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ORIGINAL ARTICLE

Vestibulotoxicity Assessment using Video Head Impulse Test (v-HIT) in Cancer Patients Receiving Platinum-Based Chemotherapy at Hospital Canselor Tuanku Muhriz

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ABSTRAK

Matlamat kajian ini adalah untuk mengkaji vestibulotoksisiti dalam kalangan pesakit kanser yang menerima ejen kemoterapi berasaskan platinum, menggunakan ujian video Head Impulse Test (v-HIT). Sebanyak 23 orang pesakit telah direkrut sepanjang tempoh Julai 2020 hingga Disember 2022 dari Unit Onkologi dan Hematologi di Hospital Censelor Tuanku Muhriz. Pengambilan sejarah pesakit, otoskopi dan penilaian visual telah dilakukan. Penilaian vestibular menggunakan v-HIT dilakukan sebelum memulakan kemoterapi, selepas rawatan dan sebulan selepas rawatan selesai. Penilaian vestibular prarawatan kemoterapi telah dijalankan ke atas 23 pesakit kanser yang menerima rawatan. Lapan (34.8%) pesakit berjaya melengkapkan semua penilaian yang dijalankan. Lima (21.7%) pesakit dapat melengkapkan penilaian semasa rawatan selesai. Sepuluh (43.5%) pesakit tidak dapat melengkapkan penilaian disebabkan oleh perkembangan penyakit atau kematian. Dua daripada 13 (15.4%) pesakit yang berjaya melengkapkan penilaian menunjukkan penurunan dalam refleks vestibulo-okular. Dalam kajian ini, kadar vestibulotoksisiti berdasarkan penurunan refleks vestibulo-okular adalah sebanyak 15.4% (2 daripada 13 pesakit). Faktor umur ialah salah satu faktor yang mungkin menyumbang kepada penurunan dalam keuntungan refleks vestibulo-okular. Jenis

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kanser juga boleh mempengaruhi fungsi vestibular akibat daripada perubahan hormon. Sebagai kesimpulan, kajian ini mendapati bahawa 15.4% pesakit kanser yang menerima kemoterapi berasaskan platinum menunjukkan "vestibulotoxicity" yang dibuktikan melalui penurunan gain refleks vestibulo-okular pada v-HIT. Faktor umur dan jenis kanser mungkin menyumbang kepada risiko ini, sekali gus menekankan keperluan pemantauan fungsi vestibular yang teliti dalam populasi ini.

Kata kunci: *Kehilangan pendengaran; kemoterapi, keuntungan refleks vestibulo-okular; ujian impuls kepala video; vestibulotoksisiti*

ABSTRACT

The aim of the research was to study vestibulotoxicity among cancer patients receiving platinum-based chemotherapy agents, using video Head Impulse Test (v-HIT). A total of 23 patients were recruited throughout July 2020 until December 2022 from the Oncology and Haematology Unit in Hospital Censelor Tuanku Muhriz. History taking, otoscopy and visual assessments were performed. Vestibular assessments were performed with v-HIT prior to initiation of chemotherapy, post treatment and one month after treatment completion. Pre-chemotherapy vestibular assessment was performed in 23 cancer patients who received treatment. Eight (34.8%) patients were able to complete the assessments conducted. Five (21.7%) patients were able to complete assessments at treatment completion. Ten (43.5%) patients were unable to complete the assessments due to disease progression/ death. Two out of 13 (15.4%) patients who completed the assessments had decreased vestibulo-ocular reflex gain. In our study, vestibulotoxicity based on decrease in vestibulo-ocular reflex gain was 15.4% (2/13). Age was one of the factors that might cause decrease in vestibulo-ocular reflex gain. The type of cancer might also affect the vestibular function due to hormonal changes. In conclusion, this study found that 15.4% of cancer patients receiving platinum-based chemotherapy exhibited vestibulotoxicity as evidenced by decreased vestibulo-ocular reflex gain on v-HIT. Age and cancer type may contribute to this risk, highlighting the need for careful vestibular monitoring in this population.

Keywords: Chemotherapy; hearing loss; vestibulotoxicity; vestibulo-ocular reflex gain; video head impulse test

INTRODUCTION

Cancer care has greatly improved. With early detection, best supportive care and treatment, the 5-year survival rate for all cancer patients is now approximately 66%. However, these advancements are also associated with specific adverse effects. We discuss such adverse effects to do with ototoxicity in platinum-based chemotherapy drugs. These may reduce long term functional status, work and quality of life causing permanent hearing loss and peripheral neurotoxicity (Prayuenyong et al. 2018; Travis et al. 2014).

