EVALUATION OF RETINAL NERVE FIBRE LAYER AND MACULAR THICKNESS PRE- AND POST-CHEMOTHERAPY WITH CARBOPLATIN AND PACLITAXEL IN PATIENTS WITH ENDOMETRIAL AND OVARIAN CANCER

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DISCLAIMER

I hereby certify that the work in this my own except for the quotations and summaries which have been duly acknowledged.

Date: 9th May 2021 Dr. Chin Ju Juen

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ABSTRAK (BAHASA MELAYU)

Latar Belakang

Carboplatin dan Paclitaxel adalah dua jenis ubat kemoterapi yang sudah dikenalpasti sering memberi kesan sampingan neurotoksisiti. Kami ingin mengkaji kesan toksisiti dengan mengukur ketebalan lapisan retina dan makula pesakit barah rahim dan ovari yang menerima rawatan kemoterapi dengan ubatan ini.

Kaedah

Satu kajian prospektif kohort sepanjang tempoh setahun yang melibatkan seramai 28 orang pesakit yang menerima rawatan intravena carboplatin (200-400mg/m^2) dan paclitaxel (175mg/m^2) setiap tiga minggu untuk enam kitaran telah dijalankan. Ketebalan lapisan retina dan makula diukur dengan tomografi koheren optik sebelum diberi kemoterapi (garis dasar), selepas menerima tiga kitaran, dan satu bulan selepas siap enam kitaran. Hasil utama ukuran ialah purata ketebalan lapisan retina dan purata ketebalan lapisan makula pusat.

Keputusan

Min umur 28 peserta adalah 54.68 (sisihan piawai 9.03). Sebelas orang menghidapi barah rahim manakala 17 pesakit menghidapi barah ovari. Min purata ketebalan lapisan retina sebelum rawatan kemoterapi adalah 96.43µm (sisihan piawai 11.39). Sebulan selepas tamat kemoterapi, ia meningkat kepada 101.57µm (sisihan piawai 13.54). Analisis statistik menunjukkan peningkatan ketara nilai min ketebalan lapisan retina antara sebelum dan selepas tiga kitaran, dan juga sebelum dan sebulan selepas siap enam kitaran rawatan kemoterapi (p=<0.001) kecuali “nasal”. Peningkatan ketebalan pada semua

kuadran lapisan makula memberi perbezaan statistik yang ketara ($p < 0.05$) kecuali makula pusat.

Kesimpulan

Kajian kami menunjukkan rawatan kemoterapi intravena carboplatin dan paclitaxel menjejaskan ketebalan lapisan retina dan makula. Kajian kami mendapati kesan awal subakut subklinikal toksisiti retina disebabkan oleh ubatan ini. Tomografi koheren optik boleh digunakan sebagai alat saringan untuk mengkaji perubahan ketebalan retina sebelum dan selepas kemoterapi.

Kata kunci

Kemoterapi, Carboplain, Paclitaxel, neurotoksisiti, ketebalan lapisan retina, ketebalan lapisan makula, barah rahim, barah ovari.

ABSTRACT (ENGLISH)

Background

Carboplatin and paclitaxel are two standard chemotherapeutic agents known to cause neurotoxicity. In this study we aim to evaluate the toxicity by measuring the peripapillary retinal nerve fibre layer (RNFL) and macular thickness in patients with endometrial and ovarian cancers receiving them.

Methods

A one-year prospective cohort study involving 28 patients who were treated intravenously with carboplatin (200-400mg/m^2) and paclitaxel (175mg/m^2) three-weekly for 6 cycles was conducted. RNFL and macula thickness were measured using optical coherence tomography (OCT) before commencement of chemotherapy, after the third cycle, and one month after the sixth cycle. The main outcome measurements were the average RNFL thickness and central subfield thickness of macula.

Results

The mean age of the 28 participants was 54.68 years old (SD=9.03). Eleven had endometrial cancer while 17 had ovarian cancer. The mean of the average RNFL thickness during baseline pre-chemotherapy was 96.43µm (SD 11.39). One month after cessation of treatment the mean RNFL thickness increased to 101.57µm (SD 13.54). Statistical analysis showed a significant increment in the mean RNFL thickness (p=<0.001), from baseline to after three cycles, and baseline to one-month post six cycles

of chemotherapy, except nasal quadrant. The increment in all the macular quadrants was statistically significant ($p < 0.05$) except central subfield thickness.

