THE UNIVERSITY OF MEDICINE AND PHARMACY
"CAROL DAVILA" from BUCHAREST

THE UNIVERSITY OF MEDICINE AND PHARMACY "CAROL DAVILA", BUCHAREST

DOCTORAL SCHOOL

THE FIELD OF MEDICINE

NEW HYPOTHESIS ON THE EFFECT OF DOCETAXEL (TAXOIDE CLASS) AT THE OCULAR SURFACE LEVEL IN WOMEN WITH BREAST NEOPLASM

PhD THESIS SUMMARY

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THE CONTENT OF THE PhD THESIS

Introduction

The PhD thesis entitled "New hypothesis on the effect of docetaxel (taxoid class) on the ocular surface, in women with breast neoplasm" is a scientific approach carried out with the aim of showing the causal relationship between the administration of docetaxel, in women with breast neoplasm and the occurrence of hyperlacrimation (epiphora), taking into account the rate of administration of this medicine, the permeability of the lacrimal system and the condition of the meibomian glands. Through this study, I want to highlight that the appearance of epiphora is due to morphological changes in the Meibomius glands, changes due to the action of docetaxel on these glands.

In carrying out this doctoral research, we started from the hypothesis that docetaxel acts on the level of the Meibomius glands, producing a narrowing/shrinkage of them, which leads to the appearance of epiphora as the most frequent ophthalmological adverse reaction, in women with breast neoplasm who are treated with docetaxel .

The PhD thesis contains:

• general part including anatomy notions about the tear film, lacrimal apparatus, eyelids, general notions about chemotherapy treatment, especially about docetaxel. Also, in the general part I would also mention the current data existing in the specialized literature regarding the causal relationship between docetaxel treatment and the occurrence of hyperlacrimation (current state of knowledge).

• a special part, personal contribution, which includes the working hypothesis and general objectives, the general research methodology and 3 studies in which I analyzed 3 parameters that give me indications about the function and morphology of the Meibomius glands (Schirmer test, tear film break-up time – NKBUT). The main outcome variable is upper and lower eyelid meibography for both the group of patients treated with docetaxel alone and for the group of patients treated with docetaxel in combination with another chemotherapy.The importance and uniqueness of our research emerges from the fact that so far no causal relationship has been demonstrated between the narrowing and/or shrinking of the Meibomius glands in patients with breast cancer undergoing docetaxel treatment and the

appearance of epiphora, the most frequent ophthalmological adverse reaction in these patients and which resolves within a few weeks of stopping docetaxel.

I. GENERAL PART

Chapter 1. Theoretical aspects relevant to the researched pathology

1.1.Eyelid anatomy and lacrimal apparatus

The eyelids have as their main function, the function of protection, thus the eye is protected from the aggression of external factors (gases, liquids, foreign bodies) (Dumitrache, 2012). They also regulate how much light penetrates through the pupil and also the eyelids have a role in the distribution of the tear film on the ocular surface and in the drainage of tears towards the nasolacrimal canal (Dumitrache, 2012).

The lacrimal apparatus has as components a tear secretion system which in turn consists of the main lacrimal gland and accessory glands, and a system of canals and canaliculi (drainage system), which aim to eliminate tears externally.

The main lacrimal gland is located in the lacrimal gland fossa (antero-laterally in the ceiling of the orbit). It is a tubulo-acinous gland. The gland has 10-14 ducts that reach the superior conjunctival fornix. The main lacrimal gland produces an aqueous secretion that is a reflex secretion to: peripheral corneal and conjunctival sensory factors, sensory stimuli (eg bright light) and sympathetic stimulation (eg Basedow's disease).

Accessory lacrimal glands that include conjunctival glands (Krause glands, Wolfring glands) are found mainly in the area of the superior fornix and palpebral glands (Meibomian glands which are sebaceous glands included in the thickness of the tarsus, Zeiss glands are accessory sebaceous glands of the pilos ciliary system and Moll's glands which are sweat glands attached to the cilia, with holes that open at the free edge between two cilia).

The name of Glande Meibomius is 6uet o the one who described them for the first time in 1666, namely the German physicist, Heinrich Meibom. The cells of the Meibomius glands that secrete the lipid liquid (meibum) that is part of the tear film are called meibocytes (Pucker, 2015). These meibocytes have a holocrine secretion, this meibum being deposited with each blink, on the entire ocular surface (Verma, 2023). Meibomius glands are responsible for the lipid component of the tear film, thus these glands have a major role in

preserving and maintaining what is called the stability of the tear film. The lipid layer is the superficial layer of the tear film and its presence prevents its evaporation and thus preserves an intact ocular surface both structurally and refractively. At the level of the upper eyelid there are several Meibomius glands in number and volume, than at the level of the lower eyelid (on average at the level of the upper eyelid there are 40-50 glands per eyelid and at the level of the lower eyelid there are around 20-30 glands) (Nicolaides, 1981). Meibomius glands are placed perpendicular to the free edge of the eyelid. Their holes can be seen at the level of the free edge of the eyelid, but they do not come into direct contact with the eyelash follicles. Their trajectory is linear and they are 3-4 mm long.

