INTRODUCTION

Non-Hodgkin’s lymphoma (NHL) is the most common cancer of the lymphatic system. Since the early 1970s, the incidence of NHL has nearly doubled. Overall, the five-year survival rate is 59%.

Of the nearly 500,000 Americans with lymphoma, approximately 332,000 have NHL. Each year, more than 56,390 new cases of NHL are diagnosed and 19,200 Americans die of the disease. NHL has grown from a relatively uncommon disease to being the fifth most common cancer in the U.S. The reasons for this are not clear, but promising research is under way to improve the prognosis for patients with NHL.

Lymphoma is manifested when an error occurs in the way a lymphocyte is produced, resulting in an abnormal cell. The exact cause is unknown. The cancerous lymphocytes can grow in many parts of the body, including the lymph nodes, spleen, bone marrow, blood, or other organs. There are more than 30 subtypes of lymphoma, including five types of Hodgkin’s lymphoma (HL) and more than 25 types of NHL. Lymphoma is the most common blood cancer and the third most common cancer of childhood.

NHL is broadly divided into two major groups:

- **B-cell lymphomas**, which develop from abnormal B lymphocytes
- **T-cell lymphomas**, which develop from abnormal T lymphocytes

One type of slowly growing (indolent) NHL, **follicular lymphoma**, is classified as grade 1, 2, or 3. It is relatively common, accounting for 20% to 30% of all NHLs. Follicular lymphoma arises from B lymphocytes and is thus one of the B-cell lymphomas. It typically affects middle-aged and older adults. Because follicular lymphomas are common, they are often used as a model for the treatment of other indolent lymphomas.

Patients with follicular NHL usually have abnormal cells in many parts of the body, including the bone marrow. These cells are rarely localized. About 50% of follicular lymphomas may eventually be transformed into a more aggressive lymphoma that becomes more difficult to treat than those that are more aggressive at diagnosis.

Grade 3 NHL is considered to be more aggressive than grade 1 or 2 NHL. An aggressive, or fast-growing NHL, **diffuse large B-cell lymphoma** (DLBCL), is the most common type, making up 30% to 40% of NHLs. DLBCL may be localized or generalized.

TREATMENT

NHL comprises a highly treatable group of diseases that are very responsive to modern treatments, such as chemotherapy, radiation, and immunotherapy. Stem-cell transplantation is sometimes used. The efficacy of these treatments depends on the particular form of NHL and the precise type and stage of the lymphoma, as well as other variables.

For example, DLBCL is curable in more than 80% of patients. By contrast, follicular lymphoma is generalized in most patients; it is responsive to therapy, but it is not curable. If it is localized, however, it can often remain quiet for years or decades, with minimal treatment.

Major research efforts continue to investigate the effectiveness of new medications and novel combinations of established therapies. The science of treating NHL is advancing quickly, and many new regimens are under study.

Chemotherapy

Combination Therapy

Combination chemotherapy is often selected because different drugs damage or kill cancer cells in different ways, thereby making the cells more vulnerable. Combinations can offer an effective way to kill more tumor cells; using the drugs together, rather than individually, enhances the drug’s impact more than would be achieved if the drug were used alone or as add-on therapy.

CHOP (cyclophosphamide, doxorubicin, vincristine [Oncovin] and prednisone), for instance, which is considered the standard therapy for DLBCL, includes drugs in less toxic amounts while sustaining a full or augmented (synergistic) capacity to destroy cancerous lymphocytes. Combination therapy is also used to prevent drug resistance. A chemotherapy regimen combines anticancer drugs that are administered at a certain dose in a specific sequence according to an exact schedule.
Bendamustine (Treanda)
Bendamustine (SDX-105, Treanda, Cephalon), an investigational, bifunctional chemotherapeutic agent with both alkylator and purine-like activity, is currently in phase 2 testing for a variety of diseases. One advantage of bendamustine is that it is not cross-resistant with other alkylating agents. It has been used clinically in Germany for many years in patients with NHL, chronic lymphocytic leukemia, multiple myeloma, breast cancer, and other solid tumors such as lung cancer.

Single-drug therapy with bendamustine appears to be effective at producing durable objective responses in heavily pretreated patients with indolent NHL. In a phase 2 study of bendamustine monotherapy in 77 patients with relapsed indolent or transformed rituximab-refractory B-cell NHL, 38% of the patients had complete beneficial responses; 39% of patients had partial responses; 7% had stable disease; and 16% had disease progression. The overall objective response rate was 74%.

