Adjuvant Surgical Oophorectomy Efficacy According to Hormonally-Determined Menstrual Cycle Phase

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Methods: The data from a previously reported adjuvant randomized clinical trial addressing the timing of surgical oophorectomy in the menstrual cycle have been examined in detail, presenting here new data from pre-planned secondary analyses. Multivariable Cox models were used.

Keywords: adjuvant therapy, surgical oophorectomy, tamoxifen, menstrual cycle timing.

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Short Title: Surgical Oophorectomy Plus Tamoxifen

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Methods: The data from a previously reported adjuvant randomized clinical trial addressing the timing of surgical oophorectomy in the menstrual cycle have been examined in detail, presenting here new data from pre-planned secondary analyses. Multivariable Cox models were used.

Results: In this adjuvant trial, among randomized subjects, women in prolonged follicular phases (>14 days) with low progesterone levels at the times of their surgeries derived minimal survival benefit from surgical oophorectomy plus tamoxifen treatments. The differences at 5 years compared with luteal phase patients with elevated progesterone levels, were, for disease free survival (DFS) 20% less, multivariable p=0.02; and for overall survival (OS) 15% less, multivariable p=0.036. Other sub-group comparisons in this trial support these findings.

Conclusion: Because one third of women undergoing surgical oophorectomy have worse outcomes if they are in prolonged follicular phases at the time of their surgeries, major outcome benefits are suggested to accrue to women undergoing this treatment in hormonally confirmed follicular and luteal menstrual cycle phases.

Keywords: adjuvant therapy, surgical oophorectomy, tamoxifen, menstrual cycle timing.

I. BACKGROUND

Globally, 500,000 premenopausal women annually present with hormone receptor positive breast cancer. For these women with operable disease, surgical oophorectomy or ovarian function-suppression plus tamoxifen are the most effective adjuvant therapies[1, 2, 3]. Secondary analysis of women in a clinical trial receiving surgical oophorectomy treatment suggested that if the oophorectomy surgery was performed during the luteal phase of the menstrual cycle, long term disease-free and overall survival were significantly better than if the surgery was done in the follicular phase[4]. We have conducted and reported two phase III trials, one in metastatic and one in adjuvant patients, to investigate this finding in which we presented some data from secondary pre-planned analyses of outcomes according to hormonally confirmed menstrual cycle phases[5, 6].

In the reported metastatic study, the primary analysis showed that the randomized luteal history (beyond day 14 since beginning of last menstrual period) and follicular history (from beginning day of menstrual period through day 14) surgical oophorectomy patients had equivalent overall survival (LH=FH for OS) [6]. In pre-planned analyses of all randomized patients with hormonal levels, based on confirmed hormonal status LH patients with high progesterone (Pg) levels had better overall survival than LH patients with low progesterone levels: 27 versus 17 months (multivariable p=0.14) [6].

The primary analysis of the adjuvant trial showed that luteal phase by history(LH) patients, did not have better survival than patients in historical follicular phase, FH, by strong trends (multivariable overall survival p=0.05)[5, Figure 2]. That is, contrary to the study hypothesis, LH patients had worse disease-free (DFS) and overall survival. One exploratory analysis result was presented: In patients randomized to receive mid-luteal phase surgery, patients with higher Pg (≥2ng/ml) had better DFS than those with < 2ng/ml (aHR 0.53; 95% CI 0.34 – 0.84; p=0.006) [5].

This communication reports new data from the adjuvant study, other data, and interpretations relevant to our findings.

II. METHODS

Reports of two phase III clinical trials of surgical oophorectomy plus tamoxifen (SO + T) in adjuvant and metastatic populations have been published with the detailed designs, eligibilities, IRB approvals, treatments, laboratory studies and statistical methods[5, 6]. A
The subgroups of unconfirmed and confirmed luteal phase status had markedly different survival experiences. Among all combined randomized patients, $L^H$ patients with high progesterone levels ("$L^H$ confirmed", $n=150$) had better survival than $L^L$ patients with low progesterone levels ("$L^L$ unconfirmed", $n=112$): the differences at 5 years were for disease-free survival, 20%, HR = 1.60 (95% CI: 1.07-2.38), multivariable $p=0.02$; and for overall survival, 15%, HR = 1.63 (95% CI: 1.03-2.56), multivariable $p=0.036$. The differences between $F^H$ confirmed ($n=121$) and $L^H$ unconfirmed ($n=112$) for both DFS and OS were marginally greater.