The lacrimal glands, the tear film together with the ocular surface make up a functional unit. When there is an alteration of this unit, diseases of the ocular surface appear. Also, when the tear film undergoes a change in composition, production or distribution on the ocular surface, various conditions of the ocular surface may appear, accompanied even by a decrease in visual acuity.

The drainage system of the lacrimal apparatus removes 90% of the tears produced, the rest evaporates. The drainage system begins with the lacrimal puncta found on the inside of the eyelids and continues to the inferior nasal meatus.

1.2 The tear film

Tears spread across the conjunctiva and cornea in a layer called the tear film. The thickness of the tear film is 3 μm and its volume is 7-10 μL (Bron, 2004). It helps provide nutrients and oxygen to the cornea, provides a proper refractive environment for the eye (DelMonte, 2011). The tear film is continuously formed through its production process and is removed through absorption, drainage and evaporation (Stahl, 2012). The tear film consists of three layers (Gipson, 2007): the deep mucous layer (0.02-0.05 micrometers) attached to the cells of the corneal epithelium, the intermediate, aqueous layer (6.5-7.5 micrometers) with the role of oxygenation and nourishment and the superficial lipid layer (0.1 micrometers) with a role in protecting the ocular surface but also has an antimicrobial role. The properties of tears are protective of the cornea (through hydration but also its mechanical protection), role of nourishing the cornea through substances from the tear film, optical role (very important in maintaining the regularity of the cornea) and immunological immunological role (due to the substances it contains and which have specific and non-specific anti-microbial action). Ocular Surface Disease (OSD) was first mentioned by John

Dart, when he described a group of conditions that have different pathogenic mechanism and resulted in an imbalance of the ocular surface (Ong, 2016).

Chapter 2. The action of chemotherapy treatment on the ocular surface

Many of the chemotherapeutic (antineoplastic) drugs have ocular toxicity, demonstrated by various ocular adverse reactions, the eye having unique physiological and anatomical characteristics (Stoicescu, 2023). As new chemotherapy treatments or new combinations have emerged, the reporting of ocular adverse reactions has increased for various stages of neoplastic disease (Singh, 2012).

2.1 Alkylating agents

This type of drug has broad-spectrum tumor activity, activity on proliferative and non-proliferative cells, and acts by covalently binding to the DNA molecule, which it destroys by direct action. This class includes platinum compounds (Cisplatin, Oxaliplatin, Carboplatin), nitrogen analogs (Cyclophosphamide, Ifosfamide, Chlorambucil) and nitrosoureas (Procarbazine, Dacarbazine). As ocular side effects of Oxilaplatin, hyperlacrimation (epiphora), conjunctivitis, narrowing of the visual field, decreased visual acuity have been reported (Jack, 1981). Reversible epiphora, keratoconjunctivitis Sicca, blepharoconjunctivitis are noted among the ocular adverse reactions of cyclophosphamide (al-Tweigeri, 1996; Stevens, 2001).

2.2 Antimetabolites

They are drugs that act on proliferating cells in the S phase, inhibiting the enzymes necessary for DNA synthesis. They "mimic" the structure of some essential cellular metabolites (purines, pyrimidines, folic acid).

They are classified in:

- Purine analogues (Fludarabine, Cladribine, Thioguanine)

- Pyrimidine analogues (5-Fluorouracil, Capecitabine, Cytarabine, Gemcitabine)

- Folic acid analogs (Methotrexate, Pemetrexed).

Studies have shown that between 1% and 5% of patients who received Pemetrexed, experienced an adverse reaction on the ocular surface (epiphora most frequently, then

conjunctivitis and others) (Rollins, 2005). Methotrexate also exhibits toxicity at the level of the ocular surface but also at the level of the optic nerve (al-Tweigeri, 1996).

2.3. Antitumor antibiotics

These drugs act by inhibiting topoisomerase II (cancer cells need this enzyme to grow), leading to the unwinding of the DNA helix thus acting to stop or slow down the growth of cancer cells; they produce free radicals. This category includes anthracyclines, bleomycin, mitomycin C, mitoxantrone, actinomycin D. Anthracyclines on the ocular surface most frequently cause conjunctivitis and hyperlacrimation (epiphora) (Vizel, 1999-2002).

2.4. Hormonal agents

Tamoxifen is usually recommended as adjuvant therapy and its main indication is metastatic breast cancer. It has also been approved by the FDA as a preventive treatment in women who are at high risk of developing breast cancer (Center for Drug Evaluation and Research, 2005). Keratopathy has been described as an adverse reaction on the ocular surface (Sahyoun, 2022; Kashiwagi, 2010).

2.5. Agents on signal transduction

Everolimus is an immunosuppressant useful in preventing organ transplant rejection (Todesco-Silva, 2022). To be noted as an adverse reaction at the eye level, is an important photosensitivity and the appearance of anterior uveitis in some patients, but retinal vein occlusions have also been described during treatment with vemurafenib (Eikenberry, 2021).

2.6. Monoclonal antibodies

As ophthalmic adverse reactions in patients treated with rituximab, epiphora, burning sensation, conjunctivitis and even decrease or loss of visual acuity have been reported (Kaegi, 2019).