Conclusion

Systemic administration of carboplatin and paclitaxel affected both the peripapillary RNFL and macula thickness. This represents early evidence of subacute subclinical retinal toxicity. OCT can be used as a screening tool to assess peri-chemotherapeutic retinal alterations.

Keywords

Chemotherapy, Carboplatin, Paclitaxel, neurotoxicity, retinal nerve fibre layer, macular thickness, endometrial cancer, ovarian cancer.

Trial Registration:

This study adheres to the tenets of the declaration of Helsinki and was approved by the local ethical boards [*USM/JEPeM/19010005*] and the Medical Research Ethics Committee (MREC) [*KKM/NIHSEC/P19-353(12)*].

CHAPTER 1

INTRODUCTION

1.1 ENDOMETRIAL AND OVARIAN CANCER

Endometrial cancer is the sixth most common cancer globally for females, and the 14th most common cancer overall.[1] On the other hand, epithelial ovarian cancer has the highest mortality of all gynaecological cancers, accounting for 6% of all cancer deaths inwomen.[2]

Endometrial cancers are coded as C54 by the International Statistical Classification of Diseases and related health problems, tenth revision (ICD-10:C54) and ovarian cancer as C56 (ICD-10:C56).[3] According to the latest Malaysian Cancer Registry report 2012-2016 published in 2017,[4] cancer of the cervix uteri was reported as the third most common cancer in females and ranked ninth in Malaysia, whereas cancer of ovary ranked fourth in females and tenth in Malaysia.

The current standard of care in advanced ovarian cancer is cisplatin/carboplatin (area under curve 5/6) and paclitaxel (175mg/m^2) three-weekly for 6 cycles.[2] This is Grade A recommendation as per the Royal College of Obstetrics and Gynaecologists document.[2] Primary debulking surgery followed by post-operative chemotherapy with combination of platinum-paclitaxel is the standard of care for all patients with FIGO stage II-IV. Where this is not achievable, neo-adjuvant chemotherapy followed by interval debulking surgery is advised.

Apart from this, adjuvant platinum-based chemotherapy is recommended in all cases of early ovarian cancer other than low grade stage Is/Ib. Large prospective clinical trials have demonstrated significant improvement in both relapse-free survival and overall survival in this group. This chemotherapy regime is also used as first-line in non-serous

histological subtypes and recurrent disease which are platinum-sensitive as a part of cytoreductive surgery.

For uterine cancers, the optimal chemotherapy schedule of cisplatin/carboplatin and paclitaxel (CP) is derived from similar responses of endometrial cancer to epithelial ovarian cancer and is graded D.[1] Due to this, dosage and cycles of this chemotherapy regimen is similar to that used in ovarian cancers. Postoperative platinum-based chemotherapy is associated with a small benefit in progression free survival and overall survival regardless of radiotherapy treatment.[1] Chemotherapy also reduces the risk of developing the first recurrence outside the pelvis.

1.2 CARBOPLATIN AND PACLITAXEL CHEMOTHERAPY

Platinum-based chemotherapy is used in a wide spectrum of solid malignancies other than uterine and ovarian cancer. They are also used in lung cancer, germ cell tumours, bladder cancer, head and neck cancers.

All the main clinical guidelines (American Society of Clinical Oncology-ASCO[5] and European Society of Medical Oncology-ESMO)[6] recommend a first-line platinum-based chemotherapy as the treatment of choice in both advanced cancers as well as neoadjuvant chemotherapy.

