Commentary (Thomas/Greco): Myalgias and Arthralgias Associated With Paclitaxel

Review Article [1] | February 01, 2003
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Despite nearly a decade of paclitaxel’s commercial availability, the best strategy for managing several paclitaxel-related toxicities including myalgia/arthralgia remains to be elucidated. Most available data in the treatment of myalgia/arthralgia have been anecdotal, reported in the form of case studies or within the toxicity results of published paclitaxel-containing clinical trials. Garrison et al have provided a well-written review summarizing what is currently known about the incidence and management of this quality-of-life-impacting toxicity.

Risk Factors

This article provides an in-depth look at potential risk factors in the development of myalgia/arthralgia. Available data suggest a correlation with dose only and not infusion duration, cumulative dosing, or various baseline patient characteristics. Given that the incidence rises with single paclitaxel doses greater than or equal to 135 mg/m$^2$, the decreased incidence and severity seen with weekly dosing, for which doses are lower, is thus easily explained.

Treatment Strategies

The use of nonsteroidal antiinflammatory drugs (NSAIDs), opioid analgesics, corticosteroids, antihistamines, tricyclic antidepressants, intranasal calcitonin (Miacalcin), and gabapentin (Neurontin) are all addressed as potential treatment strategies in this article. While NSAIDs are sited most often in the literature, no randomized trials have evaluated any of these pharmacologic agents after the onset of myalgia/arthralgia.

We have experience with most of these strategies, but we have not formally evaluated any of them and, therefore, cannot recommend any one approach over another. Certainly patients with mild to moderate myalgia/arthralgia are more easily managed than patients with severe myalgia/arthralgia, who may require a combination of agents for adequate relief.

Prevention Strategies

Many of the agents used in treatment have also been employed prophylactically. Although corticosteroids have been used most often in this setting, as mentioned by Garrison et al, this is not an appropriate strategy for weekly dosing.

Glutamine

The authors briefly discuss the use of glutamine as a preventive strategy for paclitaxel-induced myalgia/arthralgia and peripheral neuropathy. We will elaborate further on these data and provide additional data for the use of glutamine here. To begin with, Savarese, Boucher, and Corey reported positive results with prophylactic glutamine in five patients with previous moderate to severe paclitaxel-related myalgia/arthralgia.[1]

In addition, Vahdat et al, reported a reduction of paclitaxel-induced peripheral neuropathy with glutamine in patients receiving high-dose paclitaxel (825 mg/m$^2$ given over 24 hours).[2] In this trial, the first cohort of patients (n = 33) did not receive glutamine, and the second cohort (n = 12)
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The investigators found a significant reduction in the severity of peripheral neuropathy, including less motor weakness, gait deterioration, and interference with activities of daily living, in the glutamine-treated patients. Vahdat et al concluded that randomized, placebo-controlled trials would be needed to assess the impact of glutamine on neuropathy. The encouraging results from the aforementioned case report and from this trial led to the development of more definitive research. Recently, Jacobson et al reported results from a placebo-controlled, double-blinded randomized crossover trial evaluating the effect of glutamine prophylaxis on the prevention of myalgia/arthralgia.[3] Thirty-six patients who had previously experienced myalgia/arthralgia related to paclitaxel were enrolled. Patients were randomized to receive glutamine, 10 g orally three times daily for 5 days, starting the day of chemotherapy or an identical placebo. With the subsequent cycle, patients were crossed over to the alternate treatment. Patients self-evaluated myalgia/arthralgia daily using numeric scales. In addition, a quality-of-life instrument was used, and myalgia/arthralgia was assessed by the physician using National Cancer Institute common toxicity criteria (CTC).

Unfortunately, this trial demonstrated no effect of glutamine on the development or severity of paclitaxel-related myalgia/arthralgia by either patients' daily assessment or physician-reported CTC grade. The mean myalgia/arthralgia grades were similar as well. Patients were asked which of the two blinded treatments they preferred. Some patients had no preference; however, of those who did, 29% preferred the glutamine cycle compared to 33% who preferred the placebo cycle. Jacobson et al concluded that this trial did not suggest a role for oral glutamine in the prevention of paclitaxel-induced toxicities. Despite these results, when we have used prophylactic glutamine in patients who had experienced myalgia/arthralgia with a previous dose of paclitaxel, some have reported a complete absence of or decrease in these symptoms.

**Amifostine**

The authors did not mention the potential usefulness of amifostine (Ethyol), but available data are not promising. Three separate trials have evaluated the cytoprotective effects of amifostine on the incidence and severity of neurotoxicity and/or myalgia/arthralgia in patients treated with paclitaxel. DiPaola et al reported the results of a phase I trial evaluating amifostine and dose-intense paclitaxel in patients with advanced malignancies.[4] A fixed dose of amifostine (910 mg/m²) was administered prior to escalating doses of paclitaxel. No grade 3/4 neurotoxicity or myalgia/arthralgia was seen in 13 cycles of paclitaxel administered at a dose of 310 mg/m². Grade 3 paresthesias were seen in only 2 of 27 cycles at 270 mg/m² and grade 3 myalgia/arthralgia in only 1 of 27. None of the typical amifostine-related toxicities—specifically nausea, vomiting, and hypotension—were seen at a severity grade greater than 2. The authors concluded that pretreatment with amifostine resulted in less than expected neurotoxicity and myalgia/arthralgia with multiple courses of high-dose paclitaxel, and that amifostine-related toxicities may be lessened with the use of standard paclitaxel premedications.

Gelmon et al published the results of a randomized phase II study evaluating paclitaxel, 250 mg/m² given over 3 hours every 3 weeks, with or without pretreatment with amifostine, 910 mg/m²[5]; 20 patients were enrolled in each treatment arm and had neurologic symptoms assessed by self-completed questionnaires as well as standardized neurologic examinations. Changes from baseline were assessed after courses 1, 2, and 3. The results of this trial showed no difference in any measures of neurotoxicity or myalgia/arthralgia with the addition of amifostine. In addition, the lack of amifostine-related toxicities reported in the phase I trial by DiPaola et al was not seen in this trial, as nausea, vomiting, dizziness, hypotension, and sneezing occurred more often among amifostine-treated patients.

The use of amifostine has also been evaluated with the combination of paclitaxel and carboplatin (Paraplatin). Mitchell and Campbell reported results of a phase II trial of amifostine at a dose of 740 mg/m² prior to paclitaxel, 200 mg/m², and carboplatin, AUC 6, in patients with advanced non-small-cell lung cancer.[6] Neurotoxicity was evaluated by physical exam, electrodiagnostic testing, quantitative sensory testing, and symptom assessment. The 19 patients who were enrolled received a total of 60 treatment cycles. Grade 3/4 neurotoxicity occurred in 5 patients (26%), and grade 2 or greater in 13 patients (68%). Grade 3 myalgia occurred in three patients (16%) and grade 2 or greater in nine patients (47%). The authors concluded that amifostine administered at this dose...
and schedule did not have an impact on the prevention of these toxicities.

Conclusions

This review article clearly supports the need for prospective randomized trials to determine the impact, if any, of these various supportive agents on the prevention or treatment of myalgia/arthralgia. With negative data beginning to emerge using strategies once thought promising, perhaps a combination approach should be formally explored.

References:


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