REVIEW

Patient-controlled transdermal 4-hydroxytamoxifen (4-OHT) vs. oral tamoxifen: A systematic review and meta analysis

Usha Sundralingam[1], Tahir Mehmood Khan[2], Sumita Elendran[1], Saravanan Muniyandy[2] and Uma D Palanisamy[1]*

[1]School of Medicine and Health Sciences, Monash University Malaysia, Jalan Lagoon Selatan, Bandar Sunway, Selangor Darul Ehsan. Malaysia

[2]School of Pharmacy, Monash University Malaysia, Jalan Lagoon Selatan, Bandar Sunway, Selangor Darul Ehsan. Malaysia

Abstract: There has been a number of studies looking into an alternative mode of therapy for the treament of breast cancer via 4-hydroxytamoxifen (4-OHT) transdermal administration.This systematic review aims to compare the safety and efficacy of a transdermal 4-OHT local therapy and oral tamoxifen (oral-T) on the treatment of ductal carcinoma *in situ* breast cancer. Through a systematic search of health science databases, eligible trials were located and the end points assessed were Ki-67 labeling index, concentration of 4-OHT in breast adipose tissue (ng/g) and plasma (ng/ml). Revman 5.3 version was used to perfom the meta-analysis. Three trials were identified (n=103), while only two were included for meta analysis. The mean difference between the two studies included were 0.40 and -10.58. Overall the I^2 value was 89.0%, (Tau^2 =53.86) and the differences between the two trials were statistically significant p=0.002. The meta analysis of the randomized controlled trials showed that the use of local transdermal therapy of 4-OHT gel is more safer than oral-T. However, due to the limited number of studies, the potential use of 4-OHT topical transdermal therapy for the treatment of breast cancer could not be concluded for healthcare professionals.

Keywords: Transdermal drug delivery, 4-hydroxytamoxifen, oral tamoxifen, breast cancer, systematic review and meta-analysis.

INTRODUCTION

Current research in mitigating breast cancer (BC) has failed to address the key issue of considering patient compliance. Studies have shown the need to reduce and manage the disease and treatment-related symptoms which could improve the quality of life among women with BC (Janz *et al.*, 2007). Cancer diagnosis and its treatment course can not only have an ongoing physical and psychologic effect on the life and well being of BC patients, but also remain an issue in long-term survival (Christiane Brems *et al.*, 2013).

In the US, the incidence of mammary ductal carcinoma *in situ* (DCIS) increased over seven-fold from 1980 to 2007, from 4.8 per 100 000 to 34.6 per 100 000. Today, approximately one in four woman with invasive BC is diagnosed with DCIS. Patients with DCIS are advised to undertake systemic therapy in the form of oral tamoxifen (oral-T) to further reduce the risk of local breast events. Although oral administration is proved to be quite effective; tamoxifen exhibits side effects such as hot flashes and vaginal symptoms (Port *et al.*, 2001, Day *et al.*, 1999), endometrial carcinoma, ocular problems, thromboembolic disorders and acquired drug resistance on long-term therapy (Morrow and Jordan, 1993, Jordan, 1995, Brigger *et al.*, 2001, Fisher *et al.*, 1998). Moreover, oral-T is a prodrug and it requires conversion by drug metabolizing enzymes to its' metabolite 4-hydroxytamoxifen (4-OHT), which has better binding affinity for estrogen receptors compared to tamoxifen.

Therefore, there arises the need for an alternative mode of treatment that will improve the drugs' bioavailability/ efficacy, reduce systemic effects, is cost saving, enhance the quality of life of primary and secondary BC patients and consequently improve patients compliance. One possible solution is transdermal delivery of the active drug (4-OHT) through the skin envelope of the breast. The embryological origins of the breast as a skin appendage (a modified eccrine gland) with a well developed internal lymphatic circulation promotes the accumulation of drug in the breast (Ackerman *et al.*, 2007).

This review was undertaken to help elucidate the scientific literature on the efficacy of a local transdermal therapy of 4-OHT against the conventional oral-T in the treatment of early stages of BC and DCIS. It is hoped to aid researchers and clinicians in making a more informed decision in considering an alternative route of administration for the treatment of DCIS. The few studies

**Corresponding author:* e-mail: usun1@student.monash.edu

addressing this issue provides sufficient data to construct a meta-analysis to compare transdermal delivery of 4-OHT over oral-T.

