is the possibility of long-term disease-free survival. Isolated limb perfusion or infusion with melphalan and hyperthermia are options for patients with extensive cutaneous regional recurrences in an extremity. High complete response rates have been reported and significant palliation of symptoms can be achieved, but there is no change in overall survival.

Patients rendered free of disease after surgery may be at high risk for a local or distant recurrence and should be considered for adjuvant therapy. Radiotherapy can reduce the risk of local recurrence after lymphadenectomy, but does not affect overall survival. Patients with large nodes (>3–4 cm), four or more involved lymph nodes, or extranodal spread on microscopic examination should be considered for radiation. Systemic adjuvant therapy is indicated primarily for patients with stage III disease, but high-risk, node-negative patients (>4 mm thick or ulcerated lesions) and patients with completely resected stage IV disease also may benefit. Either interferon α2b (IFN-α2b), which is given at 20 million units/m^2 IV 5 days a week for 4 weeks followed by 10 million units/m^2 SC three times a week for 11 months (1 year total), or subcutaneous peginterferon α2b (6 μg/kg per week for 8 weeks followed by 3 μg/kg per week for a total of 5 years) is acceptable adjuvant therapy. Treatment is accompanied by significant toxicity, including a flu-like illness, decline in performance status, and the development of depression. Side effects can be managed in most patients by appropriate treatment of symptoms, dose reduction, and treatment interruption. Sometimes IFN must be permanently discontinued before all of the planned doses are administered because of unacceptable toxicity. The high-dose regimen is significantly more toxic than peginterferon, but the latter requires 4 additional years of therapy. Adjuvant treatment with IFN improves disease-free survival, but its impact on overall survival remains controversial. Enrollment in a clinical trial is appropriate for these patients, many of whom will otherwise be observed without treatment either because they are poor candidates for IFN or because the patient (or their oncologist) does not believe the beneficial effects of IFN outweigh the toxicity. The recently approved immunotherapy and targeted agents are being evaluated in the adjuvant setting.

TREATMENT METASTATIC DISEASE

At diagnosis, most patients with melanoma will have early-stage disease; however, some will present with metastases, and others will develop metastases after initial therapy. Patients with a history of melanoma who develop signs or symptoms suggesting recurrent disease should undergo restaging that includes physical examination, CBC, complete metabolic panel, LDH, and appropriate diagnostic imaging that may include a magnetic resonance image (MRI) of the brain and total-body PET/CT or CT scans of the chest, abdomen, and pelvis. Distant metastases (stage IV), which may involve any organ, commonly involve the skin and lymph nodes as well as viscera, bone, or the brain. Historically, metastatic melanoma was considered incurable; median survival ranges from 6 to 15 months, depending on the organs involved. The prognosis is better for patients with skin and subcutaneous metastases (M1a) than for lung (M1b) and worst for those with metastases to liver, bone, and brain (M1c). An elevated serum LDH is a poor prognostic factor and places the patient in stage M1c regardless of the site of the metastases (Table 105-3). Although historical data suggest that the 15-year survival of patients with M1a, M1b, and M1c disease is less than 10%, there is optimism that newer therapies will increase the number of melanoma patients with long-term survival, especially patients with M1a and M1b disease.

The treatment for patients with stage IV melanoma has changed dramatically in the past 2 years. Two new classes of therapeutic agents for melanoma have been approved by the U.S. Food and Drug Administration (FDA). The immune T cell checkpoint inhibitor, ipilimumab, and three new oral agents that target the MAP kinase pathway: the BRAF inhibitors, vemurafenib and dabrafenib, and the MEK inhibitor, trametinib, are now available, so patients with stage IV disease now have multiple therapeutic options **(Table 105-4)**.

TABLE 105-4 TREATMENT OPTIONS FOR METASTATIC MELANOMA

Surgery: Metastasectomy for small number of lesions
Immunotherapy:
Interleukin 2
Immune checkpoint blockade
- FDA approved
▪ Anti-CTLA-4: ipilimumab
- Experimental
▪ Anti-PD-1: nivolumab, lambrolizumab
▪ Anti-PD-L1
Molecular targeted therapy:
BRAF inhibitor: vemurafenib, dabrafenib
MEK inhibitor: trametinib
Chemotherapy: dacarbazine, temozolomide, paclitaxel, albumin-bound paclitaxel (Abraxane), carboplatin

Patients with oligometastatic disease should be referred to a surgical oncologist for consideration of metastasectomy, because they may experience long-term disease-free survival after surgery. Patients with solitary metastases are the best candidates, but surgery increasingly is being used even for patients with metastases at more than one site. Patients rendered free of disease can be considered for IFN therapy or a clinical trial because their risk of developing additional metastases is very high. Surgery can also be used as an adjunct to immunotherapy when only a few of many metastatic lesions prove resistant to systemic therapy.

IMMUNOTHERAPY

The cytokine interleukin 2 (IL-2 or aldesleukin) has been approved to treat patients with melanoma since 1995. IL-2 is used to treat stage IV patients who have a good performance status and is administered at centers with experience managing IL-2-related toxicity. Patients require hospitalization in an intensive care unit–like setting to receive high-dose IL-2 600,000 or 720,000 IU every 8 h for up to 14 doses (one cycle). Patients continue treatment until they achieve maximal benefit, usually 4–6 cycles. Treatment is associated with long-term disease-free survival (probable cures) in 5% of treated patients. The mechanism by which IL-2 causes tumor regression has not been identified, but it is presumed that IL-2 induces melanoma-specific T cells that eliminate tumor cells by recognizing specific antigens. Rosenberg and his colleagues at the National Cancer Institute (NCI) have combined adoptive transfer of in vitro–expanded tumor-infiltrating lymphocytes with high-dose IL-2 in patients who were preconditioned with nonmyeloablative chemotherapy (sometimes combined with total-body irradiation). Tumor regression was observed in more than 50% of patients with IL-2-refractory metastatic melanoma.

Immune checkpoint blockade with monoclonal antibodies to the inhibitory immune receptors CTLA-4 and PD-1 has shown promising clinical efficacy. An array of inhibitory receptors are upregulated during an immune response. An absolute requirement to ensure proper regulation of a normal immune response, the continued expression of inhibitory receptors during chronic infection (hepatitis, HIV) and in cancer patients denotes exhausted T cells with limited potential for proliferation, cytokine production, or cytotoxicity **(Fig. 105-3)**. Checkpoint blockade with a monoclonal antibody results in improved T cell function with eradication of tumor cells in preclinical animal models. Ipilimumab, a fully human IgG antibody that binds CTLA-4 and blocks inhibitory signals, was the first treatment of any kind to improve survival in patients with metastatic melanoma. A full course of therapy is four IV outpatient infusions of ipilimumab 3 mg/kg every 3 weeks. Although response rates were low (~10%) in randomized clinical trials, survival of both previously treated and untreated patients was improved, and ipilimumab was approved by the FDA in March 2011.