STUDY SEES BENEFIT IN HIGH-DOSE CHEMOTHERAPY FOR BREAST CANCER

German researchers report success with high-dose adjuvant chemotherapy for women with advanced breast cancer. Their regimen of rapidly cycled tandem high-dose chemotherapy plus autologous peripheral stem cell support provided better disease-free and overall survival than traditional dose-dense chemotherapy, they write in *The Lancet* (2005;366:1935–1944).

Their results stand in contrast to those of several previous studies, which found no benefit to high-dose chemotherapy and a higher incidence of toxic side effects. But the new findings suggest researchers should take another look at the possibility of using this technique against breast cancer, said lead study author Ulrike Nitz, MD, Coordinator of the Breast Center at the University Hospital of Düsseldorf.

“The trials published so far are very heterogenous,” she said. “We need a closer look at each of them to identify promising strategies.”

Nitz said her group may have done just that. Rather than giving women a single high-dose chemotherapy cycle after a relatively long conventional induction period, as previous studies have done, Nitz and her colleagues used a short induction period followed by two high-dose cycles of chemotherapy and autologous peripheral blood stem-cell transplant.

They randomly assigned 201 women to the high-dose regimen (epirubicin and cyclophosphamide, followed by epirubicin, cyclophosphamide, and thiotepa), whereas 202 women received dose-dense conventional chemotherapy (epirubicin and cyclophosphamide, followed by cyclophosphamide, methotrexate, and fluorouracil). The women were between the ages of 18 and 60 years and each had at least nine affected lymph nodes (median 17.6 positive nodes) but no clinical evidence of distant metastasis.

Four-year event-free survival was 60% in the high-dose group and 44% in the control group (\( P = 0.0069 \)). Overall survival was 75% in the high-dose group and 70% in the conventional treatment group (\( P = 0.02 \)). There were no treatment-related deaths.
The results came as a surprise, even though the researchers had a sense that women on the experimental regimen had done well.

“After publication of the other high-dose trials, we did not expect to see such a large survival difference,” Nitz said. “As survival rates for this subgroup of patients with standard regimens have not been improved substantially over the last 20 years, we think that the rapidly cycled tandem high-dose regimen is a very good option for these patients and should be investigated further.”

One important point that is sure to generate discussion is the composition of the chemotherapy regimes the researchers used, said Larry Norton, MD, Deputy Physician-in-Chief for Breast Cancer Programs at Memorial Sloan-Kettering Cancer Center in New York. Neither the control arm nor the high-dose arm used a taxane.

“This may be an issue of an inferior control arm rather than a superior trial arm,” said Norton, who was not involved in the German study. “The single most active class of agents in breast cancer is absent in both treatments.”

Nitz and colleagues acknowledge, and dismiss, that concern in their paper.

“Another issue not raised in 1995 [the year the trial began] but unequivocally important today is the role of taxanes in the control group,” they write.

They go on to note that taxanes have been shown to be most effective in women with one to three involved lymph nodes, and less effective in women with more than four involved nodes. They also cite findings from the Breast Cancer International Research Group that taxanes may even be inferior in patients with 10 or more positive nodes.

“We therefore conclude that our dose-dense anthracycline-based regimen is up to date and appropriate,” they write. “Superiority of high-dose chemotherapy in this trial cannot be attributed to a weakness of the control regimen.”

Nevertheless, Norton said the new study is unlikely to change practice in the United States.

“Essentially, all the well-done, well-controlled, and audited clinical trials showed high-dose chemotherapy didn’t add anything except toxicity, and if it did add anything it was at enormous cost, so it did fall out of favor,” he said. “I think cytotoxic therapy has accomplished all it can.

“The real future is going to come from targeted biological agents combined with cytotoxic drugs,” he continued. “There are dozens of exciting compounds, and integrating those into the treatment regimens is something we should be focusing on.”

MODIFIABLE RISK FACTORS STILL MAJOR CAUSE OF CANCER DEATHS WORLDWIDE

Nine modifiable risk factors are responsible for more than one-third of cancer deaths worldwide, according to a recent estimate from researchers at the Harvard School of Public Health and other institutions. Of these, smoking and alcohol consumption are the most damaging, they reported in The Lancet (2005; 366:1784–1793).

The other risk factors assessed include: overweight/obesity, physical inactivity, low fruit and vegetable consumption, unsafe sex, urban air pollution, indoor smoke from household fuels, and contaminated injections in health care settings. The researchers looked at each factor’s impact on 12 different types of cancer based on age, sex, and region of the world. The data came from several sources, including the World Health Organization’s Comparative Risk Assessment project, an initiative to determine which risk factors play a role in the global burden of disease.

Of the 7 million global cancer deaths in 2001, the team estimated that 2.43 million (35%) were attributable to the cumulative effect of these nine risk factors. Smoking was by far the biggest contributor to mortality, causing