MATERIALS AND METHODS

This was a systematic review and meta-analysis aiming to summarise the clinical evidence of local transdermal therapy of 4-OHT vs. oral-T for the treatment of early stages of BC.

A systematic review was performed from inception till 1st February 2016 aiming to identify the primary full text english literature published on the effectiveness of a transdermal delivery system in the treatment of BC. The following databases were systematically searched: EMBASE, International Pharmaceutical Abstracts (IPA), Science Direct, Pub Med and Cochrane library.

Search strategy

The search strategy included initial screening of titles and abstracts, and only articles with full texts were included. No unpublished material were included in this review, and there was no limitation imposed on the year of publication for the studies.

Relevant keywords relating to breast cancer ("breast cancer" *or* "breast carcinoma" *or* ductal carcinoma *in situ*" *or* lobular carcinoma *in situ*") were used in combination using the boolean operators ("AND" & "OR") with words relating to transdermal delivery systems ("transdermal delivery" or "transdermal drug administration" or "topical drug administration" or "percutaneous" or "transdermal patch" or transdermal cream" or "transdermal gel" or "transdermal microneedle" or "transdermal ultrasound" or "transdermal emulsion"). Search was also performed using MeSH terms for PUBMED search. The reference section of included studies were examined to identify additional studies that met the selection criteria.

Search eligibility criteria

To be included in the systematic review and meta-analysis, studies had to meet the following criteria; (i) study compares the efficacy of a topical and transdermal system for the treatment of BC, (ii) articles in english full text, (iii) human studies, and all types of trials on patients of all ages, ethnicity and gender, (iv) randomized controlled trials (RCT), cohort and case controlled studies. Studies that were excluded were (i) animal studies, (ii) letter to editor, case studies, case reports, conference papers, reports, review papers or editorial papers, and (iii) had no full english text publication.

Quality asessment and data extraction

The information extracted from each study included: journal title, author and year of publication; study design and population, patient characteristics, disease condition, dose of Oral-T and 4-OHT gel administered, tumor tissue proliferation indices (Ki-67 labeling indices (LI)), breast tissue deposition and plasma concentrations; and any side effects encountered. The extracted data was verified by a second reviewer.

Review Manager (Revman)® version 5.3 was used to generate graphical summary of the risk of bias. The methodological quality of the studies included in the meta-analysis was assessed using the Cochrane collaboration's tool (Higgins *et al.*, 2011). The tool assesses the following sources of bias, attrition bias, reporting bias and other source of bias. Included studies were independently reviewed by two authors (SE and TMK). Discrepancies between articles were discussed amongst the two authors, and a third party (UDP) was consulted, if necessary, to achieve consensus.

STATISTICAL ANALYSIS

All analyses were performed using Revman® version 5.3. Only studies that contained the required variables; mean value, standard deviation and total number of patients in the trials were considered for further analysis. Dichotomous outcomes were not assessed in this review because there were insufficient data related to the number of patients that have better breast or plasma accumulation of 4-OHT after the use of transdermal therapy or oral administration. The standardized mean difference (SMD) for each clinical study is presented with its 95% confidence interval (CI). SMD is used to standardize the results of the included studies to ensure uniformity. The heterogeneity was tested using the I^2 test, an I^2 value >50 % would indicate high heterogeneity. In studies having high heterogeneity, the random effects model was used as it weighs the studies more equally than the fixed effect model. A forest plot was also constructed to graphically represent the meta-analysis.

RESULTS

The literature search returned 2915 articles with none identified from other sources. After removal of duplicates identified manually and via EndNote®, the systematic screening of titles and abstracts led to the exclusion of 2265 articles. The screening of these articles were based on the titles and abstract (i.e. those that did not address transdermal or topical route of administration for the treatment of BC, were chemoprevention based studies, hormone replacement therapies and diagnostics based studies). Nine articles were reviewed full text; of which 6 articles did not meet the eligibility criteria (i.e. not RCT or controlled trials, were *in vitro* or *in vivo* study, was not in English) . Finally, three studies were selected for inclusion in this review (total patients: n = 103) (fg.1).

