Re: Prognostic Value of Ki67 Expression After Short-Term Presurgical Endocrine Therapy for Primary Breast Cancer

In a recent study, Dowsett et al. (1) reported that among postmenopausal patients with breast cancer, the proportion of tumor cells expressing Ki67 after 2 weeks of endocrine therapy predicted recurrence after resection better than the proportion of cells expressing Ki67 before initiation of endocrine therapy.

The authors compared Ki67 expression and other tumor cell characteristics in pairs of tumor biopsy samples. One sample in each pair was obtained by a core-needle biopsy of the primary tumor. The second sample was obtained during surgical resection of the primary tumor that was performed 2 weeks after the first sample was obtained. The authors found that the Ki67 values of the second sample predicted local and distant breast cancer recurrences better than the Ki67 values of the first sample. The authors claimed that the differences in the predictive capacity of Ki67 results arose as a result of 2 weeks of treatment with one of three endocrine therapies given between the first and second tissue sampling. This conclusion is not warranted.

We have shown that surgical trauma associated with breast cancer resection may be responsible for changing the dynamics of cancer recurrence and dissemination after resection (2–4). Badwe et al. (5) have shown that comparable effects on outcome occur after core-needle biopsy.

A core-needle biopsy, in which two or three cores of a tumor are taken, is a traumatic event. This procedure results in intratumoral and peritumoral bleeding and the resulting wound healing dynamic within the tumor bed has systemic effects.

It is possible that changes in biologic markers that are measured within a tumor nodule 2 weeks after a large-bore needle has been repeatedly passed through it may be associated with the 2 weeks of endocrine therapy that follows this wound. However, it is also possible that values of such measurements may be associated with either the wounding itself or the interaction of this surgical wounding with the endocrine therapy. It is important to differentiate between these two possibilities because modulation of the effects of surgical wounding upon subsequent cancer spread may be an important strategy to increase the curability of breast cancer, which should not be ignored (6).

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Response
Hrushesky et al. suggest that in our recent report (1), the relationship between recurrence-free survival and Ki67 expression in the excision biopsy after 2 weeks of preoperative treatment with endocrine therapy may not reflect the effect of this treatment
but rather some ill-defined biologic effects that result from the trauma associated with the pretreatment needle biopsy. Specifically, they suggest that “the values of such measurements may be associated with either the wounding itself or the interaction of this surgical wounding with endocrine therapy.”

We can directly rebut the first of these suggestions on the basis of previous work in which we found that Ki67 values were not statistically significantly different between the pretreatment and excision biopsy samples from subjects in the placebo arms of three short-term (1 or 2 week) preoperative studies (2–4). In these studies, the placebo arms were specifically included to ensure that we would record any effects of wounding on our biomarker measurements.

It is not clear to us how we might directly distinguish between the effect of the endocrine therapy and a hypothetical interaction between such therapy and surgical wounding. However, others (5) have reported that a core biopsy had a measurable impact on the expression of only a few genes, suggesting that the potential for such an interaction is modest. In addition, in the presurgical studies referred to above (2–4), it is notable that the endocrine therapies had no effect on the expression of Ki67 (or other markers) in estrogen receptor (ER)–negative tumors: the absence of an effect on Ki67 expression in the ER-negative subgroup would require that any interaction with trauma also depends on the ER status of the tumor.

Trauma associated with surgery for breast cancer may indeed have effects on long-term outcome, but we find the argument that it explains our 2-week Ki67 observations unconvincing. We maintain our view that the relationship between the 2-week Ki67 value and recurrence-free survival probably relates to a combination of the intrinsic prognostic value of pretreatment Ki67 expression and the change in Ki67 expression associated with estrogen deprivation, effects that are grounded in substantive experimental data from model systems as well as clinical correlations.

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