Lymphomas, Multiple Myeloma

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Plan of lecture

- **Lymphomas, Multiple Myeloma**: etiology and pathogenesis;
- **Lymphomas, Multiple Myeloma**: diagnosis;
- **Lymphomas, Multiple Myeloma**: treatment.

Lymphomas

Lymphomas are a heterogeneous group of tumors arising in the reticuloendothelial and lymphatic systems. The major types are Hodgkin lymphoma and non-Hodgkin lymphoma Lymphomas were once thought to be absolutely distinct from leukemias. However, better understanding of cell markers and tools used to evaluate those markers now show that the distinction between these 2 cancers is often vague. The notion that lymphoma is relatively restricted to the lymphatic system and leukemias to the bone marrow, at least in early stages, is also not always true.

Malignant lymphoma cells can populate the bone marrow and the blood as well as the lymph nodes. This is more common in the low grade, or indolent, non-Hodgkin lymphomas, such as chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) or marginal zone lymphoma and the more aggressive mantle cell lymphoma.

Lymphomas

Non-Hodgkin lymphomas are a heterogeneous group of disorders involving malignant monoclonal proliferation of lymphoid cells in lymphoreticular sites, including lymph nodes, bone marrow, the spleen, the liver, and the GI tract. Presenting symptoms usually include peripheral lymphadenopathy. However, some patients present without lymphadenopathy but with abnormal lymphocytes in circulation. Compared with Hodgkin lymphoma, there is a greater likelihood of disseminated disease at the time of diagnosis. Diagnosis is usually based on lymph node or bone marrow biopsy or both. Management strategies may include watch and wait, chemotherapy, targeted drugs (eg, kinase inhibitors), and immunotherapies (eg, monoclonal antibodies, chimeric antigen receptor T cells); occasionally, radiation therapy is added. With few exceptions, stem cell transplantation is usually reserved for patients with aggressive lymphomas after incomplete remission or relapse.

Non-Hodgkin lymphoma is more common than Hodgkin lymphoma. It is the 6th most common cancer in the US and represents 4% of all new cancers in the US each year and 3% of all cancer deaths.

Lymphomas [1]

Over 70,000 new cases are diagnosed annually in all age groups. Non-Hodgkin lymphoma is not one disease but rather a category of lymphocyte cancers with a number of subgroups largely divided into aggressive and indolent types Incidence increases with age (median age, 67 years).

(By **Peter Martin**, MD, Weill Cornell Medicine; **John P. Leonard**, MD, Weill Cornell Medicine; Last full review/revision Jun 2020| Content last modified Jun 2020 **Non-Hodgkin Lymphomas;** Last full review/revision Jun 2020| Content last modified Jun 2020; https://www.msdmanuals.com/professional/hematology-and-oncology/lymphomas/non-hodgkin-lymphomas)

Etiology

The cause of non-Hodgkin lymphoma is unknown, although, as with the leukemias, substantial evidence suggests a viral cause (eg, human T-cell leukemia-lymphoma virus, Epstein-Barr virus, hepatitis B virus, hepatitis C virus, HIV, human herpesvirus 8). Bacteria such as *Helicobacter pylori* also increase lymphoma risk.

Lymphomas [1]

Patients at increased risk of non-Hodgkin lymphoma include those with

- Primary immunodeficiency
- Secondary immunodeficiency (eg, when induced by immunosuppressive drugs, such as those used in rheumatologic disorders and post-solid organ transplant)
- Exposure to certain chemicals (eg, some herbicides and insecticides)
- Chronic inflammation and reactive lymph node hyperplasia

Lymphomas [1]

- Non-Hodgkin lymphoma is the 2nd most common cancer in HIV-infected patients, and some AIDS patients present with lymphoma. Indeed, patients with non-Hodgkin lymphoma should generally be screened for HIV and hepatitis viruses.

Genetic factors appear to play a role. Recent evidence shows that certain single nucleotide polymorphisms increase the risk of lymphoma. Also, patients with a first-degree relative with Hodgkin or non-Hodgkin lymphoma have an increased risk of non-Hodgkin lymphoma.

Pathophysiology

Most (80 to 85%) non-Hodgkin lymphomas arise from B lymphocytes; the remainder arise from T lymphocytes or natural killer cells. Either precursor or mature cells may be involved. The stage of lymphocyte differentiation at which the oncogenic event occurs determines the disease presentation and outcome.

Lymphomas [1]

Most lymphomas are nodal with variable involvement of the bone marrow and peripheral blood. A leukemia-like picture with peripheral lymphocytosis and bone marrow involvement may be present in up to 50% of children and about 20% of adults with some types of non-Hodgkin lymphoma.

Hypogammaglobulinemia caused by a progressive decrease in immunoglobulin production is present in 15% of patients at diagnosis. This increases the risk of serious bacterial infection and may require replacement with IV immune globulin.

Lymphomas [1]

Classification

Pathologic classification of non-Hodgkin lymphoma continues to evolve, reflecting new insights into the cells of origin and the biologic bases of these heterogeneous diseases. The 2016 WHO classification is valuable because it incorporates immunophenotype, genotype, and cytogenetics, but numerous other systems exist (eg, Lyon classification).

Non-Hodgkin lymphomas are commonly also categorized as indolent or aggressive:

- Indolent: Slowly progressive and responsive to therapy but not typically curable with standard approaches
- Aggressive: Rapidly progressive but responsive to chemotherapy and often curable
- In children, non-Hodgkin lymphoma is almost always aggressive. Follicular and other indolent lymphomas are unusual. The treatment of these aggressive lymphomas (Burkitt, diffuse large B cell, and lymphoblastic lymphoma) presents special concerns, including gastrointestinal tract involvement (particularly in the terminal ileum); meningeal spread (requiring cerebrospinal fluid prophylaxis or treatment); and other sanctuary sites of involvement (eg, testes, brain). In addition, with these potentially curable lymphomas, treatment of adverse effects as well as outcome must be considered, including late risks of secondary cancer, cardiorespiratory sequelae, fertility preservation, and developmental consequences. Current research is focused on these areas as well as on the molecular events and predictors of lymphoma in both children and adults.