2.7. Antimicrotubule agents (mitotic inhibitors)

These drugs prevent cell division and have the ability to act in all phases. They can be classified into:

- Derivatives of Vinca: Vincristine, Vinblastine, Vinorelbine

- Taxanes: Docetaxel, Paclitaxel, Cabazitaxel)

Docetaxel is a taxane used in locally advanced or metastatic breast cancer, alone or in combination with other antineoplastic agents (eg docetaxel + doxorubicin + cyclophosphamide or docetaxel + capecitebine) (Costa, 1999). It is in the list of so-called In women, breast cancer is the most common neoplastic pathology and is the second most common type of cancer among newly diagnosed cancers worldwide.

In 2018, approximately 280,000 new cases of breast cancer were diagnosed in the United States. In young women under the age of 45, breast cancer is the leading cause of cancer death (DeSantis, 2013).

The most common ophthalmic adverse reaction reported by women with breast cancer undergoing docetaxel treatment is epiphora or hyperlacrimation (Ho, 2014).

Chapter 3. Current state of knowledge of ocular surface involvement in women with breast cancer under docetaxel treatment

In women, breast cancer is the most common neoplastic pathology and is the second most common type of cancer among newly diagnosed cancers worldwide.

In 2018, approximately 280,000 new cases of breast cancer were diagnosed in the United States. In young women under the age of 45, breast cancer is the leading cause of cancer death (DeSantis, 2013). The most common ophthalmic adverse reaction reported by women with breast cancer undergoing docetaxel treatment is epiphora or hyperlacrimation (Ho, 2014). Previous studies have shown that weekly administration of docetaxel is correlated with a higher rate of epiphora than in patients receiving docetaxel once every three weeks (Esmaeli, 2002; Noguchi, 2016; **Stoicescu, 2021).**

Burstein and colleagues showed in a phase II study that epiphora occurred in 50% of women who received weekly docetaxel (Burstein, 2000). Epiphora usually occurs 12–16 weeks after starting docetaxel treatment (Burstein, 2000).

The exact mechanism by which epiphora occurs in these patients is still not fully elucidated. In several studies, canalicular stenosis is shown to be the mechanism that leads to the appearance of epiphora, but it is not statistically significant (Esmaeli, 2001; Esmaeli, 2002; Esmaeli, 2006). The hypothesis for the production of canalicular stenosis that they support is that docetaxel is found in the tear film and its permanent contact with the mucosa of the nasolacrimal canal and tear ducts favors the appearance of inflammation and/or fibrosis at this level, leading to their narrowing and/or stenosis (Esmaeli, 2002; Esmaeli, 2005). However, there are studies showing that epiphora is also present in patients without canalicular stenosis who receive weekly docetaxel-based chemotherapy (Chan, 2013). Drainage of the lacrimal system was checked before, during and at the end of treatment by computed tomography (computed tomography dacryocystography: CT-DCG) (Chan, 2013). In patients receiving docetaxel-based chemotherapy once every 3 weeks, previous studies recommend monitoring every 6 weeks with probing and irrigation of the lacrimal system and short-term treatment with topical steroids (Esmaeli, 2005). Epiphora has also been shown to be a reversible symptom. Thus, 4 months after the last administration of docetaxel,

approximately 70% of patients no longer exhibit epiphora, 29% report intermittent epiphora and 1% still report epiphora (Chan, 2013).

II. EXPERIMENTAL PART

Chapter 4. Working hypothesis and general objectives

The purpose of this scientific research is to demonstrate the causal relationship between the appearance of epiphora in women with breast cancer treated with docetaxel and the morphological changes in the meibomian glands, changes due to docetaxel and which consist in narrowing and/or decreasing their number.

I have chosen in this doctoral thesis to compare three groups of 15 patients each, a study group in which patients with breast neoplasm receive treatment with docetaxel (in monotherapy), a control group of patients with breast neoplasm, who receive treatment with another chemotherapy and a group of 15 patients receiving docetaxel chemotherapy in combination with another chemotherapy drug.

The three studied groups performed 5 ophthalmological consultations, namely before the start of the chemotherapy treatment, 1 month after the start of the treatment, 3 months and 6 months after the start of the treatment as well as 2 months after stopping the docetaxel treatment.

The main objective of this scientific work is to carry out a comparative study between the three groups of patients. Thus, I will analyze the changes in the Schirmer test, the NKBUT and the Meiboscor (by performing the meiboscopy) during the treatment with docetaxel for the study group, compared to the changes of the same parameters for the control group, i.e. the patients who have another chemotherapy treatment (other than docetaxel) but and for the group of patients undergoing treatment with docetaxel in combination with another chemotherapy.

