Sustained Accumulation of Microtubule-Binding Chemotherapy Drugs in the Peripheral Nervous System: Correlations with Time Course and Neurotoxic Severity

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Abstract

Chemotherapy-induced peripheral neuropathy is a dose-limiting side effect of many antineoplastic agents, but the mechanisms underlying the toxicities are unclear. At their MTDs, the microtubule-binding drugs paclitaxel and ixabepilone induce more severe neuropathy in mice relative to eribulin mesylate, paralleling their toxicity profiles in clinic. We hypothesized that the severity of their neurotoxic effects might be explained by the levels at which they accumulate in the peripheral nervous system. To test this hypothesis, we compared their pharmacokinetics and distribution in peripheral nerve tissue. After administration of a single intravenous dose, each drug was rapidly cleared from plasma but all persisted in the dorsal root ganglia (DRG) and sciatic nerve (SN) for up to 72 hours. Focusing on paclitaxel and eribulin, we performed a 2-week MTD-dosing regimen, followed by a determination of drug pharmacokinetics, tissue distribution, and multiple functional measures of peripheral nerve toxicity for 4 weeks. Consistent with the acute dosing study, both drugs persisted in peripheral nervous tissues for weeks, in contrast to their rapid clearance from plasma. Notably, although eribulin exhibited greater DRG and SN penetration than paclitaxel, the neurotoxicity observed functionally was consistently more severe with paclitaxel. Overall, our results argue that sustained exposure of microtubule-binding chemotherapeutic agents in peripheral nerve tissues cannot by itself account for their associated neurotoxicity. Cancer Res; 76(11): 3332–9. ©2016 AACR.

Introduction

Chemotherapy-induced peripheral neurotoxicity (CIPN) is a major clinical problem representing a significant dose-limiting side effect of many antineoplastic drugs. Even when neuropathy is not dose limiting, residual neuropathy can severely affect quality of life in cancer survivors. The severity of neuropathy caused by a particular chemotherapeutic drug is dependent on multiple factors, including mechanism of action, frequency of administration, duration of treatment, and cumulative dose (1, 2). Within the class of microtubule-targeting drugs, high-grade neuropathy occurs more frequently with paclitaxel and epothilones, such as ixabepilone, whereas eribulin is less likely to produce dose-limiting neuropathy. Animal models of CIPN have provided data that are in broad agreement with clinical results (3–7) and thus provide an opportunity to explore the relationship between exposure and toxicity for both existing and new chemotherapies. For example, we have reported that paclitaxel and ixabepilone produce more severe neuropathy in mice compared with eribulin mesylate at their respective MTDs (3), with findings that replicate the frequency of severe neuropathy reported in comparative clinical studies (1, 8). However, it is not known whether these differences are due to the intrinsic toxicity of these agents or due to differences in exposure of the vulnerable peripheral nervous system.

It has long been recognized that cumulative chemotherapy exposure over time is the most important clinical predictor of neuropathy. This dependence on dose could either be due to an accumulation of injury produced by the toxicity of each administration or an accumulation of drug in peripheral nerve tissues that reach toxic levels only after multiple doses. Peripheral nervous tissue exposure is difficult to quantitate clinically, and is likely poorly predicted by plasma concentration because of variable distribution, often strongly influenced by factors such as formulation or route of administration (9–12). In addition, clearance mechanisms from tissues also varies, determined both by binding of chemotherapeutic agents within tissues and efflux mediated by transport mechanisms such as P-glycoproteins (13, 14).

To investigate further the potential relationship between peripheral nervous tissue accumulation and neuropathy, it would be useful to compare chemotherapeutic agents with similar mechanisms but different neurotoxic potential. In the experiments described...
Animals

Female BALB/c mice (approximately 7–8 weeks old at the onset of dosing) were obtained from Harlan Laboratories and maintained with free access to water and a standardized synthetic diet (Harlan Teklad). Animal housing and procedure room temperature and humidity were maintained at 20 ± 2°C and 55 ± 10%, respectively. Artificial lighting provided a 12-hour light/dark cycle (light 7 am–7 pm). All experimental protocols were approved by the Institutional Animal Care and Use Committee of Sobran Inc. and adhered to all of the applicable institutional and governmental guidelines for the humane treatment of laboratory animals.

