

A Randomized, Double-Blinded, Placebo-Controlled Phase II Trial of Recombinant Human Leukemia Inhibitory Factor (rhuLIF, emfilermin, AM424) to Prevent Chemotherapy-Induced Peripheral Neuropathy

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Peripheral neuropathy is an increasingly important complication of many cancer therapies, including conventional cytotoxic agents, such as platinum analogues, taxanes, and Vinca alkaloids, and newer agents, such as thalidomide, suramin, and the proteosome inhibitor bortezomib. The development of a neuropathy frequently limits the dose of the therapeutic agent that can be administered and significantly contributes to the morbidity of the treatment, reducing the quality of life of patients.

The likelihood of developing a neuropathy is dependent on the chemotherapeutic agent, dose intensity, and cumulative dose, as well as the presence of preexisting nerve injury from other causes, such as diabetes or alcohol. The precise pathogenesis of chemotherapy-induced neuropathies is poorly understood and varies with the agents involved. Most drugs produce an axonal neuropathy, although some agents, such as cisplatin, predominantly affect neurons in the dorsal root ganglion, giving rise to a neuronopathy. Vinca alkaloids, taxanes, and suramin produce a mixed sensorimotor neuropathy, sometimes accompanied by autonomic involvement. Cisplatin, oxaliplatin, thalidomide, and bortezomib result in a sensory neuropathy that may be painful.

There is currently no effective treatment for chemotherapy-induced neuropathies. Most neuropathies improve after the drug is withdrawn, but a significant number of patients continue to experience long-term sequelae. Symptomatic treatment with tricyclic antidepressants, anticonvulsants, topical capsaicin cream, and lidocaine patches provide limited relief. Attempts have been made to prevent chemotherapy-induced neuropathies by dose reduction, substitution of less neurotoxic agents, and the administration of chemoprotectants. Early studies with agents, such as the adrenocorticotrophic hormone (4-9) analogue Org 2766, suggested that it may partially protect peripheral nerves from cisplatin neurotoxicity. However, this was not confirmed by subsequent studies. There has also been interest in amifostine, an inorganic thiophosphate whose active metabolite WR-1065 acts as a free radical scavenger. Some studies suggest that amifostine may reduce neurotoxicity from cisplatin and paclitaxel, but other studies have failed to show any benefit. Currently, there is insufficient data to support routine use of amifostine to prevent cisplatin or paclitaxel-associated peripheral neuropathies.

Leukemia-inhibitory factor (LIF) is a 180-amino acid single-chain protein belonging to a group of cytokines that includes ciliary neurotrophic factor, interleukin-6, interleukin-11, cardiotropin-1, and oncostatin M. LIF acts through the LIF cell-surface receptor complex consisting of two components, LIFR and gp130. The LIF receptor is expressed on many cell types including neurons, megakaryocytes, macrophages, adipocytes, hepatocytes, osteoblasts, myoblasts, kidney, and breast epithelium.

An accumulating body of evidence suggests that LIF has potent neurotrophic activity in both motor and sensory neurons. In studies on axotomy and nerve crush models, LIF enhanced the survival of motor and sensory neurons and reduced denervation-induced muscle atrophy. LIF also decreased the rate of progression of neurologic deterioration in the wobbler mouse, an extensively studied model of axonopathy. In human nerves, the level of LIF is increased following injury, potentially contributing to up-regulation of neuropeptides involved in regeneration. These neurotrophic properties suggest that LIF may have a potential role in the prevention or treatment of chemotherapy-induced neuropathies. Importantly, preclinical studies showed that LIF did not compromise the antitumor activity of cisplatin, paclitaxel, and carboplatin.

In this issue of CCR, Davis et al. report the results of a randomized, double-blinded, placebo-controlled Phase II trial of recombinant human LIF (rhuLIF, AM424; emfilermin; AMRAD Operations) to prevent peripheral neuropathy in patients with solid tumors treated with carboplatin (AUC 6) and paclitaxel (175 mg/m² over 3 hours) every 21 days. The study drug was administered s.c. for 7 days, each cycle starting the day before chemotherapy. Patients were randomized to receive low-dose rhuLIF (2 µg/kg), high-dose rhuLIF (4 µg/kg), or placebo. The primary end point was a standardized composite peripheral nerve electrophysiology score based on nerve conduction velocities and amplitudes measured at baseline and after four cycles of chemotherapy. Secondary end points included composite peripheral nerve electrophysiology score at the last cycle, vibration perception threshold, H-reflex latency, symptom scores, and quantitative...
assessment of neurologic signs. One hundred and seventeen patients were enrolled in the study. Thirty-six patients received low-dose rhuLIF, 39 received high-dose rhuLIF, and 42 received placebo. RhuLIF was well tolerated but no differences were observed between groups in composite peripheral nerve electrophysiology or any of the individual neurologic testing parameters between baseline and cycle 4 or by the secondary efficacy variables.

The reason for the lack of efficacy of rhuLIF in patients despite extensive preclinical data suggesting that LIF had neurotrophic activity is unclear. This was a well-conducted study in which the three arms were reasonably well balanced. The use of the composite peripheral nerve electrophysiology score provided a more objective measurement of neuropathy than many previous studies. Possible explanations for the lack of efficacy include the failure of the preclinical models to reflect the human situation, inadequate dosing, failure to continuously administer rhuLIF, inadequate penetration of rhuLIF into distal nerve endings, failure of rhuLIF to act on mature neurons as opposed to the developing neurons frequently used in preclinical studies, and compensatory down-regulation of endogenous LIF and other cytokines following exogenous administration of rhuLIF.

Unfortunately, the failure of LIF to protect against chemotherapy-induced neuropathy is not unique. Attempts to treat neuropathies with other neurotrophic factors, such as the use of nerve growth factor for diabetic neuropathies, have also met with similar disappointment (19). Although there are many reasons for this lack of success, an important factor is our poor understanding of the pathogenesis of neuropathies and the role of various neurotrophic factors in nerve regeneration.

Although the results with neurotrophic factors and chemoprotective agents have been disappointing, there is emerging evidence that other therapies, such as dietary supplementation, may be helpful in preventing certain forms of chemotherapy-induced neuropathies. Infusions of calcium and magnesium seem to reduce the incidence of sensory neurotoxicity associated with oxaliplatin, possibly by counteracting the calcium and magnesium chelating effects of the oxaliplatin metabolite, oxalate (20). Vitamin E levels are decreased in patients receiving cisplatin chemotherapy and supplementation with vitamin E reduces the incidence and severity of peripheral neuropathy (21). There is also some evidence that glutathione may reduce oxaliplatin-induced neuropathy (22) and glutamine may reduce paclitaxel-induced neuropathy (23). However, the value of these approaches awaits confirmation by larger, controlled studies.

Chemotherapy-induced neuropathy is an increasingly important clinical problem and more effective therapies are urgently needed. Despite the disappointing results with neurotrophic factors to date, further work with these and other novel treatments, based on improved understanding of the pathogenesis of the neuropathies, is warranted.

REFERENCES
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