Chemotherapy in Elderly Women

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Limited data exist about the risks and benefits of adjuvant chemotherapy in elderly women. An important adjuvant trial led by Dr Hyman Muss, CALGB-49907, randomly assigns elderly women to either capecitabine versus AC or CMF. A small clinical trial in the metastatic setting has suggested that in older women with advanced breast cancer, capecitabine 1,000 mg/m^2 twice a day for 14 of 21 days may be better tolerated and result in equal or greater efficacy than the package-insert dose. Retrospective studies of women treated with adjuvant chemotherapy have found that (1) it is not offered as often to elderly women with high-risk breast cancer and (2) age does not significantly predict for any toxicity risk other than dose reductions.

ACTIVE CHEMOTHERAPY TRIALS IN ELDERLY WOMEN WITH BREAST CANCER

Protocol ID	Phase	Eligibility	Target accrual	Schema
CALGB-49907	III	Age: ≥65, Stage I-IIIC, operable breast cancer	600-1,800	CMF or AC vs capecitabine 1,000 mg/m^2 BID d1-14 q3wk*
DO03-21-022	II/III	Age: ≥60, metastatic breast cancer	NR	Pegylated liposomal doxorubicin versus capecitabine
SWS-SAKK-25/99	I/II	Age: ≥65, metastatic breast cancer	98-110	Phase I: Escalating doses of capecitabine and vinorelbine Phase II: Capecitabine and vinorelbine at dose preceding MTD
FRE-FNCLCC-GERICO-04/0406	II	Age: ≥70, metastatic breast cancer	53	Docetaxel
IBCSG 32-05/ BIG 1-05	III	Age: ≥66, endocrine-nonresponsive early breast cancer, ineligible for standard chemotherapy	1,296	R1†: Pegylated liposomal doxorubicin versus no adjuvant therapy R2†: Pegylated liposomal doxorubicin versus metronomic cyclophosphamide and methotrexate

* Patients with insufficient LVEF must receive CMF, not AC. Protocol under amendment to allow the addition of trastuzumab in patients with tumors positive for HER2 by IHC 3+ or FISH; † randomization option at physician's/patient's preference; NR = not reported; MTD = maximum tolerated dose

SOURCES: NCI Physician Data Query, October 2005; www.ibcsg.org; personal communication with CALGB, October 2005.

ADJUVANT CHEMOTHERAPY OFFERED TO BREAST CANCER PATIENTS[1]

Patients	≥70 years (n = 97)	<70 years (n = 168)	*p*-value
High-risk group*	51.6%	92.9%	<0.0001
HR-negative (HR-)	77.3%	100%	0.0002
Node-positive (N+)	60.2%	95.7%	<0.0001
Grade III tumor	57.8%	91.2%	<0.0001
pT2-pT3	50%	88.3%	<0.0001
N+, HR+	52.6%	93.4%	<0.0001
N+, HR-	94.1%	100%	0.2290

* Presenting with one or more risk factors (pT2-3, Grade III, node-positive, HR-negative); HR+ = hormone receptor-positive

RATES OF CLINICAL TRIAL PARTICIPATION IN WOMEN WITH BREAST CANCER (N = 154)[2]

Mean age (years)	Offered protocol	Consented when offered
48	51%	56%
74	35%	50%

SOURCES: [1] Brunello A et al. *Ann Oncol* 2005;16:1276-82; [2] Kemeny MM et al. *J Clin Oncol* 2003;21(12):2268-75.

CAPECITABINE DOSING IN OLDER WOMEN WITH ADVANCED BREAST CANCER

Efficacy	Capecitabine 1,250 mg/m^2 BID (n = 30)	Capecitabine 1,000 mg/m^2 BID (n = 43)
Median survival	10 months	16 months
Overall response	36.7%	34.9%
Median duration of response	4.3 months	4.3 months
Stable disease	33%	46%
Median time to progression	3.9 months	4.1 months
Grade III/IV toxicities	**Capecitabine 1,250 mg/m^2 BID (n = 30)**	**Capecitabine 1,000 mg/m^2 BID (n = 43)**
Fatigue	7%	12%
Diarrhea	13%	2%
Dyspnea	10%	5%
Nausea	7%	5%
Dose reductions required	30%	5%
Lethal toxicities	7%	2%

SOURCE: Bajetta E et al. *J Clin Oncol* 2005;23(10):2155-61.

ROLE OF AGE, CHEMOTHERAPY REGIMEN AND COMORBIDITY IN RISK OF TOXICITY FROM ADJUVANT CHEMOTHERAPY IN WOMEN OVER AGE 65 WITH BREAST CANCER

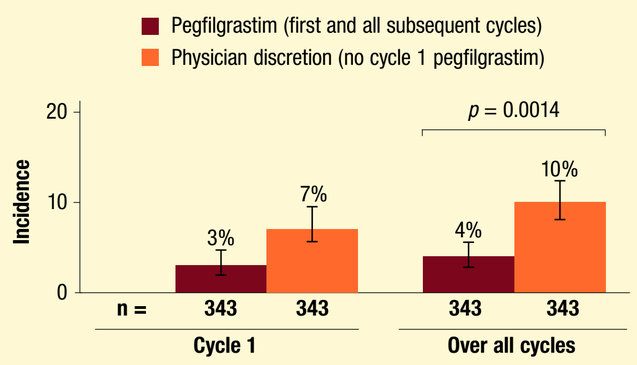
Variable	Age[1]	Chemotherapy regimen[2]	Comorbidity[3]
Toxicity outcome	***p*-value**	***p*-value**	***p*-value**
Hospitalization	0.51	**<0.01**	0.62
Fever and neutropenia	0.07	**<0.01**	0.27
Dose reduction	**0.02**	0.13	0.34
Any Grade III/IV toxicity	0.89	**0.02**	0.99
Grade III/IV nonhematologic toxicity	0.37	**0.02**	0.66
Treatment delay for low ANC	0.31	**<0.01**	0.36

"The type of chemotherapy regimen (anthracycline compared to CMF) was a better predictor for toxicity than increased age or comorbidity score."

