diagnosis. Patients with isolated or dominant cervical lymphadenopathy should undergo full endoscopic examination of the upper aero-digestive tract to evaluate for a head and neck primary. Even if a primary is not identified, treatment along a head and neck paradigm with chemotherapy and radiation therapy is often appropriate. In particular, patients with high cervical lymphadenopathy with squamous cell cancer occasionally achieve cure. Supraclavicular lymphadenopathy or adenocarcinoma makes a head and neck primary far less likely, and therapy is less efficacious.

Isolated inguinal lymphadenopathy should prompt a careful examination of the anal, perineal, and genital regions that includes anoscopy. Even in the absence of a defined primary tumor, definitive resection or radiation to inguinal or other isolated solitary or regional lymph nodes may provide long-term tumor control and cures in rare circumstances.

Peritoneal Carcinomatosis in Women

Women who have adenocarcinoma with abdominal carcinomatosis and ascites should be presumptively treated for ovarian cancer. Ovarian cancer paradigms, including initial cytoreductive surgery and ovarian cancer chemotherapy regimens, should be used.

KEY POINTS

- Patients with cancer of unknown primary who have poorly differentiated carcinoma predominantly in the midline, such as those with large retroperitoneal or mediastinal lymphadenopathy, are likely to have a germ cell tumor and should be treated for that possibility with platinum-based chemotherapy.
- Women with a cancer of unknown primary who have axillary lymphadenopathy and a negative breast MRI scan should be treated for presumptive stage II breast cancer.
- Women with adenocarcinoma with abdominal carcinomatosis and ascites should be treated for presumptive ovarian cancer.
- Patients with isolated or dominant cervical lymphadenopathy and cancer of unknown primary should be treated along a head and neck cancer paradigm with chemotherapy and radiation therapy.

Nonfavorable Subgroups of Cancer of Unknown Primary Site

Therapy for CUP that does not fall into one of the favorable subgroups is empirically directed with chemotherapy and radiation therapy based on the pattern of presentation. CUP presenting above the diaphragm should be evaluated and managed as metastatic lung cancer. CUP that is predominantly below the diaphragm should be managed as gastrointestinal cancer.

Chronic medical comorbidities and performance status of the patient greatly influences the range of treatment options. As with other solid tumors, patients with several comorbidities and poor performance status are far less likely to benefit from aggressive chemotherapy and are far more likely to experience serious or life-threatening toxicity. Palliative and hospice care should be considered in such patients. Clinical trials that may demonstrate tumor response are typically restricted to patients with normal organ function and good performance status. The results of those trials are unlikely to be informative regarding the response to therapy or prognosis for patients who are not well enough to have qualified for entry into those trials.

KEY POINTS

- Therapy for cancer of unknown primary that does not fall into one of the favorable subgroups should be managed based on pattern of presentation; cancer presenting above the diaphragm should be treated as metastatic lung cancer and cancer presenting below the diaphragm should be treated as gastrointestinal cancer.
- Palliative or hospice care is appropriate for patients with an unfavorable subtype of cancer of unknown primary site who have comorbidities and poor performance status.

Melanoma

Melanoma has been steadily increasing in incidence worldwide, with risk related to sun exposure. Most melanomas begin in and present with cutaneous disease, but they can also begin in mucosal sites. About half arise in preexisting nevi, but many begin in apparently normal skin. Melanoma can also present in nodal or visceral sites without a known cutaneous or mucosal primary. About 10% of patients with melanoma have a familial history, and mutations in certain genes, such as *CDKN2A*, have been identified in some families. Ocular melanoma is the most common cancer of the eye, and uveal melanomas have a distinct biology and behavior. Epidemiology, diagnosis, and staging of melanoma are discussed in MKSAP 18 Dermatology.

Advances in systemic therapy during the past decade have resulted in significant improvements in survival for metastatic melanoma patients. These advances include the use of molecular therapy targeted at specific gene mutations and immunotherapy, including the use of immune checkpoint inhibitors.

Treatment of Melanoma

Melanoma has the potential to behave quite aggressively, but it is a highly curable disease when detected and treated early with simple excision. For localized melanomas, prognosis is related to the depth of invasion, either by Clark level (I to V) or by Breslow's depth. A high mitotic rate, lymphovascular invasion, and the presence of bleeding or ulceration are poor prognostic signs. Surgical resection margins for melanomas do not

have to be excessive: 1-cm margins are acceptable for lesions that are less than 1 mm in thickness. Patients with melanomas between 1 mm and 2 mm in thickness should be resected with a 2-cm margin provided that a skin graft is not required for closure. Patients with lesions that are greater than 2 mm in thickness should be resected with 2-cm margins. Early-stage patients can be assessed clinically and do not need radiographic staging (for example, CT and PET) and surveillance.

