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Original article

Dosage-dependent reduction of macular pigment optical density in female breast cancer patients receiving tamoxifen adjuvant therapy

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ABSTRACT

It is now increasingly common for breast cancer patients to receive adjuvant tamoxifen therapy for a period of up to 10 years. As survival rate increases, managing tamoxifen ocular toxicities is important for patients' quality of life. Macular pigments in photoreceptor cells protect against free radical damage, which can cause macular degeneration. By reducing macular pigment concentration, tamoxifen may increase the risk of macular degeneration. Here, we compared macular pigment optical density (MPOD) and central macular thickness between breast cancer patients on tamoxifen adjuvant therapy (n = 70), and a control group (n = 72). Multiple regression analysis indicated that MPOD decreases with increasing tamoxifen dosage, up to a threshold of about 20 g, after which MPOD plateaus out. Mean MPOD in the treatment group (mean = 0.40) was significantly lower (p-value = 0.02) compared to the control group (mean = 0.47) for the left eye, and for the right eye (treatment mean = 0.39; control mean = 0.48; p-value = 0.009). No significant difference in mean central macular thickness was found between the treatment and the control group (p-values > 0.4). In the control group, MPOD and central macular thickness showed significant correlation (r~0.30; p-values < 0.01) for both eyes. However, in the treatment group, loss of significant correlation was observed in the left eye ($r = 0.21$; p-value = 0.08). The present results show that MPOD decreases non-linearly as a function of tamoxifen dosage, and highlight the potential of tamoxifen to reduce macular pigment concentration through an unknown mechanism that does not depend on macular thinning solely.

1. Introduction

Long-term adjuvant tamoxifen therapy is now firmly established as an effective clinical intervention that saves the lives of breast cancer patients [1–6].Originally, adjuvant tamoxifen therapy was continued for up to 5 years; however, data indicating enhanced efficacy with up to 10 years of therapy means that some women will be using tamoxifen for up to a decade [2]. Cumulative evidence from several large randomised clinical trials strongly indicates that tamoxifen is also effective for the prevention of breast cancer in healthy women [7–11].As more and more women benefit from the use of tamoxifen, the side effects of being exposed to long-term usage of tamoxifen need to be addressed. A potentially life-threatening side effect is the elevation of the risk of endometrial cancer [12]. However, the most commonly reported side effect is postmenopausal symptoms that can impact the patients' quality of life [13].

Tamoxifen-induced ocular toxicities such as crystalline retinal deposits were first noted in 1978 among women receiving extremely high dosage to tamoxifen (120–320 mg/day) [14]. Other complications include macular edema [15], retinopathy [16] and keratopathy [17]. Patients receiving high-dosage tamoxifen may develop extensive retinal lesions, and become visually impaired as a result of macular edema [18]. The increased risk for developing cataracts when tamoxifen was used for 5 years or more has been

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reported [19]. For some women below 50 years old, tamoxifen can affect the optic nerve head by causing subclinical swelling within the first two years of use [20]. Tamoxifen maculopathy in the form of microcystoid maculopathy [21] and crystalline maculopathy [22] have also been reported. While tamoxifen retinopathy may be uncommon (prevalence ~ 3.1%) [23], it can result in foveal cystoid spaces that increase the risk for macula holes [20].

From a theoretical point of view, tamoxifen-induced retinal pigment epithelium (RPE) cell death may be expected to correlate with a reduction in the availability of macular pigment (MP), which is measurable in the form of macular pigment optical density (MPOD). The MP comprises three isomeric carotenoids: meso-zeaxanthin, lutein, and zeaxanthin. These pigments accumulate in high concentrations at the macula [24,25]; they protect the photoreceptor cells by filtering blue light, and by quenching reactive oxygen species (ROS) [26–28]. Furthermore, by attenuating oxidative injury at the macula, MP potentially protects against age-related macular degeneration [29,30]. Supplementing diets with meso-zeaxanthin, lutein, and zeaxanthin is known to improve visual performance [31].

The present study aims to model variation in MPOD as a function of central macular thickness and tamoxifen dosage. To this end, we used a treatment group consisting of female breast cancer patients who received tamoxifen treatment, and a comparable control group.

2. Materials and methods

2.1. Study design

The present study is cross-sectional. It adheres to the Declaration of Helsinki and Good Clinical Practice guidelines. Institutional Review Board approval (MREC ID No. 20164-2395) was obtained from the Medical Ethics Board of University of Malaya Medical Centre (UMMC). Prior to enrolment of each breast cancer patient and control subject, written informed consent was obtained.

