Research To Practice: Adjuvant Chemotherapy

Clinical decisions regarding adjuvant chemotherapy are complex and multifactorial. Tumor-related factors such as nodal status, tumor size and predictors like the Onco*type* DX™ assay must be balanced against issues such as patient age and comorbidities. Computer models, such as Peter Ravdin's Adjuvant! Online program, are frequently utilized by oncologists to assist in estimating the absolute impact of adjuvant therapy, and these must be balanced against the risk of side effects and toxicities with treatment. An important facet of Adjuvant! is that it factors in nonbreast cancer sources of competing mortality based on the patient's age and general health status. Data from the 2005 *Breast Cancer Update* Patterns of Care Study, a survey of breast cancer clinical investigators and randomly selected US-based medical oncologists, are presented here. In patients with node-positive tumors, dose-dense AC → paclitaxel is the most common choice. AC is the most common regimen utilized in patients with node-negative tumors. Adjuvant chemotherapy is less frequently utilized in older patients, particularly octogenarians.

CLINICAL USE OF ONCO*TYPE* DX ASSAY

Have you ordered the Onco*type* DX assay?		
Yes	80%	34%
No	20%	66%
If you have ordered this assay, in how many patients? (Mean)	8	5
How helpful was this test in your treatment decisions? (N = 17)		
Very helpful	26%	18%
Somewhat helpful	61%	64%
Not helpful	13%	18%

☐ Breast cancer specialists (n = 45)   ☐ General oncologists (n = 50)

SOURCE: Breast Cancer Update Patterns of Care Survey, September 2005.

ADJUVANT CHEMOTHERAPY FOR NODE-POSITIVE DISEASE

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

	Age 35		Age 55		Age 75		Age 85	
AC x 4 q3wk	—	4%	—	4%	11%	14%	2%	—
AC x 4 q2wk	—	—	—	—	2%	2%	5%	2%
FAC or FEC x 6	—	—	—	—	2%	6%	—	2%
AC x 4 → paclitaxel x 4 q3wk	—	6%	—	6%	—	6%	—	—
AC x 4 → paclitaxel x 4 q2wk	53%	44%	55%	44%	24%	14%	2%	2%
AC x 4 q3wk → paclitaxel qwk x 12	7%	4%	7%	8%	9%	8%	2%	2%
AC x 4 → docetaxel x 4 q3wk	—	2%	—	4%	—	8%	—	—
AC x 4 → docetaxel x 4 q2wk	9%	18%	9%	18%	7%	6%	2%	2%
CMF	—	—	—	—	7%	18%	—	8%
TAC (docetaxel) x 6	27%	22%	20%	16%	2%	2%	—	2%
Other	4%	—	9%	—	9%	2%	—	2%
No chemotherapy	—	—	—	—	27%	14%	87%	78%

☐ Breast cancer specialists (n = 45)   ☐ General oncologists (n = 50)

SOURCE: Breast Cancer Update Patterns of Care Survey, September 2005.

CLINICAL USE OF ADJUVANT TAXANES

How many times a month do you start a breast cancer patient on a taxane?		
Mean	6	5
What percent of your patients in each of the following categories receiving adjuvant chemotherapy receive adjuvant taxanes?		
Node-negative (all)	32%	28%
High-risk, node-negative	70%	58%
Node-positive	92%	90%
What percentage of your adjuvant taxane use is with each of the following agents?		
Docetaxel	33%	42%
Paclitaxel	67%	58%
Do you most often prescribe the taxane after or combined with AC when using AC and a taxane?		
After AC	82%	86%
Combined with AC	9%	14%
Other	9%	—

☐ Breast cancer specialists (n = 45)   ☐ General oncologists (n = 50)

SOURCE: Breast Cancer Update Patterns of Care Survey, September 2005.

ADJUVANT CHEMOTHERAPY FOR NODE-NEGATIVE DISEASE

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

	Age 35		Age 55		Age 75		Age 85	
AC x 4 q3wk	39%	44%	34%	34%	2%	10%	—	4%
AC x 4 q2wk	11%	12%	7%	10%	—	6%	—	—
FAC or FEC x 6	14%	6%	5%	6%	—	2%	—	—
AC x 4 → paclitaxel x 4 q3wk	—	4%	—	2%	—	—	—	—
AC x 4 → paclitaxel x 4 q2wk	9%	10%	5%	8%	—	2%	—	—
AC x 4 → docetaxel x 4 q2wk	—	10%	—	4%	—	2%	—	—
CMF	7%	8%	5%	8%	—	10%	—	10%
TAC (docetaxel) x 6	2%	2%	2%	—	—	—	—	—
Other	2%	2%	5%	4%	—	—	—	—
No chemotherapy	16%	2%	37%	24%	98%	68%	100%	86%

☐ Breast cancer specialists (n = 45)   ☐ General oncologists (n = 50)

SOURCE: Breast Cancer Update Patterns of Care Survey, September 2005.