Ototoxicity due to various factors can result in auditory and/ or vestibular dysfunction. The effects can be temporary or permanent. Symptoms of ototoxicity include tinnitus, dizziness, hyperacusis and problems in understanding speech in a noisy environment. Vestibulotoxicity may present

with unsteadiness or ataxic gait, oscillopsia, nystagmus and/ or vertigo (Konrad-Martin et al. 2005).

Platinum-based compounds are commonly used to treat a variety of malignancies (Callejo et al. 2015; Prayuenyong et al. 2018; Waissbluth et al. 2018a; Waissbluth et al. 2018b). There are three platinum-based drugs that are used for cancer treatment which are cisplatin, carboplatin and oxaliplatin (Oun et al. 2018). However, patients can develop irreversible sensorineural hearing loss and tinnitus due to the ototoxicity.

The possibility of patients developing vestibulotoxicity after receiving platinum-based agents have been controversial (Waissbluth et al. 2018b). Both auditory and vestibular organ functions may be implicated as they have a common haematologic and nerve supply. Potential risk factors of vestibulotoxicity are cumulative dosage of platinum-based chemotherapy agents and accompanying cochleotoxicity (Prayuenyong et al. 2018).

Vasquez and Mattucci (2003) conducted a study whereby patients who were on a cochleotoxic or vestbulotoxic drugs underwent testing within 24 hours before the start of treatment. Following completion of treatment, they underwent follow up assessments at 2 weeks, 1 month, 3 months and 6 months. They concluded that stopping the drugs at first sign of vestibular irritability, might not improve prognosis and outcome. However, early cessation of the drug might spare the cochlear function.

Head Impulse Test (HIT) is a diagnostic tool used at the bedside to examine and identify patients with suspected peripheral vestibular disorders (Handelsman 2018; Halmagyi et al. 2017; MacDougall et al. 2009). With the advent of technology, clinicians are now able to use video to capture eye movements. Video Head Impulse Test (v-HIT) may now be employed for patients that are suspected to suffer from vestibular disorders. The test is fast, repeatable and provides objective quantitative data about each semi-circular canal which are the horizontal, left anterior right posterior (LARP) and right anterior left posterior (RALP) (Halmagyi et al. 2017; Handelsman 2018). V-HIT is able to measure the function of each canal. Impairment of the canal is able to be measured quantitatively.

Vestibulo-ocular response (VOR) gain is used to assess the functional state of the canals. It measures the adequacy of the VOR response. The normal range of gains for v-HIT that are often referred to for lateral and vertical manoeuvres are 0.8-1.2 and 0.7-1.2, respectively. Patients with vestibular loss have reduced VOR gain (Halmagyi et al. 2017; Jamaluddin & Omar 2019). In this study, we defined vestibulotoxicity when the patient had a reduction of VOR gain. We reported on vestibulotoxicity among cancer patients receiving platinum-based chemotherapy, utilising the v-HIT at our centre.

MATERIALS AND METHODS

This was a descriptive cross-sectional study conducted in the Oncology and Haematology Unit Hospital Canselor Tuanku Muhriz (HCTM) from July 2020 until December 2021 among newly diagnosed cancer patients receiving platinum-based chemotherapy within the age range of 6 to 75 years old. The exclusion criteria consisted of pre-existing middle ear pathology, vestibular disease, temporal bone malignancy and a history of cranial irradiation, cervical disorders, visual disturbance and ill patients. History taking and examination of the ears using otoscopy and visual assessment using Snellen chart were performed. Vestibular assessments were performed using v-HIT

prior to initiation of chemotherapy, at end of treatment and at 1-month post-treatment. Data analysis was performed using Microsoft Excel (Microsoft Corporation, Redmond, WA). The baseline demographic data were expressed as mean and standard deviation for continuous data. Descriptive analyses were performed from the data and summarised.

RESULTS

A total of 23 patients (Table 1) were recruited in the study which had fulfilled the inclusion and exclusion criteria. Among the 23 patients, 13 subjects were female (56.5%) and 10 subjects were male (43.5%). Age ranged from 30 to 74 years old. The ethnicity was recorded as Malay (n=12), Chinese (n=6), Indian (n=3) and "other" race (n=2). None of the patients reported any pre-existing vestibular symptoms (Table 2) such as vertigo/ imbalance or giddiness prior to recruitment.

