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Editorial

Simplifying Guidelines: We Only Need One Adjuvant Chemotherapy Regimen for Breast Cancer

Permissiveness is a common feature in most treatment guidelines, including the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). In general, if several treatment options are thought to be reasonable choices, they are all included. On the one hand, this makes complete sense. Not every regimen can be compared against every other regimen. Subtle variations in dosing and schedule are rarely worth evaluating in exquisite detail. Expert opinion and perceptions of efficacy and toxicity are such that people disagree in good faith. "Class effects" considerations allow similar types of drugs to be put into approved rosters. Inclusiveness is favored when there is concern that not listing a regimen might limit patient access or insurance coverage for arbitrary reasons.

But inclusiveness comes at a price. It enables variation in practice that may be confusing or unnecessary, potentially raising questions of safety and efficiency for treatment delivery. And it allows guideline panels to skirt the tough questions about which regimen would they "really" recommend or which regimens provide the most value based on activity, toxicity, and cost. I highlighted one of the weaknesses of permissiveness in a recent editorial (*JNCCN* 2012;10:425–426) that noted that 3 bone-modifying agents (denosumab, zoledronic acid, and pamidronate) were all endorsed by NCCN and ASCO guidelines. Yet these agents differ markedly in logistics and cost. Are they really all equally preferred? On what grounds?

At present, the NCCN Guidelines for Breast Cancer enumerate no fewer than 12 adjuvant chemotherapy regimens, with another 6 for HER2-positive disease. Each of these has been studied in phase III trials and has historical data to support its use. Some of these regimens are ancient artifacts at this point, more talked about than given to patients. However, events in breast cancer have evolved to a point of remarkable clarification: high-level evidence now simplifies the number of needed adjuvant chemotherapy regimens dramatically. In fact, you only need 1: AC (doxorubicin/cyclophosphamide) followed by paclitaxel.

Here is the following evidence. The Oxford overview, based on treatment of over 100,000 women in adjuvant trials, suggests that all women who need chemotherapy do better if they receive anthracycline- and taxane-based chemotherapy. No known biomarker predicts which patients need one flavor (say, anthracyclines) but not another; however, data are clear that anthracycline-based regimens (e.g., AC, FEC [FU, epirubicin, cyclophosphamide], variants) are not as good as regimens that also include a taxane. There is only non-anthracycline, taxane-based regimen (docetaxel plus cyclophosphamide [TC]), but whether 4 cycles of TC is better than a regimen that includes both an anthracycline and a taxane is not known. Therefore, the best adjuvant regimens should include an anthracycline, an alkylator, and a taxane, but do not need to include anything else. No data show that including antimetabolites (FU, gemcitabine, related congeners) make a compelling difference in outcome.

How best to pick? Cooperative group studies have made this easy. CALGB 9741 showed that every-2-week chemotherapy scheduling was superior to every-3-week dosing for women offered AC followed by paclitaxel. ECOG 1199 studied AC followed by 4 ways of delivering taxanes and showed that weekly paclitaxel was best. NSABP B-38, just reported at the 2012 ASCO Annual Meeting, compared TAC (taxotere, adriamycin, cyclophosphamide) against AC followed by paclitaxel, and showed general equivalence with less toxicity with the AC/paclitaxel arm.

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There you have it. You might have a different favorite, but no one can argue that AC/paclitaxel isn't the gold standard, and no rational clinical criteria identify a patient who needs a different anthracycline- and taxane-based regimen. Clinicians who savor choices can still decide whether to give the paclitaxel every 2 weeks x 4, or weekly x 12, at least until more data are available.

A bonus of this simplicity is that it works for HER2-positive breast cancer, too. If the tumor is HER2-positive, then give AC followed by paclitaxel and include trastuzumab with the paclitaxel. This is the most widely studied and most efficacious regimen available for management of HER2-positive breast cancer.

Some may object that not everyone needs an anthracycline or a taxane, or that lower-risk patients might get small benefits from these more-intensive regimens compared with shorter regimens. At the moment, however, those arguments are not supported by strong evidence. Many patients do not need chemotherapy at all. However, once clinical assessment suggests that a patient needs chemotherapy, all the data suggest that AC/paclitaxel provides the greatest likelihood of avoiding cancer recurrence, which is, after all, the goal of treatment, and that it is generally as well tolerated as any alternative.

A few patients cannot be treated using AC/paclitaxel, including those with preexisting conditions such as cardiomyopathy or neuropathy and those with prior anthracycline exposure or taxane hypersensitivity. For these patients, we are fortunate to have options, including nonanthracycline, nontaxane options. These alternative regimens can be properly included as footnotes in the guideline. As for the other dozen regimens, they can be included on a "B" list. If a clinician has a compelling reason to use one in a given patient, so be it. Guidelines should focus on the 80% or more of patients who have standard presentations and needs.

Here then is the proposed, simplified guidance for patients with breast cancer who warrant adjuvant chemotherapy:

- Give AC followed by paclitaxel[a,b]

Footnotes:

a. For patients with HER2-positive cancers, include trastuzumab for 1 year, beginning concurrently with paclitaxel treatment.

b. or patients with contraindications to AC/paclitaxel, consider CMF or TC (if HER2-negative) or TCH (if HER2-positive).