Combination Chemotherapy Regimens for Metastatic Disease

28TH ANNUAL San Antonio Breast Cancer Symposium 21

In E1193, the Phase III trial comparing sequential single-agent and combination chemotherapy, patients treated with doxorubicin/paclitaxel did not have an improvement in overall survival. In contrast, two Phase III trials comparing nonsequential single-agent and combination chemotherapy reported an improvement in overall survival in patients receiving capecitabine/docetaxel or gemcitabine/paclitaxel, although neither trial included crossover for the single-agent arm. Capecitabine/paclitaxel, a regimen with encouraging results, has been evaluated in two Phase II trials. Breast cancer clinical investigators generally support the use of sequential single-agent chemotherapy in most patients with metastatic disease. Ongoing clinical trials will define the role for combination regimens, which may also include biologics.

PHASE III TRIALS COMPARING SINGLE-AGENT AND COMBINATION CHEMOTHERAPY

	XT Trial[1]: Comparing docetaxel monotherapy and combination capecitabine/docetaxel		Intergroup Trial E1193[2]: Comparing doxorubicin, paclitaxel and combination doxorubicin/paclitaxel		
Treatment	**Docetaxel**	**Capecitabine/docetaxel**	**Doxorubicin**	**Paclitaxel**	**Doxorubicin/paclitaxel**
Objective response	30%	42%	36% (20% response to crossover)	34% (22% response to crossover)	47%
Median survival	11.5 months	14.5 months*	18.9 months	22.2 months	22.0 months

* $p = 0.0126$

SOURCES: [1] O'Shaughnessy J et al. *J Clin Oncol* 2002;20(12):2812-23; [2] Sledge GW et al. *J Clin Oncol* 2003;21(4):588-92.

PHASE III TRIAL OF GEMCITABINE/PACLITAXEL VERSUS PACLITAXEL AS FIRST-LINE TREATMENT IN PATIENTS WITH ANTHRACYCLINE-PRETREATED METASTATIC BREAST CANCER: INTERIM SURVIVAL REPORT

Accrual: 529 (Closed)

Eligibility	**Locally recurrent or metastatic breast cancer Prior adjuvant anthracycline treatment No prior therapy for advanced disease**
ARM 1	**Gemcitabine + paclitaxel q3wk**
ARM 2	**Paclitaxel q3wk**

Endpoint	GT (n = 267)	T (n = 262)	*p*-value
Response rate (95% CI)	40.8% (34.9, 46.7)	22.1% (17.2, 27.2)	<0.0001
Median TTP (95% CI)	5.2 mo (4.2, 8.6)	2.9 mo (2.6, 3.7)	<0.0001
Median overall survival (95% CI)	18.5 mo (16.5, 21.2)	15.8 mo (14.4, 17.4)	0.018

G = gemcitabine; T = paclitaxel; TTP = time to progression

SOURCE: Albain KS. Presentation. ASCO 2004;Abstract 510.

MULTICENTER PHASE II STUDY OF CAPECITABINE PLUS PACLITAXEL AS FIRST-LINE THERAPY (N = 47)

Efficacy endpoints	No. of responders	Response rate
Overall response (90% CI)	24	51% (38, 64)
Complete response	7	15%
Partial response	17	36%
Stable disease ≥6 mo	9	19%
Clinical benefit (95% CI)	33	70% (55, 83)

Grade III/IV adverse events	No. of patients	Percent
Neutropenia	7	15
Alopecia	6	13
Hand-foot syndrome	5	11
Fatigue	4	9
Dyspnea	4	9
Paraesthesia	3	6
Peripheral neuropathy	3	6

Capecitabine = 825 mg/m^2 twice daily, days 1-14, every three weeks
Paclitaxel = 175 mg/m^2 every three weeks

SOURCE: Gradishar WJ et al. *J Clin Oncol* 2004;22(12):2321-7.

PHASE II TRIAL OF CAPECITABINE AND WEEKLY PACLITAXEL IN TAXANE-NAÏVE PATIENTS

Response (N = 54 evaluable patients)	Percent	Grade III/IV adverse events (>5%)	No. of patients Grade III/IV	Percent Grade III/IV
Complete response	0	Hand-foot syndrome	10/0	18.2
Partial response	50	Neutropenia	3/4	12.7
Stable disease	30	Nausea	3/0	5.5
Clinical benefit (CR + PR + SD ≥6 months)	65	Leukopenia	1/2	5.5
		Diarrhea	3/0	5.5

SOURCE: Blum JL. Poster 5053. San Antonio Breast Cancer Symposium 2004.