Lymphomas [1]

Symptoms and Signs

Most patients present with

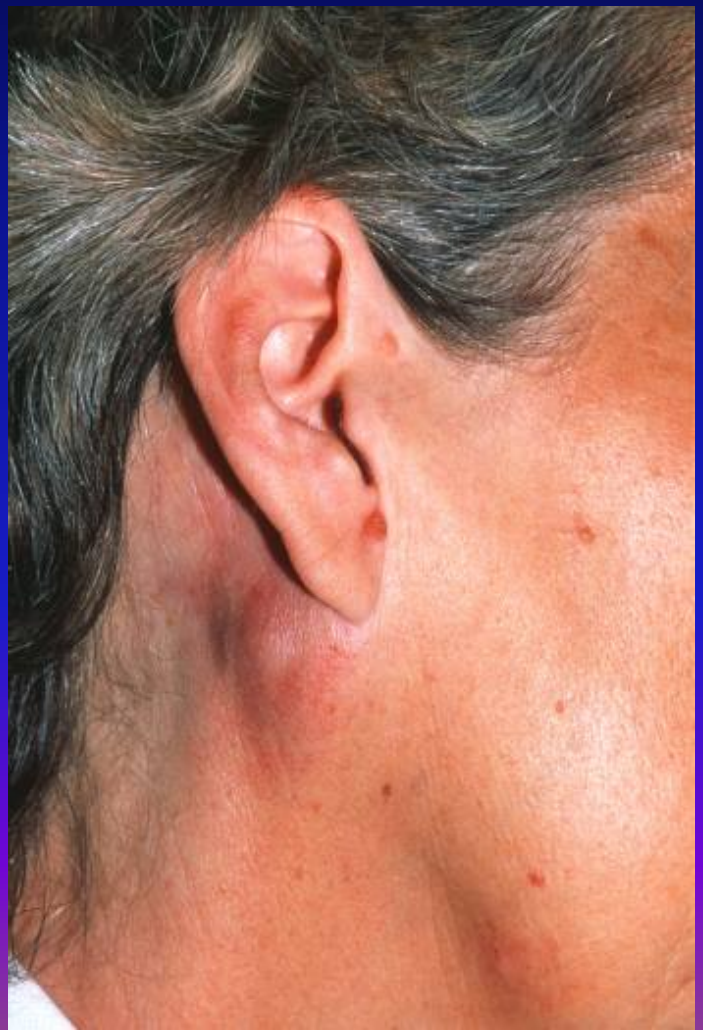
- Asymptomatic peripheral lymphadenopathy
- Enlarged lymph nodes can be rubbery and discrete and later coalesce into masses. Affected nodes are usually not painful, unlike the tender nodes that often occur with viral infections. Nodal involvement is localized in some patients, but most patients have several areas affected. The initial physical examination should carefully look for nodes in the cervical, axillary, inguinal, and femoral regions.
- In some patients, enlarged mediastinal and retroperitoneal nodes produce pressure symptoms. The most important of these are
- Compression of the superior vena cava (SVC): Shortness of breath and facial edema (SVC syndrome)
- Compression of the external biliary tree: Jaundice

Lymphomas [1]

- Compression of the ureters: Hydronephrosis
- Bowel obstruction: Vomiting and obstipation
- Interference with lymph drainage: Chylous pleural or peritoneal fluid or lymphedema of a lower extremity he **skin** is involved in some non-Hodgkin lymphomas. B-cell non-Hodgkin lymphoma can affect the scalp (follicular non-Hodgkin lymphoma) or the legs (large cell non-Hodgkin lymphoma), typically causing slightly raised, erythematous nodules. In cutaneous T-cell non-Hodgkin lymphoma, skin lesions can be diffuse, nonpalpable erythema or discrete papules, plaques, or tumors.

Systemic symptoms (eg, fatigue, fevers, night sweats, weight loss) can be the first manifestations in some patients, most commonly in aggressive lymphomas. These patients may not have noticed lymphadenopathy or not have external, palpable disease; these patients require CT or positron emission tomography (PET) imaging to discover the lesion(s).

Non-Hodgkin Lymphoma (Posterior Auricular Lymphadenopathy) DR P. MARAZZI/SCIENCE PHOTO LIBRARY



Lymphomas [1]

Anemia is initially present in about 33% of patients and eventually develops in many. It may be caused by bleeding due to gastrointestinal lymphoma, with or without low platelet levels; hemolysis due to hypersplenism or Coombs'-positive hemolytic anemia; bone marrow infiltration due to lymphoma; or marrow suppression due to chemotherapy or radiation therapy.

Manifestations of some specific lymphomas

Adult T-cell leukemia-lymphoma, which is associated with human T-lymphotropic virus 1 (HTLV-1), has a fulminating clinical course with skin infiltrates, lymphadenopathy, hepatosplenomegaly, and leukemia. The leukemic cells are malignant T cells, many with convoluted nuclei. Hypercalcemia often develops, related to humoral factors rather than to direct bone invasion.

Anaplastic large cell lymphoma may cause rapidly progressive skin lesions, adenopathy, and visceral lesions. This disease may be mistaken for Hodgkin lymphoma or metastatic undifferentiated carcinoma.

