Adjuvant Chemo Best in ER-Negative Tumors

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SAN ANTONIO — Twenty years of refinements in adjuvant chemotherapy have brought dramatically improved outcomes in lymph node–positive breast cancer patients, but the benefit has been confined to those with estrogen receptor–negative tumors, Donald A. Berry, Ph.D., said at a breast cancer symposium sponsored by the Cancer Therapy and Research Center.

In patients with node-positive, estrogen receptor–positive breast cancer, hormone therapy—first with tamoxifen, now increasingly with aromatase inhibitors—has resulted in markedly better outcomes over the past 2 decades. There are no comparable treatments specifically targeting ER-negative tumors. But the benefits of chemotherapy in node-positive patients with ER-negative disease are "enormously greater" than in ER-positive women, according to Dr. Berry, professor and chair of the department of biostatistics and applied mathematics at M.D. Anderson Cancer Center, Houston.

He illustrated his point via a review of the three most recent Cancer and Leukemia Group B (CALGB) randomized trials of various chemotherapy regimens in women with node-positive breast cancer. The three studies collectively included 6,644 patients, of whom 2,537 were ER negative. The first of the studies, CALGB 8541, began accruing patients 20 years ago. The most recent, CALGB 9741, started enrollment in the late 1990s.

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DR. BERRY

Each trial randomized patients to lower-dose, less intensive chemotherapy regimens or higher-dose, more aggressive ones. In each study, patients with ER-negative disease who were assigned to the more intensive regimens had significantly greater improvements in disease-free and overall survival than women on conservative, lower-dose chemotherapy. And in each study, the benefits of more modern, aggressive chemotherapy didn't come close to achieving significance in patients with ER-positive breast cancer who were on adjuvant tamoxifen.

The relative reductions in relapse risk in ER-negative patients assigned to high-dose, as compared with low-dose chemotherapy in the three trials were 23%-36%. Similarly, patients on high-dose chemotherapy had relative reductions in all-cause mortality of 22%-29%.

Just how far chemotherapy has come in the past 20 years was best illustrated by a comparison of outcomes between ER-negative participants in CALGB 8541 who were on the standard adjuvant chemotherapy regimen of 20 years ago—low-dose cyclophosphamide, doxorubicin, and fluorouracil—and patients in CALGB 9741 on a much more contemporary regimen of concurrent high-dose doxorubicin and cyclophosphamide followed by paclitaxel with dosing every 2 weeks. Patients on the contemporary regimen had relative risk reductions of 63% for recurrence and 59% for death.

Analysis of the follow-up data from the three trials on a year-by-year basis shows that the real benefit of chemotherapy is seen in the first several years of follow-up.

"There's an enormous hazard in the early part of follow-up. Those cancers that are aggressive recur early and are removed from the at-risk set. In the later period in every trial, the risk from about 5 years on out is only 2%-3% per year. That's comparable with what's seen in node-negative disease. This is important to tell your patients: If you're able to get over this hump and get out to 4 or 5 years, your risk is essentially the same as that of a node-negative patient. Roughly speaking, any risk factor is trumped by being able to get to this time period," Dr. Berry explained.

Why were there no improved outcomes in ER-positive patients who receive the same chemotherapy regimens so successful in ER-negative patients? "Tamoxifen so lowers their risk that it's difficult to see any benefit for chemotherapy. The number of events in the first few years of follow-up, where chemotherapy is doing its work, is so small that we can't see a statistically significant benefit," he said. ■