Among a subgroup of 28 patients whose condition was refractory to both rituximab and prior chemotherapy with an alkylating agent, the overall response rate was 64%, satisfactory for patients so far along in the course of the disease. Bendamustine is undergoing additional study for FDA approval.

Bortezomib (Velcade)
Bortezomib (Velcade, Millennium) is a modified dipetidyl boronic acid and a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome in mammalian cells. The 26S proteasome is a large protein complex that degrades ubiquitinated proteins. The ubiquitin–proteasome pathway plays an essential role in regulating the intracellular concentration of specific proteins, thereby maintaining homeostasis within cells. Inhibition of the 26S proteasome prevents targeted proteolysis, which can affect multiple signaling cascades within the cell. This disruption of normal homeostatic mechanisms can lead to cell death.

Bortezomib is cytotoxic to a variety of cancer cell types in vitro. It causes a delay in tumor growth in vivo in nonclinical tumor models, including multiple myeloma. It is approved for the treatment of multiple myeloma in patients who have received at least two prior therapies and have demonstrated disease progression while receiving the last therapy. It is under study for NHL.

Monoclonal Antibodies
Rituximab (Rituxan)
The advent of monoclonal antibodies in the treatment of NHL has marked a revolution in our understanding of cancer. Rituximab (Rituxan, Genentech/Biogen Idec) is a genetically engineered, chimeric murine (mouse)/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes. It is approved for use in patients with relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL. CD20 regulates early steps in the activation process for cell–cycle initiation and differentiation and possibly functions as a calcium-ion channel. CD20 is not shed from the cell surface and does not become internalized upon antibody binding.

Rituximab is usually given in a dose of 375 mg intravenously once a week for four to eight weeks, often with other types of chemotherapy. It is often used in combinations such as CHOP or fludarabine phosphate (Fludara, Berlex) and cyclophosphamide. Rituximab is sometimes administered with ibritumomab tiuxetan (Zevalin, Biogen Idec) (see later).

Recent work at the University of California, Los Angeles, and elsewhere has shown that rituximab can increase the sensitivity of lymphoma cells to chemotherapy. Patients with aggressive lymphoma have shown improvement in both response rates and survival after receiving a combination of rituximab and chemotherapy, compared with chemotherapy alone. It is possible that all patients might derive a benefit from rituximab whether it is administered earlier or later in the course of the disease.

Efforts to increase the efficacy of rituximab by stimulating the immune system are ongoing. Researchers hypothesize that because rituximab helps the immune system attack the antibody-covered lymphoma cells, immune-enhancing biologic drugs, such as interleukin-2 (aldesleukin [Proleukin], Chiron) interleukin-12, and cytosine–phosphorothioate—guanine (CpG) oligodeoxynucleotides, can enhance the therapy’s action. Results look promising.

Alemtuzumab (Campath)
Alemtuzumab (Campath, Berlex) is a genetically engineered, humanized immunoglobulin G1 (IgG1) kappa monoclonal antibody. It is specifically directed against a 21- to 28-kilodalton lymphocyte cell–surface glycoprotein, CD52. CD52 is expressed primarily on the surface of normal and malignant peripheral blood B-cell and T-cell lymphocytes. Alemtuzumab causes the lysis of lymphocytes by binding to CD52, a nonmodulating antigen, found on the surface of essentially all B-cell and T-cell lymphocytes, monocytes, thymocytes, and macrophages. The antibody mediates the lysis of lymphocytes via complement fixation and antibody-dependent cell-mediated cytotoxicity.

The Food and Drug Administration (FDA) has approved the antibody for the first-line treatment of chronic lymphocytic leukemia (CLL) on the basis of its efficacy in patients with refractory disease. Alemtuzumab is also being studied for the treatment of NHL.

Epratuzumab
Epratuzumab (Immunomedics, Inc.) is an anti-CD22 antibody that is being tested for patients with NHL. As monotherapy, this agent demonstrates less activity than rituximab. Results of a recent study of an epratuzumab/rituximab combination are awaited.

IDE 114
An anti-CD80 antibody, IDEC 114 (Biogen Idec), is also under investigation, and results have been encouraging in some patients with follicular lymphoma.

Radioimmunotherapy
Tositumomab and Iodine 131 Tositumomab (Bexxar)
Bexxar, a combination of two radioimmunotherapy products, is currently approved by the FDA for the treatment of NHL. Although radiolabeled antibodies seem to be highly effective, problems associated with radiation therapy are evident.
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because the radiation targets the tumor as well as neighboring healthy cells when the particles are injected. Complications may occur in the bone marrow, resulting in low levels of white blood cells, red blood cells, and platelets.