As the depth of invasion increases, the risk of nodal and ultimately distant metastasis increases. Nodal metastases are uncommon and need not be assessed if the patient has thin lesions with a Breslow depth of less than 1 mm. Assessing for lymph node metastasis with lymphatic mapping and sentinel lymph node biopsy is often recommended for intermediate and thicker melanomas. If the sentinel node is positive, a lymph node dissection commonly yields other positive nodes. Although prophylactic lymphadenectomies or completion node dissections for those with positive sentinel nodes have not definitively shown an overall survival benefit, node dissections can be curative in 20% to 50% of patients who present with or who develop regional nodal disease. The use of interferon as adjuvant therapy for resected high-risk disease has been extensively studied and is FDA approved. Although there is some demonstrated improvement in disease-free survival, the overall survival benefit is uncertain, and this therapy is associated with considerable side effects. Adjuvant ipilimumab (see below) also has shown modest benefit in disease-free survival, but as of yet, no overall survival benefit has been shown. Adjuvant nivolumab has been recently shown to be more effective than ipilimumab in node-positive disease.

For distant metastatic disease, surgery may still play a significant role. Melanoma can present with solitary or oligometastatic disease amenable to resection that is curable in some patients. Standard cytotoxic chemotherapy is associated with low response rates and no longer plays a large role in the treatment of metastatic melanoma. The biologic agents interferon-alfa and interleukin-2 can induce responses in some patients, but they cause considerable toxicity and are generally used only in specialized referral centers. The current focus is on targeted therapy for patients with specific gene mutations and on the use of checkpoint inhibitors of programmed cell death transmembrane proteins.

Approximately one half of melanomas harbor a *BRAF* gene mutation (most commonly V600E), and another 20% have a *MEK* or *NRAS* mutation; all of these mutations activate the mitogen-activated protein kinase pathway. Melanomas with these mutations may respond to oral therapy with the *BRAF* inhibitors vemurafenib and dabrafenib. Combining *BRAF* inhibitors with MEK inhibitors trametinib and cobimetinib improves the rate and duration of response. These are available as combined oral agents.

In addition to the efficacy of *BRAF* inhibitors, the use of immune checkpoint inhibitors has revolutionized the therapy and prognosis of patients with metastatic melanoma. Cellular immunity is based on T cells recognizing peptide fragments expressed on the surface of antigen-presenting cells when bound to histocompatibility complex molecules. Cytotoxic T-lymphocyte associated protein 4 (*CTLA4*) is a potent down-regulator of this process. *CTLA4* is stimulated by T-cell activation and various cytokines, serving as an inhibitory factor or braking "checkpoint" on immune activation. The antibody against *CTLA4*, ipilimumab, can result in dramatic tumor response, albeit in a small percentage of patients. Tumor response is independent of *BRAF* status.

The programmed cell death-1 (PD-1) receptor is another transmembrane protein that acts as an inhibitory molecule when bound to the PD-ligand 1 and stops tumor cell apoptosis while down-regulating other aspects of T-cell immune response. Nivolumab and pembrolizumab are both anti-PD-1 antibodies that can result in significant melanoma response rates with sometimes durable response and dramatic survival improvement. Ipilimumab alone has a relatively low response rate and is associated with considerable toxicity, with various immune-related adverse events that can include colitis, hepatitis, pneumonitis, and endocrine insufficiency syndromes. Similar side effects can occur with nivolumab and pembrolizumab but are less frequent, and these antibodies are associated with a higher response rate (30% to 40%). Combining ipilimumab with nivolumab improves results compared with ipilimumab or nivolumab alone. The best dosage, schedule, and sequence for these newer agents continue to be explored.

KEY POINTS

- Surgical resection can be curative in many patients with melanoma, including those with solitary or oligometastatic disease.
- Nodal metastases are uncommon and need not be assessed in patients with thin melanoma lesions (Breslow depth less than 1 mm). HVC
- More than one half of patients have melanoma that harbors a V600E *BRAF* or *MEK* gene mutation, which may respond to the *BRAF* inhibitors vemurafenib and dabrafenib combined with MEK inhibitors trametinib and cobimetinib.
- The combination of ipilimumab, a checkpoint inhibitor targeting cytotoxic T-lymphocyte associated protein 4 (*CTLA4*), and nivolumab, an antibody against programmed cell death-1 receptor, has shown significant improvements in survival for patients with metastatic melanoma.

Follow-up

All patients should be encouraged to perform skin self-examinations as well as receive annual skin evaluations by a dermatologist for life. Patients with early-stage melanoma need not undergo routine blood testing or imaging studies in the absence of signs or symptoms.