count and discussing sperm banking should occur before treatment is initiated unless treatment needs to start emergently. For patients with seminoma confined to the testis (stage I), orchiectomy is usually curative. Options following surgery include active surveillance, single-agent carboplatin, and radiation to para-aortic lymph nodes. Active surveillance consists of regular tumor marker and imaging assessments with the purpose of evaluating for evidence of recurrence. Patients with stage II seminomas receive adjuvant radiotherapy or cisplatin-based chemotherapy depending on the extent of lymphadenopathy. Conversely, in patients with stage I nonseminomatous germ cell tumors, depending on pathologic risk factors, post-surgical therapy can include active surveillance, one cycle of cisplatin-based chemotherapy, or retroperitoneal lymph node dissection (RPLND). High-risk patients usually receive RPLND or chemotherapy. Patients with stage II disease receive RPLND if retroperitoneal lymph nodes are small, with possible adjuvant chemotherapy depending on the extent of disease identified at surgery. For patients with bulky retroperitoneal lymphadenopathy identified on CT, cisplatin-based chemotherapy is recommended. Treatment of advanced disease depends on both histology and risk assessment based on clinical extent of disease and tumor marker levels. All patients with advanced disease receive chemotherapy, most commonly bleomycin, etoposide, and cisplatin, given for three to four cycles. Following treatment, patients are observed closely with periodic history, physical examination, and imaging and tumor marker assessments. For patients with residual radiographic abnormalities following treatment, surgery is sometimes recommended. Patients with relapsed or refractory disease are treated with salvage chemotherapy, and sometimes, autologous hematopoietic stem cell transplantation.

Survivorship issues are particularly important in men with testicular germ cell tumors because of the risk for various treatment-related complications, such as infertility from chemotherapy or RPLND, and the risk for second cancers, including some solid tumors and acute leukemia. There is an increased risk for metabolic syndrome (insulin resistance, hypertension, dyslipidemia, abdominal obesity) after chemotherapy or radiation treatment. Other potential complications include pulmonary toxicity, kidney failure, peripheral neuropathy, ototoxicity, Raynaud phenomenon, and cardiovascular disease.

KEY POINTS

- For most patients with testicular cancer, symptoms are attributable to local disease and include testicular swelling, a testicular mass, or occasionally, a dull pain in the lower abdomen, perianal region, or scrotum.
- After a palpable testicular mass is identified, patients undergo testicular ultrasonography to confirm the presence of a solid mass, following which radical inguinal orchiectomy is usually performed.
- For patients with seminoma confined to the testis (stage 1), orchiectomy is usually curative.

Renal Cell Carcinoma

Renal cell carcinomas arise in the renal cortex and are the most common type of tumors affecting the kidney. The next most common tumor, transitional cell carcinoma of the renal pelvis, is not considered a renal cell carcinoma and is treated similarly to bladder cancer. Patients with renal cell carcinoma are often asymptomatic until they have advanced disease, but possible symptoms include hematuria, an abdominal mass, abdominal pain, and unexplained weight loss. However, the classic triad of flank pain, hematuria, and a palpable abdominal mass occurs in only approximately 9% of patients. Incidental identification of asymptomatic renal mass lesions has been occurring with increasing frequency owing to the large number of abdominal ultrasounds and CT scans done for other reasons.

Renal cell carcinoma has been associated with various paraneoplastic syndromes, including erythrocytosis, AA amyloidosis, polymyalgia rheumatica, and hepatic dysfunction. For patients with symptoms suggestive of renal cell carcinoma, radiographic evaluation with abdominal ultrasonography or CT is recommended. Identification of a solid mass or complex cyst requires further intervention. Small lesions should be biopsied if possible. Larger lesions can be removed without biopsy if imaging findings are consistent with malignancy. Additionally, CT to evaluate the local disease extent and assess for metastatic disease is also recommended.

Patients with nonmetastatic disease undergo radical or partial nephrectomy. For patients who are not surgical candidates, active surveillance or ablative treatment can be considered for those with small tumors. No established adjuvant therapy for renal cell carcinoma is available, although studies using targeted agents are ongoing; consequently, patients with localized renal cell carcinoma are observed following surgery regardless of the local extent of disease. Selected patients with metastatic disease at presentation undergo cytoreductive nephrectomy, which has been associated with improved survival in some studies. Patients with lung-only metastasis and good performance status benefit most. Common sites of metastasis in renal cell carcinoma are the lung, liver, bone, and renal fossa.

Previously, metastatic renal cell carcinoma treatment was disappointing because responses to cytotoxic chemotherapy were limited and survival was often short. Although interleukin-2 can result in long-term remission in about 10% of patients, this agent is expensive, not widely available, and is associated with significant toxicity. However, because of rapidly expanding knowledge about the molecular pathogenesis of renal cell carcinoma, multiple targeted therapies are now available, and many of these agents have been shown to have significant activity against renal cell carcinoma. These agents are categorized as vascular endothelial growth factor (VEGF) inhibitors and mammalian target of rapamycin (mTOR) inhibitors. VEGF inhibitors include bevacizumab and various VEGF tyrosine kinase inhibitors, such as sunitinib, sorafenib, pazopanib, and axitinib. The mTOR inhibitors include temsirolimus and everolimus. Unfortunately, no studies comparing any of these agents have been published to date. Most patients receive a VEGF tyrosine kinase inhibitor in the first-line setting. Those with high-risk disease, which is determined by performance status, elevated serum lactate dehydrogenase level, elevated serum calcium level, and anemia, are often treated with an mTOR inhibitor, although sunitinib is also active against high-risk disease. Agents with demonstrated activity in second-line treatment include axitinib, sorafenib, and everolimus. Bevacizumab, a monoclonal antibody directed against VEGF, can also be used with interferon alfa in first-line treatment or as a single agent in second-line or later treatment.

