CORRESPONDENCE

Re: Mastectomy and Oophorectomy by Menstrual Cycle Phase in Women With Operable Breast Cancer

In their article recently published in the Journal, Love et al. *(1)* present provoking evidence that in a cohort of Vietnamese premenopausal breast cancer patients the timing of initiation of adjuvant hormone therapy (oophorectomy + tamoxifen) during the luteal phase of the menstrual cycle improves 5-year disease-free and overall survival. These data add fuel to the fire of the ongoing controversy on the role of the timing of breast cancer surgery during the menstrual cycle, and adding the new dimension of the timing of adjuvant hormone therapy initiation. Although the data are intriguing from both a biological and a clinical perspective, we believe that a note of caution in their interpretation is in order and we fully agree with the comments made by Dr. Hortobagyi in the accompanying editorial *(2)*.

In our opinion, the piece of evidence regarding the interactions between hormone receptor (HR) status and the timing of hormonal intervention is especially problematic. In fact, the statement that "similar levels of benefit of oophorectomy during the luteal phase [were] seen in patients with ER-positive or ER-negative cancers" appears to be somewhat in contrast with the observation that in the entire series, recently published in the *Journal of Clinical Oncology (3),* "only patients with hormone receptor-positive tumors benefited from the adjuvant treatment." Moreover, our group has recently shown that in premenopausal women with operable breast cancer who did not receive any adjuvant hormone treatment, the timing of surgery during the follicular or luteal phase, although not prognostic *per se,* does complement the prognostic relevance of HR status *(4)*.

Recently, we have analyzed these data further and found that the menstrual phase at the time of surgery was indeed prognostic in patients with HR-positive cancers, with patients operated upon in the follicular phase having statistically significantly better outcome ($P = .04$ for both disease-free and overall survival), but not in patients with HR-negative cancers ($P = .4$ and $P = .6$ for disease-free and overall survival, respectively); on the other hand, although of borderline prognostic significance in the whole population ($P = .07$ and $P = .02$ for disease-free and overall survival, respectively), HR status was a powerful prognostic factor for patients in the follicular phase ($P = .005$ and $P = .002$ for disease-free and overall survival, respectively), but not for patients in the luteal phase ($P = .85$ and $P = .58$ for disease-free and overall survival, respectively), even after adjusting for other prognostic factors. On the basis of this evidence, we created a hybrid prognostic variable including both parameters (follicular phase [F] at the time of surgery and positive HRs, F+) and tested it in multivariate analysis (Table 1). The results indicate that the hybrid F+ variable was an independent prognostic factor for disease-free survival and, quite surprisingly, the single most important prognostic factor for overall survival.

Table 1. Multivariate analysis of prognostic factors in 248 premenopausal patients receiving surgery followed by adjuvant chemotherapy for operable breast cancer*

	P values	
Prognostic factor	Disease-free survival	Overall survival
Tumor size	<.001	.15
Lymph-node status	<.001	.009
Hormone receptor status	.47	.26
Menstrual phase	.16	.28
Menstrual phase/HR status	.04	.003

*From October 1991 to April 1994, a cohort of 248 premenopausal women with operable breast cancer were accrued into a multicentric, prospective, randomized trial designed to evaluate the impact of the addition of lonidamine and/or granulocyte-colony stimulating factor (G-CSF) to the epidoxorubicin and cyclophosphamide (EC) chemotherapy regimen *(4,5)*. Multivariate analysis was performed by using BMDP software, release 7.0 (BMDP Statistical Software, Los Angeles, CA).

In our opinion, these results call for a more detailed analysis of the data by Love et al. *(1)* before a final conclusion can be made on whether the advantage observed for hormone treatment initiation in the luteal phase really derives from the timing of the therapeutic intervention rather than from a simple prognostic interaction. Such analysis should be performed on both adjuvant hormone-treated and untreated patients, and its results would be even more interesting in light of the unsettled question regarding differences in breast cancer hormone dependency in Asian, rather than in Western, women.

