Research To Practice: HER2-Positive Disease

Availability of the humanized monoclonal antibody trastuzumab makes it critical to accurately determine HER2 tumor status in all patients with metastatic breast cancer. About three fourths of oncologists accept IHC results of 3+ as HER2-positive, but others require FISH confirmation. The 2004 Patterns of Care Study demonstrated that, in the first-line metastatic setting, trastuzumab is generally combined with chemotherapy — usually a taxane. Although no randomized clinical trial data are available addressing the questions of continuation of trastuzumab upon disease progression, this is a common practice pattern both in tertiary care centers and community oncology practice. In the adjuvant setting, trastuzumab is rarely utilized outside the context of a clinical trial.

INTERPRETATION OF HER2 TEST RESULTS

How would you interpret the following HER2 test results?

	IHC 3+	IHC 2+	IHC 1+
HER2-positive	78%	4%	—
HER2-positive only with FISH confirmation	22%	96%	48%
HER2-negative	—	—	52%

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2004;1(1).

TREATMENT FOR *DE NOVO* ER-NEGATIVE, HER2-POSITIVE METASTATIC DISEASE

How would you generally treat a woman presenting de novo with ER-negative, HER2-positive metastatic disease?

Regimen	Asymptomatic bone mets	Asymptomatic liver mets	Moderate pain/ bone mets	Very symptomatic visceral mets
Trastuzumab only	21%	2%	—	—
Trastuzumab + chemotherapy	67%	90%	94%	94%
Chemotherapy alone	12%	8%	6%	6%

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2004;1(1).

TRASTUZUMAB AND CHEMOTHERAPY USE FOR HER2-POSITIVE METASTATIC DISEASE AFTER ADJUVANT AC

The patient is a 57-year-old woman treated two years ago with adjuvant AC for an ER-negative, HER2-positive tumor. What is your first-line treatment for this patient and your second-line treatment if she had objective progression over several months but was clinically the same?

	Rising tumor markers, asymptomatic bone metastases		Symptomatic bone and lung metastases	
	1st-line	2nd-line	1st-line	2nd-line
Chemotherapy alone	10%	14%	4%	12%
Trastuzumab alone	17%	2%	3%	1%
Trastuzumab + chemotherapy	69%	81%	93%	87%
Capecitabine + docetaxel	1%	3%	6%	5%
Docetaxel	16%	10%	14%	3%
Paclitaxel	22%	9%	15%	4%
Carboplatin + taxane	19%	5%	51%	1%
Capecitabine	4%	7%	—	6%
Gemcitabine	—	13%	—	16%
Vinorelbine	6%	29%	3%	46%
Carboplatin	—	1%	1%	1%
Other chemotherapy	1%	4%	3%	5%
No therapy	4%	3%	—	—

CONTINUATION OF TRASTUZUMAB AFTER PROGRESSION

For this patient, if you would use first-line trastuzumab (with or without chemotherapy), would you continue it upon disease progression?

	Rising tumor markers, asymptomatic bone metastases	Symptomatic bone and lung metastases
Percent continuing trastuzumab upon disease progression	95%	92%

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2004;1(3).

CLINICAL USE OF ADJUVANT TRASTUZUMAB

The patient is a woman in average health with a 1.2-cm, ER-positive, Grade II tumor and three positive lymph nodes. Her tumor is HER2-positive (as confirmed by FISH). Would you utilize trastuzumab for this patient? (Percent responding "yes")

	Age 55	Age 75
Trastuzumab off protocol	5%	5%
Trastuzumab clinical trial	76%	51%

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2004;1(3).

SELECT PUBLICATIONS

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Paik S. **Successful quality assurance program for HER2 testing in the NSABP trial for Herceptin®.** *Breast Cancer Res Treat* 2002;76(Suppl 1):31;Abstract 9.

Robert NJ et al. **Randomized phase III study of trastuzumab, paclitaxel, and carboplatin versus trastuzumab and paclitaxel in women with HER-2 overexpressing metastatic breast cancer: An update including survival.** *Proc ASCO* 2004;Abstract 573.

Roche PC et al. **Concordance between local and central laboratory HER2 testing in the breast Intergroup trial N9831.** *J Natl Cancer Inst* 2002;94(11):855-7.

Tripathy D et al. **Safety of treatment of metastatic breast cancer with trastuzumab beyond disease progression.** *J Clin Oncol* 2004;22(6):1063-70.

Vogel CL et al. **Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer.** *J Clin Oncol* 2002;20(3):719-26.

HER2-TESTING ALGORITHM

We routinely order IHC on pathology specimens. For patients with metastatic breast cancer, if the IHC is 3+ I do not generally follow up with FISH, provided the tumor stains 3+ in 75 to 100 percent of cells.

I sometimes order FISH in IHC 0 cases — not in the adjuvant setting when I'm trying to decide between tamoxifen and an aromatase inhibitor, but in metastatic disease, I test everybody. I believe every patient with metastatic disease needs one FISH assay in her lifetime. These are not perfect tests by any means, and it is worthwhile to make sure you are comfortable with the results.

— Joyce O'Shaughnessy, MD

I try to find any excuse to order a FISH. If the IHC assay is 3+, I don't, but if it is 2+, I order FISH. A minuscule number of tumors are 1+ and FISH-positive but sometimes, for a young patient who has aggressive disease and not many alternatives, I order FISH if the IHC is slightly positive. I will not do that for IHC 0 tumors.

— Gershon Locker, MD

TREATMENT ALGORITHMS FOR PATIENTS WITH HER2-POSITIVE METASTATIC DISEASE

I generally use trastuzumab alone for asymptomatic patients with HER2-positive disease. If you recommend chemotherapy to an asymptomatic patient, that patient may become symptomatic.

For a highly symptomatic patient who received adjuvant AC, I would recommend a taxane plus trastuzumab. I don't think it matters which taxane. I would either use docetaxel every three weeks or weekly paclitaxel, and I would not argue that either is right or wrong.

— Clifford Hudis, MD

I use a combination with weekly paclitaxel as my preferred partner for trastuzumab. Docetaxel is a reasonable option. In a symptomatic patient I would probably use a platinum/taxane combination. I do not often use combination chemotherapy because most of my patients are not that symptomatic, but for the ones who are, I use a platinum/taxane combination.

Second line, I tend to prefer trastuzumab, but I admit we do not know what the independent contribution of trastuzumab is in that situation. All of the retrospective data does not tell us whether chemotherapy alone would have had the same types of responses that are seen in that setting.

Theoretically, I think trastuzumab still retains the possibility of synergy with other chemotherapy drugs and, therefore, I think a biological rationale exists for continuing it. Also, patients who have not developed toxicities with trastuzumab for some time have a very low risk of additional complications, such as cardiomyopathy, over time. For those reasons, I think it is reasonable to continue trastuzumab. The downside is the cost. It depletes resources, and that is a big issue, especially in fixed-cost medical systems.

— Debu Tripathy, MD

NONPROTOCOL USE OF ADJUVANT TRASTUZUMAB

I find it somewhat surprising but very reassuring that physicians are not prescribing adjuvant trastuzumab off protocol without high-level evidence that the benefits exceed the long-term toxicities — especially with regard to cardiac toxicity.

This might be a result of the "Bezwoda effect" and physicians' experiences with high-dose chemotherapy. Years ago, many community physicians took information that was a little bit disconnected, put it together and concluded that high-dose therapy was superior to standard full-dose therapy. When they eventually were burned by fraudulent trial results, I think many of them paused and thought, "How many women died because of my recommendation, albeit well intentioned, about how to treat their breast cancer?"

— Robert W Carlson, MD