

## Original article

# Tamoxifen-induced severe hot flashes and endoxifen levels: is dose reduction a safe and effective strategy?



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## ABSTRACT

**Objectives:** Severe hot flash (HF) toxicity due to tamoxifen can compromise compliance. We previously found that HFs did not correlate with endoxifen level or *CYP2D6* genotype. In this study, we reduced tamoxifen dose in patients with severe HFs to determine whether HFs were ameliorated whilst maintaining a purported therapeutic endoxifen level of >15 nM.

**Materials and methods:** Twenty patients with severe HFs on 20 mg TAM had *CYP2D6* genotype, trough level tamoxifen and metabolites measured with Loprinzi HF scores (HFS) derived before and after DR of tamoxifen to 10 mg. Other data collected included demographics, smoking, alcohol, menstrual and breast cancer history, previous chemotherapies, concurrent medications, BMI and other tamoxifen toxicities.

**Results:** At the 20 mg tamoxifen dose, endoxifen levels were 25.6, 0–91.9 nM (median, range) with HFS 131, 22–1482 (median, range). Upon DR to 10 mg, median endoxifen level fell to 14.1, 0.6–71.9 nM (difference in means  $p = 0.11$ , two-tailed T test) with HFS 47, 5–864 (difference in means  $p = 0.24$ , two-tailed T test). Despite lacking statistical significance, 85% of patients reported subjective improvement of HFs with DR. After DR, the proportion of patients with endoxifen level <15 nM increased from 20% to 50%. HFS did not correlate with any other parameter.

**Conclusion:** DR of tamoxifen from 20 mg to 10 mg daily resulted in halving of endoxifen levels and subjective improvement of HF. While half the dose-reduced patients were below a potential therapeutic level of endoxifen, other recent studies suggest that low endoxifen levels may not indicate reduced effectiveness of tamoxifen.

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## 1. Introduction

It has been established for over three decades that tamoxifen is an effective endocrine therapy for hormone sensitive breast cancer, and it is used especially for premenopausal and perimenopausal women. Although it is well-tolerated generally, hot flashes as well as other vasomotor side effects can be a problematic toxicity for up to 78% [1] of patients and can threaten compliance in the long term

[2]. While for premenopausal women tamoxifen is still generally standard of care, it also remains an important option for postmenopausal women who develop troublesome side-effects with aromatase inhibitors.

There are discordant data in the literature as to the meaning and relevance of hot flashes in the context of tamoxifen therapy. Although a few studies have suggested that the presence of hot flashes might be a pharmacodynamic indicator of clinical effect [1,3–5] and hence desirable, other studies did not find such a relationship [6–9]. Moreover, Baxter et al. reported an inverse relationship between hot flash severity and endoxifen levels [10].

It is known that the metabolism of the pro-drug, tamoxifen is

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complex and differs significantly between individuals. Endoxifen is the main active tamoxifen-metabolite that mediates the tamoxifen effect and the enzyme Cytochrome P450 2D6 (CYP2D6) is a key determinant in its production. It is evident that polymorphisms of CYP2D6 contribute to variability in average endoxifen levels, with “extensive” metabolizer genotypes demonstrating higher average endoxifen levels, and conversely, “poor” metabolizer genotypes leading to lower levels [11], although non-genetic factors are also important in determining exposure [11].

Consequently, it has been hypothesized that CYP2D6 genotype could correlate with breast cancer outcomes following tamoxifen therapy. However, the results of the largest dataset published to date [9] found no correlation between CYP2D6 genotype and breast cancer recurrence rates, suggesting that direct measurement of endoxifen levels may be a more useful clinical indicator of tamoxifen effect than CYP2D6 genotype. Furthermore, the relationship between CYP2D6 genotype, hot flashes, endoxifen levels and clinical outcomes is unclear for individual patients on tamoxifen. We reported previously in a prospectively collected cohort of 122 women treated with tamoxifen, that neither incidence nor severity of hot flashes could be used as a surrogate marker for endoxifen levels and thus potentially clinical outcomes [11].

There has been considerable debate on the importance of endoxifen levels, and whether a therapeutic threshold can be defined. Initially, a cohort of 1370 women on tamoxifen suggested a therapeutic threshold level of 15nM<sup>12</sup>. Below this level, women were 26% more likely to recur. This was again demonstrated in a cohort of 306 women where endoxifen levels below 15 nM similarly had worse disease free survival from their breast cancer [13]. In two recently reported prospective cohorts however, there has not been demonstrable correlation between endoxifen level thresholds and efficacy in tamoxifen treated cohorts both in the metastatic and neoadjuvant setting in one study [14] and in the adjuvant setting in another [15]. In the adjuvant setting, however, we certainly know that treatment adherence [16] improves disease outcomes, and that understanding and ameliorating toxicity to achieve compliance is important.

