Corticosteroids in Advanced Cancer

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Corticosteroids play a vitally important role in the treatment of patients with advanced cancer. While the scientific data, as reviewed by Wooldridge et al, are often slim, most physicians who treat patients with cancer quickly become comfortable with prescribing synthetic glucocorticoids for a variety of indications. Wooldridge et al have provided a much needed synthesis of the medical literature on the use of steroids, both as part of chemotherapeutic treatment for a variety of malignancies and in symptom control.

Steroids and Neuro-Oncology

In his classic textbook, *Neurological Complications of Cancer*, Jerome Posner notes that steroids are "the most widely used drugs in neuro-oncology."[1] However, despite their frequent use, the precise mechanism of action of these agents remains unclear. In the setting of metastatic disease, steroids are thought to exert their action as anti-edema agents by repairing the disruption seen in the blood-brain barrier. Indeed, Dr. Posner suggests that, "many scans [magnetic resonance imaging and computed tomography] do show decreased contrast enhancement with the tumor, suggesting partial restoration of the blood-brain barrier."[1] Steroids may also control brain edema by inhibiting the effect of arachadonic acid on vascular permeability.

In the setting of spinal cord compression, steroids decrease the associated vasogenic edema and thereby substantially improve neurologic function and decrease pain. Although the one available study of high-dose vs low-dose dexamethasone cited in the review by Wooldridge et al did not demonstrate a benefit with the use of a higher dose, compelling animal data and decades of clinical experience at Memorial Sloan-Kettering Cancer Center suggest that patients with acute spinal cord compression should be treated with a 100-mg bolus of dexamethasone followed by a steroid taper while more definitive treatment—usually radiation or chemotherapy—gets underway.[2]

Although tapering the steroid to the lowest effective dose is critical, there are no reports in the medical literature of any deleterious outcomes associated with the administration of a single bolus of 100 mg. Among the available corticosteroids, dexamethasone is used most commonly because of its lack of mineralocorticoid activity and a half-life of greater than 30 hours, which allows for more convenient daily dosing.

The best time to begin other forms of therapy after steroids have been administered is unclear. Given the tissue swelling that may occur with the onset of radiation therapy to the brain, some clinicians recommend treatment with steroids, usually dexamethasone, for a short time (1 to 2 days) prior to beginning a course of radiotherapy. In the treatment of epidural spinal cord compression, there is no evidence that immediate radiotherapy worsens neurologic function.

A rapid taper or abrupt cessation may result in "steroid pseudorheumatism," which is characterized by the onset of acute arthralgias and/or myalgias.[3] Clinicians may avoid this undesirable effect by implementing gradual dose reduction schedules, although side effects due to steroid withdrawal can occur even when steroids are tapered slowly.

Malignant Bone Pain
Bone metastases are the most common cause of cancer-related pain, occurring in 60% to 84% of patients with metastatic cancer.[4] Autopsy studies demonstrate that 85% of patients who die with stage IV breast, prostate, or lung cancer have bone metastases. In an excellent review of the pathophysiology and treatment of malignant bone pain, Mercadante notes, "The presence of pain is not correlated with the type of tumor, location, number and size of metastases, gender, or age of patient." He explains that a metastasis may develop near the primary site (eg, prostate cancer via the valveless paravertebral plexus) or at a more distal location secondary to chemotactic factors responsible for the "osteotropism" of certain malignancies—namely breast, lung, thyroid, kidney, and prostate cancers.[5]

A variety of mechanisms for the bone pain caused by metastatic disease have been suggested, including invasion of the richly innervated periosteum, microfractures of the trabeculae causing bone distortion, mechanical stress, nerve entrapment, and bone destruction/collapse.[6] Recently, a murine model of bone cancer pain has been proposed that demonstrates massive astrocyte hypertrophy without neuronal loss, an increase in the neuronal expression of c-Fos, and an increase in the number of dynorphin-immunoreactive neurons in dorsal horn deep laminae neurons ipsilateral to a limb with cancer.[7] Because these changes have not been found in other murine models of inflammatory or neuropathic pain, Schwei et al suggested that bone cancer pain may have a unique "neurochemical signature."

Treatment of Bone Pain

Anti-inflammatory medications, including corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs) are often successfully used for the treatment of pain secondary to bone metastases.[8] Although there are few randomized double-blind clinical trials examining the role of NSAIDs in the management of metastatic bone pain, an understanding of the pathophysiology of malignant bone pain and the results of meta-analyses of the role of NSAIDs in cancer pain compel many cancer pain specialists to add an anti-inflammatory agent to the daily regimen of many of their patients with malignant bone pain.[9]

For patients with advanced disease whose cardiac, gastrointestinal, or renal comorbid illnesses may limit their ability to receive traditional NSAIDs safely, the COX-2 inhibitors now represent a welcome alternative. There are no data from randomized controlled trials supporting the use of COX-2 inhibitors in the setting of advanced cancer. However, their demonstrated safety and efficacy in other inflammatory pain settings make these agents an important addition to the daily regimen of many patients with malignant bone pain.

The risk of osteoporotic fracture and avascular necrosis associated with long-term steroid use in patients whose bone is already weakened from the spread of metastatic cancer limit their long-term use. However, in the setting of acute, severe cancer pain, a large bolus followed by a taper to the lowest effective dosage can be enormously beneficial. In addition, in patients who are unlikely to survive long enough to develop the well-known complications of systemic steroids, maintaining use of a daily corticosteroid can be helpful not only for analgesia but also for beneficial effects on respiration, appetite, nausea, and mood.

Conclusions

In conclusion, Wooldridge et al have offered a useful synthesis of the existing data on the use of corticosteroids in patients with advanced cancer. Competent clinical practice requires not only a thorough and critical review of the literature, but also an understanding of the relevant molecular mechanisms of action, which, taken together, may form the basis for a rational treatment strategy.

References:


