Nivolumab: Immunotherapy in Malignant Melanoma

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Background: Although patients diagnosed with melanoma that is confined to the skin have a five-year survival rate of 98%, this number drops to 16% with widely metastatic disease. Melanoma rates have been steadily increasing since the 1970s, but cytotoxic chemotherapy generally prolongs survival by about four months. Nivolumab is an effective immunotherapy agent.

Objectives: This article discusses the use of nivolumab for metastatic melanoma.

Methods: Clinical trial and early postmarketing data were reviewed.

Findings: In clinical trials, patients with advanced melanoma experienced partial sustained responses to nivolumab, a new targeted immunotherapy agent, for more than one year. Nivolumab helps the immune system mobilize lymphocytes that have been inactivated by melanoma cells, enhancing the body’s ability to recognize the cancer as abnormal. Compared to conventional chemotherapy, nivolumab has been shown to greatly improve survival in widespread, inoperable malignant melanoma. Oncology nurses will administer, monitor, and educate patients about nivolumab.

Physiologic Action

Research focusing on cancer cells’ ability to evade detection by the immune system has shown that many cancers can disable the cytotoxic T lymphocytes that normally recognize and kill cancerous cells. For T cells to recognize cancer cells as abnormal, two processes must take place. First, an antigen-presenting cell expresses specific proteins (antigens) from the cancer cell, which are recognized by T-cell receptors. Second, interactions between the T cell and the antigen-presenting cell determine whether the T cell is activated to target and kill cells expressing the specific antigens. This second step serves as a checkpoint in the immune activation process and normally helps prevent overreaction of the immune system. However, if T cells have been repeatedly activated over time, they can become exhausted. At this point, the inhibitory receptor programmed cell death protein 1 (PD-1) is induced on the T cells and they become dormant (Sullivan, Lorusso, and Flaherty, 2013).

Melanoma cells have been found to express the ligands of PD-1 (programmed death-ligand 1 or 2 [PDL-1 or PDL-2]), which prevent T lymphocytes from binding to them. In this manner, they are able to evade immune detection and destruction. Monoclonal anti-PD-1 antibodies are being designed to block this interaction, allowing T cells to recognize tumor cells as abnormal and destroy them. One such drug, nivolumab, shows promise for the treatment of several cancers, including metastatic melanoma.

Nivolumab was approved for unresectable metastatic melanoma in December 2014 and for non-small cell lung cancer in March 2015 (Bristol-Myers Squibb, 2015). Another approved drug, ipilimumab, is being tested for use in combination with nivolumab to increase effectiveness (McDermott & Atkins, 2013). The ligands to which PD-1 binds are often increased on many tumor types, including ovarian, esophageal, breast, cervical, and pancreatic cancers (Merelli, Massi, Cattaneo, & Mandalà, 2014), giving a wide range of potential indications for nivolumab.

Key words: antibodies, monoclonal; anti-programmed cell death protein 1, human; melanoma; molecular targeted therapy; nivolumab; programmed cell death protein 1 receptor

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Clinical trials investigating nivolumab combined with peptide vaccines to observe objective response and time to relapse in patients with resected stage IIIC or IV melanoma. Phase III studies are underway to compare the overall survival and objective response of nivolumab with those of dacarbazine, carboplatin, and paclitaxel. Overall survival rates for nivolumab versus ipilimumab alone or in combination is the objective for another phase III study (Merelli et al., 2014).

Nivolumab has been found to be more tumor specific and less toxic than some other immunotherapies, possibly because it reactivates T lymphocytes in the circulation and the tumor rather than activating T cells in the lymph nodes throughout the body (Merelli et al., 2014). Partial sustained responses to nivolumab were noted for more than one year in patients with advanced melanoma, prostate cancer, non-small cell lung cancer, renal cell carcinoma, and colorectal cancer (Lipson, 2013), with a median duration of response in melanoma of more than two years (Merelli et al., 2014). The overall response rate was 28% in melanoma (Menzies & Long, 2013), compared to 11% with ipilimumab (Bristol-Myers Squibb, 2013) and 40% when the drugs were combined (Merelli et al., 2014).