ACTIVE PHASE III TRIALS OF NOVEL COMBINATIONS OF CHEMOTHERAPY AND BIOLOGIC AGENTS

Protocol ID	Target accrual	Eligibility	Randomization
CA163-048	Not reported	Prior anthracycline and taxane; no more than two prior chemotherapy regimens	Ixabepilone (BMS-247550) + capecitabine Capecitabine
GSK-EGF100151	372	Progression in metastatic disease or relapse within six months after adjuvant taxane and anthracycline	Lapatinib (GW572016) + capecitabine Capecitabine
CA163-046	Not reported	Two or three prior chemotherapy regimens, one in the metastatic setting; taxane resistant and prior anthracycline	Ixabepilone (BMS-247550) + capecitabine Capecitabine
GSK-EGF30001	570	No prior chemotherapy for Stage IV HER2-negative or unknown	Paclitaxel + lapatinib (GW572016) Paclitaxel + placebo

SOURCE: NCI Physician Data Query, September 2005.

SELECT PUBLICATIONS

Albain KS et al. **Global phase III study of gemcitabine plus paclitaxel (GT) vs paclitaxel (T) as frontline therapy for metastatic breast cancer (MBC): First report of overall survival.** *Proc ASCO* 2004;Abstract 510.

Blum JL et al. **A phase II trial of combination therapy with capecitabine and weekly paclitaxel for metastatic breast cancer (MBC): Preliminary results in taxane-naïve patients.** Poster 5053. San Antonio Breast Cancer Symposium 2004.

Gradishar WJ et al. **Capecitabine plus paclitaxel as front-line combination therapy for metastatic breast cancer: A multicenter phase II study.** *J Clin Oncol* 2004;22(12):2321-7.

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.

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.

FIRST-LINE THERAPY FOR PATIENTS WITH PRIOR ADJUVANT AC AND A TAXANE

I usually consider these patients as being anthracycline and taxane refractory, but if a long period has passed (ie, two or more years) since the adjuvant therapy, one could certainly retry a taxane. Nanoparticle paclitaxel or a weekly regimen of the original paclitaxel formulation would be attractive choices. However, I'm generally treating these patients as anthracycline and taxane refractory, and I'm using capecitabine. Not only is capecitabine FDA approved for that indication, it seems to have among the higher response rates in the anthracycline- and taxane-refractory group of patients.

Alternatives to capecitabine would include vinorelbine and gemcitabine. I believe combinations of these drugs are also something to consider. We're so geared toward thinking of single agents, but combinations do have a role, particularly for more symptomatic patients. It's hard to know which combination wins out. Data exist on combinations of vinorelbine/capecitabine, gemcitabine/vinorelbine and gemcitabine/capecitabine.

— Debu Tripathy, MD.* Breast Cancer Update *2005 (5)

CAPECITABINE/PACLITAXEL IN PATIENTS WITH TAXANE-NAÏVE METASTATIC BREAST CANCER

In our trial evaluating capecitabine plus weekly paclitaxel, patients could have undergone one prior chemotherapy regimen for metastatic breast cancer, which is in contrast to the front-line trial conducted by Bill Gradishar that evaluated a similar regimen but used paclitaxel 175 mg/m^2 every three weeks. Our response rate was very exciting, with 50 percent of patients achieving a partial response and an additional 30 percent of patients with stable disease for greater than six months, which is comparable to the 70 percent clinical benefit seen in Dr Gradishar's trial. The median progression-free survival is 12.1 months, and overall median survival has not yet been reached. The combination was remarkably well tolerated, and the hand-foot syndrome that occurred in 18 percent of patients was easily managed with dose modification.

— Joanne L Blum, MD, PhD. Meet The Professors Session at the 2004 San Antonio Breast Cancer Symposium

PHASE II TRIAL OF CAPECITABINE/PACLITAXEL AS FIRST-LINE THERAPY

The rationale behind our study was to determine whether we could see a similar benefit to that observed in Joyce O'Shaughnessy's docetaxel/capecitabine randomized trial. There were differences in the two trials. Our study was largely in the first line, whereas O'Shaughnessy's trial had a mix of patients receiving first-, second- and third-line therapy. The other distinction was the dose of the capecitabine. We started at 825 mg/m^2 twice a day for 14 days out of 21 days, as opposed to the FDA-approved dose (1,250 mg/m^2 BID) utilized in the other trial. We found the lower dose was better tolerated, which reflects the experience of most physicians using capecitabine as a single agent or in combination.

Dose reduction is usually necessary when starting at the FDA-approved dose. In practice, most physicians utilize 1 g/m^2/BID. So when combining with paclitaxel, the decision was made that we would use a lower starting dose. There was a very good response rate of approximately 50 percent, which is similar to O'Shaughnessy's results in patients treated first line.

If one is making the decision to combine capecitabine with a taxane, one could choose either docetaxel or paclitaxel and expect a robust response rate. It's a reasonable combination if one is wedded to the idea of using a combination in a particular patient. Joanne Blum evaluated another regimen of capecitabine with paclitaxel and demonstrated results similar to ours. Multiple studies have evaluated capecitabine plus a taxane. All of the studies are imperfect because none of them address the fundamental issue of whether one might accomplish the same objective with sequential, rather than combination, therapy. Studies are ongoing to address that issue.

— William J Gradishar, MD.* Breast Cancer Update *2005 (4)