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Meet the Professors: A case-based discussion on the integration of chemotherapy into the management of metastatic breast cancer

STATEMENT OF NEED/TARGET AUDIENCE

Management of metastatic breast cancer in women is one of the many challenges faced by medical oncologists. As new data continues to emerge from clinical trials of chemotherapeutic, endocrine and biologic agents in the metastatic setting, oncologists must integrate this information into clinical practice in order to provide optimal patient care. To bridge the gap between research and practice, this activity is designed as a roundtable discussion in which community oncologists discuss their challenging cases of metastatic breast cancer with one another and with research leaders.

LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

- Describe and implement a management strategy integrating chemotherapy, endocrine therapy and biologic therapy in the treatment of metastatic breast cancer in women.
- Determine the clinical implications of emerging data on the use of platinum analogs in combination with chemotherapy in the management of metastatic breast cancer in women.
- Determine the role of trastuzumab as part of these combination chemotherapeutic regimens for patients diagnosed with HER2-positive metastatic breast cancer.
- Determine the appropriate use of follow-up studies to monitor progression in patients with primary and metastatic breast cancer.

EDUCATIONAL METHOD

To receive CME credit, the participant should listen to the CDs or tapes, review the monograph and complete the post-test and evaluation form.

ACCREDITATION STATEMENT

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CREDIT DESIGNATION STATEMENT

NL Communications Inc designates this educational activity for a maximum of 4 category 1 credits towards the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent on the activity.

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Pharmaceutical agents discussed in this program

GENERIC	TRADE	MANUFACTURER
anastrozole	Arimidex®	AstraZeneca Pharmaceuticals LP
buserelin	Suprefact®, Suprefact Depot®	Hoechst Marion Roussel
capecitabine	Xeloda®	Roche Laboratories Inc
carboplatin	Paraplatin®	Bristol-Myers Squibb Company
cisplatin	Platinol®	Bristol-Myers Squibb Company
cyclophosphamide	Cytoxan®	Bristol-Myers Squibb Company
	Neosar®	Pfizer Inc
docetaxel	Taxotere®	Aventis Pharmaceuticals Inc
doxorubicin hydrochloride	Adriamycin®, Rubrex®	Pfizer Inc
etoposide	VePesid®, Toposar™, Etopophos®	RP Scherer GmbH Eberbach, Pfizer Inc, Bristol-Myers Squibb Company
fluorouracil, 5FU	Various	Various
fulvestrant	Faslodex®	AstraZeneca Pharmaceuticals LP
gemcitabine HLC	Gemzar®	Eli Lilly & Company
goserelin acetate implant	Zoladex®	AstraZeneca Pharmaceuticals LP
letrozole	Femara®	Novartis Pharmaceuticals Corporation
leucovorin calcium	Wellcovorin®	Immunex Corporation
mitoxantrone	Novantrone®	Amgen Inc
methotrexate	Various	Various
paclitaxel	Taxol®	Bristol-Myers Squibb Company
tamoxifen citrate	Nolvadex®	AstraZeneca Pharmaceuticals LP
trastuzumab	Herceptin®	Genentech Inc
vinorelbine tartrate	Navelbine®	GlaxoSmithKline
warfarin	Coumadin®	Bristol-Myers Squibb Company

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Editor's Note

A Successful "Phase I" Trial

In a recent interview for the *Breast Cancer Update* audio series, Dr Mark Pegram discussed a breast cancer patient who presented with extensive pulmonary metastases. Histology from a supraclavicular node confirmed that the patient had a HER2-positive recurrence, and she agreed to participate in one of the first Phase I trastuzumab plus chemotherapy trials conducted at UCLA. Based on laboratory data demonstrating synergy between the plantinum salts and trastuzumab, the woman received this combination and her cancer quickly had a complete response. The trial called for treatment discontinuation after a few months, and the patient has been followed for more than 10 years in complete remission without further treatment.

Dr Pegram cited this case as perhaps providing important insight into the biology of HER2-positive breast cancer, and as part of the rationale for the current major BCIRG adjuvant trial evaluating trastuzumab, docetaxel and carboplatin. Another intriguing lesson from this remarkable story is the human impact of entering a Phase I trial — in which there is usually minimal or no hope for significant benefit — and experiencing such an extraordinary response to treatment. We always hold out hope for such an occurrence, but unfortunately, the result is usually disappointing. To see such a profound response in such an early trial is truly extraordinary.

A similar analogy might be made to this CME program. Clinicians form the core of our "*Breast Cancer Update*" continuing medical education group, and we have a research-like orientation to our work that is objectively evaluated both internally and externally. In March of this year, we decided to pilot a "Phase I" program. We invited attendees to the 20th annual Miami Breast Cancer Conference to present challenging cases from their practices to breast cancer research leaders. A similar format has been used for many years at the San Antonio Breast Cancer Symposium lunch meetings.

The interactivity of our pilot program was very dynamic. We were so encouraged that we implemented another "Phase I" endeavor, this time in Dallas during the American Society of Breast Disease meetings, and we audiotaped the proceedings and developed this CME program based upon the discussions. Our four faculty members — Drs Perez, Robert, Seidman and Tripathy — walked into these sessions without any preparation for the cases about to be presented by the 11 community-based medical oncologists who practice in the Dallas area.

We are very interested in your feedback about this novel CME approach. Did you find real cases more relevant than hypothetical ones? How useful were the discussions about psychosocial issues, such as the emotional impact of metastatic disease on the patient and physician? Was this format as useful as a more didactic, topic-based CME approach? What other topics related to these cases could have been discussed? What other challenging clinical situations would be of interest? As with Dr Pegram's case, only prolonged follow-up will determine whether this type of "therapy" holds promise for the future.

—Neil Love, MD

CASE 1: Disease recurrence and brachial plexopathy during the third trimester of pregnancy (from the practice of Dr Cheryl Harth)

- A mother in her early 30s with two young children
- 1.7-cm infiltrating ductal carcinoma (ER-negative, PR-negative, HER2-positive [FISH])
- Lumpectomy and AND (7/9 positive nodes) and radiation therapy
- Received AC x 4, paclitaxel x 4
- Became pregnant 4 months post-treatment
- Developed right arm/shoulder pain and numbness in hand 1 month later
- Exam: Supraclavicular fullness
- MRI: 4 x 4 cm right supraclavicular mass involving the brachial plexus
- FNA and open biopsy: Negative for tumor
- Pain increased, developed shortness of breath
- At 25 weeks gestation, right pleural effusion was discovered; fluid was positive for adenocarcinoma

Key discussion points:

1. Defining the goals of therapy for a pregnant patient with metastatic disease
2. Risks and benefits of systemic therapy for metastatic disease in pregnancy
3. Effects of pregnancy on breast cancer progression
4. Emotional impact of practice on the oncologist

Dr Love: Dr Harth, would you describe your discussions with this woman and her family in terms of their expectations and goals for therapy and for the future?

Dr Harth: The extent of the disease was not determined until she was at 25 weeks gestation, and she wanted to be aggressive with therapy and try to live as long as possible. Her family was very dependent on her. The main question was: What therapies could we offer?

Dr Love: How did you discuss the potential effects of therapy on the fetus?

Dr Harth: I told her we were unsure of the impact many chemotherapy agents could have on the fetus. In addition, we discussed the fact that we didn't know whether she would respond to treatment. She had a very aggressive tumor, which relapsed within a short period of time after adjuvant therapy.

Dr Love: Dr Seidman, how would you think through this case?

Dr Seidman: Thank God we don't see this situation very often. This is an incredibly difficult case in which we're actually considering the fates of two lives — one confronted with metastatic breast cancer and another that hasn't yet begun.

This woman needs to understand that treatment is unlikely to have any curative potential. Hopefully, this will factor into her decision regarding the potential toxicities of therapy to which her fetus would be exposed. Some of these concerns are probably not as great as we might imagine, because she is well into her second trimester; therefore, most organ system formation has already occurred.

I would consider trastuzumab, because this agent doesn't have the classic toxicities of chemotherapy, but I do not know whether trastuzumab crosses the placenta nor do I know its potential toxicity to the fetus.

This patient's disease is rapidly progressing, causing brachial plexopathy, a malignant pleural effusion, and she still has to go through childbirth. I would want to medically maximize her chances of a good outcome in delivering this child. It will take eight to twelve weeks before this woman reaches steady state concentrations of trastuzumab; therefore, in addition to trastuzumab, I would likely add a cytotoxic agent. My bias would be to use carboplatin, vinorelbine, or gemcitabine in combination with trastuzumab because she recently received an anthracycline and a taxane.

Dr Tripathy: I would try very hard to hold off on any therapy until she delivers. Apart from the pleural effusion, which can be tapped for symptomatic relief, I don't think there is a pressing, life-threatening reason to treat her. I think she should wait until delivery, which is 10 weeks away, at most.

We have ample evidence that antibodies do cross the placental barrier, and I would suspect that trastuzumab crosses through the placenta. The HER2 pathway is important in cardiac and neural development, and I am concerned about using trastuzumab in pregnancy at any stage of fetal development. I am postulating all of this, but I don't think we can exclude harm.

I would let her deliver and then institute palliative chemotherapy. At that point, your choices are much greater, and I would certainly use trastuzumab-based therapy.

Dr Love: Debu, what would it take for you to give her chemotherapy? For example, how would you deal with the situation if two weeks later her pleural effusion was becoming worse, she had mediastinal lymph nodes, and her pain was increasing?

Dr Tripathy: I would probably use induction chemotherapy with an anthracycline and cyclophosphamide. These chemotherapy agents are not optimal because she has already received them, but there is data from MD Anderson looking at this combination as adjuvant or neoadjuvant therapy. Fluoropyrimidines, such as capecitabine, would also be a reasonable choice if we are up against the wall. As soon as she delivers, I would add trastuzumab and revert to a combination like vinorelbine/trastuzumab in a patient like this who has received a taxane.

Dr Love: Andy, a related issue in this case is advising premenopausal women about becoming pregnant after having breast cancer. How do you approach this?

Dr Seidman: Because this woman's risk of relapse was high, particularly in the short term, and because she was in her early 30s, I would have urged her to wait before conceiving. This is always a long and careful discussion, but for a younger woman, I would strongly urge the "watch-and-wait" approach. I don't tell these women they can never become pregnant. We do not have good evidence that pregnancy increases the risk of relapse.

Dr Love: Would you have advised her against pregnancy if she had a lower risk of relapse, for example, if she had a smaller tumor with negative nodes?

Dr Seidman: Because of her young age, I still would have taken a "watch-and-wait" approach. Her fertility in her late 30s would still probably be quite acceptable, and I would like for there to be some "water under the bridge" so to speak.

Dr Love: Debu, how do you advise patients about pregnancy?

Dr Tripathy: The two large retrospective studies available do not suggest that pregnancy itself increases the risk of relapse (Table 1). These studies, looking at outcomes of patients who became pregnant compared to age and stage-matched patients who did not, did not show an excess risk of relapse, even in patients with ER-positive tumors. However, as clinicians, we know that some patients with ER-positive tumors associated with pregnancy seem to have more rapid tumor growth. I honestly don't understand why that has not been seen in these studies. It is possible that these retrospective studies simply don't have the sensitivity to detect what might be a true risk. Therefore, we cannot say absolutely that pregnancy is safe, but these studies have not shown any harm.

I advise patients to make decisions about pregnancy based on their individual risk of relapse. I agree with Andy that, in high-risk patients, most of the risk of relapse occurs within the first few years. The "watch-and-wait" approach allows them to put some of that risk behind them before making such an important decision.

However, different women make different decisions. For example, a woman with a support structure in place that would allow a child to be raised with security even without a mother might be more inclined to go forward with pregnancy sooner. The discussion needs to be individualized.

Dr Harth: I think the "watch-and-wait" approach is reasonable. Many of my young breast cancer patients have the option of waiting four or five years before becoming pregnant. I tell patients that we don't know the absolute answer, and I generally recommend, if at all possible, that they wait at least five years before becoming pregnant.

Dr Tripathy: This makes sense, because they put some of the risk of relapse behind them in the first few years. However, there is sometimes the competing problem that these women are likely to go through menopause early — even in their 30s— because they received chemotherapy. With each successive year, their chances of fertility decrease. It's a difficult decision.

Dr Love: One of the lessons here is that medical oncologists have a really, really difficult job. I applaud Dr Harth for presenting this case in which there is no good answer. That's the nature of metastatic breast cancer and that's what is involved in the practice of medical oncology. Dr Harth, what was it like for you to take care of this woman?

Dr Harth: I've been in practice for over 15 years now, and this was probably one of the most difficult cases with which I've dealt. Treating metastatic disease in young women is always hard, especially in cases like this.

Table 1. The Effect of Pregnancy on Overall 5- and 10-year Breast Cancer Survival

	Study Group	Comparison Group
Overall 5-year survival (%)	92 ± 3	85 ± 3
Overall 10-year survival (%)	86 ± 4	74 ± 4

CONCLUSION: "Subsequent pregnancy does not adversely affect the prognosis of early-stage breast cancer. The superior survival seen in this and other controlled series may merely reflect a healthy patient selection bias, but is also consistent with an antitumor effect of the pregnancy."
Gelber S et al. **International Breast Cancer Study Group: Effect of pregnancy on overall survival after the diagnosis of early-stage breast cancer.** *J Clin Oncol* 2001;19(6):1671-5.

We become involved with our patients' social issues, and it makes our jobs even tougher.

Dr Love: Taking care of women with metastatic breast cancer has an impact on the oncologist. What are some of the ways oncologists cope with these tragedies?

Dr Cohen: It helps to have a strong support system within your practice. We have very good social workers who run patient support groups targeted to the needs of different patients. We have an on-site psychiatrist who practices only oncologic psychiatry. These people help a tremendous amount.

Dr Brooks: Medical oncologists are a modern day manifestation of the myth of Prometheus — chained to the rock, and each day the big predatory bird eats away part of him, and overnight he regrows, just to be partially consumed again the next day. There are many things that we as oncologists can do to renew ourselves, including seeking support among colleagues. One thing I've also learned from your Breast Cancer Update audio series is that no one knows how to take care of some of these very challenging cases — and in a way, that is comforting. Even though it may be painful from time to time, there is comfort in the fact that we are all in the same large boat.

Dr Tripathy: When I'm dealing with a patient who is likely to die, I remind myself of the many beneficial things I do for them and their family. I explain what we can and can't do and make them aware that we need to harness the capacity we all have to experience tremendous loss. I give examples of patients who have told me how comfortable they feel with their situation. They are at peace with themselves, even though they know they are dying. I share my amazement at this attitude with my patients and their families, and I confess that I myself, hope that I could reach this point if I were in their position.

Sharing these experiences with our patients and their families is rewarding. We have all had family members tell us, after patients die, how important we were, how much they appreciated our work and how they'll never forget what we did. This is the reward that keeps us going. If this is our goal, death is not always a failure. Not helping the family to feel security is a failure. In this regard, there can always be some success no matter how terrible the outcome.