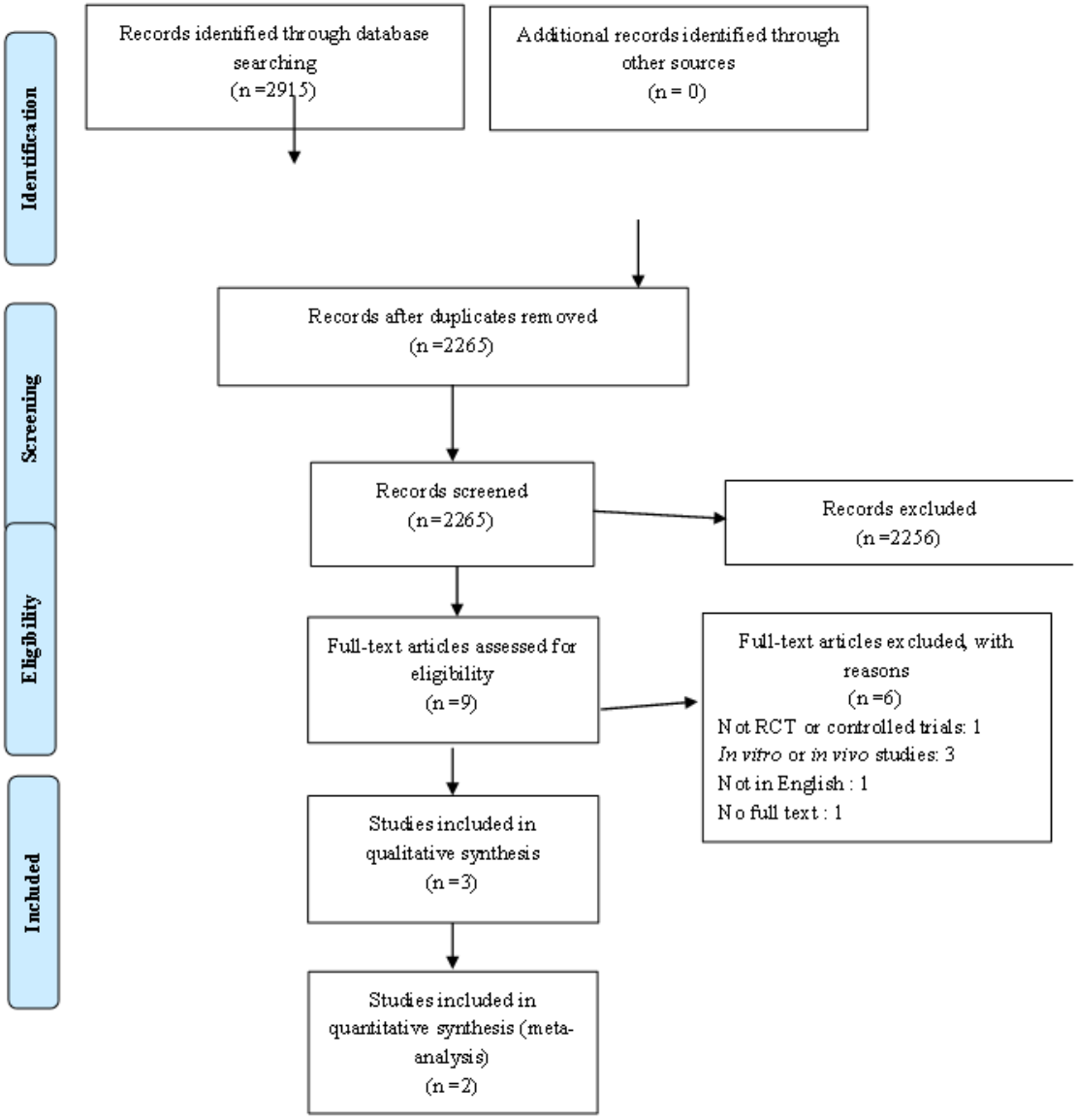

Fig. 1: PRISMA flow diagram of study selection

Study caracteristics

A summary of the studies included in this review is as shown in table 1 (Lee *et al.*, 2014, Pujol *et al.*, 1995, Rouanet *et al.*, 2005). The table includes the study design, interventions compared, sample size, patient eligibility criteria, patient age and key endpoints.One of the above studies, presented its data in median form possibly due to its small sample size (Rouanet *et al.*, 2005). Due to the inability to contact the author(s) to obtain the mean values, data from this particular study was not included in the meta-analysis. Oddly enough, the three articles were published almost ten years apart of each other (1995, 2005, and 2015) (Rouanet *et al.*, 2005, Lee *et al.*, 2014, Pujol *et al.*, 1995). One of the three studies was double blinded placebo-controlled (Lee *et al.*, 2014), while the other two did not mention double blinding. The initial number of participant enrollment ranged from 31 (Lee *et al.*, 2014, Pujol *et al.*, 1995) to 55 (Rouanet *et al.*, 2005). However, the final number of patients included were on average about 87% of the initial enrollment number. Reasons given for drop out included ineligible participants (Lee *et al.*, 2014, Pujol *et al.*, 1995, Rouanet *et al.*, 2005), participants who withdrew consent before randomization (Lee *et al.*, 2014, Pujol *et al.*, 1995, Rouanet *et al.*, 2005) and withdrawal of participant due to the lack of drug supply (Lee *et al.