A one-day workshop, entitled “Innovations in Lymphoma Treatments,” was held on November 16, 2002, in New York City. The sessions provided a forum for patients, caregivers, and clinicians to learn about current and future clinical trials in lymphoma research. The workshop also provided an opportunity to gain knowledge of the promising new therapies under clinical investigation and to reflect on the combination of currently approved therapies with new drug classes to treat follicular B-cell non-Hodgkin’s lymphoma (NHL) and other lymphomas. This is an era of exciting new developments in drugs and biologicals for the therapy of NHL; breakthroughs will eventually prolong the lives of patients of all ages with the disease.

A new age of lymphoma therapy began in 1997 with the approval of rituximab (Rituxan®, IDEC/Genetech) by the Food and Drug Administration (FDA). This therapeutic monoclonal antibody has been found to be safe and effective for many patients with NHL. Rituximab therapy is now viewed as a complementary treatment to the earlier effective but dangerous chemotherapeutic combination for NHL patients, CHOP, composed of cyclophosphamide (Cytoxan®, Bristol-Myers Squibb), hydroxydaunomycin (doxorubicin [Adriamycin®], Pharmacia and Upjohn), Oncovin® (vincristine, Eli Lilly), and prednisone. Rituximab attacks the increased CD20+ antigen target proteins on the cancerous B cells and eventually kills the cells.

Another variation of the composition of a monoclonal antibody was to attach a toxic substance to enhance the antibody’s ability to attack and kill its target cancer cell through apoptotic immunotoxicity. An additional spinoff was a radioactive particle conjugated to a monoclonal antibody. These radiolabeled antibodies would eventually kill the targeted cancerous cells. With therapeutic antibodies, the main objective is to kill cancer cells without damaging normal tissue.

One of the latest innovations is the development of various vaccine types for lymphoma treatment. Once a diagnosis of lymphoma is confirmed, the approach to treatment is to use vaccine therapy to prevent a recurrence of the disease. This type of immunotherapy uses a patient’s own immune system to recognize and eradicate the lymphoma; vaccines trigger the immune system to attack the disease by stimulating an entire range of immune cells.

Indolent cases of NHL respond well to first-time treatment with rituximab–CHOP (R–CHOP) chemotherapy but are generally not curable. These lymphomas are candidates for vaccine therapy because they grow slowly and permit sufficient time for the manufacture of the patient-specific vaccine. The goal of vaccine therapy is to establish an active immune response against these residual lymphoma cells so that each time they try to surface, the immune system repels them. While the vaccine is being developed, patients undergo chemotherapy to lower the body’s quantity of lymphoma. Vaccines seem to work better when the number of lymphoma cells is low. Patients who respond to chemotherapy will be vaccinated after a rest period to allow the immune system to recover. In general, patients receive a series of vaccinations over time.

Table 1 presents a summary of many of the proposed and ongoing clinical trials of new medications for treating NHL.

### VACCINE STUDIES

A phase III randomized trial is currently in the patient-accrual stage to evaluate the safety and efficacy of GTOP-99 (Genotope), a specific immunotherapeutic recombinant idiotype conjugated to keyhole limpet hemocyanin (KLH) vaccine with granulocyte-macrophage colony-stimulating factor (GM-CSF), compared with nonspecific immunotherapy, KLH with GM-CSF in patients with follicular NHL. Two-thirds of patients will receive the specific agent, and one-third will receive the control substance. The inclusion criteria for patients are as follows:

- stage III or IV follicular lymphoma
- no prior chemotherapy, biological therapy, or radiotherapy
- no prior or concurrent primary central nervous system lymphoma
- age 18 years or older
- lymphoma tissue or a site accessible for biopsy to enable the therapy

A phase II trial of rituximab plus tumor-specific idiotype-KLH vaccine (Favid™, Favrire), and GM-CSF immunotherapy in patients with grade 1 or 2 follicular B-cell lymphoma is in the patient-recruiting stage. Favid™ is a patient-specific vaccine generated from a lymph node biopsy. The vaccine consists of the tumor-specific idiotype (unique to each B-cell lymphoma), coupled to a strong immune stimulant (KLH). Idiotype (Id) immunotherapies belong to a class of drugs known as biological therapeutic agents, which stimulate a patient’s own immune system to fight infection or cancer. Idiotype immunotherapy boosts the immune system in a patient who already has the disease. Id protein is unique to each lymphoma and is shared by every lymphoma cell. It is not normally found in the body, and it can be attacked by the immune system.