Lymphomas [1]

Diagnosis

- Lymph node biopsy
- Often unilateral bone marrow aspiration and biopsy
- FDG-PET/CT of chest, abdomen, and pelvis for staging
- MRI of brain and/or spinal cord if neurologic symptoms are present
- As with Hodgkin lymphoma, non-Hodgkin lymphoma is usually suspected in patients with
- Painless lymphadenopathy
- Mediastinal adenopathy detected on a chest x-ray or CT done for other reasons
- Painless lymphadenopathy can also result from infectious mononucleosis, toxoplasmosis, cytomegalovirus infection, primary HIV infection, or leukemia.
- Similar chest x-ray findings can result from lung carcinoma, sarcoidosis, or tuberculosis.
- Less commonly, patients present after a finding of peripheral lymphocytosis on a complete blood count (CBC) done for nonspecific symptoms. In such cases, the differential diagnosis includes leukemia, Epstein-Barr virus infection, and Duncan syndrome (X-linked lymphoproliferative syndrome).
- Tests needed to make the diagnosis are followed by tests to complete staging and assess etiology and prognosis (1).

Lymphomas [1]

Diagnostic tests

- Enlarged lymph nodes are biopsied. If a node is palpable, no imaging is required initially, although CT or ultrasonography may be needed to properly plan subsequent tests.
- If the lesion is easily palpable, an excisional biopsy is preferred. If the lesion is in the lung or abdomen, a core needle biopsy (18- to 20-gauge needle) done using CT or ultrasound guidance can often obtain an adequate specimen for diagnosis. A fine needle biopsy (percutaneous or bronchoscopic) frequently will not produce adequate tissue, especially for initial diagnosis; core biopsy is preferred if deemed safe.
- Biopsies should be reviewed by a pathologist with expertise in lymphoma diagnosis. If this review is not available locally, the slides should be sent to a reference laboratory with hematopathology expertise. The proper classification of non-Hodgkin lymphoma is critical for treatment planning. Non-Hodgkin lymphomas are potentially curable, but without a precise diagnosis, optimal therapy may not be chosen.

Lymphomas [1]

- Histologic criteria on biopsy include destruction of normal lymph node architecture and invasion of the capsule and adjacent fat by characteristic neoplastic cells. Immunophenotyping studies to determine the cell of origin are of great value in identifying specific subtypes and helping define prognosis and management; these studies also can be done on peripheral cells if they are present, but typically these stains are applied to formalin-fixed, paraffin-embedded tissue. Demonstration of the leukocyte common antigen CD45 by immunoperoxidase rules out metastatic cancer, which is often in the differential diagnosis of “undifferentiated” cancers. The test for leukocyte common antigen, most surface marker studies, and gene rearrangement (to document B-cell or T-cell clonality) can be done on fixed tissues. Cytogenetics and flow cytometry require fresh tissue.

Lymphomas [1]

Staging tests

- Once the diagnosis of lymphoma is made, staging tests are done.
- A combined fluorodeoxyglucose (FDG)-PET/CT scan of the chest, abdomen, and pelvis is recommended. PET/CT provides accurate location of lesions, their size (from CT) and tumor metabolism (from FDG-PET). If combined FDG-PET/CT is not available, a contrast-enhanced CT scan of the chest, abdomen, and pelvis is done.
- Bone marrow aspiration and biopsy is often done in patients with non-Hodgkin lymphoma. Although bilateral posterior iliac crest biopsies can be done, unilateral biopsy is typically sufficient. Bone marrow biopsy may not be needed for staging large cell non-Hodgkin lymphoma if a PET scan has been done because FDG-PET is sensitive for bone marrow involvement. Bone marrow assessment in low-grade (indolent) non-Hodgkin lymphoma or T-cell non-Hodgkin lymphoma can also be limited to cases where findings will change management or are needed to assess cytopenias.

Lymphomas [1]

Testing for complications and prognosis

- Blood tests typically include CBC with white blood cell differential, kidney function and liver tests (including serum creatinine, bilirubin, calcium, AST, albumin, alkaline phosphatase, and lactate dehydrogenase), uric acid, beta-2 microglobulin, and vitamin D levels. Serum protein electrophoresis with IgG, IgA, and IgM immunoglobulin levels are also done.
- Other tests are done depending on findings (eg, MRI of brain and/or spinal cord for neurologic symptoms). If uric acid levels are high, serum glucose-6-phosphate dehydrogenase (G6PD) level is checked because G6PD deficiency precludes treatment with rasburicase (to prevent tumor lysis syndrome).

Lymphomas [1]

Testing for etiology

- Patients with non-Hodgkin lymphoma are initially screened for HIV and hepatitis B and C viruses. Patients diagnosed with adult T-cell leukemia/lymphoma (ATLL) are also checked for human T-cell lymphotropic virus type 1 (HTLV-1).
- **Staging**
- After diagnosis, stage is determined to guide therapy. The commonly used Lugano staging system (see table Lugano Staging of Hodgkin Lymphoma and Non-Hodgkin Lymphoma) incorporates
- Symptoms
- Physical examination findings
- Results of imaging tests, including CT of the chest, abdomen, and pelvis, and functional imaging with FDG-PET
- Bone marrow biopsy (in selected cases)
- Although stage I non-Hodgkin lymphoma does occur, the disease is typically disseminated when first recognized.

Lymphomas [1]

Diagnosis reference

1. Cheson BD, Fisher RI, Barrington SF, et al: Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: The Lugano classification. J Clin Oncol 32(27):3059-3068, 2014.

Prognosis

- Prognosis varies by the type and stage of lymphoma and individual patient factors. In general, patients with peripheral T-cell or natural killer (NK)/T-cell lymphomas typically have a worse prognosis than those with B-cell non-Hodgkin lymphoma. Within each non-Hodgkin lymphoma variant, prognosis is related to differences in tumor cell biology.
- The most commonly used prognostic scoring system is the International Prognostic Index (IPI) for diffuse large B-cell lymphoma). The IPI score is used only for diffuse large B-cell lymphoma (DLBCL). There are also scoring systems for follicular lymphoma (FLIPI) and mantle cell lymphoma (MIPI). Online calculators are available to estimate prognosis in other types of non-Hodgkin lymphoma as well.

