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REFERENCES

1. Leppäluoto PA: Nonsmoking: A surrogate factor in primary lung cancer in survivors of cervical adenocarcinoma? J Clin Oncol 27:3065-3066, 2009
2. Chaturvedi AK, Kleinerman RA, Hildesheim A, et al: Second cancers after squamous cell carcinoma and adenocarcinoma of the cervix. J Clin Oncol 27:967-973, 2009
3. Appleby P, Beral V, Berrington de González A, et al: Carcinoma of the cervix and tobacco smoking: Collaborative reanalysis of individual data on 13,541 women with carcinoma of the cervix and 23,017 women without carcinoma of the cervix from 23 epidemiological studies. Int J Cancer 118:1481-1495, 2006
4. Moreno V, Bosch FX, Munoz N, et al: Effect of oral contraceptives on risk of cervical cancer in women with human papillomavirus infection: The IARC multicentric case-control study. Lancet 359:1085-1092, 2002
5. Lacey JV Jr, Brinton LA, Abbas FM, et al: Oral contraceptives as risk factors for cervical adenocarcinomas and squamous cell carcinomas. Cancer Epidemiol Biomarkers Prev 8:1079-1085, 1999
6. Castellsagué X, Díaz M, de Sanjosé S, et al: Worldwide human papillomavirus etiology of cervical adenocarcinoma and its cofactors: Implications for screening and prevention. J Natl Cancer Inst 98:303-315, 2006

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Metronomic Schedule of Paclitaxel Is Effective in Hormone Receptor–Positive and Hormone Receptor–Negative Breast Cancer

To the Editor: Hugh et al[1] are to be lauded for their comprehensive analysis of the benefit estimation of a docetaxel-based regimen compared with the standard fluorouracil-based regimen in various breast cancer subsets. After comparing trials in which paclitaxel rather than docetaxel was used, they suggest that the benefit seen with docetaxel in hormone receptor–positive subsets may have resulted from either docetaxel being a more efficacious taxane, or a docetaxel-specific schedule that was better than the schedule of paclitaxel once every 3 weeks. However, they do not expand on paclitaxel scheduling; we believe this is a crucial omission in their discussion. In fact, missing from their discussion is a major phase III randomized trial that clearly established the superiority of paclitaxel once per week over paclitaxel once every 3 weeks,[2] whereas the overall survival benefit of docetaxel once every 3 weeks over paclitaxel once every 3 weeks has yet to be demonstrated. In fact, the superiority of paclitaxel once per week over paclitaxel once every 3 weeks was first predicted by Green et al,[3] who showed paclitaxel once per week compared with paclitaxel once every 3 weeks increased pathologic complete response—a surrogate of disease-free and overall survival—in the neoadjuvant setting in operable breast cancer, in both hormone receptor–positive and hormone receptor–negative subsets. In the confirmatory trial by Sparano et al,[2] which evaluated the 5-year disease-free and overall survival end points and compared the two taxanes and the two taxane schedules in a 2×2 factorial design, paclitaxel once per week compared with paclitaxel once every 3 weeks significantly improved 5-year progression-free survival in hormone receptor–negative breast cancer, including triple-negative and human epidermal growth factor receptor 2 (HER2) –positive subsets of breast cancer, and hormone receptor–positive breast cancer, which combines luminal-A and luminal-B subtypes of breast cancer. This was seen despite the fact that patients with HER2-positive breast cancer (including luminal-B breast cancer, an HER2-positive subtype) were preferentially enrolled onto the alternate trastuzumab trials; these patients were more likely to have chemotherapy-sensitive disease and therefore more likely to benefit from weekly paclitaxel. It is likely that the small subgroup of patients with hormone receptor–positive breast cancer with low Ki-67 proliferation index that did not benefit from a docetaxel-based regimen in the study by Hugh et al[1] may not have benefited from paclitaxel once per week either. This subgroup may be akin to the group identified by multigene assay that did not benefit from first-generation chemotherapy regimens. Until this subset of patients who will not benefit from paclitaxel once per week is identified, weekly paclitaxel after anthracyclines should be standard in all subsets of breast cancer, including triple-negative, hormone receptor–positive (estrogen receptor–positive and/or progesterone receptor–positive and either HER2-positive and/or $Ki67^{high}$ breast cancer), HER2–positive, and luminal-A (estrogen receptor–positive and/or progesterone receptor–positive but not HER2-positive or $Ki67^{high}$ breast cancer)[2-7] breast cancer. Moreover, drug-specific optimal schedules of chemotherapy must always be compared when comparing across trials and/or assessing outcome in different subsets of breast cancer, because optimal schedules of various chemotherapies are an important advancement in the treatment of various malignancies, demonstrated convincingly in Ewing's sarcoma and ovarian cancer,[8,9] in addition to breast cancer.