*, 2014). All three studies reported the concentration of tamoxifen and its metabolites in plasma and breast tissue; while only Lee et al., additionally reported concentration of 4-OHT in nipple aspirated fluid (NAF) (Lee *et al.*, 2014). Ki-67 LI was only reported in two of the studies (Rouanet *et al.*, 2005, Lee *et al.*, 2014). Risk of bias for each study is

shown in fg.2 and no studies fulfilled all criteria. The risk of selection bias was high in all three studies due to its failure in reporting adequate sequence generation and/or allocation concealment (Lee *et al.*, 2014, Rouanet *et al.*, 2005, Pujol *et al.*, 1995). In summary, the three studies exhibited a low risk bias.

Patient Characteristics

Median patient age was reported in two of the studies (Rouanet *et al.*, 2005, Lee *et al.*, 2014). A similarity in the inclusion criteria of the trials was that it required at least 12 months postmenopausal patients (Pujol *et al.*, 1995, Rouanet *et al.*, 2005); while one study included both pre- and post menopausal patients (Lee *et al.*, 2014). Additionally, Lee *et al*., and Rouanet *et al*.,(Lee *et al.*, 2014, Rouanet *et al.*, 2005) required estrogen positive BC patients, while Pujol *et al*.,(Pujol *et al.*, 1995) did not specify the type of BC. The study by Pujol *et al.*, and Rouanet *et al*. recruited patients to have operable infiltrative BC of more than 1 cm (Pujol *et al.*, 1995, Rouanet *et al.*, 2005), while Lee *et al.*, recruited patients who were in between diagnostic core needle biopsy and surgical excision (Lee *et al.*, 2014).

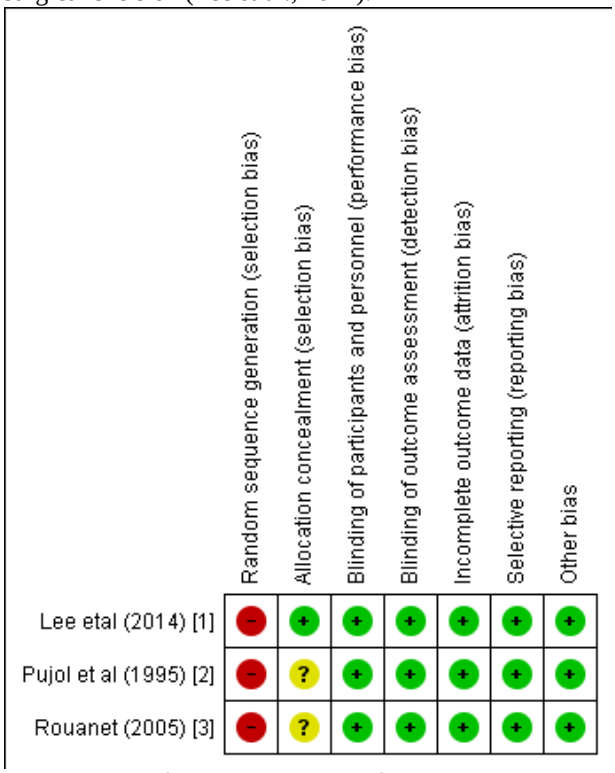

Fig. 2: Risk of bias assessment of the included studies using the Cochrane risk of bias tool