Dr Love: Debu, what advice would you give to a medical oncology fellow starting to deal with these difficult issues?

Dr Tripathy: As Dr Brooks pointed out, we need the support of our colleagues. We are all under a lot of stress, and we've all seen colleagues burn out. We're faced with death all the time, but we have a lot of the same stresses that other people have. Oncologists are not alone in difficult jobs. Accountants and lawyers also burn out. We all have the ability to handle these kinds of stresses if we allow ourselves the support that we need.

We must understand the limits of what we can and can't do. We must be proud of educating and advancing ourselves. We must hope that we can help our patients to the greatest extent possible, and we must take care of ourselves.

Case follow-up:

- Patient received trastuzumab and vinorelbine with initial response, then progression
- Pain increased requiring oral narcotics; pleural effusion recurred, leading to respiratory arrest (necessitating mechanical ventilation) and fetal demise
- Continued treatment while on ventilator; was taken off ventilator and did reasonably well for several months until imaging studies revealed liver and bone metastases

Select publications: ***Pregnancy and breast cancer***

Ajarim D et al. **Pregnancy-associated breast cancer: Case-controlled study.** *Proc ASCO* 2000;Abstract 518.

Avisar E et al. **Tumor biology of pregnancy-associated breast cancer.** *Proc ASCO* 2000;Abstract 560.

Crivellari D et al. **Breast cancer and pregnancy.** *Tumori* 2002;88(3):187-92.

Dohollou N et al. **What about breast cancer during pregnancy? Experience of the Institute Gustave Roussy (IGR) from 1954 to 1995.** *Proc ASCO* 1997.

Falkenberry SS. **Breast cancer in pregnancy.** *Obstet Gynecol Clin North Am* 2002;29(1):225-32.

Gelber S et al. **International Breast Cancer Study Group: Effect of pregnancy on overall survival after the diagnosis of early-stage breast cancer.** *J Clin Oncol* 2001;19(6):1671-5.

Gemignani ML, Petrek JA. **Pregnancy after breast cancer.** *Cancer Control* 1999;6(3):272-76.

Germann N et al. **Anthracyclines during pregnancy: Factors influencing fetal outcome.** *Proc ASCO* 2003;Abstract 3037.

Gottlieb S. **Pregnancy does not increase mortality from breast cancer.** *BMJ* 1999;318:1577. Full Text

Gwyn K, Theriault R. **Breast cancer during pregnancy.** *Oncology (Huntingt)* 2001;15(1):39-46.

Gwyn K et al. **Treatment of breast cancer (BrCa) during pregnancy (Pg) using a standard protocol: Update of the MD Anderson experience.** *Proc ASCO* 2001;Abstract 1821.

Hasan C et al. **Cytotoxic therapy during pregnancy — A literature search for a prospective national study.** *Proc ASCO* 1999.

Ives A et al. **A growing dilemma — breast cancer and pregnancy.** *Aust Fam Physician* 2002;31(10):929-32.

Keleher AJ et al. **Multidisciplinary management of breast cancer concurrent with pregnancy.** *J Am Coll Surg* 2002;194(1):54-64.

Lozada JA et al. **Effects of pregnancy following treatment for breast cancer on survival and risk of recurrence.** *Proc ASCO* 2001;Abstract 145.

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Samuel J et al. **Incidence of malignant and/or pre-malignant lesions seen with pregnancy.** Proc ASCO 2003;Abstract 2190.

Velentgas P et al. **Pregnancy after breast carcinoma: Outcomes and influence on mortality.** *Cancer* 1999;85(11):2424-32.

Ward RM, Bristow RE. **Cancer and pregnancy: Recent developments.** *Curr Opin Obstet Gynecol* 2002;14(6):613-7.

Woo JC et al. **Breast cancer in pregnancy: A literature review.** *Arch Surg* 2003;138(1):91-8.

CASE 2: Unresectable local recurrence in the pectoralis major after breast-conserving surgery (from the practice of Dr Ashwani Argawal)

- 63-year-old woman with a 6-cm, ER/PR-negative, HER2-negative, poorly differentiated IDC of the right breast
- Received neoadjuvant CAF x 3, excellent response (tumor decreased to 1.5-cm)
- Underwent lumpectomy and AND (1/16 positive nodes) and XRT
- Received adjuvant CAF x 3
- Two years after initial diagnosis developed discomfort in right arm and infraclavicular region
- Physical examination: Infraclavicular mass, palpable axillary nodes, mild swelling of arm and infraclavicular region
- Biopsy of mass: ER/PR-negative, HER2-negative, poorly differentiated infiltrating ductal carcinoma
- Bone scan: Negative
- Chest CT: 7-cm mass in the right pectoral region (involving the pectoralis muscle), enlarged axillary nodes (See Figure 1a, Page 14)

Key discussion points:

1. Local versus systemic therapy for local recurrence
2. Taxane/platinum chemotherapy combinations
3. Treatment of women with Stage IV NED
4. The role of tumor markers and imaging as follow-up in metastatic disease

Dr Love: Debu, this woman initially presented with locally advanced disease and is now presenting with local recurrence after breast conservation. What are your thoughts?

Dr Tripathy: Generally speaking, the standard treatment for patients with local recurrence has always been surgical excision. Treatment beyond that has not been studied in prospectively randomized trials, so my first approach would be to attempt to provide local therapy.

Additional imaging, specifically an MRI, looking at the depth of penetration into the muscle, might help determine resectability of the lesion. Hopefully, a dissection could be done without removing a significant amount of pectoral muscle, but if there is pectoral muscle involvement, there needs to be some resection of the muscle.

Dr Love: This woman received neoadjuvant chemotherapy for her primary tumor. If her recurrence weren't amenable to surgery, would you consider giving her chemotherapy prior to

attempting to resect the recurrence to make the surgery easier?

Dr Tripathy: Although I generally do not like to use chemotherapy in these situations, if there was sufficient muscle involvement and the surgeon felt the resection would be easier with a smaller mass, neoadjuvant chemotherapy — probably with single agent paclitaxel or docetaxel — would be a reasonable option.

After the mass was removed, I would generally not use additional chemotherapy, especially in a patient like this who has already received a significant amount of chemotherapy. A caveat is that biologically speaking — people have proposed, but never tested — the interval of time since the patient received chemotherapy might guide the decision. The longer the time interval that has passed, the more likely there is retained chemosensitivity. As a general concept, I believe this is true. In the metastatic setting, we generally see higher responses and better outcome in patients with a longer disease-free interval. However, transferring that to the pure adjuvant setting has not been done. Even though we all vacillate in cases like this, my enthusiasm about chemotherapy is less when the time interval is shorter; therefore, in this particular case, my enthusiasm would be rather low.

Dr Love: Dr Argawal, what did the surgeon say about the possibility of resecting the mass?

Dr Argawal: After reviewing the CT scan, they felt the mass was inoperable without radiotherapy or chemotherapy because of significant invasion into the pectoralis major muscle.

Dr Love: Andy, how would you have thought through this case?

Dr Seidman: You have to ask yourself and the entire multidisciplinary healthcare team whether the goal of therapy is palliation or cure. Most people would expect the goal here to be palliation. Disease-free interval can be an important predictor for a long-term outcome. This woman's high risk of distant metastases — based on her initial presentation — would temper my enthusiasm about administering chemotherapy to treat distant metastases. However, if resection is needed for palliation, and the surgeon felt this lesion was unresectable, chemotherapy would be warranted.

This is one of the few scenarios in which I might employ combination chemotherapy, because the higher response rate and greater chance of shrinking the tumor could make a palpable difference for that surgeon — and be the difference between resectability with clear margins or not.

Dr Love: Which chemotherapy combination would you use?

Dr Seidman: The basic ingredient would be a taxane, and many other agents could be added. We have Phase II data for taxanes and carboplatin (Table 2) and equally impressive data for the taxanes and gemcitabine. We also have limited data for taxanes and vinorelbine. Because this patient received fluorouracil two years ago, I probably wouldn't use capecitabine. I would likely use carboplatin or gemcitabine.

Dr Love: What are your major clinical concerns in this situation?

Dr Seidman: Brachial plexopathy, subclavian vein thrombosis and all of the upper extremity problems that go along with this woman's presentation come to my mind immediately. Most of us rely on radiotherapy as a solution — often when it is too late. Here, we are considering the possibility of chemotherapy followed by resection of both the axillary nodes — which is a challenge when the axilla has been dissected — and of this infraclavicular mass with part of the pectoralis muscle. Certainly radiotherapy would be a part of the whole recipe.

Dr Love: Debu, How often do you see axillary node recurrence in a woman who's had axillary node dissection?

Dr Tripathy: In the published literature, we see axillary node recurrence in five to ten

Table 2. Phase II Trials of Taxanes Plus Carboplatin as First-line Chemotherapy for Women with Metastatic Breast Cancer: Efficacy and Toxicity Data

	Paclitaxel + Carboplatin NCCTG-953252	Docetaxel + Carboplatin NCCTG-N9932
Efficacy		
Overall response rate	62% (95% CI: 48-75%)	58% (95% CI: 44-72%)
Median progression-free survival	7.3 months	9.8 months
1-year survival rate	72% (95% CI: 61-86%)	72% (95% CI: 59-88%)
Grade III/IV toxicities		
Neutropenia	82%	94%
Febrile neutropenia	0%	15%
Thrombocytopenia	18%	15%
Neurotoxicity	16%	4%

DERIVED FROM: Perez EA et al. **A Phase II study of paclitaxel plus carboplatin as first-line chemotherapy for women with metastatic breast carcinoma.** *Cancer* 2000;88(1):124-31.
Fitch TR et al. **Phase II cooperative group trial of docetaxel (D) and carboplatin (CBDCA) as first-line chemotherapy for metastatic breast cancer (MBC).** *Proc ASCO* 2003.

percent of women who have had axillary node dissection. There are obviously different determinants in the risk, such as number of involved axillary nodes, grade of the tumor, etc. In the Canadian study of postmastectomy radiation, local recurrence rates were 35 to 40 percent.

As Dr Seidman pointed out, brachial plexopathy and axillary recurrence, especially with lymphedema, is a very challenging clinical problem. I would rely on systemic chemotherapy in the palliative setting, very similar to the way you would treat someone with, for example, symptomatic pulmonary metastases. As we hear more about this case, it sounds unlikely that the patient will be a surgical candidate. The changes in her arm and the possibility of lymphedema and brachial plexus involvement are concerns.

I disagree with the use of radiation therapy in this case. This patient probably received 5,000 cGy. It's hard to conceive that an additional 2,000 cGy, which would be the absolute most you could deliver, would help much. In fact, causing an iatrogenic brachial plexopathy and lymphedema is more likely. I think we're left with palliative chemotherapy as our main option.

Dr Love: Dr Argawal, what did you decide to do?

Dr Argawal: I gave her four cycles of carboplatin and docetaxel, and she had an excellent response — actually, I was amazed. The response was so good that she didn't want to come for the second cycle — her daughter convinced her to continue. The mass was much smaller, the node was smaller and the swelling in her arm had almost completely resolved.

After four cycles of chemotherapy, the surgeon was able to perform a mastectomy with a part of the pectoral muscle dissected, completely resecting the mass. Six of lymph nodes out of seven were positive.

She is now completely healed and there is no evidence of disease. She will also receive additional radiation.

Dr Seidman: If she is very motivated, she could enter a vaccine clinical trial. Otherwise, I don't believe there is anything else you should be doing for her. I would not continue the chemotherapy because we lack evidence of its benefit, and the only thing we can be certain of is additional toxicity in this scenario.

Case follow-up:

- Patient received carboplatin and docetaxel weekly (3 weeks on, 1 week off) x 4; tolerated chemotherapy well but had several treatment delays due to grade III and IV hematological toxicity
- Excellent response; beginning after the first cycle, mass and lymph nodes smaller on physical exam and CT (Figure 1b); arm swelling resolved
- Underwent a mastectomy, partial resection of pectoralis muscle and axillary node dissection (6/7 nodes positive); recovered well with no evidence of disease
- Will receive additional infraclavicular and axillary radiation

Figure 1a. Pretreatment Chest CT
October 2002

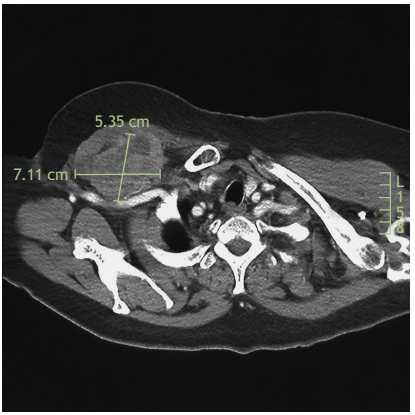
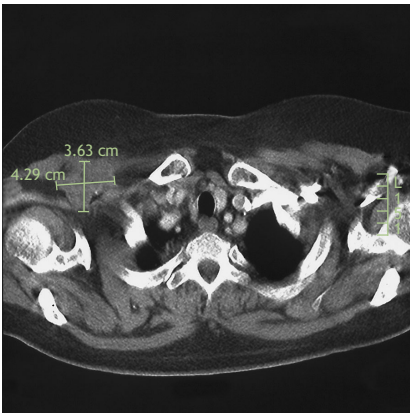


Figure 1b. Post-treatment (carboplatin/ docetaxel) Chest CT
January 2003



Dr Tripathy: This patient is technically NED. You could argue that the likelihood of recurrence is so high that an additional two cycles of chemotherapy might delay that recurrence, but it's hard to believe this would improve long-term outcome and survivability. This patient has completed local therapy and has negative margins. I would probably stop at this point.

Radiation will probably lower the risk of local recurrence, but the trade-off will be a fair amount of toxicity, especially with taxanes and I would be concerned about radiation recall phenomena. Careful shielding and careful attention to detail in port planning is essential if the patient is going to undergo radiation.

Dr Brooks: How would you follow a patient like this? My experience is that physical examination is not very sensitive after these salvage surgical procedures in the infraclavicular and axillary regions.

Dr Seidman: I agree, but I would add that routine imaging studies to detect subpalpable disease radiographically will probably not change the ultimate outcome for the patient.

So, from a cost-effectiveness standpoint, physical examination and imaging directed by physical examinations and by symptoms would be indicated.

Dr Brooks: I disagree. I am a proponent of using tumor markers. I would also use CT scans. I favor the imaging approach because of the availability of more tolerable chemotherapeutic agents, such as capecitabine, which almost deserves its own class. I wouldn't give her multi-agent chemotherapy based on a CT scan finding, but I believe that you can intervene early with capecitabine in a case like this. I think that you can treat an ER/PR-negative cancer with capecitabine early on with a good conscience.

Dr Seidman: In a patient like this with a very high risk of tumor recurrence — particularly if I knew she had elevated markers at the time of her six-centimeter mass — I, too, would keep my antenna up by following tumor markers to intervene early.

Dr Love: Dr Argawal, did this patient have tumor markers checked?