KEY POINTS

- The classic triad of flank pain, hematuria, and a palpable abdominal mass occurs only in approximately 9% of patients with renal cell carcinoma.
- For patients with suspected renal cell carcinoma, radiographic evaluation with abdominal ultrasonography or CT is recommended, with histologic sampling done on identification of a kidney lesion that is characterized by a mass or a complex cyst.
- Patients with nonmetastatic renal cell carcinoma undergo radical or partial nephrectomy.
- The response of metastatic renal cell carcinoma to traditional cytotoxic chemotherapy is limited and associated with short survival; however, multiple targeted therapies, including vascular endothelial growth factor inhibitors, have significant activity against renal cell carcinoma and may improve survival in select patients.

Bladder Cancer

Bladder cancer is the most commonly diagnosed cancer of the urinary tract. In the United States, almost all bladder cancer is transitional cell carcinoma, which will be the focus of this section. The incidence of bladder cancer has increased by more than 50% during the past 20 to 30 years. Risk factors include advanced age, white ethnicity, various occupational exposures, and cigarette smoking; smoking is the most important risk factor and encompasses current and former smokers and individuals exposed to second-hand smoke. Individuals at occupational risk include metal workers, painters, miners, textile workers, and leather workers, among others.

The most common presenting symptom is painless hematuria, although some patients experience other urinary symptoms, such as frequency, urgency, or dysuria. Identification of new-onset hematuria in patients older than 40 years mandates urologic evaluation with cystoscopy. Biopsy or resection can be performed during initial cystoscopy, depending on the status of the lesion. Most bladder cancer is superficial and does not invade into muscle. These lesions often can be treated locally with transurethral resection of the bladder tumor. Following resection, additional treatment with intravesical bacillus Calmette-Guérin or chemotherapy is usually given, with the amount of treatment determined by risk assessment. The risk of recurrence and of new primary tumors is high following a diagnosis of superficial bladder cancer; consequently, careful surveillance is essential following initial treatment.

Cystectomy is recommended only for patients with frequent, high-grade recurrences occurring within a short period. Conversely, patients with muscle-invasive disease often are treated with radical cystectomy, although bladder-sparing approaches can be considered in some patients. Neoadjuvant cisplatin-based chemotherapy is also recommended, as it can improve survival in patients with muscle-invasive disease; however, the role of adjuvant chemotherapy is much less clear.

Treatment outcomes for patients with metastatic bladder cancer are disappointing. Although cisplatin-based regimens have been shown to improve survival, cures are uncommon, and median survival is only about 15 months.

KEY POINTS

- Identification of new-onset hematuria in patients older than 40 years mandates urologic evaluation with cystoscopy.
- Most bladder cancer is superficial, does not invade into muscle, and can usually be treated locally with transurethral resection of the bladder tumor.
- Patients with muscle-invasive bladder cancer often are treated with radical cystectomy, although bladder-sparing approaches can be considered in some patients.

Lymphoid Malignancies

Epidemiology and Risk Factors

Transient palpable lymphadenopathy is a common physical finding, particularly among young patients, and is virtually always benign, with less than 1% of cases persisting and later found to be lymphoma. Local or systemic infection with bacteria or viruses, drug reactions, and autoimmune disease can all be characterized by transient lymphadenopathy.

Lymphoma is the most common subtype of the hematologic malignancies and is heralded by lymphadenopathy. The fifth most common malignancy, lymphoma constitutes 5% of all cancers and 3% of cancer-related deaths in the United States. In 2013, the American Cancer Society estimated there would be 79,030 new cases of lymphoma diagnosed in the Unites States, 88% of which would be non-Hodgkin lymphoma (NHL) and 12% of which would be Hodgkin lymphoma. The incidence of lymphoma has doubled over the past 30 years; however, Surveillance Epidemiology and End Result statistics (SEER) reported a drastic improvement in 5-year relative survival rates for both non-Hodgkin (47% in 1975-1977

versus 71% in 2002-2008) and Hodgkin lymphoma (72% in 1975-1977 versus 87% in 2002-2008).

NHL occurs more often in men, and the incidence increases with age. Hodgkin lymphoma has a bimodal age distribution, occurring between ages 15 and 45 years and after age 55 years. The cause of some subtypes of lymphoma remains unknown. One exception is mucosa-associated lymphoid tissue (MALT) lymphoma, which is caused by an underlying infection with *Helicobacter pylori*. Other infections, including Epstein-Barr virus, HIV, human T-cell lymphotrophic virus type-1 (HTLV-1), and hepatitis B and C viruses, can also directly drive transformation of lymphoid tissue to lymphoma or contribute indirectly to transformation by causing immunodeficiency, which is also a risk factor for lymphoma. For example, patients who receive immunosuppressive drugs such as cyclosporine or tacrolimus following transplantation may develop lymphoproliferative disorders that evolve to high-grade B-cell NHL.

In addition to chronic inflammation caused by infectious agents, genetic factors and occupational risk factors predisposing to lymphoma include exposure to herbicides, chlorinated organic compounds, and other fertilizing material used in farming. Hodgkin lymphoma survivors have an increased lifetime risk of acquiring NHL, presumably because of the lifelong T-cell defect associated with Hodgkin lymphoma.

KEY POINTS

- The cause of some lymphoma subtypes is underlying infection, including *Helicobacter pylori*, Epstein-Barr virus, HIV, human T-cell lymphotrophic virus type-1, and hepatitis B and C virus infections.
- In addition to chronic inflammation caused by infectious agents, genetic factors and occupational risk factors predisposing to lymphoma include exposure to herbicides, chlorinated organic compounds, and other fertilizing material used in farming.

