clinical and immunologic standpoint—that may bring us closer to a cure for these patients.

Other ongoing studies are looking at the use of talimogene laherparepvec, which is known as T-VEC. This agent secretes the cytokine granulocyte-macrophage colony-stimulating factor (GM-CSF).

I think neoadjuvant therapy may ultimately allow us to avoid or reduce the need for aggressive surgery for this group of patients. Neoadjuvant immunotherapy has the potential to cure a significant proportion of these patients, in many cases without surgery.

Suggested Readings

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