Among all randomized $L^H$ patients: those with high progesterone had better survival than those with low progesterone ($p=0.001$).

IV. Discussion

a) Interpretation

The reported new results show that in preplanned exploratory analyses in a second phase II adjuvant study, among the randomized patients, those patients found to be in prolonged follicular phase (that is beyond day 14 of their menstrual cycle) with low progesterone levels at the times of their oophorectomy surgeries, showed limited evidence of long-term disease-free and overall survival benefits, despite receiving additionally tamoxifen treatment. A conservative interpretation is that these observations define a new hypothesis. The major limitation of the results is that they are secondary study findings, whose statistical significance cannot be reliably estimated. The major strength of the results is that they have been found among randomized patients in two studies (5, 6).

As I have previously written, which critically bears repetition here: "the corollary to this new observation is that were such unconfirmed luteal phase patients (in these and other studies usually one third of patients) identified a priori, and not treated with this surgery at this time, those patients treated in hormonally-confirmed follicular or luteal phases would be expected to have better outcomes that the average outcomes that are seen from this treatment applied to all premenopausal women regardless of hormonal status and menstrual cycle phase. Thus, if in a high-risk group of women with operable breast cancer receiving SO (+T) (without paying any attention to their menstrual cycle history and blood levels of progesterone), 65% have no recurrence in 5 years; if patients have their SO in the first half of their menstrual cycles by history and with confirmation showing low progesterone blood levels, 72% will have no recurrence in 5 years. This increased level of benefit from appropriately timed SO, suggests that timed SO + T is more effective than GnRH + tamoxifen, and equivalently effective or better than GnRH + aromatase inhibitor[2].

III. Results

In pre-planned analyses based on hormonally-confirmed hormonal status, the explanation for the definitive primary analysis result is clear.[The result described above: luteal phase by history patients, did not have better survival than patients in historical follicular phase, (multivariable overall survival $p=0.05$)].

The consort figure for the adjuvant trial populations that are the subject of this report is presented in figure 1. In this study, 383 patients (of 509 randomized because they would not be by history in luteal phase—that is beyond day 14 since last menstrual period began—for the next 1-6 days) had: 1. menstrual cycle history data; 2. day-of-surgery blood hormone level determinations showing levels of <2ng/ml or 5 or greater ng/ml; and 3. complete follow up data. In the current report, Cox model subgroup analyses are based on data from these 383 subjects. In this adjuvant trial are three subgroups of the combined two randomized groups, defined by menstrual cycle dates history and hormonal levels on the dates of oophorectomy surgery (Figure 1). In this report luteal phase history patients with progesterone levels of $\geq$2 but < 5 ng/ml have been removed to provide information on the most well-defined follicular and luteal groups. The three subgroups of patients are: Follicular phase patients-by-history with progesterone levels <2ng/ml—"$F^H$ confirmed"; luteal phase-by-history patients with progesterone levels = >5ng/ml—"$L^H$ confirmed"; and luteal phase-by-history patients with progesterone levels <2 ng/ml or prolonged follicular phase patients, or anovulatory patients—"$L^L$ unconfirmed". If the less well-defined subgroup of 49 luteal phase by history patients with progesterone levels of between 2 and 5 ng/ml, half of whom were in follicular phase by history, is included as confirmed luteal phase patients, the results reported here are unchanged.

A multivariable Cox proportional hazards model was used to estimate adjusted hazard ratios between pairs of luteal phase-confirmed and unconfirmed, and luteal phase-unconfirmed and follicular phase-confirmed groups. In these analyses, the other prognostic variables included were: adjuvant radiotherapy, stage, nodal status, tumor size and patient age. As in the report of the primary analyses "proportionality assumptions for the Cox models were assessed by diagnostic plots of the scaled Schoenfeld residuals and log-minus-log survival plots. Substantial deviations from proportionality were not observed."