Biomarkers in Development

The presence of PDL-1 on an individual’s tumor cells may predict the patient’s response to nivolumab (Lipson, 2013); however, the quantity varies with changes in the tumor’s microenvironment (Ascierto, Kalos, Schaer, Callahan, & Wolchok, 2013). Techniques, such as flow cytometry and immunohistochemistry, can be used to evaluate a patient’s T-cell number, phenotype, and levels of activation and suppression (Ascierto et al., 2013). Immune function can also be measured indirectly via assessment of cytokines and chemokines produced by T cells (Ascierto et al., 2013). However, clinicians may need access to specialized or research laboratories to perform these tests. Research continues to develop standardized testing and interpretation measures to yield consistent, reliable results among multiple laboratory sites.

Adverse Reactions

Adverse reactions to nivolumab can be categorized as drug-related or immune-mediated adverse events. Drug-related events, including fatigue, rash, pruritis, diarrhea, decreased appetite, and nausea, occurred in 11% of patients in initial trials (Merelli et al., 2014) and did not appear to be related to dose. Skin reactions, such as erythema, acnecform rash, or inflammation of melanoma sites, were the most common adverse event, occurring in 36% of those who experienced side effects (Topalian et al., 2014). Nurses should assess patients’ skin prior to each nivolumab infusion. Corticosteroids may be prescribed to relieve rash and inflammation (Bristol-Myers Squibb, 2015).

Immune-mediated adverse events included vitiligo, colitis, hepatitis, thyroiditis, autoimmune endocrine dysfunction, and pneumonitis (Merelli et al., 2014). Only 5% of patients who had adverse reactions experienced grade 3 or 4 toxicities (Topalian et al., 2014).

Questions related to the frequency, severity, and duration of immune reactions; treatment of side effects; and treatment impact on patients’ quality of life are being addressed as research into novel immunotherapy agents and combinations continues.

Drug Development, Indications, and Dosing

In 2013, nivolumab was granted fast track designation by the U.S. Food and Drug Administration to expedite approval for its use in non-small cell lung cancer, melanoma, and renal cell carcinoma (Bristol-Myers Squibb, 2015). It is approved as an immunotherapy agent against unresectable or metastatic melanoma and metastatic squamous cell non-small cell lung cancer that has progressed during or after platinum-based chemotherapy (Bristol-Myers Squibb, 2015).

Nivolumab is given at a dose of 3 mg/kg via IV every two weeks until the patient’s tumor shows a complete response or the disease progresses (Bristol-Myers Squibb, 2015; Merelli et al., 2014). Tumor regression was observed in 71% of patients for more than 16 weeks after nivolumab was stopped (Topalian et al., 2014).

Clinical Trials

Nivolumab continues to be studied for safety and efficacy in a variety of cancers, which includes monitoring patients after completion of therapy. Melanoma trials include phase I studies investigating nivolumab combined with peptide vaccines to observe objective response and time to relapse in patients with resected stage IIIC or IV melanoma. Phase III studies are underway to compare the overall survival and objective response of nivolumab with those of dacarbazine, carboplatin, and paclitaxel. Overall survival rates for nivolumab versus ipilimumab alone or in combination is the objective for another phase III study (Merelli et al., 2014).

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Implications for Practice

As immunotherapies and targeted agents become more commonplace, oncology nurses will need to keep up to date on new therapies and monitoring parameters. For example, immune-stimulating agents, such as nivolumab and ipilimumab, cause an inflammatory response that results in edema and can make tumors appear larger on the skin and on radiographic images before the tumors regress. Low-grade immune reactions and tumors that appear worse in the first two to three months of treatment may be associated with better clinical outcomes in malignancies (Torino et al., 2013).

Because of a risk of systemic immune reactions, nurses will need to learn how to recognize and manage immune-related adverse effects of this new class of monoclonal antibodies. Nurses should perform and document a thorough skin assessment and ask the patient about symptoms prior to each infusion. The prescriber should be notified if the patient experiences new or worsening cough, chest pain, abdominal pain, jaundice, gastrointestinal symptoms, or edema (Bristol-Myers Squibb, 2015). Corticosteroids can be used to decrease immune-related symptoms without decreasing the effectiveness of nivolumab (Moffitt Cancer Center, 2015). Nurses should advise patients that skin rash may take as many as seven months to resolve.

Conclusion

Immune checkpoint inhibitors, such as nivolumab, show great promise to control tumor growth, promote survival, and enhance quality of life in patients with advanced melanoma and several other cancers. Nurses will play an important role in educating patients and caregivers and ensuring safe and effective use of these agents.

References


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