Lymphomas [1]

- The IPI considers 5 risk factors:
- Age > 60 years
- Poor performance status (can be measured using the Eastern Cooperative Oncology Group tool)
- Elevated lactate dehydrogenase (LDH) level
- > 1 extranodal site
- Stage III or IV disease
- Outcome is worse with an increasing number of risk factors. Patients in the highest risk groups (patients with 4 or 5 risk factors) now have a 50% 5-year survival. Patients without any of the risk factors have a very high cure rate. The original IPI score uses the 5 factors as discrete variables (eg, either age over 60 or under 60). A recent modification, the Diffuse Large B-cell Lymphoma Prognosis (IPI24), which calculates the chance of being disease free at 24 months from diagnosis, includes the above factors as continuous variables and also includes absolute lymphocyte count.

Lymphomas [1]

Treatment

- Watch and wait (for indolent, largely asymptomatic lymphomas)
- Chemotherapy
- Radiation therapy (most common in patients with limited-stage disease and sometimes in those with advanced-stage disease)
- Immunotherapy (eg, monoclonal antibodies targeting CD20, CD19, or CD79, or chimeric antigen receptor T cells [CAR T cells])
- Targeted drugs (eg, BTK [Bruton tyrosine kinase] inhibitors, PI3K [phosphoinositide 3-kinase] inhibitors, cereblon inhibitors)
- Sometimes hematopoietic stem cell transplantation (autologous or allogeneic)
- Treatment varies considerably with cell type, which are too numerous to permit detailed discussion. Generalizations can be made regarding limited vs advanced disease and aggressive vs indolent forms. Burkitt lymphoma and cutaneous T-cell lymphomas are discussed separately. For patients with indolent lymphomas and no significant signs or symptoms of lymphoma, a "watch and wait" approach (withholding treatment while closely monitoring) can be used.

Lymphomas [1]

- **Limited disease (stages I-II)**
- For stage I indolent non-Hodgkin lymphoma (uncommon because most patients have stage II to IV when diagnosed), external beam radiation therapy can be the sole initial treatment. Regional radiation therapy may offer long-term control and possibly cure in about 40% of stage I patients. Stage II indolent non-Hodgkin lymphoma is most commonly treated as advanced-stage disease.
- Limited-stage aggressive non-Hodgkin lymphomas can be managed with a combination of chemotherapy plus radiation therapy or with chemotherapy alone (plus anti-CD20 monoclonal antibodies for B-cell lymphomas).
- Patients with stage I lymphoblastic lymphomas or Burkitt lymphoma are treated with intensive combination chemotherapy with meningeal prophylaxis.
- **Advanced disease (stages II-IV)**
- Stage II non-Hodgkin lymphoma is managed as advanced stage disease in many circumstances. Most patients with all types of non-Hodgkin lymphoma who have stage II to IV disease are candidates for chemoimmunotherapy. In these cases, radiation therapy may be used to limit the number of cycles of chemoimmunotherapy or provide localized treatment for residual sites of bulk disease.

Lymphomas [1]

- For indolent lymphomas, treatment varies considerably. Because these lymphomas are highly treatable but not reliably curable, treatment may not be recommended initially for asymptomatic patients, although with the advent of rituximab anti-CD20 immunotherapy, some of these patients may be given immunotherapy alone. This strategy can delay the need for myelosuppressive chemotherapy, but early immunotherapy alone has not been shown to impact overall survival. Patients with symptoms or bulky disease that puts vital organs at risk are treated with chemoimmunotherapy. In selected cases, radiolabeled anti-CD20 antibody can be used to target radiation to the tumor cell with potentially fewer effects on nearby normal organs.
- In patients with aggressive B-cell lymphomas (eg, diffuse large B cell), the standard drug combination is rituximab plus cyclophosphamide, hydroxydaunorubicin (doxorubicin), vincristine, and prednisone (R-CHOP). A complete response with disease regression is expected in 80% of cases, with an overall cure rate of about 60%. These results vary significantly by IPI score. Patients who are disease free at ≥ 24 months from diagnosis have a lifetime expectancy similar to that of the age- and sex-matched population. This key factor can guide follow-up strategies in this patient population.

Lymphomas [1]

- Cure rates have improved with the use of R-CHOP, so autologous transplantation is not used as adjuvant therapy in patients who achieve complete metabolic response (ie, determined by PET) at the end of therapy.
- The approach in peripheral T-cell non-Hodgkin lymphoma and primary central nervous system lymphoma is different. In these patients, autologous stem cell transplantation may be offered to initial responders before relapse occurs with the intention of improving the likelihood of cure. Similarly, in some younger patients with mantle cell lymphoma who have responded to initial therapy, autologous stem cell transplantation may be is done to prolong remission.

Lymphomas [1]

Lymphoma relapse

- Patients with aggressive non-Hodgkin lymphoma not in remission at end of therapy or who relapse are treated with second-line chemotherapy regimens followed by autologous stem cell transplantation if they are relatively young and in good health. In autologous stem cell transplantation, stem cells are obtained from the patient by peripheral blood leukopheresis and are transfused back into the patient after high-dose chemotherapy. In some patients at very high risk of relapse as well as in those for whom autologous transplant is not feasible or has already failed, stem cells from a matched sibling or unrelated donor (allogeneic transplants) can be effective. In general, the older the patient, the less likely an allogeneic transplantation will be offered because they have higher rates of transplantation complications.
- Patients with diffuse large B-cell lymphoma (DLBCL) who have persistent lymphoma despite at least 2 prior lines of therapy may be candidates for chimeric antigen receptor (CAR) T cells. CAR T cells are T cells (most commonly autologous T cells) that have been genetically engineered to recognize a tumor antigen (eg, CD19). After infusion, they undergo activation and expansion. About one third of patients achieve a durable response from this therapy.