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According to Love et al. *(1),* premenopausal women with breast cancer had better disease-free and overall survival when they received mastectomy and oophorectomy with adjuvant tamoxifen therapy during the luteal phase rather than during the follicular phase of the menstrual cycle, regardless of hormone receptor status. Commenting on these data in his editorial, Dr. Hortobagyi *(2)* underlines that "despite reports to the contrary, there is no scientifically valid evidence that any endocrine intervention is effective for patients with estrogen receptor-negative tumors" and "there is no compelling biologic rationale to think that ovarian ablation will work in patients with estrogen receptor-negative tumors."

Estrogen affects cell signaling by binding to the estrogen receptor (ER) and promoting the transcription of ER-responsive genes. However, estrogen may also have ER-independent activity. Estrogen activates Akt and downstream anti-apoptotic signaling molecules through the phosphatidylinositol 3-kinase pathway *(3).* Estrogen has also been found to activate the mitogen-activated protein kinases, extracellular signal-regulated kinase Erk-1 and Erk-2, driving growth factor-dependent cellular responses through the G protein-coupled receptor homolog GPR30 *(4).* By contrast, tamoxifen can induce apoptosis and growth arrest by ER-mediated or ER-independent mechanisms *(5).* Although these preclinical data are not yet documented to be of clinical significance in breast cancer, the ability of tamoxifen to work independently of the ER has been shown in melanoma and glioma clinical trials *(5).*

We agree with Dr. Hortobagyi that the data from Love et al. "raise again the spectrum of the utility of an endocrine intervention in patients with estrogen receptor-negative tumors" *(2).* In fact, patients with ER-negative cancers in the oophorectomy and tamoxifen arm who had a mastectomy during the luteal phase of the menstrual cycle had better overall survival ($P = .02$) than did those who had surgery during the follicular phase *(1).* Some interesting evidence could explain these results. Although estrogen represents a major stimulant of mammary cell proliferation, the effect of progesterone remains controversial. Breast cell mitotic activity reaches its peak during the progesterone-dominant luteal phase. However, it has been suggested that progesterone decreases the invasiveness and metastatic potential of breast cancer cells, and that raised progesterone levels at the time of surgery confer a better prognosis to breast cancer patients. Moreover, although rats are protected from breast cancer by levels of estrogen and progesterone resembling those detected during pregnancy *(6),* neither hormone alone is sufficient to induce the same protective effect. It is noteworthy that the increased survival of breast cancer patients with subsequent full-term pregnancy could be consistent with an antitumor effect of pregnancy itself *(7).* This evidence could be associated with the sustained release of balanced levels of both estrogen and progesterone, partially observed also during the luteal phase.

Tumor expression of genes (such as p53 and matrix metalloproteinase-9) affecting the proliferation, metastatic potential, and postoperative production of angiogenic factors in the surgical wound could vary during the menstrual cycle and thus could potentially explain the improved survival of some patients who were operated on during the luteal phase of the menstrual cycle. Whether and how these factors could be responsible for the favorable outcome related to endocrine interventions in the luteal phase, as reported by Love et al. *(1),* is still unknown.

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The recent paper by Love et al. *(1)* describing the effect of the menstrual cycle timing of breast cancer resection upon outcome represents the first prospective investigation of this question. The findings are consistent with those of our earlier retrospective studies *(2–4).* The outcome for patients undergoing mastectomy or lumpectomy and receiving concurrent oophorectomy is profoundly dependent on the menstrual cycle timing of surgery. The optimal time, during the luteal phase, is as predicted by our original murine and clinical studies *(2,5,6).*

The menstrual cycle phase-based outcome difference, though gratifying, was unexpected because the median follow-up of these patients should not have been adequate to demonstrate it. Almost all retrospective studies demonstrating similar outcome differences require an actual median follow-up in excess of 5 years. Interestingly, the earlier retrospective data showed that patients with more advanced breast cancer had the largest and earliest differences in outcome depending on surgery timing. The

patient population studied by Love et al. *(1)* had, on average, more advanced breast cancer than did patients comprising a recent study *(4),* with average tumor sizes in the study by Love et al. *(1)* of more than 3 cm and involvement of an average of more than four axillary nodes. The prominence of menstrual cycle-dependent outcome in these patients may be the result, in part, of the extent of surgical wounding. Larger tumors with axillary node involvement require larger operations. The women in the study by Love et al. *(1)* who underwent both breast and ovarian resections also had more extensive surgical wounding by virtue of their concurrent abdominal surgery. The extent of the surgical wound is an important determinant of how soon the effect of its timing within the cycle becomes visible.