Evaluation and Diagnosis

Initial workup of patients with lymphadenopathy includes a detailed history of recent travel, insect bites, sexual encounters, injection drug use, blood product transfusions, and all new medications. Fever, night sweats, or unexpected weight loss should be documented. A comprehensive physical examination determines the number of sites, size (small versus large), and consistency (firm and fixed versus soft and moveable) of lymphadenopathy. In addition, careful assessment for enlarged Waldeyer tonsillar ring nodes and hepatic and splenic enlargement is warranted. Patients with soft, small, freely moveable lymph nodes that are limited to one or two adjacent sites and who have no other significant history or physical examination findings can be followed with serial examinations over 6 to 8 weeks and require no other laboratory studies or imaging. Persistent or enlarging lymphadenopathy, particularly when associated with systemic symptoms, may require further assessment, including a chest radiograph, complete blood count with differential, and a serum chemistry panel.

To establish a diagnosis of lymphoma, it is optimal to perform an excisional biopsy to preserve lymph node architecture. Core needle biopsy can be used for deep lymph nodes in place of excision, but fine-needle aspiration should be avoided. The biopsy specimen is used for histopathologic, cytogenetic, fluorescence in situ hybridization (FISH), and immunophenotypic analysis and gene expression profiling. Routine blood tests should include a complete blood count with differential, erythrocyte sedimentation rate, and chemistry panel, including serum urate levels. Serum levels of lactate dehydrogenase, β_2-microglobulin, and immune globulins should also be assessed to assist in diagnosis and establish prognosis. Screening for viral infections, including hepatitis B and C viruses, HIV, HTLV-1, human herpesvirus-8, Epstein-Barr virus, and when indicated in gastric lymphoma, *H. pylori* infection, is appropriate to identify possible causative drivers of lymphoma.

After a histologic diagnosis of lymphoma is made, a total-body PET/CT scan and an iliac crest bone marrow biopsy are done to complete staging. Patients with aggressive lymphoma with involvement of the testes, sinuses, bone marrow, and ocular sites require a lumbar puncture owing to an increased risk for central nervous system involvement.

KEY POINTS

- Patients with small, soft, freely moveable lymph nodes that are limited to one or two adjacent sites and who have no other significant history or physical examination findings can be followed with serial examinations and require no laboratory studies or imaging.
- Persistent or enlarging lymphadenopathy, particularly when associated with systemic symptoms, may require further assessment, including a chest radiograph, complete blood count with differential, a serum chemistry panel, and assessment for viral infections.
- Excisional biopsy and core biopsy for deep lymphadenopathy are appropriate for diagnosing lymphoma; however, fine-needle aspiration should not be used.

Classification, Staging, and Prognosis of Malignant Lymphoma

NHL consists of more than 20 lymphoma subtypes defined by cell surface antigen expression and other morphologic features, including unique molecular profiles. NHL falls into two categories based on a B-cell immunophenotype or a T-cell or natural killer (NK)–cell lineage immunophenotype. B-cell lymphomas account for 85% of all cases of NHL, with T-cell (13%) and NK-cell (2%) lymphomas constituting the remainder. Classification of NHL and Hodgkin lymphoma is summarized in the 2008 World Health Organization 2008 classification system.

Staging of lymphoma consists of structural disease assessment using physical examination, CT imaging, and biopsy of

potential disease sites and disease activity assessment using PET scanning to quantify the standard uptake value (SUV). SUV activity is an indicator of glucose uptake and metabolism, with more aggressive, quickly growing lymphomas using more glucose and thus associated with a higher SUV score. The Ann Arbor staging criteria can be used for determining disease extent for most forms of lymphoma (**Figure 16**).

Lymphomas are classified into three prognostic groups: indolent, aggressive, and highly aggressive. Traditional methods of staging used for other cancers are inadequate for prognosis and treatment planning for NHL. Because of this, the International Prognostic Index (IPI) was developed which generates a score based on patient age, performance status, serum lactate dehydrogenase level, disease stage, and degree of extranodal involvement. The IPI score correlates with progression-free and overall survival after standard therapy, and separate IPI scoring systems have been developed for diffuse large B-cell lymphoma (DLBCL) (revised IPI), mantle cell lymphoma (MIPI), and follicular lymphoma (FLIPI); however, new therapies, plus treatment with rituximab, have lessened the predictive value of these indices.

Indolent lymphomas may not require therapy for decades but are difficult to cure. Conversely, aggressive lymphomas, and particularly, highly aggressive lymphomas such as Burkitt lymphoma, require immediate therapy and often can be cured. Newer modalities of prognostic testing are available, including next-generation sequencing that assesses major portions of tumor genomes to identify mutations predictive of outcome to available therapies. Consequently, classic staging and IPI scores will likely become less relevant over time.

KEY POINTS

- The Ann Arbor staging criteria can be used for determining extent of disease for most forms of lymphoma.
- Use of International Prognostic Index (IPI) scores can help determine the prognosis of patients with diffuse large B-cell lymphoma (revised IPI), mantle cell lymphoma (MIPI), and follicular lymphoma (FLIPI), although new therapies, in addition to treatment with rituximab, have lessened the predictive value of these indices.

Overview and Treatment of Indolent Lymphomas

Follicular Lymphoma

Follicular lymphoma constitutes 20% of all cases of NHL in the United States and Europe and 70% of all cases of indolent