We hypothesised that since a potential strategy to reduce hot flash symptoms might be to reduce tamoxifen dose, it may be clinically relevant to know whether this causes endoxifen levels to become purportedly sub-therapeutic according to the previously reported 15 nM threshold. There are reports of measures other than dose modification to ameliorate hot flushes including non-hormonal pharmacological strategies [17–20]. To our knowledge however, the effect of dose reduction of tamoxifen as a strategy to ameliorate hot flash toxicity has not previously been tested, and the effect this has on endoxifen levels is unknown. Additionally, though a dose of 5 mg has been examined in the context of breast cancer prevention [21,22], the efficacy and utility of dose reduction in the face of severe toxicity has not been previously reported in patients treated with tamoxifen for invasive breast cancer.

We therefore aimed to test whether reducing the dose of tamoxifen from 20 mg per day to 10 mg per day would ameliorate hot flashes and whether in doing so, endoxifen levels remained above the suggested threshold of 15 nM. In this pilot study, we recruited patients who were taking 20 mg tamoxifen daily and who had sufficient vasomotor toxicity to consider stopping the drug. We then compared symptom severity scores and endoxifen levels before and after dose reduction.

## 2. Materials and Methods

### 2.1. Patients

The study cohort included 20 women with a history of breast

cancer, who were experiencing severe vasomotor and hot flash toxicity due to tamoxifen and who felt that the degree of this toxicity was severe enough to threaten treatment continuation. Informed consent was obtained from participants and the study was conducted with approval from the local Human Research Ethics Committee, Westmead Hospital, Sydney.

### 2.2. Study protocol

Once enrolled, the women completed a Loprinzi hot flash diary for seven consecutive days from which a total hot flash score (HFS) was derived [23]. Blood samples were collected for CYP2D6 genotyping and tamoxifen-metabolite levels. Other data collected included tamoxifen-mediated toxicities, anthropometric indices, ECOG performance status (PS), smoking history, alcohol intake, previous chemotherapies, menopausal status and ethnicity. Patients were dose reduced to 10 mg of tamoxifen for 8 weeks prior to repeating the Loprinzi hot flash diary and blood tests at the 10 mg level dose.

### 2.3. CYP2D6 genotyping and tamoxifen metabolite measurements

CYP2D6 genotyping categorized patients into Extensive, Moderate and Poor metabolizers as previously described [11]. Metabolite levels were performed to assess levels of tamoxifen, N-desmethyltamoxifen (NDMT), 4-OH-tamoxifen (4OHT), Z-endoxifen (endoxifen) and 4'-OH N-desmethyltamoxifen (Z'-endoxifen) levels via a validated mass spectrometry technique as previously described [11].

### 2.4. Statistical analysis

Analyses were then carried out to test whether there were any significant relationships between dose reduction and amelioration of hot flashes and fall in metabolite levels, particularly endoxifen. We compared the distribution of genotype in these twenty patients with the genotype distribution in the previous unselected cohort of 122 patients [11]. The Spearman rank correlation coefficient was utilized to assess any association between patient-related variables including smoking and alcohol history, breast cancer history, previous chemotherapies, concurrent medications, menstrual history, body mass index (BMI) and other toxicities recognized to be associated with tamoxifen and HFS.