Mice were treated with single and multiple doses of a previously determined 6-dose MTD regimen administered intravenously on an every other day for three injections with a 2 day rest between weekly cycles (Q2D × 3 × 2 week) schedule (for method, see ref. 3). MTD was defined as the maximal dose of eribulin mesylate, ixabepilone, or paclitaxel administered at which no more than one animal in the treatment group died spontaneously. In addition, this was the maximal dose tested at which no mice in the dose group required euthanasia due to ≥20% individual weight loss, showing overt clinical signs of distress or inability to eat and/or drink. The MTD when administered intravenously 6 times on a Q2D × 3 × 2-week schedule was found to be 1.125 mg/kg for eribulin, 2 mg/kg for ixabepilone, and 30 mg/kg for paclitaxel.

Drugs and formulations

Eribulin mesylate [synthesized at Eisai Research Institute (Andover, MA) and stored at −80°C in the dark] was dissolved in 100% anhydrous DMSO (Sigma-Aldrich) to produce a 10 mg/mL stock solution, which was separated into aliquots and stored at −80°C until the day of administration. Each administration day, the stock solution was thawed and diluted with saline to a final concentration of 0.112 mg/mL in 2.5% DMSO/97.5% and administered in a 10 mL/kg volume.

Paclitaxel (purchased from LC Laboratories and stored at −20°C in the dark) was dissolved in ethanol (100%) at 10% of final volume. An equal volume of cremophor (10% of final volume) was then added and the mixture vortexed for about 10 minutes. Immediately prior to injection, ice-cold saline was added to final volume (as 80% of final), and the solution was maintained on ice during dosing. Dosing solutions of 3 mg/mL were made fresh daily and administered in a 10 mL/kg volume.

Ixabepilone (Ixempra, Bristol-Myers Squibb), was prepared according to the package insert. The formulated ixabepilone stock solution (2 mg/mL) was immediately aliquoted and stored at −80°C until use. On each experimental day, the stock solution was diluted by adding 50% ethanol/50% cremophor, with subsequent vortexing to yield a resultant solution that was 5 times the required dosing concentration. Finally, 4 volumes of PBS were added, while vortexing, to achieve a final dosing concentration of 10 mL/kg.

Pharmacokinetic studies

Pharmacokinetic studies were performed in female BALB/c mice to determine the plasma, DRG, and SN exposure of eribulin and paclitaxel after single and multiple MTD administrations as described above. For the single dose pharmacokinetics, plasma and tissue were taken at the following time points: time zero (no treatment), 0.25, 0.5, 1, 3, 6, 24, 72, 72 hours, and 7 days after drug administration. For pharmacokinetics following multiple doses, plasma and tissues were taken at the following time points during/after the Q2Dx3 × 2-week 6-dose administrations: 1 hour before third, fourth, fifth, and sixth dose and then 24 hours, 7, and 14 days following the last (sixth) dose. At sacrifice, blood was removed via cardiac puncture. Plasma was derived from the whole blood by centrifugation at 3,000 rpm at 4°C in plasma separator tubes for 10 minutes. The SN and DRG were removed and pooled from 3 mice per time point and homogenized with 3 times their respective weights of mouse plasma using a MiniBead Beater-96. All samples were stored at −80°C until subsequent analysis. Samples were analyzed for eribulin, ixabepilone, and paclitaxel using reversed phase chromatography on a LC/MS-MS (API-4000 with a Shimadzu autosampler) using methods based on procedures described previously (15–17). The lower limits of quantification were 0.5, 2, and 10 ng/mL in plasma and 5, 10, and 50 ng/g in DRG, for eribulin, paclitaxel, and ixabepilone, respectively, and 8ng/g for each analyte in SN. Pharmacokinetic parameters were calculated using noncompartmental analysis in WinNonLin v 5.0.3.