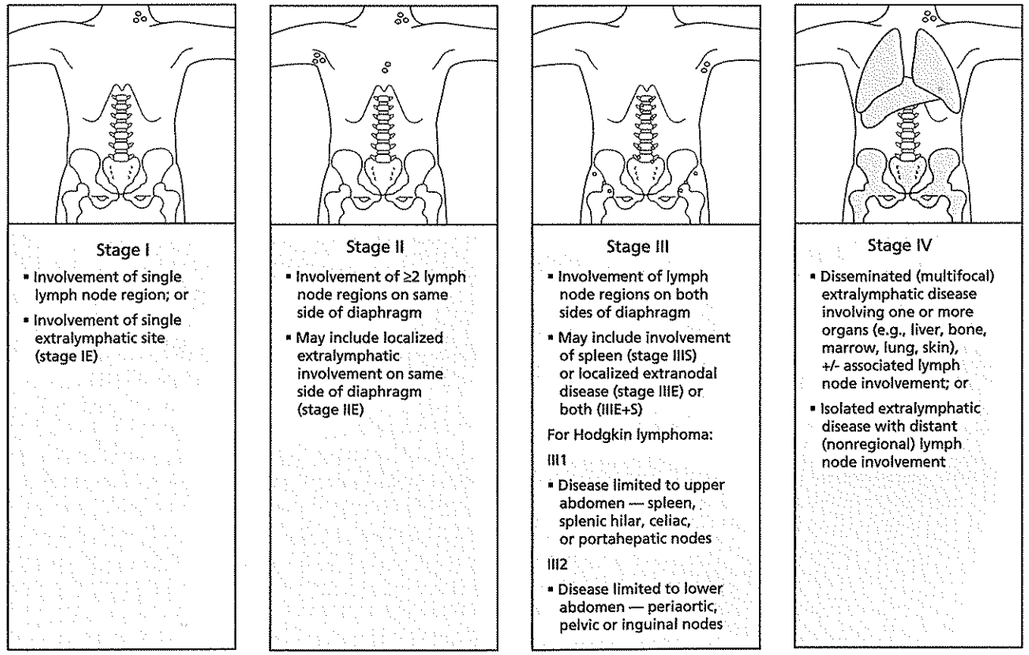

FIGURE 16. Ann Arbor Staging System for Hodgkin and non-Hodgkin lymphoma.

NHL, ranking second in incidence to DLBCL (30%). Follicular lymphoma is characterized by the presence of surface B-cell markers (CD10, 19, 20, and 22) and small cells on morphologic analysis. Incidence increases with increasing age (median age at presentation, 60 years). Invariably, patients present with advanced-stage disease, including bone marrow involvement (stage IV). However, unlike patients with large cell lymphoma, patients with follicular lymphoma have an indolent clinical course (that is, disease is slow to progress), with most patients having lymphadenopathy but no other symptoms at presentation, and some patients not requiring therapy for decades. Diagnosis is confirmed by biopsy of a palpable lymph node and cytogenetic analysis identifying a translocation [t(14:18)] that causes an overexpression of the *BCL2* oncogene.

An international prognostic score specific for follicular lymphoma (FLIPI) has been created that provides prognostic information and helps to guide therapeutic choices. Routinely, therapy is withheld until patients become symptomatic because it is generally not curative, and early initiation of therapy does not change long-term prognosis. Disease causing localized symptoms can be treated effectively with involved-field radiation therapy combined with rituximab. Symptomatic systemic disease requires multiagent therapy that traditionally includes rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP); rituximab plus cyclophosphamide, vincristine, and prednisone (R-CVP); or rituximab and bendamustine. Radioimmunoconjugates that consist of an anti-CD20 antibody directed against CD20-expressing lymphoma and that deliver targeted cytotoxic radiation by being conjugated with a radioisotope (tositumomab and ibritumomab) have been used effectively to induce long-term remissions. Autologous and allogeneic hematopoietic stem cell transplantation (HSCT) is used in younger patients with advanced symptomatic follicular lymphoma whose disease is responsive to standard chemotherapy. Allogeneic transplantation remains the only curative therapy but is associated with a significant risk for morbidity and mortality. New therapeutic approaches include maintenance rituximab for 2 years after completion of rituximab and chemotherapy. Combining rituximab with immune modulators such as lenalidomide may also be effective and may eliminate the need for cytotoxic chemotherapy. Salvage therapy with ibrutinib, a Bruton tyrosine kinase inhibitor, has recently been shown to be highly effective.

KEY POINTS

- The clinical course of patients with follicular lymphoma is usually indolent, with most patients having lymphadenopathy but no symptoms at presentation, and some patients requiring no therapy for decades.
- Allogeneic hematopoietic stem cell transplantation remains the only curative therapy for follicular lymphoma but is associated with a significant risk for morbidity and mortality.

Mucosa-associated Lymphoid Tissue Lymphoma

MALT lines the entire gastrointestinal tract, providing for immune surveillance and initiating immunologic responses to pathogens. Chronic antigen stimulation can lead to clonal expansion of MALT and progress to malignant transformation manifesting as lymphoma. The lymphoma originates in B cells in the marginal zone of MALT and expresses the CD20 surface antigen. The clinical course of MALT lymphoma is usually indolent, and presentation is usually localized. Gastric MALT lymphoma occurs most commonly, but MALT lymphoma can occur throughout the gastrointestinal tract and can also be characterized as extranodal marginal-zone lymphoma when involving a tissue independent of a lymph node. Constituting 50% of all cases of gastric lymphomas, gastric MALT lymphomas usually are localized (stage I and II) and almost always (70% to 98%) are caused by chronic inflammation of an ulcer bed resulting from infection with *H. pylori* diagnosed by upper endoscopy and biopsy. Strikingly, complete remissions are achieved in greater than 70% of patients with limited disease without chemotherapy after completion of antimicrobial therapy directed against *H. pylori* infection and concomitant proton pump inhibitor treatment.

For MALT lymphoma that is not localized to the stomach, or rarely, that is localized to the stomach but does not respond to eradication of *H. pylori* infection, surgical removal, involved-field radiation therapy, and, when indicated, anti-CD20–directed therapy with R-CVP may be effective. Isolated splenic MALT lymphoma is characterized by asymptomatic splenomegaly, circulating lymphocytosis, and a low level of monoclonal serum proteins. Complete responses can occur following splenectomy.

