INTRODUCTION

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Non-Hodgkin’s lymphoma (NHL) is a cancer of the lymphatic system. Approximately 54,000 new cases of NHL are recorded each year. The disease affects 19 in 100,000 persons, equivalent to a rate of 4% of all cancers. From the 1970s to the 1980s, the incidence of NHL accelerated by 3% to 4% each year. In the 1990s, the rate declined and is now slowing down. The etiology is unclear, but the disease predominates in males. Possible etiologic factors include:

- infectious organisms, such as human T-cell leukemia/lymphoma virus (HTLV-1), Epstein-Barr virus, Helicobacter pylori, hepatitis C virus
- genetic and environmental factors and family aggregation of hematolymphoproliferative neoplasms, or families with two or more NHL cases, which have shown a two-fold to three-fold increase
- agricultural and pesticide exposures, which have been observed repeatedly but not consistently, or local exposure, such as those encountered in lawn care
- lifestyle factors, such as an increased dietary intake of animal fats and proteins; hair coloring; and benzene from cans, which might damage the DNA in cells.

There is no clear association of NHL with vitamin supplementation, alcohol, or smoking. Human immunodeficiency virus (HIV) infection, immunosuppressive therapy, and improved diagnostic techniques probably account for one third of the recent increases in NHL. There is great concern regarding the environment, diet, and identification of other unknown risk factors.

B-cell lineage NHL is classified into three groups:

- Indolent (low-risk, low-grade) NHL:
  - chronic lymphocytic leukemia (CLL)
  - small lymphocytic lymphoma (SLL)
  - lymphoplasmacytic lymphoma
  - Waldenström’s macroglobulinemia
  - marginal zone lymphoma
- follicular center-cell lymphoma
- follicular lymphoma
- Aggressive (intermediate-risk, intermediate-grade) NHL:
  - mantle-cell lymphoma
  - follicular large B-cell lymphoma
  - diffuse large B-cell lymphoma
  - primary mediastinal large B-cell lymphoma
- Very aggressive (high-risk, high-grade) NHL, which is the precursor to B-lymphoblastic Burkitt’s lymphoma or leukemia

The entire pathology of CLL involves the accumulation of leukemia cells, which in turn increase the size of the lymph nodes and spleen and expand the number of lymphocytes in bone marrow and the number of white blood cells.

THE ROLE OF GENES

In most follicular and diffuse lymphomas and in CLL, there is an overproduction of bcl-1 and bcl-2 proteins. The bcl-2 family of genes was originally noted when bcl-2 protein was cloned from the chromosome 18q contribution to the t(14; 18) translocation in follicular lymphoma. The bcl-2 protein is localized to the endoplasmic reticulum nuclear envelope of mitochondria. The physiological function of the gene (bcl-2 protein) is to prolong the life of cells that are destined to die in the lymphoid follicle.

The gene confers longevity on memory B and T cells by blocking apoptosis (regulated normal cell death) and prolonging cell survival. Excessive cell production increases bcl-1 protein concentrations, and insufficient cell death increases bcl-2 protein concentrations. Apoptosis increases bcl-1 and bcl-2 protein production, and this can lead to indolent lymphoma. Bcl-2 protein prevents the normal p53-mediated destruction of cells with damaged DNA and also appears to prevent the death of cells that have been severely damaged by cancer chemotherapy. The overexpression of bcl-2 prevents B-cell and T-cell death by apoptosis.

TREATMENT

Biological Agents (Monoclonal Antibodies: Rituexan®)

One of the most significant developments in cancer treatment today is the use of targeted therapies. Rituexin® (Rituexan®, Genentech/Idec) is the major therapy for NHL. It
targets the CD20 antigen on the surface of B cells. In targeting malignant lymphoma cells, rituximab is a nonradioactive antibody that is used alone or combination with the standard of care known as CHOP (cyclophosphamide, doxorubicin, Oncovin, and prednisone), the chemotherapeutic regimen for lymphoma. Some immediate side effects of rituximab include fever, a tickling sensation in the throat, and shortness of breath. This drug should be infused slowly.

Re-treatment of low-grade NHL with rituximab results in a longer duration of remission in patients: an average duration of 9.8 months with the first treatment and 15 months after re-treatment.

Radioimmunotherapy (Zevalin™ and Bexxar®)

The newest targeted therapy provides the added benefit of radiation. Radioimmunotherapy consists of monoclonal antibodies that have radioisotopes attached to them so that whatever the antibody binds to can be irradiated.