Cisplatin is a cytotoxic heavy-metal compound. It induces apoptosis of tumour cells by substituting hydrogen atoms with alkyl groups.[7] Carboplatin has a similar mechanism of

action with a more favourable toxicity profile.[9] It is superior to cisplatin due to reduced toxicity and deliverability.[1] Their molecular structure consists of a parent platinum compound with their difference being in the leaving groups, namely the cyclobutane-decarboxylate group for carboplatin and the chloride group for cisplatin. [10] They form DNA crosslinks which interrupts cellular DNA functioning thereby causes apoptosis. They also form covalent DNA adducts with other cell components. They have been proven to be therapeutically equivalent. Side effects of carboplatin are thrombocytopenia and myelotoxicity. It is less nephrotoxic and neurotoxic compared to cisplatin. Cisplatin has many other side effects including leukopenia, emesis, renal dysfunction, neurotoxic and ototoxic. In gynaecological cancers, carboplatin-doublet was better tolerated with significantly less renal and gastrointestinal toxicities.

Drugs that can be combined with platinum include third-generation cytotoxic drugs docetaxel, paclitaxel, gemcitabine, irinotecan and pemetrexed.

Paclitaxel belongs to taxane class of chemotherapy drugs. It is a mitotic inhibitor which stabilizes microtubules and interferes with its usual breakdown during cell division.[8] Other than its use in uterine and ovarian cancer, it is also widely used in lung cancer.

1.3 SYSTEMIC CHEMOTHERAPY AND OCULAR TOXICITY

The human eye is small and has a rich vascular supply. This makes it particularly vulnerable to systemically administered drugs. The major hurdle for systemic drugs to

reach the eye is the blood ocular barriers, namely the blood-aqueous barrier and blood-retina barrier.

Optic neuropathy and macular degeneration can occur following systemic drug administration.[10,11] Neurotoxicity is the major dose-limiting toxicity of cisplatin. Its other well-known complications are nephrotoxicity and peripheral neuropathy.[12]

Visual impairment has been considered as a rare and infrequent form of neurotoxicity. Long-term intravenous carboplatin therapy causes various ocular complications. Severe orbital inflammation, proptosis, loss of eye movements, loss of vision, optic neuropathy, maculopathy, sore eyes, chorioretinitis to optic neuritis have been described.[13-15] Previous studies showed reversible visual disturbances after drug cessation.

Neurotoxicity of paclitaxel is widely known. Visual impairment and transient scintillating scotoma have been reported. Reversible scotoma with visual evoked potential abnormalities similar to that of demyelinating optic neuropathy was reported by Capri et al.[16] Photopsia has been reported to occur during the last half an hour of intravenous infusion of paclitaxel. This resolves totally within 3 hours and usually occurs with higher doses of 250mg/m^2 or more.[17] It rarely occurs at 175mg/m^2 doses used in treatment of uterine and ovarian cancers. Taxanes have also been reported infrequently to cause cystoid macular edema which is angiographically silent. Glaucoma has also been reported to occur with taxanes in literature.[18,19]

A case report and literature review by Li Y et al[20] in 2014 summarized the ocular toxicities induced by cisplatin and paclitaxel combination which were reported in prior studies as seen below.

Table 1 Summarized paclitaxel- and/or cisplatin-induced ocular toxicity reported in prior and present studies

Author(s)	Case number	Toxicity	Drug	Diagnosis
Kwan et al[4]	1	Hemianopia	CDDP	Nonseminomatous germ cell testicular tumor
Berman and Mann[8]	1	Cortical blindness	CDDP	Embryonic cell carcinoma of the testicle
Wilding et al[9]	13	Blurred vision	CDDP	Ovarian carcinoma
Tan and Walsh[10]	2	Photopsia	CDDP, PTX	Lung cancer
Wang et al[11]	1	Bilateral blindness	Carmustine, CDDP	Breast carcinoma
Watanabe et al[12]	1	Visual disturbance	Carboplatin	Glioblastoma
Wu et al[13]	1	Intraorbital and intraocular pain	CDDP	Glioblastoma multiforme
Scaioli et al[14]	1	Optic neuropathy	PTX, doxorubicin	Breast cancer
Modi and Dubovy[15]	1	Maculopathy	PTX	Breast cancer
Joshi and Garretson[16]	1	Cystoid macular edema	PTX	Breast cancer
Li et al (present study)	1	Bilateral blindness	CDDP, PTX	Nasopharyngeal cancer

Abbreviations: PTX, paclitaxel; CDDP, cisplatin.