Patients with chronic autoimmune disease, such as Sjögren syndrome or Hashimoto thyroiditis, can present with MALT lymphoma of the salivary glands and thyroid, respectively. Other less frequent sites of presentation include the orbits, lungs, and bladder, all usually associated with a form of chronic inflammation. The large cell variant of MALT lymphoma requires the aggressive chemotherapy used to treat DLBCL.

KEY POINTS

- In patients with mucosa-associated lymphoid tissue lymphoma, complete remission is achieved in most patients with limited disease without chemotherapy after completion of antimicrobial therapy directed against *Helicobacter pylori* infection and concomitant proton pump inhibitor therapy.
- For mucosa-associated lymphoid tissue lymphoma that is not localized to the stomach or is not responsive to *Helicobacter pylori* infection eradication, treatment includes surgical removal, involved-field radiation therapy, and, when indicated, anti-CD20–directed therapy with rituximab combined with multiagent chemotherapy.

HVC

Chronic Lymphocytic Leukemia

B-cell chronic lymphocytic leukemia (CLL) is the most common form of adult leukemia, accounting for 10% of hematologic malignancies. Patients with CLL present at a median age of 70 years, and, with newer therapies, median survival for affected patients is approaching that of age-matched controls. Patients are usually asymptomatic at presentation, with CLL identified by a relative lymphocytosis on a routine complete blood count. Although common in western countries, CLL occurs uncommonly in Japan and China and usually is characterized by a T-cell phenotype. Younger patients develop CLL less frequently, and, when they do, they usually have more aggressive disease. No definitive causative factors are associated with CLL, although it is more common among first-degree relatives.

Diagnosis is confirmed by flow cytometry indicating co-expression of cell surface antigens CD5 and CD23. Several staging criteria from the Rai or Binet staging systems are used. Early-stage disease (stage 0) is limited to patients with elevated lymphocyte counts, mid-stage disease (stage I and II) is associated with lymphadenopathy and splenomegaly, and late-stage disease (stage III and IV) is characterized by suppression of normal hematopoiesis (anemia and thrombocytopenia).

Prognosis is determined by gene mutation status (immune globulin variable heavy-chain mutation) and FISH or array-based karyotyping. In patients with CLL, a deletion of chromosome 17p is concerning because it is associated with a short median survival (<3 years). Whether to initiate therapy depends on several factors, including disease stage, patient age and comorbidities, lymphocyte doubling time, and other prognostic markers. Asymptomatic patients with low-stage disease (stage 0 to II) can be observed without therapy, often for decades. When therapy is indicated, the goal in most patients is palliation. Combination therapy with rituximab and multiagent chemotherapy (fludarabine, cyclophosphamide, and prednisone or rituximab and bendamustine) has been the most effective treatment regimen. Curative therapy (allogeneic HSCT) is reserved for younger patients with aggressive symptomatic disease.

Concomitant autoimmune disease, including immune thrombocytopenia and hemolytic anemia, is common among patients with CLL. Regardless of therapy, patients with CLL have a chronic immunodeficiency that may be characterized by recurrent sinus and pulmonary infections and low serum IgG levels requiring replacement therapy. Surveillance for viral infections and early initiation of antimicrobial agents for presumed bacterial infections are essential. Consideration for live virus vaccines including herpes zoster should be made early in the course of disease before a more profound immunodeficiency develops. Patients are at increased risk for second malignancies and transformation from CLL to a large cell lymphoma (Richter transformation) requiring aggressive multiagent chemotherapy with R-CHOP.

KEY POINTS

- Patients with chronic lymphocytic leukemia usually have no symptoms on presentation, with disease identified by incidentally discovered relative lymphocytosis.
- Diagnosis of chronic lymphocytic leukemia is confirmed by flow cytometry indicating co-expression of cell surface antigens CD5 and CD23, and prognosis is determined by gene mutation status (immune globulin variable heavy-chain mutation) and fluorescence in situ hybridization or array-based karyotyping.
- Asymptomatic patients with low-stage chronic lymphocytic leukemia (stage 0 to II) can be observed without therapy for decades.

HVC

Hairy Cell Leukemia

Hairy cell leukemia is a rare disorder with only 2000 new cases diagnosed annually in the United States and Europe. The incidence is higher in men (5 to 1) and older patients. This disorder is characterized by an accumulation of malignant B cells in the bone marrow and spleen that manifests as pancytopenia and progressive splenomegaly without lymphadenopathy. Typically, an attempt at bone marrow aspiration is unsuccessful (a "dry tap") owing to reticulin fibrosis and packing of the marrow with B cells that have the classic appearance of thread-like projections emanating from the cell surface ("hairy" cells) (Figure 17). Diagnosis is established by bone marrow biopsy results and confirmed by expression of specific cell surface antigens. Treatment with a purine analog such as cladribine plus rituximab for resistant disease results in complete and durable remission in most patients.

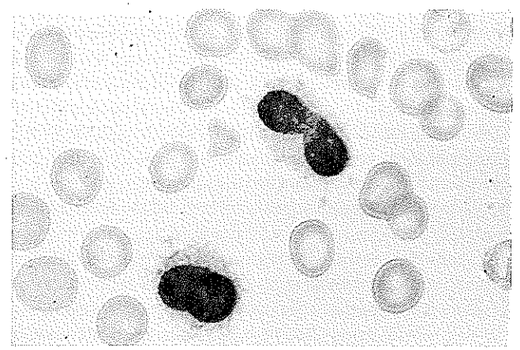

FIGURE 17. Hairy cell leukemia depicted by a peripheral blood smear showing atypical lymphocytes with thread-like cytoplasmic projections from the cell surface.

KEY POINTS

- Hairy cell leukemia is characterized by an accumulation of malignant B cells in the bone marrow and spleen that manifests as pancytopenia and progressive splenomegaly without lymphadenopathy.
- Treatment of hairy cell leukemia with purine analogs plus rituximab for resistant disease results in complete and durable remission for most patients.