Pre-chemotherapy vestibular assessment was done in 23 cancer patients. The drugs used in this study were cisplatin, carboplatin and oxaliplatin. Eight (34.8%) patients (Table 3) completed the assessments conducted (completed post-chemotherapy assessment twice, which was at end of treatment and at 1-month post-treatment). Only five (21.7%) patients completed assessments done at end of treatment. Ten (43.5%) patients were unable to complete the tests due to disease progression and/or death. The systems involved based on the type of cancer among patients recruited were the highest among gastrointestinal 56.5%, followed by respiratory 13%, both head and neck and gynaecology 8.7% each and endocrine and breast, haematological, genitourinary 4.3% respectively (Figure 1).

TABLE 1: Demographic description

Demographics	**n = 23**
Age (mean)	53.4 (31 to 75 years old)
Gender	Male 43.5% (n=10) Female 56.5% (n=13)
Race	Malay 52.2% (n=12) Chinese 26.1% (n=6) Indian 13.0% (n=3) Others 8.7% (n=2)
Co-morbidity	No known medical illness 52.2% (n=13) Diabetes Mellitus 17.4% (n=4) Hypertension 34.8% (n=8) Hyperthyroidism 4.4% (n=1) Dyslipidemia 8.7% (n=2)

Two out of 13 patients, (15.4%) had decreased VOR gain (VOR gain<0.7). Both patients who developed decrease in VOR gain were within the age range of 45-60 years old. The first case is a 45-year-old Malay female. She was diagnosed with endocervical endometrial adenocarcinoma. She had received cisplatin (total dosage of 280 mg), which was given at 40 mg/m^2 body surface area (BSA). She had persistent decrease in VOR gain at one month post treatment assessment. The second case was a 56-year-old Malay female with hepatic flexure adenocarcinoma. She had received a regime in combination of oxaliplatin (total dosage of 1970 mg), which was given at 130 mg/m^2 BSA. She had a decrease in VOR gain at completion of treatment. Her repeated assessment at one month revealed improvement in VOR gain. Both patients did not have any co-morbidities.

DISCUSSION

Vestibular dysfunction may seriously impact a patient's daily life. This affects not just the personal life but also economically with days off work, injuries due to balance and falls. Prevention and successful intervention is needed to protect the population from the possible effects of cancer treatment (Prayuenyong et al. 2018).

TABLE 2: Demographic table according to co-morbidity and type of malignancy

Patient	Age	Gender	Race	Comorbidity	Diagnosis
Case 1	53	Female	Malay	Diabetes mellitus, hypertension	Adenocarcinoma of the lung
Case 2	40	Female	Malay	No known medical illness	Metastatic lung adenocarcinoma
Case 3	35	Male	Malay	No known medical illness	Non-Hodgkin lymphoma
Case 4	62	Male	India	Diabetes mellitus, hypertension	Alveolar squamous cell carcinoma
Case 5	45	Female	Malay	No known medical illness	Endocervical endometrial adenocarcinoma
Case 6	70	Female	Malay	No known medical illness	Invasive urothelial bladder papillary carcinoma
Case 7	74	Male	Chinese	No known medical illness	Rectal adenocarcinoma
Case 8	56	Female	Malay	No known medical illness	Hepatic flexure adenocarcinoma
Case 9	31	Female	Malay	No known medical illness	Rectosigmoid adenocarcinoma with liver metastasis
Case 10	38	Female	Malay	No known medical illness	Periampullary adenocarcinoma with liver metastasis
Case 11	56	Female	Malay	Hypertension	Locally advanced pancreatic adenocarcinoma
Case 12	53	Male	Malay	Dyslipidaemia	Metastatic sigmoid colon carcinoma
Case 13	69	Female	Indian	Diabetes mellitus, hypertension	Rectal adenocarcinoma with lung metastasis

