

Hodgkin's Disease

Introduction Lymphomas

Lymphomas are malignancies of the lymph system that are generally subdivided into two groups, Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL). Non-Hodgkin's lymphoma is discussed in another report. [*See Well-Connected Report #84, Non-Hodgkin's Lymphomas.*]

Hodgkin's Disease and Biologic Process Involved in Malignancy

Hodgkin's disease (HD) is the major tumor in a group known as malignant lymphomas. Most often HD starts in B-cell lymphocytes located in lymph nodes in the neck area, although any lymph node may be the site of initial disease.

The following is a possible description of the process leading to Hodgkin's disease:

- In early development, B cells normally undergo a series of genetic rearrangements until they create *immunoglobulins*, which are proteins that act as antibodies.
- Antibodies are immune factors that contain receptors that match and bind to a wide array of foreign substances (such as viral proteins) called antigens. With the assistance of helper-T-cells, the antibody primes the antigen for destruction by other components of the immune system.
- B-cells normally undergo limited cycles of genetic rearrangement that result in immunoglobulin production. In rare cases, however, the genetic arrangements create a mutation that does produce immunoglobulins. The results are large, abnormal cells referred to as Reed-Sternberg cells.
- Without immunoglobulin, Reed-Sternberg cells can be infected by certain viruses (notably the Epstein-Barr virus—the cause of infectious mononucleosis). Genetic byproducts of these viruses appear to inhibit a natural process of self-destruction (called apoptosis) that would normally kill off these natural cells. Instead, the abnormal B-cells proliferate unceasingly, causing most forms of Hodgkin's disease.

It should be noted that only a very small percentage (about 1%) of cells found in the affected lymph tissues of Hodgkin's disease are actually Reed-Sternberg cells. Researchers are unable to completely explain why so few cells can cause such severe symptoms. One explanation is that these cells trigger production of very powerful agents of the immune system, called *cytokines* (including those known as interleukin-1, interleukin-6, and tumor necrosis factor). These cytokines produce an inflammatory response that can cause local pain, fever, and other symptoms typical of Hodgkin's disease. The dominance of different kinds of cytokines may also explain why Hodgkin's disease takes different forms.

Subtypes of Hodgkin's Disease

Classical Hodgkin's Lymphoma. Based on the variations and numbers of Reed-Sternberg cells, as well as other features, four major subtypes of classical Hodgkin's disease have been identified:

- *Nodular Sclerosis.* Nodular sclerosis is the most common, representing almost 60% of HD cases. Younger patients are more likely to have this type. The nodes first affected are often those located in the center of the chest (the mediastinum).
- *Mixed Cellularity.* Mixed cellularity is the next most common HD form, occurring in about 25% of patients, mostly in older patients, children, and those with immune disorders, such as AIDS. It usually indicates a more severe condition.
- *Lymphocyte Depleted.* Lymphocyte-depleted Hodgkin's disease occurs in about 4% of patients, nearly always in elderly people. It indicates extensive disease and a poor outlook. It can easily be confused with non-Hodgkin's lymphoma.
- *Lymphocyte-Rich Classical Hodgkin's Lymphoma.* This form is similar to nodular lymphocyte predominant HD, but has more cell characteristics that conforms to classical HD.

Nodular Lymphocyte-Predominant Hodgkin's Disease. Nodular lymphocyte-predominant Hodgkin's disease (LPHD) occurs in about 5% of patients. The cells in LPHD are known as lymphocytic and histolytic cells; they are proving to be distinctly different from classic Reed-Sternberg B-cells. Patients with lymphocyte predominance are usually young men, who often have no symptoms. LPHD is very slow growing and may be associated with long survival. There is a 3% risk, however, that LPHD will transform to non-Hodgkin's lymphoma. In fact, lymphocyte-predominant Hodgkin's disease may eventually be defined as a non-Hodgkin's lymphoma.

The Lymphatic System

Lymphomas, such as non-Hodgkin's lymphomas and Hodgkin's disease, represent tumors of the lymphatic system. This system is a network of organs, ducts, and nodes that interacts with the blood's circulatory system to transport a watery clear fluid called lymph throughout the body. The lymphatic system contains lymphocytes, which are important cells involved in defending the body against infectious organisms. This system also restores 60% of the fluid that leaks out from blood capillaries back into circulation, and its ducts provide transportation for fats, proteins, and other substances collected from the body's tissues.

Lymphocytes

The lymphatic system is involved in the production and transportation of lymphocytes, white blood cells that are a primary component of the immune system. Among other vital functions, certain lymphocytes are responsible for producing *antibodies*, factors that can target and attack specific foreign agents (antigens). To understand the lymphatic system, it is helpful to track part of the life cycle of these lymphocytes:

- Lymphocytes develop in the bone marrow or thymus gland and are, therefore, categorized as either *B-cells* (bone marrow-derived cells) or *T-cells* (thymus gland-derived cells).
- B-cells complete their structural growth and definition (known as differentiation) and mature in the bone marrow.
- T-cells also start out in the bone marrow but differentiate and mature in the *thymus gland*, located beneath the breastbone (*sternum*). This small gland is active mostly in the fetal stage through the first 10 years of life, after which it atrophies (shrinks).
- B-cell and T-cell lymphocytes leave these organs through the bloodstream, which eventually branches out into the tiny blood vessels called capillaries.
- Some lymphocytes, along with fluid, proteins, and other substances, migrate out of the capillaries into the surrounding tissues. A proportion of these lymphocytes and other substances then enter the *lymphatic vessels*.
- Lymphatic vessels begin as tiny, blind-ended tubes and lead to larger lymphatic ducts and branches until they drain into two ducts in the neck, where the fluid re-enters the bloodstream.
- Along the way, the fluid passes through *lymph nodes*, which are oval structures composed of lymph vessels, connective tissue, and white blood cells. Here, the lymphocytes either are filtered out or are added to the contents of the node.

Lymph Nodes

The lymph node provides an environment where lymphocytes can receive their initial exposure to foreign agents (antigens) such as bacteria or other microorganisms, which then activates the lymphocytes to perform their immune functions. The size of a lymph node varies generally from that of a pinhead to a bean. Most nodes are in clusters located throughout the system; important node clusters are found in the neck, lower arm, armpit, and groin.

Other Structures in the Lymphatic System

The tonsils and adenoids are secondary organs composed of masses of lymph tissue that also play a role in the lymphatic system. The spleen is another important organ that processes lymphocytes from incoming blood.

Risk Factors

An estimated 7,600 new cases of Hodgkin's disease (HD) were diagnosed in the US in 2003. The incidence has declined significantly over the past two decades at a rate of nearly 1% a year. Experts believe that the malignant process leading to Hodgkin's disease is triggered by a combination of environmental and genetic factors along with a susceptible immune system. The exact triggers, however, are unknown.

Gender and Hormonal Factors

Hodgkin's disease is more common in males than in females. In the last few years, however, the incidence of HD has increased dramatically in young women. Women who get Hodgkin's disease appear to have a slightly lower risk for relapse after treatment than men.

Age

Initial Risk by Age Group. Hodgkin's disease is the most common malignancy in people ages 10 to 30. The average age for developing Hodgkin's is about 28 years old. There are two periods of peak incidence in HD over a lifetime. The major peak occurs in young people between the ages of 15 and 24, with a lesser peak after age 55. The disease can, however, occur at all ages, even in children.

A 2001 Scandinavian study reported an increase in cases among young people. The rate of the disease in older people has declined, however, possibly because better diagnostic procedures are identifying elderly people with non-Hodgkin's lymphomas who would previously have been diagnosed with Hodgkin's.