Lymphomas [1]

- Patients not eligible for the above therapies, or for whom they have failed, may receive treatment with various therapies, mostly for palliation. These therapies vary widely and are constantly changing as new agents are developed.
- In indolent lymphomas, patients may be managed using a wide variety of strategies depending on lymphoma-related factors (eg, histopathology, stage, molecular and immunologic characteristics), patient-related factors (eg, age, comorbidities), and the type of and response to prior therapy. Many of the same agents used in for first-line treatment may be given. In some cases, the same treatment may be repeated if it was previously effective and well tolerated. High-dose chemotherapy with autologous stem cell transplantation is used occasionally in patients who have high-risk lymphoma biology (including a poor response to chemotherapy), and although cure remains unlikely, remission may be superior to that with secondary palliative therapy alone. Reduced intensity allogeneic transplantation is a potentially curative option in some patients with indolent lymphoma.

The mortality rate of patients undergoing myeloablative transplantation has decreased dramatically to 1 to 2% for most autologous procedures and to 15 to 20% for most allogeneic procedures (depending on age).

Lymphomas [1]

Complications of treatment

- An immediate complication of most therapies is infection that occurs during periods of neutropenia. Although use of growth factors that stimulate white blood cell production has helped, infection continues to pose a problem.
- The gastrointestinal adverse effects of chemotherapy can be largely relieved and prevented by antiemetics and bowel programs. Patients receiving anthracyclines are at risk of cardiomyopathy and/or arrhythmias.
- After successful treatment, patients should be referred to a cancer survivorship clinic for a care plan that can be implemented by the patient's primary care team. This plan is tailored to the patient's comorbidities and risks specific to the treatment they received.
- Drugs and radiation have late complications. In the first 10 years after treatment, there is a risk of myelodysplasia or acute leukemia due to bone marrow damage from certain chemotherapy agents. After 10 years, the risk of secondary cancers increases, especially in patients who received radiation to the chest.

Lymphomas [1]

Key Points

- Non-Hodgkin lymphomas are a group of related cancers involving lymphocytes; they vary significantly in their rate of growth and response to treatment.
- The disease is usually already disseminated at the time of diagnosis.
- Molecular and genetic tests are essential for diagnosis and management.
- Limited indolent disease may be treated with radiation therapy.
- Treat more advanced disease with immunotherapy, chemotherapy, hematopoietic stem cell transplantation, or a combination depending on the type and stage of non-Hodgkin lymphoma.

Multiple Myeloma

Multiple Myeloma (Myelomatosis; Plasma Cell Myeloma) by **James R. Berenson**, MD, Institute for Myeloma and Bone Cancer Research; Last full review/revision Sep 2019| Content last modified Sep 2019; https://www.msdmanuals.com/professional/hematology-and-oncology/plasma-cell-disorders/multiple-myeloma?query=multiple%20myeloma

Multiple Myeloma [2]

Multiple myeloma is a cancer of plasma cells that produce monoclonal immunoglobulin and invade and destroy adjacent bone tissue. Common manifestations include lytic lesions in bones causing pain, and/or fractures, renal insufficiency, hypercalcemia, anemia, and recurrent infections. Diagnosis typically requires demonstration of M-protein (sometimes present in urine and not serum but rarely absent entirely) and/or light-chain proteinuria, and excessive plasma cells in the bone marrow. Specific treatment most often includes some combination of conventional chemotherapy, corticosteroids, and one or more of the newer agents such as proteasome inhibitors (eg, bortezomib, carfilzomib, ixazomib), immunomodulating agents (eg, lenalidomide, thalidomide, pomalidomide), or monoclonal antibodies (eg, daratumumab, elotuzumab). High-dose melphalan followed by autologous peripheral blood stem cell transplantation may also be used.

The incidence of multiple myeloma is 2 to 4/100,000. Male:female ratio is 1.6:1, and the median age is about 65 years. Prevalence in blacks is twice that in whites. Etiology is unknown, although chromosomal and genetic factors, radiation, and chemicals have been suggested.

Multiple Myeloma [2]

Pathophysiology

- The M-protein (monoclonal immunoglobulin protein) produced by the malignant plasma cells is IgG in about 55% of myeloma patients and IgA in about 20%; of patients producing either IgG or IgA, 40% also have Bence Jones proteinuria, which is free monoclonal kappa (κ) or lambda (λ) light chains in the urine. In 15 to 20% of patients, plasma cells secrete only Bence Jones protein. IgD myeloma accounts for about 1% of cases. Rarely, patients have no M-protein in blood and urine, although the currently used serum free light chain assay now demonstrates monoclonal light chains in many of these formerly so-called nonsecretory patients.
- Diffuse osteoporosis or discrete osteolytic lesions develop, usually in the pelvis, spine, ribs, femur, humerus, and skull. Lesions are caused by bone replacement by expanding plasmacytomas or by cytokines that are secreted by malignant plasma cells that activate osteoclasts and suppress osteoblasts. The osteolytic lesions are usually multiple; occasionally, they are solitary intramedullary masses. Increased bone loss may also lead to hypercalcemia.

Multiple Myeloma [2]

- Extraosseous solitary plasmacytomas are unusual but may occur in any tissue, especially in the upper respiratory tract.
- In many patients, renal failure is present at diagnosis or develops during the course of the disorder. Renal failure has many causes, and most commonly, it results from deposition of light chains in the distal tubules (myeloma-related kidney disease) or hypercalcemia. Patients also often develop anemia usually due to kidney disease or suppression of erythropoiesis by cancer cells but sometimes also due to other unrelated causes, including iron deficiency or vitamin B12 deficiency.
- Because of lack of normal antibodies and other immune dysfunction, some patients have increased susceptibility to bacterial infection. Viral infections, especially herpes zoster infections, are increasingly occurring as a result of newer treatment modalities, especially use of the proteasome inhibitors bortezomib, ixazomib, and carfilzomib and monoclonal antibodies such as daratumumab and elotuzumab. Amyloidosis occurs in 10% of myeloma patients, most often in patients with lambda-type M-proteins.
- Variant expressions of multiple myeloma occur