[1] Age continuous variable; [2] anthracycline vs CMF; [3] comorbidity score: 0 vs ≥1 (patients with score ≥1 = 17%); ANC = absolute neutrophil count

SOURCE: Hurria A et al. *Breast Cancer Res Treat* 2005;92:151-6.

INCIDENCE OF FEBRILE NEUTROPENIA*



The proportion of patients experiencing febrile neutropenia was statistically significantly lower for patients receiving pegfilgrastim in all cycles compared to patients in the physician discretion arm.

Error bars represent 95% confidence intervals.

* Febrile neutropenia is defined as ANC <1 x 10^9/L and temperature ≥38° C.

SOURCE: Balducci L et al. Presentation. ASCO 2005.

SELECT PUBLICATIONS

Bajetta E et al. **Safety and efficacy of two different doses of capecitabine in the treatment of advanced breast cancer in older women.** *J Clin Oncol* 2005;23(10):2155-61.

Balducci L et al. **A large study of the older cancer patient in the community setting: Initial report of a randomized controlled trial using pegfilgrastim to reduce neutropenic complications.** *Proc ASCO* 2005;Abstract 8111.

Biganzoli L et al. **Adjuvant therapy in elderly patients with breast cancer.** *Clin Breast Cancer* 2004;5(3):188-95.

Brunello A et al. **Adjuvant chemotherapy for elderly patients (> 70 years) with early high-risk breast cancer: A retrospective analysis of 260 patients.** *Ann Oncol* 2005;16(8):1276-82.

Hurria A et al. **Patterns of toxicity in older patients with breast cancer receiving adjuvant chemotherapy.** *Breast Cancer Res Treat* 2005;92:151-6.

Kemeny MM et al. **Barriers to clinical trial participation by older women with breast cancer.** *J Clin Oncol* 2003;21(12):2268-75.

INCLUSION OF OLDER PATIENTS IN TRIALS OF ADJUVANT CHEMOTHERAPY

Our study adds to the increasing number of trials that suggest that older patients in fair to good health tolerate standard chemotherapy regimens, and even more intensive regimens, almost as well as younger patients. Moreover, and more importantly, this study suggests that the added value gained from more intensive chemotherapy regimens commonly used in the adjuvant setting might be shared by older patients and not limited to younger age groups.

— Hyman B Muss, MD et al. JAMA *2005;293(9):1073-81.*

ENROLLMENT OF ELDERLY IN CLINICAL TRIALS

…The number of patients at low risk who can be spared adjuvant chemotherapy appears to be markedly increased when the prognostic genetic signature is used. These findings are of great interest, especially in elderly patients, who more frequently have comorbidities and/or impaired organ functions than younger people, and the real benefit from tolerance of adjuvant chemotherapy is still a major issue. Clinical trials specifically designed for elderly patient subpopulations with breast cancer are critically needed and must incorporate gene expression profiling as a potential way of identifying those patients who can be spared adjuvant systemic treatment despite having traditionally defined high-risk disease (ie, node-positive, high grade). The prognostic genetic signature could have this potential, but it has been investigated only in younger women and therefore needs to be prospectively validated in elderly patients as well.

— Laura Biganzoli, MD et al. Clin Breast Cancer *2004;5(3):188-95.*

CALGB-49907

Hyman Muss has made some changes to try to make the eligibility more streamlined and easier for physicians and patients to participate in the study.

We strongly believe that this trial will address a very good question: How does an oral agent compare to traditional intravenous chemotherapy? In patients with metastatic disease, capecitabine has been shown to be better than CMF, so we might even have an efficacy advantage.

— Jeffrey Abrams, MD. Breast Cancer Update *2004 (5)*

CAPECITABINE DOSE IN ELDERLY WOMEN WITH ADVANCED BREAST CANCER

This study has shown in a large series that oral capecitabine is well tolerated and effective in older women with advanced breast cancer. Older patients may frequently exhibit diminished capacity to eliminate drugs, resulting in unusual sensitivity to standard dosing regimens. In light of this, the overall results of the study suggest that although the dose groups are small and nonrandomized, the capecitabine dose of 1,000 mg/m^2 twice daily merits consideration as 'standard' for women aged 70 years and older who are candidates to cytotoxic therapy for metastatic breast cancer and do not have severely impaired renal function.

— Emilio Bajetta, MD et al. J Clin Oncol *2005;23(10):2155-61.*

PEGFILGRASTIM FOR FEBRILE NEUTROPENIA IN THE ELDERLY

This large, prospective, community-based trial in older patients was both feasible to conduct and demonstrated that myleosuppressive chemotherapy can be given to older patients with cancer.

Pegfilgrastim from the first cycle of chemotherapy resulted in reduced incidence of febrile neutropenia, hospitalizations, IV anti-infective use and chemotherapy dose reductions and delays compared with current community practice, which may include pegfilgrastim in later cycles.

Pegfilgrastim use from the first cycle was associated with fewer serious adverse events compared with pegfilgrastim given at physician discretion in later cycles.

— Lodovico Balducci, MD. Presentation. ASCO 2005.