The phase II trial is being conducted to evaluate the objective response rate in patients receiving rituximab plus Favid™ and GM-CSF compared with historical data at nine months in patients receiving rituximab alone. After a lymph node biopsy,

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patients receive standard treatment with rituximab (375 mg/m² weekly infusions for four weeks), followed approximately eight weeks later by six monthly 1-mg subcutaneous injections of Favid™ GM-CSF, which brings immune cells to the vaccine site, is administered together with Favid™ on day one of each month and separately on days two, three, and four. Patients are assessed by computed tomography (CT) scanning for a baseline reading and every three months thereafter.

Other vaccine types in the very early stages of clinical development are idiotype/hybridoma, lymphoma/CD-40-L, chronic lymphocytic leukemia/CD40-L-adenovirus, and idiotype/heat shock protein. These types are not discussed in this article.

**COMBINATION RITUXIMAB TRIALS**

Patient recruitment is under way for a phase II research study of rituximab plus interleukin-2 (IL-2) (Chiron) for a nine-week treatment period with a two-year follow-up. IL-2 is a protein produced by T-helper cells that, when stimulated by infection, can cause large increases in T-cell counts in patients with CD20+, B-cell, relapsing, or refractory NHL of intermediate-grade or high-grade histological findings who have not responded to chemotherapy. Rituximab will be given intravenously once a week, and IL-2 will be given subcutaneously three times a week. Not all patients with refractory lymphoma can enter the study. Patients with the following conditions are excluded:

- autoimmune disease
- positive status for human immunodeficiency virus (HIV)
- positive status for hepatitis C
- serious infection
- pneumonia or bronchitis within two weeks of the study
- pregnancy
- a previous total doxorubicin dose greater than 400 mg/m²

A phase II/III research study of rituximab plus IL-2 in patients with relapsing low-grade or follicular NHL who have not responded to rituximab therapy alone is in the patient-accrual stage. The treatment schedule and the length of the study are the same as the study just mentioned. The inclusion criteria are patients with CD20+, B-cell, relapsed low-grade or follicular lymphoma who have been unresponsive to rituximab alone or who have had no response, or a short-term response (less than six months), to rituximab therapy.

Pegylated interferon alfa-2b (PegIntron®, Schering-Plough/IDEC) is a long-acting interferon preparation used in the treatment of hepatitis C. The drug is also active against low-grade NHL and has been used for many years, but it was associated with adverse side effects. Peg-interferon, which is polyethylene glycol conjugated to interferon, can be administered once a week and produces fewer side effects than regular interferon does. It also appears to raise the number of CD20+ antigen sites on lymphoma B cells.

It is theorized that peg-interferon alfa-2b might increase the effectiveness of rituximab when the two drugs are given together. Investigators are currently recruiting patients with previously treated, advanced-stage, low-grade lymphoma for a phase II study of pegylated interferon alfa-2b plus rituximab. The patient eligibility criteria for inclusion in the study are as follows:

- A diagnosis of follicular NHL has been confirmed.
- Patients have tested positive for the CD20+ antigen; patients with intermediate-grade or high-grade NHL are ineligible.
- Patients may have had up to three previous regimes of radiation therapy, chemotherapy, immunotherapy, and chemotherapy with immunotherapy or chemotherapy with regional radiation therapy; no prior treatment with alfa interferon is permitted.
- Earlier treatment with rituximab is permitted if the patient received the drug for at least six months before entering the study.