Chapter 5. General research methodology

5.1 Paraclinical investigations used to perform the work of Research

The examination of patients will be done in the following order so that one measurement does not interfere with another:

 Personal pathological history (only at visit 1)

 Personal medication

 Autorefraction (visit 1 only)

 Biomicroscope examination

 Meibography/Meibogram (using Ocular Keratograph 5)

Tear film breakup time (NKBUT)

 Schirmer test

 Probing the 4 canaliculi and irrigation of the lacrimal system

The patients will perform 5 ophthalmological consultations, before the start of the chemotherapy treatment (docetaxel or other), at t1 - 1 month after the start of treatment, at t3 - 3 months after the start of treatment, at t 6 - 6 months after the start treatment and 2 months after the end of chemotherapy treatment.

5.1.1. Autorefractometry – is an objective method of determining refraction. Autorefractometry is performed with a high-precision device called a refractometer. The autorefractometer used by us in the research study is a Huvitz Autorefractometer / keratometer, HRK -8000A, model 2021.

5.1.2. Biomicroscopic examination - the biomicroscopic examination was carried out with the Argus 5000 Slit Lamp Biomicroscope (class I, type B), in the ophthalmology department of the Bucharest Emergency University Hospital.

5.1.3. Meibography/meibogram – meibography/meibogram is a non-invasive technique for examining the morphology of the Meibomius glands, glands found on both the

upper and lower eyelids. Through this investigation it is possible to observe their number, their path, the degree of narrowing or obstruction by calculating the degree of narrowing or atrophy of these glands by taking serial images for both eyelids. It is an investigation that produces minimal discomfort but provides many morphological details very important in the normal functioning of the ocular surface. Meibography was performed using Ocular Keratograph, in the Ophthalmology department of the Bucharest University Emergency Hospital. After storing the images, they are analyzed by a special program that shows the degree of narrowing/obstruction of the Meibomian glands. Three parameters are followed namely gland distortion, gland disappearance and meibomian gland shortening/narrowing resulting in a score of 0 to 3 for each eyelid (Arita, 2010). Meiboscores can be compared and help to diagnose meibomian gland pathology, follow the evolution of meibomian gland pathology as well as to follow the response to treatment.

5.1.4. Tear film break-up time (NKBUT) - the tear film break-up time is a non-invasive investigation, very important in determining the stability of the tear film and in the diagnosis of evaporative dry eye syndrome. It has been described since 1969 by Norn (Norn, 1969). Tear film breakup time is the time from the last complete eyelid blink to the first dry spot on the cornea. By analyzing the NKBUT, an indirect evaluation of the function of the Meibomius glands is thus achieved. It is performed by instillation of fluorescein and then the moment when "breaks" (discontinuities) appear in the tear film is observed with the help of the Ocular Keratograph. The stability of the tear film is good when it is maintained for more than 10 seconds.

5.1.5. The Schirmer test - is used in order to evaluate the production of tears and is often used in the diagnosis of dry eye syndrome, keratoconjunctivitis Sicca but also in hyperproduction of tears. An indirect assessment of meibomian gland function is performed, but alone cannot diagnose meibomian gland dysfunction. To make it, two special strips of paper are used, one for each eye, strips that will be bent at one end and will be applied with this end in the outer corner of the eye, between the palpebral conjunctiva and the bulbar conjunctiva. It is normal if a level greater than 10 mm appears on the paper strip within 5 minute.

5.1.6. Probing the 4 canaliculi and irrigating the lacrimal system - if the cannula meets an obstacle in its path, the physiological serum does not reach the patient's throat and then it means that there is an obstruction on the path of the lacrimal system (reflux may occur

and dilatation of the lacrimal sac can also be observed) . If physiological serum appears in the patient's throat, then the lacrimal drainage system is permeable, there is no obstruction on its path.

5.2 Characteristics of the study groups

5.2.1 Inclusion criteria

Criteria for including patients in the research:

1) Patients older than 18 years (for the 3 groups of patients)

2) Patients who provide signed informed consent before performing study-related procedures (for the 3 groups of patients)

3) Patients able to understand and comply with the requested procedures (for the 3 groups of patients)

4) Patients with breast neoplasm receiving docetaxel as chemotherapeutic treatment (monotherapy) (for group 0)

5) Patients with breast neoplasm receiving other chemotherapy treatment (for group 1)

6) Patients with breast neoplasm who are treated with docetaxel in combination with another chemotherapy (for group 2)

5.2.2 Exclusion criteria

Criteria for excluding patients in research:

1) History of severe damage to the ocular surface, before the start of chemotherapeutic treatment (for the 3 groups of patients)

2) Ophthalmological surgery in the last 3 months preceding the study (for the 3 groups of patients)

3) The presence of an eye disease, such as glaucoma and/or any other eye damage that threatened visual acuity (for the 3 groups of patients)

5.3. Ethical considerations

The research within the Doctoral Thesis was carried out at the Ophthalmology Department of the Bucharest University Emergency Hospital, receiving the approval of the Ethics Commission of the hospital on 26.02.2021 with number 11285. Enrollment of patients in the study was carried out only after reading the patient's Informed Consent, understanding and signing it. Consent from the patients was obtained for the purpose of collecting and using the data for scientific purposes, ensuring the confidentiality of the data, according to the rules in force.

