# Mono- and Combination Chemotherapy for Metastatic Breast Cancer: An Incremental Step Forward

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## INTRODUCTION

For decades, combination chemotherapy regimens have been exhaustively studied for the treatment of metastatic breast cancer. The fact that curative combination chemotherapy regimens for other advanced cancers exists has been one motivating force behind this relentless research. Clinical results in breast cancer have unfortunately not been as encouraging for this approach, as for, let us say, germ cell tumors or lymphomas. The recently reported ECOG 1193 study(*1*) showed no clear advantage for combination therapy over the use of sequential single agents. Thus, oncologists who have been motivated by phase II data(*2-6*) might reconsider the use of anthracycline/taxane combination chemotherapy as a reasonable option for selected patients, but certainly this is not "CHOP" for metastatic breast cancer.

Exactly *which* patients should receive combination chemotherapy as opposed to single agent therapy presently falls as much within the domain of the art of clinical oncology as the science. We currently lack high level evidence-based medicine to guide such choices. Many oncologists consider anthracycline/taxane combinations for patients with rapidly progressing visceral disease, for younger patients who might tolerate it best, while others believe this to be most suited to the adjuvant or neoadjuvant setting. For example, it is disappointing that the substitution of docetaxel for fluorouracil in the "FAC" regimen to create "TAC" did not prolong time to progression or improve survival as first-line chemotherapy of metastatic breast cancer,(*7*) yet the same substitution (with doxorubicin/cyclophosphamide) has improved disease-free survival in a large adjuvant trial.(*8*) Certainly specific combinations in specific circumstances may be beneficial, yet evidence-based guidelines for selecting such patients are lacking.

In asking the question: "is A+B together superior to A, then B?" in the chemotherapeutic management of metastatic breast cancer, it is essential to clarify what indeed defines superiority. Many medical oncologists rate regimens based on objective responses, whereas patients seem to care more about whether or not a given treatment will prolong survival, or the time until progression, as opposed to whether the treatment might happen cause a 50% reduction in the sum of the products of the bi-perpendicular diameters of their measurable tumor lesions (i.e., a PR). While response proportion could be a surrogate for quality of life, or symptom relief, rigorous prospective evaluation of quality of life in ECOG 1193 unfortunately does not demonstrate this parallel - the higher objective response rate for the doxorubicin/paclitaxel combination did not translate into improved quality of life.

Joensuu, et al. found no advantage in time to progression or overall survival for the use of combinations as first- and second-line therapy as opposed to single agents, with less toxicity and superior quality of life seen in the sequential monotherapy arm.(*9*) Single-agent docetaxel outperformed a prior standard post-anthracycline doublet, mitomycin C plus vinblastine, with superior response, time to progression, and survival.(*10*) Single-agent paclitaxel compared quite favorably to the 4-drug combination regimen CMFP, (cyclophosphamide, methotrexate, 5-fluorouracil, and prednisone) as first-line chemotherapy.(*11*) Single-agent mitoxantrone likewise compared favorably to the combination of 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) in another multicenter randomized trial, with prospective evaluation of quality of life favoring monotherapy.(*12*) The NCI of Canada found no therapeutic advantage (RR, TTP, OS) for vinorelbine combined with doxorubicin as opposed to doxorubicin alone

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(again, with more toxicity for the combination arm).(*13*) A recent phase III trial demonstrated that time to progression in metastatic breast cancer patients treated with epirubicin is not improved by the addition of either cisplatin or lonidamine.(*14*)

We have the recent report of a randomized trial of single agent docetaxel compared to the combination of docetaxel plus capecitabine.(*15*) O'Shaugnessy et al. reported a higher response rate, a longer time to progression, and improved overall survival for the combination versus docetaxel alone. However, the lack of subsequent (i.e. crossover) use of capecitabine in 73% of patients who received post-study chemotherapy, makes the superiority of this doublet uncertain. Might the sequential use of docetaxel first, then capecitabine at progression, have yielded the same overall survival as the combination (perhaps with less toxicity)? This tenable hypothesis was indeed tested in ECOG 1,193, where the sequential use of paclitaxel and doxorubicin offered no disadvantage as compared to the combination. The lack of predesigned crossover in the O'Shaugnessy trial precludes one from addressing this hypothesis, although an exploratory subset analysis of the patients treated sequentially with docetaxel and then capecitabine (as opposed to other agents) is supportive of the use of these agents sequentially.