## 3. Results

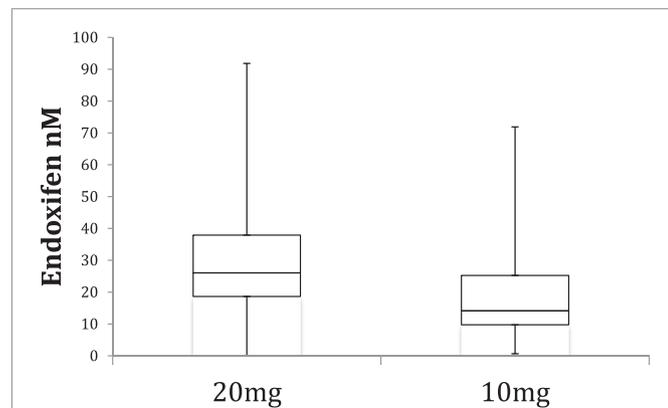
### 3.1. Cohort characteristics

Twenty women were enrolled in the study (median age 52, range 34–73). The median time on tamoxifen treatment was 14 months, range 2–43 months. At diagnosis of breast cancer, 16 (80%) were pre or peri menopausal and four (20%) were postmenopausal. At time of study entry, nine (45%) of women were postmenopausal. Three (15%) of the women were experiencing menstrual cycles whilst on study. In all patients, PS was 0 or 1 excepting one patient who was PS 2. BMI was varied in the cohort: 27 median, 28 mean, 19–44 range. Fourteen (70%) of patients received prior chemotherapy. Of these all had received anthracyclines and nine (45%) received taxanes. One patient was concomitantly treated with the weak CYP2D6 inhibitor, sertraline and still experiencing significant hot flushes. This patient had been on sertraline for depression and was stable from a depression point of view. Her antidepressant did not change during tamoxifen treatment. No other patients were on CYP2D6 inhibitors.

There was no association between baseline HFS and menopausal

**Table 1**  
Spearman's rank correlation coefficients demonstrating lack of correlation between patient variables and baseline HFS.

Patient Variables	Correlation coefficient HFS
Tamoxifen dose	
Endoxifen at 20 mg	−0.17
Endoxifen at 10 mg	−0.01
Trough levels	
Tamoxifen	−0.09
4 OH tamoxifen	−0.37
NDMTamoxifen	−0.18
4OHNDMTamoxifen	−0.67
Clinical factors	
Smoking	0.29
ETOH	−0.13
Receipt of previous chemotherapy	0.06
Receipt of previous anthracycline	0.06
Receipt of previous taxane	0.11
Menopausal status	0.14
Time since Last Menstrual Period	−0.04
BMI	0.02
ECOG	0.23



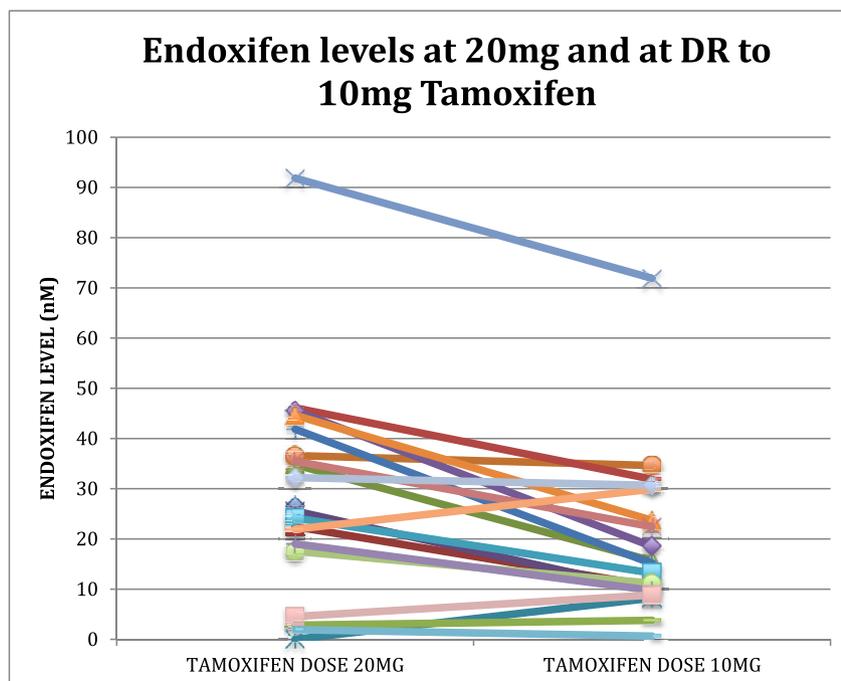
**Fig. 1.** Endoxifen level at 20 mg and 10 mg tamoxifen. Two-tailed t-test  $p = 0.11$ .

state of the patient, nor with duration since last menstrual period if postmenopausal. HFS did not correlate with BMI or ETOH consumption, receipt of or type of chemotherapy (Table 1).

At 20 mg dose of tamoxifen, baseline endoxifen levels were 25.6, 0–91.9 nM (median, range), consistent with the high variability seen in our previous 122 patient cohort [11]. Following dose reduction to 10 mg, endoxifen levels fell to 14.1, 0.6–71.9 nM (difference in means  $p = 0.11$ , two-tailed T test) as shown in Fig. 1 (note one patient had an unrecordable endoxifen level at baseline but level of 8.1 nM at dose reduction, suggesting a lack of compliance). Fig. 2 demonstrates individual endoxifen level changes. It is important to note that 4/20 (20%) of patients at baseline had endoxifen levels below 15 nM, the suggested threshold for therapeutic efficacy [12,13]. After dose reduction this proportion rose to 10/20 (50%). Of note endoxifen levels were 26 nM at 20 mg and 13 at 10 mg for the one patient who was on sertraline.