5.4 Statistical analysis

For the statistical processing of the data we used SPSS (Statistical Package for the Social Sciences) version 22, the ANOVA function and Microsoft Excel, 2016. The statistical significance (p) or the probability value - the p value - is the probability that the hypothesis null to be true, i.e. the probability that the obtained result is due to an error. Through the statistical analysis carried out, we studied whether significant statistical differences appear for each batch separately, but also comparatively, between them.

Chapter 6. Study I – Analysis of the Schirmer test and tear film breakup time (NKBUT) in breast cancer patients under Docetaxel treatment and in breast cancer patients undergoing other chemotherapy

6.1. Introduction (working hypothesis and specific objectives)

The objective of this study was to observe if there are changes in the Schirmer test and the NKBUT, during the treatment with docetaxel in patients with breast cancer undergoing this treatment, and also to observe if these changes occur in the other batch of patients, who undergo another chemotherapy treatment.

6.2. Materials and methods - were presented in chapter 5

6.3 Results - 2 parameters were analyzed: the Schirmer test and tear film break-up time, for both eyes, in 15 patients with breast neoplasm treated only with docetaxel (group 1) and 15 patients with breast neoplasm treated with another chemotherapy (group 0).

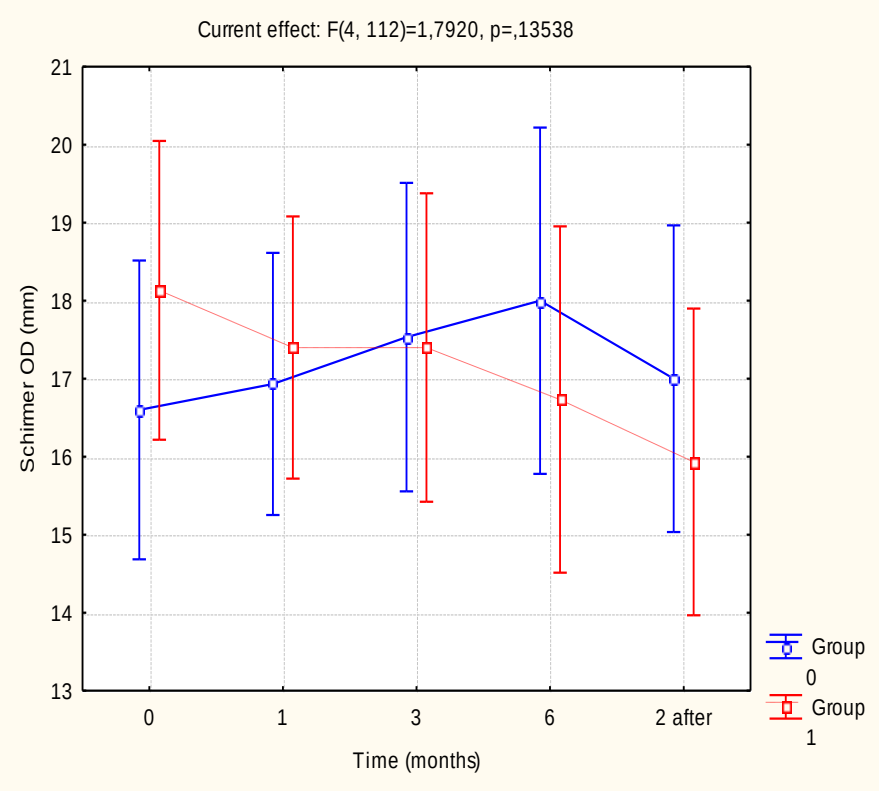


Fig. 6.1. Graphical results of the Schirmer test at the 5 visits, for the 2 groups of patients studied, in the right eye