Overview and Treatment of Aggressive Lymphomas

Diffuse Large B-Cell Lymphoma

DLBCL is the most common form of lymphoma, and when considered together along with the other less common form, diffuse large T-cell lymphoma, represents 30% of all lymphoma cases. Most patients with DLBCL present with advanced (stage III and IV) disease, fever, night sweats, or weight loss (B symptoms), and experience rapid disease progression without therapy. The way in which the T-cell variant presents depends on the course and subtype of disease.

The IPI is used to assist in determining prognosis before therapy and considers age, serum lactate dehydrogenase level, number of extranodal sites, disease stage, and performance status. Standard therapy for all patients with DLBCL, regardless of stage or prognosis, is R-CHOP. Studies evaluating more aggressive initial therapy for advanced disease in patients with high IPI scores including rituximab plus hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (R-hyper-CVAD), as well as the addition of novel agents, including immune modulators such as lenalidomide, are ongoing. Involved-field radiation therapy is added for patients with bulky disease, with expected cure rates ranging from less than 20% for those with advanced disease and high IPI scores to more than 80% for those with localized disease and low IPI scores. Autologous HSCT is used as salvage therapy in patients with recurrent, chemotherapy-sensitive disease who experienced a disease-free interval of longer than 1 year from initial therapy. The use of allogeneic transplantation in patients with DLBCL remains investigational. Patients with the T-cell variant of large cell lymphoma are treated with CHOP, but outcomes for these patients vary significantly.

The most aggressive forms of large cell lymphoma are Burkitt lymphoma and lymphoblastic lymphoma. Onset of disease is acute, and patients usually present with life-threatening metabolic and structural abnormalities. Treatment is the same as that used to treat acute lymphoblastic leukemia (R-hyper-CVAD for CD20-positive disease), and it is associated with high response rates (80%) and is curative in nearly 50% of patients.

KEY POINTS

- Most patients with diffuse large B-cell lymphoma present with advanced (stage III and IV) disease, have B symptoms (fever, night sweats, or weight loss), and will experience rapid disease progression without therapy.
- Standard therapy for all patients with diffuse large B-cell lymphoma, regardless of stage or prognosis, is rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).

Mantle Cell Lymphoma

Overexpression of cyclin D1, a cell-cycle gene regulator, is associated with a chromosomal translocation [t(11:14)] and can result in mantle cell lymphoma, a rare form of NHL that has a varied clinical course depending on the extent of disease. Usually, patients present with advanced disease characterized by lymphadenopathy, weight loss, and sometimes fever, and have diffuse sites of involvement, including the gastrointestinal tract, bone marrow, and bloodstream. Previously, most patients with mantle cell lymphoma treated with R-CHOP experienced brief remissions and limited median survival (<3 years). Newer approaches using more intensive chemotherapy such as R-hyper-CVAD and including autologous HSCT have increased median survival rates and, occasionally, resulted in durable complete remissions. Allogeneic HSCT, although associated with a significant risk of morbidity and mortality, can produce long-term remissions, even in patients with relapsed disease. Newer FDA approved agents active against relapsed disease include bortezomib, a proteasome inhibitor; temsirolimus; and ibrutinib.

Fifteen percent of patients with mantle cell lymphoma present with localized and indolent disease. This group is younger (<65 years), has normal serum lactate dehydrogenase and serum β_2-microglobulin levels, and has no B symptoms. Median survival in these patients exceeds 6 years, and initiation of therapy can be delayed until symptoms develop. The variable course of mantle cell lymphoma led to the development of a graded prognostic score (MIPI) to guide therapy.

KEY POINTS

- Most patients with mantle cell lymphoma present with advanced disease characterized by lymphadenopathy, weight loss, and occasionally fever, and have diffuse sites of involvement, including the gastrointestinal tract, bone marrow, and bloodstream.
- Allogeneic hematopoietic stem cell transplantation, although associated with a significant risk of morbidity and mortality, can produce long-term remissions in patients with mantle cell lymphoma, even in those with relapsed disease.

Hodgkin Lymphoma

Hodgkin lymphoma encompasses four classic histologic subtypes (nodular sclerosing, mixed cellularity, lymphocyte predominant, and lymphocyte depleted) and one nonclassic subtype (nodular lymphocyte-predominant subtype expressing the CD20 cell surface antigen). Hodgkin lymphoma is distinctive among lymphomas because it commonly presents locally, is associated with firm lymphadenopathy, and allows for therapy to be more readily limited in intensity and duration based on stage and risk factors compared with other types of lymphoma. The presentation is consistent among subtypes and is characterized by palpable, firm lymph nodes, and, in some patients, B symptoms. Other physical examination findings include splenomegaly (30%) and hepatomegaly (5%).

Hodgkin lymphoma is curable in most patients, even those with advanced disease. Therapy is not based on histology in classic Hodgkin lymphoma but rather on stage. The staging evaluation consists of PET scanning and a bone marrow biopsy after lymph node biopsy results confirm a diagnosis.

Stage I and II disease in patients without B symptoms (limited to lymph nodes and the same side of the diaphragm) can be treated effectively with radiation alone or radiation combined with a short course of chemotherapy. Patients with advanced disease (stage III and IV) or those with B symptoms, regardless of stage, usually require a full course of chemotherapy. The combination of doxorubicin, bleomycin, vinblastine, and dacarbazine remains the standard of care for all stages of classic Hodgkin lymphoma when chemotherapy is indicated. Rituximab is added to this combination in patients with CD20-positive disease (nodular lymphocyte–predominant subtype).