In all comparisons of these randomized patient subgroups, treatment group assigned at random assignment was compared regardless of the treatment received(5). P values are reported for completeness: because these are exploratory/explicative analyses, they cannot be considered hypothesis testing results.
Further discussion is warranted. The adjuvant therapy primary analysis results are definitive that patients in historical luteal phase are extremely unlikely to have better outcomes than patients in historical follicular phase[5]. The data presentation in the primary publication, while reporting the one exploratory analysis finding of better DFS in confirmed luteal versus unconfirmed luteal patients, was conservative in combining all patients in the trial, randomized and non-randomized. Because for unexplained reasons the nonrandomized patients enjoyed better-than-expected survival, the striking finding in the randomized patients reported here above, was not found. Differences in outcomes in non-randomized versus randomized groups of patients have been repeatedly observed, explained by selection bias, so these findings are not unusual, and are the basis for the current report emphasizing the clear explicable findings for the primary trial result, and their consistency with the results of the metastatic trial[6, 7].

b) The hypothesis-generating study data and their interpretation

The previous hypothesis-generating study also deserves comment[4]. The discussed adjuvant study was designed to test the hypothesis that surgery during historical luteal phase (L\textsuperscript{H}) of the menstrual cycle had superior efficacy [5]. This design followed from secondary exploratory analyses of an adjuvant study of surgical oophorectomy plus tamoxifen, which strongly suggested that L\textsuperscript{H} was superior [4]. How can the findings from these 3 studies be reconciled [4, 5, 6]? The hypothesis-generating study categorized patients as being F\textsuperscript{H} or L\textsuperscript{H} based on reported “day one” of their menstrual cycle at the time of their breast and surgical oophorectomy surgeries (done under the same anesthesia on the same days) [4]. Without careful discussion of this time point, we assumed that day one of the menstrual cycle according to the Vietnamese women was the day they began their menstrual bleeding. In discussions with Vietnamese, now American immigrant women, who had resided in Vietnam during the same period the study was conducted and who were in the same age range as the study subjects, these women indicated that their definition of day one of their menstrual cycle when they were in Vietnam, was the day they had no further menstrual bleeding. In exploring this possibility with the 3 Vietnamese investigating physicians, they agreed that this misunderstanding was very plausible. If we assume that this alternative definition was operative in the study for at least some of the women and their reported LMP dates, then the classifications made in the reported secondary analyses were wrong and the conclusion that L\textsuperscript{H} oophorectomy surgery gives better outcomes was grounded in mis-classifications[4]. If the conclusions from the new adjuvant (reported here) and metastatic studies are correct and represent ‘truth’, given this different definition, theoretically the original study might be expected to show the same result. This is because if we make the assumption that day of surgery in the menstrual cycle is always F\textsuperscript{H} + 6, and L\textsuperscript{H} + 6, new L\textsuperscript{H} defined patients will all be beyond day 21 in their cycles and more likely to be in hormonally-confirmable luteal phase (which patients in the new adjuvant and metastatic studies did well), and new F\textsuperscript{H} patients will include true F patients, and prolonged F patients (or “L\textsuperscript{H} unconfirmed”); the latter subgroup of whom did badly in the new studies as discussed above [5, 6]. Thus, conceivably the original study could in fact, with appropriate definitions of day one of the cycle, give the same L\textsuperscript{H} (very likely confirmable) better result than in a combined group of F\textsuperscript{H} (likely confirmable) and F\textsuperscript{H} (prolonged) (=L\textsuperscript{H} unconfirmed). When re-analyses were done under these new definitions, no DFS and OS differences were seen between the two redefined L\textsuperscript{H} and F\textsuperscript{H} groups. Given the now-likely poor and mixed patient and physician definitions quality of the menstrual cycle history data in this study, this revised result is not surprising [4].

c) Menstrual cycle hormonal biology which may explain the new surgical oophorectomy timing findings