ONCO*TYPE DX AND COMPUTERIZED RISK MODELS*

Peter Ravdin notes that in the Adjuvant! program, the relative benefit of chemotherapy is presumed to be equal for patients at higher and lower risk, but it's likely that the estimation of chemotherapy benefit in the group with low-risk disease is an overestimation. Conversely, the benefit in the group with higher-risk disease may be underestimated. I believe our studies with Onco*type* DX demonstrate this, and Ravdin's model may need to be modified slightly. My prediction is that when people see these data from NSABP-B-20, they will want the Onco*type* assay performed because nobody wants to receive chemotherapy when it will not work.

— *Soonmyung Paik, MD. Breast Cancer Update 2005 (3)*

CHEMOTHERAPY AND RECEPTOR STATUS

The estrogen and progesterone receptor status may be important in determining the potential benefit from adjuvant chemotherapy. SWOG-8814 demonstrated that patients with highly ER- and PR-positive tumors received no benefit from FAC chemotherapy. Similarly, data from the Ludwig group showed that highly endocrine-responsive patients received little or possibly no benefit from chemotherapy. Finally, Don Berry's analysis of a series of CALGB/Intergroup studies suggested little or no additional benefit for taxanes added to AC or for dose-dense chemotherapy in the ER-positive group of patients.

— *C Kent Osborne, MD. Breast Cancer Update 2005, Special CME Meeting Edition*

SELECTION OF ADJUVANT CHEMOTHERAPY

For patients with ER-positive disease and multiple positive nodes, I usually use AC with or without a taxane, often dose dense. As we learn more about the biology of these diseases and separate out the cancers by more than just ER-positive and ER-negative, I hope that we can give fewer people chemotherapy.

— *Ann H Partridge, MD, MPH. Patterns of Care 2005 (1)*

AC → docetaxel, the control arm in our current US Oncology study, is a very reasonable treatment that doesn't require growth factors. TAC would also be an option. TAC requires growth factors but has about the same treatment duration as dose-dense therapy, and I use this regimen. We also saw in San Antonio [2004] that FEC/docetaxel was significantly better than the standard six cycles of FEC. This is also a legitimate treatment option. In the patient at higher risk, I would pick one of these regimens, and I tend to use AC → docetaxel.

— *Stephen E Jones, MD. Patterns of Care 2005 (1)*

One of the things that's interesting about Dr Berry's presentation at San Antonio in 2004 is that in the three CALGB/Intergroup studies, the particular correlation between a greater degree of benefit in the ER-negative population than the ER-positive population was absolutely consistent. That's not consistent across all trials, however, and in many trials that correlation is not seen. One of the trials in which that's not seen is the TAC versus FAC trial. In fact, there was an equivalent amount of benefit for the TAC regimen over FAC in both the ER-negative population and the ER-positive population.

It's interesting that, if you look at the dose-dense study, there was essentially no additional benefit for making the therapy dose-dense in terms of overall survival in the ER-positive population. Almost all of the benefit was carried by the ER-negative population. Theoretically, if you compared TAC and dose-dense chemotherapy, maybe they would be fairly equal in the ER-negative populations, but in ER-positive populations, TAC might be better. I think that's a very speculative thing to say, but it will be tested.

There's an NSABP trial that has the dose-dense regimen being compared to the TAC regimen. It will be interesting to see which of the regimens is better, specifically to see if there can be identifiers that select one regimen over the other in given subsets of the patients.

— *Peter M Ravdin, MD, PhD. Breast Cancer Update 2005 (8)*

SELECT PUBLICATIONS

Budman DR. **Dose and schedule as determinants of outcomes in chemotherapy for breast cancer.** *Semin Oncol* 2004;31(6 Suppl 15):3-9.

Campos SM. **Evolving treatment approaches for early breast cancer.** *Breast Cancer Res Treat* 2005;89(Suppl 1):1-7.

Di Leo A et al. **Controversies in the adjuvant treatment of breast cancer: The role of taxanes.** *Ann Oncol* 2004;15(Suppl 4):iv17-21.

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.

Hudis C et al. **Five year follow-up of INT C9741: Dose-dense (DD) chemotherapy (CRx) is safe and effective.** San Antonio Breast Cancer Symposium 2005;Abstract 41.

Mamounas EP et al. **Paclitaxel after doxorubicin plus cyclophosphamide as adjuvant chemotherapy for node-positive breast cancer: Results from NSABP B-28.** *J Clin Oncol* 2005;23(16):3686-96.

Mano MS et al. **Adjuvant anthracycline-based chemotherapy for early breast cancer: Do the dose and schedule matter?** *Cancer Treat Rev* 2005;31(2):69-78.

Martin M et al. **Adjuvant docetaxel for node-positive breast cancer.** *N Engl J Med* 2005;352(22):2302-13.

Nowak AK et al. **Systematic review of taxane-containing versus non-taxane-containing regimens for adjuvant and neoadjuvant treatment of early breast cancer.** *Lancet Oncol* 2004;5(6):372-80.

Olivotto IA et al. **Population-based validation of the prognostic model Adjuvant! for early breast cancer.** *J Clin Oncol* 2005;23(12):2716-25.

Paik S et al. **A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer.** *N Engl J Med* 2004;351(27):2817-26.

Vogel CL et al. **First and subsequent cycle use of pegfilgrastim prevents febrile neutropenia in patients with breast cancer: A multicenter, double-blind, placebo-controlled phase III study.** *J Clin Oncol* 2005;23(6):1178-84.