Bahrain Medical Bulletin, Volume 18, No.3, September 1996

TOXIC ENCEPHALOPATHY AS AN ADVERSE EFFECT TO PACLITAXEL IN THE TREATMENT OF HEPATOCELLULAR CARCINOMA: A CASE REPORT

Jalal H Al-Maskati, CABM*
Farid F Khalifa, MD**

We report a 31 year old patient who developed central neurotoxicity manifested as transient loss of consciousness when treated for an advanced hepatocellular carcinoma by the new drug Taxol (Paclitaxel). This side effect is the least reported and documented toxicity of this agent.
Bahrain Med Bull 1996;18(3):

The Taxanes are a new class of anticancer drugs. Taxol was the first drug in this class to enter clinical practice, and initial reports that suggest high activity in refractory solid tumours, in particular ovarian, breast and lung cancers have generated high expectations among clinicians and also in the media[1]. Taxol toxicity has been well described and various methods have been developed to reduce some of the side effects.

The least recognized of taxol adverse effect is the central neurotoxicity. The aim of this report is to draw the attention to this adverse effect of in a patient treated by Taxol presenting with altered sensation due to an unexplainable cause.

THE CASE

A 31 year old Bahraini male presented in October 1995 with a 3 months history of upper abdominal pain, anorexia and weight loss of 6 kg. He had a left varicocoelectomy in 1989. On presentation he had a huge hard liver but no ascites and the testes were normal. A CT scan of the abdomen showed a hepatomegaly with large hypodense lesion occupying almost the whole of the right lobe measuring 17 x 15 cm with satellite hypodense foci around. A CT scan of the chest showed multiple rounded shadows throughout both lung fields. Testicular ultrasound was normal. Liver biopsy confirmed a hepatocellular carcinoma with extensive areas of necrosis.

---

* Chief Resident in Medical Oncology
** Consultant Oncologist
Department of Medicine
Section of haematology/Medical Oncology
Salmaniya medical Centre
State of Bahrain

Investigations showed impaired liver function with a total protein of 6.2 gm/dl, albumin 1.9 and Globulin 4.3 gm/dl. Alkaline phosphatase 271 U/L (N 50-135 U/L), Alanine Amino transferase (SGPT) 147 U/L (N 30-65 U/L) and G-Glutamyltransferase (GGT) 185 U/L (N 15-85 U/L). Serum electrolytes, renal function tests and adjusted serum calcium was all normal. Carcinoembryonic antigens (CEA), Beta human chorionic gonadotrophin (BHCG) were normal but Alpha-foetoprotein (AFP) was raised to 23 IU/ml (N 1-8 IU/ml). Hepatitis and anti HIV serology was negative.

He was given Taxol (Paclitaxel) as part of a pilot study using this drug to treat advanced and metastatic gastrointestinal tumours including hepatic tumours. Taxol was given in a dose of 200 mg/m2 as a three hour infusion with

the standard precautions and premedications including the use of Dexamethasone 8 mg intravenously 6 and 12 hours before Taxol and premedicated with diphenhydramine 50 mg iv and Cimetidine 200 mg iv, 30 minutes before the infusion. He received a total dose of 340 mg of Taxol with no hypersensitivity reaction.

Sixteen hours following the infusion, he was found to be very restless, partly unresponsive and profusely diaphoretic. Clinically he was semiconscious with a raised blood pressure (160/110 mm Hg), and sinus tachycardia of 120/minutes. There was no neck rigidity and the pupils were widely dilated but equal and reactive. There was no definite limb weakness and the plantares were flexor. An urgent CT scan of the head showed no focal brain lesion or haemorrhage and CSF examination showed only a raised protein of 85 mg/dl (N 20-40 mg/dl). Other tests including CSF glucose, chloride, lactic acid and CSF cytology were all normal. Repeated serum electrolytes, serum creatinine and blood sugar were normal and there was no further deterioration of liver function.