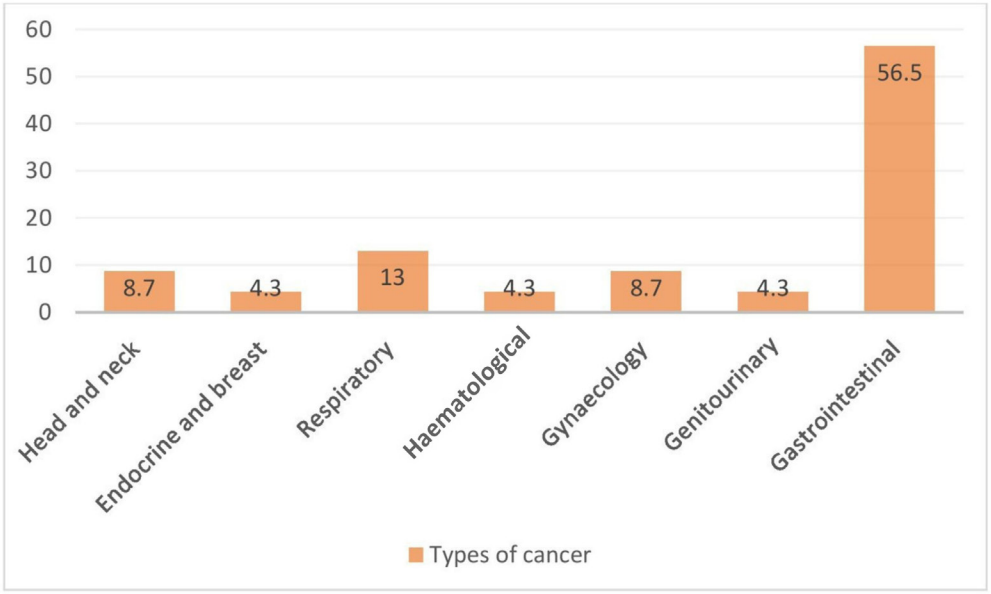

FIGURE 1: Percentage of cancer cases based on system

TABLE 3: VOR gain in subjects pre chemotherapy and post chemotherapy assessment

No	Regime received	Dose received (mg)	VOR gain pre-chemo						VOR gain post-chemo						VOR gain 1 month post-chemo					
			Rt lat	Rt ant	Rt post	Lt lat	Lt ant	Lt post	Rt lat	Rt ant	Rt post	Lt lat	Lt ant	Lt post	Rt lat	Rt ant	Rt post	Lt lat	Lt ant	Lt post
1	Cisplatin	660	1.0	0.6	0.71	1.01	0.72	0.77	1.52	0.93	0.8	1.63	0.72	0.93	1.3	0.8	0.78	1.38	0.65	0.88
2	Cisplatin	347	0.96	0.84	0.83	0.98	0.76	0.84	0.88	0.93	0.87	0.99	0.83	0.95	1.09	0.85	0.96	0.98	0.88	1.0
3	Carboplatin	3200	0.96	0.89	0.79	0.85	0.81	0.86	0.96	0.85	0.86	0.92	0.72	0.9	0.97	0.87	0.89	0.91	0.86	0.96
4	Cisplatin	224	0.98	0.99	0.9	0.9	0.76	1.08	1.02	0.92	0.86	0.94	0.76	0.96	1.01	0.82	0.74	0.9	0.71	0.91
5	Cisplatin	280	1.05	0.77	0.85	0.9	0.88	0.86	0.97	0.67	0.7	0.91	0.7	0.71	0.88	0.66	0.75	0.83	0.75	0.71
6	Cisplatin	425	1.15	0.89	0.94	1.05	0.96	0.79	1.18	0.99	0.84	1.09	0.83	0.98	0.94	0.82	0.75	0.84	0.82	0.71
7	Oxaliplatin	580	1.06	0.88	0.85	0.93	0.88	0.86	1.07	0.91	0.82	0.97	0.85	0.9	0.94	0.88	0.84	1.0	0.84	0.84
8	Oxaliplatin	1970	0.99	0.71	0.8	0.96	0.85	0.7	1.03	0.75	0.72	0.98	0.63	0.7	1.05	0.84	0.7	1.01	0.82	0.77
9	Oxaliplatin	1743	0.93	0.82	0.89	0.83	0.9	0.82	1.05	0.9	0.81	1.0	0.81	0.71	-	-	-	-	-	-
10	Oxaliplatin	1330	0.99	0.54	0.41	0.98	0.45	0.51	1.02	0.6	0.47	0.97	0.54	0.47	-	-	-	-	-	-
11	Cisplatin	120	1.48	1	0.94	1.49	0.82	0.97	1.25	1.0	0.88	1.2	0.89	0.91	-	-	-	-	-	-
12	Oxaliplatin	415	1.01	0.87	0.71	0.93	0.70	0.71	0.95	0.90	0.77	0.86	0.79	0.84	-	-	-	-	-	-
13	Oxaliplatin	800	0.87	0.85	0.74	0.92	0.73	0.80	1.02	1.2	0.97	0.87	0.94	1.05	-	-	-	-	-	-