Prognosis by Age Group. Studies suggest that children with Hodgkin's disease have a better outlook than adults — particularly elderly adults. One 2000 study suggested, however, that the reason is due to better HD treatments in pediatric medical centers than in adult centers. In support of this, another 2000 study reported that when elderly patients were treated successfully for relapse they did as well as younger people. (In any case, unrelated illness would affect treatment complications and outlook in elderly people.) Some evidence, however, suggests that Hodgkin's disease associated with the Epstein-Barr virus is more severe in the elderly (although possibly not in younger people) than other forms of HD.

Epstein-Barr Virus Infection and Infectious Mononucleosis

Young people who have had infectious mononucleosis ("mono"), which is caused by the Epstein-Barr virus (EBV), are at significantly higher risk for Hodgkin's disease. According to a 2003 study, if the malignancy develops in young people who have had mono, it does so on average about four years afterward, with a peak incidence at two and half years. The risk persists, however, for about 20 years after the infection.

EBV most likely plays a role in about half of HD cases. Research suggests that the virus activates some pathway within the lymphocyte cell that leads to cell proliferation.

Only one in 1000 patients with mononucleosis develops Hodgkin's disease, however. It should also be noted that Epstein-Barr virus itself is present in 90% of the population and, in the great majority of these cases, causes a mild infection or none at all, and very few develop HD. Other factors must be present to trigger the malignancy.

EBV appears to be more common in the mixed cellularity subtype of Hodgkin's disease and to occur less often in the nodular sclerosis subtype. In fact, there have been reports of a decline in EBV-associated HD, which coincides with an increasing incidence of nodular sclerosis HD.

Some evidence suggests that ethnic differences may be involved in a lower or higher susceptibility to Hodgkin's disease after an Epstein-Barr infection, with Northern Europeans being at higher risk than other groups.

Family and Ethnic Factors

Hodgkin's disease runs in families in about 5% of cases. Siblings have a threefold higher risk than the general population. Studies suggest, however, that such family clusters are more likely to be due to environmental than genetic factors.

Environmental Toxins

Although high exposure to industrial chemicals has been linked to non-Hodgkin's lymphomas, it is not clear if this is a major risk factor in HD. In a 1999 analysis of studies on the subject, woodworking posed the most consistent risk, although no specific chemical was implicated and not all studies reported a risk. In a 2000 study, automobile workers exposed to cutting oil had a much higher incidence of HD as well as cancers of the lung and testis. Dioxin may also be associated with a higher risk for HD.

Other Factors Associated with Hodgkin's Disease

The following are groups that have a slightly higher than normal risk for HD:

- People who are from small families, have higher educational levels, and are from homes with good hygiene.
- Geographically, people living in developed countries have the highest incidence of Hodgkin's disease. Hodgkin's disease is very uncommon in people who live in Eastern Asia and the Pacific Islands.
- A 2002 study reported a much higher risk for HD in smokers than in non-smokers.
- People who are HIV-positive are at increased risk for Hodgkin's and the incidence is increasing.
- Some studies have reported an association between inflammatory bowel disease (ulcerative colitis or Crohn's disease) and HD. (One study suggested that this relationship may be due to Epstein-Barr virus, which could play causal role in both disorders.)

Symptoms

The onset of Hodgkin's disease symptoms is highest during late winter months, with lymph node enlargement usually being the first sign. Lymph nodes may be enlarged in the following regions:

- The most common first sign of Hodgkin's disease is painless enlargement of one or more lymph nodes above the diaphragm, most often those in the neck, chest, or armpits.
- Enlarged lymph nodes are often detected in the chest cavity between the lungs (the *mediastinum*), particularly in younger patients.
- Only about 15% of cases occur exclusively below the diaphragm.

Hodgkin's disease usually progresses in an orderly way from one lymph node region to the next. This process may be slow, particularly in younger people, or very aggressive. The disease typically spreads downward from the initial site.

- If it spreads below the diaphragm, it usually reaches the spleen first; the disease may then spread to the liver and bone marrow.
- If the disease starts in the nodes in the middle of the chest, it may spread outward to the chest wall and areas around the heart and lungs.

Symptoms

Symptoms in or around the Lymph Nodes. Occasionally, patients may have a cough or chest pain if the disease is located in the middle of the chest, but usually the enlarged nodes produce no symptoms. Sometimes patients experience pain in the diseased lymph nodes after drinking alcohol.

Systemic (B) Symptoms. Between 20% and 40% of patients have *systemic* symptoms that affect the whole body rather than just the specific location of the disease. Some of systemic symptoms are referred to as B symptoms. Patients who have B symptoms have a more severe condition than asymptomatic patients with the same cancer stage or tumor location or size.

Systemic symptoms include the following:

- Drenching night sweats and weight loss (B symptoms).
- Fever is often present, which may occur only at night in episodes that last several days followed by periods of no fever (B symptoms).
- Itching all over the body can also occur. This is caused by the release of histamines, substances ordinarily triggered by an allergic response. In the case of Hodgkin's disease, histamine release is due to abnormalities in the immune system. (It should be noted that although itching is a systemic symptom, it is not usually considered a B symptom if other systemic symptoms are not also present.)
- In late stages, some patients develop a skin rash.

Diagnosis

The physician will take a medical history and perform a physical examination. If these simple procedures point to Hodgkin's disease, a number of additional tests may be needed to either rule out other diseases or to confirm HD and determine the extent of the cancer.

Ruling Out Other Conditions

Many patients seek medical help for abnormally swollen lymph nodes (commonly referred to as "swollen glands"). Swollen glands can be caused by many conditions, most often infections, and are rarely serious.

Infections. In the great majority of cases, swollen glands are caused by an infection:

- For example, although Hodgkin's often first appears in the neck, enlarged lymph nodes in that location are much more likely to be a sign of a strep or other throat infections.
- In young people, infectious mononucleosis (caused by the Epstein Barr virus) is a common cause of swollen lymph nodes.
- The patient should report any recent travel, particularly to countries with a high incidence of tropical diseases, which can trigger similar symptoms.
- Other infections that cause similar symptoms include cat scratch fever, Lyme or other tick-borne disease, HIV, tularemia, tuberculosis, syphilis, herpes simplex virus, cytomegalovirus, and hepatitis.

Non-Hodgkin's Lymphomas. Although both Hodgkin's disease and non-Hodgkin's lymphomas are malignancies of the lymph nodes, they can usually be distinguished by certain characteristics. It is extremely important to differentiate between Hodgkin's lymphomas and non-Hodgkin's lymphomas, since the treatments for these two conditions differ. In particular, a subtype of lymphoma called anaplastic large-cell lymphoma (ALCL) might be confused with Hodgkin's disease under some circumstances. [For more information, see Well-Connected Report #84 *Non-Hodgkin's Lymphomas.*]

Comparison Between Hodgkin's Disease and Non-Hodgkin's Lymphomas		
Characteristics	Hodgkin's Disease	Non-Hodgkin's Lymphomas
Age and Prevalence	Average age is 27.7 with two age peaks, the major one between 15 and 24 with a lesser peak after age 55. It is less common than NHL.	Average age is about 67. It is more common than HD.
Location	In both malignancies, the disease occurs most often in lymph nodes above the collarbone. However, in HD it is also more likely to appear in the chest cavity between the lungs (the mediastinum), particularly in younger patients. Only about 15% to 20% of cases are found in areas below the diaphragm. Disease occurs outside the nodes in about 4% of cases.	In both malignancies, the disease occurs most often in lymph nodes above the collarbone. In NHL, however, it is also more likely to appear in the nodes in the abdomen (called the mesenteric nodes). The disease occurs in the chest cavity in less than 40% of patients. (An exception, lymphoblastic lymphoma, which is seen most often in young people, is likely to first appear in the chest.) Disease occurs outside the nodes in about 23% of patients. Slow-growing lymphomas are common in the liver and bone marrow.
Symptoms	More likely than NHL (40%) to have systemic symptoms (such as fever and night sweats) at the time of diagnosis.	Less likely to have systemic symptoms (27%) at the time of diagnosis.
Progression	Less likely than NHL to be diagnosed in stage IV (10%). Hodgkin's disease usually progresses in an orderly way from one lymph node region to the next. This process may be slow, particularly in younger people, or very aggressive. The disease typically spreads downward from the initial site. If it spreads below the diaphragm, it usually reaches the spleen first; the disease then may spread to the liver and bone marrow. If the disease starts in the nodes in the middle of the chest, it may spread outward to the chest wall and areas around the heart and lungs.	More likely than HD to be diagnosed in stage IV (36%). The lymphomas are less predictable in their course than Hodgkin's disease and they are more apt to spread.

