The Biology Behind

Prevention of Chemotherapy-Induced Neuropathy: Leukemia Inhibitory Factor

Commentary on Davis et al., p. 1890

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Peripheral neurotoxicity is a dose-limiting and disabling side effect of several important chemotherapeutic agents. In particular, vincristine, cisplatin, oxaliplatin, paclitaxel, and docetaxel are frequently used antineoplastic agents, which are known causes of a peripheral neuropathy. The recently registered proteasome inhibitor bortezomib, which is effective in multiple myeloma, is the latest example of an effective antineoplastic agent, which may cause a severe—and often painful—neuropathy. Most of these agents cause an axonal neuropathy, leading to damage of the core of the peripheral neuron, but there are actually quite large differences between the neuropathies each of these agents cause.

- Vincristine causes an axonal sensorimotor neuropathy often early on during treatment, heralded by paresthesias and followed by severe motor weakness if treatment is continued (1). Pain is not a prominent feature. Autonomic neuropathy is often prominent (ileus, orthostatic hypotension). Even in cases with a more severe neuropathy, in time, recovery may be good. The cause is probably a vincristine-induced interference with microtubuli, affecting axonal transport. Neurotoxicity is the dose-limiting toxicity of vincristine, in particular related to dose per cycle. Other Vinca alkaloids are far less neurotoxic.

- Cisplatin predominantly affects the sensory nerve bodies, which are located in the sensory root ganglia. This may be due to the absence of the blood-nerve barrier of this part of the nervous system, resulting in a higher accumulation inside the sensory nerve body. The clinical feature is that of an axonal sensory neuronopathy, which is cumulative, dose-dependent, usually occurring at cumulative dose levels of 420 mg/m² or higher. The gnostic senses are most severely affected, leading to the typical loss in vibration sense and joint position sense, with only minimally affected pain and temperature sense. This pattern of sensory loss and the disabling chorea that may ensue in more severe causes may result in the inability to walk, despite the complete absence of motor deficits. A particular troublesome aspect of cisplatin neurotoxicity is that it takes a relatively long period to develop. Often signs and symptoms do not start until the end to treatment, or considerably worsen after the cessation of treatment (“coasting”; ref. 2). This prevents timely discontinuation of treatment in most patients with neurotoxicity. For cisplatin, neurotoxicity and renal toxicity is dose-limiting. In more severe cases, recovery is limited. Carboplatin is hardly neurotoxic, in contrast to cisplatin, the major toxicity of this drug is myelosuppression.

- Oxaliplatin is a third-generation platinum derivate, with activity against a variety of tumors like colorectal cancer, breast cancer, and lung cancer. It may induce an acute sensory axonal neuropathy, which is probably caused by an acute channelopathy (3). This acute neuropathy has rather typical clinical sensory features: besides distal paresthesias, patients complain of perioral and pharyngolaryngeal dyesthesias. These are generally mild and short-lived, and can be avoided by prolongation of the infusion (which decreases peak levels). Oxaliplatin may also cause a chronic cumulative axonal sensory neuropathy, which occurs after treatment of a cumulative dosage of >800 to 1,000 mg/m² oxaliplatin. In contrast to cisplatin neuropathy, it is generally a reversible neuropathy.

- Paclitaxel neuropathy is particularly dependent on the dose per cycle, and is rarely severe if this dose is kept <200 mg/m² per cycle (4). It is more of an axonal sensory rather than a motor neuropathy. In susceptible individuals, signs and symptoms begin early after the start of treatment, and they tend to improve prior to the next cycle, only to deteriorate with further cycles. The dysesthesias are often prominent, and if treatment is continued, weakness may be profound. If treatment is not modified, recovery is limited and the dysesthesias may prove to be disabling. Docetaxel induces a similar neuropathy, but because other toxicities are usually present, it is rarely dose-limiting. It is assumed that taxanes also interfere with tubular intra-axonal transport.

- Because the taxanes and cisplatin are effective against similar tumor types (head and neck cancer, lung cancer, and ovarian cancer) these agents are often combined. As one would expect, in combination, the neurotoxicity is increased, although it is not clear if the combined toxicity is additive or synergistic (5). Neuropathic pain is often a prominent feature of the combination regimens, and neurotoxicity is certainly dose-limiting. If treatment is continued in patients with neurotoxicity, persistent disabling dysesthesias are the rule.

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Chemotherapy-Induced Neuropathy and LIF

• Bortezomib is a novel agent, effective against multiple myeloma. It may cause a sensory neuropathy with predominant small fiber involvement, often burning sensations that can be very painful (6). It may be more severe in patients with a preexisting neuropathy. The neuropathic pain is usually resistant to medical treatment. At present, the only existing strategy is to immediately dose reduce or discontinue treatment once a patient develops neuropathic pain.

