Non-Hodgkin’s Lymphoma Trials In Elderly Look Beyond CHOP

Researchers in December launched a new randomized trial for elderly patients with intermediate-grade non-Hodgkin’s lymphoma (NHL) to test a novel alternative to CHOP (cyclophosphamide, vincristine, doxorubicin, and prednisone), the standard chemotherapy for this form of NHL. The phase III trial will compare CHOP alone to CHOP plus the new monoclonal antibody, IDEC-C2B8 (Rituxan®).

The trial stands out on one hand for its new approach to intermediate-grade NHL; Rituxan’s recent Food and Drug Administration approval was for low-grade NHL. But it may be even more notable for its specific focus on older patients and the need to find alternatives to CHOP in this age group. It is the first U.S. randomized trial exclusively for older NHL patients, according to principal investigator Thomas Habermann, M.D., of the Mayo Clinic in Rochester, Minn.

Up to now, few clinical trials of any type have even included older patients, a problem highlighted recently by the President’s Cancer Panel (see News, Oct. 1 1997). But the need for trials in the elderly is particularly acute in lymphomas. The incidence of NHL in this age group is rising rapidly — up by 75% between 1973 and 1994, according to NCI’s Surveillance Program.

In addition, the aging of the population will compound the problem, say experts. “It is not unreasonable to expect more than a doubling of the absolute numbers of patients with lymphoma who are over the age of 65 years during the next 20 to 25 years,” according to Joseph M. Connors, M.D., and Susan O’Reilly, M.B., of the British Columbia Cancer Agency, Vancouver, writing last October in Hematology/Oncology Clinics of North America.

Cures Only Half

Demographics are not the only reason researchers are focusing more on NHL in older people. Another impetus is the fact that treatment for intermediate-grade lymphoma — common among elderly NHL patients — is markedly less successful in older patients. CHOP cures only about half as many elderly patients as younger patients, according to Connors and O’Reilly. And a recent international study of prognostic indicators in NHL found that age — being over age 60 — was the most important factor independently associated with poorer survival in patients with intermediate- and high-grade lymphoma.

“We know from this prognostic index that we should be looking for an alternative for patients age 60 and above,” said Habermann.

One alternative could be CHOP plus the monoclonal antibody. The new trial, organized by the Eastern Cooperative Oncology Group (ECOG), will recruit 630 patients age 60 and over, and randomly assign them to receive either CHOP alone or CHOP with Rituxan, which targets the B-cell protein CD20.

Another possible improvement on CHOP in the elderly is the addition of maintenance therapy, and the new ECOG trial will also test this possibility. After initial therapy, patients who responded will be again randomly assigned to receive the maintenance regimen — Rituxan every 6 months for 2 years — or observation. This is the first randomized trial to address maintenance therapy of any kind in NHL, Habermann said.

CHOP alternatives could also turn out be less toxic chemotherapy regimens, another area where several NHL studies are underway in the elderly. One reason for poorer outcomes in older patients is thought to be that CHOP, like some other chemotherapy regimens, is more toxic in this age group.

“Older patients with good performance status can quite often take three or four treatments, but they have a hard time getting to six or eight [the standard number],” said British Columbia’s O’Reilly in an interview. “And the 75-80 year olds have great difficulty.”

So far, no drug combinations have emerged as clearly superior to CHOP in this age group, at least in terms of overall survival. Most recently a report from the European Organization for Research and Treatment of Cancer concluded that VMP (etoposide, mitoxantrone, and prednimustine), a drug combination devised specifically for the elderly, was less effective than CHOP in patients age 69 and above.
Even patients who did not complete the entire CHOP regimen did better, said lead investigator Umberto Tirelli, M.D., of the Centro diRiferimento Oncologico, Aviano, Italy. The study, reported in the Journal of Clinical Oncology last month, confirms CHOP as the standard therapy for the elderly, Tirelli said.

Another recent, multicenter trial by a cooperative group in France found that CTVP (cyclophosphamide, tenoposide, prednisone, and pirarubicin) did better than the same combination minus pirarubicin, which is an anthracycline similar to doxorubicin, in patients older than 69 years of age. Because CTVP is quite similar to CHOP, this finding provides more support for the use of the stronger, antracyclin-based regimens.

**Less Toxic Options**

Meanwhile, the search for other drug combinations that may be as effective but less toxic than CHOP continues. At Aviano, for instance, investigators led by Vittorina Zagonei, M.D., have launched a trial comparing CHOP to CIEP, in which the less toxic idarubicin and VP16(P) are substituted for CHOP’s doxorubicin and vincristine.

Still another strategy is the use of fewer doses of CHOP in elderly patients who cannot tolerate the full regimen. O’Reilly said that Vancouver scientists have a phase II study in progress looking at a four-treatment “mini-CHOP,” called COPA, in elderly patients. COPA uses the same drugs as CHOP given in reduced doses along with supportive agents, such as an antibiotic and an antifungal. Preliminary data, O’Reilly said, suggest that outcomes are similar to CHOP in the elderly with less chance of side effects.

One more approach to NHL in the elderly involves peripheral stem cell transplants an approach that is combined with low-dose chemotherapy regimens,” according to Julie Vose, M.D., at the University of Nebraska. The idea is that stem cells from a sibling donor may induce a graft vs. tumor effect, i.e., the sibling stem cells will mount an immune response against the host cancer cells. Trials are under way at the University of Nebraska and the University of Texas M.D. Anderson Cancer Center in Houston where there have been some “impressive responses,” said M. D. Anderson’s Richard Champlain, M.D.

In these studies and others focusing on the elderly, data on length of disease-free and overall survival will be key. Often elderly people respond to therapy initially but do not maintain remissions as long as younger people. “The elderly have a higher relapse rate,” said Vose, “and we don’t really understand why. So we’re always looking for something better.”

— Caroline McNeil

**Stat Bite**

**Pancreatic Cancer Incidence Trends in U.S. Men and Women**

Pancreatic cancer is the 12th most frequently diagnosed cancer in the United States but the fifth most common cause of cancer death. Little is known about its etiology; cigarette smoking is the only proven cause. From 1973 to 1994, incidence rates declined 20% for white males and 4.5% for white females. Rates for blacks were less stable, but overall rates for black males decreased slightly and for black females remained the same.

*Rates are age-adjusted to the 1970 U.S. standard population.