Research To Practice: Adjuvant Chemotherapy

27TH ANNUAL
San Antonio Breast Cancer Symposium 15

One of the most important factors affecting the use of adjuvant chemotherapy in clinical practice has been the use of computerized web- and PDA-based models estimating risk of relapse and death with and without specific adjuvant chemotherapy and hormonal therapy regimens. About half of practicing oncologists in the United States currently use these models to assist in clinical decision-making, and a particularly common scenario is the patient with an ER-positive, node-negative tumor for whom the incremental benefit of chemotherapy is a key issue. In terms of selection of regimens, the most important recent research databases are the CALGB-9741 trial evaluating dose-dense adjuvant chemotherapy and multiple trials addressing the inclusion of taxanes, including CALGB-9344, NSABP-B-28 and BCIRG-001. The patterns of care survey demonstrates that taxane-containing regimens are commonly utilized in patients with node-positive and high-risk node-negative tumors. Dose-dense AC → T is the most frequently utilized regimen in this setting, and pegfilgrastim is more commonly utilized than filgrastim for growth factor support.

USE OF COMPUTER MODELS IN CLINICAL PRACTICE

In which of the following situations do you* tend to use computer models to estimate breast cancer patients' risk of relapse and/or mortality?

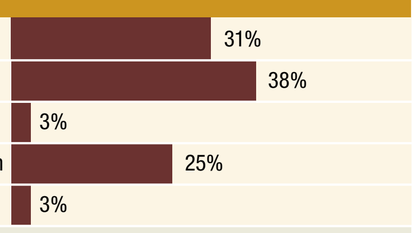
To review risk estimates with patients	98%
To decide whether to use chemotherapy in node negative cases	81%
To decide whether to use endocrine therapy in node negative cases	44%
To select type of chemotherapy to use	19%
To select type of endocrine therapy to use	10%
Other situations	5%

* 25% of oncologists surveyed use the Adjuvant! model, 12% use the Mayo clinic model, 22% use both models and 41% of physicians do not use either model.

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2004.

CHOICE OF GROWTH FACTORS FOR DOSE-DENSE ADJUVANT CHEMOTHERAPY

When using dose-dense chemotherapy*, which growth factor(s) do you use?



* 64% of oncologists report having utilized dose-dense adjuvant chemotherapy in a nonprotocol setting.

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2004.

ADJUVANT CHEMOTHERAPY FOR NODE-POSITIVE DISEASE

The patient is a woman in average health with a 1.2-cm, ER-positive, HER2-negative (as confirmed by FISH), Grade II tumor and 3 positive lymph nodes. Which chemotherapy regimen, if any, would you most likely recommend?

	Age 35	Age 55	Age 65	Age 75
AC x 4 q3wk	3%	4%	7%	11%
AC x 4 q2wk with pegfilgrastim	3%	3%	2%	2%
AC x 4 q2wk with filgrastim	1%	1%	—	—
FAC or FEC x 6	2%	3%	4%	7%
AC x 4 followed by paclitaxel x 4 q3wk	7%	8%	13%	7%
AC x 4 followed by paclitaxel x 4 q2wk with pegfilgrastim	38%	33%	26%	11%
AC x 4 followed by paclitaxel x 4 q2wk with filgrastim	7%	7%	5%	3%
AC x 4 q3wk followed by weekly paclitaxel x 12	2%	1%	3%	5%
AC x 4 followed by docetaxel x 4 - no growth factors	15%	17%	16%	8%
AC x 4 followed by docetaxel x 4 - with growth factors	11%	10%	10%	6%
CMF	—	—	—	10%
TAC (docetaxel)	9%	9%	7%	2%
Other chemotherapy	2%	2%	2%	2%
Would not recommend chemotherapy	—	2%	5%	26%

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2004.

ACCURACY OF PHYSICIAN-ESTIMATED RISK OF RELAPSE AND MORTALITY

The patient is a 65-year-old woman in average health with a 1.2-centimeter, ER-positive, HER2-negative (as confirmed by FISH), Grade II tumor and negative lymph nodes. How would you estimate this patient's 10-year risk of relapse and mortality?

Therapy	Estimated 10-year risk of relapse	Actual* 10-year risk of relapse	Estimated 10-year risk of mortality	Actual* 10-year risk of mortality
With no systemic therapy	20%	23%	12%	7%
With hormonal therapy alone	13%	Anastrozole 13% Tamoxifen 15%	8%	Tamoxifen 6%
With both hormonal therapy and chemotherapy (AC x 4)	10%	Anastrozole 11% Tamoxifen 14%	6%	Tamoxifen 5%

* Based on Adjuvant!

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2004.

SELECT PUBLICATIONS

Baum M, Ravdin PM. **Decision-making in early breast cancer: Guidelines and decision tools.** *Eur J Cancer* 2002;38(6):745-9.