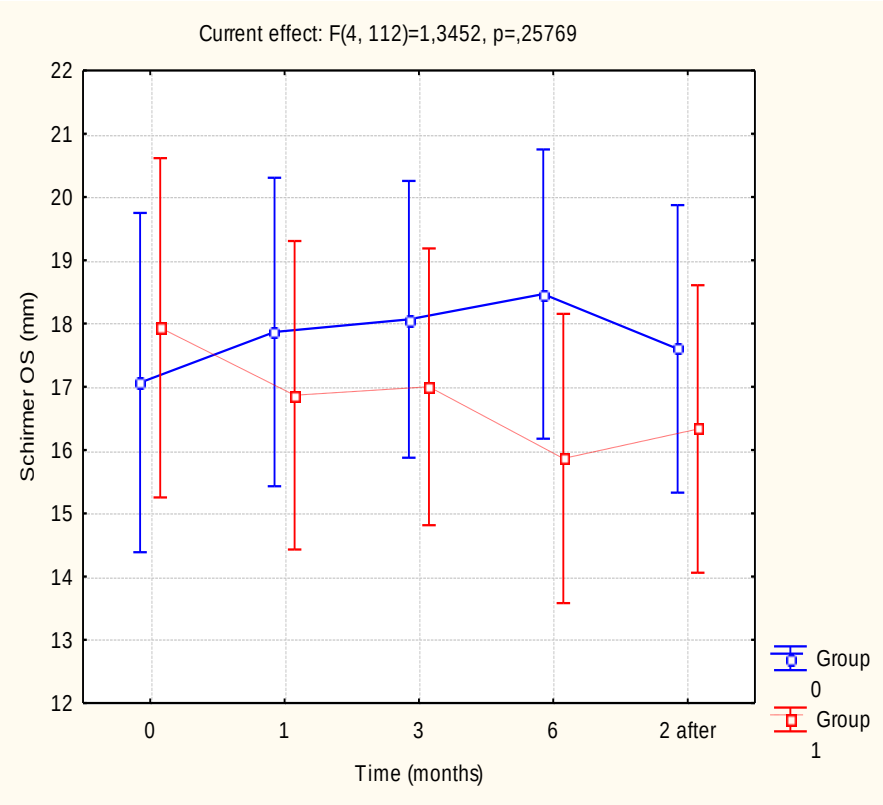
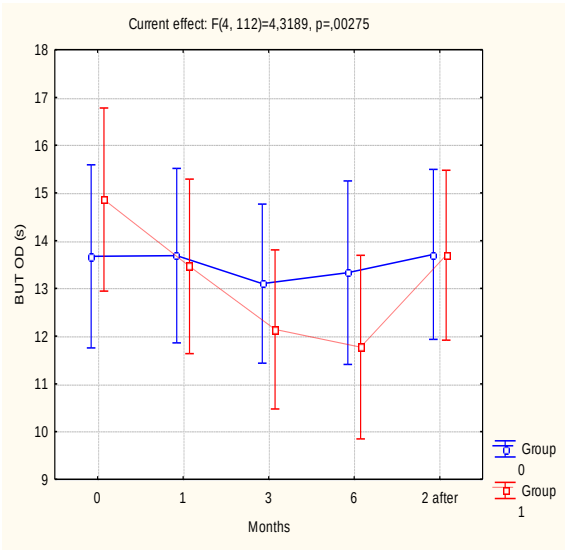


Fig 6.2. Graphical results of the Schirmer test at the 5 visits, for the 2 groups of patients studied, in the left eye

In patients with breast neoplasm undergoing treatment with docetaxel (group 1), as well as in patients with breast neoplasm undergoing other chemotherapy treatment (group 0), the mean variation of the Schirmer test and the NKBUT have fairly uniform values during the treatment period . Following the statistical analysis performed, the coefficient of statistical significance has values $p > 0.05$, for each individual batch (Fig. 6.1. and Fig. 6.2.; Fig. 6.3. and Fig. 6.4.) both for the right eye and for the left eye, for the 2 parameters.



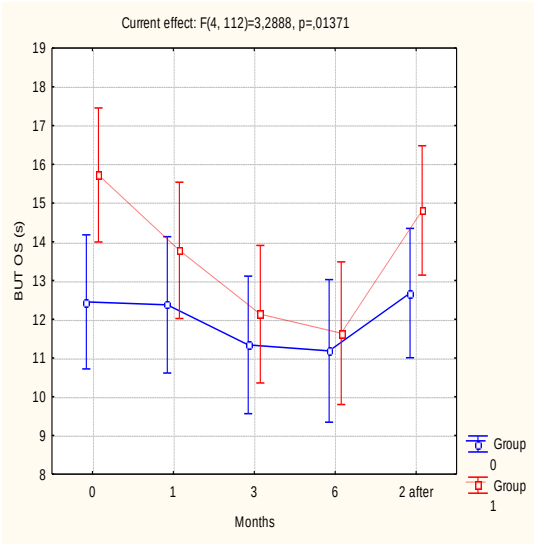


Fig. 6.3 (left) and Fig. 6.4 (right) Graphical results of tear film breaking time (NKBUT), in the 2 studied groups, for the 5 ophthalmological consultations for both eyes

6.4. Discussions and conclusions

The statistical analysis of the two parameters, for the two groups of patients studied, shows that there are no statistically significant differences in the Schirmer test and tear film break-up time, for each group separately, nor for the group under treatment with docetaxel compared to the group who is doing other chemotherapy treatment. That is, we cannot say that the two parameters are modified by the treatment followed by the patients, either docetaxel or another chemotherapy.

Chapter 7. Study II – Meiboscore analysis in patients with breast neoplasm under Docetaxel treatment and in patients with breast neoplasm undergoing other chemotherapy treatment

7.1. Introduction (working hypothesis and specific objectives)

The objective of this study was to observe if there are changes in the level of the meiboscore calculated by performing meibography, during docetaxel treatment in patients with breast cancer undergoing this treatment, and also to observe if these changes occur in the other group as well of patients who undergo other chemotherapy treatment. This parameter gives us useful information about the morphology of the Meibomius glands, by directly visualizing them on meibography.

7.2. Materials and methods - were presented in chapter 5

7.3. Results

In this study, we analyzed the meiboscore by performing meibography with the Ocular Keratograph 5 device, of the Ophthalmology department, of the Bucharest University Emergency Hospital, in all 15 patients from group 1 - the patients undergoing treatment with docetaxel and in the 15 patients from group 0 who are undergoing another chemotherapy treatment. We observe that at this level, for the group of patients treated with docetaxel (group 1), there are changes with statistical significance, in both eyes and especially after 3 weeks from the start of the treatment with Docetaxel.