## Global Phase III Trial of Gemcitabine Plus Paclitaxel Versus Paclitaxel

At the 2003 Annual Meeting of the American Society of Clinical Oncology, Dr. Joyce O'Shaughnessy presented the results of a large (n=-529), global, randomized phase III trial comparing paclitaxel 175 mg/m$^2$ via 3-hour infusion every 3 weeks to the same plus gemcitabine 1,250 mg/m$^2$ on day 1 and day 8, every 3 weeks, as first line therapy of metastatic breast cancer.(*25*) Treatment arms were well balanced for demographic characteristics, and over 70% of patients had visceral metastases; 76% had two or more organ systems involved. The delivered dose intensity of gemcitabine was 90% of the planned dose intensity, and it was almost 100% for paclitaxel. Only 7% of gemcitabine doses were omitted, and only 8% dose-reduced for toxicity.

The median time to progression was 5.4 months (95% CI: 4.6～6.1 months) for gemcitabine/paclitaxel and 3.5 months (95% CI: 2.9～4.0 months) for single-agent paclitaxel, a highly significant difference (P=0.0013 by log rank test). Women receiving the combination had an approximately 50% chance of being progression-free at 6 months. The overall response rate for the combination was 39.3% (95% CI: 33.5～45.2%), and 25.6% (95% CI: 20.3～30.9%) for paclitaxel (P=0.0007). In addition to these advantages for the paclitaxel/gemcitabine combination, numerical improvements in analgesic level, pain relief, and global quality of life scores were observed.

Toxicity was largely manageable and expected. Grade 4 neutropenia was observed in 17% of patients receiving the combination, versus 7% for paclitaxel monotherapy. Febrile neutropenia was generally uncommon, occurring in 5% of patients receiving the combination and 2% receiving paclitaxel. Ten percent of patients receiving the combination required red blood cell transfusion, as compared with 4% in the monotherapy arm. Severe thrombocytopenia was rare in both arms. Non-hematologic toxicity was modest in both arms: grade 3/4 peripheral neuropathy occurred in 6% and 4%, and fatigue in 7% and 2% respectively for combination and single agent therapy. These differences appear to stand in some contradistinction to the toxicity differences reported between docetaxel monotherapy and the capecitabine-docetaxel combination.

## Moving Forward

Those who look to high level evidence-based medicine would point to the ambitious meta-analysis of Fossati et al., (*16*) as justification for the routine use of combination chemotherapy in metastatic breast cancer. This effort combined the results of numerous, rather small randomized clinical trials of combination therapy compared to single-agent chemotherapy. Individual trials were insufficiently powered to discern a statistically significant survival advantage for combinations versus monotherapy. Collectively, however, there appeared to be a signal that indeed combinations could be superior to single agents. A few qualifying caveats are worth noting here. Firstly, the trials in the meta-analysis were conducted in the pre-taxane era; taxane monotherapy is not considered. Secondly, although this is technically a meta-analysis, it is quite modest in scale compared with, as an example, the "Early Breast Cancer Trialists Collaborative Group" effort.(*17*) Given the results of the recent randomized trials mentioned, there certainly seems to be a significant amount of high-level, evidence-based medicine challenging the conventional wisdom that combination chemotherapy is the gold standard for treatment of metastatic breast cancer.

Should we abandon the search for additional active chemotherapeutic combinations in metastatic breast cancer? Or would this be overly nihilistic? This question seems to be

beginning to answer itself. With the preclinical and clinical development of more targeted biologic agents (e.g. monoclonal antibodies), many of which are expected to possess a higher therapeutic index as compared to conventional cytotoxic chemotherapy, certainly a significant amount of refocusing of energy away from combination cytotoxic chemotherapy seems in order - and is fortunately already occurring. If uncoupling chemotherapeutic agents from one another dose not adversely impact outcome in the adjuvant setting(*18*) (CALGB 9741), why should sequential single- agent therapy be expected to be suboptimal for metastatic disease? Over three decades of innumerable combination chemotherapy trials has taught us that metastatic breast cancer does not behave as certain very chemosensitive lymphomas, nor most testicular cancers, do.