The goal of treatment is to administer the least amount of chemotherapy sufficient to achieve a durable remission (cure) while avoiding early and late (chronic) therapy-related toxicity. Therapy-related toxicities include bleomycin-induced pneumonitis, doxorubicin-induced cardiac dysfunction, vincristine-induced neuropathy, and late second malignancies and myelodysplasia. Early repeat PET scanning provides important prognostic information in patients with Hodgkin lymphoma, but not in those with NHL. Patients with Hodgkin lymphoma who have a normal PET scan after two to three cycles of chemotherapy, regardless of residual lymphadenopathy, have more than a 90% likelihood of long-term disease response compared with those with residual PET activity, who have less than a 15% likelihood of being cured with standard therapy. Multiple prognostic risk scores are available to assist in determining long-term prognosis, but PET findings in response to two to three cycles of chemotherapy may be more predictive.

Multiple effective salvage therapies are available for patients with recurrent and resistant Hodgkin lymphoma. Patients with recurrent chemotherapy-sensitive disease are usually candidates for autologous HSCT, whereas those with disease resistant to salvage chemotherapy may achieve long-term remissions with allogeneic HSCT. Brentuximab, an anti-CD30 monoclonal antibody, is also effective as salvage therapy. Patients with Hodgkin lymphoma, including those cured by therapy, may have long-term deficits in T-cell function and should be monitored for late reactivation of viruses.

KEY POINTS

- Hodgkin lymphoma is curable in most patients, even those with advanced disease.
- Patients with stage I and II Hodgkin lymphoma without B symptoms can be treated effectively with radiation alone or radiation combined with a short course of chemotherapy, whereas those with stage III and IV disease or with B symptoms, regardless of stage, usually require a full course of chemotherapy.
- Patients with recurrent chemotherapy-sensitive Hodgkin lymphoma usually are candidates for autologous hematopoietic stem cell transplantation, whereas those with disease resistant to salvage chemotherapy may achieve long-term remissions with allogeneic hematopoietic stem cell transplantation.

Cutaneous T-Cell Non-Hodgkin Lymphoma

The more common forms of cutaneous T-cell NHL are lymphomas expressing T-cell surface antigens (CD4) that infiltrate skin and initially cause rash (mycosis fungoides), and occasionally, circulate in the blood (Sézary syndrome). The large CD4-expressing malignant T cells have classic cerebriform-appearing nuclei and clonal T-cell receptor gene rearrangements. Presentation begins with small areas of pruritic erythema. Disease progression manifests with raised plaques, diffuse skin erythema, and skin ulcers. In the final stages of disease progression, organ infiltration and evolving immunodeficiency cause recurrent bacterial infections, sepsis, and death.

Therapy is guided by disease stage. Early-stage disease (stages I and II) is limited to the skin only and is associated with a median survival of more than 20 years. Early-stage disease is treated effectively with topical glucocorticoids and, when needed, additional retinoids such as bexarotene as well as psoralen and ultraviolet A (PUVA) therapy that can be combined with interferon alfa. Advanced-stage disease (stages III and IV) is characterized by extensive skin and organ involvement and is associated with a median survival of 4 years. Advanced-stage disease requires more aggressive therapy, including electron-beam radiation therapy; photopheresis; chemotherapy including methotrexate, gemcitabine, and CHOP; purine analogs such as pentostatin; histone deacetylase inhibitors such as romidepsin and vorinostat; and monoclonal antibodies such as alemtuzumab. Allogeneic HSCT may be curative in young patients with an appropriate donor.

KEY POINTS

- Early-stage cutaneous T-cell non-Hodgkin lymphoma is treated with topical glucocorticoids, retinoids (when needed), and psoralen and ultraviolet light with interferon alfa.
- Advanced-stage cutaneous T-cell non-Hodgkin lymphoma is treated with chemotherapy, purine analogs, histone deacetylase inhibitors, and monoclonal antibodies.
- Allogeneic hematopoietic stem cell transplantation may be curative in young patients with an appropriate donor.

Cancer of Unknown Primary Site

Introduction

In the United States, approximately 35,000 patients receive a diagnosis of cancer of unknown primary site (CUP) annually. Continued improvements in diagnostic imaging have resulted in decreased frequency of CUP diagnosis.

Diagnosis and Evaluation

CUP is a diagnosis of exclusion established in patients with a solid metastatic tumor after a detailed medical history and physical examination have been done and imaging studies or other diagnostic studies have not identified a primary tumor site.

Diagnostic efforts should focus on identifying whether a patient is among the approximately 20% of patients with CUP who have a more favorable prognosis and who can benefit from a specific treatment strategy. A biopsy obtained from the site that can be sampled in the safest, least invasive manner is performed, and specimens are evaluated by immunohistochemical stains consistent with the tumor's pattern of presentation to attempt to establish a diagnosis of a more treatable subtype of CUP. The clinical evaluation should not involve an exhaustive search for a primary site because detection of an asymptomatic and occult primary tumor does not improve outcome. Physicians should discuss with patients and their families that focusing on identification of the primary tumor can distract from the more important issue of managing the metastatic cancer. Efforts to identify primary tumors should focus only on those tumors that are suggested by the clinical presentation or could be managed with a specific, effective therapy. For example, upper endoscopy and colonoscopy are warranted in patients with evidence or symptoms of gastrointestinal bleeding but should not be done routinely. Men should undergo a testicular examination, a prostate examination, and serum prostate-specific antigen measurement. Women should undergo breast examination, mammography, and a full gynecologic examination.

Measurement of serum tumor marker levels, such as carcinoembryonic antigen, CA-19-9, CA-15-3, and CA-125, is rarely helpful and virtually never diagnostic. Although PET scans may sometimes suggest the location of a primary tumor, these findings are rarely definitive and do not improve long-term outcome.

Although several companies currently offer molecular analyses such as gene expression profiling or microRNA profiling to attempt to identify the site of tumor origin in patients with CUP, these approaches have yet to be validated in randomized prospective trials and are not considered standard practice.