Radioimmunotherapy is effective for patients whose disease is resistant to both chemotherapy and rituximab. Many oncologists are unsure about how and when to use radioimmunotherapy, but the two agents may play a role in treating follicular lymphoma.

A recent study was conducted with CHOP, followed by Bexxar, in patients with advanced follicular lymphoma who had received no previous treatment. These patients responded to CHOP therapy; with Bexxar therapy, 69% of treated patients achieved a 100% response, 22% had a partial response, and 2% had stable disease. The four-year progression-free survival rate was 70%. This rate is comparable to that in other studies of CHOP in similar patients whose four-year progression-free survival rate was 46%. The rate of four-year overall survival was 91% with combined therapy, compared with 69% observed with CHOP alone.

The Bexxar therapeutic regimen is indicated for patients with CD20 antigen–expressing relapsed or refractory, low-grade, follicular, or transformed NHL, including patients with rituximab-refractory NHL. The original indication specified that patients had to have disease that was refractory to rituximab and they had to have experienced relapse after receiving chemotherapy. The determination of the effectiveness of the Bexxar regimen was based on overall response rates in patients whose disease was refractory to chemotherapy alone or to chemotherapy and rituximab.

The regimen is not indicated for the initial treatment of patients with CD20-positive NHL, and it is intended as a single course of treatment.

Yttrium 90 Ibritumomab Tiuxetan (Zevalin)

90Y Ibritumomab tiuxetan (Zevalin, Biogen Idec) was the first FDA-approved radioimmunotherapy modality for the treatment of NHL. Ibritumomab is indicated for patients with relapsed or refractory low-grade, follicular, or transformed B-cell NHL, including patients with follicular NHL who are no longer responding to treatment with rituximab. 90Y Ibritumomab tiuxetan is used with rituximab, which locks on to the CD20 protein, present on the surface of B-cell lymphocytes. Ibritumomab differs in many ways from conventional chemotherapy or external-beam radiation therapy. This agent combines the cell-targeting ability of a monoclonal antibody with the additional cell-killing ability of a radioactive particle, or radioisotope (yttrium 90). Treatment can be completed within a week on an outpatient basis. This regimen is generally well tolerated by patients and does not cause the hair loss and nausea that often accompany chemotherapy treatments.

The most common adverse effect is a temporary reduction in blood cell counts. This regimen has also been associated with severe cutaneous or mucocutaneous reactions, some of which have been fatal.

Antisense Therapy

Oblimersen (Genasense)

Oblimersen sodium (Genasense, Genta) is a novel type of agent known as an antisense drug. It is designed to block the production of specific proteins, thus targeting cancer cells while producing minimal adverse effects on normal cells.

Antisense drugs are small, chemically modified strands of DNA that are complementary to the specific messenger ribonucleic acid (mRNA)—hence the term “anti”, which codes for the protein (the “sense”). Antisense drugs are designed to bind to these mRNAs. After binding occurs, subsequent protein production is stopped. Oblimersen inhibits the production of bcl-2, a protein made by cancer cells that is thought to block chemotherapy-induced cell death. By reducing the amount of bcl-2 in cancer cells, oblimersen may enhance the effectiveness of current anticancer therapy.

Oblimersen has been granted orphan drug status for treating myeloma and is now being studied for the treatment of acute myelogenous leukemia. A combination of rituximab and oblimersen is in phase 2 development for the treatment of NHL.

Epothilones

The epothilones are a family of compounds that are produced by soil bacteria. Their mechanism of action is similar to that of the taxanes (e.g., paclitaxel). Both types of compounds bind to the cell protein tubulin, thereby preventing cancer cells from dividing and leading to apoptosis.

Epothilones are a new class of natural, potent antineoplastic agents that stabilize microtubules, although only two 13-epoxide derivatives are potent antiproliferative agents. Several of these agents are being investigated for treating various types of cancer, including lymphoma.

CONCLUSION

Over the past five to 10 years, there have been vast improvements in the delivery of important curative therapeutics for the treatment of NHL and other lymphomas. Better therapies are still needed, especially for follicular lymphoma. Many novel, possibly effective anticancer agents are undergoing clinical trials in the U.S. and internationally. The introduction of monoclonal antibodies in studies of lymphoma may well alter the way we understand and treat cancer.