Electrophysiology

Electrophysiologic measurements were performed as described previously (3, 18). In brief, baseline caudal and digital nerve conduction velocities (NCV) and amplitudes were measured in all mice one week prior to initiation of dosing. Mice were anesthetized with 2% isoflurane (by inhalation, for induction and maintenance) and placed on a heating pad with rectal temperature monitored and maintained between 37.0°C to 40.0°C. Platinum subdermal needle electrodes (Grass Technologies) were used. Caudal NCV was recorded from electrodes in a bipolar configuration at the base of the tail (at the hairline); the stimulating cathode being positioned 35 mm further distal. Digital NCV was recorded using stimulation at the base of the second toe and recording at the level of the lateral malleolus. Amplitudes were measured as the baseline to peak neural response. Each nerve segment stimulation was repeated at least 3 times, up to a maximum of 6 times, with increasing voltage until the maximal response was achieved, using AcqKnowledge software version 3.7.3 (BIOPAC Systems Inc.). Mice were assigned into a vehicle, paclitaxel, or eribulin treatment group (10 mice/group). Following MTD dosing on a Q2Dx3 for 2-week schedule, mice were again tested for NCV at 24 hours, 7, and 14 days following the last dose.

Results

Pharmacokinetic studies

Following intravenous administration, plasma concentrations of eribulin, paclitaxel, and ixabepilone declined rapidly, presumably due to rapid distribution to peripheral compartments...
(19–21). Limitations of assay sensitivity prevented characterization of terminal elimination. After a single infusion, all three drugs rapidly distributed into DRG and SN, remaining above the limit of detection for over 72 hours. Concentration–time analyses of eribulin, paclitaxel, and ixabepilone in their respective matrices after single dose are depicted in Fig. 1A–C.

As shown by the pharmacokinetic parameters (Table 1), the three drugs varied widely in relative penetration into tissue after intravenous administration. Accumulation during the early tissue distribution, reflected as maximal exposure (C\textsubscript{max}) reached in tissue compared with plasma, was greatest for ixabepilone followed by eribulin. Peak paclitaxel concentration in tissue was lower than peak plasma concentration, whereas eribulin and ixabepilone displayed greater C\textsubscript{max} in tissue than in plasma. Peak exposure was greater in DRG than SN for all three compounds. The overall DRG and SN exposures relative to plasma were characterized by calculating a tissue penetration index for both C\textsubscript{max} and AUC. As shown in Table 1, the relative exposure by either measure was greater in DRG than SN for all three drugs, with ixabepilone having the highest exposure, eribulin being intermediate, and paclitaxel relatively lower.

As CIPN develops in the mouse model only after repeated administration, the tissue exposure was subsequently examined following a multiple MTD dosing paradigm of eribulin and paclitaxel (Fig. 2A and B, respectively). Similar to observations after acute dosing, the chemotherapies rapidly entered SN and DRG from plasma. In all cases, plasma concentrations declined within 24 hours of last dosing and were not detectable thereafter. In contrast, concentrations of eribulin and paclitaxel were maintained in SN and DRG for up to 26 days after the completion of dosing (Fig. 2A and B). As shown in Fig. 2, paclitaxel exposure reached maximal levels in the DRG after the first dose, while in the SN, there was accumulation with multiple doses. Eribulin exposure showed increasing accumulation in both DRG and SN with multiple administrations.

Electrophysiology

Following the 2-week MTD dosing regimen, caudal nerve conduction velocity was significantly slowed by paclitaxel at every time point measured (ranging from 23%–38% of vehicle; Fig. 3A). Similarly, caudal amplitude was significantly reduced by paclitaxel administration, remaining suppressed by 77 ± 4% (mean ± SEM) at 28 days after first dosing (Fig. 3B). Digital nerve conduction velocity also showed significant deficits at every time point measured (between 10% and 25% of vehicle; Fig. 3C). Paclitaxel also significantly affected digital nerve amplitude at all time points, remaining suppressed by 53 ± 7.8% at 28 days after dosing (Fig. 3D). Overall, the pattern of deficit was present the first day following dosing, showing a trend toward recovery for the conduction velocity measurements but mild gradual worsening for the sensory nerve amplitude measures. These patterns did not appear to be related to the prolonged tissue exposure.