Study results

Lee et al. (Lee et al., 2014)

In the study of Lee et al. (Lee *et al.*, 2014), the primary endpoint was Ki-67 LI in DCIS lesions, while the secondary endpoints were to compare concentrations of tamoxifen and its metabolites (4-OHT, endoxifen, N-desmethyltamoxifen (NDT)) in plasma, breast tissue, and nipple aspirated fluid (NAF). The mean Ki-67 LI significantly decreased from baseline in both the oral-T group and topical 4-OHT group (P=0.0008 and 0.03, respectively). There were significant increases in plasma sex hormone-binding globulin (SHBG), factor VIII, and von Williebrand factor (P=0.002, 0.03 and 0.02, respectively) and a significant decrease in plasma insulin-like growth factor-1 (IGFI) (P = 0.003) from baseline in the oral-T group, but not with the topical 4-OHT group. This supported the notion that the systemic effects of 4-OHT gel were insignificant. The major biologically active form, (Z) isomer of 4-OHT were found to be similar in breast adipose tissue in both the oral and topical group (P = 0.88). Given the small sample sizes (Oral-T = 13; Topical 4-OHT = 10); the magnitude of change was not significant between the treatment groups. NAF concentrations obtained from 4 women, indicated that high mammary concentrations of 4-OHT was achieved with the transdermal therapy. The incidence of hot flashes were similar in both groups. Major outcomes are presented in table 2. The author concluded that 4-OHT gel application was as effective as oral-T, with low systemic exposure. However, further evaluation of local transdermal therapy for DCIS and BC prevention were needed to support this. *Pujol et al., (Pujol et al., 1995).*

Pujol et al., analyzed 4-OHT concentrations in tissue and plasma of women with BC given oral-T. The study compared oral-T administration at 20 mg/day against percutaneously administered 4-OHT to the breast tissue at 1 and 2 mg/day; and percutaneously delivered 4-OHT to large cutaneous areas excluding the breast at 1 and 2 mg/day (table 2). The primary end point of this study was the quantitative measurements of 4-OHT in the plasma, tumoral breast tissues and normal breast tissues. Oral-T resulted in a higher 4-OHT plasmatic concentrations in both BC and normal breast tissues. The study showed that percutaneous 4-OHT gel administration on the breast lead to a very low plasma concentration (P < 0.002) of 4-OHT together with a breast tissue concentration of 4-OHT significantly lower than treated with oral-T (P <0.0001). No modification of coagulation or lipid metabolism was seen at all doses tested. Pre- and post- treatment levels of Estradiol (E^2), Follicle-stimulating hormone (FSH), Luteotrophic hormone (LH) and SHBG did not differ significantly. Intratumoral concentration of estrogen receptors, progestrone receptors and cathepsin D did not show significant difference between all the groups tested. The study also exhibited that the concentration of 4-OHT in both the oral and topical groups were higher in tumoral tissue as compared with normal breast tissue. Hence, the author concluded that at the doses described in this study, 4-OHT percutaneous gel cannot be proposed as an alternative tamoxifen treatment and further study is required *(*Rouanet *et al.*, 2005)

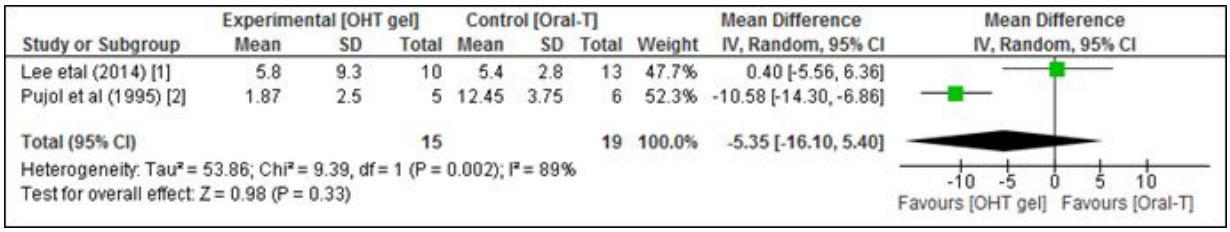

Fig. 3: Forest plot comparison of 4-OHT gel to Oral-T for breast adipose tissue (ng/g)