**ANTISENSE THERAPY**

In multicellular organisms, apoptosis (the programmed death of cells) is necessary for proper development. In mature individuals, apoptosis is essential to accommodate the billions of new cells manufactured daily and to destroy aged or damaged cells. Apoptosis is ultimately eliminated by intracellular proteases called *caspases* that affect widespread proteolysis.

The regulation of the process to initiate cell death is per-

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**Table 1** Summary of Lymphoma Drugs and Biologicals Under Study

<table>
<thead>
<tr>
<th>Biological or Drug</th>
<th>Sponsor</th>
<th>Study Site</th>
</tr>
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<tbody>
<tr>
<td>GTOP-99 vaccine</td>
<td>Genitope</td>
<td>Various locations</td>
</tr>
<tr>
<td>Tumor-specific idiotype-KLH vaccine (Favid™)</td>
<td>Favrille, Inc.</td>
<td>Various locations</td>
</tr>
<tr>
<td>Oncophage-idiotype vaccine</td>
<td>Antigenics, Inc.</td>
<td>MD Anderson Cancer Center</td>
</tr>
<tr>
<td>Interleukin-2 + rituximab</td>
<td>Chiron</td>
<td>Various locations</td>
</tr>
<tr>
<td>Peg-interferon alfa-2b (PegIntron®) + rituximab</td>
<td>Schering-Plough/IDEC</td>
<td>Memorial Sloan-Kettering Cancer Center</td>
</tr>
<tr>
<td>Antisense blocker of bcl-2</td>
<td>Genta</td>
<td>MD Anderson Cancer Center</td>
</tr>
<tr>
<td>Proteosome inhibitor (PS-341 [Velcade™])</td>
<td>Millennium</td>
<td>St. Bartholomew’s Hospital</td>
</tr>
<tr>
<td>Ibritumomab tiuxetan (Zevalin™)</td>
<td>IDEC</td>
<td>Memorial Sloan-Kettering Cancer Center</td>
</tr>
<tr>
<td>Iodine 131 (¹³¹I) tositumomab (Bexxar®)</td>
<td>Corixa/GlaxoSmithKline</td>
<td>Memorial Sloan-Kettering Cancer Center</td>
</tr>
<tr>
<td>Pentostatin/cyclophosphamide/rituximab</td>
<td>SuperGen, Inc.</td>
<td>Mount Sinai Medical Center</td>
</tr>
<tr>
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<td>Various locations</td>
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</table>
formed primarily by the bcl-2 protein family. As a regulator of cell survival, the bcl-2 family of proteins plays a pivotal role in the etiology and progression of cancer and in the development of acquired resistance to anticancer treatment. Bcl-2, expressed in hematological or solid-tumor types, is a key regulator of apoptosis by slowing or preventing cell death. A decrease in apoptosis promotes carcinogenesis.

Antisense compounds are small, chemically modified, single strands of deoxyribonucleic acid (DNA) that are complementary to specific target messenger ribonucleic acid (mRNA) sequences. Protein is produced by the translation of genetic information from mRNA. Antisense/RNA binding triggers degradation of the mRNA, which prevents production of the target protein (i.e., bcl-2). Bcl-2 overexpression blocks the release of cytochrome C, which activates caspases, reduces the efficacy of cancer therapy, and thereby promotes survival of cancer cells. Bcl-2 antisense profoundly decreases bcl-2 production in tumors and unblocks the pathway of programmed cell death triggered by cancer therapy. Inhibiting bcl-2 production may potentiate the pro-apoptotic effects of anticancer agents. Bcl-2 antisense can target several molecular targets, including CD20+ sites on B cells involved in NHL.

Clinical phase I studies showed that bcl-2 protein concentrations could be safely reduced in lymphoma cells in patients receiving antisense therapy. The next step was to add conventional anticancer therapy. Trials involving patients with follicular lymphoma, mantle cell lymphoma, and chronic lymphocytic leukemia are expected to commence shortly. These studies will use antisense therapy for five days to reduce the bcl-2 protein in patients who will then receive anticancer therapy. For mantle cell lymphoma, the anticancer therapeutic agent might be rituximab, because lymphoma cells express high amounts of CD20+ antigen in addition to bcl-2 protein.

