Novel neurosensory testing in cancer patients treated with the epothilone B analog, ixabepilone

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Background: We have previously established the recommended phase II dose (RPTD) of ixabepilone as 40 mg/m² administered over 1 h repeated every 3 weeks with neuropathy as a cumulative dose-limiting toxicity. We expanded the cohort at the RPTD to include detailed assessment of nerve damage in these patients. We report our findings on vibration perception threshold (VPT) and neuropathy.

Patients and methods: Forty-four patients were treated with a median (range) of three (1–14) cycles of ixabepilone. The VPT (5-min duration) and nerve conduction test (NCT, 10-min duration) were carried out in the office, before ixabepilone dosing, and every two cycles thereafter.

Results: Neuropathy (grade 1 and grades 2–3) was observed in 17 (38.6%) and 11 (25%) patients, respectively. The mean increase in VPT as a function of grade 0–1 versus grades 2–3 neuropathy was 0.235 ± 0.09 (P = 0.049) vibration units. The F-wave frequency and distal motor latency, as assessed using the NCT, did not correlate with clinical neurotoxicity.

Conclusion: The change in VPT is observed early and likely reflects early vibration perception change. Mean change in VPT correlates with the severity of clinical neuropathy. Whether VPT change predicts onset of severe neuropathy warrants prospective testing and validation.

Key words: ixabepilone, nerve conduction test (NCT), phase I, solid tumors, vibration perception threshold (VPT)

introduction

Ixabepilone (Ixempra®, Bristol Myers Squibb, Princeton, NJ) is an esterase-resistant semisynthetic analog of epothilone B that is US Food and Drug Administration (USFDA) approved for the treatment of taxane and anthracycline refractory metastatic breast cancer [1]. Drug dosing is limited by toxic effects of neutropenia and neuropathy. The rate of grade 3 peripheral neuropathy approaches 20% in patients who have been exposed to prior neurotoxic agents [1, 2]. Early data suggested that the incidence of neuropathy was lower in patients receiving 6 mg/m²/day for 5 days every 3 weeks [3]. More recent studies comparing a 5-day versus a single dose every 3 weeks in the same patient population, however, suggest that the neuropathy rates may be similar [4], with neuropathy being related to cumulative ixabepilone dose, baseline neuropathy, as well as previous treatment with neurotoxic agents [5–7]. Dose duration has been increased from 1 h to 3 h on an every 3-week schedule in an attempt to decrease the incidence and severity of neuropathy and is the recommended method of drug administration in the package insert.

Standardized criteria for evaluating the degree of peripheral neuropathy have been developed for patients receiving chemotherapy; however, these are highly subjective and rely on patient self-reporting [8]. More recently, however, specific instruments have been evaluated to assess peripheral neuropathy in these patients. In patients treated with ixabepilone, the Jepsen Test of Hand Function and the Grooved Pegboard Test were found to predict for severe neuropathy; however, the results were not conclusive and required specialized tests that are not readily available [6]. Therefore, facile predictive tests of function-limiting neuropathy are desirable particularly since the drug may become widely used including the adjuvant setting.

As part of a National Cancer Institute (NCI) Cancer Therapy Evaluation Program-sponsored phase I clinical study of ixabepilone, we evaluated the utility of the vibration perception threshold (VPT) and nerve conduction tests (NCTs) as measures of nerve damage following drug therapy. The VPT is a simple office-based semi-objective evaluation of distal sensory threshold that can be administered by a physician extender such as a physician assistant or a nurse practitioner (NP). The assessment is rapid (~5 min), the obtained values are parametric, and the degree of deficit can be determined against an age-matched normal population [9]. NCT is an...
index of the integrity of peripheral axons and can now be rapidly obtained (~10 min) at the bedside using newly developed methodology (i.e. NeuroMetrix, Waltham, MA) [10].

**patients and methods**

**patient selection study design and treatment plan**

The dose escalation component (25 patients) of the trial has been previously reported [11]. At the recommended phase II dose (40 mg/m²), additional patients were enrolled. This paper focuses on previously unreported findings in all patients treated at the dose of 40 mg/m² (including 12 patients from the prior report). Patients were entered onto this prospective trial between March 2000 and May 2003, and all patients gave informed consent as approved by the Institutional Review Board at Montefiore Medical Center.