Other Cancers or Serious Conditions in the Lymphatic System. Other cancers that can travel to lymph nodes include breast cancer and leukemia.

Very serious causes of enlarged lymph nodes include disorders of the lymph system that include Castleman's disease, lymphomatoid granulomatosis, and angioimmunoblastic lymphadenopathy. These lymph system disorders, although noncancerous, involve abnormal lymph cells. They are often fatal and can be very difficult to distinguish from lymphomas. Many of the other serious illnesses involving diseased lymph nodes develop simultaneously at multiple sites, while Hodgkin's nearly always starts at one location before spreading to nearby nodes. [See Well-Connected Report #84, *Non-Hodgkin's Lymphomas* or Report #86 *Acute Lymphocytic Leukemia.*]

Exposure to Chemicals. Exposure to industrial chemicals or certain medications, such as phenytoin (Dilantin), may cause enlarged nodes. In addition, other drugs, such as cephalosporins, penicillins, or sulfonamides, can cause enlarged nodes and other symptoms, including fever and rash that may resemble Hodgkin's disease.

Physical Examination

The physician will examine not only the affected lymph nodes but also the surrounding tissues and other lymph node areas for signs of infection, skin injuries, or tumors. The consistency of the node is sometimes indicative of certain conditions. For example, a stony, hard node is often a sign of cancer, usually one that has metastasized (spread to another part of the body). A firm, rubbery node may indicate lymphoma (including Hodgkin's). Soft nodes suggest infection or inflammatory conditions.

Blood Tests

Blood tests are performed to measure white and red blood cells, blood protein levels, the uric acid level, blood proteins, and the liver's function. Another blood test is the erythrocyte sedimentation rate (ESR), which is sometimes elevated in Hodgkin's disease (although it is not specific for this condition).

Imaging Techniques

Chest X-Ray. A chest X-ray allows a view of the lymph nodes in the chest and neck area, where Hodgkin's disease usually starts and is a useful step for detection of enlarged lymph nodes.

Computer Tomography. Computed tomography (CT) scans are more accurate and can detect abnormalities in the chest and neck area, as well as revealing the extent of the cancer and whether it has spread outside the nodes. In one study, CT scans provided evidence of disease in 15% of sites that were considered normal on chest X-ray. A CT scan also is useful in detecting cancer below the diaphragm in the abdomen and pelvic areas.

Other Advanced Imaging Techniques. Other newer advanced imaging techniques, including positron emission tomography (PET) and gallium-67 scintigraphy, are proving to be very helpful. Gallium scintigraphy has also been proven to detect the presence of HD, relapse, progression, and helps physicians to predict outcome. A specific PET scan technique called FDG-PET may be even more useful, because it can detect more disease sites both above and below the diaphragm. These imaging techniques can be used for staging the disease, often reducing the need for invasive procedures, which are required for examining areas undetectable using standard imaging techniques. Magnetic resonance imaging (MRI) has been used but has not yet proven to be very useful beyond the evaluation of the chest wall.

Lymphangiography. Lymphangiography is an X-ray of the lymph glands and vessels after an injection of a dye. It might provide additional information on lower parts of the body, but it is generally not performed routinely. By itself, lymphangiography misses cancer in 20% of cases. It may be used after a diagnosis of stage I or II Hodgkin's disease to pinpoint the location of lymph nodes that are scheduled to be treated. There is a small risk that the dye will affect the lungs, so this test should not be used in patients with severe lung disease. The test is usually not necessary in patients who are receiving multidrug chemotherapy. It is also not usually performed on children.

Biopsy

A biopsy of the suspicious lymph node is the most definitive way to diagnose Hodgkin's disease. A biopsy has risks, some serious, and should only be performed by a qualified and experienced physician. Sometimes a physician may choose to wait and observe the involved lymph nodes, which will usually regress on their own if a temporary infection is causing the enlargement. (It should be noted, however, that some lymphomas may regress and appear to be benign, only to reappear at a later time.)

The Procedure. During a biopsy, the physician usually removes the node and checks the surrounding areas. The tissue in the node is then examined for signs of infection and blood cell or other abnormalities. Biopsies of bone marrow may also be performed in patients with existing Hodgkin's disease if the physician suspects that it may have spread to the marrow.

Results. Warning signs include the presence of B symptoms with low counts of certain blood cells, such as low red blood cells (indicating anemia), low white blood cells (leukopenia), or low platelets, the blood-clotting cells (thrombocytopenia). If the disease is detected in the bone marrow, then more invasive diagnostic procedures, such as laparotomy, are unnecessary.

Laparotomy and Laparoscopy

Laparotomy and laparoscopy are abdominal surgeries that have been used to examine internal organs and stage the disease in patients who were candidates for radiation. The goal was to determine whether the disease had spread or not. They play a more limited role in HD management now than previously, however, since many patients receive a combination of chemotherapy (which fights cancer throughout the body) and radiation for local disease, making this procedure unnecessary.

Laparotomy. Laparotomy is abdominal surgery used to examine the internal organs, particularly the liver, spleen, and any nodes not detectable using noninvasive imaging techniques. During this procedure, the spleen is removed (*splenectomy*) and tissue samples in the abdominal area are taken for biopsy. Because removal of the spleen affects the body's resistance to infection, after laparotomy some patients are susceptible to infection, which can be life-threatening. This risk has been greatly minimized with use of preoperative vaccinations and chemotherapy treatments that have less of a negative effect on the immune system. Children are at higher risk for infection than adults. It is advisable to be vaccinated against *Hemophilus influenzae* type b, meningococcal, and pneumococcal organisms at least one week before splenectomy. Some investigators recommend re-immunization with all three vaccines two years after completion of treatment and pneumococcal vaccine every six years thereafter.

Laparoscopy. A less-invasive technique called laparoscopy is sometimes considered to avoid the invasive laparotomy. This procedure uses small abdominal incisions and the insertion of fiberoptic tubes and tiny cameras for viewing the internal areas. The laparoscopy has a high incidence of missing cancers, but if cancer is observed and confirmed with a biopsy, then the patient does not need a laparotomy.

Biologic Markers

Biologic markers, called biomarkers for short, are high levels of substances that are released by tumors and indicate the level of cancer activity. Biomarkers can be found in sputum, blood, and tissue samples. Biomarkers can be enzymes, hormones, amino-acid compounds, antigens (identified by antibodies that specifically target them), growth factors, and other chemicals. Some under investigation include the following:

- CD44 is a molecule that binds to the surface of cells and may be involved in metastasis. High levels of this molecule may suggest a more aggressive disease.
- Interleukin (IL) 10 is another immune factor that may indicate a poor outlook when it occurs in high levels.

Outlook

Studies indicate that survival rates 15 years after treatment are 85% of all patients. More than 80% of Hodgkin's patients reach complete remission after initial treatment. Unlike other cancers, Hodgkin's disease is even potentially curable in late stages, with up to 85% of patients in late stages surviving 10 years and longer.

The disease recurs after treatment in about 20% to 35% of patients after an average of 10 years, but it is still potentially curable even in these cases. In one study, of those who relapsed two or more years after remission, survival was over 80%. (In other cancers, late stages or relapses are very rarely curable.)

Survival rates are poorest in the following:

- Those who relapse within a year of treatment.
- Patients who do not respond to the first-line therapy, and the disease continues to progress.

