All Nodes Lead to Chemo...

PRESENTATION OF THE CASE

A 51-year-old woman presents with an abnormal screening mammogram. Core biopsy shows an invasive ductal cancer that stains strongly for estrogen receptor (ER) and progesterone receptor (PR) and does not overexpress human epidermal growth factor receptor 2. She underwent a partial mastectomy and sentinel node biopsy. The invasive tumor measured 2.1 cm in greatest diameter and was grade 1. There was a 0.4 cm metastatic deposit in one of two sentinel lymph nodes (pT1cN1/stage IIA). There was no tumor within 0.2 cm of all margins and no lymphatic or vascular invasion noted. She was evaluated in the breast multidisciplinary clinic by a medical, surgical, and radiation oncologist. The question for our colleagues is what is the optimal adjuvant therapy for this woman and, more specifically, is chemotherapy necessary? *The Oncologist* 2011;16:722–725

PRO

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I agree that our newly diagnosed patient deserves a thoughtful discussion of treatment options, including the pros and cons of adjuvant chemotherapy. I would start the conversation by acknowledging that there are several reasonable approaches to her systemic treatment and they deserve attention. More treatment may not necessarily lead to a better outcome, may require a considerable expenditure of personal resources, and may leave a lasting physical and emotional impact. Personalizing the treatment plan based on tumor-derived predictive and prognostic factors and patient preference is ideal, but we simply do not have the tools to guide this patient with such a fine level of precision. Our recommendation needs to be based as much as possible on evidence derived from clinical trials.

How patients make such decisions sometimes remains a bit mysterious. We can present numerical data, graphs, icons, and even videos to help inform and provide estimates of benefit and risk both with and without interventions but know very little about the true “value” of such presentations. Decision scientists in general agree that women often and consistently overestimate the personal benefit from adjuvant therapy [1–4]. Some women will accept chemotherapy even for a very small expected benefit, such as a modest

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CON

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A new diagnosis of breast cancer is frightening for all women. It may disturb the sleep of the oncologist as well! Most of us are wary of withholding any potentially beneficial therapy from an otherwise healthy, young mother/sister/daughter. The stakes are high and your patient expects to stay alive and well for the next three decades or so. However, “throwing the book” at a patient, in this case prescribing a modern chemotherapy regimen in addition to optimal adjuvant endocrine therapy, does not guarantee disease-free survival. Instead, a thoughtful consideration of the available evidence and additive benefit of each therapy is required, so that both patient and physician are comfortable with the final decision.

We all agree that a patient with a large triple-negative breast tumor should have adjuvant chemotherapy, and few would argue that an elderly woman with a 1-cm ER⁺ tumor needs more than hormonal therapy, but unfortunately there is a large grey area between these extremes. The National Comprehensive Cancer Center Network recommends chemotherapy for all node-positive (>2 mm deposit) breast tumors [1]. As a European, I have always felt most convinced by the sensible St. Gallen expert consensus guidelines [2].

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prolongation in life expectancy of several months [2]. Perhaps the way the information is conveyed also sways decision making. We certainly know that framing things positively (the chance of being well and free of cancer) or negatively (the chance of relapse or death) can affect the mood and hopefulness of vulnerable patients. I think it is best in this case to take a close look at the evidence derived from large clinical trials and then provide the necessary interpretation and guidance for our patient.

Data from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview convincingly established that there is a survival benefit for women aged <50 years treated with 6 months of anthracycline-based chemotherapy, irrespective of their hormone receptor status [5]. The overall 7% lower relapse rate and 10% lower mortality rate for the group of women aged <50 years is certainly well worth the investment in treatment and above the commonly accepted threshold for the use of cytotoxic therapy [5]. For women in the 50–69 year age group, treatment resulted in a 15-year probability of recurrence that was only 5% lower and a 3% lower breast cancer mortality rate [5]. Because these studies were conducted prior to the introduction of taxanes and did not analyze results according to receptor status, and because our patient may still be in the premenopausal group, I think it is fair to assume that she can derive meaningful benefit from treatment.