In contrast, eribulin had no significant effect on caudal velocity at any time point tested, although a nonsignificant deficit (ranging between 7% and 17%) was consistently observed (Fig. 4A). Eribulin-treated mice showed a less severe, but statistically significant suppression of caudal amplitude at 14 and 28 days following the last dose (30 ± 9.8 and 52 ± 5.0%, respectively; Fig. 4B). Similarly, eribulin produced small but significant deficits in digital nerve velocity from 7 days postdose, ranging from 8% to 12% of vehicle (Fig. 4C). Digital amplitude in eribulin-treated mice was significantly attenuated at 7 days (19 ± 4.9%) and 14 days (26 ± 5.2%) postdosing but recovered back to predosing values at the 28-day time point (Fig. 4D). As observed for paclitaxel, the time course of functional deficit was not directly
correlated with the drug exposure time course, particularly the late decline in caudal nerve amplitude that occurred when tissue exposure was no longer detectable.

**Discussion**

After a single intravenous dose, paclitaxel, ixabepilone, and eribulin cleared rapidly from plasma but accumulated and dramatically persisted in DRG and SN, with limited clearance three days postadministration. In repeated dose studies, eribulin and paclitaxel also rapidly declined in plasma but accumulated and persisted in peripheral nervous tissues for up to 26 days after dosing. This neurotoxic class of drugs appears to exert toxic effects directly through prolonged exposure within sensitive tissues. However, although eribulin consistently showed greater tissue penetration than paclitaxel, neurotoxicity was minimal and less severe than with paclitaxel. This is in concordance with the milder morphologic deficits induced by eribulin in this paradigm compared with paclitaxel reported previously (3). Together, these data suggest that dramatic and sustained exposure of chemotherapeutic agents in peripheral nerve tissues alone cannot account for their neurotoxicity.

The paclitaxel concentrations we observed in DRG using a 2-week MTD model of paclitaxel-induced neuropathy are significantly higher than those previously reported by Cavaletti and colleagues (22) and Xiao and colleagues (4), both performed in rats. Cavaletti reported a mean tissue concentration in DRG of 366 ng/g after 5 mg/kg/day i.v. on 5 alternating days. Xiao and colleagues reported concentrations of 446 ng/g 24 hours after 7 days of administration (2 mg/kg i.p. on 4 alternate days) with no morphologic deficits, whereas in our current study, we observed 4,000 ng/g 24 hours after 6 injections of 30 mg/kg i.v. (Q2Dx3 for 2 weeks), a concentration that also induced morphologic deficits in our earlier study (3). Differences in paclitaxel administration route as well as cumulative dose may underlie these reported differences. Also, given the reported higher paclitaxel exposures from a cremophor formulation (23) versus ethanol/tween formulation (4), some accumulation in tissue may occur due to the depot effect of the formulation (24, 25). In addition to the higher DRG concentration, we observed a concentration in SN that was approximately 50% of that measured in DRG, whereas Xiao and colleagues reported SN concentrations only 10% of that measured in DRG. This is consistent with our observation that paclitaxel accumulates in SN with repeated doses. Interestingly, in the weeks after administration, the tissue concentration of paclitaxel in SN was actually higher than that in DRG, reversing the relative tissue concentration during the period of administration. This pattern of gradual accumulation in nerve might explain why a cumulative dose of paclitaxel is the critical clinical metric for neuropathy risk.

### Table 1. Pharmacokinetic parameters of a single intravenous dose of eribulin mesylate, paclitaxel, and ixabepilone in mice

