Research To Practice: Chemotherapy in Metastatic Disease

The Patterns of Care Study indicates that key factors determining choice of systemic treatment in the metastatic setting are patient age, performance status, site of disease, and ER and HER2 assay results. Endocrine therapy alone is generally utilized in patients with good performance status and ER-positive tumors. Trastuzumab, usually in combination with chemotherapy, is widely utilized as first-line therapy for women with HER2-positive disease. A key issue in selection of chemotherapy is the choice between sequential single agents and combinations. Oncologists often use single agents for patients with good performance status, and the decisions regarding sequencing vary. Side-effect profiles alter choices in individual situations. Anthracycline-based regimens are commonly utilized in patients who have not previously received adjuvant chemotherapy. The combination of docetaxel and capecitabine is frequently utilized in women who have previously received chemotherapy.

CHEMOTHERAPY FOR ASYMPTOMATIC PATIENTS WITH METASTASES: PRIOR AC → DOCETAXEL

The patient is a woman treated two years ago with adjuvant AC → docetaxel for an ER-negative, HER2-negative tumor who now has rising tumor markers and asymptomatic bone metastases. What is your first-line treatment for this patient and your second-line treatment if she had objective progression over several months but was clinically the same?

	Age 40 (premenopausal)		Age 57		Age 75	
	1st-line	2nd-line	1st-line	2nd-line	1st-line	2nd-line
Capecitabine + docetaxel	6%	3%	6%	4%	2%	2%
Docetaxel	8%	6%	7%	6%	4%	6%
Paclitaxel	13%	6%	16%	5%	14%	4%
Carboplatin + taxane	13%	4%	10%	4%	2%	1%
Capecitabine	24%	22%	26%	24%	35%	25%
Gemcitabine	18%	18%	17%	21%	16%	24%
Vinorelbine	6%	25%	7%	20%	8%	23%
Carboplatin	—	1%	—	1%	—	1%
AC	2%	3%	1%	4%	—	—
AC + paclitaxel	1%	—	1%	—	—	—
Doxorubicin	—	1%	—	1%	—	—
Other chemotherapy	3%	7%	4%	6%	3%	2%
No chemotherapy	6%	4%	5%	4%	16%	12%

CHEMOTHERAPY FOR SYMPTOMATIC PATIENTS WITH METASTASES: PRIOR AC → DOCETAXEL

Same patient but with bone and lung metastases and is very symptomatic.

	Age 40 (premenopausal)		Age 57		Age 75	
	1st-line	2nd-line	1st-line	2nd-line	1st-line	2nd-line
Capecitabine + docetaxel	11%	10%	11%	10%	6%	3%
Docetaxel	1%	2%	1%	2%	6%	4%
Paclitaxel	9%	1%	10%	1%	23%	2%
Carboplatin + taxane	33%	2%	32%	2%	9%	—
Capecitabine	4%	23%	5%	25%	20%	37%
Gemcitabine	9%	28%	9%	28%	16%	24%
Vinorelbine	2%	21%	3%	21%	7%	25%
AC	3%	1%	2%	1%	1%	—
AC + docetaxel	3%	—	3%	—	—	—
AC + paclitaxel	3%	—	3%	—	—	—
Cyclophosphamide	1%	—	1%	—	—	—
Other chemotherapy	21%	12%	20%	10%	12%	4%
No chemotherapy	—	—	—	—	—	1%

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

TREATMENT OF CHEMOTHERAPY-NAÏVE PATIENTS WITH RECEPTOR-NEGATIVE DISEASE

The patient is a 57-year-old woman with no prior systemic therapy who has an ER-negative, HER2-negative tumor with metastases. What are your first- and second-line treatment recommendations in the following clinical scenarios?

	Rising tumor markers, asymptomatic bone metastases		Symptomatic bone and lung metastases	
	1st-line	2nd-line	1st-line	2nd-line
Capecitabine + docetaxel	4%	4%	14%	5%
Docetaxel	16%	17%	7%	15%
Paclitaxel	18%	8%	3%	10%
Platinum + taxane	4%	5%	17%	8%
Capecitabine	14%	19%	—	11%
Gemcitabine	—	18%	—	15%
Vinorelbine	—	16%	—	10%
AC	15%	5%	22%	9%
AC + docetaxel	13%	—	27%	1%
Other chemotherapy	10%	5%	10%	16%
No chemotherapy	6%	3%	—	—

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2004;1(2).

