ONCOLOGY

Paraclinical evaluation of side-effects of Taxanes on auditory system

Valutazione degli effetti collaterali dei Taxani sull'apparato uditivo

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SUMMARY

Ototoxicity is one of the major causes of hearing loss and balance system disorders. Taxanes are a new group of anti-neoplastic agents used for chemotherapy; examples include Paclitaxel and Docetaxel. In this study, ototoxicity of these drugs has been evaluated in order to provide a means of adjusting the doses to avoid these complications. A prospective analytical study was carried out on103 known cases of breast and ovarian cancer, during 2004 to 2006 (20 months), in the Otolaryngology, Head and Neck Surgery Department of Ahwaz University of Medical Sciences of Tehran. All patients (mean age 45 ± 2.3 years) were treated with Taxanes. The first evaluation of hearing (using pure tone audiometery) was performed before starting treatment, the second in the middle of the treatment period and the last at the end of treatment. Results showed that nausea and vomiting were the most common side-effects of the drugs used. No significant side-effects of Taxanes, on the audiovestibular system, were observed. In conclusion, little information concerning the ototoxic effect of Taxanes has been reported in other studies, and, in the present investigation, no significant effect on the auditory system was found.

KEY WORDS: Taxanes • Side-effects • Hearing loss • Ototoxicity • Pure tone audiometery

RIASSUNTO

L'ototossicità è una delle cause più comuni di ipoacusia e di alterazioni dell'equilibrio. I Taxani sono un nuovo gruppo di farmaci antineoplastici utilizzati per la chemioterapia; esempi di questi farmaci sono rappresentati dal Paclitaxel e dal Docetaxel. In questo studio è stata valutata l'ototossicità di questi farmaci, al fine di fornire un mezzo di aggiustamento delle dosi finalizzato alla prevenzione di questo effetto collaterale. A questo scopo è stato realizzato, presso l'Otolaryngology, Head and Neck Surgery Department della Ahwaz University of Medical Sciences di Tehran, uno studio prospettico su 103 pazienti affetti da carcinoma della mammella o dell'ovaio, nel periodo compreso tra il 2004 e il 2006 (20 mesi). Tutti i pazienti (età media: 45 ± 2,3 anni) sono stati trattati con Taxani. La prima valutazione dell'udito, mediante esecuzione di audiometria tonale, è stata eseguita prima dell'inizio del trattamento, la seconda a metà di esso, e la terza alla fine del trattamento. I risultati hanno evidenziato che la nausea e il vomito rappresentano gli effetti collaterali più frequenti di questi farmaci. Non sono invece stati riscontrati effetti collaterali dei Taxani sull'apparato uditivo. In conclusione poche informazioni sono disponibili in letteratura sugli effetti ototossici dei Taxani, ed in questo studio non è stato evidenziato nessun effetto significativo di essi sull'apparato uditivo.

PAROLE CHIAVE: *Taxani • Effetti collaterali • Ipoacusia • Ototossicità • Audiometria tonale*

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Introduction

Ototoxicity is one of the major causes of hearing loss and balance disturbance [1]. This complication often occurs during the treatment of severe systemic disorders such as breast and ovarian cancers [2]. Ototoxic drugs include antibiotics, diuretics, anti-neoplastic agents, chelators, anti-inflammatory agents and anti-malaria drugs; some new drugs have recently been introduced which have no immediate ototoxicity effect and their ototoxic side-effects will appear only during long-term adminstration,. When it is mandatory to use an ototoxic drug, screening audiologic testing, at brief intervals, can detect ototoxic side-effects and the drug should be discontinued [2 3]. The most common signs and symptoms of ototoxicity are hearing loss, tinnitus, balance disturbance and vertigo [3]. Tinnitus is usually the most common symptom that may occur in the early stages and should be considered as a warning sign of other serious complications [4]. Hearing loss and tinnitus are often bilateral and symmetric but also unilateral symptoms are not uncommon [2]. Mild or severe imbalance is a sign of vestibular system damage and may present with nausea, vertigo and, in severe cases, even with osilopsia [4]. Hepatic or renal failure, immune deficiency, old age, history of previous hearing loss and collagen vascular disease are the major risk factors for ototoxicity [2].