**neurological assessments**

Neurological assessments included a detailed neurological history and toxic effects graded as per the NCI common toxicity criteria (CTC) version 2.0 [8]. All patients also underwent a comprehensive neurological exam that included cognitive function (mental status examination), cranial nerves, and the peripheral and autonomic nervous system. In addition, VPT and NCT were carried out in all patients. VPT was determined using a Vibratron II device (Physitemps Instruments Inc., Clifton, NJ) combined with a two alternative forced choice test algorithm [9]. This device has been used in oncology, including therapeutic clinical trials evaluating paclitaxel and docetaxel [12–16]. It consists of two units, each with a rod set to vibrate at 128 Hz. At any time only one rod is vibrating. The intensity of vibration is set in a range from 0.1 to 20 vibration units (VU, 0.05–200 μM) and is continuously displayed on a digital readout. During the evaluation, the subject contacts the two rods in sequence and must determine which rod is actually vibrating. For the initial trials, the vibration intensity is set at a level easily detected by the subject; the intensity is systematically lowered in subsequent trials until the subject fails to correctly identify the vibrating rod. The VPT is defined as the lowest value correctly identified.

NCT of the median nerve was accomplished using the NC-Stat device (NeuroMetrix Instruments, Waltham, MA) [10]. A compound electrode is positioned with respect to bony landmarks overlying the distal segment of the median nerve at the wrist and a simple button is pressed. The device delivers a series of electrical pulses of appropriate duration and intensity to stimulate the nerve at supramaximal levels. The compound motor response is then recorded and automatically scored at the onset and peak of the depolarization. Recording and stimulation parameters are displayed in real time on a liquid crystal display screen and the waveforms are checked for signal-to-noise ratio, artifacts, and appropriate NC-Stat biosensor contact. The final report includes a median distal motor latency (DMML), which represents conduction in the distal segment of the motor nerve and median F-wave latency, which reflects conduction in the long-loop motor pathway including proximal segments of the nerve and spinal roots. At the conclusion of the study, the instrument is placed on a docking station, wherein all gathered data are transmitted to the on-call information system and a report is generated summarizing the results of the test.

Patients were tested at multiple time points that included a baseline test on the first day or within 2 weeks of the first dose of ixabepilone. Subsequently, tests were carried out before the next ixabepilone dosing and at the time when patients came off study. The tests were administered by a physician or other personnel trained to administer and monitor the tests.

**statistical analysis**

Descriptive statistics were used to describe patient characteristics on study. Toxicity relationships (e.g. VPT and neurotoxicity) were determined using the t-test. All analyses were carried out using the SPSS statistical package version 10.0 (SPSS Inc., Chicago, IL).

**results**

**patient characteristics**

Forty-four patients with a median (range) age of 57 (30–81) years received 165 cycles (median 3, range 1–14) of ixabepilone at a dose of 40 mg/m² (Table 1). Ninety percent were women; the majority (55%) had gynecological cancer; and 98% had received prior chemotherapy. Only two patients had grade 1 neuropathy at protocol entry. Forty-two patients were assessable for cycle 1 dose-limiting toxicity; however, only 35 patients were assessable for response. Two patients withdrew from the study before completion of one cycle and withdrew consent. An additional seven patients did not complete two cycles and were not assessable for disease response.

**neurotoxicity**

Neurotoxicity was observed in 28 of the 44 (63.6%) patients (Figure 1). Of the 28 patients with neuropathy, 26 (92.9%) experienced sensory neuropathy, while only two (7.1%) developed motor symptoms. In all, grade 2 and 3 neuropathy was observed in eight (18.2%) and three (6.8%) patients, respectively. Among patients with neuropathy, 85.7% (24 of 28) developed symptoms within the first two cycles [67.9% (19 of 28) within first cycle] of therapy. In contrast, for patients...
developing grades 2–3 neuropathy, only 36.4% (4 of 11) manifested it within the first two cycles, while 63.6% (7 of 11) developed it beyond the second cycle.