Long-Term Effects of Treatments

The good news about Hodgkin's disease is that treatment can cure the disease. The bad news is that survivors face a higher than average risk for long-term complications of these treatments, some very serious.

Many patients may experience chronic fatigue that could persist for years. One study indicated that aerobic exercise may significantly improve fatigue; in doing so it could have a positive effect on mood as well.

The most serious complications are second cancers and heart disease, which occur over the two or three decades following treatments. Secondary cancers include non-Hodgkin's lymphoma, leukemia, melanoma, stomach and lung cancers, and breast and uterine cancers. Combinations of radiation and chemotherapies are especially associated with these problems. Non-Hodgkin's lymphomas may be treatment-related but is more highly associated with having HD itself.

The risks for second cancers are highest in younger people and most likely to develop between the ages of 50 and 60 years. The danger for nonsolid tumors declines after five to 10 years although the risk persists for solid tumors for 25 years or more, particularly for stomach, breast, and uterine cancers. Long-term care and monitoring are important. [Complications for the specific treatments are discussed *under* What Are the Specific Therapies for Hodgkin's Disease?]

Still, in a 2000 study, 20 years after treatment, 90% of patients who had survived treatments were still living.

Researchers are constantly looking for treatments that will be both effective and also reduce the risk for these complications

Quality of Life in Long-Term Survivors

Although HD is highly curable, it can have many psychologic consequences. Depression and anxiety are common in survivors, particularly those who suffer additional medical conditions. Fatigue persists in the majority of patients for years. Still, a 2003 Swedish study reported that although survivors worried about their health and loss of energy, their quality of life did not differ from other people in the population. In fact, they tended to worry less about finances and leisure and placed more importance on family, work, and their relationships with other people.

Staging and Treatment Guidelines

Multiple treatment approaches are available for patients with Hodgkin's disease at nearly every stage, often resulting in similar rates of cure. Ultimately, the choice of treatment is based on a consideration of various prognostic factors as well as treatment side effects, both short and long term. Treatment decisions are individualized, and patients should discuss the pros and cons of various approaches with their physicians.

Staging the Disease

Staging the disease according to how far the cancer has spread (I through IV) is a primary method for determining both treatment options and prognosis. There are two levels of staging: clinical staging and pathological staging.

- Clinical stages are determined by conducting a thorough examination, which may include blood tests and different kinds of X-rays.
- Pathologic staging is conducted after a laparotomy and biopsy of the tissue to help determine treatment options. It involves a much more detailed examination, but is not required as often as in the past for making treatment decisions.

In general, the prognosis according to stage is as follows:

- If the disease is treated in stages I or II, the cure rates are as high as 90%. (About 55% of patients are diagnosed in these stages.)
- Patients in stages III or IV are usually diagnosed with advanced Hodgkin's disease. (Even in such stages, survival at five years can be as high as 85%.)

Staging Refinements

The staging system can be further refined according to other features or factors that indicate a more or less severe condition and can help determine whether treatments should be more or less aggressive.

Presence or Absence of B Symptoms. For example, Stages I through III are further categorized as either A or B according to whether certain widespread symptoms are absent (A) or whether they are present (B). The presence of B symptoms increases the risk of relapse.

- The patient is classified as "B" if he or she has unexplained weight loss of more than 10% within six months, unexplained fever, and drenching night sweats. Fever and weight loss are the most important indications of B symptoms; night sweats alone do not always mean that such symptoms are present. Itching by itself is not considered a reliable B symptom.
- If the patient has *none* of these symptoms, then the disease is considered at A, which is less severe than the B form at any stage.
- Another letter used to further refine a stage is E, which indicates that the malignancy is still local but has gone beyond the lymph node into surrounding tissue.

Indicators for Aggressive Treatments. Certain factors are indicators of a more serious case at any stage and the need for aggressive treatment:

- The malignancy is "bulky" (a large mass).
- Blood tests show high levels of erythrocyte sedimentation rates.

- Multiple tumors in the spleen.
- Greater involvement in the abdomen.

So, for example, even if patients have stage II disease, if any such factors are present then the patients may be treated as if they had advanced Hodgkin's disease.

Cell Types. The cell type of Hodgkin's disease may also influence treatment. For example, those with mixed cellularity type might require more aggressive therapy in certain cases than those with a slower-growing form, such as lymphocyte-predominant Hodgkin's disease (LPHD). In fact, some studies are suggesting LPHD is the mildest form of Hodgkin's disease and that patients with LPHD are more likely to die of treatment-related disease than from Hodgkin's itself. Some experts, then, are investigating the role of limiting radiation doses in such patients, although the most optimal approach is not yet known.

Other Prognostic Risk Factors. The International Prognostic Factors Project on Advanced Hodgkin's Disease has developed seven factors that help determine which patients with advanced Hodgkin's disease would benefit from more or less aggressive chemotherapy. They are also useful to help determine success in patients with relapsed or persistent HD who are undergoing stem cell transplantation. The score is determined by the number of yes answers to the following questions. The more yes answers the more likely the patient needs to be treated aggressively:

- Is the patient male?
- Is the patient older than 45?
- Does the patient have stage IV disease?
- Does the patient have blood tests showing lower than normal albumin levels? (Albumin is a protein found throughout the body.)
- Does the patients have abnormally low hemoglobin levels? (Hemoglobin is the oxygen-carrying compound in red blood cells, so low levels suggest anemia.)
- Does the patient have an abnormally high white blood cell count (15,000 or more)?
- Does the patient have abnormally low levels of lymphocytes?

Preparing for Side Effects Before Treatment

To avoid putting patients through unnecessary treatments that may actually be as or even more lethal than the disease itself over time, physicians are attempting to identify more specifically those patients who would or would not benefit from aggressive therapy.

Preventing Infection. Both the disease and some of the treatments suppress the immune system, increasing the risk for infections. Widespread, life-threatening infection is a particular danger if the spleen has been removed and both radiation and chemotherapy are administered. A week before any treatment, patients are often vaccinated against three bacteria: the pneumococcus, the meningococci, and *Haemophilus influenza*.

Measures for Infertility. People who wish to have children should discuss the possibility for receiving treatments that may lessen the risk for infertility. Examples include the following:

- Men with Hodgkin's disease may want to consider sperm freezing and assisted reproductive techniques. One encouraging study on male survivors of childhood Hodgkin's disease, reported that although treatments had reduced their sperm count and quality, the actual genetic material was healthy. Such men, then, would still be good candidates for assisted reproductive techniques.
- Women should ask their physicians about the possibility for preserving fertility by taking hormonal agents called GnRH analogs before and during chemotherapy.

Considerations During Pregnancy. Women who are pregnant need special preparation and treatments.

Monitoring after Treatment

Periodic examination for recurrent Hodgkin's disease is necessary for years after treatment, since relapse is not uncommon, even after treatment for early stages, and can occur a decade or more after treatment. Chest X-rays and CT scans of the abdomen are useful for detecting relapsed disease. Relapse is more likely to occur in early-stage disease, probably because limited radiation normally used in such cases did not destroy all malignancies. Patients who had large tumors in the chest are also at higher risk for recurrence. Patients also need to be monitored for long-term effects of the treatments themselves. Conditions to watch for include inflammation in the lungs and thyroid disease from radiation in the chest and heart disease and cancers from combined treatments, chemotherapy (particularly the use of MOPP), and blood stem cell transplantation.

Treatment of Pregnant Women

Because Hodgkin's disease often occurs in young adults, treatment for pregnant women is of particular concern. Therapy must be effective enough to protect the mother without hurting the fetus. Treatment choice must be

individualized, taking into consideration the mother's wishes, the severity and pace of the disease, and the length of the remaining pregnancy. The treatment plan may need to be changed as the pregnancy progresses.