TREATMENT OF PATIENTS WITH RECEPTOR-NEGATIVE DISEASE AFTER ADJUVANT AC → PACLITAXEL

The patient is a 57-year-old woman who previously received adjuvant AC → paclitaxel who has an ER-negative, HER2-negative tumor with metastases. What are your first- and second-line treatment recommendations in the following clinical scenarios?

	Rising tumor markers, asymptomatic bone metastases		Symptomatic bone and lung metastases	
	1st-line	2nd-line	1st-line	2nd-line
Capecitabine + docetaxel	9%	2%	41%	7%
Docetaxel	29%	14%	10%	5%
Paclitaxel	8%	4%	1%	1%
Platinum + taxane	6%	3%	24%	4%
Capecitabine	20%	19%	1%	17%
Gemcitabine	9%	26%	6%	31%
Vinorelbine	7%	18%	—	21%
AC	—	2%	1%	1%
AC + docetaxel	3%	—	4%	—
Other chemotherapy	2%	8%	12%	13%
No chemotherapy	7%	4%	—	—

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2004;1(2).

SELECT PUBLICATIONS

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CAPECITABINE/PACLITAXEL TRIAL IN METASTATIC DISEASE

We are currently investigating capecitabine, 1,650 mg/m^2 total daily dose, for 14 days with paclitaxel 80 mg/m^2, days one and eight of a three-week cycle in patients with metastatic breast cancer. The regimen has been extremely well tolerated and the side effects we have seen have been those we expected from paclitaxel — some alopecia, fluid retention, Grade I neuropathy, skin and nail changes — but capecitabine doesn't seem to add much to the toxicity and the clinical benefit is extraordinary. We have had some patients on this trial for one to two years.

In the taxane-naïve subset, we found this regimen to be exceedingly effective and well tolerated. It's been more difficult to accrue patients who have taken a taxane, so we don't have that data yet. However, this is an ideal trial for patients who have received docetaxel in the past and progressed.

We have seen long, durable responses with capecitabine/paclitaxel, and it is more tolerable than capecitabine/docetaxel. Capecitabine has also been combined with vinorelbine, which is also a very well-tolerated regimen.

— Joanne L Blum, MD, PhD

SELECTION OF CHEMOTHERAPY IN THE METASTATIC SETTING

I think I am consistent with the responses to the survey in that I am remarkably inconsistent and do not follow a single regimen. Little evidence exists to suggest that any one chemotherapy regimen provides a meaningful advantage in terms of response rates, duration of response, survival and so on, relative to other combinations or single agents.

I tend to discuss what she expects from her treatment, how much toxicity she is willing to tolerate and when she would be willing to do so; however, in an asymptomatic woman I try to minimize toxicity. Why should I make a woman sick when she feels well?

In the asymptomatic patient with chemotherapy-naïve disease, I often start with an agent such as capecitabine regardless of her age; however, I can't be critical of the choices that have been made. My second-line therapy tends to be a taxane.

— Robert W Carlson, MD

There are several combinations for which good data exists, including capecitabine/docetaxel and paclitaxel/gemcitabine. The doxorubicin/docetaxel combination improved response rate but didn't improve overall survival. Since George Sledge's ECOG trial 1193, demonstrated sequential therapy was as good as combination treatment in terms of overall survival, I tend to use sequential single agents for the vast majority of my patients.

In a patient who is chemo-naïve and needs a rapid response, I would consider an anthracycline-based combination regimen. It would probably be doxorubicin/docetaxel, but it could also be doxorubicin/paclitaxel. If a patient had dose-dense AC/paclitaxel in the adjuvant setting, I'd be very interested in incorporating a gemcitabine-based combination or a capecitabine-based combination. I use a lot of capecitabine. I think it's a great drug. It's generally well-tolerated when given at non-package-insert doses.

For the patient who's had adjuvant AC → T, I frequently use capecitabine or vinorelbine as first-line therapy. For someone who's chemo-naïve, my first choice would probably be weekly paclitaxel followed by either vinorelbine or capecitabine.

I seldom use early-line doxorubicin up front in my asymptomatic patients, because I think it causes a lot of fatigue and alopecia. Weekly paclitaxel also results in alopecia, but I prefer to use weekly paclitaxel more than doxorubicin in the metastatic setting.

— Maura N Dickler, MD