Rouanet et al., performed a randomized study to analyze if 4-OHT gel, administered percutaneously on the breast skin, can inhibit proliferation of malignant breast cells to the same extent as orally administered tamoxifen. The biological endpoints of this study includes the analysis of the proliferation-associated antigen expression (Ki-67 LI and proliferating cell nuclear antigen (PCNA) labeling indices); estrogen and progestrone expressions and 4-OHT breast tissue and plasma concentrations (table 2). Administration of 4-OHT gel resulted in reduction in Ki-67 LI and PCNA, with approximate equivalence between the 1.0 mg/day and 2.0 mg/day 4-OHT dose, and oral-T. Plasma levels of 4-OHT were consistently higher in the oral-T group compared to the gel groups. No dose-related pattern was shown for estrogen or progestrone receptor levels, and topical 4-OHT gel appeared to be generally well tolerated. Hot flushes was found to be common in the two higher gel doses as with tamoxifen. Thus, the author concluded that percutaneous 4-OHT gel has a local impact on tumor proliferation and further studies should be conducted to confim this in future.

Meta-analysis

Upon extraction of the quantitative data, two studies were found to meet the requirements of meta-analysis. The pooled comparison of 4-OHT gel to Oral-T was assessed from two randomized controlled trials (Pujol *et al*., 1995, Lee *et al*., 2014). fg.3 shows the pooled odds ratio of 4-OHT in relation to the route of administration (oral vs. topical). I^2 value was 89.0%, (Tau^2 = 53.86, p=0.002).

DISCUSSION

The three studies included in this systematic review and meta-analysis, recruited post menopausal women, of which two studies specified the type of BC to be estrogen receptor – positive BC. These studies also included patients who were in the window between diagnostic biopsy and surgical excision; making them comparable. Similar dose (20 mg/day) for oral-T in all the three studies were based on adjuvant tamoxifen clinical trials that exhibited the efficacy of 20mg/day dose of tamoxifen to be equivalent to that of higher doses of the drug (30 to 40 mg/day) (Early Breast Cancer Trialists' Collaborative, 1998). Lee et al., administered higher (4 mg/day) topical 4-OHT dose on the breast areas compared to the other two studies (1 mg/day and 2 mg/day). In terms of duration of therapy, Lee et al., conducted the therapy for a longer duration (6-0 weeks) compared to the 3 weeks of therapy in the other two studies. This reportedly was to allow an assessment of vasomotor symptoms (Lee *et al*., 2014).

The common key endpoint among all the three studies were the; Ki-67 LI, concentrations of tamoxifen and its' metabolites in plasma and breast tissue. Lee et al., (Lee *et al.*, 2014) exhibited a decrease in Ki-67 LI than baseline in both the oral and transdermal group; mean reduction of 5.1% in the oral-T group (*P*=0.008) and 3.4% in the topical 4-OHT (4 mg/day) group (*P*=0.03).This study was comparable with Rouanet et al., which saw a reduction in Ki-67, with approximate equivalence between 1mg/day or 2 mg/day 4-OHT dose and oral-T. However, Rouanet et al., could not show significance in the relationship due to insufficient sample size (Rouanet *et al*., 2005).