Early in the Term. Unfortunately, an abortion may sometimes be the most prudent approach if the disease occurs in the first trimester. Chemotherapy is rarely used during that period, because it poses a risk for birth defects. Deciding on a course of action when Hodgkin's disease occurs in the first trimester is very difficult and emotionally wrenching. Prospective parents should not be shy about consulting with more than one physician if they are uncertain about how to proceed.

Later in the Term. If the disease develops in the second half of the pregnancy, it *may* be possible to postpone therapy until after an early induced delivery. Alternatively, some evidence suggests that chemotherapy in pregnant women after the first trimester may be beneficial without harming the fetus. If full-dose standard chemotherapy is not deemed possible, vinblastine alone may be beneficial; this drug is not usually associated with fetal abnormalities in the second half of pregnancy.

Steroids may also be employed late in the pregnancy both because of their antitumor effect and their effect in hastening fetal lung maturity. As an alternative, a short course of radiation (with extensive shielding of the fetus) can sometimes be considered prior to delivery if the mother is experiencing lung problems because of a rapidly enlarging mass in the chest. Combination chemotherapy may also be safe in the second half of pregnancy.

In one study, the 20-year survival rate of pregnant women with Hodgkin's disease was no different from that of nonpregnant women matched for similar stage of disease and age at diagnosis.

Treatment Options by Stage

Treatment is guided by the stage of the disease and usually relies on the location and extent of the disease. Treatment may vary within a stage, depending on whether it is categorized as either A or B. (Systemic symptoms are absent in "A" and present in "B.") The presence of B symptoms increases the risk of relapse, and so may require more aggressive treatments for that stage.

Early Stages (I or II). For non- disease in stages I or II, the following treatments may be used:

- Treatment in Adults. Physicians usually recommend radiation first for adults with HD. It provides excellent remission rates, although studies have reported a number of serious long-term complications in some patients. Selected patients in early stages may also be candidates for radiation limited only to areas above the diaphragm (called the *mantle field*), which can also have excellent results although still poses a considerable risk for late serious complications.
- Treatment in Children. Chemotherapy and low-dose radiation is the standard treatment for most children and adolescents who have not reached full growth. Specific chemotherapy combinations have been developed to reduce the risks for infertility, leukemia, and toxic effects on the heart and lungs. Researchers are studying the use of chemotherapy alone in this group.

Later Stages. For stage III disease, chemotherapy, often with radiation, is a standard treatment. For stage IV disease, chemotherapy alone is generally recommended. The latest chemotherapy regimens are achieving survival rates that reach 90%.

Relapse. Relapse after treatment occurs in 20% to 35% of patients. Treatments for relapse include chemotherapy, radiation, and bone marrow or blood stem cell transplantation. Many patients respond favorably to such treatments, although another relapse is still possible.

Stage I Hodgkin's Disease

Disease is limited to a single node region (I) or has involved one neighboring area or a single nearby organ (IE). The standard treatment for stage I disease is usually radiation for adult patients who have determined the stage using pathologic staging with laparotomy. Chemotherapy with low-dose radiation is now the standard approach for children and adolescents. Cure rates can be greater than 90%.

Stage IA. Treatments depend on location:

- Malignancy is above the diaphragm and does not involve a large part of the chest: 1. Radiation therapy to the mantle field (chest, neck, and arm pits) and to the lymph nodes in the upper abdomen and spleen. 2. Radiation therapy to a mantle field in certain patients (best candidates are females with nodular sclerosis or lymphocyte predominant cell types, who are no older than 40 years, have no "B" symptoms, and have erythrocyte sedimentation rate (ESR) levels less than 50). 3. Radiation therapy to a mantle field, the lymph nodes in the upper abdomen, and the spleen (subtotal node irradiation). 4. Chemotherapy alone is under investigation.

- Malignancy is bulky (above the diaphragm but involves a large part of the chest). 1. Chemotherapy plus radiation therapy to a mantle field is a common approach.
- Malignancy is below the diaphragm: 1. Chemotherapy with or without radiation therapy. 2. Radiation therapy to the lymph nodes in the upper abdomen and pelvis or total nodal irradiation (which includes these regions plus the mantle field). The spleen or the groin may also be treated if needed.

Stage IB. Treatments depend on location:

- Malignancy is above the diaphragm and does not involve a large part of the chest: 1. Chemotherapy plus radiation therapy to a mantle field (in patients who have severe symptoms and did not undergo laparotomy to determine the extent of the disease below the diaphragm). 2. Radiation therapy to the mantle field and to the lymph nodes in the upper abdomen is sometimes considered, but relapse rate can be high if significant B symptoms are present. 3. Chemotherapy alone under investigation for children.
- Malignancy is bulky (above the diaphragm but involves a large part of the chest): 1. Chemotherapy plus radiation therapy to a mantle field is a common approach.
- Malignancy is below the diaphragm, the treatment may be one of the following: 1. Chemotherapy with or without radiation therapy to the upper abdomen and pelvis, to the areas that contain cancer, or to the spleen. 2. Total nodal irradiation or radiation to lymph nodes in the upper abdomen and pelvis.

Stage II Hodgkin's Disease

Disease is limited to two or more lymph nodes on the same side of the diaphragm (II) or involvement of a single neighboring organ or area and one or more nearby lymph nodes; other lymph nodes on the same side of the diaphragm may be involved (IIE).

There are few differences between treatments for State IIA and IIB and the approach for both depends on the extent and location of the disease:

- Nonbulky disease. Standard treatments are usually radiation alone for adult and possibly adolescent (especially male) patients and chemotherapy with low-dose radiation for children.
- Malignancy is above the diaphragm and does not involve a large part of the chest. The treatment may be one of the following: 1. Radiation therapy to a mantle field and to the lymph nodes in the upper abdomen. 2. Radiation therapy to a mantle field only (in certain patients). (See Stage I above.) 3. Chemotherapy alone or with radiation therapy (combined modality) being evaluated for those with non-bulky stage IIA. 4. Under investigation: Radiation therapy to a mantle field only in patients with lymphocyte predominant cell types, who are no older than 40 years.
- Malignancy is above the diaphragm but involves a large part of the chest. 1. Chemotherapy plus radiation therapy to a mantle field is a common approach
- If the malignancy is below the diaphragm, the treatment may be one of the following: 1. Chemotherapy alone or with radiation therapy (combined modality). 2. Radiation therapy to the lymph nodes in the upper abdomen and pelvis. The spleen may also be treated if needed. 3. Total nodal irradiation.

Stage III Hodgkin's Disease

Disease is in lymph nodes on both sides of the diaphragm (III), which may also be accompanied by localized involvement of an associated organ or site outside the lymph node (IIIE), by involvement of the spleen (IIIS), or by both (IIIE+S). In addition, Stage III may be further categorized by the extent of its spread into the spleen or where it has spread in the abdominal area. Survival rates in some cases can be as high as 90%.

Stage IIIA. Chemotherapy is the most common treatment approach for most adults and children. Radiation may be added under certain circumstances, especially to provide localized treatment of bulky areas. (Radiation does not appear to offer any survival advantage for patients whose disease is in complete remission after chemotherapy.)

- The malignancy does not involve a large part of the chest: 1. Chemotherapy alone. 2. Chemotherapy with radiation therapy (combined modality). 3. Total or subtotal nodal radiation therapy alone in adults if disease is only in the upper abdomen and fewer than five nodes in the spleen are affected, although relapse rate may be high.
- The malignancy involves a large part of the chest: 1. Standard chemotherapy regimens. 2. Chemotherapy plus radiation therapy (combined modality). 3. Investigative treatments.

Stage IIIB. Chemotherapy alone is the standard treatment for most adults and children. Radiation is often added to treat areas of bulky tumor. 1. Chemotherapy. 2. Chemotherapy and radiation to areas where the cancer is found or to more extended areas. (Radiation does not appear to offer any survival advantage for patients whose disease is in complete remission after chemotherapy.)