Multiple Myeloma [2]

Symptoms and Signs:

Persistent bone pain (especially in the back or thorax), renal failure, and recurring bacterial infections are the most common problems on presentation, but many patients are identified when routine laboratory tests show an elevated total protein level in the blood, proteinuria, or unexplained anemia or renal failure. Pathologic fractures (ie, fractures that occur with minimal or no trauma) are common, and vertebral collapse may lead to spinal cord compression and paraplegia. Symptoms of anemia predominate or may be the sole reason for evaluation in some patients, and a few patients have manifestations of hyperviscosity syndrome. Peripheral neuropathy, carpal tunnel syndrome (especially with associated amyloid disease), abnormal bleeding, and symptoms of hypercalcemia (eg, polydipsia, dehydration) are common. Patients may also present with renal failure. Lymphadenopathy and hepatosplenomegaly are unusual.

Multiple Myeloma [2]

Diagnosis

- Complete blood count (CBC) with platelets, peripheral blood smear, erythrocyte sedimentation rate (ESR), and chemistry panel (blood urea nitrogen [BUN], creatinine, calcium, uric acid, lactate dehydrogenase [LDH])
- Serum and urine protein (on a 24-hour urine collection) electrophoresis followed by immunofixation; quantitative immunoglobulins; serum free light chains
- X-rays (skeletal survey)
- Bone marrow examination, including conventional cytogenetics and fluorescent in situ hybridization studies (FISH)
- Multiple myeloma is suspected in patients > 40 years with persistent unexplained bone pain, particularly at night or at rest, other typical symptoms, or unexplained laboratory abnormalities, such as elevated blood protein or urinary protein, hypercalcemia, renal insufficiency, or anemia. Laboratory evaluation includes routine blood tests, LDH, serum beta-2 microglobulin, urine and serum immune and protein electrophoresis, serum free light chains, x-rays, and bone marrow examination (for review, see [1, 2]).

Multiple Myeloma [2]

- Routine blood tests include CBC, ESR, and chemistry panel. Anemia is present in 80% of patients, usually normocytic-normochromic anemia with formation of rouleaux, which are clusters of 3 to 12 red blood cells that occur in stacks. White blood cell and platelet counts are usually normal. ESR usually is > 100 mm/hour; BUN, serum creatinine, LDH, beta-2 microglobulin, and serum uric acid may be elevated. Anion gap is sometimes low. Hypercalcemia is present at diagnosis in about 10% of patients.
- Immune and protein electrophoresis is done on a serum sample and on a urine sample concentrated from a 24-hour collection to quantify the amount of urinary M-protein. Serum electrophoresis identifies M-protein in about 80 to 90% of patients. The remaining 10 to 20% are usually patients with only free monoclonal light chains (Bence Jones protein) or IgD. They almost always have M-protein detected by urine protein electrophoresis.
- Immunofixation electrophoresis can identify the immunoglobulin class of the M-protein (IgG, IgA, or uncommonly IgD, IgM, or IgE) and can often detect light-chain protein if serum immunoelectrophoresis is falsely negative; immunofixation electrophoresis is done even when the serum test is negative if multiple myeloma is strongly suspected.

Multiple Myeloma [2]

- Serum free light-chain analysis with delineation of kappa and lambda ratios helps confirm the diagnosis and can also be used to monitor efficacy of therapy and provide prognostic data.
- Serum level of beta-2 microglobulin is measured if diagnosis is confirmed or very likely and along with serum albumin is used to stage patients as part of the international staging system. Beta-2 microglobulin is a small protein on the membrane of all cells. Its concentration varies directly with tumor mass and severity of renal dysfunction.
- X-rays include a skeletal survey (ie, plain x-rays of skull, long bones, spine, pelvis, and ribs). Punched-out lytic lesions or diffuse osteoporosis is present in 80% of cases. Radionuclide bone scans usually are not helpful. MRI can provide more detail and is obtained if specific sites of pain or neurologic symptoms are present. PET-CT may provide prognostic information and can help determine whether patients have solitary plasmacytoma or multiple myeloma.

Multiple Myeloma [2]

- Bone marrow aspiration and biopsy are done and reveal sheets or clusters of plasma cells; myeloma is diagnosed when >10% of the cells are of this type. However, bone marrow involvement is patchy; therefore, some samples from patients with myeloma may show <10% plasma cells. Still, the number of plasma cells in bone marrow is rarely normal. Plasma cell morphology does not correlate with the class of immunoglobulin synthesized. Chromosomal studies on bone marrow (eg, using cytogenetic testing methods such as fluorescent in situ hybridization [FISH] and immunohistochemistry) may reveal specific karyotypic abnormalities in plasma cells associated with differences in survival.
- Diagnosis and differentiation from other malignancies (eg, metastatic carcinoma, lymphoma, leukemia) and monoclonal gammopathy of undetermined significance typically require multiple criteria:
- Clonal bone marrow plasma cells or plasmacytoma
- M-protein in plasma and/or urine
- Organ impairment (hypercalcemia, renal insufficiency, anemia, or bony lesions)

Multiple Myeloma [2]

- In patients without serum M protein, myeloma is indicated by Bence Jones proteinuria > 200 mg/24 hour or abnormal serum free light chain levels, osteolytic lesions (without evidence of metastatic cancer or granulomatous disease), and sheets or clusters of plasma cells in the bone marrow.