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Dose (mg/kg)</th>
<th>Matrix</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (ng/g)</th>
<th>AUC&lt;sub&gt;(0—t)/C&lt;sub&gt;0&lt;/sub&gt;&lt;/sub&gt; (h/ng/g)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>AUC&lt;sub&gt;(0—∞)/C&lt;sub&gt;0&lt;/sub&gt;&lt;/sub&gt; (h/ng/g)</th>
<th>TPI&lt;sup&gt;b&lt;/sup&gt;</th>
<th>AUC&lt;sub&gt;TPI&lt;/sub&gt;</th>
<th>TPI&lt;sup&gt;c&lt;/sup&gt; AUC&lt;sub&gt;TPI&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eribulin mesylate</td>
<td>1.125</td>
<td>Plasma</td>
<td>203</td>
<td>487</td>
<td>491</td>
<td>2.1</td>
<td>8.8</td>
<td></td>
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<tr>
<td>Eribulin mesylate</td>
<td>1.125</td>
<td>DRG</td>
<td>428</td>
<td>4,270</td>
<td>7,080</td>
<td>2.1</td>
<td>8.8</td>
<td></td>
</tr>
<tr>
<td>Eribulin mesylate</td>
<td>1.125</td>
<td>SN</td>
<td>121</td>
<td>731</td>
<td>NR&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.6</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>Ixabepilone</td>
<td>2.0</td>
<td>Plasma</td>
<td>117</td>
<td>260</td>
<td>304</td>
<td>--</td>
<td>--</td>
<td></td>
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<tr>
<td>Ixabepilone</td>
<td>2.0</td>
<td>DRG</td>
<td>1,940</td>
<td>9,250</td>
<td>125,000</td>
<td>16.6</td>
<td>35.6</td>
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<tr>
<td>Ixabepilone</td>
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<td>SN</td>
<td>333</td>
<td>920</td>
<td>NR&lt;sup&gt;d&lt;/sup&gt;</td>
<td>2.8</td>
<td>3.5</td>
<td></td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>30.0</td>
<td>Plasma</td>
<td>95,000</td>
<td>114,000</td>
<td>114,000</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>30.0</td>
<td>DRG</td>
<td>9,280</td>
<td>94,000</td>
<td>279,000</td>
<td>0.1</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>30.0</td>
<td>SN</td>
<td>2,250</td>
<td>12,100</td>
<td>60,200</td>
<td>0.02</td>
<td>0.3</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: TPI, tissue penetration index.

<sup>a</sup> AUC<sub>(0—t)/C<sub>0</sub></sub>, 0—24 hours for eribulin mesylate and paclitaxel; 0—6 hours for ixabepilone.

<sup>b</sup> TPI = C<sub>max</sub>(tissue)/C<sub>max</sub>(plasma).

<sup>c</sup> TPI = AUC<sub>(0—t)/C<sub>0</sub></sub>/AUC<sub>(0—t)/C<sub>0</sub></sub>.

<sup>d</sup> NR, not reported because extrapolation area >30%.

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**Figure 2.**

A and B, pharmacokinetic profile of eribulin mesylate and paclitaxel in plasma, DRG, and SN from mice receiving Q2Dx3 for 2-week MTD dosing regimen of 1.125 mg/kg per dose for eribulin mesylate and 30 mg/kg per dose for paclitaxel. Plasma levels were below detection at all time points. In contrast, eribulin mesylate was quantifiable in DRG and SN samples up to 19 and 26 days after initial dose, respectively. Paclitaxel remained quantifiable in the DRG and SN up to 26 days postdose. Note: Eribulin data for day 20 were BLQ. Arrows represent actual dosing days, which occurred on days 1, 3, 5, 8, 10, and 12.
if nerve rather than DRG exposure in vulnerable patients is responsible for toxicity. Correlation in actual clinical samples would be needed to further explore this relationship.

The pharmacokinetics observed in these experiments can be understood as the sum of three dynamic processes: (i) distribution of drug into tissue; (ii) retention of drug in tissue, likely at specific binding sites; and (iii) efflux from tissue by active transport. Regarding uptake into tissues, paclitaxel, eribulin, and ixabepilone all exhibited a similar pattern of rapid peripheral nerve tissue distribution, even though they each differ in lipophilicity and formulation. Tissue distribution of these drugs is complex and can depend on formulation. For example, the distribution of paclitaxel in cremophor differs substantially from albumin-bound paclitaxel pharmacokinetics (9, 27). Tissue distribution is not purely passive; active uptake into tumors by carriers (28) such as OATP1B-mediated transport (11, 29) has been described. However, the cellular pharmacokinetics and specific transport mechanisms of these drugs in cultured peripheral neurons or glial cells are completely unexplored. Such studies are warranted to elucidate the potential for unique accumulation and retention of microtubule-targeting chemotherapies in peripheral neural cells versus tumor cells.