The Food and Drug Administration (FDA) has approved two drugs for the treatment of B-cell indolent NHL:

1. Indium 111 (111In) ibritumomab tiuxetan, a monoclonal antibody (111In Zevalin™, Biogen Idec), and yttrium 90 (90Y) ibritumomab tiuxetan (90Y Zevalin™, Biogen Idec) became the first radiopharmaceuticals to be approved for patients with NHL. The antibody moiety of Zevalin™ is ibritumomab, a murine (mouse) IgG1 kappa monoclonal antibody directed against the CD20 antigen, which is found on the surface of normal and malignant B lymphocytes. The Zevalin™ regimen is administered in two steps: one infusion of rituximab precedes 111In Zevalin™; after seven to nine days, another infusion of rituximab is followed by 90Y Zevalin™.

2. Tositumomab (Bexxar®, Corixa/GlaxoSmithKline) is a murine immunoglobulin G (IgG2a) lambda monoclonal antibody that is directed against the CD20 antigen. The Bexxar® regimen is administered in two discrete steps: a dosimetric step (nominal protein and activity concentrations of 0.1 mg/ml and 0.61 mCi/ml) and a therapeutic step (nominal protein and activity concentrations of 1.1 mg/ml and 5.6 mCi/ml). Each step consists of a sequential infusion of tositumomab, followed by iodine 131 (131I) tositumomab. The therapeutic step is administered seven to 14 days after the dosimetric step.

Zevalin™ and Bexxar® are recommended for patients with NHL that is refractory to rituximab and that has recurred after chemotherapy and rituximab. These agents are not indicated for the initial treatment of patients with CD20-positive NHL.

Zevalin™ utilizes radioactive yttrium, and its very short half-life enables it to be given on an outpatient basis. Zevalin™ can be safely administered by patients, family members, and health care workers. Zevalin™ radioimmunotherapy is a safe and effective alternative for outpatient therapy in 67% of an intent-to-treat population of patients with relapsed or refractory NHL; 26% of patients showed complete responses, and 41% showed partial responses in phase 1 and 2 studies. Patients with relapsed or refractory low-grade NHL showed an 82% positive response to Zevalin™ treatment.

Bexxar® utilizes 131I. When 131I is linked to an antibody, it is easy to sense where the radioisotope is going after only one dose. The disadvantage is its fairly long half-life, which means that patients must often be hospitalized overnight.

The response rate to rituximab, the “naked” antibody, has been approximately 50% in patients with relapsed, low-grade NHL. A naked antibody has no drug or radioactive material attached to it.2) Few of these patients experience complete remissions.

The overall response rate to radioimmunotherapy with Bexxar® is generally 70%; the response to rituximab is 50%. For patients with complete remissions, the response rate is 30%, compared with the very low numbers of patients treated with naked antibodies.

The primary immediate side effect after radioimmunotherapy is a decreased blood count. The decline does not occur for four, five, or even six weeks after treatment. Generally, the counts are low for a period of two to three weeks and then return to normal.

The distinct advantage of radioimmunotherapy is that it is usually given only once. The treatment course takes two weeks. During the first week on the first day, patients receive the tracer dose so that the clinician can determine whether the radioactive isotope is being delivered to normal organs. One week later, the patients receive the therapeutic dose, which ends the treatment.

Purine Nucleoside Analogues (Leustatin®, Leustat®, Fludara®, and Nipent®)

Cladribine (Leustatin®, Janssen–Ortho; Leustat®, Janssen–Cilag), fludarabine (Fludara®, Berlex Labs), and pentostatin (Nipent®, Parke-Davis) have been used to treat advanced indolent NHL.

Cladribine. Cladribine is a form of chemotherapy that is indicated mainly as a treatment for hairy-cell leukemia and (more rarely) for CLL. It is also used to treat some types of low-grade lymphoma. It is structurally related to fludarabine and pentostatin but has a different mechanism of action. Cladribine is phosphorylated to its corresponding nucleotide, CdaTP, which accumulates and is incorporated into the DNA of cells such as lymphocytes. High concentrations of CdaTP lead to broken DNA strands, inhibition of DNA synthesis, and cell death. Unlike other antimetabolite drugs, cladribine has cytotoxic effects on both resting and proliferating lymphocytes.

Fludarabine. The purine analogue antimetabolite fludarabine phosphate can induce remission in 40% to 50% of patients with relapsed or refractory indolent B-cell NHL, although complete remission is uncommon (in only 10% of cases). Fludarabine phosphate appears to be particularly active in the subset of small B-lymphocytic lymphoma and is effective for low-grade NHL. Minimal or no response has been observed in the treatment of the intermediate or high-grade lymphomas.