He remained in a critical condition with further deterioration of his level of consciousness as he became unresponsive, for about a week, during which he was fully supported. After one week, he started to improve gradually but his level of consciousness continued to fluctuate before stabilizing 2 weeks after the initial episode. Since then he continued to improve with the help of an intensive course of physiotherapy.

One month after receiving the dose of Taxol; he was discharged home fully conscious and able to walk unaided with no significant residual damage. His disease status was reassessed again by a repeated CT scan of the abdomen that has demonstrated a stable disease state.

DISCUSSION

Paclitaxel (Taxol; Bristol-Myers Squibb Company, Princeton, NJ), the first of the Taxane antimicrotubule agents, is an important new anticancer agent that has demonstrated efficacy in the treatment of ovarian, breast and lung cancers[1]. It is derived from the bark of the pacific Yew tree Taxus brevifolia and acts by promoting microtubular assembly and stabilizing the microtubules against depolymerisation leading to arrest of the cells in the G_2 and M phase of the cell cycle[4].

Taxol has been used in patients with advanced gastrointestinal malignancies including stomach, oesophagus or pancreatic carcinoma. The result has shown an overall response rate of 31 % in one report, but in another report using the same drug in the treatment of adenocarcinoma of the pancreas, the response rate was less than 10 %2.

The primary dose limiting toxicity of Taxol is myelosuppression, mainly neutropenia, with thrombocytopenia occurring less frequently. An additional cumulative toxicity is a predominantly sensory peripheral neuropathy which may be seen after multiple courses of Taxol at conventional doses[4]. In the initial phase I studies, hypersensitivity reactions to Paclitaxel were seen as a dose limiting toxicity of the drug (41 %) -- such reactions have been reduced by prolongation of the infusion time and premedication with steroids and antihistamines[4]. Other frequent adverse effects include transient myalgia/ arthralgia in about 56 % of patients. The frequency and severity of neurologic manifestations were dose-dependent, but were not influenced by infusion duration mostly manifested as peripheral neuropathy. Other than peripheral neuropathy, serious neurologic events following Taxol administration have been rare (Less than 1 %), and have included grand mal seizures, syncope, ataxia and neuroencephalopathy[4]. Rare reports of autonomic neuropathy resulting in paralytic ileus have been received as part of the continuing surveillance of

Taxol safety. In various reports; there was no consistent evidence of neurotoxicity. The central nervous system depression reported in dogs was attributed to the Cremophor/ethanol vehicle, which is used because of aqueous insolubility of taxol.

There is no available information as regards the clinical picture of this rarely reported neuro-encephalopathy especially as regard the reversibility and sequelae of this toxicity. Our patient has mild impairment of his liver function tests; whether this is related with regard to the metabolism of Taxol, is unclear but unlikely since his liver function has shown no change after the treatment with the drug. It would be of interest to learn about others' experience regarding the neurotoxicity.

So far we cannot trace any report that is published in this regard, particularly in view of the serious nature of our case.

CONCLUSION

Neuro-encephalopathy is the least recognized adverse effect of Taxol and the exact nature of this complication is not well documented. The condition is reversible if patients developing this condition are recognized early. .

REFERENCES

1. Kearns CM, Gianni L, Egorin MJ. Paclitaxel pharmacokinetics and pharmacodynamics. Sem Oncol 1995;22[Suppl 6]:16-23.

2. Ajani JA, Ilson DH, Kelsen DP. The activity of Paclitaxel in gastrointestinal tumours. Sem Oncol 1995;22[Suppl 12]:46-50.

3. Ozols RF. Current status of chemotherapy for ovarian cancers. Sem Oncol 1995;22[Suppl 12]:61-6.

4. Document of Bristol-Myers Squibb Company. Therapy of recurrent metastatic breast cancer. Taxol - Clinical Studies. Proceedings of a panel discussion, October 1995.

5. Rowinsky EK, Donehower RC. Paclitaxel (Taxol). N Engl J Med 1995;322:1004-14.OFR mediated mechanisms13.