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EDITORIAL

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Chemotherapy-associated neurotoxicity: an important side effect-impacting on quality, rather than quantity, of life

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Through trial and error, oncologists have learned to communicate with each other about the side effects of cancer chemotherapy by developing "objective toxicity scales" (Miller et al. 1981). These measurements make it possible for investigators to compare the toxicity profile of one drug (or regimen) to another, either though the results of phase 2 studies of phase 3 randomized trials. The "grade" of a particular side effect reflects its severity, with the most serious toxicities being labeled as "life threatening".

The most common "life threatening" toxicity of cancer chemotherapy is severe bone marrow suppression. It is well recognized from extensive clinical experience that very low granulocyte counts can be associated with serious infectious events, including death. However, the vast majority of these short-term "severe neutropenic events" are relatively asymptomatic, completely reversible (with the use of antibiotics, bone marrow colony stimulating factors, or observation only), and severe morbidity is very uncommon. Additional well-recognized and noteworthy characteristics of cancer chemotherapy-associated bone marrow toxicity include the fact it is often anticipated, is readily recognized, and can be quantified easily.

The clinical features of the neurotoxic side effects of antineoplastic agents are strikingly different from those described for bone marrow toxicity. Neurotoxicity is often difficult to predict and may become clinically evident late in the treatment course or even after therapy has been completed. Although symptoms can be quite debilitating (e. g., difficulty writing or even buttoning a blouse), they are often difficult to measure or quantify. In addition, despite the severity of neurotoxicity, such events are rarely (if ever) "life threatening", exerting their impact on the quality of life of the cancer patient, rather than on its duration.

Finally, neurotoxic events are usually of prolonged duration, often measured in months, rather than days. Neurological dysfunction may improve, but never completely disappear in many patients. In fact, subjective improvement may be due as much to patients "learning to live with the discomfort or dysfunction", as to actual reversibility of the pathologic process.

In patients receiving chemotherapy administered with legitimate "curative intent", many toxicities (including both acute life threatening and more chronic side effects) can be justified to accomplish this goal. However, at the present time, the ultimate goal of most chemotherapy delivered to patients with metastatic cancer is to *palliate symptoms* and optimize the quality of fife for some limited period of time. Under these circumstances it is difficult to justify toxicity which directly impairs normal neurological function and causes significant chronic patient discomfort.

A recent reported experience with a combination cisplatin and paclitaxel regimen emphasizes the importance of the neurotoxicity of cancer chemotherapy (Connelly et al. 1996). In this trial, previously untreated patients with gynecologic malignancies received cisplatin (75 mg/m^2) plus paclitaxel (175 of 135 mg/m^2 delivered over 3 h). A 70% incidence (20% severe) of neurotoxicity (principally peripheral neuropathy) was noted, with most patients developing initial symptoms after three or more courses of the planned six cycle treatment program. While the majority of patients exhibited improvement within a few months of the completion of therapy, several individuals were reported to continue to experience significant discomfort more than one year after discontinuing treatment.

It is likely the neurotoxicity observed in this study was the direct result of relatively high concentrations of two potentially neurotoxic agents reaching the peripheral nerves at essentially the same time. A regimen consisting of the same dose of cisplatin, but with paclitaxel administered over 24 h, has reported a much lower incidence and severity

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of neurotoxicity (McGuire et al. 1996). The major difference between the two regimens is the lower peak serum concentrations of paclitaxel achieved when the drug is delivered over 24 hours, providing indirect support for the above noted explanation of excessive neurotoxicity observed with the 3 hour paclitaxel infusion schedule.

Neurotoxicity can present in a number of forms, including peripheral sensory neuropathy, autonomic dysfunction, hearing loss and tinnitus. With several drugs neurotoxicity appears to be related more to *cumulative* dose levels (e. g., cisplatin-induced peripheral neuropathy), while in other situations high *peak* drug concentrations appear to be responsible for the toxicity observed (e. g., cisplatin-induced hearing loss, paclitaxel-associated peripheral neuropathy) (Alberts and Noel 1995; Schiller et al. 1994; Chaudhry et al. 1994; Warner 1995).

At the present time there are no drugs which have been documented to either successfully prevent or treat cancer chemotherapy-induced neurotoxicity (Alberts and Noel 1995; Warner 1995). However, several agents have shown promise, either in clinical studies or in pre-clinical evaluation. Well-designed *randomized* clinical trials will be required to examine these agents in both the prevention and treatment of neurotoxicity before they can be considered for routine use in standard oncologic practice.

For the present, practicing oncologists and clinical cancer investigators must continue to carefully monitor patients receiving potentially neurotoxic agents and discontinue such therapy when necessary to minimize the risk of significant neurotoxic events. The clinical relevance and potential severity of this "non-life threatening" toxicity of antineoplastic therapy cannot be overemphasized.

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