All three studies reported a significantly lower plasmatic concentrations of topical 4-OHT compared to the oral-T group (table 2) (Rouanet *et al*., 2005, Lee *et al*., 2014, Pujol *et al.*, 1995). These findings supported the similar hypothesis of these studies that the effective breast accumulation can be achieved with low systemic exposures (Lee *et al*., 2014, Rouanet *et al.*, 2005, Pujol *et al.*, 1995). Lee et al., recorded equivalent breast tissue concentrations of 4-OHT in both the oral and topical groups (more than 5.0ng/g tissue in both groups) despite the difference in dose (Lee *et al.*, 2014). An administration of 2.0mg/day topically in both Pujol and Rouanet et al., exhibited similar accumulation of 4-OHT in the breast tissue (1.7ng/g and 1.9 ng/g, respectively) (Rouanet *et al.*, 2005, Pujol *et al*., 1995). When 4-OHT concentrations were also administered on normal breast tissues, it was observed that its concentrations were far lower than that at tumoral breast tissues (Rouanet *et al.*, 2005, Pujol *et al.*, 1995). This could be due to the leaky vasculature of the tumor tissues compared to normal tissues (Brown and Giaccia, 1998).

Interpreting the results of meta-analysis revealed that 4-OHT gel might be superior in comparison to oral-T in terms of plasma concentration and breast tissue concentration. However, the result of meta-anlysis based on the I^2 revealed a high heterogeneity. Therefore it is hard to rule out which study is better, as a higher I^2 is an indicator that these two studies are not combinable, perhaps due to a smaller sample size and the number of studies investigating the comparison of 4-OHT vs Oral-T

Table 1: Overview of characteristics of included studies

Author (year)	Study design/ Intervention comparison/ duration	Sample size	Patient eligibility criteria	Age (years)	Key endpoints
Lee et al., (2014)	Randomized, double blind, placebo-controlled phase II trial / transdermal 4-OHT vs Oral-T / Duration (therapy): 6 – 10 weeks; Duration (study): 29 months	26	Pre- and post-menopausal women ER-positive DCIS	45-86	Ki-67 LI Tamoxifen and its metabolites in plasma, breast tissue and NAF.
Pujol et al., (1995)	Randomized / percutaneous 4-OHT versus oral-T / Duration (therapy): 21 days; Duration (study): 8 months	28	Women with histologically proven breast cancer. Postmenopausal women (>1 year) Operable infiltrative breast cancer (> 1cm in diameter).	NR	Tamoxifen and its metabolites in plasma and breast tissue.
Rouanet et al., (2005)	Controlled randomized study / percutaneous 4-OHT gel vs. Oral-T / Duration (therapy): 2 – 3 weeks; Duration (study): 35 months.	49	Postmenopausal women Women who had Tru-cut biopsy. T1 or T2 ER-positive breast cancer.	>50	Ki-67 LI Tamoxifen and its metabolites in plasma and breast tissue.

ER = Estrogen receptor; DCIS = Ductal Carcinoma in situ; 4-OHT = 4-hydroxy tamoxifen; Oral-T = oral tamoxifen; NR = Not reported; LI = Labeling index; NAF = Nipple aspirated fluid

Table 2: Reported outcomes of the included studies

No	Author	Number of samples	Formulation	Dose Regimen (mg/day)	Ki-67 LI (%)		Breast Adipose Tissue (ng/g)		Plasma (ng/ml)	
					Mean	SD	Mean	SD		
1	Lee et al., (2014)	13	Oral -T	20	5.1	5.5	5.4	2.8	1.1	0.7
		10	4-OHT gel	4	3.4	5.0	5.8	9.3	0.2	0.2
2	Pujol et al., (1995)	6	Oral -T	20	NR		12.45	3.75	2.3	0.6
		6	4-OHT gel	1			1.45	2.7	0.017	0.03
		5	4-OHT gel	2			1.87	2.5	0.062	0.07
	Rouanet et al., (2005)	11	Oral -T	20	-3.8	-10.2-1.0	4.23	2.39-7.39	1.5	0.03-1.995
		8	4-OHT gel	0.5	-0.8	-4.1-1.9	0.69	0.08-1.98	0.03	0.02-0.14
		9	4-OHT gel	1	-4.5	-5.9-1.1	1.38	0.56-2.96	0.04	0.02-0.08
		10	4-OHT gel	2	-3.9	-7-0.6	1.7	0.33-5.12	0.16	0.03-0.31

* Data presented in median and range

are only two. Overall assessing the individual results of studies, it was revealed that the study by Pujol *et al.*, clearly supports the superiority of 4-OHT gel vs Oral-T (Pujol *et al.*, 1995).