Guidelines from expert consensus convened in St. Gallen, and last published in 2009, specifically capture our dilemma in the following statement: “the threshold for use of cytotoxic chemotherapy is the most difficult to define” [6]. These experts list relative indications for chemohormonal therapy, such as grade 3, lower ER and PR levels, high proliferation index, presence of peritumoral vascular invasion, tumor size >5 cm, node positivity (four or more involved nodes), high recurrence score, and patient preference [6]. The indications for endocrine therapy alone include higher ER and PR levels, grade 1, low proliferation index, node negativity, size ≤2 cm, a low score on a gene signature assay, as well as patient preference [6]. Our patient falls in between these two groups given the size of the tumor and involvement of the sentinel node—expert oncologists may differ on just what constitutes the perfect management and we certainly do not know anything about the patient's preference from this case presentation.

When oncologists are in doubt, they often order tests or look for additional data. In this case, some colleagues may reach for *Oncotype DX*® (Genomic Health, Inc., Redwood City, CA), but I would caution them that this test has not been validated for premenopausal women with node-positive disease. Because our patient was 51 years old at

Their most recent opinion makes the point that patients with tumors that exhibit high expression of ER and PR, a low proliferation rate, negative axillary lymph nodes, no peritumoral vascular invasion, and a tumor size ≤2 cm may be treated with endocrine therapy alone. But our patient in question had macrometastases in an axillary node. I hear you say: Yes, indeed she did, but there are now data available to inform our decision for such patients.

Breast cancer represents a molecularly heterogeneous group of diseases, but the notion that all patients with a higher risk for relapse (i.e., with positive nodes) benefit equally from chemotherapy does not make biological sense and may simply be untrue. The 21-gene recurrence score (RS) assay developed and validated for women with node-negative breast cancers provides useful estimates of recurrence risk for these patients, and guides the selection of treatment with hormonal therapy for these patients. Albain et al. [3] performed a retrospective analysis of the prognostic and predictive value of the RS in postmenopausal women with node-positive, ER⁺ breast cancer. The subjects for their study were participants in the Southwest Oncology Group (SWOG) 8814 study of adjuvant tamoxifen or cyclophosphamide, doxorubicin, and 5-fluorouracil (CAF) chemotherapy followed by tamoxifen [3]. There was a lack of progression-free survival benefit from anthracycline-containing chemotherapy in patients with a low RS (score <18; log-rank $p = .97$; hazard ratio [HR], 1.02; 95% confidence interval [CI] 0.54–1.93), as opposed to patients with a high RS (score ≥31; log-rank $p = .033$; HR, 0.59; 95% CI, 0.35–1.01). That study finally provided evidence, albeit retrospective, to support my gut feeling that a higher risk for recurrence does not necessarily translate into significant benefit from adjuvant chemotherapy. There is a subset of women with node-positive breast cancers who do not benefit from chemotherapy—the challenge is to identify them, and the RS assay may provide a way to do so.

Importantly, the SWOG 8814 study included only postmenopausal women and cannot be used to predict prognosis for similarly treated premenopausal women. At 51 years of age, our patient may or may not have reached physiologic menopause, and the value of adding chemotherapy to hormonal therapy for node-positive breast cancer in this age group is unclear. From the INT 0101 study, which randomized 1,503 such premenopausal women to either six cycles of CAF, CAF followed by 5 years of OS, or CAF followed by 5 years of OS and daily tamoxifen, we learned that combined endocrine therapy after chemotherapy improves disease-free survival [4]. However, the absolute benefit of adding chemotherapy to endocrine treatment remains unclear and has not been elucidated in any EBCTCG overview [5–7].