Bonneterre J et al. **Long-term cardiac follow-up in relapse-free patients after six courses of fluorouracil, epirubicin, and cyclophosphamide, with either 50 or 100 mg of epirubicin, as adjuvant therapy for node-positive breast cancer: French adjuvant study group.** *J Clin Oncol* 2004;22(15):3070-9.

Citron ML et al. **Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: First report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741.** *J Clin Oncol* 2003;21(8):1431-9.

Fumoleau P et al. **Randomized trial comparing six versus three cycles of epirubicin-based adjuvant chemotherapy in premenopausal, node-positive breast cancer patients: 10-year follow-up results of the French Adjuvant Study Group 01 trial.** *J Clin Oncol* 2003;21(2):298-305.

Henderson IC et al. **Improved outcomes from adding sequential paclitaxel but not from escalating doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer.** *J Clin Oncol* 2003;21(6):976-83.

Loprinzi CL, Thome SD. **Understanding the utility of adjuvant systemic therapy for primary breast cancer.** *J Clin Oncol* 2001;19(4):972-9.

Martin M et al. **TAC improves disease free survival and overall survival over FAC in node positive early breast cancer patients, BCIRG 001: 55 months follow-up.** *Breast Cancer Res Treat* 2003;Abstract 43.

Ravdin PM et al. **Computer program to assist in making decisions about adjuvant therapy for women with early breast cancer.** *J Clin Oncol* 2001;19(4):980-91.

USE OF COMPUTERIZED RISK ESTIMATE MODELS

I am really pleased about how many practitioners are actually using computer-based models in their practice. My expectation is that the number is rapidly increasing. I have found that it is difficult to convince practitioners to try these models; however, once they do, I believe that they see the power of the numbers and how the presentation of absolute benefits to the patient can make decision-making an easier and much more objective process.

I use these models for every patient who comes in the door for a discussion of adjuvant therapy. For the past two years I have printed out the results and usually give them to the patient. I love the Adjuvant! model because it helps me to avoid biases. There are all types of factors that influence how physicians think about a specific patient — personality type, type of relationship that is established, referral source — these models totally remove those from the equation.

— Robert W Carlson, MD

NONPROTOCOL ADJUVANT MANAGEMENT OF PATIENTS WITH POSITIVE NODES

Right now, I believe that TAC and dose-dense AC followed by T are among the two best choices for adjuvant chemotherapy in node-positive patients. I use more dose-dense therapy, and by limiting anthracyclines to four courses, perhaps we will have somewhat less cardiotoxicity in the long run. I've occasionally observed cardiotoxicity with some of the six or more cycle anthracycline regimens. This is more of a gut feeling than a scientific observation, and I believe both regimens are excellent. In terms of quality of life and toxicity, my interpretation is that the regimens are not drastically different. You must use growth factors with TAC because the rate of neutropenic fever can be ameliorated with filgrastim or preferably pegfilgrastim.

— Hyman B Muss, MD

The most effective regimens are perceived to be TAC and dose-dense AC followed by paclitaxel. Without a comparative trial, it's difficult to say whether one is better than the other. A direct comparison is required to obtain a clear answer. I am most likely to use dose-dense AC followed by paclitaxel, but I helped to develop that regimen, and we often use what we have the most experience with. I believe Marc Citron and Cliff Hudis were surprised that dose-dense therapy wasn't more toxic; they feel that the dose-dense regimen is less toxic than the every three-week regimen, and the data support that.

— I Craig Henderson, MD

I've heard doctors state that they don't want to use a more aggressive dose-dense regimen unless the patients are at very high risk. Frankly, the dose-dense regimen is less toxic, more effective and faster. If CALGB-9741 had demonstrated that the regimens had equal efficacy, there would be real arguments for using a dose-dense regimen just from the toxicity point of view.

— Larry Norton, MD

RATIONALE FOR THE EFFECTIVENESS OF DOSE-DENSE SCHEDULING

The results of CALGB-9741 support the basic hypothesis I've had since the late 1980s, which is if you achieve a critical concentration necessary for cell kill, you're more likely to get an effective result in direct proportion to the amount of time, or area under the curve, that the tumor cells are exposed. That may sound a little simple-minded, and the explanation is probably more complex, but I think the exposure of cells to effective concentrations of chemotherapy over a longer period of time is the key to why dose-dense therapies work better.

A second reason, which may be very important, is the antiangiogenic hypothesis. We now have good preclinical data that demonstrate that with continuous exposure, certain classes of agents — cyclophosphamide, the vincas and the taxanes — result in much better cell kill and tumor regressions than intermittent exposure. There is solid evidence in preclinical systems that an antiangiogenic effect is the primary reason for that cell kill.

— Robert B Livingston, MD