Diagnosis references

1. Rajkumar SV, Kumar S: Multiple myeloma: Diagnosis and treatment. Mayo Clinic Proc 91(1):101-119, 2016. doi: 10.1016/j.mayocp.2015.11.007
2. Rajkumar SV: Myeloma today: Disease definitions and treatment advances. Am J Hematol 91(1):90-100, 2016. doi: 10.1002/ajh.24392

Multiple Myeloma [2]

Prognosis

- The disease is progressive and incurable, but median survival has recently improved to > 5 years as a result of advances in treatment. Unfavorable prognostic signs at diagnosis are lower serum albumin, higher beta-2 microglobulin levels, elevated LDH levels, and specific cytogenetic abnormalities in the tumor cells. Patients initially presenting with renal failure also do poorly unless kidney function improves with therapy (which typically happens with current treatment options).
- Because multiple myeloma is ultimately fatal, patients are likely to benefit from discussions of end-of-life care that involve their doctors and appropriate family and friends. Points for discussion may include advance directives, the use of feeding tubes, and pain relief.

Multiple Myeloma [2]

Treatment

- Chemotherapy for symptomatic patients
- Thalidomide, lenalidomide, or pomalidomide, and/or bortezomib, carfilzomib, or ixazomib, plus corticosteroids and/or conventional chemotherapy
- Monoclonal antibodies, including elotuzumab and daratumumab
- Maintenance therapy with corticosteroids, thalidomide, and/or lenalidomide, and proteasome inhibitors, especially oral ixazomib
- Possibly autologous stem cell transplantation
- Possibly radiation therapy to specific symptomatic areas that do not respond to systemic therapy
- Treatment of complications (anemia, hypercalcemia, renal insufficiency, infections, and skeletal lesions---especially those associated with high risk of fracture)

Treatment of myeloma has improved in the past 2 decades, and long-term survival is a reasonable therapeutic target (1–4). Therapy involves direct treatment of malignant cells in symptomatic patients or those with myeloma-related organ dysfunction (anemia, renal dysfunction, hypercalcemia, or bone disease).

Multiple Myeloma [2]

Risk factors for requiring rapid treatment of myeloma among patients initially presenting with organ dysfunction include > 60% plasma cells in bone marrow, > 1 lesion on MRI, and serum free light chain levels > 100 mg/L. Thus, these patients are now considered to have active myeloma and require immediate treatment even though nearly all randomized clinical trials of early treatment of these patients have not yet shown an improvement in overall survival. Patients without these risk factors or end-organ dysfunction probably do not benefit from immediate treatment, which is usually withheld until symptoms or complications develop.

Multiple Myeloma [2]

Treatment of malignant cells

- In the past, initial treatment of multiple myeloma consisted of conventional chemotherapy with oral melphalan and prednisone given in cycles of 4 to 6 weeks for 8 to 12 cycles with monthly evaluation of response. However, superior outcomes have been achieved with the addition of either the proteasome inhibitor bortezomib (or carfilzomib) or the immunomodulatory agents lenalidomide or thalidomide. Other chemotherapeutic drugs, including cyclophosphamide, bendamustine, doxorubicin, and its analog, liposomal pegylated doxorubicin, also are more effective when combined with an immunomodulatory drug (thalidomide, lenalidomide) or bortezomib. Studies suggest better survival when initial treatment includes both bortezomib and lenalidomide with corticosteroids. In addition, the addition of the monoclonal antibody daratumumab to bortezomib and dexamethasone as part of initial treatment appears to improve outcomes.

Multiple Myeloma [2]

- Response to treatment (see table Defining Response to Cancer Treatment) is indicated by decreases in serum and urine M-protein, decreases in levels of the involved serum free light chain, increases in numbers of red blood cells, improvement in renal function among patients presenting with renal failure, and normalization of calcium levels among those presenting with elevated levels. Bone pain and fatigue should also decrease.
- Autologous peripheral blood stem cell transplantation may be considered for patients who have adequate cardiac, hepatic, pulmonary, and renal function, particularly those whose disease is stable or responsive after several cycles of initial therapy. However, studies suggest that the newer treatment options are highly effective and may make transplantation less often necessary or unnecessary altogether.
- Allogeneic stem cell transplantation after nonmyeloablative chemotherapy (eg, low-dose cyclophosphamide and fludarabine) or low-dose radiation therapy can produce myeloma-free survival of 5 to 10 years in some patients. However, allogeneic stem cell transplantation with myeloablative or nonmyeloablative chemotherapy remains experimental because of the high morbidity and mortality resulting from graft vs host disease.

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Treatment of relapsed or refractory myeloma

- In relapsed or refractory myeloma, combinations of a proteasome inhibitor (bortezomib, ixazomib, or carfilzomib) with an immunomodulatory agent (thalidomide, lenalidomide, or pomalidomide) and chemotherapy or corticosteroids may be used. These drugs are usually combined with other effective drugs that the patient has not yet been treated with, although patients with prolonged remissions may respond to retreatment with the same regimen that led to the initial remission. Patients who fail to respond to a given combination of drugs may respond when another drug in the same class (eg, proteasome inhibitors, immunomodulatory agents, chemotherapeutic drugs) is substituted.
- Newer monoclonal antibodies may also be highly effective in relapsed or refractory myeloma and include daratumumab and elotuzumab. Both antibodies are more effective when combined with lenalidomide or pomalidomide and dexamethasone. Daratumumab also shows better results when combined with bortezomib and dexamethasone.

Multiple Myeloma [2]

Maintenance therapy

- Maintenance therapy has been tried with nonchemotherapeutic drugs, including interferon alfa, which prolongs remission but does not improve survival and is associated with significant adverse effects. Following a response to corticosteroid-based regimens, corticosteroids alone are effective as a maintenance treatment. Thalidomide may also be effective as a maintenance treatment, and studies show that lenalidomide alone or with corticosteroids is also effective maintenance treatment. However, there is some concern about secondary malignancy among patients receiving long-term lenalidomide therapy, especially after autologous stem cell transplantation, and the risk of developing secondary cancers must be weighed against improved survival. In addition, the oral proteasome inhibitor ixazomib is effective as a single agent in the maintenance setting. Whether the combination of ixazomib with lenalidomide is more effective in this setting is yet unknown.