1.4 PERIPAPILLARY RNFL AND MACULAR THICKNESS IN OCULAR TOXICITY

The RNFL is made up of axons of retinal ganglion cells. They carry electrical impulses from the retina to the optic nerve and optic chiasm. RNFL thickness is a morphological measurement which can be affected in the early stages of many optic nerve conditions such as glaucoma and optic neuropathy. A decrease in thickness implies loss of axons of ganglion cells. An increase in thickness is found in cases of inflammation or toxicity.

Early changes in these thicknesses can be detected using OCT before any visual field defects appear.[21] Using near-infrared light, the OCT provides quantitative and reproducible

measurements of RNFL and macular thickness parameters.[22] Normal measurements of RNFL and macular thickness are 92.63±4.80 µm and 262.8±13.34 µm respectively.[23,24]

The mechanism of ocular neurotoxicity remains unknown. The ischaemic and electrophysiological hypothesis does not fully explain their occurrence.[20] Previous studies suggested retinal vascular dysregulation or optic nerve ischaemia to be the possible mechanism. Electrophysiological changes in patients with reversible scotoma was comparable to those changes observed in ischaemic neuropathies, suggesting that the optic nerve may be the main target site of these drugs.[25,26]

Besides DNA dysfunction and apoptosis, platinum-based compounds are known to cause mitochondrial dysfunction. This leads to reduced axonal transport, particularly affecting small calibre axons (parvo-cellular RGC axons) of the optic nerve and papillomacular bundle. This was based on an in vitro Leber's hereditary optic neuropathy (LHON)-mimicking mice model study report.[27-29]

Paclitaxel is known to cause angiographically-silent macular oedema.[30] The mechanism of this oedema is not clearly understood. One theory suggests that the permeability of retinal vessels due to breakdown of blood-ocular barrier is so minute that larger fluorescein molecules are unable to pass through.[31] Another theory explains that it is due to the toxicity of Muller cells which leads to disturbances in the osmotic gradient within the neurosensory retina, which results in intracellular fluid accumulation.[32]

Bakbak et al[8] assessed CP-associated toxicities in the optic nerve by measuring the RNFL thickness and visual field changes in patients with lung cancer. They found statistically

significant decrement in RNFL thickness and visual field changes recorded by OCT and Humphrey visual field analyser (HFA) respectively. The measurement of RNFL was done at baseline and three months after cessation of chemotherapy.

Another similar study by Simon Dulz et al[33] investigating the ocular toxicity of cisplatin-based chemotherapy in patients with germ cell cancer showed similar decrements in RNFL thickness which correlated with cumulative cisplatin doses. This shows that alterations in RNFL thickness reflect the underlying subclinical retinal toxicity of CP.

1.5 RATIONALE OF THE STUDY

Neurotoxicity represents the major dose-limiting toxicity of carboplatin, cisplatin and paclitaxel. Optic neuropathy and maculopathy are considered forms of neurotoxicity. Since these chemotherapeutic agents are recommended as first-line in combating endometrial and ovarian cancers, it is imperative to quantify the ocular neurotoxicity effects. There have been limited studies on determination and comparison of macular and RNFL thicknesses among cancer patients receiving carboplatin and paclitaxel chemotherapy. To the best of our knowledge, there is no study on endometrial and ovarian cancer patients receiving CP chemotherapy.

We hope to provide reliable parameters on detection of subclinical optic nerve and retinal changes before significant functional changes occur. If the changes of CP-induced optic neuropathy and CP-induced retinopathy can be detected early in the course of treatment, it may be possible to prevent permanent damage to the optic nerve and the potential

outcome of irreversible visual reduction. As there is no specific treatment plan proposed in literature for ocular toxicity induced by these agents, the common decision is the discontinuation of the causative factor, possible change of chemotherapeutic agents, or adjustment of dose intervals of the regimen. All these should be in consultation with the managing gynae-oncologist.

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CHAPTER 2

OBJECTIVES

2.0 RESEARCH OBJECTIVES

2.1 General Objective

To evaluate the change in RNFL and macula thickness pre- and post-chemotherapy with carboplatin and paclitaxel in patients with endometrial and ovarian cancer.