KEY POINTS

- The clinical evaluation in patients with cancer of unknown primary site should not involve an exhaustive search for a primary tumor because finding an asymptomatic and occult primary site does not improve outcome. **HVC**
- In patients with cancer of unknown primary site, measurement of serum tumor marker levels, such as carcinoembryonic antigen, CA-19-9, CA-15-3, and CA-125, is rarely helpful and virtually never diagnostic. **HVC**
- Although PET scans may sometimes suggest the location of a primary tumor, these findings are rarely definitive and do not improve long-term outcome in patients with cancer of unknown primary site. **HVC**

Prognostic Subgroups of CUP

If a primary tumor site is identified, the patient no longer has CUP and should receive treatment that is appropriate for the new diagnosis. For those patients who retain a CUP diagnosis, evaluation is focused on identifying the prognostic subgroups into which their disease is categorized.

Favorable Subgroups

Isolated Regional Lymphadenopathy

Patients with CUP who have lymphadenopathy in a single lymph node or single lymph node region belong to a potentially more treatable subgroup of patients with CUP.

Women with adenocarcinoma limited to lymph nodes in one or both axillae have locoregional breast cancer until proved otherwise and should undergo MRI of the breasts. If a primary tumor is identified on MRI imaging, the patient should be managed as appropriate for her breast cancer. However, even patients with negative MRI findings should be treated for presumptive stage II breast cancer and undergo mastectomy and appropriate axillary lymph node management. Although a primary breast cancer tumor is identified on pathologic inspection of resected breast specimens in 50% women with CUP and axillary lymphadenopathy, the management and prognosis of these patients are similar to that of

women with breast cancer whether or not a primary breast cancer tumor is identified.

Patients with isolated cervical lymphadenopathy should undergo triple endoscopic examination (upper endoscopy, bronchoscopy, and laryngoscopy) to identify a head and neck primary tumor site. However, even patients in whom a primary tumor site is not identified should receive chemotherapy and radiation therapy for head and neck cancer, which yields a high response rate and can be curative in some patients, especially those with squamous cell histology and nonbulky cervical lymphadenopathy. Patients with adenocarcinoma or supraclavicular lymphadenopathy have a worse prognosis; however, treatment recommendations for adenocarcinoma and squamous cell histology in these patients are similar in the absence of identification of other disease sites.

Patients with isolated inguinal lymphadenopathy should undergo a thorough anorectal, perineal, and genital examination. In the absence of identification of a primary site, resection or locoregional radiation therapy may result in a favorable outcome. Resection or localized radiotherapy may also be used to manage other isolated solitary or regional enlarged lymph nodes.

Peritoneal Carcinomatosis in Women

Women with CUP characterized by ascites and abdominal carcinomatosis are regarded as having ovarian cancer until proved otherwise and are managed with cytoreductive surgery and ovarian cancer chemotherapy regimens.

Poorly Differentiated Nonadenocarcinoma

Certain groups of patients with poorly differentiated CUP that cannot be identified as adenocarcinoma may benefit from specific chemotherapeutic approaches. Young men with poorly differentiated carcinoma that is relatively symmetrical around the midline and is characterized by bulky retroperitoneal or mediastinal lymphadenopathy may have an unrecognized germ cell tumor. These patients require measurement of serum α-fetoprotein and β-human chorionic gonadotropin levels, a testicular examination, and testicular ultrasonography. Management consists of platinum-containing germ cell tumor regimens and germ cell treatment paradigms.

Poorly differentiated neuroendocrine tumors constitute another nonadenocarcinoma CUP subgroup that may benefit from specific chemotherapeutic strategies. Metastases predominantly to the liver and to bone are common. Therapy with platinum-based chemotherapy using a regimen similar to that used to treat small cell lung cancer often results in responses, and occasionally, complete clinical responses. Note that only high-grade, poorly differentiated neuroendocrine tumors are sensitive to platinum-based regimens; well-differentiated neuroendocrine tumors do not respond to this approach.

KEY POINTS

- Patients with cancer of unknown primary site and isolated cervical lymphadenopathy should undergo triple endoscopic examination (upper endoscopy, bronchoscopy, and laryngoscopy) to identify a head and neck primary tumor site.
- Women with adenocarcinoma limited to lymph nodes in one or both axillae have locoregional breast cancer until proved otherwise and should undergo MRI of the breasts.
- Patients with cancer of unknown primary site and isolated inguinal lymphadenopathy should undergo a thorough anorectal, perineal, and genital examination.
- Young men with poorly differentiated carcinoma that is relatively symmetrical around the midline and characterized by bulky retroperitoneal or mediastinal lymphadenopathy may have an unrecognized germ cell tumor.

Nonfavorable Subgroups

There are no accepted standard treatment regimens for patients with nonfavorable CUP (those patients with CUP who do not fit into one of the favorable subgroups); therapy tends to be empiric, and the prognosis is often poor. The use of gastrointestinal cancer regimens for CUP that is mostly below the diaphragm and lung cancer regimens for CUP that is mostly above the diaphragm is reasonable. Accurate assessments of performance status, as well as liver, kidney, and bone marrow function, are important when developing treatment strategies. Patients who are medically fit (Eastern Cooperative Oncology Group performance status of 0 or 1; see Table 48) are most likely to benefit from and tolerate aggressive chemotherapy compared with those who are debilitated or have multiple comorbidities and for whom supportive therapy may be appropriate.

KEY POINT

- Gastrointestinal cancer regimens are used to treat cancer of unknown primary site (CUP) that is mostly below the diaphragm, and lung cancer regimens are used for CUP that is mostly above the diaphragm.

Melanoma

Epidemiology, diagnosis, and staging of melanoma are discussed in MKSAP 17 Dermatology.

Treatment

Wide local excision is the standard of care for patients with nonmetastatic melanoma. Recommended margins are 0.5 cm for in situ lesions, 1 cm for melanomas with less than 1 mm of invasion, and 2 cm for melanomas with deeper invasion.