diagnosis, we cannot make any assumptions about her menopausal status. Age alone is unhelpful, but a detailed menstrual history and determinations of serum estradiol and luteinizing hormone and follicle-stimulating hormone levels could certainly help us to clarify this point. It is disappointing that we remain collectively uncertain about the benefit of chemotherapy for this subset of women and decades of research have not provided the answer to this most basic question. Since the 1988 EBCTCG overview presented evidence that patients aged <50 years did not benefit from tamoxifen alone [8], trials in premenopausal women in the 1980s and 1990s included chemotherapy in all arms. Trials aiming to study the role of endocrine therapy alone accrued very slowly. As Dr. Higgins recounts, The International Breast Cancer Study Group (IBCSG) Trial 11–93 enrolled only 174 premenopausal patients from May 1993 until November 1998 [9]. Participants who had ER⁺ and PR⁺ tumors and at least one involved axillary lymph node were randomized to treatment with endocrine therapy (with ovarian suppression) for 2 years and tamoxifen for 5 years or the same endocrine therapy plus chemotherapy with four cycles of doxorubicin and cyclophosphamide [9]. This protocol closed early because of poor accrual. Dr. Higgins discusses these results from an underpowered trial that showed no advantage for patients who received chemotherapy in addition to ovarian suppression (OS) and tamoxifen [9]. Two other trials also addressed by Dr. Higgins, the Premenopausal Endocrine Responsive Chemotherapy (PERCHE) and Premenopausal Optimal Management Is Endocrine Therapy (PROMISE) trials, closed early and unfortunately will not resolve this question of the true “added value” of chemotherapy for this subset of patients.

In real time, many oncologists may turn to Adjuvant! Online to estimate the benefit of chemotherapy [10]. For our patient, the calculated absolute reduction in mortality was 3% using a chemotherapeutic regimen that includes anthracyclines and taxanes. It is reasonable to ask whether this low estimate of personal benefit justifies the toxicity of treatment. I think the most conservative approach is to recommend chemoendocrine therapy, but to explain the small magnitude of possible benefit and the added toxicity of chemotherapy. And there the conversation begins.

DISCLOSURES

Lidia Schapira: None.

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Two trials attempted to determine the need for chemotherapy in premenopausal women with hormone receptor-positive disease, but both the PERCHE and PROMISE trials were closed early because of poor patient accrual. A third trial, the IBCSG Trial 11–93, closed after the accrual of only 174 patients, and yet is the largest available trial evaluating the addition of chemotherapy to OS and tamoxifen in premenopausal patients with ER⁺ early breast cancer [8]. In that study, patients with at least one positive lymph node were randomly assigned to receive OS and 5 years of tamoxifen with or without chemotherapy. At 10 years of follow-up, there was no difference in the disease-free survival rate—76.4% (95% CI, 65.8%–84%) for tamoxifen plus OS alone versus 74.9% (95% CI, 64.5%–84%) for combined chemoendocrine therapy—or overall survival rate between the two groups [8].

An additional factor influencing my decision is the strongly ER⁺ status of this patient's tumor. An interesting subanalysis of IBCSG Trial 11–93 compared observed relapse-free survival rates obtained in the study with those predicted by the Web-based tool Adjuvant! Online and demonstrated that the online predictions significantly underestimated the effectiveness of adjuvant endocrine therapy among these premenopausal women with node-positive disease receiving tamoxifen and OS [9]. I am particularly comfortable with employing endocrine therapy alone when staining for hormone receptors is strong within the tumor [10].

It is unlikely that statistically robust prospective trials of endocrine therapy with or without chemotherapy will ever be completed in premenopausal women. Thus, although there is no definite proof that chemotherapy does not add measurable benefit to endocrine therapy for any specific subset of node-positive patients, Dr. Schapira is unlikely to convince me that every node-positive breast cancer patient benefits from systemic chemotherapy. I suspect that chemotherapy provides little, if any, benefit over endocrine therapy alone as adjuvant therapy for women with low-grade, hormone receptor-positive and node-positive breast cancers and certainly exposes them to greater toxicity.

The adjuvant systemic therapy discussion is rarely a 15-minute clinic visit. Rather than proclaiming at the door whether you are a “believer in chemo” or a “fan of hormones,” oncologists should now be ready for both, or either, when appropriate. It is our job to interpret the available evidence for the woman before us and make rational recommendations. The choice of treatment should ultimately take into consideration a number of factors, both medical and emotional, including a patient's fears, understanding, and preference.

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DISCLOSURES

Michaela J. Higgins: None.

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