Dr Argawal: No, I didn't follow tumor markers.

Dr Love: Dr Seidman, if, for example, this woman's CA 27.29 was very elevated, then dropped down by a quantum amount after the carboplatin/docetaxel, and dropped down further after surgery but was still elevated, what would you do?

Dr Seidman: I would reiterate Dr Brooks' comments about capecitabine. I would not treat a patient with rising tumor markers with any cytotoxic chemotherapy agent other than capecitabine. I would have a discussion with the patient about the watch-and-wait approach — beginning therapy at the onset of symptoms as opposed to the onset of a rise in biochemical markers. But having said that, once you open the box, it's hard to close it.

Dr Tripathy: I agree with Dr. Argawal's approach. I would not check tumor markers in the first place. I don't know of any reason to use markers, because it's not clear that initiating therapy based on marker elevations helps patients' outcomes in the long term.

I don't want to be absolute about it. The fact of the matter is that I actually have this discussion with patients. I tend to sway them away from using markers, but I do tell them that there are very rare potential scenarios in which one, in retrospect, might say, "I wish I'd used a marker." For example, in a patient who develops a fairly rapid complication, such as a tumor-related brachial plexus problem, by the time you start them on chemotherapy you cannot alleviate symptoms. You might have saved, or at least delayed, the onset of that problem.

The risk of using tumor markers in this type of situation is that we might over-react. We take a patient who perhaps didn't need to be exposed to the side effects of chemotherapy for quite some time, and expose them much earlier because of elevated serum markers, but we don't affect their overall clinical course or their survival. The serum marker problem can cut both ways in terms of helping you or hurting you.

Dr Love: If you believe that adjuvant systemic therapy increases survival by treating micrometastatic disease, why would you not believe that treating Stage IV NED — particularly when you have an in vivo demonstration of active chemotherapy agents — might give her a chance of surviving?

Dr Tripathy: If we had more effective drugs, it's quite possible that a rising serum marker, or even a positive PET scan might actually result in an improvement in outcome. In fact, we know that is the case in lymphoma and testicular cancer. However, in breast cancer we don't have good enough agents to do that at this point.

The second point is that two Italian studies have looked at serum markers, and there was no difference in outcome between patients who had them checked versus those who did not. The markers did predict in which patients cancer was going to recur. A serially rising serum marker is associated with an 80 percent

likelihood of developing metastases. However, in some cases, these metastases do not develop radiographically for two or three years. So you have a patient in limbo, and you can't do anything. At this point, there's no evidence that rising serum markers can help you treat a patient. They are predictive, and that's why the FDA approved them, but they just don't help with patient management.

Select publications: ***Tumor markers in metastatic breast cancer***

Bast RC Jr et al. **2000 update of recommendations for the use of tumor markers in breast and colorectal cancer: Clinical practice guidelines of the American Society of Clinical Oncology.** *J Clin Oncol* 2001;19(6):1865-78.

Clinton SR et al. **A comparative study of four serological tumor markers for the detection of breast cancer.** *Biomed Sci Instrum* 2003;39:408-14.

Duffy MJ. **Biochemical markers in breast cancer: Which ones are clinically useful?** *Clin Biochem* 2001;34(5):347-52.

Gion M et al. **CA27.29: A valuable marker for breast cancer management. A confirmatory multicentric study on 603 cases.** *Eur J Cancer* 2001;37(3):355-63.

Gion M et al. **Tumor markers in breast cancer monitoring should be scheduled according to initial stage and follow-up time: A prospective study on 859 patients.** *Cancer J* 2001;7(3):181-90.

Guadagni F et al. **A re-evaluation of carcinoembryonic antigen (CEA) as a serum marker for breast cancer: A prospective longitudinal study.** *Clin Cancer Res* 2001;7(8):2357-62.

Jager W et al. **Serial CEA and CA 15-3 measurements during follow-up of breast cancer patients.** *Anticancer Res* 2000;20(6D):5179-82.

Kurebayashi J et al. **Significance of Serum Carcinoembryonic Antigen and CA 15-3 in monitoring advanced breast cancer patients treated with systemic therapy: A large-scale retrospective study.** *Breast Cancer* 2003;10(1):38-44.

Lauro S et al. **Comparison of CEA, MCA, CA 15-3 and CA 27-29 in follow-up and monitoring therapeutic response in breast cancer patients.** *Anticancer Res* 1999;19(4C):3511-5.

Lufter D et al. **A comparison of bone-related biomarkers and CA27.29 to assess response to treatment of osseous metastatic breast cancer.** *Anticancer Res* 2000;20(6D):5099-105.

Robertson JF et al. **The objective measurement of remission and progression in metastatic breast cancer by use of serum tumour markers. European Group for Serum Tumour Markers in Breast Cancer.** *Eur J Cancer* 1999;35(1):47-53.

Smith TJ et al. **American Society of Clinical Oncology 1998 update of recommended breast cancer surveillance guidelines.** *J Clin Oncol* 1999;17(3):1080-2.

Sutterlin M et al. **Predictive value of CEA and CA 15-3 in the follow up of invasive breast cancer.** *Anticancer Res* 1999;19(4A):2567-70.

Valenzuela P et al. **The contribution of the CEA marker to CA 15.3 in the follow-up of breast cancer.** *Eur J Gynaecol Oncol* 2003;24(1):60-2.

CASE 3: Pulmonary metastases and mild shortness of breath (from the practice of Dr Paschal Wilson)

- 5 years ago, the patient in her 50s, received ACT followed by tamoxifen for ER/PR-positive, HER2-negative breast cancer
- Returns for routine follow-up, while on tamoxifen, with mild shortness of breath and fatigue
- Chest X-ray and CT: Multiple small pulmonary nodules (largest 1.5-cm)

Key discussion points:

1. Discuss goals of treating metastatic breast cancer
2. Chemotherapy versus endocrine therapy in metastatic disease
3. Sequential single agents versus combination chemotherapy in metastatic disease
4. Selection and scheduling of taxanes
5. Combining trastuzumab with chemotherapy in the metastatic setting
6. Determining ER- and PR-positivity
7. Optimal dosing of docetaxel

Dr Love: What kind of questions did this woman ask you about what to expect in the future? What was her overall approach to this in terms of how aggressive to be in treating the disease?

Dr Wilson: Like most patients with metastatic disease, she experienced some shock at the diagnosis. She was able to appreciate that she still had a very good quality of life without major symptoms and that we had an approach to fight this. She also has good family support from her husband and her children.

I stressed that while we didn't expect to cure her, we had number of treatment options available. I also emphasized my expectation that a strong patient with relatively few symptoms would do well for a relatively long time. She certainly wanted to be treated, but she wanted treatment that would not significantly interfere with her life, because to that point, her symptoms were not interfering with her daily activities.

Dr Love: Debu, how would you think through this case?

Dr Tripathy: I tell patients that there is a spectrum of disease, ranging from chronic to a more acute and life-threatening disease. I try to give them a sense of what they might expect from different therapies, both in terms of the likelihood of response and toxicity. Finally, I give them my recommendation balancing these two issues.

In this case, I would start her on a hormonal therapy with an aromatase inhibitor. I would follow symptoms closely, but the lungs are an area one could follow most accurately with CT scans.

Dr Love: One of the things I find most interesting about interviewing research leaders and interacting with physicians in practice is that there is a real dichotomy in some situations. In this patient, I think the lung metastases and shortness of breath would make many physicians nervous. I'm not saying what is right or wrong, but I think many community-based oncologists would start this woman on chemotherapy. One strategy I often see in this kind of situation is to use chemotherapy to elicit a response and then switch to hormonal therapy.

Dr Harth: I agree. Not having seen the patient, I would choose chemotherapy first, because the suggestion of shortness of breath is unnerving. In addition, this patient progressed on tamoxifen. In my experience, those patients do not do as well on hormonal agents. I would treat her with chemotherapy initially and then start her on an aromatase inhibitor.

Dr Brooks: I'd like to dissent. Aromatase inhibitors work pretty quickly, and I believe you can start patients like this on an aromatase inhibitor and follow tumor markers, CT scans and symptoms. I don't think you lose very much, because if the tumor responds, you have a therapy that may work for 6, 12, 18, 24, or more months. This is your opportunity to "hit it out of the ball park" with essentially no symptoms.

If you put this patient's disease into remission with chemotherapy and then use aromatase inhibition, you don't know if you are looking at a nice remission from chemotherapy or a small hormone effect. As long as you have time, trying hormones first is preferable.

Dr Love: When we face the decision between hormonal therapy and chemotherapy, we classically think about how quickly we need a response. This is based on the idea that hormones don't work as fast as chemotherapy. However, Mike Dixon, who studies neoadjuvant endocrine therapy, says that changes occur in the biopsy within days after an aromatase inhibitor is started. Debu, how much do we really know about how long it takes to have an effect with hormonal therapy versus chemotherapy?

Dr Tripathy: We know very little about the timing of response. This has typically not been reported in clinical trials, so it's hard to determine. I can't answer on a clinical basis, although, as you pointed out, studies have looked at the biological effects, examining proliferative status, and shown very rapid effects.

People also have the common conception, which may or may not be true, that visceral disease responds less often to hormonal therapy than nonvisceral disease. In most of the hormonal therapy trials, the response rates are generally comparable between soft tissue and visceral disease.

I agree with Dr Harth that the likelihood of response with an aromatase inhibitor is probably slightly lower in this patient; however, the speed of response and the ability to monitor the patient for a response is such that using an aromatase inhibitor is a reasonable option.

Dr Love: Let's change some of the variables in this case and see how it affects treatment. Andy, assume this patient had much more shortness of breath and the chest CT scan was much worse — she's not ready to be hospitalized, but you're a little bit concerned about her situation. What would you recommend?

Dr Seidman: A single-agent taxane would be the standard of care in that situation.

Dr Love: Okay, now we'll go even further and say that she's very short of breath and has lymphangitic disease.

Dr Seidman: I would stand by my original answer to give her a single-agent taxane.

Dr Tripathy: I disagree with Dr Seidman here. Although I very rarely use combination chemotherapy, I probably would in this situation because the patient is in visceral crisis. I agree with Dr Seidman that the long-term survival may not be different with combination versus sequential therapy; however, in this patient, a higher chance of response might justify the added toxicity of a combination. I try to estimate the degree of benefit for a patient based on symptoms — the more symptoms, the greater the potential benefit, which might outweigh the added toxicity of combination therapy.

The docetaxel/capecitabine combination is a completely reasonable choice for this situation. There is a published trial demonstrating a benefit, and this patient has not previously received a taxane (Figure 2, Table 3). One could consider a combination of anthracyclines and taxanes, but this patient has previously received anthracyclines.

Dr Love: Dr Aks, how would you have managed this patient's disease if she were very symptomatic?

Dr Aks: Because of the pending respiratory failure that you suggested, I would have been very aggressive and taken my chances with at least a doublet to try to avoid the crisis of ventilator support. I would be comfortable with a taxane and capecitabine. Could either Dr Seidman or Dr Tripathy comment on the recent emerging data on combining taxanes with carboplatin in this clinical setting?

Dr Seidman: There is a much higher level of evidence supporting the addition of carboplatin in the HER2-positive setting than in the HER2-negative setting. Nick Robert presented data from the US Oncology trial last December in San Antonio, in which the addition of carboplatin to paclitaxel and trastuzumab significantly improved patient outcome. The Phase II data for paclitaxel and carboplatin in HER2-negative tumors are also impressive.

Dr Tripathy: A platinum-containing combination would be reasonable as would vinorelbine in combination with taxanes and a variety of others. Data have been published on many combinations in the Phase II

Figure 2. Phase III Trial of Capecitabine/Docetaxel (XT) Combination Therapy vs Docetaxel Monotherapy (T) in Metastatic Breast Cancer — Closed Protocol

Eligibility	Metastatic breast cancer patients resistant to or relapsing after anthracycline-based therapy
ARM 1	Capecitabine 1,250 mg/m^2 po twice daily days 1-14 + docetaxel 75 mg/m^2 IV q 3 weeks
ARM 2	Docetaxel 100 mg/m^2 IV q 3 weeks

Table 3. Efficacy of XT vs T in Patients with Anthracycline-Pretreated Metastatic Breast Cancer

	Capecitabine/Docetaxel (XT) n=255	Docetaxel (T) n=256	*p* value
Median time to progression	6.1 months [95% CI: 5.4-6.5]	4.2 months [95% CI: 3.4-4.5]	log rank $p = 0.0001$
Objective tumor response	42% [95% CI: 36-48]	30% [95% CI: 24-36]	$p = 0.006$
Stable disease	38% [95% CI: 32-44]	44% [95% CI: 38-50]	
Median survival	14.5 months [95% CI: 12.3-16.3]	11.5 months [95% CI: 9.8-12.7]	log rank $p = 0.0126$

DERIVED FROM: O'Shaughnessy J et al. **Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: Phase III trial results** *J Clin Oncol* 2002;20:2812–2823.

setting, but there are not many randomized studies in HER2-negative populations, by which we can compare outcomes and toxicities relative to a single agent. This is one of the reasons I chose the particular combination of docetaxel and capecitabine.

I must emphasize, as we discussed, that treating breast cancer is an art, and one has to look at and be able to present numerous options to patients. Sometimes, I present these multiple options to my patients just to illustrate the number of possibilities available to them. In the end, I'm not as dogmatic with my patients as I may be in this setting. I think it's only fair to say that there are several reasonable regimens, including the platinum-based regimens.

Dr Love: Andy, you said you would start this patient on a taxane — which agent would you choose?

Dr Seidman: Presently, we don't have evidence to make this decision, but I understand in the not too distant future we will have some prospective randomized comparisons between paclitaxel and docetaxel. Right now, I can't give you the evidence-based answer.

Sometimes the symptom of shortness of breath helps me choose between the taxanes. Docetaxel in cumulative doses that exceed 400 to 600 milligrams per meter squared can sometimes lead to a syndrome of fluid retention, including pleural effusion. We started seeing this back in the early 1990s, and the use of corticosteroid premedication has made it much less common. But, in this scenario, I would favor paclitaxel because it would be less likely to confound my assessment of her primary symptom of shortness of breath.

Dr Firstenberg: In general, in a patient who is taxane-naïve, is there any data to suggest whether it's better to use paclitaxel followed by docetaxel, or the opposite?

Dr Seidman: Is one taxane more active after the other in terms of cross-resistance? I don't think we know that. But we also don't necessarily know that answer for steroidal and nonsteroidal aromatase inhibitors, for which there has been a lack of cross-resistance. I wouldn't select an agent based on that notion.

Dr Love: What would you do if she had a dramatic response to paclitaxel and was doing great after two or three cycles?

Dr Seidman: What is the optimal duration of therapy? Do you treat for some arbitrary number of cycles, stop and observe? Do you treat to the maximum response as assessed by CT scan and stop? Do you treat to the maximum response as assessed by CT scan and then add a few extra cycles? Or do you treat until disease progression, as long as there's no intolerable toxicity? I tend to do the latter.