Together, these agents are effective against a wide variety of human cancers, and their neurotoxicity interferes with the effective treatment of these cancers. Strategies to deal with the neurotoxicity are dose reductions (or use of alternative drugs), the use of preventive drugs, and symptomatic agents. Symptomatic agents are mainly directed at the control of dysesthasias and pain. The drugs most frequently used for this indication are gabapentin, amitryptiline, tramadol, carbamazepine, and fentanyl patches. Pain and/or dysesthasia relief is rarely complete, and often side effects interfere with effective symptom control. Dose reductions are of course hampering effective anticancer treatment, and especially in patients responding to treatment this is very unfortunate measure. Any drug that prevents neurotoxic side effects would not only allow the continuation of treatment in these patients, but might also circumvent dose-limiting side effects, allowing a further dose escalation. Thus, a true protective agent would not only improve quality of life, but might also lead to a better tumor control. Candidate neuroprotective agents have to fulfill three requirements:

• They must be well tolerated, without significant side effects
• They should not interfere with antitumor treatment
• They should be effective in preventing the development of chemotherapy-induced neuropathy

Several agents have been investigated in clinical trials, like the adrenocorticotropic hormone analogue, ORG27776 (7), the thiols, gluthathione (8) and amifostine (WR-2711; ref. 9), the mesna prodrug BNP7787 (10), and vitamin E (11). For some of these agents, the mechanisms of action seems to be the decreased accumulation of the neurotoxic compounds in normal (neural) cells. Although some of these compounds showed some neuroprotective action, none has gained wide acceptance as a neuroprotective agent.

A totally different class of agents that have received attention are the nerve growth factors, such as the neurotrophins, nerve growth factor, and neurotrophin-3, the gp130 cytokines, ciliary neurotrophic factor, and leukemia inhibitory factor (LIF), and insulin-like growth factor-I. For each of these factors, high-affinity receptors are present on neural cells. In a large number of experimental studies, specific trophic actions of these growth factors on neurons were shown. This suggested a role for these agents in degenerative diseases like motor neuron disease and Parkinson’s disease, as well as in mood disorders and nerve trauma. Chemotherapy-induced neuropathy is in fact an ideal model to investigate the role of protective agents in neuronal trauma, as the exposure to the toxic agent is exactly known and is usually limited in time. This allows treatment throughout the entire period of the insult to the nervous system. In several animal models using a variety of chemotherapeutic agents, different growth factors proved to indeed be effective in preventing chemotherapy-induced neuropathy (12–15). As a result, insulin-like growth factor-I (Cephalon Inc., West Chester, PA) and LIF (Amrad, Melbourne, Australia) were actually investigated in clinical trials.

This issue of Clinical Cancer Research contains a report on the placebo-controlled randomized phase II trial that investigated the role of two dose levels of LIF in the prevention of paclitaxel/carboplatin-induced neurotoxicity (16). LIF was found to be effective in the prevention of paclitaxel and cisplatin without affecting antitumor activity in animal models (17–19). Despite the promising results of experimental animal studies, the clinical study failed to identify the protective role of LIF. The question is why?

The first question that arises is of course whether the study design was appropriate. In general, the designs of clinical studies on chemotherapy-induced neurotoxicity are complicated. First of all, due to the nature of the disease, the dropout rates are usually high. The authors have tried to deal with this by choosing the principle evaluation after cycle four, although six cycles of treatment were foreseen. Then, trials that explore protection against neurotoxicity should use a significantly neurotoxic regimen. The present trial does not meet this requirement: the used combination of carboplatin and paclitaxel at a dose level of 175 mg/m² per cycle is only modestly neurotoxic. This marginal neurotoxicity is further limited by the use of the assessments after cycle four as the primary outcome measure. It is also shown by the return to baseline for most neurologic parameters at the exit evaluation well after the end of treatment, showing that the induced neuropathy was clinically not significant. Next, no generally agreed upon single end point is available for studies like this. In most studies, the end points are either a sum score of a list of signs and symptoms, some peripheral nerve toxicity score (e.g., the National Cancer Institute Common Toxicity Criteria for neuropathy), a quantitative assessment of nerve function like sensory threshold determination (often vibration sense), or nerve conduction velocity studies. The authors used several of these end points, but their primary end point is rather surprising. Although paclitaxel predominantly causes a sensory axonal neuropathy (resulting in reduced sensory nerve amplitudes), the chosen primary end point is nerve conduction slowing.

Still, the authors carried out a thorough evaluation of many levels of nerve function, including sensory nerve amplitudes, sensory threshold testing, and a composite score of signs, symptoms, and functions (the CIPNS-32). An important strength of the study is the blinded design. Despite the limited neurotoxicity of the chemotherapy regimen, the tests did give evidence of the development of neuropathy during treatment and none showed any indication of a preventive effect of LIF. Thus, this study does not provide the “proof of principle” of a protective effect of LIF on paclitaxel-induced neuropathy. The paper mentions that in response to chemotherapy, no adverse effect of LIF was observed, but these data are not presented.

Unfortunately, the negative outcome of trials on growth factors for neurologic diseases is not exceptional. Despite the high expectations of these growth factors for degenerative neurologic diseases (diabetic neuropathy, amyotrophic lateral sclerosis, and Parkinson’s disease) clinical trials were negative...
There is ample evidence that the role of these neurotropic factors in the regulation of neuronal growth/function is complex, with different growth factors having different functions on different types of neurons. Although all neurotropic chemotherapeutic agents cause paresthesias, the mechanism of chemotherapy-induced neurotoxicity differs for each agent, and at first glance, it seems illogical to assume that any single drug might counteract neurotoxic effects of a variety of agents. Another critical issue is the question of whether or not the target was actually reached, as a blood brain-nerve barrier protects nerves and neurons. While preparing this review, I was unable to identify the report on insulin-like growth factor-I, which was investigated in a trial on cisplatin and paclitaxel in non–small cell lung carcinoma. It cannot be overemphasized that negative trials should be reported. However unfortunate the negative outcome may be, in this respect, the present report is very important: no other report on a proper evaluation of a neurotropic factor on chemotherapy-induced neuropathy is available. In view of the present outcome, it is unlikely the compound will ever be investigated in a more neurotoxic regimen.

**REFERENCES**

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