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REFERENCES

1. Hugh J, Hanson J, Cheang MC, et al: Breast cancer subtypes and response to docetaxel in node-positive breast cancer: Use of an immunohistochemical definition in the BCIRG 001 trial. J Clin Oncol 27:1168-1176

2. Sparano JA, Wang M, Martino S, et al: Weekly paclitaxel in the adjuvant treatment of breast cancer. N Engl J Med 358:1663-1671, 2008

3. Green MC, Buzdar AU, Smith T, et al: Weekly paclitaxel improves pathologic complete remission in operable breast cancer when compared with paclitaxel once every 3 weeks. J Clin Oncol 23:5983-5992, 2005

4. Mehta RS: Dose-dense and/or metronomic schedules of specific chemotherapies consolidate the chemosensitivity of triple-negative breast cancer: A step toward reversing triple-negative paradox. J Clin Oncol 26:3286-3288, 2008; author reply 3288

5. Mehta RS: Hormone receptor, grade, human epidermal growth factor receptor 2, and topoisomerase II as predictors of response to chemotherapy. J Clin Oncol 26:2596, 2008; author reply 2596-2597

6. Mehta R: HER2 and response to paclitaxel in node-positive breast cancer. N Engl J Med 358:197-198, 2008; author reply 198

7. Mehta RS, Hsiang D, Lane K, et al: Association between pathologic complete response and survival in patients treated with sequential anthracyclines and concomitant taxanes and trastuzumab in HER2-positive breast cancer. San Antonio Breast Cancer Symposium, San Antonio, TX, December 10-14, 2008 (abstr 3141)

8. Womer RB, West DC, Krailo MD, et al: Randomized comparison of every-two-week v. every-three-week chemotherapy in Ewing sarcoma family tumors (ESFT). J Clin Oncol 26:554s, 2008 (suppl; abstr 10504)

9. Isonishi S, Yasuda M, Takahashi F, et al: Randomized phase III trial of conventional paclitaxel and carboplatin (c-TC) versus dose dense weekly paclitaxel and carboplatin (dd-TC) in women with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer: Japanese Gynecologic Oncology. J Clin Oncol 26:294s, 2008 (suppl; abstr 5506)

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Reply to R.S. Mehta et al

We would like to thank Mehta et al[1] for their insightful comments on and elaboration of those points to which we alluded in our article.[2] We are in substantial agreement with most of them. We agree there is convincing evidence that the standard regimen of paclitaxel once every 3 weeks is inferior to the regimen of docetaxel once every 3 weeks used in the BCIRG (Breast Cancer International Research Group) 001 trial,[3,4] and we apologize for omitting the study by Sparano et al.[4] This is probably the reason why we found benefit in docetaxel once every 3 weeks when administered to the human epidermal growth factor receptor 2–negative, hormone receptor–positive population, whereas Hayes et al[5] did not in the CALGB (Cancer and Leukemia Group B) 9344 trial of paclitaxel once every 3 weeks. We also agree that the subgroup of women with hormone receptor–positive breast cancer with low Ki-67 proliferation index (luminal A) is probably the same group identified by multigene assay that did not benefit from first-generation chemotherapy regimens, because there is proven high concordance between classification systems.[6] As regards the assertion by Mehta et al that standard therapy for all women with breast cancer should not be altered as a result of our findings, we do not advocate an immediate change, and we do state that these data are hypothesis generating only.[2] However, there is increasing support for the concept of all subtypes of breast cancer requiring targeted/individualized treatments.[7] Although the impulse to apply the most aggressive treatment in all women is a laudable application of the equity principle, we must remain open to more individualized therapy, if only to be mindful of the original Hippocratic oath: "Above all, do no harm."

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