Single-Agent versus Combination Chemotherapy for Metastatic Disease

27TH ANNUAL San Antonio Breast Cancer Symposium 20

Randomized clinical trials of chemotherapeutic agents and regimens not only help better define clinical care but also provide important clues to future adjuvant therapy strategies. A series of recent studies have resulted in encouraging results with new combinations, including capecitabine/docetaxel, capecitabine/paclitaxel, and gemcitabine/paclitaxel. Adjuvant trials are now being planned and conducted utilizing these regimens. However, most breast cancer clinical research leaders support nonprotocol therapy with sequential single-agent chemotherapy in the metastatic setting, and the choice of agents is mainly based on prior adjuvant treatment and toxicity considerations.

PHASE III TRIALS COMPARING SINGLE-AGENT AND COMBINATION CHEMOTHERAPY FOR METASTATIC BREAST CANCER

	XT Trial*: Comparing docetaxel monotherapy and combination capecitabine/docetaxel		Intergroup Trial E1193**: 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

SOURCES: * 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.

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

Accrual: 529 (Closed)

Eligibility	**Locally recurrent or metastatic breast cancer Prior adjuvant anthracycline treatment No prior therapy for metastatic disease**
ARM 1	**Gemcitabine 1250 mg/m² + paclitaxel 175 mg/m² q3wk**
ARM 2	**Paclitaxel 175 mg/m² 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	18.5 mo (16.5, 21.2)	15.8 mo (14.4, 17.4)	0.018

SOURCE: KS Albain. 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**	**%**
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/m² twice daily, days 1-14, every three weeks
Paclitaxel = 175 mg/m² day 1 every three weeks

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

ACTIVE PHASE III TRIALS OF CHEMOTHERAPY IN METASTATIC BREAST CANCER

Protocol ID	Target accrual	Eligibility	Randomization
EORTC-10001	406-452	Prior taxanes	Vinorelbine Capecitabine
DO03-21-022	NR	≥65 years old No prior chemotherapy for Stage IV No anthracycline resistance	Pegylated liposomal doxorubicin Capecitabine
CA163-048	NR	Prior anthracycline and taxane. No more than 2 prior chemotherapy regimens	Ixabepilone (BMS-247550) + capecitabine Capecitabine
GSK-EGF100151	372	Progression in metastatic disease or relapse within 6 months after adjuvant taxane and anthracycline	GW572016 + capecitabine Capecitabine
CA163-046	NR	2-3 prior chemotherapy regimens; 1 in the metastatic setting Taxane resistant and prior anthracycline	Ixabepilone (BMS-247550) + capecitabine Capecitabine
XRP9881B/3001	NR	Prior anthracycline and taxane	Investigational drug Capecitabine
GSK-EGF30001	570	No prior chemotherapy for Stage IV HER2-negative or unknown	Paclitaxel + GW572016 Paclitaxel + placebo
MDA-ID-99242	160	≤2 prior chemotherapy regimens; 1 in the metastatic setting No taxane for Stage IV and ≥12 months since adjuvant taxane	Docetaxel day 1 q3wk Docetaxel days 1, 8 and 15 q4wk

NR = Not reported

SOURCE: NCI Physician Data Query, October 2004.

SELECT PUBLICATIONS

Alba E et al; Spanish Breast Cancer Research Group. **Multicenter randomized trial comparing sequential with concomitant administration of doxorubicin and docetaxel as first-line treatment of metastatic breast cancer: A Spanish Breast Cancer Research Group (GEICAM-9903) phase III study.** *J Clin Oncol* 2004;22(13):2587-93.

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.

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.

Moinpour C et al. **Gemcitabine plus paclitaxel (GT) versus paclitaxel (T) as first-line treatment for anthracycline pre-treated metastatic breast cancer (MBC): Quality of life (QoL) and pain palliation results from the global phase III study.** *Proc ASCO* 2004;Abstract 621.

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 CAPECITABINE/PACLITAXEL

"This phase II study supports the concept that the complementary mechanisms of action and non-overlapping major toxicities of capecitabine and taxanes create a highly effective and well-tolerated combination chemotherapy regimen for MBC. Both capecitabine and taxanes are effective when used as monotherapy, and preclinical studies in tumor xenograft models demonstrate synergistic antitumor activity when the drugs are used in combination. …The high clinical activity of capecitabine plus paclitaxel documented in this phase II study is consistent with that reported from the recent large international phase III trial of capecitabine combined with docetaxel, compared with docetaxel alone, in anthracycline-pretreated patients."

— Gradishar WJ et al. J Clin Oncol *2004;22(12):2321-27.*

COMBINATION VERSUS SEQUENTIAL DOXORUBICIN AND PACLITAXEL AS FIRST-LINE THERAPY

"Trial E1193 tested whether the combination of two active drugs, representing what are arguably the two most active classes of agents (anthracyclines and taxanes) used in breast cancer, might prove superior to sequential, single-agent therapy with the same agents. Combination therapy resulted both in a superior overall response rate and a superior TTF, two frequent measures of efficacy in metastatic chemotherapy trials. Despite this superiority, combination therapy failed to improve overall survival. Perhaps more importantly, given the usually fatal nature of the disease, combination therapy did not improve quality of life."

— Sledge GW et al. J Clin Oncol *2003;21(4):588-92.*

GEMCITABINE (G) PLUS PACLITAXEL (T) VERSUS PACLITAXEL AS FIRST-LINE THERAPY

"GT had phase II safety and efficacy in MBC after anthracyclines, so it was compared to T in a phase III study of frontline therapy. …GT provides significant OS advantage over T when both are given on a q3 week cycle, a result to be confirmed in the final planned analysis in late 2004. The TTP benefit predicted OS improvement with longer follow-up. GT should be considered a frontline regimen in MBC."

— Albain KS et al. Proc ASCO *2004;Abstract 510.*

CAPECITABINE/DOCETAXEL VERSUS DOCETAXEL IN HEAVILY PRETREATED PATIENTS WITH METASTATIC BREAST CANCER

"This phase III study demonstrates that capecitabine/docetaxel combination therapy is more effective than a current standard treatment, single-agent docetaxel, and is thus a significant development for patients with breast cancer whose disease has progressed after an anthracycline containing regimen. The addition of capecitabine to docetaxel 75 mg/m² resulted in a significant improvement in overall survival, time to disease progression, and response rate compared with docetaxel 100 mg/m² alone. The addition of capecitabine to docetaxel resulted in a 23% reduction in risk of death compared with docetaxel, with an increase in median survival of 3 months. The survival benefit with capecitabine/docetaxel combination therapy was seen early in the course of treatment and persisted throughout the study."

— O'Shaughnessy J et al. J Clin Oncol *2002;20(12):2812-23.*

SELECTING A COMBINATION REGIMEN: ANTHRACYCLINE/TAXANE VERSUS CAPECITABINE/DOCETAXEL

We typically use a combination regimen of an anthracycline and a taxane, but capecitabine/docetaxel is equally reasonable. We know a survival advantage exists with capecitabine/docetaxel, and no survival advantage exists with an anthracycline/taxane combination; however, that's like comparing apples and oranges, because many of the trials of anthracycline/taxane combinations — including the largest ECOG-1193 trial — included a crossover. The capecitabine/docetaxel trial didn't. Had they conducted the study using the ECOG-1193 model — combination therapy versus each single-agent with a crossover — I believe they would have seen the same results as in ECOG-1193.

— Kathy Miller, MD