When the degree of neurotoxicity was evaluated in association with prior chemotherapy, both in terms of number of prior regimens and the prior class, i.e. platinum and/or taxane, unlike prior reports, none of the factors appeared to influence the degree of neuropathy. The only nonstatistical difference was that the mean degree of neuropathy in patients with prior exposure to taxanes (1.03) was higher than that in those without (0.75), with a P value of 0.37.

neurological testing
Adapted from VPT results are available for 25 patients. Nineteen patients did not have valid VPT measurements due to inability to complete two cycles (nine patients), lack of adequately trained personnel at one site (four patients), patient’s refusal or inability to cooperate (three patients), and poor documentation (three patients). Neurotoxicity was graded as per NCI CTC version 2.0. As one objective of the VPT testing is to facilitate early prediction of delayed neurotoxicity, we considered the change in VPT (measured in VU) from baseline to cycle 2 as the variable of interest. The outcome data considered were the worst-grade neuropathy experienced by each patient at any time in the trial. We also observed that patients often had different VPT measurements in the two sides (left and right) and this combined with the fact that some patients noted neuropathic symptoms particularly in a single hand (or foot), or digit (asymmetric neurotoxicity), we considered the VPT measurement from each hand as an individual observation.

The mean change (increase) in VPT from baseline to cycle 2 was 0.48 ± 0.02 (mean ± SEM) VU. The mean increase in VPT as a function of grade 0–1 versus grades 2–3 neuropathy was 0.235 ± 0.03 versus 0.869 ± 0.09 (P = 0.049) VU (Figure 2). However, neither the F wave nor the DML scores were different in the patients with grades 2–3 neuropathy relative to those with grade 1 neuropathy (data not shown).

toxic effects
Overall, toxic effects are summarized in Table 2. Cycle 1 dose-limiting toxic effects were observed in six patients and included neuropathy (one patient) and neutropenia (five patients).

![Figure 2. VPT change in patients with different grades of neuropathy. Difference in the increase in vibration perception threshold in vibration units between patients who experienced grade 0–1 neuropathy versus those who developed grades 2–3 neuropathy.](https://academic.oup.com/annonc/article-abstract/19/12/2048/167550)

**Table 2.** Toxicity across all cycles among all patients

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Insomnia, fracture, renal function abnormality, dizziness, itching, lower extremity edema.

Bloating, abnormal liver function test (LFT), gastrointestinal bleed.

n, number of patients; CTC, common toxicity criteria.
Among all treated patients, neuropathy was observed in 28 patients (three patients with grade 3 neuropathy). Grade 3 or greater neutropenia was observed in 18 (40.9%) patients. A drug-related death was observed in an 81-year-old woman with metastatic colon cancer who died of complications of febrile neutropenia and sepsis on the 11th day of the first cycle. Other common toxic effects included anemia (95.5%), fatigue (70.5%), and myalgia (68.2%).

**antitumor response**

Of the 35 patients assessable for response, three [9% (two breast and one ovarian cancer)] had a partial response and two [6% (one breast and one ovarian cancer)] had a minimal response. All five patients had previously received a taxane-based therapy (paclitaxel or docetaxel) and had progressive cancer before entering this study.

**discussion**

In this report, we generate the hypothesis that a simple office-based objective test for neurological function, the VPT, can distinguish between patients who will develop clinically significant neuropathy (grades 2–3) from those patients who will not (grade 0–1).

We observed that of the 28 patients who developed neuropathy, a majority (24 patients, 85.7%) did so within the first two cycles. In contrast, of the 11 patients with clinically significant grades 2–3 neuropathy, only four (36.4%) manifested it in the first two cycles. While this indicates that the VPT at the end of cycle 2 can predict and possibly prevent 63.6% of symptomatic neuropathy, one may also speculate that performing the VPT at the end of the first cycle may identify patients who are likely to develop this as early as in cycle 2. This would, however, require confirmation in a prospective clinical trial.

Vibration (pallesthesia) is a touch sense that is perceived predominantly by the Pacinian mechanoreceptor (with some contribution by the Meissner’s corpuscle and Merkel’s discs) and is transmitted from the periphery to the central nervous system via the large myelinated fibers that also transmit the sense of light touch and joint position [17]. The impulse is then transmitted through the dorsal (posterior) columns in the spinal cord to the dorsal column nucleus in the midbrain, to the ventral posterior lateral nucleus to finally reach the primary sensory cerebral cortex. The loss of the vibration sense could therefore be secondary to damage to the Pacinian receptor, or the large myelinated fibers or anyplace in the tract to the cortex. While the reports with the use of ixabepilone have not focused on the issue of joint position and imbalance as toxicity, it is possible that the visual input along with an intact vestibular system are able to overcome a dysfunctional joint position sense. We would also propose that future trials looking at neurotoxicity of ixabepilone consider mandating a Rhomberg’s test to evaluate for dorsal column anomalies or detailed testing for joint position abnormalities.

