Axonal neuropathy caused by epothilone B

Sir,

Epothilones are non-taxane, tubulin polymerizing agents that have pre-clinical activity in taxane resistant cell lines.\(^1\) Several phases 1 and 2 trials have been conducted with Epothilone B for therapy of colorectal, prostate and other solid tumors.\(^2-3\) Neuropathy is one of the toxicities encountered in these trials and may be significant enough to limit further treatment.

A 31-year-old woman was diagnosed with a carcinoid tumor 5 years prior to evaluation, which was initially treated surgically. Eight months earlier, the tumor had recurred several times and she was enrolled in a dose escalation trial with epothilone B in which it was initiated at 20 mg/m\(^2\) with monthly increments achieving a final
dose of 50 mg/m². Three months after the last treatment, she presented with numbness and tingling in her feet.

Physical examination revealed a thin woman with decreased pin prick sensibility, light touch, proprioception in a stocking distribution worse distally in the legs. The ankle jerks were not elicited. There was mild distal atrophy and weakness (Grade 5-5 MRC grade) of the intrinsic muscles of her feet. She had gait imbalance and could not tandem walk.

Electrophysiological examination showed normal motor and sensory nerve parameters in the right ulnar and median nerves. In the right peroneal and tibial nerves, the motor distal latencies were both normal. Recording the extensor digitorum brevis muscle, the evoked potential in the peroneal showed both a mildly reduced amplitude response (1.2 mV; nl > 2 mV) and conduction velocity (37 m/s; nl > 40 m/s). In the tibial nerve, recording the adductor hallucis muscle, the evoked response amplitude and conduction velocity were also mildly reduced (4.5 mV; nl > 5 mV), (33 m/s; nl > 40 m/s). The F-wave latencies were mildly prolonged in both tibial and peroneal nerves. Needle electromyogram was normal in the tibialis anterior and medial gastrocnemius muscles, however the extensor digitorum brevis muscle showed the presence of scattered high amplitude polyphasic units and a decreased interference pattern with maximal effort. Overall, the study was consistent with a length dependent axonal neuropathy affecting both motor and sensory fibers.

Routine laboratory investigations were either negative or normal including the following: cell count and differential, serum vitamin B₁₂, folate, serum protein electrophoresis and immunofixation, thyroid function studies, routine liver and kidney tests, vitamin E level, anti-Hu antibody.

This patient developed the clinical and electrophysiological features of an axonal length dependent polyneuropathy affecting both motor and sensory fibers. Given the history and time course, it is likely that the etiology of this neuropathy is epothilone B exposure rather than another cause. Applying Naranjo’s algorithm in this case reveals a probability score of 8 indicating a ‘probable’ adverse drug reaction.[4] The exact mechanism of epothilone neurotoxicity is unknown, however, it is probably similar to that of taxane associated neuropathy and involves an interaction with microtubules.[5] Increased awareness of this neuropathy is important as it may limit the medication that a patient can tolerate. Furthermore, research into the mechanism of the neuropathy could facilitate measures that could prevent, attenuate or prevent the neurotoxicity of this drug.

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References