PROTEOSOMES

The 26 SS proteosome is universally present and abundant in all human cells, including tumor cells. Its chief function is to degrade cellular proteins, including damaged or misfolded proteins, as well as numerous regulatory proteins that control cell growth and death. Proteosome inhibition interferes with a tumor’s growth and causes death in tumor cell lines, in vivo and in vitro.

PS-341 (VelcadeTM, Millenium), a proteosome inhibitor, has been shown to be safe in phase I clinical studies. The major dose-limiting toxicities include thrombocytopenia, peripheral neuropathy, rash, and diarrhea. All toxicities resolved following the completion of the phase I drug study.

A phase II study of PS-341 in patients with indolent lymphoma, including follicular lymphoma, mantle cell lymphoma, marginal zone lymphoma, and small lymphocytic lymphoma/chronic lymphocytic leukemia, is currently in progress. A dose of 1.5 mg/m² of PS-341, administered twice weekly for two weeks, followed by a one-week rest period, is initiated. Patients must have adequate liver, kidney, heart, and pulmonary function. To date, 13 patients have been treated and many patients experienced a partial, durable remission of disease. Patients continue to be recruited, and a possible combination with other known drugs that have been used to treat lymphoma is under consideration.

PROMISING MONOCLONAL ANTIBODIES

The radiolabeled monoclonal antibody ibritumomab tiuxetan plus yttrium-2B8 (Zevalin™, IDEC) attaches to the CD20+ antigen on B cells and attacks and kills the targeted cancerous cells by irradiation. Radioimmunotherapy represents a new treatment modality that has proved effective in the management of low-grade NHL.

A phase II study of the combination of R-CHOP chemotherapy and ibritumomab tiuxetan plus yttrium-2B8 will be conducted in elderly patients with previously untreated diffuse, large B-cell lymphoma. Eligible patients will receive R-CHOP for six cycles every three weeks with G-CSF (for neutropenia) and darbepoetin alfa (for anemia). After completing chemotherapy, patients who achieve a complete or partial response to the regimen will be eligible to receive radioimmunotherapy with ibritumomab tiuxetan. The primary goal of the trial is to assess improvements in the overall and progression-free survival for the trial of aggressive, diffuse, large B-cell lymphoma.

Recruitment of previously untreated follicular NHL that expresses CD20+ antigen is in progress to determine whether the addition of either rituximab or iodine 131 (131I) tositumomab (Bexxar®, Corixa and GlaxoSmithKline) to CHOP chemotherapy affects the progression-free and overall survival of patients with newly diagnosed follicular lymphoma. Final FDA approval for 131I tositumomab is expected sometime next year.

NEW DRUGS UNDER STUDY

Alemtuzumab, or humanized anti-CD52 monoclonal antibody (CamPath-1H®, Berlex Oncology), and a combination of ifosfamide (Ifnex®, Bristol-Myers Squibb), carboplatin (Paraplatin®, Bristol-Myers Squibb), and etoposide (Vepesid®, Baxter)—ICE—are to be studied in a new clinical trial to improve the response rates, particularly the complete response rate, in patients with relapsing peripheral T-cell lymphomas. ICE is used as second-line therapy for patients with aggressive B-cell and T-cell lymphomas. CamPath-1H® is effective against a variety of lymphomas, including T-cell lymphomas.

Pentostatin (Nipent®, Parke-Davis), an antibiotic used in the treatment of chronic lymphocytic leukemia, will be combined with rituximab (by SuperGen) for the treatment of patients with NHL. In a phase I/II study, pentostatin will be combined with cyclophosphamide and rituximab (by SuperGen) for the treatment of patients with chronic lymphocytic leukemia and other low-grade B-cell malignancies.

REFERENCE