Biologic Therapies Combined with Chemo/hormonal Agents

25TH ANNUAL SAN ANTONIO BREAST CANCER SYMPOSIUM 18

Many of the newer, targeted, biologic antitumor agents are being combined with chemotherapeutic and endocrine agents in Phase II and Phase III clinical trials, because of presumed synergy and the absence of overlapping toxicities. In the first important evaluation of this principal, a number of trials have combined trastuzumab with cytotoxic agents. Many chemotherapeutic and hormonal agents in combination with trastuzumab are currently being explored in a new generation of clinical trials. At this meeting, Robert is presenting initial results of a randomized trial evaluating carboplatin, paclitaxel and trastuzumab demonstrating an advantage compared to paclitaxel and trastuzumab. A number of novel antiangiogenic agents are also being evaluated in clinical trials, including the anti-vascular endothelial growth factor (VEGF) monoclonal antibody, bevacizumab. At this meeting, Miller is reporting initial results of a randomized trial in the metastatic setting comparing capecitabine to capecitabine plus bevacizumab.

CLINICAL TRIALS OF TRASTUZUMAB COMBINATIONS IN THE METASTATIC SETTING

Protocol IDs	Target Accrual	Eligibility Criteria	Randomization Arms
CWRU-030118, GENENTECH-H2223G, ROCHE-1100, ROCHE-B016216C, ROCHE-BO16216	202	Postmenopausal, ER/PR+, HER2+ (IHC 3+ or FISH-positive) metastatic disease	Arm 1: Anastrozole qd + trastuzumab qw Arm 2: Anastrozole qd
BCIRG-007, GENENTECH-UCLA-0109024, NCI-G02-2116, ROCHE-UCLA-0109024, UCLA-0109024	444	Stage IIIB or IV, HER2-positive breast cancer	Arm 1: [(T+C) q3w + H qw] x 8, then H q3w Arm 2: (T q3w + H qw) x 8, then H q3w
EU-99028, SWS-SAKK-22/99	170-250	HER2-overexpressing metastatic breast cancer	Arm 1: H qw until DP, then [H qw + (paclitaxel qw x 3, followed by 1 w rest)] Arm 2: [H qw + (paclitaxel qw x 3, followed by 1 w rest)]
CLB-9840, CTSU	580	Inoperable, recurrent or metastatic breast cancer with measurable disease and known HER2 status	**HER2 non-overexpressing** Arm 1: paclitaxel q3w Arm 2: paclitaxel qw Arm 3: paclitaxel q3w + H qw Arm 4: paclitaxel qw + H qw **HER2 overexpressing** Arm 1: paclitaxel q3w + H qw Arm 2: paclitaxel qw + H qw
DFCI-01087, GSK-2001-P-000473/2	250	HER2+ metastatic breast cancer (IHC 3+ but FISH- are ineligible)	Arm 1: (H + vinorelbine) qw x 8 w Arm 2: H qw x 8 w + (paclitaxel qw x 8 w OR docetaxel on w 1, 2, 3, 5, 6 and 7)

H=trastuzumab; T=docetaxel; C=cisplatin or carboplatin; DP=disease progression

Source: NCI Physician Data Query, October 2002

PHASE III RANDOMIZED STUDY OF BEVACIZUMAB WITH CAPECITABINE VERSUS CAPECITABINE ALONE IN WOMEN WITH PREVIOUSLY TREATED METASTATIC BREAST CANCER — Closed Protocol

Protocol IDs: GENENTECH-AVF2119g, GUMC-00299, MSKCC-01008, UAB-0028, UAB-F001009003
Projected Accrual: 400 patients

Eligibility: Metastatic breast cancer previously treated with 1-2 chemotherapy regimens for metastatic disease or no prior chemotherapy for metastatic disease if previously treated with an adjuvant anthracycline or taxane regimen and relapsed within 12 months

ARM 1: Capecitabine bid (days 1-14) q3w

ARM 2: Capecitabine bid (days 1-14) + bevacizumab (day 1) q3w

Treatment repeats for up to 35 courses in the absence of disease progression or unacceptable toxicity.