What biological explanation is consistent with the summarized data that prolonged follicular phase patients derive minimal benefit from surgical oophorectomy plus tamoxifen treatments? To begin, it is important to note that typical human levels of progesterone are < 1 nanogram (ng) to about 20 ng/ml, while levels of estradiol are 50-200 picograms (pg)/ml. Thus, a typical luteal phase level of progesterone of 10 ng/ml is 50-fold greater than a typical estradiol level of 200pg/ml. When ovulation is delayed, there are sustained high estradiol levels for as many as 14 days or more. Indeed, in our data, the mean estradiol levels on the day of surgery were higher in the prolonged follicular phase (or L\textsuperscript{H} unconfirmed) group of patients than in the confirmed follicular patients. In the surgical oophorectomy situation, no progesterone “rescue” follows. In normal follicular phase, estradiol exposure is short, and in normal luteal phase exposure to some duration of progesterone “rescue” occurs before the oophorectomies. In anovulatory patients, the high and prolonged estradiol levels stimulate growth of micro-metastases as the last hormonal signal that these lesions receive. When it is done during the follicular phase of a cycle, oophorectomy appears to send a strong anti-growth signal. A flare of the metastatic disease is often seen about 7-10 days after starting the treatment. This kind of flare may be what is occurring with follicular phase oophorectomy. In a normal luteal phase, oophorectomy may have relatively small acute effects because of the last signals, which are high progesterone level-mediated.
The data from our two trials collectively are showing extraordinarily limited effects (in the sense of limited/no benefit from oophorectomies plus tamoxifen) in designated prolonged follicular phase-low progesterone patients from limited-time hormonal differences, while showing strong effects when this surgery is done in usual follicular or high progesterone luteal phases.

d) Other data which bear on the new hypothesis/interpretations

There are five observations which validate our findings because they are consistent with our observation of limited benefit from prolonged follicular phase patient-surgical oophorectomy. First, there are immediate and severe vasomotor symptoms in women following surgical oophorectomy. Second, men with metastatic prostate cancer have immediate responses with decreases in bone pain following orchiectomy. Third, Badwe et al. found that short-term adjuvant, parenteral peri-operative progesterone, which was associated with better outcomes in axillary node positive patients [8]. These results are consistent with our observation of absence of benefit with low-progesterone prolonged follicular phase patients. Four, the peaks of hazards for recurrence of breast cancer at 2-3 years post diagnosis and treatment have most strongly been related to peri-operative changes. Baum et al. suggested that minor peri-operative changes can lead to major long-term effects [9, 10]. Finally, other peri-operative conditions of limited duration have been suggested to have major longer-term impacts[11].

V. Conclusions

The potential greater efficacy with timing in the menstrual cycle of the surgical oophorectomy would make this treatment combined with tamoxifen, already the first global option adjuvant treatment based on efficacy, practicality and cost-efficacy, an even more compelling therapy [2, 3]. A practical interpretation is that acting on this observation and performing surgical oophorectomies whenever possible in hormonally confirmed follicular or luteal phases appears very unlikely to be harmful in terms of efficacy. Were surgical oophorectomy plus tamoxifen adjuvant therapy widely promoted and applied across the world, a reasonable estimate is that 100,000 women a year would be saved, women who otherwise would get little or no effective adjuvant treatment (12). Were timed surgical oophorectomy widely promoted and applied as host-personalized therapy, an additional 20,000 women per year might be saved.

If a conservative position is taken with regard to these timing data, that the case that women in prolonged follicular phase with low progesterone levels benefit little from oophorectomy done at this time, has but limited support, then the rational approach is to do a clinical trial of timed SO+T (excluding prolonged follicular phase confirmed women) vs. GnRH/LHRH +T (or aromatase inhibitor). With provision of the drugs, this would not be a difficult trial to do, certainly with low- and middle-income county participation.

Declarations

Ethics approval and consent to participate

The data reported in this manuscript have come from previously approved clinical trials. The approvals have been both in the home countries of the patients and in the United States.

Consent for publication

With this submission the sole author implicitly provides consent to publish.

Availability of data and material

The primary study data and files are available. ClinicalTrials.govnumbers, NCT 00201851 and NCT00293540

Competing interests

The author reports no conflicts of interest.

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Scheduled surgeries were assigned to be in mid-luteal phase by history. For these patients, by history, 96% of surgeries were done in luteal phase.

For these patients, 66% had surgeries by history in follicular phase.

These percentages make clear the rationale for the secondary analyses based on the better menstrual cycle phase status of study patients using day of surgery progesterone levels.

Figure 1: CONSORT diagram for the trial.

1Scheduled surgeries were assigned to be in mid-luteal phase by history. For these patients, by history, 96% of surgeries were done in luteal phase.

2For these patients, 66% had surgeries by history in follicular phase.

These percentages make clear the rationale for the secondary analyses based on the better menstrual cycle phase status of study patients using day of surgery progesterone levels.