The natural history of metastatic breast cancer is to grow, progress and cause death. If I've changed that natural history, as long as the treatment is reasonably well-tolerated, my bias is to continue. However, if this woman had, as Dr Wilson presented, estrogen receptor-positive disease, I have the option of backing off and using second-line anti-estrogen therapy.

Dr Love: What schedule of paclitaxel would you use?

Dr Seidman: I am the principal investigator of CALGB-9840, which randomizes patients to weekly dose-dense or conventional paclitaxel every three weeks. We don't yet know the right answer. Until we do, the practical, logistic issues influence me.

It's not a major issue for my patients living on East 79th Street to come in for weekly therapy. Weekly therapy, however, for my patients commuting from New Jersey, Connecticut, or Long Island, could be inconvenient, especially in the absence of any randomized Phase III data showing benefit.

Dr Love: For ER-positive disease, you mentioned the strategy of giving chemotherapy to induce response and stabilize the patient and then switching to a hormonal

therapy. Let's say this patient has been treated for four months and is having a good response but with some neurotoxicity. Is that something you would be likely to do?

Dr Seidman: Absolutely. I think the best thing we can do for patients with potentially hormone-sensitive breast cancer is to give them antiestrogen therapy. The only thing in this scenario that pushed me to cytotoxic chemotherapy was the more symptomatic, aggressive profile you illustrated. I would welcome the first opportunity to back off of chemotherapy and to start an aromatase inhibitor.

Dr Love: Now, for example, let's make this woman HER2-positive by FISH, with lymphangitic disease and severe shortness of breath. Debu, how would you treat her?

Dr Tripathy: I would certainly use trastuzumab therapy in this situation. We know that it improves the response rate, quality of life, duration of response and survival when used in combination with chemotherapy compared to chemotherapy alone.

The question is what trastuzumab-containing regimen to use. The comparative trials are with paclitaxel/trastuzumab, and this would be the standard and my initial choice. However, with recent data suggesting that higher response rates can be achieved with the addition of carboplatin, this would be an important option to discuss with the patient.

I wouldn't offer the triplet in a knee-jerk way, but I probably would use it. There is not that much more toxicity, but there is more fatigue and more severe cytopenias. In this particular case, I probably would consider the triplet therapy with trastuzumab, carboplatin and paclitaxel.

Dr Love: Ok, now you put her on the triplet and after three months of therapy she's having a good response and doing well. What would you do at that point?

Dr Tripathy: As soon as her disease has plateaued and I felt additional therapy would not result in much further benefit, I would stop the chemotherapy and continue trastuzumab alone. The point at which that plateau is reached varies with each patient, the symptomatology and the tolerability of therapy. In the published trial, patients needed to receive at least six cycles before having their treatment discontinued. The vast majority did discontinue chemotherapy around that time or shortly thereafter.

Case follow-up:

- Patient received docetaxel (75 mg/m^2) q 3 weeks; tolerated chemotherapy well with symptomatic improvement
- CT scan after the third cycle indicated a response; additional 3 cycles were given

Dr Love: Let's follow up with Dr Wilson and find out exactly what happened.

Dr Wilson: She agreed to receive six cycles of docetaxel at 75 mg/m^2 every three weeks. She tolerated therapy well with symptomatic improvement, and her CT scan after the third cycle showed some response.

Dr Seidman: Dr Wilson, I'm just wondering why you chose a dose of docetaxel of 75 mg/m^2? Were you concerned about the impact of 100 mg/m^2 on her quality of life?

Dr Wilson: Yes, I was concerned about that. There was a question of giving her hormonal therapy up front. Since she had visceral metastases and symptoms, I wanted to give

her chemotherapy, but she was working. She wanted to be treated, but she also wanted to minimize toxicity. I thought it was reasonable to give docetaxel at that dose and monitor her response.

Dr Seidman: One of the questions posed to me was which taxane would I use. The randomized data comparing these two taxanes compares docetaxel at 100 mg/m^2 to paclitaxel at 175 mg/m^2.

We also have randomized Phase III data on docetaxel dosing, comparing 100 to 75 to 60 mg/m^2, indicating a higher response rate and longer time to progression with the higher dose (Table 4). It's interesting that some of my colleagues in the community still aren't comfortable with the 100 mg/m^2 dose, despite its positive impact on quality of life.

Dr Tripathy: This issue is critical. Whereas with paclitaxel there doesn't seem to be much of a dose-response relationship increasing from 175 to 225 to 250 mg/m^2, with docetaxel, it does matter. And the toxicities are clearly different at 75 versus 100 mg/m^2.

Dr Cohen: I generally have used 75 mg/m^2 of docetaxel, because there's less of an issue with fluid retention and also fatigue. Isn't it true that a significant number of patients in many of the studies start at 100 mg/m^2 and have to decrease to 75 mg/m^2 because of toxicity?

Dr Tripathy: Yes, so the dose delivered may actually be lower than 100 mg/m^2, but in an intent-to-treat analysis, this is generally presented as the 100 mg/m^2 dose. One can extrapolate to say: We can probably just start at 75 mg/m^2. While it is very hard to say, I believe the answer might be somewhere in between.

Table 4. Randomized Phase III Data on Docetaxel Dosing, Comparing 100 to 75 to 60 mg/m^2

	100 mg/m^2 (n=139)	75 mg/m^2 (n=146)	60 mg/m^2 (n=122)
Complete response rate	6.5%	1.4%	2.5%
Overall response rate	36.0%	23.3%	22.1%
Median overall survival (months)	12.3	10.3	10.6
Discontinuation due to toxicity	17%	7%	5%
Febrile neutropenia	14%	7%	5%

CONCLUSION: "There was a significant dose-response relationship in the range 60-100 mg/m^2, and RR [response rates] differed between the groups. Overall the 100 mg/m^2 group had the best efficacy and was associated with higher but manageable toxicity."
DERIVED FROM: Mouridsen H et al. **Phase III study of docetaxel 100 versus 75 versus 60 mg/m^2 as second line chemotherapy in advanced breast cancer.** *Breast Cancer Res Treat* 2002:Abstract 327.

Case follow-up:

- CT scan indicated stable disease
- Patient switched to anastrozole as maintenance therapy
- Remained on anastrozole, working and feeling well for 7-8 months

Select publications: *Recent clinical trial data regarding taxane use in the metastatic setting*

Aihara T et al. **Phase II study of concurrent administration of doxorubicin and docetaxel as first-line chemotherapy for metastatic breast cancer.** *Oncology* 2003;64(2):124-30.

Aihara T et al. **Phase II study of weekly docetaxel in patients with metastatic breast cancer.** *Ann Oncol* 2002;13(2):286-92.

Alba E et al. **Sequential doxorubicin and docetaxel as first-line treatment in metastatic breast cancer: A GEICAM-9801 phase II study.** *Breast Cancer Res Treat* 2003;77(1):1-8.

Baltali E et al. **Paclitaxel and doxorubicin combination in the first-line treatment of metastatic breast cancer.** *Tumori* 2002;88(3):200-3.

Biganzoli L et al. **Doxorubicin and paclitaxel versus doxorubicin and cyclophosphamide as first-line chemotherapy in metastatic breast cancer: The European Organization for Research and Treatment of Cancer 10961 Multicenter Phase III Trial.** *J Clin Oncol* 2002;20(14):3114-21.

Gennari A et al. **Weekly docetaxel/paclitaxel in pretreated metastatic breast cancer.** *Clin Breast Cancer* 2002;3(5):346-52.

Gori S et al. **Weekly paclitaxel in metastatic breast cancer patients: A phase II study.** *Tumori* 2002;88(6):470-3.

Loesch D et al. **Phase II multicenter trial of a weekly paclitaxel and carboplatin regimen in patients with advanced breast cancer.** *J Clin Oncol* 2002;20(18):3857-64.

Mavroudis D et al. **Salvage treatment of metastatic breast cancer with docetaxel and carboplatin. A multicenter phase II trial.** *Oncology* 2003;64(3):207-12.

Nabholtz JM et al. **Docetaxel and doxorubicin compared with doxorubicin and cyclophosphamide as first-line chemotherapy for metastatic breast cancer: Results of a randomized, multicenter, phase III trial.** *J Clin Oncol* 2003;21(6):968-75.

O'Shaughnessy J et al. **Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: Phase III trial results.** *J Clin Oncol* 2002;20(12):2812-23.

Perez EA et al. **A randomized phase II study of sequential docetaxel and doxorubicin/cyclophosphamide in patients with metastatic breast cancer.** *Ann Oncol* 2002;13(8):1225-35.

Sledge GW et al. **Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer: An intergroup trial (E1193).** *J Clin Oncol* 2003;21(4):588-92.

Smith RE et al. **Phase II trial of doxorubicin/docetaxel/cyclophosphamide for locally advanced and metastatic breast cancer: Results from NSABP trial BP-58.** *Clin Breast Cancer.* 2002;3(5):333-40.

Talbot DC et al. **Randomised, phase II trial comparing oral capecitabine (Xeloda) with paclitaxel in patients with metastatic/advanced breast cancer pretreated with anthracyclines.** *Br J Cancer* 2002;86(9):1367-72.

Venturini M et al. **Capecitabine in combination with docetaxel and epirubicin in patients with previously untreated, advanced breast carcinoma.** *Cancer* 2003;97(5):1174-80.

CASE 4: HER2-positive metastases to the lung and residual local breast cancer after lumpectomy (from the practice of Dr Norman R Cohen)

- Patient in her 30s with a past history of a positive tuberculin test (no treatment for TB)
- Lumpectomy, axillary dissection at another hospital for a 5-cm ER/PR-negative, HER2-negative (IHC by outside lab) left breast cancer (7/7 positive nodes)
- Postoperative examination: Left breast tenderness at surgical site
- Disabled by aseptic necrosis of right hip unrelated to breast cancer
- Chest X-Ray: Multiple, nonspecific nodules too small to biopsy
- Repeat TB test: Positive
- Started TAC chemotherapy
- Developed staphylococcal bacteremia from infected port-a-cath within the first week of treatment before blood counts fell
- Treatment delayed 3-4 weeks, port-a-cath removed and resistant staphylococcal infection treated
- Pulmonary nodules increased in size and there was swelling in left breast and increasing pain and tenderness
- FNA of pulmonary nodules: Positive for metastatic adenocarcinoma
- Ultrasound of tumor cavity: Solid elements present
- Core breast biopsies: Positive for residual cancer, ER/PR-negative, but HER2-positive (IHC 3+)

Key discussion points:

1. HER2-testing with IHC versus FISH
2. Selection of chemotherapy in combination with trastuzumab in patients with HER2-positive metastatic disease
3. Monitoring cardiac function in patients on trastuzumab
4. Carboplatin versus cisplatin
5. Duration of trastuzumab therapy
6. Scheduling of taxane/carboplatin combination

Dr Love: Tell us a little bit more about this woman, her attitude, and how she and her family reacted to the news of her metastatic disease?

Dr Cohen: She was depressed during the separation from her family when she was hospitalized for the staphylococcal bacteremia. She was not very talkative and just laid in bed, sleeping most of the time. After she was able to leave the hospital and move around, she was much more animated.

When we talked about the lung disease she realized she had metastatic disease and asked whether she was going to be cured. I had to convert the discussion from one of cure to control and prolongation of her life in the best possible way. She understood, but it set her back for a while. Her husband was extremely supportive; they have a very strong, mutually supportive relationship.

Dr Love: Dr Cohen, were you concerned that HER2-negative status of her primary tumor may have been incorrect? Did you consider submitting her tumor for analysis by FISH?

Dr Cohen: We did not obtain a FISH due to financial concerns. If we were going to send it out, she would have been required to sign a financial obligation to pay for anything that wasn't covered by insurance, and she refused to do that.

Dr Perez: We cannot forget the financial burden that some tests and therapies we recommend might have on patients and families. In this particular situation, knowing the HER2 status is critical to making an appropriate recommendation, and I'm not completely comfortable that this patient has HER2-positive disease. I would want to review the initial slides to determine whether a mistake was made in the immunohistochemistry. Perhaps a review of those slides wouldn't cost as much as ordering FISH.

Dr Cohen: We did review the initial slides, but our pathologist agreed with the histologic diagnosis, and we didn't repeat the biopsy at that time. This is one reason I decided to rebiopsy the lesion when she was not doing well. I wanted the IHC done in our lab — our lab's IHC 3+ results have all been positive on FISH.

Dr Perez: Good. If the pathology has been evaluated in a laboratory like yours, with a high volume of HER2 testing corroborated with FISH analysis, then I would be content that this patient's tumor is HER2-positive based on immunohistochemistry. If her test is read as IHC 3+, I do not see any need to corroborate that with FISH analysis. Clinical trials have demonstrated that the benefit of trastuzumab is similar for patients with IHC 3+ positivity or FISH positivity, so, I wouldn't go any further in terms of retesting her tumor.

Dr Robert: As a former pathologist, I must add that immunohistochemistry is much easier and less expensive than FISH, and FISH usually has to be sent out. However, IHC has to be done by a high-volume pathology department to be reproducible. We have a financial block in our thinking that an inexpensive immunohistochemistry test is adequate and we don't want to spend money on FISH, yet we're willing to give trastuzumab, which has a significant cost.

In reviewing Dr Chuck Vogel's experience with first-line single-agent trastuzumab (Table 5, page 26) and Dr Melody Cobleigh's experience with trastuzumab given after chemotherapy — of the IHC 3+ patients who responded, only one patient out of more than 60 was not FISH-positive. There is a very good linkage between FISH positivity and response to trastuzumab.

It has become my routine practice in metastatic breast cancer, not to be comfortable with IHC evaluation but to order a FISH test. The flip side is also true —

Table 5. Efficacy of First-Line Trastuzumab In HER2-Overexpressing Metastatic Breast Cancer

Subset	Objective Response	Clinical Benefit*
All assessable patients (n=111) (95% CI)	26%	38%
Trastuzumab		
2 mg/kg weekly (n=58) [95% CI]	24%	34%
4 mg/kg weekly (n=53) [95% CI]	28%	42%
Estrogen receptor		
positive (n=52)	23%	36%
negative (n=54)	30%	39%
HER2		
IHC 3+ (n=84)	35%	48%
IHC 2+ (n=27)	0%	7%
FISH		
positive (n=79)	34%	48%
negative (n=29)	7%	10%
Previous adjuvant doxorubicin (n=57)	32%	41%

*Clinical Benefit = complete, partial or minor response or stable disease > 6 months

DERIVED FROM: 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;20:719-726.

patients with IHC 1+ or 2+ tumors that are FISH-positive have a very good chance of responding to trastuzumab.

Dr Capistrano: We know that our laboratory has a good correlation between IHC 3+ and FISH positivity. But, for example, if you send an IHC 2+ to the reference laboratory and they can't make a decision about a tumor being FISH-positive or not, would you subject that patient to the potential risks of long-term trastuzumab?