We should look to the highest available level of evidence-based medicine to decide what is nihilistic, and what is realistic, in the management of hormone-insensitive metastatic breast cancer. The ECOG 1,193 trial, considered together with other recent randomized trials that have failed to show consistent survival benefit for anthracycline-taxane combinations versus non-taxane containing combinations,(*19-24*) do *not* support the notion that anthracycline/taxane combinations are a reference regimen for metastatic breast cancer, unless perhaps a major goal of treatment is to increase the response rate, a goal seemingly more suited to neoadjuvant therapy. The only trial to report a survival advantage for such a combination(*19*) (paclitaxel plus doxorubicin compared to fluorouracil plus doxorubicin plus cyclophosphamide) is notable for the fact that only 25% of FAC-treated patients ever received a taxane as part of subsequent therapy for their metastatic disease.

Metastatic breast cancer often behaves biologically ("reads") like a novel with many chapters (fortunately), rather than a "short story". It could indeed be short-sighted to expect to know how the book will end based solely on what happens in Chapter One (i.e. first-line therapy). Thus, while survival data are awaited from the recent gemcitabine plus paclitaxel versus paclitaxel alone trial,(*25*) it would seem that this trial has already answered the relevant questions posed and inherent in the trial design for this disease: this is a kinder, gentler doublet that should be thoughtfully applied in the art of managing selected patients with metastatic breast cancer.

## REFERENCES


1) Sledge GW, Neuberg D, Bernardo P, Ingle JN, Martino S, Rowinsky EK, Wood WC. 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;21:588-92.
2) Gianni L, Munzone E, Capri G, Fulfaro F, Tarenzi E, Villani F, et al. Paclitaxel by 3-hour infusion in combination with bolus doxorubicin in women with untreated metastatic breast cancer: high antitumor efficacy and cardiac effects in a dose-finding and sequence-finding study. J Clin Oncol 1995; 13:2688-99.
3) Gehl J, Boesgaard M, Paaske T, Vittrup Jensen B, Dombernowsky P. Combined doxorubicin and paclitaxel in advanced breast cancer: effective and cardiotoxic. Ann Oncol 1996;7: 687-93.
4) Dieras V, Barthier S, Beuzeboc P, Misset JL, Cottura E, Aussel JP, et al. Phase II study of taxotere in combination with doxorubicin as 1st line chemotherapy of metastatic breast cancer. Breast Cancer Res Treat 1998;50:262a.
5) Sparano JA, O'Neill A, Schaefer PL, Falkson CI, Wood WC. Phase II trial of doxorubicin and docetaxel plus granulocyte colony-stimulating factor in metastatic breast cancer: Eastern Cooperative Oncology Group Study E1196. J Clin Oncol 2000;18:2369-77.
6) Sparano JA, Hu P, Rao RM, Falkson CI, Wolff AC, Wood WC. Phase II trial of doxorubicin and paclitaxel plus granulocyte colony-stimulating factor in metastatic breast cancer: an Eastern Cooperative Oncology Group Study. J Clin Oncol 1999;17:3828-34.
7) Mackey JR, Paterson A, Dirix LY, Dewar J, Chap L, Martin M, et al. Final results of the phase III randomized trial comparing docetaxel (T), doxorubicin (A) and cyclophosphamide (C) to FAC as first line chemotherapy (CT) for patients (pts) with metastatic breast cancer (MBC). Proc Am Soc Clin Oncol 2002;21:35a(abstract 137).
8) Nabholtz J-M, Pienkowski T, Mackey J, Pawlicki M, Guastalla J-P, Vogel C, et al. Phase III trial comparing TAC (docetaxel, doxorubicin, cyclophosphamide) with FAC (5-fluorouracil, doxorubicin, cyclophosphamide) in the adjuvant treatment of node positive breast cancer (BC) patients: interim analysis of the BCIRG 001 study. Proc Am Soc Clin Oncol 2002:21:36a (abstract 141).
9) Joensuu H, Holli K, Heikkinen M, Suonio E, Aro AR, Hietanen P, et al. Combination chemotherapy versus single-agent therapy as first- and second-line treatment in metastatic breast cancer: a prospective randomized trial. J Clin Oncol 1998;16: 3720-30.
10) Nabholtz JM, Senn HJ, Bezwoda WR, Melnychuk D, Deschenes L, Douma J, et al. Prospective randomized trial of doce-

taxel versus mitomycin plus vinblastine in patients with metastatic breast cancer progressing despite previous anthracycline-containing chemotherapy. 304 Study Group. J Clin Oncol 1999; 17:1413-24.

11) Bishop JF, Dewar J, Toner GC, Smith J, Tattersall MH, Olver IN, et al. Initial paclitaxel improves outcome compared with CMFP combination chemotherapy as front-line therapy in untreated metastatic breast cancer. J Clin Oncol 1999;17:2355-64.

