Acetyl-L-Carnitine and Prevention of Chemotherapy-Induced Peripheral Neuropathy: Can Anything Work?

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Disclosures of potential conflicts of interest may be found at the end of this article.

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Oncologists, ever the optimists, continue to look for the perfect drug—effective and without side effects. Failing this, we then look for drugs or therapies that can mitigate side effects. Successes have been achieved. Antiemetics that diminish or abolish nausea and vomiting have made once intolerable drugs such as most alkylating agents much more tolerable, and growth factors often help us manage neutropenia. But success has thus far eluded the management of peripheral neuropathy (PN), a common toxicity with many of our most effective therapies, most notably microtubule targeting agents (MTAs). In this issue of *The Oncologist*, in the Clinical Trial Results section, Campone et al. report their results using acetyl-L-carnitine (ALC) to mitigate chemotherapy-induced PN [1].

The current study describes a well-executed, prospective, placebo-controlled, double-blind, randomized trial. Ninety-eight patients with ovarian cancer (OC) and fifty-two with castration-resistant prostate cancer (CRPC) were enrolled. None had PN at enrollment. All were treated with sagopilone, a microtubule-targeting epothilone, with ALC (1,000 mg every 3 days) or placebo. The primary endpoint was the incidence of PN within ≤ 6 cycles in both treatment groups. While in OC patients the sagopilone/ALC arm had a significantly lower incidence of grade 3 or 4 PN than OC patients in the sagopilone/placebo arm, the administration of ALC with sagopilone did not result in a significant difference in overall PN incidence compared with a placebo.

Preclinical data with ALC examined the prevention of axonal damage and mitochondrial dysfunction and appeared promising [2]. However, together with other studies (Table 1), the current report indicates ALC will not be an effective therapy for chemotherapy-induced PN, and other strategies will need to be pursued. But as in all oncology, nothing is ever quite so simple and straightforward. For example, published randomized studies are not all in agreement and not readily comparable. Different chemotherapies have been used, with paclitaxel and

docetaxel used in previous studies and sagopilone in the current report. Similarly, the scoring of toxicity has varied with the Common Terminology Criteria for Adverse Events grade used by Campone et al. and the Functional Assessment of Cancer Therapy (FACT) by others. And while the study “failed to meet” its primary endpoint, patients with OC may have had a reduction in more severe PN. How that difference might occur is not clear and, at some level, counterintuitive. Clinical trialists know some toxicity is more difficult to score than others, and neuropathy is very difficult. Given its often-subjective description, grading of neuropathy varies among investigators [3]. New assessment methods with robust verification are needed.

But we can also wonder if MTA-induced PN will ever be preventable. Emesis control, for example, has been achieved by targeting active neurotransmitters and their receptors in the central nervous system and the GI tract that mediate afferent inputs to the vomiting center [4]. This has nothing to do with the mechanism of action of alkylating agents. Similarly, growth factors target the quiescent stem cells chemotherapy spares [5]. But in the case of MTAs, the toxicity—PN—is a direct result of the drug mechanism of action: interference with microtubule trafficking. Given their high specificity, most MTAs have only one target—the microtubules—and it is this that is responsible for both their efficacy and their toxicity. Unless we think we can identify a compound that preferentially “nourishes” peripheral neurons whose crucial microtubule trafficking is being disrupted, prevention will be difficult if not impossible. Symptom control may still be possible, as with duloxetine, for example [6]. But symptom control and prevention of toxicity are different strategies. Still, try we must and report we should. Campone and his associates did just that and we are now the wiser.

DISCLOSURES

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Table 1. Prospective clinical trials of acetyl-L-carnitine for the treatment or prevention of chemotherapy induced peripheral neuropathy

Author	Study	N	Tumor	Chemotherapy drug and schedule	Result
Bianchi et al. 2005	Phase II	25	N/R	Paclitaxel and cisplatin (schedules N/R)	TNS improved in 92% of patients
Sun et al. 2012 (Abstract)	Phase III	249	Various tumors	N/R	Improvement of at least one grade in neuropathy
Campone et al. 2013	Phase II randomized	150	OC and CRPC	Sagopilone q3 weeks	Incidence of grade 3/4 PN decreased with ALC in OC patients
Hershman et al. 2013	Phase III	409	Adjuvant breast cancer	Taxol weekly Taxol q3 weeks Docetaxel q3 weeks	CIPN significantly increased by 24 weeks with ALC

ALC, acetyl-L-carnitine; CIPN, chemotherapy-induced peripheral neuropathy; CRPC, castration-resistant prostate cancer; N/R, not reported; OC, ovarian cancer; PN, peripheral neuropathy; TNS, total neuropathy score

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