Dr Perez: That is a very good question. Sometimes, technically, it's impossible to obtain a result of the test — even in big laboratories. A CALGB study led by Andy Seidman will help us address this issue (Figure 3). They are enrolling patients with HER2-positive or HER2-negative breast cancer to receive paclitaxel either alone or with trastuzumab. This trial is almost complete, so we'll eventually have an answer. At this point, I have not treated patients with HER2-negative breast cancer with trastuzumab.

We know that a percentage of IHC 2+ tumors are actually FISH-positive. In a study we did at the Mayo Clinic — in more than 200 specimens tested as IHC 2+ (the largest study to date) — we found a 12 percent rate of FISH positivity. More data will be forthcoming in the next couple of years regarding that issue.

Dr Love: Dr Perez, how would you treat this patient?

Dr Perez: The FDA indication for trastuzumab in combination with chemotherapy is based on the pivotal study done with weekly trastuzumab and paclitaxel given every three weeks, which demonstrated improvement in response rate, time to progression, one-year survival, and median survival (Figure 4). Since that pivotal trial was completed, many other Phase II studies have been published, and a Phase III trial led by Dr Nick Robert provides data on carboplatin with paclitaxel and trastuzumab. I would treat this patient first-line with paclitaxel, carboplatin and trastuzumab. I also believe Dr Cohen's decision to use adjuvant TAC chemotherapy at the initial diagnosis was appropriate.

Figure 3. Phase III Randomized Study of Paclitaxel via One-Hour Infusion Every Week versus Three-Hour Infusion Every 3 Weeks with or without Trastuzumab (Herceptin) in Patients with Inoperable, Recurrent, or Metastatic Breast Cancer with or without Overexpression of HER2-Neu — Open Protocol

Protocol ID: CLB-9840, CTSU
Projected Accrual: 580 patients within 3 years

Eligibility: Inoperable, recurrent or metastatic breast cancer with known HER2 status and LVEF at east 45%. Patients are stratified according to prior chemotherapy for metastatic disease and HER2 status.

Group A: HER2-negative		Group B: HER2-positive	
ARM 1	Paclitaxel q 3 w	ARM 5	Paclitaxel q 3 w + trastuzumab q w
ARM 2	Paclitaxel q w	ARM 6	Paclitaxel q w + trastuzumab q w
ARM 3	Paclitaxel q 3 w + trastuzumab q w		
ARM 4	Paclitaxel q w + trastuzumab q w		

Both groups: Courses repeat in the absence of disease progression or unacceptable toxicity. Quality of life is assessed at baseline and then at 3, 6 and 9 months.

SOURCE: NCI Physician Data Query, December 2002; personal communication, CALGB, June 2003.

Dr Love: In which patients with HER2-positive metastatic disease would you use trastuzumab alone or with some other chemotherapy? What about this woman's disease is causing you to use the full triplet?

Dr Perez: Despite the excellent data published by Dr Chuck Vogel using single-agent trastuzumab (Table 5), I've actually never used trastuzumab alone in my practice. If a patient has hormone receptor-positive breast cancer that is HER2-positive, I tend to use hormonal therapy rather than first-line trastuzumab or trastuzumab in combination with hormonal therapy. I try to extend the duration of hormonal therapy as long as possible. In a patient like this, with a rapidly progressive tumor, I want to rely on the best therapy I have with the highest possibility of tumor control right away.

Dr Love: What if this woman was in her 70s rather than her 30s?

Dr Perez: I would use the same approach regardless of the patient's age. Actually, in our original paclitaxel and carboplatin study, we had patients up to 82 years of age. I use the patient's physiological condition, rather than chronologic age, to make these decisions. The velocity of growth and the site of tumor involvement guide my approach.

Dr Love: Nick, what are your thoughts about single-agent trastuzumab, and how would you have thought through this case?

Dr Robert: HER2-positive metastatic breast cancer is usually an aggressive disease, but there are patients in whom it isn't aggressive. In cases of slowly progressing, ER-positive disease, we often give endocrine agents and delay chemotherapy even though chemotherapy might produce a faster response or a higher response rate. Similarly, there will be patients with slowly progressive HER2-positive disease who can be treated with trastuzumab monotherapy for a period of time.

This patient, however, is a young woman with aggressive Stage IV disease. I agree that trastuzumab with chemotherapy is the most appropriate combination, given the pivotal trial data demonstrating that trastuzumab with chemotherapy produces a better response rate, time to progression, and overall survival than chemotherapy alone. Keep in mind that this trial had two chemotherapy arms — doxorubicin/cyclophosphamide/trastuzumab versus paclitaxel/trastuzumab.

Figure 4. Phase III Randomized Study of Chemotherapy with versus without Monoclonal Antibody HER2 in Women with Metastatic Breast Cancer Overexpressing HER2/neu and Previously Untreated with Cytotoxic Chemotherapy (Closed to accrual)

Protocol IDs: GENENTECH-HO648G, NCI-V95-0714

Eligibility Patients with HER2-overexpressing tumors and without prior chemotherapy for metastatic breast cancer

No Prior Anthracyclines → doxorubicin/cyclophosphamide → ARM 1 Trastuzumab
→ ARM 2 No further treatment

Prior Anthracyclines → Paclitaxel → ARM 3 Trastuzumab
→ ARM 4 No further treatment

Clinical Benefit, Duration of Response and Cardiotoxicity in Chemotherapy versus Chemotherapy Plus Trastuzumab Regimens

	AC (n=138)	AC + H (n=143)	Paclitaxel (n=96)	Paclitaxel + H (n=92)	Chemo (total) (n=234)	Chemo (total) + H (n=235)
Median time to progression (months)	6.1	7.8	3.0	6.9	4.6	7.4
Median duration of response (months)	6.7	9.1	4.5	10.5	6.1	9.1
Median survival (months)	21.4	26.8	18.4	22.1	20.3	25.1
Complete + partial response	58/138 42%	80/143 56%	16/96 17%	38/92 41%	74/234 32%	118/235 50%
Any cardiac dysfunction	8%	27%	1%	13%	5%	22%
Severe cardiac dysfunction	3%	16%	1%	2%	2%	10%

A = anthracycline; C = cyclophosphamide; H = trastuzumab

DERIVED FROM: Slamon DJ et al. *NEJM* 2001;344(11):783-792.

The paclitaxel/trastuzumab arm had improvements in response rate and time to progression but, in that subset, there wasn't an overall survival advantage. You had to look at all 400-plus patients in the trial to see an improvement in survival.

For this patient, I would recommend paclitaxel, carboplatin and trastuzumab trial (Figure 5). We did a Phase III randomized trial, building upon the results of the pivotal trial to try to improve the outcome. *In vitro* data demonstrated that carboplatin is synergistic with either paclitaxel or docetaxel. Our trial addressed the very simple question: How does the addition of carboplatin affect outcomes?

We utilized the same schema used in the pivotal trial — paclitaxel every three weeks at 175 mg/m^2 and carboplatin with an AUC of six. Our carboplatin dose was based on some of Edith's work evaluating paclitaxel/carboplatin every three weeks. We were very pleased that this laboratory work was carried through to the bedside.

In our trial of patients with HER2-positive

Figure 5. Phase III Study Comparing Trastuzumab and Paclitaxel with and without Carboplatin in Patients with HER2-positive, Advanced Breast Cancer

HER2-positive, metastatic breast cancer patients with no prior chemotherapy for metastatic disease

n = 96 ↙ ↘ n = 95

HTC: Trastuzumab qw + Paclitaxel/Carboplatin q3w

HT: Trastuzumab qw + Paclitaxel q3w

Study Results

Parameters	HTC Regimen	HT Regimen	*p* Value
Response Rate (RR)	48/92 (52%)	34/94 (36%)	$p = 0.04$
RR in HER2 IHC 3+	35/61 (57%)	23/63 (37%)	$p = 0.03$
Time to progression (TTP)	11.2 months	6.9 months	$p = 0.007$
TTP in HER2 IHC 3+	13.5 months	7.2 months	$p = 0.006$

HTC = trastuzumab, paclitaxel, carboplatin; HT = trastuzumab, paclitaxel

SOURCE: Robert N. Presentation, 2002 San Antonio Breast Cancer Symposium

(IHC 3+) metastatic disease, adding carboplatin to paclitaxel improved response rates to about 57% and doubled the time to progression to 14 months. We also saw an improvement of survival by nine months, although it's not statistically significant. I don't expect to see statistically significant improvement in survival — just as it wasn't seen in the paclitaxel arm of the original pivotal trial — because we only had 191 patients. It's also interesting to note that it took less than two months to see a response. This is a fast-acting regimen, considering that we don't look for measurable disease more than once every two months.

Another important factor is that trastuzumab, like endocrine therapy, may be continued after chemotherapy. The pivotal trial mandated six cycles of chemotherapy, and we designed our trial in very much the same way. Three-quarters of the responding patients stopped chemotherapy after six cycles. In this strategy, chemotherapy is given in a synergistic combination with trastuzumab to induce a remission — in the parlance of leukemia — and after you have achieved the maximum response, then trastuzumab can be continued as maintenance therapy.

Dr Love: What was the tolerability of this combination regimen?

Dr Robert: Generally, this regimen was well-tolerated. We were concerned about myelosuppression from adding carboplatin to paclitaxel, and we did see more neutropenia and thrombocytopenia but no neutropenic fever. There was not an increased incidence of neuropathy. We saw slightly more fatigue, but we did not control for treatment with erythropoietin, so we cannot comment on whether or not this was related to anemia. It is important to note that this was not a dose-dense regimen, and we did not utilize prophylactic growth factors. If the counts were not adequate, then we would dose-reduce or dose-delay, and that partly explains the relatively favorable side-effect profile.

Dr Chittoor: When you give trastuzumab long-term, how do you monitor the cardiac status? I've had three patients who didn't go into failure but had significant decreases in ejection fraction (EF). I checked EFs every six months. I realize that it is touted to be a reversible left ventricular dysfunction. Nonetheless, let us presume you do stop it and the EFs improve. Can you restart trastuzumab again?

Dr Perez: That's a great question. When trastuzumab first became available, the package insert indicated that you should monitor left ventricular ejection fraction. We were routinely doing those evaluations, but we have completely abandoned that in our practice because we haven't seen any correlation between asymptomatic decreases of ejection fraction and the development of congestive heart failure. Now the patients are managed on the basis of their physical symptoms.

In terms of clinical trials, we are doing very intense monitoring not only of left ventricular ejection fraction, but we are also looking at potential serum or plasma markers that may be predictive. Those studies are still in the investigational stages.

One of the challenges we have is that there is really not a database telling us that there's a good correlation even between MUGAs and ECHOs when we look at ejection fractions. There's a vacuum in knowledge, and that's one of the reasons we've abandoned routine evaluation of left ventricular ejection fraction.

It appears that in the few patients who have had endomyocardial biopsies after the development of trastuzumab-induced congestive heart failure, there is no documented anatomical vacuolization. This is very different than what is seen in anthracycline-induced cardiomyopathy, in which you see the vacuoles and can look at the damage. With trastuzumab, there's no damage that is readily seen under the microscope. One of the theories is that this drug may be associated with stunning the myocardium, and many patients improve after decreases in ejection fraction.

One thing that we're learning, just recently, is that this can also happen with chemotherapy. We have become very comfortable using anthracyclines, and we usually do not check ejection fractions. At the ASCO meeting this year, there was a wealth of information regarding this issue. We give AC x 4, the ejection fraction drops; we follow ejection fraction, and a few months later that number improves.

I think we have been sensitized to the issue of trastuzumab. We've been seeing a lot of ejection fractions, and we don't really know how much that translates into the clinical symptomatology of our patients.

Dr Robert: Increasingly, I've heard that people are becoming more comfortable dropping the ventricular ejection fraction evaluation. The argument has been, if trouble arises, it will be early, within the first few months. That's a good reason to initiate that test in the first few months. Afterwards, it doesn't seem to be a problem — unlike with the use of doxorubicin.

What I haven't heard is evidence that the hypothesis is true — whether two or three years later, cardiac functioning is okay. Now, there aren't that many patients who stay on trastuzumab or any regimen for years, but there are a few. If I'm giving a patient a drug that may affect their heart in a deleterious way, I should share those concerns with the patient. For patients who are responding to trastuzumab but develop congestive heart failure, you can continue trastuzumab and treat their cardiac condition with diuretics and ACE inhibitors and maintain a positive quality of life and good cardiac function.

Dr Love: Any comments from the group about the new data that Dr Robert was discussing with regard to carboplatin, docetaxel and trastuzumab?

Dr Firstenberg: We've been a big proponent of using platinums — both cisplatin and carboplatin — in patients with HER2-positive tumors, and then we use trastuzumab and vinorelbine.

Dr Love: Edith, what went into the evolution of using carboplatin versus cisplatin in some of these studies?

Dr Perez: We selected carboplatin based on the tolerability compared to cisplatin. A lower dosage of cisplatin needs to be studied,

but we don't have as much data on that drug, compared to carboplatin.

Dr Robert: The BCIRG has Phase II experience, in which cisplatin and carboplatin were used in combination with trastuzumab, and the response rates are comparable. The patient populations are not the same. (Table 6) Patients who received carboplatin had prior therapy, but the time to progression was longer in the carboplatin group. It's a little bit like comparing "apples and oranges," but I think all of us are convinced that carboplatin is better-tolerated than cisplatin.

Dr Robert: Another question for which we do not have an answer is how long should we continue trastuzumab after first-line therapy? For example, a patient receives carboplatin and paclitaxel, progresses, then you give them vinorelbine and the tumor progresses. Does it make sense to continue evaluating drugs that are either synergistic or additive? Is it time to stop?

We don't have any evidence to direct us. One trial attempted to take patients who failed trastuzumab/taxane therapy and randomize them to vinorelbine versus vinorelbine and trastuzumab. That trial had poor accrual and it's closed. It may resurface as an Intergroup trial.

Another issue is the schedule of trastuzumab. We have pharmacokinetic data from Brian Leyland-Jones that supports giving trastuzumab every three weeks instead of weekly, so our patients do not have to come into the office every week. This was a proof of principle trial, so we didn't become involved with what was the best schedule for administering paclitaxel or carboplatin. We just wanted to demonstrate that adding carboplatin made a difference. Clearly, there are scheduling questions, and Dr Perez can tell us about her experience using weekly paclitaxel/carboplatin and trastuzumab, as opposed to the every-three-week schedule.

Dr Perez: At the NCCTG we have been interested in the taxane/carboplatin and the paclitaxel/carboplatin/trastuzumab combinations for a few years. We are completing a randomized Phase II trial — NCCTG-983252 — in which the basic question was the scheduling of the three drugs (Figure 6).