Stage IV Hodgkin's Disease

Disease has spread to organs outside the lymph system, such as liver, lung, or bone marrow. Even in this population, high long-term survival rates of over 85% are possible, including in children.

Treatment may be one of the following: 1. Chemotherapy alone. 2. Chemotherapy with limited radiation to places of bulky disease. 4. A clinical trial of novel chemotherapy regimens or of stem-cell transplantation.

Relapsed or Refractory Hodgkin's Disease

When disease recurs or persists after initial treatment either in the same area or in another part of the body, the next round of therapy depends on where the disease returns and the previous treatment used.

- If the previous treatment was radiation therapy without chemotherapy, salvage chemotherapy is the usual choice.
- If the patient was previously treated with chemotherapy, then the choice may be radiation therapy to the lymph nodes with or without salvage chemotherapy.
- In some patients, if the disease has persisted or if relapse has occurred after chemotherapy with or without radiation, high-dose chemotherapy and stem cell transplantation may be given.

Radiation Treatments

High-dose radiation therapy, which shrinks the tumors, has been used for 50 years for treating Hodgkin's disease. High-dose radiation is generally reserved for adults. The treatment is highly toxic for children and adds little benefit. In such young age groups it is mostly used if there are large areas of disease in the chest; otherwise, chemotherapy with possibly low-dose radiation is the best option with excellent survival rates.

Radiation Target

Radiation is directed in specific areas depending on the location of the disease:

- If HD is above the diaphragm, radiation is delivered to the neck, chest, and under arms (called the *mantle-field*) and sometimes to lymph nodes in the upper abdomen or spleen or both. (The use of mantle-field radiation only to the mantle field is usually limited to selected younger patients.) Best candidates may be females under 40 years old with nodular sclerosis or lymphocyte predominant cell types, who have no "B" symptoms, who and have erythrocyte sedimentation rate (ESR) levels less than 50.
- If cancer is below the diaphragm, a so-called "inverted Y" field is sometimes used, in which radiation is directed lymph nodes in the upper abdomen, spleen, and pelvis.

Radiation Treatment Approaches

It is very important that radiation treatments cover the entire diseased area and that the radiation therapy be powerful enough to destroy the malignant cells' capacity to grow and divide. Unfortunately, this means that normal cells are also affected, which can cause serious side effects. Different approaches may be used to prevent complications.

- Devices called *planning simulators* allow physicians to plan X-ray treatments that accurately conform to the patient's anatomy so that protective shields can be created to precisely protect the regions outside the treatment areas.
- Long-term complications generally occur at higher radiation doses (over 35 Gy). Investigators are studying the doses as low as 20 Gy (in children). Studies are now reporting that radiation alone in doses under 35 Gy can control the disease as well as higher doses in most Stage I and II patients, although some patients may require more aggressive treatment.
- To protect ovaries, a technique called *ovarian transposition* may sometimes be performed. For example, in one successful small study the procedure was performed within one month of pelvic radiation in women who had either received no chemotherapy or less than two cycles. (Chemotherapy often stops menstruation.) The procedure employs a laparoscope (a thin tube containing tiny instruments and cameras) that is introduced through a small incision. The physician uses the laparoscope to move the ovaries out of the range of areas being treated with radiation. In this study, four out of five women who desired children achieved pregnancy.

Complications of Radiation

Infections. Infections may be a particular problem with radiation combined with chemotherapy. All patients should be vaccinated against pneumonia and influenza.

Inflammation in the Lungs. With carefully conducted therapy, the risks for lung complications are small. Lung impairment may not even be evident, and the lungs usually recover after two or three years.

Infertility. Radiation therapy to the pelvic area can adversely affect later fertility in women and men. Such negative effects may be worse in women; sperm usually recover within five years.

Heart Disease. Radiation is associated with a future risk of heart disease, which includes atherosclerosis (hardening of the arteries) and valvular disease. Lower doses pose less risk. Such conditions can develop even without symptoms. Preventive treatments are important and can be effective.

Fatigue. Fatigue is significant and chronic in many survivors. It is more highly associated with intensive chemotherapy, but it also may be a late response to radiation treatment.

Secondary Cancers. Second cancers (e.g., breast, stomach, lung, melanoma) may develop later in areas within or at the edge of the radiation area. The risks are twice as high with treatments that are combined with chemotherapy.

Among children, those treated less than 10 years face a higher risk for thyroid and respiratory tract cancer later on. Older children (10 to 16 years) are at higher risk for cancers in the digestive tract.

Lung cancer in survivors is highly associated with smoking after treatment, and no survivor should smoke.

The incidence in breast cancer increases significantly in young women after treatment, particularly with high radiation doses and combined modality (chemotherapy plus radiation). The risk can persist for 25 years or more after radiotherapy and lifetime monitoring is essential. Newer treatment advances may reduce this risk. (It should be noted that cancer in the breast has also appeared in a few men.)

Thyroid Disorders. Hypothyroidism (low thyroid hormone levels) occurs in a number of patients treated with radiation treatments. There is also a 5% chance for hyperthyroidism.

Impaired Growth in Children. Children and adolescents are at special risk for impaired bone growth.

Other Treatments

Chemotherapy uses cytotoxic (cell-killing) drugs to kill cancer cells throughout the body, and it is therefore referred to as *systemic therapy*.

Cytotoxic agents may be given orally or as injections. Treatment may be administered at a medical center, physician's office, or even a patient's home. Some patients receiving chemotherapy may need to remain in the hospital for several days so the effects of the drug can be monitored.

Patients may receive up to 8 cycles of chemotherapy, depending on the stage. A cycle is usually 28 days and consists of several doses of drug administration followed by a period of rest.

Specific Agents and Drug Combinations Used in Hodgkin's Disease

A number of chemotherapy regimens have proven to be effective. Different drugs in each regimen may need to be taken orally or by injection. Toxicity varies depending on the combination. Researchers are investigating the use of chemotherapy regimens used alone, taken in alternate cycles with another regimen, or as hybrids (combining one or two drugs from one regimen with drugs from another).

The following are regimens that are very effective in the treatment of Hodgkin's disease.

- ABVD [doxorubicin (Adriamycin), bleomycin, vinblastine, dacarbazine] is now the first choice for most patients who need chemotherapy. It is the most effective and least toxic regimen available to date. Unlike MOPP, for example, it does not pose a significant risk for leukemia or infertility.
- MOPP and MOPP-ABV. The introduction of MOPP [mechlorethamine (Mustargen), vincristine (Oncovin), procarbazine, prednisone] in the 1960s resulted in dramatic reductions in mortality rates from HD. A hybrid of MOPP and ABV [doxorubicin (Adriamycin), bleomycin, vinblastine] has often been used for advanced HD. MOPP can cause infertility and carries a 3% risk for leukemia, however.
- BEACOPP (bleomycin, etoposide, Adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone). This regimen is proving to be very effective, particularly in advanced stages, with studies reporting remission

rates of over 90% in patients with advanced Hodgkin's. The risk of long-term side effects, such as leukemia, requires longer follow-up.

- Stanford V (Seven drugs administered over a shorter time but more frequently than MOPP or ABVD). Mechlorethamine (Mustargen), doxorubicin (Adriamycin), vinblastine (Velban), vincristine (Oncovin), bleomycin (Blenoxane), etoposide (VP-16), prednisone by mouth every other day. This regimen is proving to be effective for extensive and advanced HD, although it is not known whether it is superior to more standard regimens, such as ABVD.

Other regimens continue to be tested for effectiveness and safety in both early and late stage HD. They include the following:

- ChlVPP (chlorambucil, vinblastine, procarbazine, and prednisone). Studies are showing that it is effective in specific patients. For example, it is proving to be to beneficial and less toxic for children. In one 2002 study, a hybrid regimen using ChlVPP and another regimen containing doxorubicin improved response compared to ChlVPP alone for elderly patients.
- VAPEC-B (vincristine, doxorubicin, prednisolone, etoposide, cyclophosphamide, and bleomycin). This is a short-course regimen that might be useful in some patients, although it is not as effective as others.