2.2 Specific Objectives

2.2.1 To compare the change in RNFL thickness using OCT pre-chemotherapy, after 3 cycles and after 6 cycles of treatment with platinum-based chemotherapy (carboplatin) and paclitaxel among patients with endometrial and ovarian cancer.

2.2.2 To compare the change in macula thickness using OCT pre-chemotherapy, after 3 cycles and after 6 cycles of treatment with platinum-based chemotherapy (carboplatin) and paclitaxel among patients with endometrial and ovarian cancer.

CHAPTER 3

MANUSCRIPT

Evaluation of Retinal Nerve Fibre Layer and Macular Thickness Pre- and Post-Chemotherapy with Carboplatin and Paclitaxel in Patients with Endometrial and Ovarian Cancer

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3.0 MANUSCRIPT

3.1 Abstract

Background

Carboplatin and paclitaxel are two standard chemotherapeutic agents known to cause neurotoxicity. In this study we aim to evaluate the toxicity by measuring the peripapillary retinal nerve fibre layer (RNFL) and macular thickness in patients with endometrial and ovarian cancers receiving them.

Methods

A one-year prospective cohort study involving 28 patients who were treated intravenously with carboplatin (200-400mg/m^2) and paclitaxel (175mg/m^2) three-weekly for 6 cycles was conducted. RNFL and macula thickness were measured using optical coherence tomography (OCT) before commencement of chemotherapy, after the third cycle, and one month after the sixth cycle. The main outcome measurements were the average RNFL thickness and central subfield thickness of macula.

Results

The mean age of the 28 participants was 54.68 years old (SD=9.03). Eleven had endometrial cancer while 17 had ovarian cancer. The mean of the average RNFL thickness during baseline pre-chemotherapy was 96.43µm (SD 11.39). One month after cessation of treatment the mean RNFL thickness increased to 101.57µm (SD 13.54). Statistical analysis showed a significant increment in the mean RNFL thickness (p=<0.001), from baseline to after three cycles, and baseline to one-month post six cycles

of chemotherapy, except nasal quadrant. The increment in all the macular quadrants was statistically significant ($p < 0.05$) except central subfield thickness.

Conclusion

Systemic administration of carboplatin and paclitaxel affected both the peripapillary RNFL and macula thickness. This represents early evidence of subacute subclinical retinal toxicity. OCT can be used as a screening tool to assess peri-chemotherapeutic retinal alterations.

Keywords

Chemotherapy, Carboplatin, Paclitaxel, neurotoxicity, retinal nerve fibre layer, macular thickness, endometrial cancer, ovarian cancer.

Trial Registration:

This study adheres to the tenets of the declaration of Helsinki and was approved by the local ethical boards [*USM/JEPeM/19010005*] and the Medical Research Ethics Committee (MREC) [*KKM/NIHSEC/P19-353(12)*].

3.2 Introduction

Carboplatin and paclitaxel (CP) are first-line chemotherapy drugs used worldwide to treat endometrial and ovarian cancers.[1,2] The current standard of care in advanced ovarian cancer is carboplatin (area under curve 5/6, 200-400mg/m^2) and paclitaxel (175mg/m2) three-weekly for 6 cycles. This is Grade A recommendation as per the Royal College of Obstetrics and Gynaecologists document.[2] For uterine cancers, the optimal chemotherapy schedule of carboplatin and paclitaxel is derived from similar responses of endometrial cancer to epithelial ovarian cancer and is graded D.[1]

Neurotoxicity represents the major dose-limiting toxicity of CP.[3-5] Optic neuropathy and maculopathy are considered forms of neurotoxicity. Early optic nerve damage is reflected by changes in the peripapillary RNFL. Since these chemotherapeutic agents are recommended as first-line in combating endometrial and ovarian cancers, it is imperative to quantify the ocular neurotoxicity effects, especially in cumulative dose regimens. To date, there are no published reports available on the evaluation of the ocular changes due to toxicity during the course of chemotherapy in patients receiving CP combination.