Dr Robert and colleagues undertook a study that would answer the question of how much carboplatin should be added to paclitaxel/trastuzumab, so we elected to look

Table 6. Results from BCIRG 101 and 102: First-line Therapy in Women with HER2-overexpressing Metastatic Breast Cancer

	Cisplatin/docetaxel/trastuzumab BCIRG 101			Carboplatin/docetaxel/trastuzumab BCIRG 102		
Response Rate	All (N=62)	FISH + (N=35)	FISH - (IHC 2+/3+) (N=19)	All (N=59)	FISH + (N=38)	FISH - (IHC 2+/3+) (N=19)
Overall	79%	77%	84%	56%	64%	41%
Complete	5%	6%	5%	14%	19%	6%
Partial	74%	71%	79%	42%	44%	35%
Median Time to Progression (months)	All (N=62)	FISH + (N=35)	FISH - (N=19)	All (N=59)	FISH + (N=38)	FISH - (N=19)
	9.9	12.7	7.9	12	17	7.4

DERIVED FROM: Nabholtz JM et al. **Results of two open label multicentre phase II pilot studies with Herceptin in combination with docetaxel and platinum salts (Cis or Carboplatin) (TCH) as therapy for advanced breast cancer (ABC) in women with tumors over-expressing the HER2-neu proto-oncogene.** *Eur J Can* 2001;37(suppl 6);190.Poster 695.

Figure 6. Phase II Study of Paclitaxel, Carboplatin and Trastuzumab as First-Line Chemotherapy in Women with Overexpressed HER2, Metastatic Breast Cancer — Open Protocol

Protocol ID: NCCTG-983252
Projected Accrual: 36-92 patients

Eligibility	Women with metastatic HER2-positive (IHC 3+ or FISH+) breast cancer
ARM 1	Paclitaxel + carboplatin day 1 x 8 cycles + trastuzumab weekly x 8 cycles → trastuzumab every week until disease progression
ARM 2	Paclitaxel + carboplatin days 1, 8, 15 x 6 cycles + trastuzumab weekly x 6 cycles → trastuzumab every week until disease progression

ARM 1 1 cycle = 21 days
ARM 2 1 cycle = 28 days
Patients are stratified according to prior adjuvant therapy, ER/PR status, menopausal status and performance status.

Study Contact:
Edith Perez, Chair, Tel: 507-284-2111, North Central Cancer Treatment Group

SOURCE: NCCTG-983252 protocol

at paclitaxel/carboplatin/trastuzumab every-three-weeks versus given on a weekly basis.

In the every-three-week regimen, patients received paclitaxel 200 mg/m^2 and carboplatin with AUC of six. The chemotherapy in the weekly regimen consisted of paclitaxel 80 mg/m^2 with carboplatin AUC of two. The combination was given three out of four weeks. During the fourth week, patients received trastuzumab alone.

Our target accrual is 92 patients and enrollment is nearly completed.

We submitted an abstract to ASCO, documenting a significant difference in tolerability between the two regimens. Although the every-three-week regimen was fairly well-tolerated, we saw myelosuppression, some cases of febrile neutropenia, and some neuropathy.

However, when we looked at the tolerability of the weekly regimen, it was remarkably different in that we essentially did not see any myelosuppression or febrile neutropenia. And the difference in myelosuppression was not only in the white blood cell count but also with anemia. We also saw very few cases of neuropathy. Our conclusion was that we would recommend the weekly regimen be utilized in view of tolerability (Table 7).

The efficacy data on the first 70 patients is quite favorable. This is a randomized Phase II study, so we have to be a little bit careful. This is not really a randomized Phase III comparison of one regimen versus another, but it is a multi-institutional trial in which many of the patients were enrolled in community settings, so the patients actually were not enrolled at the Mayo Clinic.

Although the 95 percent confidence intervals of response rate overlapped a little bit, it's actually much better to give the combination on a weekly schedule rather than every three weeks. We are currently using the weekly regimen in patients, even outside this trial. Based on the data from NCCTG-983252, weekly paclitaxel/carboplatin/trastuzumab has a better therapeutic ratio than using the drugs once every three weeks.

Table 7. NCCTG-983252: Randomized Phase II Trial of Weekly versus Every 3-week Administration of Paclitaxel, Carboplatin and Trastuzumab in Women with HER2-Positive Metastatic Breast Cancer (MBC): Toxicity Data

Grade 3/4 Toxicities	Weekly Regimen (n=34)	Every 3-week Regimen (n=36)	*p*
Neutropenia	56%	86%	<0.01
Thrombocytopenia	3%	36%	<0.01
RBC transfusion	6%	28%	0.02
Neurosensory	3%	22%	0.03
Febrile neutropenia	0%	17%	0.03
Anemia	3%	17%	0.11
Myalgia	0%	17%	0.03
Arthralgia	3%	14%	0.20

CONCLUSION: "The addition of carboplatin to combination therapy with paclitaxel and trastuzumab has recently been demonstrated to significantly improve response rate and time to progression in patients with HER2 positive MBC. (Robert N, et al. *Breast Cancer Res Treat* 2002; 76(suppl 1):S37). Our data demonstrate that the combination of paclitaxel, carboplatin and trastuzumab is better tolerated when administered by the weekly regimen than the every-3-week regimen. Response and survival data will be available in 2003."

SOURCE: Rowland KM et al. **NCCTG 983252: Randomized Phase II trial of weekly versus every 3-week administration of paclitaxel, carboplatin and trastuzumab in women with HER2 positive metastatic breast cancer (MBC).** *Proc ASCO* 2003.

Case follow-up:

- Patient treated with trastuzumab/carboplatin and docetaxel (75 mg/m^2)
- Very rapid clinical improvement; breast became less swollen and painful
- After 3 cycles, no palpable abnormality in breast, ultrasound with marked improvement, pulmonary nodules decreased in size
- Plan is for patient to complete 6 cycles of chemotherapy, undergo breast irradiation, and continue trastuzumab

Select publications: ***Addition of carboplatin to combination chemotherapy for the treatment of metastatic breast cancer***

The addition of carboplatin to trastuzumab/paclitaxel improves efficacy in HER2-overexpressing metastatic breast cancer. *Clin Breast Cancer* 2003;3(6):378-80.

Alberti AM. **A Phase II study of docetaxel (T) and carboplatin (CBP) as second line chemotherapy in metastatic breast cancer.** *Proc ASCO* 2000:Abstract 438.

Brufsky AM et al. **A phase II study of carboplatin and docetaxel as first line chemotherapy for metastatic breast cancer.** *Proc ASCO* 2002:Abstract 2020.

Crown JP. **The platinum agents: A role in breast cancer treatment?** *Semin Oncol* 2001;28(1 Suppl 3):28-37.

Donaldson LA et al. **A phase I/II study of carboplatin, vinorelbine and capecitabine in patients with metastatic breast cancer.** *Proc ASCO* 2002:Abstract 1960.

Franco S et al. **Neoadjuvant (NEO) treatment of locally advanced and inflammatory breast cancer with weekly taxotere and carboplatin in tumors that do not overexpress HER-2.** *Proc ASCO* 2002:Abstract 2048.

Hanna N et al. **Phase I trial of carboplatin and paclitaxel with escalating doses of oral topotecan in patients with solid tumors.** *Am J Clin Oncol* 2003;26(2):200-2.

Kallab AK et al. **A phase II study of weekly paclitaxel and carboplatin in metastatic breast cancer.** *Proc ASCO* 2002:Abstract 1953.

Kosmas C et al. **Phase I study of vinorelbine and carboplatin combination in patients with taxane and anthracycline pretreated advanced breast cancer.** *Oncology* 2002;62(2):103-9.

Loesch D et al. **Phase II multicenter trial of a weekly paclitaxel and carboplatin regimen in patients with advanced breast cancer.** *J Clin Oncol* 2002;20(18):3857-64.

Martin M. **Platinum compounds in the treatment of advanced breast cancer.** *Clin Breast Cancer* 2001;2(3):190-208;discussion 209.

Mavroudis D et al. **Salvage treatment of metastatic breast cancer with docetaxel and carboplatin. A multicenter phase II trial.** *Oncology* 2003;64(3):207-12.

O'Rourke M et al. **Efficacy and tolerability of a weekly taxol (T) plus carboplatin (C) regimen in patients <65 years versus ? years with advanced breast cancer (ABC).** *Proc ASCO* 2002:Abstract 1967.

Patton JF et al. **Weekly paclitaxel, doxorubicin, and carboplatin in the treatment of metastatic breast cancer: A Minnie Pearl Research Network Phase II trial.** *Proc ASCO* 2001:Abstract 2032.

Robert N et al. **Phase III comparative study of trastuzumab and paclitaxel with and without carboplatin in patients with HER-2/neu positive advanced breast cancer.** *Breast Cancer Res Treat* 2002;Abstract 35.

Robert NJ et al. **Toxicity profiles: A comparative study of Herceptin (trastuzumab) and taxol (paclitaxel) versus herceptin, taxol, and carboplatin in HER-2 positive patients with advanced breast cancer.** *Breast Cancer Res Treat* 2001;Abstract 529.

Rodenhuis S et al. **Randomized Phase III study of high-dose chemotherapy with cyclophosphamide, thiotepa and carboplatin in operable breast cancer with 4 or more axillary lymph nodes.** *Proc ASCO* 2000:Abstract 286.

Slamon DJ et al. **Phase II pilot study of herceptin combined with taxotere and carboplatin (TCH) in metastatic breast cancer (MBC) patients overexpressing the HER2-Neu proto-oncogene a pilot study of the UCLA Network.** *Proc ASCO* 2001:Abstract 193.

Yardley DA et al. **Final results of the Minnie Pearl Cancer Research Network first-line trial of weekly paclitaxel/carboplatin/trastuzumab in metastatic breast cancer.** *Breast Cancer Res Treat* 2002;Abstract 439.

CASE 5: Liver metastases and mild hepatic encephalopathy (from the practice of Dr Barry Brooks)

Presentation:

- This woman in her 40s presented with 2-cm, hard, right breast mass within a 4-cm area of mild erythema and a palpable 2-cm, hard, ipsilateral axillary lymph node
- Breast biopsy revealed a high-grade infiltrating ductal carcinoma
- ER: 70 percent positive with moderate staining, PR: 20 percent positive with moderate staining
- MIB-1 block: 80 percent positive; HER2 1+ by IHC, negative by FISH
- Biopsy of overlying skin revealed lymphatic channels plugged with carcinoma
- Staging scans of chest, abdomen, pelvis and bone were all negative
- CA 27.29 was 48 U/mL

Primary therapy:

- Received neoadjuvant AC x 4, tumor became nonpalpable after the first cycle; patient continued menstruating
- Mastectomy, no residual tumor
- Patient declined recommendation of four cycles of taxane therapy postoperatively
- Received regional radiotherapy and adjuvant tamoxifen
- Three months after beginning adjuvant tamoxifen, patient developed pulmonary embolus
- Warfarin started, tamoxifen continued

Key discussion points:

1. Patient compliance with adjuvant therapy
2. Pulmonary embolus during adjuvant tamoxifen in a premenopausal patient

Dr Perez: The patient's refusal of a postoperative taxane reminds me of the challenge we face when we know the data, we have enough experience to match the data to the patient in front of us, and the patient still refuses our treatment recommendation. This is always a difficult situation because we want our patients to receive the best therapy and to survive this disease, but at the same time, we have to respect their wishes, which is obviously what Dr Brooks did in this situation. When the

disease recurs, we can't help wondering what would have happened if the patient had followed our initial recommendations.

Dr Brooks: Three months after the patient began adjuvant tamoxifen she developed a pulmonary embolus and was hospitalized for about one week. It was significant pulmonary embolus, but being a half-time hematologist, I continued her on tamoxifen and put her on a full dose of warfarin. She was still having regular menstrual periods. Clearly, the four cycles of AC did not ablate her ovaries.

Dr Love: Dr Robert, what would you have done in this situation?

Dr Robert: I would have done everything Dr Brooks did up to the point of the pulmonary embolus. This is retrospective, but in this ER-positive, premenopausal woman on tamoxifen, when she had her pulmonary embolus, I would have had her ovaries removed. This cancer is behaving a bit aggressively, and there is a meta-analysis of randomized trials looking at ovarian ablation via LHRH analog plus or minus tamoxifen that shows the combination is better (Table 8). One could extrapolate and use an aromatase inhibitor. Today, I would consider the options of tamoxifen plus Coumadin® versus a bilateral oophorectomy, and then add an aromatase inhibitor when she progresses.

Dr Love: Dr Brooks, can you give us some more follow-up on this patient?

Dr Brooks: One year after completing her radiation therapy, her tumor markers were elevated. We did not suspect hepatic metastases, and her liver was not easily palpable; however, her liver function tests were markedly elevated, and a CT scan of her abdomen showed very extensive and impressive disease.

Case continued:
One year after radiation therapy, while on tamoxifen

- Patient was asymptomatic but CA 27.29 was 186 U/mL; CT scan of the abdomen showed extensive hepatic metastasis
- Liver function studies were abnormal — elevated alkaline phosphatase, bilirubin 1.8, transaminases in the 100s

Dr Love: Dr Robert and Dr Perez, what would you do at this point?

Dr Robert: I saw a similar patient not long ago. Her CA 27.29 was 14,000 U/mL and her liver function studies were abnormal. She was naïve to any chemotherapy, so an anthracycline-based regimen was an option, but I don't routinely use these up front for metastatic disease. I started the patient on weekly carboplatin/paclitaxel and I would have done the same for Dr Brooks' patient. I think there is an advantage to giving the weekly regimen in a patient with increased LFTs in whom you need to be careful about giving a taxane. When you give it weekly, you can see how they react and then decide if they can tolerate day eight or not. If not, you can postpone it, as opposed to giving it every three weeks.

Dr Perez: Regarding the weekly regimen, I think the issue that Nick brings up is appropriate. It's important to remember the relationship between liver enzymes and toxicities associated with taxanes. Clearly, the last thing we want to do is harm the patient.

Case continued: *Patient enrolled in a study comparing carboplatin/paclitaxel versus weekly paclitaxel and randomized to weekly paclitaxel, 90 mg/m²*

- Received 10 doses over 11 weeks, missed one dose because of myelosuppression
- While on treatment, CA 27.29 rose from 186 to 4,600 U/mL; repeat abdominal CT showed massive ascites
- Taken off clinical trial and within two weeks developed hepatic encephalopathy necessitating hospitalization

Dr Love: Dr Brooks, at this point what happened with the patient?

Dr Brooks: At that time, we were participating in a trial comparing carboplatin/paclitaxel versus paclitaxel, and she was randomized to paclitaxel. She received 10 weekly doses, but had a relentless rise in her tumor markers and developed a palpable liver and massive acites. I took her off the clinical trial and while we were discussing what to do next, in sort of a heart-stopping fashion, she developed hepatic encephalopathy and had be hospitalized.

Dr Love: Was this patient so impaired that you couldn't turn to her for a decision as to whether she should be treated?

Dr Brooks: The hepatic encephalopathy happened quickly and caught me off guard. The patient and I hadn't yet discussed what to do in a situation like this. At this point she wasn't in a coma, rather she was alert, but confused. When she took narcotics, she was impaired. Her children were too young, so I had "end-of-life" discussions with her brother and sister. I explained that I didn't think we would be able to alter her course with treatment. They agreed to a DNR order, but they wanted to try one more therapy because of her young age.