Taxanes (Paclitaxel and Docetaxel) are the new generation of anti-neoplastic agents. These drugs affect intra-cellular

microtubules and inhibit depolarization of microtubules by binding with the B portion which leads to stopping of the cell cycle in the G2 phase [5-8]. The side-effects of Taxanes include nausea, vomiting, diarrhoea, bone marrow suppression, bradycardia and hypotension. Underlying disorders, such as renal or hepatic failure, may increase their toxicity by increasing serum drug levels. Simultanous use of Taxanes, with other drugs, may also increase their side-effects [9 10].

Few studies concerning the ototoxic effects of Taxanes have appeared in the literature and textbook referrences [6 7 11 12]. Furthermore, nothing is mentioned about their ototoxic effects in the information and usage guide provided in drug package. Although ototoxic effects of Cisplatin and Vinblastin are well documented, the ototoxicity dose not appear to be a problem with Paclitaxel [3 6 10].

Nevertheless, given the frequent use of Taxanes in patients with various types of malignancies, especially in patients with conditions making them more susceptible to ototoxicity, and due to the irreversible nature of these toxic effects on hearing, we decided to evalutate the side-effects of Taxanes on the audiovestibular system using a low cost and easy paraclinical screening in pure tone audiometery (PTA), in order to produce guidelines for dose adjustment in the attempt to avoid audiovestibular toxicity.

Methods

Included in the investigation were 138 known cases of breast or ovarian cancer from the Gynaecology ward of Imam Khomeini Hospital and the Haematology ward of Shafa Hospital (Adults) and Oncology Clinic of Shafa Hospital in Ahwaz, from 2004 to 2006 (20 months). All patients (101 female and 2 male) were treated with Taxanes. A questionnaire was completed for each patient throughout the entire treatment period. Patients with anaemia (Hb < 10 in females, Hb < 12 in males), chronic otitis media (COM) or previous vestibular were excluded.

Each patient was examined and all medical history and physical examination findings were recorded. Thereafter, each patient underwent complete audiologic evaluation consisting of pure tone audiometry (PTA), speech discrimination score (SDS), speech recognition test (SRT), and tympanogram. The first evaluation was performed at the beginning of treatment, the second, in the middle of the treatment period and the last one 4 months after the end of the treatment period. Treatment consisted of 6 single doses of a Taxane every 3 weeks, for 18 weeks (4.5 months). Drug dosage was approximately 100-140 mg/m^2 for Docetaxel and 180 mg/m^2 for Paclitaxel.

During the course of treatment, ototoxicity signs and symptoms, such as tinnitus, hearing loss, balance system disturbance and vertigo, were checked in all cases. Bilateral hearing loss of about 10-20 dB, in any pattern or frequency, in the audiometeric tests, we considered as the indicators of ototoxicity. Other data such as the presence of pulmonary or hepatic metastasis were also recorded.

Results

Of these 138 patients, 35 were treated with Cisplatin and carboplatin simultaneously by Taxanes, and were excluded due to the ototoxicity of these durgs. Of the remaining 103 patients, 101 (98.05%) were female and 2 (1.94%) were male. Ages of these patients ranged between 41 and 62 years (mean ± SD: 45 ± 4.3), and 96 cases (93.2%) were in the 40-55 years age group. The 101 female patients (98.05%) presented breast or ovarian cancer. Overall, 66 patients (64.7%) were treated with Docetaxel and 37 cases (35.92%) by Paclitaxel. One patient (1%) had chronic renal failure; 2 cases had urogenital cancer; 2 cases (1.94%) had hepatic disorders with impaired liver function tests. They were suspected to present liver metastasis.