Multiple Myeloma [2]

Treatment of complications

- In addition to direct treatment of malignant cells, therapy must also be directed at complications, which include
- Anemia
- Hypercalcemia
- Hyperuricemia
- Infections
- Renal insufficiency
- Skeletal lesions
- **Anemia** can be treated with recombinant erythropoietin (40,000 units subcutaneously once a week) in patients whose anemia is inadequately relieved by chemotherapy. If anemia causes cardiovascular or significant systemic symptoms, packed red blood cells are transfused. Plasma exchange is indicated if hyperviscosity develops. Often patients are iron deficient and require intravenous iron. Patients with anemia should have periodic measurement of serum iron, transferrin, and ferritin levels to monitor iron stores as well as vitamin B12 levels.

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- **Hypercalcemia** is treated with vigorous saluresis, IV bisphosphonates (preferably zoledronic acid) after rehydration, and sometimes with calcitonin o prednisone. Patients should avoid calcium-containing foods, calcium supplements, and vitamin D.
- **Hyperuricemia** may occur in some patients with high tumor burden and underlying metabolic problems. However, most patients do not require allopurinol. Allopurinol or rasburicase is indicated for patients with high levels of serum uric acid or high tumor burden and a high risk of tumor lysis syndrome with treatment.
- **Infection** is more likely during chemotherapy-induced neutropenia. In addition infections with the herpes zoster virus are occurring more frequently in patient treated with newer antimyeloma drugs, especially the proteasome inhibitors bortezomib, carfilzomib, or ixazomib and the monoclonal antibodies daratumumab or elotuzumab. Documented bacterial infections should be treated with antibiotics; however, prophylactic use of antibiotics is not routinely recommended.

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- Prophylactic use of antiviral drugs (eg, acyclovir, valganciclovir, famciclovir) is indicated for patients receiving a proteasome inhibitor (bortezomib, carfilzomib, ixazomib) or a monoclonal antibody (daratumumab, elotuzumab).
- Prophylactic IV immune globulin may reduce the risk of infection but is generally reserved for patients with frequent recurrent infections. Pneumococcal vaccine and influenza vaccine are indicated to prevent infection. However, use of live vaccines is not recommended in these immunocompromised patients. However, the newer recombinant zoster vaccine, unlike the earlier live-attenuated zoster vaccine, may be given to prevent herpes zoster.

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- **Renal compromise** can often be ameliorated with adequate hydration. Even patients with prolonged, massive Bence Jones proteinuria (≥ 10 to 30 g/day) may have intact renal function if they maintain urine output > 2000 mL/day. Dehydration combined with high-osmolar IV contrast may precipitate acute oliguric renal failure in patients with Bence Jones proteinuria. Plasma exchange may be effective in some cases.
- **Skeletal lesions** require multiple supportive measures. Maintenance of ambulation and supplemental calcium and vitamin D help preserve bone density. Vitamin D levels should be measured at diagnosis and periodically, and dosing of vitamin D adjusted accordingly. Analgesics and palliative doses of radiation therapy (18 to 24 gray) can relieve bone pain. However, radiation therapy may cause significant toxicity and, because it suppresses bone marrow function, may impair the patient's ability to receive cytotoxic doses of systemic chemotherapy.
- Most patients, especially those with lytic lesions and generalized osteoporosis or osteopenia, should receive a monthly IV bisphosphonate (either pamidronate or zoledronic acid). Bisphosphonates reduce skeletal complications and lessen bone pain and may have an antitumor effect. For patients with potentially reversible renal failure resulting from myeloma but unrelated to hypercalcemia or with ongoing infusion reactions after bisphosphonate infusion, an option is monthly denosumab (given subcutaneously), which, unlike bisphosphonates, is not cleared by the kidneys and does not cause infusion reactions. Both bisphosphonates and densousmab may uncommonly cause osteonecrosis of the jaw. Maintaining excellent dental health and avoiding dental explants and implants are important to minimize the risk of this complication.

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Approach Considerations

The purpose of establishing the etiology of an anemia is to permit selection of a specific and effective therapy. For example, corticosteroids are useful in the treatment of autoimmune hemolytic anemia.

Therapy and medical care vary considerably in the group of hereditary disorders. Splenectomy has been advantageous in hereditary spherocytosis and hereditary elliptocytosis, in some of the unstable hemoglobinopathies, and in certain patients with pyruvic kinase deficiency. It has little value in most other hereditary hemolytic disorders.

Drugs and chemicals capable of producing aplasia or a maturation arrest of erythroid precursors should be discontinued or avoided. Similarly, diseases known to be associated with anemia should be appropriately treated. Guidelines for the treatment of chemotherapy-associated anemia are available.

Surgery is useful to control bleeding in patients who are anemic. Most commonly, bleeding is from the GI tract, uterus, or bladder. Patients should be hemodynamically stable before and during surgery. A blood transfusion may be needed.

Multiple Myeloma [2]

Treatment references:

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Key Points

- Malignant plasma cells produce monoclonal immunoglobulin and invade and destroy bone.
- Expanding plasmacytomas and cytokine secretion cause multiple, discrete, osteolytic lesions (usually in the pelvis, spine, ribs, and skull) and diffuse osteoporosis; pain, fractures, and hypercalcemia are common.
- Anemia and renal failure are common.
- Amyloidosis develops in about 10%, typically patients who produce excess lambda light chains.
- Do serum and urine protein electrophoresis followed by immunofixation, quantitative immunoglobulins, and measurement of serum free light chains.
- Do bone marrow aspiration and biopsy.
- Symptomatic patients and those with organ dysfunction should be treated with drug therapy, which may include corticosteroids, proteasome inhibitors, immunomodulatory agents, monoclonal antibodies, and chemotherapy drugs.
- Stem cell transplantation is an option for stable patients, but newer, highly effective treatment options may make transplantation less often necessary.