Dr Love: Out of curiosity, do most of you try to have those kinds of discussions earlier on? It's such a difficult topic to bring up. Dr Cohen?

Dr Cohen: We encourage patients to execute a Durable Power of Attorney for Healthcare, so at least there will be something on paper identifying a responsible person who can make decisions when the patient is *non compos mentis*. But as in this case, often it's the last item on your agenda, and you don't want it to come up. And then when it does, it's usually not convenient. So we tend to put it off more than we should.

Dr Love: You had a very difficult human decision to make at this point. Nick, what do you think you would have done?

Dr Robert: Let me just say that what's even worse is being the on-call oncologist when this patient comes in and you don't even know them. It's a very unpleasant conversation to have with patients. You send a mixed message, saying, "We're trying to make you better," and then adding, "but what do you want us to do when you're near your death?" It is easier to have that discussion in the office when the patient isn't doing so well, and it's easier to deal with the family then as well.

At this point, if you are going to treat the patient, you're looking for a "Hail Mary" intervention. I've heard anecdotes of similar patients having good responses. With all the options you have after that, I wouldn't start with capecitabine, but I would consider liposomal doxorubicin HCL, vinorelbine, and gemcitabine.

Dr Love: Dr Perez, the patient has a bilirubin of 18. What would you have done at this point?

Dr Perez: This is a very difficult situation from an ethical perspective. If I were going to treat this patient, I would use capecitabine, because it is not metabolized in the liver — that's assuming she still has good renal function. However, my general approach is not to treat a patient with chemotherapy unless the patient can understand the risk/benefit ratio.

Dr Harth: I agree with Dr Perez, I wouldn't treat this patient without her understanding the implications. But even if she did understand, I would have serious reservations about treating her given her performance status and abnormal liver functions. I would do everything possible to explain to her and her family that even though we have drugs available, I don't think they would offer her anything in terms of response, and they have a lot of toxicity.

Dr Capistrano: I agree with Dr Harth. It would be very difficult for me to treat this patient with chemotherapy. I think chemotherapy is something patients have to participate in, in terms of whether they want to continue therapy or not. This patient's performance status and abnormal laboratory data almost preclude you from giving chemotherapy.

Dr Chittoor: I would not treat this patient. I believe that from day one, this patient did not have good insight into her disease or the implications of treatment. I don't believe treatment is justified in this case.

Dr Say: I agree. It's difficult to obtain an informed consent when the patient is confused. In my experience, I've found the primary care doctor can be very helpful at this point in obtaining a Durable Power of Attorney. They have a long-term relationship with the patient, and we can invoke their help.

Dr Love: Dr Brooks, can you give us a follow-up on what happened?

Dr Brooks: I didn't really think of capecitabine as chemotherapy because of the favorable risk/benefit ratio. While I feel patients need to consent to chemotherapy, this family was pushing for treatment, and capecitabine seemed like a good in-between solution. I gave a "Hail Mary" round of capecitabine at a generous dose, and within three weeks her bilirubin dropped to 3.2, her ascites resolved, and she went home.

Frankly, I was treating the family more than the patient when this unexpected response occurred. She had one of the most dramatic and fastest responses to capecitabine that I've ever seen.

Case follow-up:

- The patient did well for five months, but then experienced right upper quadrant pain
- CA 27.29 rose to 1100 U/mL
- Patient switched to hormonal therapy with goserelin
- CT scan and tumor markers are stable, although she still has abnormal liver function that may be unrelated to the breast cancer

Select publications: *Capecitabine in metastatic breast cancer*

Capecitabine/bevacizumab compared to capecitabine alone in pretreated metastatic breast cancer: Results of a Phase III study. *Clin Breast Cancer* 2003;3(6):375-7.

Ahn Sr J et al. **Phase II study of a combination chemotherapy of capecitabine and vinorelbine in metastatic breast cancer with previous exposure to anthracycline and taxane: Preliminary results.** *Proc ASCO* 2002: Abstract 2030.

Andres R et al. **Capecitabine plus gemcitabine is an active combination for patients with metastatic breast cancer refractory to anthracyclines and taxanes.** *Proc ASCO* 2003;Abstract 356.

Bauer-Kosinska B et al. **Capecitabine monotherapy in the treatment of patients with chemotherapy pre-treated metastatic breast cancer.** *Proc ASCO* 2003;Abstract 320.

Biganzoli L et al. **Moving forward with capecitabine: A glimpse of the future.** *Oncologist* 2002;7(Suppl 6):29-35.

Blum J. **The role of capecitabine, an oral, enzymatically activated fluoropyrimidine, in the treatment of metastatic breast cancer.** *Oncologist* 2001;6(1):56-64.

Chan S et al. **A phase II study on an all-oral regimen of capecitabine (Xeloda™) (X), idarubicin (I) and cyclophosphamide (C) (XIC) for metastatic breast cancer — Safety, efficacy and quality of life.** *Proc ASCO* 2002: Abstract 2023.

Crown J. **Nonanthracycline containing docetaxel-based combinations in metastatic breast cancer.** *Oncologist* 2001;6(Suppl 3):17-21.

Fumoleau P et al. **Capecitabine (Xeloda) in patients with advanced breast cancer (ABC), previously treated with anthracyclines and taxanes: Results of a large phase II study.** *Proc ASCO* 2002: Abstract 247.

Ghosn M et al. **Vinorelbine (Navelbine) IV and capecitabine (VINOCAP) as front line chemotherapy in metastatic breast cancer (MBC).** *Proc ASCO* 2002: Abstract 1978.

Gligorov J et al. **Capecitabine and oral vinorelbine in metastatic breast cancer: Preliminary experience.** *Proc ASCO* 2003;Abstract 351.

Kaklamani VG, Gradishar WJ. **Role of capecitabine (Xeloda) in breast cancer.** *Expert Rev Anticancer Ther* 2003;3(2):137-44.

Lago S et al. **Quality of life (QoL) in metastatic breast cancer (MBC) patients taking capecitabine.** *Proc ASCO* 2003;Abstract 2994.

Leonard RC et al. **Capecitabine named-patient programme for patients with advanced breast cancer. The UK experience.** *Eur J Cancer* 2002;38(15):2020-4.

Maher JF, Villalona-Calero MA. **Taxanes and capecitabine in combination: Rationale and clinical results.** *Clin Breast Cancer* 2002;2(4):287-93.

Miles D et al. **Combination versus sequential single-agent therapy in metastatic breast cancer.** *Oncologist* 2002;7(Suppl 6):13-9.

O'Shaughnessy J. **Capecitabine and docetaxel in advanced breast cancer: Analyses of a phase III comparative trial.** *Oncology (Huntingt)* 2002;16(10 Suppl 12):17-22.

O'Shaughnessy J. **Clinical experience of capecitabine in metastatic breast cancer.** *Eur J Cancer* 2002;38(Suppl 2):10-4.

O'Shaughnessy JA et al. **Randomized, open-label, phase II trial of oral capecitabine (Xeloda) vs a reference arm of intravenous CMF (cyclophosphamide, methotrexate and 5-fluorouracil) as first-line therapy for advanced/metastatic breast cancer.** *Ann Oncol* 2001;12(9):1247-54.

O'Shaughnessy J et al. **Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: Phase III trial results.** *J Clin Oncol* 2002;20(12):2812-23.

O'Shaughnessy J et al. **Treatment for anthracycline-pretreated metastatic breast cancer.** *Oncologist* 2002;7(Suppl 6):4-12.

Procopio G et al. **A Phase II study of capecitabine in elderly patients with advanced breast cancer.** *Proc ASCO* 2001:Abstract 3134.

Procopio G et al. **Safety and activity of capecitabine in elderly patients (pts) with advanced breast cancer (ABC).** *Proc ASCO* 2003;Abstract 3050.

Scarfe AG et al. **Interim results of a phase II study of weekly docetaxel (Taxotere®) combined with intermittent capecitabine (Xeloda®) for patients with anthracycline pre-treated metastatic breast cancer.** *Proc ASCO* 2002:Abstract 1984.

Seidman AD. **Monotherapy options in the management of metastatic breast cancer.** *Semin Oncol* 2003 Apr;30(2 Suppl 3):6-10.

Seidman AD et al. **Single-agent capecitabine: A reference treatment for taxane-pretreated metastatic breast cancer?** *Oncologist* 2002;7(Suppl 6):20-8.

Semiglazov TY et al. **Oral capecitabine (Xeloda) in the treatment of anthracycline-refractory, anthracycline and docetaxel-refractory metastatic breast cancer (MBC).** *Proc ASCO* 2002: Abstract 2061.

Soto C et al. **Capecitabine (X) plus docetaxel (T) vs capecitabine plus paclitaxel (P) vs sequential capecitabine then taxane in anthracycline pretreated patients (pts) with metastatic breast cancer: Early results.** *Proc ASCO* 2003;Abstract 28.

Talbot DC et al. **Randomised, phase II trial comparing oral capecitabine (Xeloda) with paclitaxel in patients with metastatic/advanced breast cancer pretreated with anthracyclines.** *Br J Cancer* 2002;86(9):1367-72.

Venturini M et al. **Capecitabine in combination with docetaxel and epirubicin in patients with previously untreated, advanced breast carcinoma.** *Cancer* 2003;97(5):1174-80.

Wagstaff AJ et al. **Capecitabine: A review of its pharmacology and therapeutic efficacy in the management of advanced breast cancer.** *Drugs* 2003;63(2):217-36.

Wilke H. **Future treatment options with capecitabine in solid tumours.** *Eur J Cancer* 2002;38 (Suppl 2):21-5.

CASE 6: Ascites and pleural effusion ten years after primary breast cancer (from the practice of Dr Narayana Pillai)

- 1989: 5-cm ER/PR-negative, right breast cancer, treated with mastectomy, axillary node dissection (negative nodes); received FAC x 8 chemotherapy and regional radiation therapy
- 2000: Patient is now in her 60s and asymptomatic; pleural effusion detected on clinical examination, confirmed by CT of the chest
- Bone scan, CBC, liver function studies normal
- CT of the abdomen and pelvis showed ascites, enlarged uterus and retroperitonial lymph nodes; ovaries not visible
- CA.125 = 20,728 U/mL; CA 27.29 = 355 U/mL; CEA = 0.8 ng/mL
- Thoracentesis showed poorly differentiated carcinoma, most likely an adenocarcinoma but unable to determine whether the primary tumor was breast or ovarian

Key discussion points:

1. The utility of tumor markers in breast cancer management
2. Differential diagnosis: Metastatic breast cancer versus advanced ovarian cancer
3. Treating a patient with advanced disease and an unknown site of origin
4. Discordance between primary and metastatic hormone receptors
5. Treatment of the postmenopausal patient with ER/PR-positive metastatic disease

Dr Pillai: I don't usually follow tumor markers in my practice because they may become elevated three or four months before a clinical diagnosis is made and, in a stage IV situation, I don't think that makes a big difference in the treatment outcome. But in this patient, since I thought that she might have an ovarian primary, I decided to do markers.

Dr Argawal: A CA.125 of 20,000 U/mL screams ovarian cancer.

Dr Love: Nick, what do we know about CA.125 in breast cancer?

Dr Robert: CA.125 can be elevated in all the epithelial cancers, but tumor markers are selected based on a particular tumor. For example, an elevated CA 27.29 is more typical of breast cancer. I would agree that this patient's tumor marker profile is certainly consistent with ovarian cancer.

Dr Love: Edith, have you ever heard of a CA.125 as high as 20,000 U/mL in breast cancer?

Dr Perez: No, I haven't.

Dr Brooks: I do markers on all my breast cancer patients, specifically CA 27.29, but inadvertently some patients are also tested for CA.125. I don't think I've ever seen results in the range of 20,000 U/mL, but I have seen results in the thousands. I know it's anecdotal and totally random, but I've ended up with these high numbers in my metastatic breast cancer patients, ordered sonograms of ovaries and everything else, but it turns out to be breast cancer.

Dr Aks: The lack of fidelity of these tumor markers is a genuine issue. I certainly see markedly elevated levels of CA.125 in patients with non-small cell lung carcinoma. This particular patient could have colon cancer with carcinomatosis. You definitely have to go after some tissue and do a full characterization.

Dr Pillai: I'm old fashioned in that I still try to make the diagnosis at the bedside. My clinical impression was that this patient had ovarian cancer because of the pleural effusion, negative disease in the liver, and the fact that 11 years had passed since her breast cancer diagnosis. However, I did not want to treat her without a tissue diagnosis, and I felt the easiest way to obtain tissue was a thoracentesis. The results showed a poorly differentiated carcinoma, probably an adenocarcinoma, but the pathologists couldn't say whether it was from the breast or ovary.

Dr Perez: In a case like this, I would take the CT scans to the radiologist and request a pleural biopsy. To make a diagnosis by cytology alone is very difficult. It may be easier with a core biopsy.

Dr Robert: There's a breast cystic protein stain that could be performed on the primary tumor and then the fluid to see if it's positive, but I don't know if I'd hang my hat on it. I think the biggest mistake we can make in a case like this is to assume the patient has recurrent breast cancer because of her history, and miss a diagnosis. Where I was trained, we were instructed "if there's an issue, get some tissue." My initial impression is that this woman has ovarian carcinoma, but we have to establish a tissue diagnosis. She could have pseudo-Meig's syndrome, which is malignant pleural effusion associated with ovarian carcinoma. The bottom line is you need to get some tissue.

Dr Aks: If the retroperitonial lymphadenopathy is accessible by CT scan, a fine needle aspiration may be possible for diagnosis.

Dr Harth: The strong suspicion is that this patient has ovarian cancer. The next approach would be to enter her abdomen in some manner to establish a tissue diagnosis, but I don't know whether a laparoscopy would be realistic with such ascites. Therefore, I think we would have to treat her assuming she has ovarian cancer.

Dr Brooks: This patient has a large uterus, and they can't see the ovaries. I think if she has a gynecologic malignancy, it's more likely to be endometrial cancer.

Dr Cohen: I'd do a PET scan to see if you can identify the ovaries. That would help you decide whether you needed to perform a laparotomy.

Dr Wilson: I, too, am in favor of obtaining more tissue. I would recommend approaching a gynecologic oncologist with this case and discussing the idea of doing a laparoscopic procedure with the intent of obtaining more tissue. Then, if ovarian cancer is confirmed, debulking could take place as well.

Dr Pillai: My differential diagnoses for this patient included ovarian cancer and metastatic breast cancer. If it was ovarian cancer, it was Stage IV and she was quite symptomatic. I didn't think she would be able to go through a laparotomy. I decided to treat her with a regimen that would work for both breast and ovarian cancer and then consider interval debulking. I gave her three cycles of paclitaxel, 175 mg/m^2 over three hours, and carboplatin at an AUC of six — standard doses for ovarian cancer.