HFS at baseline were 131, 22–1482 (median, range) and fell to 47, 5–864 with dose reduction (difference in means  $p = 0.24$ , two-tailed T test), Fig. 3. Despite this lack of statistical significance, 85% of patients reported subjective improvement in symptomatic hot flashes with dose reduction. Fig. 4 shows the individual HFS changes. In all patients but two, there was a reduction of hot flash score with dose reduction. In these two patients, there was an increase in hot flash score with dose reduction and no subjective improvement of hot flashes reported. No patients on study reported subjective exacerbation of hot flashes with dose reduction, despite the increase in Loprinzi hot flash score in those two patients. Also, despite the lack of statistical significance, eight of twenty patients demonstrated inpatient reduction of HFS of greater than 50%. There was no statistically significant association between HFS with tamoxifen and its metabolites, smoking/alcohol use, previous chemotherapy use, menopausal status, time since last menstrual period, BMI and ECOG performance status (Table 1).

Nineteen of 20 patients were CYP2D6 genotyped, and the distribution of genotypes of these patients selected for severe hot flashes was similar to those in our previous 122 patient cohort [11], who were not selected for severe hot flashes. Categorised into



**Fig. 2.** Individual patient data of endoxifen levels at 20 mg and 10 mg TAM.

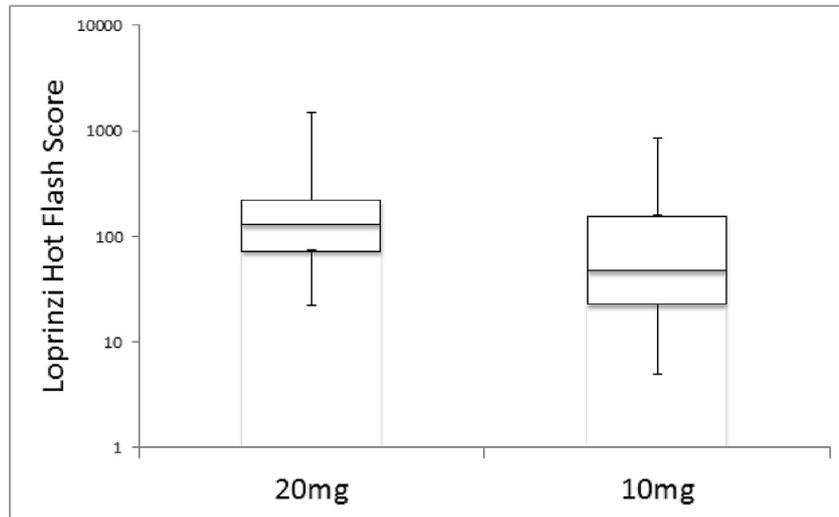


Fig. 3. Trend to modest fall in HFS upon dose reduction from 20 mg to 10 mg TAM shown in log. Comparison of means without statistical significance (two tailed t-test  $p = 0.24$ ).

metabolizer groups of CYP2D6, 84% were extensive metabolisers, 11% intermediate metabolisers and 5% poor metabolisers.

**4. Discussion**

Though generally well tolerated, tamoxifen can cause symptomatic toxicity that poses a barrier to effective treatment due to threatened compliance in some patients. The importance of committed adherence to daily dosing during a long-term endocrine therapy regimen for five years or more is paramount to derive maximal adjuvant benefit.

Our study tested the effects of dose reducing tamoxifen on endoxifen levels and hot flash scores in a small cohort of women selected for problematic hot flashes. We demonstrated falls in both

endoxifen levels and hot flash scores though these differences were not statistically significant, likely due to the small sample size.

Though there was not a statistically significant improvement in hot flashes upon dose reduction when measured by the Loprinzi instrument, there was subjective reporting of improvement by the majority of women enrolled in the study. In these women who experienced subjective improvement of hot flashes, adherence and motivation to persist with tamoxifen endocrine therapy at the lower dose was observed, and in fact a number of women have continued to be treated with 10 mg post-study.