Limitations and weakness of the included studies

A duration of more than four weeks is required to obtain stable plasma concentration of a drug after its treatment (Therasse *et al.*, 2000). Lee et al's study complied to this study duration but not Pujol and Raouanet et al.,. However, Lee et al., reported a slow accrual in their trial, as majority of eligible subjects were unwilling to experience the surgical delay of six weeks despite consensus among physicians that it was not risky (Lee *et al.*, 2014). The small sample size in all the three studies was also insufficient to draw definite conclusions. For instance, patients receiving 1mg/day and 2 mg/day 4-OHT reported hot flushes, suggesting that even low plasma level of 4-OHT might be enough to produce a systemic effect. However, this is not conclusive as these women were post menopausal and hot flushes are clinically related, whether driven by physiologic estrogenic deprivation or due to tamoxifen effect (Rouanet *et al.*, 2005, Lee *et al.*, 2014). Pujol *et al.*,(Pujol *et al.*, 1995) reported that the tissue concentration needed to achieve chemoprevention was possibly lower than that needed to obtain therapeutic effect, since the optimal breast tissue concentration of an effective 4-OHT dose is

not yet known. Lee et al., had also specified other reasons behind the slow accrual for their trial; (i) initial restrictive eligibility criteria resulted in recruitment of women with very small DCIS lesions, leading to an attrition of almost 30% in the assessment of biomarkers in matched pre- and post- therapy lesions. (ii) due to the slow accumulation of patients led to the expiration of study agent and refusal of manufacturer to produce additional supplies. Hence, they suggest that the enrollment criteria should be open as possible in future studies.

Strengths and weakness of the study

Based on our database search, research on BC have so far only focused on hormone replacement therapies, chemoprevention, pain management and diagnostics methods. Very few studies have focused on addressing the need for an alternative route of administration for the treatment of BC. This is the first systematic review and meta-analysis that provides a quantitative assessment of the efficacy of BC treatment among users of oral-T and 4-OHT gel. The present meta-analysis investigates the impact of transdermal therapy of 4-OHT among pre- and post-menopausal women.

It studies the efficacy of oral-T and 4-OHT gel users in BC treatment based on relatively few data (Pujol *et al.*, 1995, Lee *et al.*, 2014). There was a lack of randomized controlled trials studying the efficacy of a transdermal therapy in the treatment of BC. Results should therefore be interpreted with caution and further investigation of transdermal 4-OHT is needed.

Clinical implications

Primary care physicians are often perceive tamoxifen as 'cancer drug' that has challenging side effects. Effective and safer drugs that potentially could replace tamoxifen as preventive agents in high-risk women are being developed. However, these drugs are limited to postmenopausal women, leaving tamoxifen as the only chemopreventive drug for premenopausal women who are at high-risk of BC (Vogel *et al.*, 2010, Lazzeroni and DeCensi, 2013). Topical transdermal application of tamoxifen metabolites offers promising strategies for reducing side effects relative to conventional oral tamoxifen in the BC prevention setting. Studies on the transdermal application of 4-OHT conducted this far, shows very low plasma concentration of drug. These low plasma levels in the setting of a topical approach that bypasses first pass metabolism in liver suggests reduction in systemic toxicity (Mauvais-Jarvis *et al.*, 1986, Pujol *et al.*, 1995, Goyal *et al.*, 2009). Consequently, reducing the adverse side effects associated with it. Further, the reduced cost following the localized treatment of BC is also an added advantage for clinicians. The development of a localized intervention for early stages treatment of BC or its prevention will improve patients compliance. An improved experience will ensure patients adhere to the medical treatment, hence improving the course of disease.

CONCLUSION

The meta analysis of the randomized controlled trials showed that the current use of local transdermal therapy of 4-OHT gel is better than oral-T. Results from the studies show that drugs applied to the breast skin are selectively concentrated in the breast, whereas drugs applied to the skin of the other regions of the body penetrate the skin into the vascular system and are distributed systemically. However, due to the limited number of studies, the potential use of a topical transdermal therapy for the treatment of BC could not be concluded for healthcare professionals. Larger population and more studies should be conducted to strengthen this hypothesis.

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