Pentostatin. Pentostatin is a purine nucleoside analogue with demonstrated activity in low-grade lymphoid malignancies. Formerly known as deoxycoformycin, it is a profound inhibitor of the enzyme adenosine deaminase, resulting in the accumulation of metabolites that inhibit ribonucleotide reductase, which in turn inhibits DNA synthesis. It is under study.
alone and in combination with chlorambucil and prednisone in the treatment of B-cell chronic lymphocytic leukemia (B-CLL). Combined therapy with pentostatin and alkylating agents is active in B-CLL. The pentostatin/rituximab combination is well tolerated and active in low-grade NHL.

**Vaccines**

The surface immunoglobulin (Ig) on each B-cell lymphocyte has unique proteins (*idiotypes*) that are recognized by the immune system. Idiotype (Id) refers to the entire collection of *idiotopes* found on a single antibody/Ig molecule. Idiotype immunotherapies use or stimulate the patient’s own immune system to fight infection and cancer. Anti-idiotype vaccines can be manufactured and adapted for individual patients so that the patient’s own immune system has the greatest opportunity to respond in a specific way. Vaccine therapy can be used to trigger the immune system to attack indolent NHL by stimulating an entire range of immune cells.

Because lymphomas grow slowly, there is sufficient time for the manufacture of a patient-specific vaccine if the lymphoma is detected early. The vaccine helps to trigger the immune system to recognize the tumor as a foreign protein and targets only the tumor cells. The goal of idiotype vaccine therapy is to establish an immune response against residual lymphoma cells, so that each time they attempt to emerge, the immune system is activated and attacks them.

Idiotype immunotherapy differs from the traditional vaccines; it is used to delay or prevent lymphoma recurrence or progression, whereas standard vaccine therapy does not prevent the initial occurrence of the original cancer. Thus, the idea of anti-idiotype vaccine arises from a relatively simple concept: that the unique idiotype-containing Ig synthesized by and exhibited on neoplastic B cells also appears to be a tumor-specific antigen (TSA). TSA acts like a monoclonal antibody that has already been unable to activate the patient’s immune system and to stimulate it against the tumor clone that carries it.

There are two main approaches in an active immune therapy strategy to produce idiotype vaccines:

- purifying the TSA
- converting the TSA into an immunogen that is potent enough to be beneficial for lymphoma patients

Anti-idiotype vaccines can be manufactured in several ways:

- **Id vaccines.** The most common option uses cancer-associated proteins to prepare protein vaccines.
- **DNA vaccines.** The DNA of cancer-associated genes is used.
- **Dendritic cells.** These cells are used to help the immune system recognize cancer-associated proteins and initiate an attack against the cancer cells.

**Antisense Oligonucleotide (Genasense™ and Campath®)**

The basis of *antisense therapy* is that many diseases are associated with either inappropriate or inadequate production of proteins. Antisense technology is the process of creating synthetic segments of DNA or RNA, called *oligonucleotides*, to prevent these problems by blocking the production of these faulty proteins. Antisense molecules are designed to interact with messenger ribonucleic acid (mRNA) before it can be translated into the amino acids that make up proteins. In this way, disease-associated proteins can be prevented from forming. These molecules are called “antisense” because they are the opposite of the “sense” of the original RNA or DNA.

Oblimersen sodium (Genasense™, Genta) inhibits production of bcl-2, a protein that is highly expressed in malignant cells from patients with both NHL and CLL. Bcl-2 is widely believed to be a fundamental cause of resistance to anticancer therapy in both illnesses. Genasense™ penetrates the cells, destroys the precursor of bcl-2, and down-regulates bcl-2 expression, making cells more sensitive to anticancer therapy. It blocks the expression of the bcl-2 gene through degradation of the RNA–DNA complex by ribonuclease H (RNase H), preventing translation. The limitation of the antisense oligonucleotide is its short half-life.

The FDA has approved Genasense™ with an orphan drug approval for lymphoma...
status for malignant melanoma and three additional cancer indications: multiple myeloma, acute myelocytic leukemia, and CLL. Currently, Genasense™ is under study in patients with CLL either alone or in combination with alemtuzumab (Campath®, Berlex Labs), a humanized monoclonal antibody against CD52 on lymphocytes. In combination with rituximab, Genasense™ is also under study in patients with NHL.

CONCLUSION

A brighter future awaits the unfortunate victims of lymphoma. Today’s treatment options include new biological products, vaccines, and small synthetic molecules as well as evolving targeted therapies. Clinicians will gain the ability to optimize chemotherapy by scheduling and combining drugs. The combination of new biological agents and successful “traditional” favorites should improve patient outcomes and survival.

REFERENCES