Madlensky et al. and Saladores et al. suggested that women with endoxifen levels  $<15$  nM had an increased risk of recurrence [12,13]. Two more recent studies challenge this finding [14,15]. Our previous 122 patient dose escalation cohort revealed that 24% of

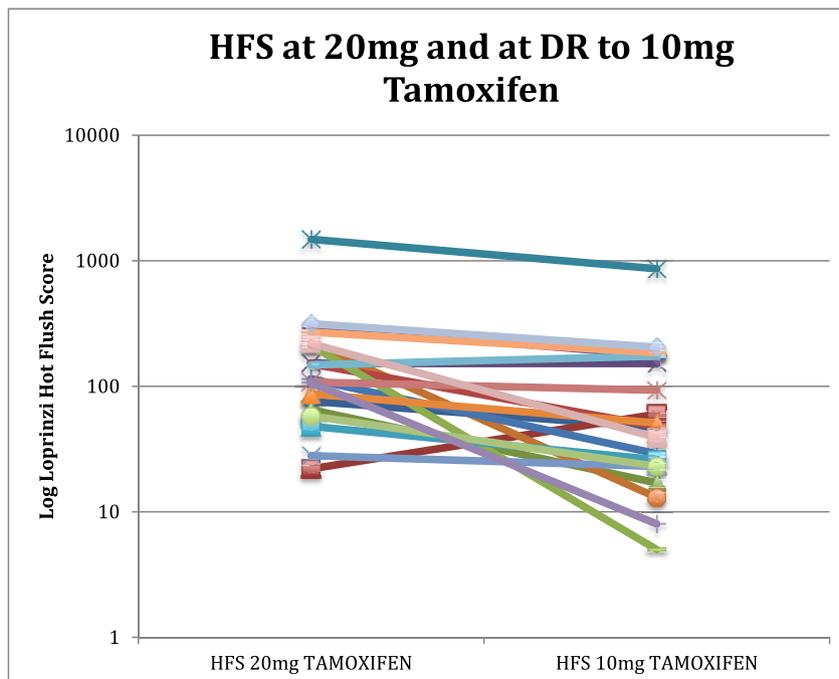


Fig. 4. Individual patient data of log HFS at 20 mg and 10 mg TAM showing trend to modest subjective improvement of HFS upon dose reduction.

patients at the baseline dose of 20 mg of tamoxifen once per day had endoxifen levels below 15nM<sup>11</sup>. Upon tamoxifen dose escalation in this study, only 6% of patients were below the 15 nM therapeutic threshold. We also demonstrated that dose escalation consistently resulted in increased levels of endoxifen [11].

In our current study, we found that endoxifen levels generally reduced upon dose reduction. Importantly, we found that the proportion of women with a potentially subtherapeutic endoxifen level increased from 22% at 20 mg to 50% at the reduced dose of 10 mg, although the clinical relevance of this remains unclear. A recent report showed that a 5 mg dose of tamoxifen was effective in patients with non-invasive disease [22], and this is somewhat reassuring. Consistent with our small study, women in that cohort had low levels of vasomotor toxicity.

In this group of patients selected for severe hot flash toxicity, *CYP2D6* genotype, endoxifen and other metabolite levels varied in line with other cohorts. Our previous study demonstrated that hot flash severity was not associated with increased tamoxifen dose or endoxifen level. In the current study, although there was subjective improvement of hot flashes with dose reduction, there was no statistically significant improvement in hot flash score as measured by the validated Loprinzi instrument. Because there was no blinding, factors other than endoxifen level may have contributed to the reported improvement including personal expectations of benefit (placebo effect).

In our previous dose escalation paper, we concluded that hot flashes in the presence of tamoxifen treatment are not related to tamoxifen dose, endoxifen level or *CYP2D6* genotype [11]. We conclude from the current study, that tamoxifen dose reduction in patients with severe hot flashes leads to subjective improvement in symptoms in a majority of patients and a non-statistically significant improvement in objective Loprinzi score. While 50% of these patients developed a potentially subtherapeutic endoxifen level upon dose reduction, recent studies suggest that this may not be as much of a concern as previously suspected.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.breast.2019.05.009>.

## Conflicts of interest

Clara Inkyung Lee, Peter Fox, Bavanthi Balakrishnar, Rosemary L Balleine, Bo Gao, Pamela Provan, Sally Coulter, Christopher Liddle, Mark Wong, and Nicholas Wilcken have no conflicts of interest to declare.

Rina Hui has conflicts to declare including: Advisory board member for Merck Sharp and Dohme, Astra Zeneca, Novartis, Roche and Bristol-Myers Squib, speaker honorarium for Merck Sharp and Dohme.

Howard Gurney has conflicts to declare including: Advisory board/consulting role for Bristol-Myers Squib, Ipsen, Merck Sharp and Dohme, Astra Zeneca, Janssen-Cilag Honorarium for Pfizer.

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## Ethical approval

Informed consent was obtained from participants and the study was conducted with approval from the local Human Research Ethics Committee, Westmead Hospital, Sydney.

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