Source: NCI Physician Data Query, October 2002

PHASE III RANDOMIZED STUDY OF PACLITAXEL WITH OR WITHOUT BEVACIZUMAB IN PATIENTS WITH LOCALLY RECURRENT OR METASTATIC BREAST CANCER — Open Protocol

Protocol IDs: E-2100, CTSU
Projected Accrual: 316-650 patients

Eligibility: Locally recurrent disease not amenable to resection with curative intent or metastatic disease

ARM 1: Paclitaxel qw + bevacizumab q2w

ARM 2: Paclitaxel qw

In both arms, treatment repeats q 4 w x 18 in the absence of disease progression or unacceptable toxicity.

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Source: NCI Physician Data Query, October 2002

SELECT PUBLICATIONS

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Pegram MD, O'Callaghan C. **Combining the anti-HER2 antibody trastuzumab with taxanes in breast cancer: Results and trial considerations.** *Clin Breast Cancer* 2001;2 Suppl 1:S15-9.

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Saaristo A et al. **Mechanisms of angiogenesis and their use in the inhibition of tumor growth and metastasis.** *Oncogene* 2000;19:6122-6129.

Toi M et al. **The predictive value of angiogenesis for adjuvant therapy in breast cancer.** *Breast Cancer* 2000;7:311-314.

Winer EP, Burstein HJ. **New combinations with Herceptin in metastatic breast cancer.** *Oncology* 2001;61 Suppl 2:50-7.

TRASTUZUMAB PLUS CHEMOTHERAPY

For the time being, trastuzumab should not be given with an anthracycline because of potential cardiotoxicity. The standard of care is trastuzumab plus paclitaxel. Given the activity of docetaxel in women with metastatic breast cancer and the potential preclinical synergy, there are many physicians who also administer trastuzumab plus docetaxel.

Approximately three years ago, we started studying trastuzumab plus vinorelbine. In our first Phase II study with 40 women, trastuzumab plus vinorelbine was well tolerated with an overall response rate of 75%. There is an on-going multicenter Phase III trial, with 50 sites in the United States, comparing vinorelbine/trastuzumab to a taxane/trastuzumab regimen.

—Eric P Winer, MD

TRASTUZUMAB SYNERGY WITH OTHER AGENTS

Systemic therapy is individualized to the patient. It depends on her prior treatment, general health, comorbid diseases and a number of other factors. All things being equal and the patient being capable, I opt for the most optimum interactive combination of carboplatin or cisplatin plus docetaxel/trastuzumab (CTH). Trastuzumab can, however, be combined with vinorelbine, capecitabine or gemcitabine.

I am quite comfortable, in a patient who cannot tolerate or does not want chemotherapy, to offer trastuzumab monotherapy. It is not, however, my usual recommendation, which is to exploit any potential synergies. HER2-positive breast cancer is very aggressive, and we want to take our best shot at the disease.

—Dennis J Slamon, MD, PhD

TRASTUZUMAB COMBINED WITH ENDOCRINE AGENTS

The HER2 and the estrogen-receptor pathways talk to one another, and co-regulate one another. Preclinical data clearly demonstrate that trastuzumab can reverse tamoxifen resistance, but that question needs to be asked in the clinic. We also need to ask whether combining trastuzumab with an aromatase inhibitor might be effective, but, fulvestrant may be the most promising, because it gets rid of the estrogen receptor.

— Dennis J Slamon, MD, PhD

ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF) MONOCLONAL ANTIBODY

The ECOG trial randomizes patients with metastatic breast cancer to weekly paclitaxel with or without a recombinant humanized monoclonal antibody to vascular endothelial growth factor (rhuMAb-VEGF, bevacizumab). This is the first large trial evaluating an antiangiogenic agent as front-line therapy in metastatic breast cancer. In anthracycline and taxane refractory breast cancer, a trial evaluating capecitabine with or without bevacizumab has been completed.

In preclinical models, the taxanes have demonstrated antiangiogenic activity. They kill vascular endothelial cells, affect capillary tubule formation and affect capillary migration. Hopefully, combining an antiangiogenic agent, such as bevacizumab, with a taxane, will lead to an additive or synergistic effect. Indeed, in some preclinical models, there was a synergistic effect against endothelial cells when a taxane was combined with anti-VEGF antibodies. Similarly, there is preclinical data suggesting that capecitabine may have some antiangiogenic activity. In the next few years, we will know if antiangiogenic agents contribute significantly to the management of breast cancer.

—George W Sledge, Jr, MD