PARA-CLINICAL EVALUATION OF TAXANE SIDE EFFECTS ON AUDITORY SYSTEM (PTA -TRESHOLD)

MOZAFFAR S. AFRAZ*
KHASHAYAR AHMADI*

SUMMARY: Ototoxicity is one of the major causes of hearing loss and balance system disorders.Taxans are new of anti-neoplastic agents chemotherapy with these agents include Paclitaxel and Docetaxel. In this study we have been evaluated ototoxicity of these drugs to adjust dose if necessary to avoide their complications. This is a study of 103 known cases of breast and ovarian cancer with mean age 45 ± 2.3 years during may 2004 to jun 2006 (20 months) in Ahwaz That were treated with Taxans (in a 20 months period).The first evaluation of hear ing (with PTA) was performed before initiation of treatment and the second was performed at the middle of treatment period and the last one at the end of treatment. Nausea and vomiting was the most common side effect of these drugs in this study. We did not any significant side effects of taxanes on audiovestibular system. There is few information about ototoxicity effect of Taxanes in the other studies, and we did not find any significant effect on Auditory system in the PTA standard (0/5 - 8 KHZ).

Key words: Ototoxicity, Anti-neoplastic agents, Pure tone audiometery, Taxenes, Hearing loss.

INTRODUCTION

Ototoxicity is one of the major causes of hearing loss and balance disturbance (1). This complications often occur during the treatment of severe systemic disorders like breast and ovarian cancers. Ototoxic drugs, including Antibiotics, Diuretics, Anti-neoplastic agents, Chelators and Anti-inflammatory agents and antimalaria drugs and some new drugs are introduced recently which have no immediate ototoxicity effect and only in long term adminstration, their ototoxic side effects will apear therefore screening audiologic testing in short intervals can detect ototoxic side effects and drug would be discontinued. The most common signs and symptoms of ototoxicity are hearing loss, tinnitus, balance disturbance and vertigo. Tinnitus is almost the most common symptom that may occur in early stages and warn us about happening other serious complications (4). Hearing loss and tinnitus are often bilateral and symetric but unilateral symptoms also is not uncommon. Mild or severe imbalance is a sign of vestibular system damage and may presented with nausea, vertigo and in severe cases even osilopsia (4). Hepatic or renal failure, immune deficiency, old age, history of previous hearing loss and colagen vascular disease are risk factors for ototoxicity. Taxanes (Paclitaxel and Doceytaxel) are new generation of Anti-neoplastic agents. These drugs affect intra-cellular microtubules and inhibit depolarization of microtubules by binding with B portion which leads to stoping the cell cycle in G2 phase (5, 7, 8). Underlying disorders such as

* From Department of Otorhinolaryngology, Ahwaz Jondi-Shapour of Medical Science, Imam Hospital, Ahwaz, Iran.

renal or hepatic failure may agraviate their toxicity by increasing drug serum level. Simultaneity use with other drugs may increase their side effects too (9,10).

There is few studies about ototoxic effects of taxanes in the literature and textbook referrences (6, 7, 11, 12). Also nothing is mentioned in the information and usage guide provided in drug package aboout their ototoxic effects. According to their frequent usage in patients with different type of malignancies specially in patients with conditions susceptible to ototoxicity and because of irreversible nature of toxic effect on hearing, we decided to evalutate side effects of taxenes on audiovestibular system specially by using a low cost and easy Para-clinical screening in Pure Tone Audiometery (PTA) and we will produced a guideline for dose adjustment to avoid audiovestibular toxicity. Althogh ototoxic effects of Cisplatin and Vinblastin is well documented, ototoxicity dose not appear to be a problem with Paclitaxel (3, 6,10). In this study we have been evaluated ototoxicity of these drugs and have been try to creat a guidline for dose adjustment to avoid audiovestibular ototoxicity.

MATERIALS AND METHODS

Patients and Methods

This study contains 138 known cases of breast and ovarian cancer in gynecology ward of Imam Hospital and Hematology Ward of Shafa Hospital (adults) and patients of oncologic clinic of Shafa Hospital from May 2004 to Jan 2006 (20 months) in Ahwaz, all treated with Taxanes. A questionare was filled out for every patient from begining to the end of treatment. Those who were treating by Cisplatin or Carboplatin as an adjuvant were excluded. Patients with Anemia (Hb < 10 in females; Hb < 12 in males), Chronic Otitis Media (COM) and patients with previous vestibular were excluded. Each patient was examined and all medical history and physical examination findings were recorded, then each patient underwent complete audiologic evaluation consist of verbal tests (PTA, SDS, SRT, and tympanogram). The first evaluation was performed at initiation of treatment and the second one was performed in the middle of treatment period and the last one was performed after four months at the end of treatment period. They were treated by six single doses of drug every three weeks during eighteen weeks (4.5 months). Drug dosage was approximately 100-140 mg/m^2 Docetaxel,180 mg/m^2 Paclitaxel. During this time, ototoxicity signs and symptoms were detected in these cases such as tinitus, hearing loss, balance system disturbance and vertigo, all these were recorded. Bilateral hearing loss about 10-20 db in any pattern or frequency in audiometeric tests are considered for ototoxicity. Other datum like presence of pulmonary or hepatic metastasis were also recorded.