As far as concerns the otological examinations, 9 cases (8.4%) had tympanic membrane perforation (chronic otitis media), one of which had vertigo. The tympanic membrane was intact in the remainder of the patients (Table I). One patient had acute otitis media which was treated before commencing Taxanes therapy. Hearing loss, tinnitus, true vertigo, dizziness, nausea and vomiting were assessed at the onset of treatment. Eleven patients (10.48%) had tinnitus before treatment, 4 of whom (3.9%) had chronic otitis media and 7 (6.5%) had hearing loss at the frequency of 4-8 KHz. A total of 16 patients (15.5%) had hearing loss, while 3 patients (2.7%) complained of slight dizziness.

After the treatment period, 4 new cases (3.9%) of tinnitus were reported. This increase in the number of patients with tinnitus was not statistically significant ($p = 0.125$). Of these 4 cases, 3 were treated by Docetaxel and 2 of them presented hearing loss in the 4-8 KHz range. Interestingly, nei-

Table I. Incidence rate (% of total) of signs and symptoms in patients under treament with Paclitaxel and Docetaxel.

Sign or symptom	Paclitaxel	Docetaxel
Hearing loss	–	–
Hearing loss in audiogram (10 dB)	–	2 (1.94%)
Tinnitus	1 (0.97%)	3 (2.91%)
Dizziness	15 (14.56%)	22 (21.35%)
Nausea and vomiting	28 (27.18%)	18 (17.47%)
Vertigo	–	–
Total	37 (35.9%)	66 (64.1%)

Table II. Incidence rate (%) of signs and symptoms in all patients under treatment with Taxanes.

Sign or symptom	Before treatment	After treatment
Hearing loss	16 (15.5%)	2 (1.94%)
Tinnitus	11 (10.2%)	4 (3.9%)
Dizziness	3 (2.91%)	37 (35.91%)
Nausea and vomiting	–	42 (40.8%)
Vertigo	1 (1%)	–

ther of these two cases complained of hearing loss despite a demonstrated hearing loss in the primary audiogram. Both cases used Docetaxel or Paclitaxel (Table II). With regard to the 3 cases of renal or hepatic failure, none complained of tinnitus and, in these cases, no hearing loss was observed in audiometeric studies.

Overall, 37 new cases (36%) presented dizziness by the end of the study; 22 of whom were in the Docetaxel group and none had true vertigo. Nausea and vomiting were observed in 46 cases (44.6%) during the first days of treatment, most of these cases being in the Paclitaxel group.

Fatigue is another common side-effect of Taxanes which can present as dizziness. This complaint occurred in 36% of our patients, but all patiants had normal vestibular tests. Four patients (3.9%) had tinnitus. All of them had been treated with Docetaxel (findings were not statistically significant). Only two of our patients (1.9%) had sensory-neural hearing loss.

Discussion

Nausea and vomiting are reported to be two common side-effects of Taxanes, especially in patients which are treated with Paclitaxel, which may occur just after the first dose of drug usage [5]. In our study, nausea and vomiting were the most common side-effects of Taxanes and they were more common with Pacetaxel ($p = 0.001$).

Although tinnitus is a common side-effect of ototoxic drugs which can occur immediately after the first dose of drug [2 3], in our study, only four patients (3.9%) had tinnitus. Only two of our patients had sensory-neural hearing loss. Interestingly any of patients with history of previous sensory-neural hearing loss or previous hepatic or renal disease had new onset sensorineural hearing loss in standard PTA. In a review of the literature, we did not find any evidence of side-effects for Taxanes like vertigo, tinnitus and hearing loss [10-14]. There is no warning about these side-effects in drug information sheets provided by drug companies. There are some reports of ototoxic effects of Taxanes when used with other anti-neoplastic drugs such as Cisplatin. All these side-effects were attributed to drugs other than Taxanes [15 16].

The audiovestibular effects of Taxenes remain questionable. Evaluation of ototoxicity with otoacoustic emissions (OAE) or high frequency PTA is superior to standard PTA but it is more expensive and less prevalent in Iran. Anyway, we can say that Taxanes have no obvious effects on hearing in speech frequencies, i.e., 0.5-8 KHz.

All in all, our study shows that auditory side-effects of Taxanes should be considered, regardless of their low incidence. Standard PTA is the minimum diagnostic test to help with the diagnosis, accompanied with OAE when available.

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