The sustained retention of all three drugs in DRG and SN is most likely due to a combination of intracellular binding and lack of efflux mechanisms. Complex computational models of intracellular pharmacokinetics of paclitaxel have been developed in vitro using cell lines (23, 30, 31) in which intracellular target binding is a critical factor in the absence of active efflux mechanisms because of the high concentration of their binding target, microtubules. Although the binding sites of paclitaxel and eribulin on microtubules vary (32, 33), as do their effects on microtubule function (34, 35), their affinity and the density of binding sites appear to be sufficient to result in prolonged intracellular DRG and SN retention.

Cellular efflux mechanisms, if present, appear to be insufficient to overcome retention through target binding. Although extensive work has been completed to understand how efflux through P-glycoproteins affects exposure of chemotherapeutics in solid tumors (36, 37), little is known regarding efflux mechanisms in peripheral nervous system tissue. It is known that paclitaxel and ixabepilone do not achieve high levels of exposures in the brain in patients (19, 38), but this is presumed due to active efflux by P-glycoproteins across the blood brain barrier, not lack of CNS distribution (14, 39, 40). Although the efflux transporters found

Figure 3.
A–D, mice receiving a 2-week MTD dosing regimen of paclitaxel (Q2Dx3 dosing of 30 mg/kg i.v. for 2 weeks) exhibited significant deficits in caudal and digital nerve conduction velocity and amplitude. The deficits were maintained for up to 28 days after completion of dosing. Mean ± SEM values at each time point. Black, vehicle; gray, paclitaxel. *, P ≤ 0.05; ***, P ≤ 0.001.
in the blood brain barrier have been found in blood vessels in peripheral nerve (41, 42), the DRGs appear to exist outside the blood brain barrier and thus are exposed to greater plasma components (43), possibly leading to the observed rapid accumulation and retention. We are not aware of in vitro studies of intracellular binding and efflux of these microtubule-binding drugs in cultured neurons or DRGs. Such studies might illuminate mechanisms of peripheral nervous system vulnerability to toxicity and development of better-tolerated agents.

Even though persistent levels of the chemotherapies were achieved in the mice peripheral nervous system, the results do not provide a pharmacokinetic explanation for the relative neurotoxicity of these agents. The more subtle functional and pathologic changes produced by eribulin compared with paclitaxel and ixabepilone are not predicted by relative exposure, accumulation, or retention in peripheral nervous system tissues. Although tissue accumulation may be necessary to produce the profound neurotoxicity of paclitaxel and ixabepilone, differential interaction with microtubules must explain differences in neurotoxicity. Eribulin may have less neurotoxic potential because it primarily affects microtubule growth in contrast to paclitaxel and ixabepilone, which affect microtubule function more broadly (34, 44). Differences in microtubule-binding properties may have significant effects on the toxicity profile of each microtubule-targeting agent (45, 46). In this context, eribulin mesylate has a 10-fold lower affinity for microtubule sides than its positive ends (47), possibly resulting in a lesser disruption of axonal transport of essential molecules, which may be the underlying reason for its lower propensity to induce neuropathy (48). In addition to the functional and pharmacokinetic findings reported, we recently showed differential effects of paclitaxel and eribulin on α-tubulin expression, tubulin acetylation, and EB1 abundance in the peripheral nerve following acute dosing (44) and are currently investigating the longitudinal course of these effects. This type of comparative study may prove useful in the design of more potent chemotherapeutic agents with less neurotoxicity. In conclusion, the dramatic and sustained exposure of chemotherapeutic agents in peripheral nervous tissue itself cannot account for their ensuing neurotoxicity profiles, and other factors must be implicated.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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Study supervision: K.M. Wozniak, K. Nomoto, G. Lai, N. Wong, B.S. Slusher

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