The patient had an excellent clinical response. The pleural effusion and ascites disappeared; the CA.125 dropped to the 500 to 600 U/mL range; the CA 27.29 dropped about 50 percent; and the CT of the abdomen and pelvis were normal, except for a smaller but still bulky uterus. At that point, the gynecologic oncologist consult recommended continuing chemotherapy. The patient received three more courses and developed some neuropathy. At the completion of treatment, the only evidence of disease was a CA.125 of 197 U/mL.

Dr Argawal: This is the kind of response you see in ovarian cancer.

Dr Perez: This is the kind of response we see with paclitaxel and carboplatin in breast cancer as well (Table 9), and while it's great for the patient, it doesn't help us in our differential diagnosis. If she's tolerating the treatment, I would continue therapy.

Dr Robert: If you assume this is a metastatic adenocarcinoma, you can give her carboplatin and a taxane to "cover the waterfront." But if she really has an ovarian cancer, the procedure that most gynecologic oncologists recommend is to debulk the patient. That means not only a laparoscopy but a laparotomy. You can't just treat her broadly with chemotherapy. You still need to know with what you are dealing. When patients are too sick for surgery, the gynecological oncologists will recommend starting chemotherapy and will want to see the patients later. If she has a great response, a laparotomy and debulking procedure can be done after treatment.

Dr Aks: If you obtain additional tissue and it shows a poorly differentiated carcinoma or adenocarcinoma, then the primary site is still unknown. If she has good organ function and performance status, you could fall back on the so-called Vanderbilt regimen, which incorporates paclitaxel, carboplatin and etoposide and covers all the bases.

Dr Firstenberg: I would be interested in seeing whether she has either ovarian cancer or an extraovarian papillary carcinomatosis. I am a principal investigator for a CA.125 antibody trial for which she would be eligible after she goes into remission.

Table 9. Efficacy Data from Phase II Trials Combining Carboplatin and Paclitaxel as First-Line Therapy in Patients with Advanced Breast Cancer

	Fountzilas G et al.	Perez EA et al.	Loesch D et al.
Number of assessable patients	--	50	95
Overall response rate	54%	62%	62%
Complete response	12%	16%	8%
Partial response	42%	46%	54%
Median time to progression	8.6 months	7.3 months	4.8 months
Median survival	20.4 months	--	16 months
12-month survival estimate	--	72%	64%

SOURCE: Fountzilas G et al. **First-line chemotherapy with paclitaxel by three-hour infusion and carboplatin in advanced breast cancer (final report): A Phase II study conducted by the Hellenic Cooperative Oncology Group.** *Ann Oncol* 1998;9(9):1031-4.

Perez EA et al. **A Phase II study of paclitaxel plus carboplatin as first-line chemotherapy for women with metastatic breast carcinoma.** *Cancer* 2000;188:124-31.

Loesch D et al. **Phase II multicenter trial of a weekly paclitaxel and carboplatin regimen in patients with advanced breast cancer.** *J Clin Oncol* 2002;20:3857-64.

Dr Pillai: After the chemotherapy, a hysterectomy and bilateral salpingo-oophorectomy revealed microscopic residual breast cancer in the uterus, ovaries and fallopian tubes. The hormone receptors were positive. I believe it's the same breast cancer, but I think the methodology for testing has changed.

Dr Perez: The problem of discordance in hormone receptors between a primary and metastatic site is not uncommon. A presentation at ASCO addressed this and reported a discordance rate of almost 25 percent. In our practice, it's becoming increasingly common to obtain biopsies when patients develop metastatic disease and re-test the hormone status. We do this not only because we're interested in hormone receptors, but also to test the tumors for HER2.

Just this week I saw a similar case of a 47-year-old patient who had breast cancer nine years ago. Originally the tumor was ER/PR-negative. When it recurred in the pleural fluid, it was ER-positive. She was then treated with an aromatase inhibitor and the disease was controlled for one year. Now she has progressive disease, and we'll perform another biopsy in order to help us decide how best to treat her today.

Dr Robert: When Dr Pillai's patient was diagnosed 14 years ago, she might have had a charcoal ligand method used to assess her hormone receptor status. This older method was associated with a false-negative rate, especially in premenopausal women, because they were only looking at unoccupied receptors. The tip-off was that sometimes you would get ER-negative, PR-positive phenotypes. If an immunohistochemistry had been done on the original blocks, it might have been positive rather than negative. Dr Perez's example, on the other hand, is a bit more recent, and it might have been tested by immunohistochemistry the first time around.

Dr Perez: At this point, I would treat this patient with an aromatase inhibitor rather than tamoxifen in view of the improved response rate and, in at least one trial, survival, when compared in the metastatic setting. She has already experienced toxicity from chemotherapy. It would be easier to maintain her quality of life with a hormonal therapy than further chemotherapy.

Dr Robert: I would do the same, and I would use either letrozole or anastrozole. This is a great case in which the physician treated the patient wisely, and he continued to ask questions that led to better outcomes for the patient. Now we have the opportunity to stop chemotherapy because we know she's receptor-positive. I agree that the aromatase inhibitors would be a better choice than tamoxifen, but if she progresses, a number of hormonal alternatives can be tried. When necessary, she can be switched from a nonsteroidal aromatase inhibitor to a steroidal aromatase inhibitor, tamoxifen, fulvestrant, high-dose estrogens, or androgens.

Dr Pillai: At the time of surgery, the patient was 60 years old, her performance status was excellent and she had good family support. I gave her only six courses of chemotherapy preoperatively and was able to do so within a period of about four months. She still had an elevated CA.125 of 197 U/mL, so I felt that I should give her more chemotherapy. I did not want to use a taxane because of the peripheral neuropathy. I had previously given her doxorubicin, up to 400 mg/m^2, so I was concerned about cardiac toxicity.

I elected to treat her with a protocol first published by Dr Hainsworth from Vanderbilt called the NFL regimen, which is a combination of mitoxantrone, 5-FU and leucovorin. It's an easy protocol to use, and it doesn't cause alopecia or peripheral neuropathy. Myelosuppression is a little more than what you see with a paclitaxel-based combination. After I gave her six courses, her CA.125 was normal. I then started her on tamoxifen.

Select publications: *Treatment of carcinoma of unknown primary origin*

Culine S et al. **Alternative bimonthly cycles of doxorubicin, cyclophosphamide, and etoposide, cisplatin with hematopoietic growth factor support in patients with carcinoma of unknown primary site.** *Cancer* 2002;94(3):840-6.

Elkordy M et al. **A phase II study of weekly paclitaxel (Taxol®) and carboplatin in advanced carcinoma of unknown primary origin.** *Proc ASCO* 2001:Abstract 1603.

Fizazi K et al. **Carcinoma of unknown primary (CUP): Are the tyrosine kinase receptors HER-2, EGF-R, and c-Kit suitable targets for therapy?** *Proc ASCO* 2003;Abstract 3549.

Greco FA et al. **Carcinoma of unknown primary site.** *Cancer* 2000;89(12):2655-60.

Greco FA et al. **Carcinoma of unknown primary site: Phase II trials with docetaxel plus cisplatin or carboplatin.** *Ann Oncol* 2000;11(2):211-5.

Greco FA et al. **Gemcitabine, carboplatin, and paclitaxel for patients with carcinoma of unknown primary site: A Minnie Pearl Cancer Research Network study.** *J Clin Oncol* 2002;20(6):1651-6.

Greco FA et al. **Taxane-based chemotherapy for patients with carcinoma of unknown primary site.** *Cancer J* 2001;7(3):203-12.

Guardiola E et al. **Combination of cisplatin-doxorubicin-cyclophosphamide in adenocarcinoma of unknown primary site: A phase II trial.** *Am J Clin Oncol* 2001;24(4):372-5.

Hainsworth JD et al. **Gemcitabine in the second-line therapy of patients with carcinoma of unknown primary site: A phase II trial of the Minnie Pearl Cancer Research Network.** *Cancer Invest* 2001;19(4):335-9.

Hainsworth JD, Greco FA. **Management of patients with cancer of unknown primary site.** *Oncology (Huntingt)* 2000;14(4):563-74;discussion 574-6, 578-9.

Karapetis CS et al. **Epirubicin, cisplatin, and prolonged or brief infusional 5-fluorouracil in the treatment of carcinoma of unknown primary site.** *Med Oncol* 2001;18(1):23-32.

Macdonald AG et al. **A phase II study of mitomycin C, cisplatin and continuous infusion 5-fluorouracil (MCF) in the treatment of patients with carcinoma of unknown primary site.** *Br J Cancer* 2002;86(8):1238-42.

Mahomed R et al. **Age as a prognostic factor in metastatic cancer of unknown primary (CUP). Long term follow up results.** *Proc ASCO* 2003;Abstract 3590.

Mukai H et al. **A safety and efficacy trial of docetaxel (D) and cisplatin (P) in patients with cancer of unknown primary (CUP).** *Proc ASCO* 2003;Abstract 2597.

Saghatchian M et al. **Carcinoma of an unknown primary site: A chemotherapy strategy based on histological differentiation – Results of a prospective study.** *Ann Oncol* 2001;12(4):535-40.

Sumi H et al. **Treatable subsets in cancer of unknown primary origin.** *Proc ASCO* 2000:Abstract 2279D.

Veach SR et al. **Cancer of unknown primary, trends in diagnosis and care.** *Proc ASCO* 2003;Abstract 2238.

Voog E et al. **Multicentric phase II study of cisplatin and etoposide in patients with metastatic carcinoma of unknown primary.** *Am J Clin Oncol* 2000;23(6):614-6.

Post-test: Meet the Professors

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **Two large retrospective studies suggest that pregnancy increases the risk of breast cancer relapse.**
   a. True
   b. False

2. **Two Italian studies comparing patients who had serum markers followed versus those who did not, found:**
   a. The markers predicted in which patients cancer was going to recur
   b. A serially rising serum marker was associated with an 80 percent likelihood of developing metastases
   c. There was no difference in outcome between the two patient groups
   d. All of the above

3. **In the Phase III trial of docetaxel/capecitabine combination therapy versus docetaxel monotherapy in metastatic breast cancer, the combination therapy significantly improved survival.**
   a. True
   b. False

4. **Dr Robert presented data at the 2002 San Antonio Breast Cancer Symposium on a Phase III study comparing trastuzumab (H) and paclitaxel (T) with and without carboplatin (C) in patients with HER2-positive, advanced breast cancer that showed:**
   a. Improved response rate and time to progression in the group receiving HTC
   b. Improved response rate but decreased time to progression in the group receiving HTC
   c. Improved response rate and time to progression in the group receiving HT
   d. Improved response rate but decreased time to progression in the group receiving HT

5. **In a randomized Phase III trial comparing docetaxel dosing of 60 mg/m^2 to 75 mg/m^2 to 100 mg/m^2, which dose was found to have the best efficacy along with manageable toxicities?**
   a. 60 mg/m^2
   b. 75 mg/m^2
   c. 100 mg/m^2

6. **Clinical trials have demonstrated that the benefit of trastuzumab is greater for patients with IHC 3+ positivity compared to FISH-positivity.**
   a. True
   b. False

7. **In a Phase III trial comparing chemotherapy to chemotherapy plus trastuzumab in patients with HER2-positive metastatic breast cancer, the addition of trastuzumab resulted in:**
   a. Improved response rate
   b. Improved time to progression
   c. Improved median survival
   d. All of the above

8. **In discussing the evolution of using carboplatin versus cisplatin in breast cancer, Dr Perez states that carboplatin was selected primarily based on its improved tolerability.**
   a. True
   b. False

9. **NCCTG-983252, which evaluated administering paclitaxel/carboplatin/trastuzumab every-three-weeks versus weekly, demonstrated that the following regimen was better tolerated:**
   a. Weekly regimen
   b. Every-3-week regimen

10. **A meta-analysis of four randomized trials show the combination of tamoxifen and luteinizing hormone-releasing hormone (LHRH) agonist is less effective than a LHRH agonist alone in premenopausal women with advanced breast cancer.**
    a. True
    b. False

Post-test Answer Key: 1b, 2d, 3a, 4a, 5c, 6b, 7d, 8a, 9a, 10b

Evaluation Form: Meet the Professors

NL Communications Inc respects and appreciates your opinions. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please complete this evaluation form. A certificate of completion is issued only upon receipt of a completed evaluation form.

Please answer the following questions by circling the appropriate rating:
5 = Outstanding 4 = Good 3 = Satisfactory 2 = Fair 1 = Poor

LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

- Describe and implement a management strategy integrating chemotherapy, endocrine therapy and biologic therapy in the treatment of women with metastatic breast cancer 5 4 3 2 1
- Determine the clinical implications of emerging data on the use of platinum analogs in combination with chemotherapy in the management of women with metastatic breast cancer 5 4 3 2 1
- Determine the role of trastuzumab as part of these combination chemotherapeutic regimens for patients diagnosed with HER2-positive metastatic breast cancer 5 4 3 2 1
- Determine the appropriate use of follow-up studies to monitor progression in patients with primary and metastatic breast cancer 5 4 3 2 1

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of Subject Matter	Effectiveness as an Educator
Edith Perez, MD	5 4 3 2 1	5 4 3 2 1
Nicholas Robert, MD	5 4 3 2 1	5 4 3 2 1
Andrew Seidman, MD	5 4 3 2 1	5 4 3 2 1
Debu Tripathy, MD	5 4 3 2 1	5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

Objectives were related to overall purpose/goal(s) of activity 5 4 3 2 1

Related to my practice needs 5 4 3 2 1

Will influence how I practice 5 4 3 2 1

Will help me improve patient care 5 4 3 2 1

Stimulated my intellectual curiosity 5 4 3 2 1

Overall quality of material 5 4 3 2 1

Overall, the activity met my expectations 5 4 3 2 1

Avoided commercial bias or influence 5 4 3 2 1

Evaluation Form: Meet the Professors

Please Print Clearly

Name: _____

Specialty: _____ ME#: _____ Last 4 digits of SS# (required): _____

Street Address: _____Box/Suite: _____

City: _____ State: _____ Zip Code: _____

Phone Number: _____ Fax Number: _____Email: _____

NL Communications Inc designates this educational activity for a maximum of 4 category 1 credits towards the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent on the activity. I certify my actual time spent to complete this educational activity to be ___ hour(s).

Signature: _____

Will the information presented cause you to make any changes in your practice?

____Yes ____No

If Yes, please describe any change(s) you plan to make in your practice as a result of this activity.

_____

_____

What other topics would you like to see addressed in future educational programs?

_____

_____

What other faculty would you like to hear interviewed in future educational programs?

_____

_____

Degree:

☐ MD ☐ DO ☐ PharmD ☐ RN ☐ NP ☐ PA ☐ BS ☐ Other _____

To obtain a certificate of completion and receive credit for this activity, please complete the post-test, fill out the evaluation form and mail or fax both to: NL Communications Inc, 400 SE Second Avenue, Suite 401, Miami, FL 33131-2117, FAX 305-377-9998.