Regular ophthalmic examination which includes visual acuity, slit lamp bio microscopy and photography has been used to detect ocular toxicity during clinical practice. However, these assessments may not be useful in detecting subclinical CP-induced optic neuropathy or retinopathy. Currently, newer imaging equipment such as the Optical Coherence Tomography (OCT) can reveal changes in the RNFL and macular thickness before visual defects surface.[6]

The purpose of this study is to evaluate the changes in RNFL and macula thickness in endometrial and ovarian cancer patients receiving carboplatin and paclitaxel at baseline before commencement of chemotherapy, after three cycles and one month after six cycles.

3.3 Methodology

3.3.1 Subjects

This is a prospective cohort study conducted in the ophthalmology clinic of a tertiary care centre, Hospital Raja Permaisuri Bainun (HRPB), Perak, Malaysia from July 2019 to July 2020. This was done in collaboration with the Gynae-oncology team of the same centre. This study adheres to the tenets of the declaration of Helsinki and was approved by the local ethical boards [*USM/JEPeM/19010005*] and the Medical Research Ethics Committee (MREC) [*KKM/NIHSEC/P19-353(12)*].

All participants had given their written informed consent prior to their inclusion in the study. A total of 35 subjects who were newly diagnosed cases of endometrial or ovarian cancer were selected. Diagnosis was confirmed based on histopathological examination and made by the gynae-oncology team. These patients were planned for commencement of chemotherapy with carboplatin and paclitaxel.

Those patients with underlying ocular diseases such as optic nerve and macula diseases, past history of ocular surgery or trauma, current and past history of intake of other neurotoxic drugs, brain metastasis, concurrent nervous system disorders (Parkinson's disease, Alzheimer's disease, stroke, bipolar disorder) were excluded. Systematic randomise sampling was applied. During our study period, the total number of newly diagnosed endometrial and ovarian cancer patients planned for chemotherapy was 43. Every alternate patient was enrolled in our study.

Each patient received intravenous Carboplatin (area under curve 5/6, 200-400mg/m^2) and Paclitaxel (175mg/m^2) consecutively, over a four-hour period, every three-weekly for a maximum of six cycles of treatment.

3.3.2 Sample Size Calculation

Sample size calculation was calculated using G*Power 3.0.10. The sample size calculated was 28 to achieve the power of 0.80 and the samples that were expected to be withdrawn from this study was 20%. Therefore, the exact sample size was 35 patients that abide with inclusion and exclusion criteria will undergo complete ocular examination and OCT using specific research tools.

3.3.3 Data Collection and Analysis

The demographic data (age and race), systemic co-morbidities, type of cancer (endometrial or ovarian) were obtained through history taking. Those who fulfilled the selection criteria were explained the nature of the study and written consent were obtained. All patients underwent a comprehensive ophthalmological examination which included best corrected visual acuity, anterior segment examination, applanation tonometry, dilated fundus examination and OCT. They underwent these examinations at three different times which were at pre-chemotherapy (baseline), after 3 cycles (just prior to commencement of 4^{th} cycle) and after 6 cycles of chemotherapy (one-month post cessation of chemotherapy). We chose one month post cessation to be the last time point of measurement as the total plasma clearance of carboplatin and paclitaxel is 1-2 weeks.[7,8] This ensures the total of six doses of drug received and taken effect. Patients who had

abnormality in the initial OCT were excluded from this study. The same OCT Machine was used for measurement throughout the entire study.

The peripapillary RNFL thickness and macular thickness were performed by a single qualified and trained personnel using Stratus OCT (Carl Zeiss Meditec Inc., Dublin, CA). Good quality scans comprising of a signal strength of more than five were used, with proper centring and focused images. Only the findings of the right eye of each patient were used. The software automatically compares an average RNFL thickness and macular thickness with a normative database.

All statistical analyses were calculated using the Statistical Package for Social Science (SPSS) version 26. Descriptive statistics was conducted to describe the demographic profile. Repeated measures ANOVA was used to compare the changes of RNFL and macula thickness at pre-chemo, after 3-cycles, and one-month post 6-cycles. The quantitative data was expressed as mean (standard deviation) since it showed a normal distribution. A p value <0.05 was considered statistically significant.