12) Heidemann E, Stoeger H, Souchon R, Hirschmann WD, Bodenstein H, Oberhoff C, et al. Is first-line single-agent mitoxantrone in the treatment of high-risk metastatic breast cancer patients as effective as combination chemotherapy? No difference in survival but higher quality of life were found in a multicenter randomized trial. Ann Oncol 2002;13:1717-29.

13) Norris B, Pritchard KI, James K, Myles J, Bennett K, Marlin S, et al. Phase III comparative study of vinorelbine combined with doxorubicin versus doxorubicin alone in disseminated metastatic/recurrent breast cancer: National Cancer Institute of Canada Clinical Trials Group Study MA8. J Clin Oncol 2000; 18:2385-94.

14) Berruti A, Bitossi R, Gorzegno G, Bottini A, Alquati P, De Matteis A, et al. Time to progression in metastatic breast cancer patients treated with epirubicin is not improved by the addition of either cisplatin or lonidamine: final results of a phase III study with a factorial design. J Clin Oncol 2002: 20:4150-9.

15) O'Shaughnessy J, Miles D, Vukelja S, Moiseyenko V, Ayoub JP, Cervantes G, 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;20:2812-23.

16) Fossati R, Confalonieri C, Torri V, Ghislandi E, Penna A, Pistotti V, et al. Cytotoxic and hormonal treatment for metastatic breast cancer: a systematic review of published randomized trials involving 31,510 women. J Clin Oncol 1998;16: 3439-60.

17) Early Breast Cancer Trialist's Collaborative Group. Polychemotherapy for early breast cancer: An overview of the randomized trials. Lancet 1998;352:930-42.

18) Citron M, Berry D, Cirrincione C, Carpenter J, Hudis C, Gradishar W, et al. Superiority of dose-dense (DD) over conventional scheduling (CS) and equivalence of sequential (SC) vs. combination adjuvant chemotherapy (CC) for node-positive breast cancer (CALGB 9741, INT C9741). San Antonio Breast Cancer Symposium 2002.

19) Jassem J, Pienkowski T, Pluzanska A, Jelic S, Gorbunova V, Mrsic-Krmpotic Z. Central & Eastern Europe and Israel Paclitaxel Breast Cancer Study Group, et al. Doxorubicin and paclitaxel versus fluorouracil, doxorubicin, and cyclophosphamide as first-line therapy for women with metastatic breast cancer: final results of a randomized phase III multicenter trial. J Clin Oncol 2001;19:1707-15.

20) Nabholtz JN, Falkson G, Campos D, Szanto J, Martin M, Chan S, et al. A Phase III Trial Comparing Doxorubicin (A) and Docetaxel (T) (AT) to Doxorubicin and Cyclophosphamide (AC) as First Line Chemotherapy for MBC. Proc Am Soc Clin Oncol 1999;18:127a(abstract 485).

21) Biganzoli L, Cufer T, Bruning P, Coleman RE, Duchateau L, Rapoport B, et al. Doxorubicin-paclitaxel: a safe regimen in terms of cardiac toxicity in metastatic breast carcinoma patients. Results from a European Organization for Research and Treatment of Cancer multicenter trial. Cancer 2003;97: 40-5.

22) Luck H, Thomssen C, Untch M, Kuhn W, Eidtmann H, Bois AD, et al. Multicentric Phase III Study in First Line Treatment of Advanced Metastatic Breast Cancer (ABC). Epirubicin/ Paclitaxel (ET) Vs Epirubicin/Cyclophosphamide (EC). A Study of the Ago Breast Cancer Group. Proc Am Soc Clin Oncol 2000;19:73a(abstract 280).

23) Bonneterre J, Dieras V, Tubiana-Hulin M, Bougnoux P, BonneterreM-E, Delozier T, et al. 6 Cycles of Epirubicin/ Docetaxel (ET) Versus 6 Cycles of 5FU Epirubicin/Cyclophosphamide (FEC) as First Line Metastatic Breast Cancer (MBC) Treatment. Proc Am Soc Clin Oncol 2001;20:22a(abstract 84).

24) O'Shaughnessy J, Nag S, Calderillo-Ruiz G, Jordaan J, Llombart A, Pluzanska A, et al. Gemcitabine plus paclitaxel (GT) versus paclitaxel (T) as first-line treatment for anthracycline pre-treated metastatic breast cancer (MBC): Interim results of a global phase III study. Proc Am Soc Clin Oncol 2003;2 2:7(abstract 25).