2.2. Study population

Breast cancer patients were recruited from the UMMC Breast Clinic, and the UMMC Oncology Clinic. Healthy volunteers were recruited from relatives of accompanying patients, and UMMC hospital staff. The study was conducted from 1 December 2016 until 1 June 2017 at the UMMC Eye Clinic.

2.3. Patient selection

In this study, the case subjects were recruited from female breast cancer patients attending the UMMC Oncology Clinic who received tamoxifen (standard dosage of 20 mg per day) as an adjuvant endocrine therapy. If they received radiotherapy, only those who had it confined to the thoracic region were included. The acceptable cancer stage was limited to stage 0, I or II. Diabetic patients were included only if diabetic retinopathy has been excluded at screening.

Subjects were excluded from the study if they met any of the following criteria: having received chemotherapy, had late stage (stage III) or metastatic breast cancer, had history of radiotherapy applied to the head and neck (inclusive of supraclavicular) region, or had one or more of the following ocular pathologies: pre-existing retinal diseases, macular diseases, glaucoma, cataract or vitreoretinal surgery, ocular trauma, optic neuropathy, intraocular pressure of 21 mmHg or higher, media opacity (corneal scar, dense cataract, dense asteroid hyalosis, etc.), and poor optical coherence tomography (OCT) signal (<6/10). We also excluded patients who had taken the following medications: hydroxychloroquine, chloroquine, thioridazine, desferoxamine, topiramate, epinephrine, digoxine, sildenafil and/or lutein and zeaxanthin supplements.

Female control subjects were recruited from healthy volunteers who had best corrected visual acuity of 6/12 or better, and normal morphology on spectral domain optical coherence tomography (SD-OCT). As far as possible, the control and the case subjects were matched with respect to age (±3 years difference), ethnicity, and diabetes status.

2.4. Data collection

Subjects who passed the inclusion-exclusion criteria underwent sequential examination consisting of visual and refraction acuity test, spherical equivalent measurement (TopCon KR-8100 Autorefractor Keratometer), undilated slit-lamp biomicroscopy examination, OCT of macula (Model 4000; Carl Zeiss Meditec AG, Germany), measurement of MPOD (MPS II; Tinsley Precision Instruments, UK) and finally, a fully-dilated fundus examination. Relevant demographic and clinical data were collected from the subjects. For calculation of total tamoxifen dosage ever received, the daily consumption dosage of 20 mg/day was multiplied by the number of days from the date of commencing tamoxifen treatment until the day when subjects had their MPOD measured.

2.5. MPOD measurement

MPOD was measured at 0.5° and 7.0° foveal eccentricities. The target was a solid disk of 0.5° arc radius. A small black dot at the centre of the solid disks is meant to facilitate fixation. The wave length composition of the test stimulus alternated between 460 nm (peak MP absorbance) and 540 nm. To measure the parafoveal region, the subjects were asked to fixate on a red light located precisely at 7.0° from the central fixation area.

The patients were trained so that they were able to recognize the null zone (zone of no or minimal flicker). The subjects only had to respond when they first perceive a flicker by pressing a button. Throughout a series of pre-set blue-green luminance ratio, the frequency of blue-green alternation automatically decreases. The MPs in the fovea attenuate the blue component of the stimulus; thus, to perceive a minimal flicker, a greater intensity of blue light is required. This is more so while looking at the stimulus directly as compared to when the stimulus is viewed from the periphery.

Viewing the target eccentrically (while the eye being tested fixates on the peripheral fixation target) means that the observer is actually utilising a part of the retina where MPs are presumed to be absent. As the MPs are absent there, the intensity ratio at which minimum flicker is obtained would differ from the foveal one. The MPOD is calculated as the $\log_{10}$ of the ratio of the intensity of blue light needed to perceive minimal flicker directly, to the intensity of blue light needed to perceive minimal flicker from peripheral fixation.

2.6. Statistical analyses

To demonstrate comparability of the control and the treatment group, we performed two-sample t-tests to assess whether mean age, body mass index (BMI), spherical equivalent, and best corrected visual acuity differed significantly between the two groups. For ethnicity and diabetes status, we used the chi-squared test of association between two categorical variables.

For testing whether mean macular thickness and mean MPOD differed between the control and the treatment group, the two-sample t-test was also used. Multiple linear regression analysis was used to evaluate whether central macular thickness, dosage of