VOR: vestibulo-ocular response; Rt/ Lt lat: Right/ left lateral; Rt/ Lt ant: Right/ left anterior; Rt/ Lt post: Right/ left posterior; VOR: Vestibular ocular response

Platinum-based chemotherapy is a type of treatment of anti-neoplastic drugs used for malignancies including testicular, ovarian, bladder, head and neck, and non-small cell lung cancer (Callejo et al. 2015; Prayuenyong et al. 2018; Waissbluth et al. 2018b). Ototoxicity is a common side-effect which may in turn limit its use. Ototoxicity refers to drug-induced damage affecting the inner ear structures causing cochlear (such as hearing loss or tinnitus) and/or vestibular dysfunction (such as vertigo, dizziness, or imbalance), or both (Konrad-Martin et al. 2005; Prayuenyong et al. 2021).

This study evaluated patients receiving platinum-based chemotherapy and its vestibulotoxicity. Two (15.4%) patients developed decrease in VOR gain (VOR gain <0.7). None of the patients were symptomatic after completion of chemotherapy. Vestibular dysfunction develops gradually. It is subtle, and may not be picked up by the clinician. This may be why they did not complain of vestibular dysfunction at the time of the study.

Drug-induced vestibular loss may affect both ears symmetrically or asymmetrically and gradually result in insidious imbalance, postural problems and oscillopsia (Prayuenyong et al. 2018). Vestibular dysfunction may be masked by central nervous system compensation or substitution by vision and proprioception, thus masking or vestibular problems. Compare this with cochlear damage, whereby the patient complains of hearing loss, which is much more obvious. Non-specific symptoms of imbalance or subtle disequilibrium may be attributed to the underlying cancer and general wellbeing of patients during and after treatment. (Prayuenyong et al. 2018)

Previous reports showed that objective test findings and patient symptoms did not always parallel with each other. Previous studies show abnormal vestibular function tests in asymptomatic patients. Possible risk factors identified are cumulative dosage and prior vestibular loss (Prayuenyong et al. 2018).

One of our patients with decrease in VOR gain has endocervical endometrial adenocarcinoma. Studies have reported on pathologies of the uterus and breast, including endometrial cancer, uterine fibroids, and breast cancer, pertaining to oestrogen and its receptors in the inner ear (Kim et al. 2013). Jian et al. (2019) previously reported on oestrogen and its role as a neurotransmitter, which therefore, causes problems with the peripheral balance system. Oestrogen regulates vascular endothelial tone, cerebral blood flow, the neurotransmitter system and neuroactive metabolites. Oestrogen receptors (ER) are found in the inner ear, where ER has specific localisation in the spiral ganglion type I cells while ERβ in the stria vascularis involved in the ion and fluid balance of the endolymph and cochlear and vestibular sensory transduction. Oestrogen could enhance receptors in the brainstem vestibular nucleus, regulating the eyeball movement, vestibular ocular reflex and vestibular spinal reflex. Oestrogen levels may also be involved in the microcirculatory disturbance of the inner ear, affecting vestibular hypofunction (Jian et al. 2019).

With regards to age and vestibulotoxicity, our study revealed 2 (15.4%) patients, 45-56 years old who had decreased vestibular function. The oldest patient recruited in the study is a 74-year-old male, revealed a normal VOR gain for pre-chemotherapy and post-chemotherapy. Vestibular function can be affected in the elderly, as the bony labyrinth undergoes degenerative changes. The semi-circular canals lose about 40% of their hair cells causing reduced function (Jian et al. 2019). Older adults with degenerating auditory systems are likely to have degenerating vestibular systems – and are likely to have

reduced saccular function. Due to these findings, the older adult patient should be assessed for balance testing including cervical vestibular evoked myogenic potential evaluation to determine saccular involvement, prior to vestibulotoxic therapy (Jian et al. 2019).

CONCLUSION

Platinum based chemotherapy drugs are known to affect the vestibular system. We suggest the assessment of the vestibular system with tools such as the v-HIT prior, during and after treatment with platinum-based chemotherapy drugs in order to better manage deteriorating vestibular function due to the treatment provided. The elderly in particular, often have reduced vestibular function due degenerative changes. Hopefully with planned assessments of the vestibular system, any deterioration in function may be addressed better and in a timely manner.

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