RESULTS

Among our 138 patients, 35 cases were treated by cisplatin and carboplatin simultaneity by taxanes and because of ototoxicity of these durgs, the cases were excluded. 101 cases (98.05%) were female and 2 cases (1.94%) were male 2 cases. Two cases had urogenital cancer. The patients ages are between 41 and 62 (mean SD=45 $\pm$ 2.3). 96 cases (93.2%) were in 40-55 years old group.101 cases (98.05%) were women with breast and ovarian cansers. 66 patients (64.7%) were treating by Docetaxel and 37 cases (35.92%) were treating by paclitaxel.one patient (1%) had chronic renal failure. Two cases (1.94%) had hepatic disorders with

Table 1: Incidence rate of symptome and sign In total patients under treatment with Taxanes.

Symptome and sign	Before treatment		After treatment	
	Incident	Percent (%)	Incident	Percent (%)
Hearing loss	16	15/5	2	1/94
Tinnitus	11	10/2	4	3/9
Dizziness	3	2/91	37	35/91
Vomiting and Nausea	-	-	42	40/8
Vertigo	1	1	-	-

impaired liver function tests. They were suspected to liver metastasis. In otological exams, 9 cases (8.4%) had tympanic membrane perforation (chronic otitis media). Tympanic membrane was intact in other patients (Table 1). One patient had acute otitis media who was treated before initiation thrapy of Taxanes. Hearing loss, tinnitus, true vertigo, dizziness and nausea and vomiting were assessed at the onset of treatment. only in one case of nine patient with chronic otitis media had vertigo.eleven patients (10.48%) had tinnitus before treatment which four of them (3.9%) had chronic otitise media.seven cases (6.5%) had hearing loss in the frequency of 4-8 KHz. In all otological tests, 16 patients (15.5%) had hearing loss which nine (8.4%) of them had chronic otitis media with conductive hearing loss and seven patints (6.8%) had sensory-neural hearing loss in 4-8 KHz. Three patients (2.7%) were complained by slight dizziness. After treatment period, 4 new cases (3.9%) of tinnitus were reported which wasn't significant statistically (P=0.125) three of these four cases were treated by Docetaxel and two of them (1.94%) had hearing loss in 4 -8 KHz. We notify that these two cases have been not complained by hearing loss despite demonstrated hearing loss in the primary audiogram. Both of these cases used Dacetaxol or taxotere (Table 2). Among three cases of renal or hepatic failure, no one complained by tinnitus and there was no hearing loss in audiometeric studies of these cases. Thirty seven new cases (36%) presentation of dizziness were reported which twenty two of them were in Doctaxel group. No one had true vertigo. Nausea and vomiting were seen in fourty six cases (44.6%) in the first days of treatment and most of these cases were in Paclitaxol group.

DISCUSSION

Nausea and vomiting are common side effects of Taxanes, especially in patients which were treated with Paclitaxel and this may occur just after first dose of drug usage (5). In our study nausea and vomiting was the most common side effect of taxanes and they were more common with Pacetaxel (p=0.001). Fatigue is another common side effects of Taxanes which can be presented as dizziness. 36% of patients had this complaint but all patiants had normal vestibular tests. Although tinnitus is a common side effects of ototoxic drugs which can occur immediately affer first dose of drug in our study only four patients (3.9%) had tinnitus (2, 3). All of them had been treated with Docetaxel (findings were not significant statistically). In our study only two patients (1.9%) 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 sensory-neural hearig loss in standard PTA. In review of literatures we did not find any evidence for side effects for Taxans like vertigo, tinnitus and hearing loss (10, 11, 12, 13, 14). There is no warning about these side effects in drug information sheet provided by drug companies. There are some reports of ototoxic effects of Taxans

Table 2 : Incidence rate of symptome and sign In patients under treament with Paclitaxel and Docitaxel.

Symptome and sign	Paclitaxel		Docetaxel	
	Incident	Percent (%)	Incident	Percent (%)
Hearing loss	-	-	-	-
Tinnitus	1	0/97	3	2/91
Dizziness	15	14/56	22	21/35
Vomiting and Nausea	28	27/18	18	17/47
Vertigo	-	-	-	-
Hearing loss in Audiogram (10dB)	-	-	2	1/94
Total	37	35/9	66	64/06

when used with other anti-neoplastic drung like Cisplatin. All these side effects attributed to drugs other than Taxanes (16,18).

There are few issues about audiovestibular effects of Taxenes. Evalution of ototoxicity with OAE or high frequency PTA is superior to standard PTA but they are more expensive and less prevalent in IRAN we know that it is not possible for fully evaluation the effect of Taxanes on audiovestibolar system just by using standard PTA but it is possible to say that Taxanes have no obvious effects on hearing in speech frequencies "0.5-8 KHZ" .

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Correspondence:
Khashayar Ahmadi
Department of Otorhinolaryngology,
Ahwaz Jondi-Shapour of Medical Science,
Imam Hospital, Ahwaz, IRAN.
e-mail: dr.khashayar.ahmadi@gmail.com