Thus, we find a coefficient of high statistical significance in the right eye, at t 6, i.e. 6 months after the start of docetaxel treatment (for group 1)($p = 0.0014$), (Table 7.1., Fig. 7.1.) and at t3 (3 months after starting docetaxel treatment) $p = 0.01$. We also find statistically significant values for the left eye ($p = 0.0504$, at t6).

Table 7.1. Time variation of meiboscore,

in the 2 studied groups, for OD, at

upper eyelid

	Mean G1	**Mean G0**	**p**
Meiboscor OD pleoapă super. la t0	1,933333	1,833333	0,637736
Meiboscor OD pleoapă super. la t1	2,166667	1,766667	0,109086
Meiboscor OD pleoapă super. la t3	2,400000	1,866667	**0,010044**
Meiboscor OD pleoapă super. la t6	2,566667	1,900000	**0,001497**
Meiboscor OD pleoapă super. la 2luni după	2,233333	1,800000	**0,043659**

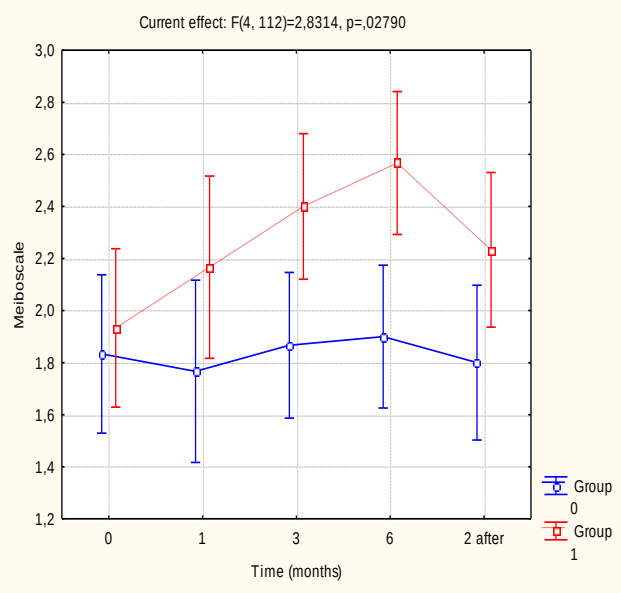


Fig 7.1. Graphic representation of meiboscore

for the 2 groups, at OD, Upper eyelid

7.4 Discussion and Conclusions

Our results support our hypothesis, namely that there are morphological changes in the meibomian glands in women treated with Docetaxel, quantifiable by evaluating the meiboscore. They narrow and/or decrease in number on the eyelids.

Chapter 8. Study III – Analysis of the Schirmer test, NKBUT and meiboscore in patients with breast neoplasm treated with Docetaxel as monotherapy compared to patients treated with docetaxel in combination with another chemotherapy

8.1. Introduction

Taking into account the other 2 studies presented previously, I tried to analyze in this study whether docetaxel in combination with another chemotherapy also produces morphological changes in the meibomian glands or only when administered as monotherapy.

8.2 Materials and methods - are presented in chapter 5, with the difference that the patient groups studied include:

- 15 patients with breast neoplasm receiving docetaxel chemotherapeutic treatment in combination with another chemotherapeutic drug (group 2)

- 15 patients with breast neoplasm receiving chemotherapeutic treatment with docetaxel (as monotherapy) (group 1).

8.3 Results

In this study we analyzed the Schirmer test, the NKBUT and the meiboscore (by performing the meibogram) in group 1 of patients (15 patients with breast cancer treated with docetaxel monotherapy) and in group 2 of patients (15 patients with breast cancer breast that are treated with docetaxel in combination with another chemotherapy). What we aim to highlight through this research. is that the presence of docetaxel in the treatment of these patients is what determines the morphological changes in the meibomian glands, changes responsible for the appearance of epiphora as an ophthalmological adverse reaction in these women.

As for the Schirmer test and the NKBUT, in this study too, there was no change in them, with statistical significance, for the 2 groups of patients studied, both for each group separately and compared between the groups.

Instead, we found statistically significant changes in meiboscore for both groups of patients, in both eyes and both eyelids (Table 8.1).

Table 8.1 The values of the coefficient of statistical significance for the 2 groups of patients studied

ANOVA				
GRUP	*OD pleoapă super.*	*OD pleoapă infer*	*OS pleoapă super*	*OS pleoapă infer*
Grup 1	**p = 0,00512**	**p =0,012**	**p=0,0057**	**p=0,032**
Grup 2	**p=0,050**	**p =0,023**	**p = 0,0141**	**p= 0,049**

8.4 Discussion and Conclusions

As meiboscor quantifies the morphological changes at the level of the Meibomius glands, we can conclude that these changes in the Meibomius glands, in the sense of decreasing their number, their narrowing may be responsible for the appearance of epiphora in patients treated with docetaxel either as monotherapy or in combination with another drug chemotherapy.