Regimens with fewer toxic effects, such as ChlVPP and others, are being tested in children and adolescents in early stages, with some showing promise. Certain agents, such as etoposide, cause less injury to male reproductive organs and can be substituted for more toxic agents, notably procarbazine.

Specific regimens are also being studied for elderly patients.

Agents Used with Relapsed or Previously Untreatable HD. For patients who relapse or have only partial remissions other agents, called salvage chemotherapy, may be needed or high-dose chemotherapy may be used in combinations with stem cell transplantation.

Common regimens include the following:

- BEAM [carmustine (BCNU), VP-16, cytosine arabinoside, and melphalan]. Used with stem cell transplantation. (An alternative regimen known as mini-BEAM uses lower doses and is used without stem cell transplantation.)
- CBV [cyclophosphamide, carmustine (BCNU), etoposide (VP-16)]. Used with stem cell transplantation.

Other agents or combinations are showing promise for relapsing or previously untreatable Hodgkin's and including the following:

- ASHAP [doxorubicin (Adriamycin), methylprednisolone (Solumedrol), high-dose cytosine arabinoside, and cisplatin (platinum)].
- DHAP (dexamethasone, cytarabine, cisplatin).
- GEM-P (gemcitabine, cisplatin and methylprednisolone).
- Agents that have shown some effectiveness in combinations for relapsed or progressive HD in children and adolescents include cisplatin plus regimens with high-dose cytarabine, ifosfamide, carboplatin, and etoposide and ifosfamide plus vinorelbine. Gemcitabine has shown promise as a single agent in patients with relapsed Hodgkin's disease.

Sequential High-Dose Chemotherapy. A promising approach called sequential high-dose chemotherapy employs few drugs given at the highest possible doses and administered at intervals of one to three weeks.

Side Effects and Complications

Side effects and complications of any chemotherapeutic regimen are common, are more severe with higher doses, and increase over the course of treatment, though some trials suggest that toxicities can be reduced by administering the drugs for shorter duration without loss of cancer-killing effects.

Common Side Effects. Common side effects include the following:

- Nausea and vomiting. Drugs known as serotonin antagonists, such as ondansetron (Zofran) or granisteron (Kyril), can relieve these side effects in nearly all patients given moderate drugs and most patients who take more powerful drugs. In one study, nearly all patients who took a combination of dexamethasone (a steroid) in combination with ondansetron within 24 hours of chemotherapy experienced either a significant or complete reduction in nausea and vomiting.
- Diarrhea.
- Hair loss.
- Weight loss.
- Anemia. Studies are investigating the use of epoetin (Procrit), which increases production of red blood cells, to reduce this effect and improve quality of life.

- Depression.

These side effects are nearly always temporary. Most patients are able to continue with normal activities for all but perhaps one or two days a month.

Serious Side Effects. Serious side effects can also occur and may vary depending on the specific agents used. They include the following:

- Increased chance for infection from suppression of the immune system and severe drops in white blood cells (*neutropenia*). White blood cell count may be improved with the addition of a drug called granulocyte colony-stimulating factor (filgrastim, pegfilgrastim, and lenograstim). (There is no evidence that these agents have any effect on survival or cancer recurrence, however.)
- Liver and kidney damage.
- Abnormal blood clotting (*thrombocytopenia*).
- Allergic reaction.
- The drug BCNU (carmustine) carries a significant risk for life-threatening pneumonia, particularly in women.

Long-Term Complications.

- Fatigue and Somatic Symptoms. Chemotherapy has been associated with long-term somatic symptoms, which are general conditions, such as fatigue and aches and pains that have no apparent physical basis. Fatigue is especially common after chemotherapy and can even last for years.
- Leukemia. Risk is highest with MOPP, particularly combined with radiation therapy.
- Infertility. Risk is highest with MOPP and less so with ABVD. Investigators are testing an agent called a gonadotropin-releasing hormone analogue that puts women in a temporary pre-pubescent state during chemotherapy and which may preserve fertility in many women.
- Bone injury. This may be related to steroid treatments.
- Heart failure. Certain agents, including anthracyclines (such as doxorubicin) and similar drugs called anthracenediones (e.g., mitoxantrone) pose specific risks to the heart.
- Lung toxicity. Bleomycin (Blenoxane), an antibiotic used in some regimens, is particularly toxic to the lungs. Vinblastine and methotrexate may also pose a risk when used in combination with radiation therapy.

In general, these serious late side effects are dependent on the cumulative drug dose and rate of administration.

Combinations of Chemotherapy and Radiation (Combined Modality)

Regimens. Chemotherapy (usually ABVD) plus radiation, referred to as combined modality, is a common treatment approach for patients with more advanced-stage disease and for those who have early-stage bulky (large mass) disease. In a 2000 study, the Stanford V regimen combined with radiation produced excellent survival and remission rates among patients with early-stage bulky and with stage III/IV disease. A comparison study with ABVD is under way. A 2003 study indicated, however, that radiation added no additional advantages for patients with advanced HD who showed no signs of disease after initial chemotherapy. It also significantly increases the risk for secondary cancers compared to chemotherapy alone. More research is needed to confirm this.

Chemotherapy with low-dose radiation is being used in children with excellent results, even for late stage cancer. In one study, 82% of the children were still disease free at five years. Some chemotherapy drugs or high doses of radiation may be more deleterious to a boy's future fertility than to a girl's. A gender-specific combined regimen for pediatric Hodgkin's reduces the amount of radiation given to boys and also substitutes etoposide for procarbazine in the chemotherapy mixture (procarbazine, vincristine, prednisone, and doxorubicin).

Side Effects and Long-Term Complications. Side effects of combination treatments can be very serious. They not include the adverse effects of the individual treatments but some may be compounded. Examples include the following:

- Combined modality poses a higher risk for secondary cancers than the use of radiation or chemotherapy alone. They, include breast, lung, thyroid, melanoma, and gastrointestinal cancers, which usually develop in or near or in the areas treated with radiation. Of note, the risk for breast cancer is lower when chemotherapies using alkylated agents or radiation treatments damage the ovaries, suggesting that hormone stimulation plays a role in this higher risk. Newer agents used in combined modalities may reduce the risk, at least for breast cancer.
- ABVD and other regimens containing bleomycin increase the risk for severe effects on the lungs when used before or after mantle-field radiation. EVA [etoposide, vinblastine, and doxorubicin] is considered to be an effective substitute in patients with lung disease for whom bleomycin and radiation present an unacceptable risk.

Transplantation

Patients with relapsed or progressive HD are often treated with high-dose chemotherapy followed by stem cell transplantation procedures. (It does not appear to offer an advantage compared to standard chemotherapy as initial treatment for patients with high-risk advanced HD.)

This treatment involves removal and replacement of *stem cells*, which are produced in the bone marrow. This allows the patient to receive high-dose chemotherapy without destroying these important cells. Stem cells are the early forms for all blood cells in the body (including red, white, and immune cells). Cancer treatments harm growing cells as well as cancer cells, and so the healthy stem cells must be replaced by transplanting them, usually using the patient's own cells (called an autologous procedure) or, less commonly, from a donor (allogeneic procedure).

Collecting the Stem Cells

Sources of Cells. Stem cells must first be collected in one of the following ways:

- Directly from blood (peripheral blood stem cell transplantation).
- From bone marrow (bone marrow transplantation).

- From umbilical cords or placentas. This procedure uses donor cells but has a lower risk for immune system rejection of the cells than with a standard donor transplant. It takes longer to restore blood cells with this process, however, so at this time its use is limited to children and sometimes adults with low weight. (A small 2001 study on adults suggested it might also be useful for adults with normal weights.)

Current evidence suggests that the stem cell and bone marrow procedure produce similar benefits in terms of survival. However, because stem cell transplantation seems to be superior in terms of cost, quality of life, and the need for less supportive care, it is discussed here.

