Commentary (Markman): Myalgias and Arthralgias Associated With Paclitaxel

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In this review, Dr. Garrison and her colleagues present a general overview of the development of myalgias and arthralgias associated with taxane chemotherapy. As noted by the authors, these side effects of treatment can be quite distressing, although clearly not life-threatening. Fortunately, only a minority of patients experience such severe symptoms that consideration needs to be given to discontinuing treatment or substantially altering the planned taxane dose and schedule.

Nonsteroidal anti-inflammatory agents have been the mainstay of treatment, although occasionally the pain is of such severity that narcotic analgesia is required. In patients demonstrated to be prone to the development of taxane-induced myalgias and arthralgias, it is reasonable to conclude that prevention will be a more effective management strategy than treatment of existing moderately severe or severe symptoms.

Timing of Side Effects

As noted by Dr. Garrison, the pathophysiology of taxane-induced myalgias and arthralgias remains poorly understood, as does any relationship between this condition and the more persistent, potentially disabling side effect of peripheral neuropathy.[1,2] Of particular interest is the fact that patients do not experience the initial discomfort ("achiness") following each treatment course until 24 to 48 hours after drug delivery. The time course suggests that dexamethasone, which is routinely administered as a component of the prophylactic program designed to prevent taxane-induced hypersensitivity reactions, has either delayed the onset or masked the symptoms of this process. This observation led our group to attempt to employ a low-dose oral prednisone regimen (10 mg twice a day for 5 days beginning 24 hours following the completion of the paclitaxel infusion) in an effort to reduce or eliminate the discomfort in a group of women with gynecologic malignancies (n = 46) who, with the previous paclitaxel cycle, had experienced myalgias and/or arthralgias that were unrelieved by nonsteroidal anti-inflammatory drugs.[3] As anticipated, there were no reported side effects associated with this low-dose steroid regimen, independent of what one might observe in any patient population receiving this cytotoxic drug, either given alone or with a platinum agent (carboplatin [Paraplatin] or cisplatin).

Eighty-five percent of the patients who had experienced unacceptable discomfort during the prior paclitaxel course (most commonly administered at a dose of 175 mg/m²) noted substantial improvement following the prophylactic use of oral prednisone. Some patients continued to require nonsteroidal medications, but the severity of the symptoms was reduced. Confirmation of the clinical utility of this approach was achieved when patients were asked whether they would choose to receive the oral prednisone regimen with a subsequent treatment course, and the almost universal response was "yes." As all individuals treated in this report were female, it remains somewhat uncertain if male patients will respond in a different manner to the oral steroid regimen, although it is difficult to conceive of a biologic reason why there would be any difference.

Emphasis on Prevention

It is important to note the steroids are not being administered to treat existing symptoms, but rather, to prevent their development. Thus, even if a patient is having no discomfort 48 to 72 hours after the completion of paclitaxel, it will likely be important to continue the steroid regimen for the
full 5 days, to minimize the risk that whatever process leads to the myalgias and arthralgias has not run its full course.

Dr. Garrison and her group note that their own use of steroids to prevent myalgias and arthralgias "has been disappointing," although they further state this use is anecdotal. I submit that the generally favorable experience of the 46-patient series noted above—which included women who had previously developed considerable discomfort resulting from paclitaxel-associated myalgias and arthralgias—provides more than "anecdotal" support for the use of this program in appropriately selected individuals.

**Alternative Agents**

Further, Dr. Garrison and colleagues state there is "considerable enthusiasm for gabapentin, glutamine, and, potentially, antihistamines." However, there remains preciously limited information in the peerreviewed medical literature to support the use of any of these agents in this particular clinical setting. As noted by Dr. Garrison, the nonsteroidal management strategies may have particular appeal when delivered in association with a weekly taxane delivery regimen, due to concern over possible adrenal suppression and chronic immunosuppression.

We will await with considerable interest data from well-designed clinical trials to document the utility of these and other pharmaceutical agents, with particular reference to their superiority (efficacy, toxicity, cost-effectiveness) compared to treatment with nonsteroidal anti-inflammatory agents or prophylaxis with low doses of oral corticosteroids.

**References:**

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