This is a very practical finding for implementation in the office or in the clinic. It is our experience that the test only takes 5 min to administer and is ideal to be carried out during a regular follow-up visit in a busy clinician’s office. While it does require an initial investment in the purchase of the instrument ($3000), and some initial training, it is extremely easy to administer. It takes ~2 h to train a physician extender in the process of administering the test, and ~5 min to perform. The cost of administering the test is estimated at $15 per test (5 min of the NP time at $60/h and $10 of capital cost of the instrument presuming that it will depreciate >300 tests). Moreover, while the Vibratron II device has been extensively explored in the diabetic population and diabetes research [18–20], there is precedence for its use in cancer research particularly with chemotherapeutic agents such as the taxanes and the platinates [12–16, 21, 22]. Future large-scale trials should consider prospective assessments analogous to ours with the objective of determining the frequency of required tests and a prediction model for calculating a percentage probability of development of clinically significant neuropathy.

One limitation of our study is that we administered ixabepilone over 1 h, while it was administered over 3 h in the pivotal phase III trial and the USFDA approved product label [1]. One reason for prolonging the infusion duration was to reduce neuropathy (suggesting dependency on Cmax). Similar speculations were raised for diminishing paclitaxel-induced neuropathy and its relation to Cmax until this was clearly negated in a prospective clinical trial that demonstrated its relationship to total paclitaxel exposure and duration above a threshold concentration [23]. Paclitaxel pharmacokinetics (namely, duration above a concentration of 0.05 μM) also bears a clear relationship with the intensity of neutropenia [24]. However, no such association has been found with ixabepilone pharmacokinetics. Additionally, considering the fact that the rate of neuropathy in our trial was similar to that observed in trials utilizing other schedules, our findings may indeed be applicable to the 3-h infusion schedule. The rate of neuropathy in our trial was 63.6% [95% confidence interval (CI) 47.8%–77.6%] while across multiple trials carried out with ixabepilone, the incidence of reported neuropathy has been between 44% and 71% [1–5; 25, 26].

Moreover, there have been suggestions that the daily times three or daily times five schedule [3] will lower incidence of neuropathy. However, in spite of these claims of lower neuropathy with the manuscript reporting ‘mild’ neuropathy, 63% of the patients demonstrated some form of neuropathy, with 26% grade 2 neuropathy; again, well within the 95% CI of our current trial with the 1-h infusion.

We also failed to find any association of the neuropathy with prior exposure to a platinum or taxane. While we did find some difference in the degree of neuropathy developed in patients with prior exposure to taxanes, this was not statistically significant. One explanation for this is that the number of patients without prior exposure to any of these agents was too small to make a statistically significant difference. Another possible reason is that patients were carefully screened for preexisting neuropathy before entry to this trial, thereby limiting the influence of prior exposure to neurotoxic agents. The third possible explanation is that patients stayed on trial for a median of three cycles, thereby not allowing sufficient exposure to drug to manifest its true neurotoxicity.
In prior reports, there have been suggestions that using nerve growth factors such as neurotrophin 3 may reverse cisplatin-induced vibratory sense loss [27]. Amifostine to prevent peripheral nerve pathology has also been tested but the evidence is not sufficient for USFDA approval [28]. The best clinical strategy for drug-induced neuropathy may well be prevention of severe toxicity. In this context, the use of VPT as a predictive tool warrants further study. The performance of the VPT may aid physicians in altering or delaying the dose before development of clinically significant neuropathy.

In conclusion, we present here the largest experience of ixabepilone at 40 mg/m² administered over a 1-h infusion schedule. We find that using the VPT can help predict which patient is likely to develop clinically significant neuropathy such that the dose may be held, delayed, or discontinued. Our findings should prompt further testing with the use of this drug and validation of the VPT as a simple detection tool in other trials. Specifically, critical data are required over the longer term administration of ixabepilone where VPT test scores are collected and assessed at least twice per week in a prospective manner. One would then need to develop ROC curves with different thresholds for using VPT change as a predictor of grades 2–3 neuropathy, and use one with the most practical value, such that the number of patients developing grade 2 neuropathy is minimized while those deriving clinical benefit from this drug is maximized.

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references