The effect of resection timing is not yet visible in those women undergoing mastectomy or lumpectomy but not subjected to oophorectomy because inadequate follow-up is available. This effect will show up in the data when each of these women has been followed for at least 5 years (median follow-up 7–10 years).

I agree with Dr. Hortobagyi's penultimate conclusion in the accompanying editorial *(7)* that adequate prospective study of whether operative timing within the menstrual cycle is essential. Unfortunately, all of the ongoing prospective studies are seriously flawed. Any trial with a *bona fide* chance to determine whether the timing of surgery affects breast cancer cure must minimally require the following: 1) meticulously locate when in the hormonal cycle the operation is performed, 2) shield any resection timing assignment from bias by some form of randomization, and 3) make absolutely certain that any and all surgical interventions are carried out at the same time within each woman's cycle. If any of these three essential requirements is absent, the results of the trial in question are uninterpretable. All ongoing studies violate at least one and sometimes all three of these essential requirements, as does Love's study.

Finally, I cannot agree with the ultimate conclusion that Dr. Hortobagyi reaches, namely that ". . . there is no reason to time either breast surgery or ovarian ablation according to the phase of the menstrual cycle." It is really hard to understand what argument could be made for not employing a strategy with no risk and no cost that has the potential to save 10 000–12 000 American and 200 000–240 000 young women's lives, worldwide, annually. This recommendation is, to me, unfathomable.

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RESPONSE

Like our reported analysis *(1),* the analysis reported by Milella et al. is exploratory. The similar levels of benefit seen in the estrogen receptor-positive and estrogen receptor-negative luteal phase operated subsets [*see* Fig. 4 in *(2)*] are not inconsistent with the overall results [*see* Figs. 2 and 3 in *(1)*], showing a statistically significant benefit from oophorectomy plus tamoxifen for estrogen receptor-positive but not estrogen receptor-negative tumor-bearing patients *(1).* There is, however, a suggested benefit in the estrogen receptor-negative group [*see* Fig. 3 in *(1)*]. The data presented in Fig 4, B *(2)* present a breakdown of the results for 90 of 105 patients in Fig. 3 *(1).* That this is also of borderline statistical significance is simply suggestive of luteal/follicular oophorectomy impact differences.

The results of Milella et al. show benefit from follicular phase breast surgery, a conclusion opposite that of another study *(3).* As we reported for similar numbers of patients treated with mastectomy alone *(2),* we did not find any menstrual cycle phase impact on survival overall, and in multivariate analyses including hormone receptor status as a variable, we found no interaction between hormone receptor status and menstrual cycle phase. In oophorectomized women where menstrual cycle differences were found, there was a suggestion of an interaction with hormone receptor status, but the interaction favored luteal phase oophorectomy for disease-free survival in estrogen receptor-positive patients and favored luteal phase oophorectomy for overall survival in estrogen receptor-negative patients. This finding is best seen in the comparative risk ratios for these hormonal status subsets [*see* subsets in Table 2 in *(2)*]. Thus, our results regarding the relationship of menstrual cycle phase and breast surgery alone are different than those of Milella et al. but not contradictory to their results. Our results regarding the relationship of menstrual cycle phase and oophorectomy, presuming they are confirmed by others and in prospective trials, may reflect the operation of completely different signaling mechanisms.

With respect to differences in breast cancers among Asian and western breast populations, the prognostic factors in our Vietnamese and Chinese patients were similar qualitatively and quantitatively to those seen in Western populations *(1).* We found the frequency of estrogen and progesterone receptor-positive tumors to be very similar to those found in western populations *(1).* We believe that the often reported lower frequencies of these proteins in Asian populations are more likely to reflect laboratory methologic differences rather than population differences.

We agree with Ferretti and colleagues that there are several possible mechanisms that could explain our results. We are particularly struck by the attempt of Baum et al. *(4)* to describe

the unpredictable natural history of breast cancer with a mathematical model. They suggested that micrometastases present at diagnosis are in a state of dynamic equilibrium, exquisitely sensitive to perioperative conditions, which luteal or follicular phase oophorectomy could dramatically change.

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