Chapter 9. Conclusions and personal contributions

This doctoral thesis is a scientific research designed to analyze a subject that is not yet elucidated in the specialized literature. Working in a multidisciplinary hospital, I had ophthalmological control of patients from the oncology ward, under docetaxel treatment (either as monotherapy or in combination with another chemotherapy) who had epiphora as the reason for presenting to the ophthalmology consultation. Hence the idea and theme of my research thesis. Searching in the specialized literature, I noticed that in the published studies, various causes of epiphora production were invoked, but the data have no statistical significance. So, the production mechanism of hyperlacrimation in these patients is still unexplained. Hence, the originality of my research thesis. Thus, we started the study of 3 groups of 15 patients each: a group of patients with breast neoplasm undergoing treatment with docetaxel (monotherapy), a group of patients with breast neoplasm undergoing other chemotherapy treatment and a group of patients undergoing treatment with docetaxel in combination with other chemotherapy.

The studies were prospective, comparative and descriptive. The doctoral research was carried out in the Department of Ophthalmology of the Bucharest University Emergency Hospital, using the specific equipment necessary for studies in this department. The duration of the research was carried out between 2019 and 2023. The patients with breast neoplasm from the oncology department of the Bucharest University Emergency Hospital, who were going to start an antineoplastic treatment for this pathology, were included. The patients performed 5 ophthalmological consultations, namely before the start of the chemotherapy treatment (t 0), 1 month after the start of the chemotherapy treatment (t1), 3 months after the start of the chemotherapy treatment (t3), 6 months after the start of the chemotherapy treatment (t6), and 2 months after stopping chemotherapy treatment (t 2 months after). We performed and studied mainly 3 parameters: the Shirmer test (performed with the help of specific disposable strips), the tear film break-up time (NKBUT) and the meiboscore by performing the meibography for each eyelid (the last 2 parameters performed with the Ocular device Keratograph, from our department).

The objective of this doctoral thesis is to find a causal relationship between the morphological changes that occur in patients with breast cancer treated with docetaxel and the occurrence of epiphora.

Carefully analyzing each batch of patients separately, we came to the following findings:

1. In study I, we studied 15 patients with breast cancer undergoing treatment with docetaxel (as monotherapy) and 15 patients with breast cancer undergoing other chemotherapy treatment. We evaluated the Schirmer test and tear film breakup time (NKBUT) for each eye at each of the 5 ophthalmological consultations performed. Following the statistical analysis of the 2 parameters, we find that there are no statistically significant differences in the Schirmer test and the NKBUT for each group of patients separately, nor for the group of patients under docetaxel treatment compared to the group of patients receiving other treatment chemotherapy ($p>0.05$).

2. In study II we studied the same 2 groups of patients but evaluating another parameter, namely the meiboscore by performing the meibogram, for each eyelid in both eyes, this being a parameter that can give us morphological details of the Meibomius glands. Thus, following the careful analysis of the meiboscore for each batch of patients separately, we observe that in patients treated with docetaxel there are statistically significant changes in this parameter, in the sense that the meiboscore increases, that is, the number and thickness of the Meibomius glands decrease. (6 months after treatment, in the right eye both for the upper and lower eyelid $p < 0.05$, for the upper eyelid the coefficient of statistical significance is highly statistically significant, $p = 0.0014$). We also observe statistically significant changes in the meiboscore from the left eye, especially for the lower eyelid, after 6 months of treatment ($p = 0.05$).

For the group of patients undergoing other chemotherapy treatment, no statistically significant changes can be observed, both for the right eye and for the left eye.

So, we find that there are statistically significant differences for each group of patients separately as well as in the comparison between the group of patients undergoing treatment with docetaxel and the group of patients undergoing other chemotherapy treatment, in the sense that the patients undergoing treatment with docetaxel present morphological changes

of meibomian glands, during treatment, which supports our hypothesis that epiphora could be due to these meibomian morphological changes.

3. In study III we analyzed 15 patients with breast neoplasm who are treated with docetaxel (as monotherapy) and 15 patients with breast neoplasm who are treated with docetaxel in combination with another chemotherapy. For both groups of patients, we analyzed the three parameters: the Schirmer test, the tear film break-up time (NKBUT) and the meiboscore (by performing the meibogram). And from this study we find that changes with statistical significance are found at the meiboscore level, i.e. morphological changes occur at the level of the Meibomius glands once a patient with breast neoplasm starts treatment with docetaxel either as monotherapy or in combination with another chemotherapy. As for the Schirmer test and tear film breakup time, no statistically significant changes were observed for any group of patients. If there were also changes in the Schirmer test and/or tear film breakup time, we could have said that these changes would have occurred due to the other chemotherapeutic drugs in patients receiving docetaxel treatment in combination with other drugs chemotherapy.

Thus, this study supports our hypothesis, namely that the presence of docetaxel in the treatment regimen of breast cancer patients leads to morphological changes in the level of the Meibomius glands, in the sense of decreasing their number, their narrowing, changes responsible for the appearance of hyperlacrimation in these patients. What I tried to demonstrate in this research is a new hypothesis, since from our research in the specialized literature, until this moment, this hypothesis was not taken into account as a mechanism for producing epiphora.

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