Donor or Patient Cells. The marrow or blood stem cells can be taken from the patient (autologous) or from a matched donor (allogeneic):

- An *autologous* transplant is one in which marrow or blood cells used are the patient's own. Autologous stem cell transplantation is the current preferred choice for HD patients who need these procedures. The advantage to an autologous procedure is that the patient is not at risk for rejection by the immune system. There is some danger, however, that the cells used may contain tumor cells and the cancer can regrow. There is also a higher risk for leukemia (This risk is lower in peripheral stem cells transplants than in bone marrow transplants.) A number of studies, however, are reporting good success with this transplant.
- An *allogeneic* transplant is one in which bone marrow or stem cells are taken from a donor. The donor and recipient must be matched as closely as possible to avoid rejection by the immune system, a serious complication called graft-versus-host disease. Siblings are the best possibility.

The Blood Stem Cell Collection Procedure

- The donor is usually given a drug called granulocyte colony-stimulating factor, or G-CSF (filgrastim, lenograstim) to stimulate stem cell growth.
- The patient (or donor in an allogeneic procedure) then undergoes apheresis. With this process the blood is withdrawn from one of the patient's veins, then passes through a machine that filters out the white cells and platelets, which contain the stem cells. The blood is returned through another vein. The entire procedure takes three to four hours but needs to be repeated several times.
- The stem cells are treated to remove contaminants and then are frozen to keep them alive until the patient is ready to receive them back.

The Transplantation Procedure

- Allogeneic transplants are preceded by chemotherapy treatment known as *conditioning*. The point of this treatment is to inactivate the immune system and to kill any residual malignant cells. It is extremely toxic since it also destroys non-malignant marrow cells. Agents used are typically cyclophosphamide, carmustine, and etoposide. Alternative conditioning to reduce toxicity includes total-body radiation plus one agent.
- A few days after treatment, the patient is *rescued* using the stored stem cells, which are administered through a vein. This may take several hours. Patients may experience fever, chills, hives, shortness of breath, or a fall in blood pressure during the procedure.
- The patient may be treated with granulocyte colony-stimulating factor *after* chemotherapy. The goal is to stimulate the growth of infection-fighting white blood cells. Because this increases immune factors, there is some concern that it might also heighten the immune attack against the donor cells, but studies to date have been encouraging and are reporting a low risk. (Adding another substance, thrombopoietin, may prove to enhance stem cell production.)
- The patient is kept in a protected environment to minimize infection, and he or she usually needs blood cell replacement and nutritional support.

Candidates and Success Rates

The following patients may be appropriate transplantation candidates:

- Patients with advanced or relapsed Hodgkin's disease, particularly for young patients with a poor outlook.
- Some studies suggest benefits using stem cell transplantation for early-stage patients who do not respond to initial therapy. (This includes those who achieve an initial partial remission, those who progress during therapy, and those who have evidence of residual disease on biopsy.)

Patients with B symptoms or those who are in poor condition at the time of the procedure are more likely to experience poorer results.

Overall, studies report five-year survival rates of between 30% and 93%, with the rates being higher or lower depending on different factors. The success rates appear to be the same in children, adolescents, and adults. Prognosis is best in the following:

- If the patient has had only one relapse that occurred more than 12 months after the completion of previous treatment, and
- If the cancer recurred within a lymph node, not outside it.

In such patients, the four-year survival rate was 93% in one study. Even when these factors were not present, the survival rate, with equivalent treatment, was 43%, and experts suggest it could be higher with more aggressive therapies. (It should be noted that there was a 6% mortality rate from the treatment itself.)

Side Effects and Complications

Common side effects include nausea, vomiting, fatigue, mouth sores, and loss of appetite.

The procedures themselves are fairly dangerous and carry a small risk for death. When it was first used, transplantation procedures had 10% to 25% mortality rates. Now mortality rates are below 5%. Potentially serious complications are the following:

- Infection resulting from a weakened immune system. This is the most common side effect and can persist for several months after the transplant. Because the stem cell procedure is done more swiftly, the risk period is shorter than with bone marrow transplantation. Many patients develop severe herpes zoster virus infections (shingles) or have a recurrence of herpes simplex virus infections (cold sores and genital herpes). Pneumonia, cytomegalovirus, aspergillus (a type of fungus), and *Pneumocystis carinii* (a protozoan) are among the most important life-threatening infections.
- Graft-versus-host disease (GVHD) is a serious attack by the patient's immune system triggered by the donated new marrow in allogeneic transplants. Acute GVHD occurs in over half of allogeneic transplants, usually within 90 days. Its severity ranges from very mild symptoms to a life-threatening condition (more often in older patients). In some cases it can become chronic, which usually develops after the third month following the transplant but may not develop for a year or more. GVHD can cause gastrointestinal problems, severe skin reactions, hair loss, mouth and throat ulcers, and liver damage. Careful matching of the donor and preventive immunosuppressive drugs, such as corticosteroids, methotrexate, and cyclosporine (Sandimmune), may reduce the risk. T-lymphocyte depletion is another approach for preventing GVHD, which involved reducing the number T-cells infused with the stem cells.
- Secondary cancers. There is a small long-term risk for leukemia after transplantation in young people. Use of newer chemotherapeutic agents, however, may not pose as high a danger as older treatments.
- Bleeding because of reduced platelets. This risk is highest within the first four weeks after BMT.
- Infertility.
- Organ complications to the liver, heart, kidney, or lungs.
- Failure of the transplant. The marrow graft may fail or new marrow cells may now grow.

Immunotherapy

Investigative approaches to Hodgkin's disease are immunotherapies, agents that take advantage of the patients' own immune factors to attack the disease.

One important approach uses genetically designed immune factors called monoclonal antibodies (MAb) that recognize and attack specific molecules found on the surface of cells associated with HD.

Rituximab (Rituxan) was the first monoclonal antibody to be approved for any cancer. It is an unconjugated MAb that targets the CD-20 antigen, which is found on most B-cell lymphomas and normal mature B-cells (although not stem cells). It is used in non-Hodgkin's lymphomas but it may have benefits for some patients with Hodgkin's disease as well. For example, an early study reported very good results in patients with lymphocyte-predominant Hodgkin disease (LPHD), which contains the CD-20 antigen.

Investigators are also studying very specific tumor-killing agents composed of fragments of MAbs or plant or bacterial targets that deliver the agent to into the tumor cells.

Another approach uses radioimmunotherapy, which binds tiny amounts of radioactive materials to antibodies for delivery into the tumor.

One experimental therapy is based on certain immune factors called killer T-cells that specifically attack a subtype of the Epstein-Barr virus (EBV) expressed by Hodgkin's cells in certain patients. Researchers draw these T-cells from the patient and expand them in the laboratory. They are then infused back into the patient with the expectation that the T-cells will attack the virus in the Hodgkin's cells, killing the cancer cells as well. To date, this therapy has shown some activity, but no cure.

Resources

- www.nci.nih.gov -- National Cancer Institute (800-422-6237)
- www.cancer.org -- American Cancer Society (800-ACS-2345)
- www.lymphoma.org -- The Lymphoma Research Foundation of America (310-204-7040)
- www.cfl.org -- Cure for Lymphoma Foundation (800-CFL-6848)
- www.leukemia.org -- The Leukemia and Lymphoma Society (800-955-4572)
- www.cansearch.org -- National Coalition for Cancer Survivorship (877-622-7937)
- www.marlow.org -- National Marrow Donor Program (800-627-7692)
- www.jco.org -- The Journal of Clinical Oncology
- www.lymphomainfo.net -- Lymphoma Information Network
- <http://cancertrials.nci.nih.gov> -- Find clinical trials
- www.clinicaltrials.gov -- Find clinical trials
- www.asco.org/people/db/html/m_db.htm -- Find an Oncologist

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