Corticosteroids in Advanced Cancer

By James E. Wooldridge, MD, Clay M. Anderson, MD, and Michael C. Perry, MD, FACP

Despite the fact that there are only a few controlled trials demonstrating the benefits associated with the use of corticosteroids in specific situations, these agents are administered frequently to patients with advanced cancer. Corticosteroids may be used alone or as adjuvants in combination with other palliative or antineoplastic treatments. For example, corticosteroids may help prevent nausea, vomiting, and hypersensitivity reactions to treatment with chemotherapy or radiation. They are also commonly used as appetite stimulants in patients with advanced cancer. In the adjuvant setting, corticosteroids help to alleviate pain in advanced cancer patients, including specific situations such as back pain related to epidural compression. This article reviews the evidence supporting the use of corticosteroids in a broad range of situations seen in patients with advanced cancer.

Introduction

Corticosteroids are commonly used in the treatment of patients with advanced cancer. However, much of this use stems from the experience of practitioners rather than from data collected in controlled clinical trials. Although little is known about the actual mechanisms by which corticosteroids exert their effects in patients, a substantial amount of evidence supports their monitored use in specific situations. This article will review the available evidence on the use of corticosteroids in advanced cancer, including treatment of refractory malignancies, use as premedication with chemotherapy, and symptom palliation.

Background Information

The most commonly used corticosteroids in the United States include prednisone, prednisolone, methylprednisolone, dexamethasone, and hydrocortisone, all of which were approved by the Food and Drug Administration in the 1950s. There does not appear to be evidence to support the use of one corticosteroid over another in any given situation, although physicians have their preferences.

Corticosteroids exhibit varying glucocorticoid and mineralocorticoid effects. More potent glucocorticoid effects are desirable in inflammatory states, whereas mineralocorticoid effects are needed to treat adrenal insufficiency. Corticosteroids inhibit inflammatory and immune responses, most likely through alteration of cellular transcription and protein synthesis as well as through effects on lipocortins, which inhibit the release of arachidonic acid. The use of corticosteroids in advanced cancer revolves around their glucocorticoid effects, combined with an avoidance of the salt-retaining properties that characterize mineralocorticoids.

That said, it is important to remember that patients previously treated with corticosteroids may have some degree of adrenal suppression and, therefore, may require supplemental corticosteroid therapy during stressful situations. In this setting, mineralocorticoid properties are desired.

Effects of Long-Term Use

Chronic use of corticosteroids causes adrenal suppression and may blunt or prevent normal adrenal response to physiologic stress. To avoid this effect, many cancer patients may receive intermittent doses of steroids as antiemetics to prevent hypersensitivity reactions, or as adjuvants for pain control. Spiegel and colleagues performed adrenocorticotropic hormone (ACTH)-stimulation tests in 14 patients receiving high-dose prednisone for emesis prophylaxis prior to chemotherapy. Adrenal function was suppressed in 13 patients at 24 hours and remained suppressed in 5 patients for more than 1 week.
Investigators at the University of Rochester performed ACTH-stimulation tests in nine women with ovarian cancer before and during chemotherapy in which dexamethasone premedication was used.[5] They noted effects on the hypothalamic-pituitary axis for up to 8 days, but reported no long-term suppression. It is probably not necessary to taper steroids when they are administered in brief, intermittent doses, but adrenal suppression should be considered when patients who have received such treatment present with hypotension and severe illness. The use of replacement-dose steroids in patients with cancer who are undergoing surgery was recently reviewed by Lefor.[6]

The risks associated with corticosteroid use in patients with advanced cancer have been reviewed extensively.[2] Acute side effects include dyspepsia, peptic ulcer disease, insomnia, oral and vaginal candidiasis, anxiety, and glucose intolerance. Side effects from chronic use include development of a cushingoid appearance, weight gain, edema, cataracts, osteoporosis, proximal myopathy, thinning of the skin, infection, and impaired wound healing. Corticosteroids can also lead to neuropsychiatric changes including depression, agitation, and delirium.[6]

It is important, therefore, to carefully weigh the potential benefits of corticosteroid therapy against potential side effects, and to closely monitor the efficacy of therapy. If no improvement is noted, treatment should be adjusted or discontinued.

Corticosteroids as Anticancer Agents

Corticosteroids have been used as anticancer agents since the 1940s,[8] with activity reported in a wide variety of solid tumors, including breast and prostate cancer, and the lymphoid hematologic malignancies. They are commonly found in regimens for acute lymphocytic leukemia, Hodgkin’s and non-Hodgkin’s lymphoma, myeloma, and chronic lymphocytic leukemia. This section will focus on the use of corticosteroids as palliative anticancer treatment once chemotherapeutic options have been exhausted or abandoned.

Multiple Myeloma

Several studies have been reported suggesting a benefit with the use of corticosteroids in refractory multiple myeloma. Alexanian et al reported the use of pulse prednisone therapy in patients with myeloma refractory to melphalan (Alkeran).[9] Prednisone was administered at 60 mg/m\(^2\)/d for 5 of 8 days, for three pulses followed by a 3-week rest, with the cycle repeated. The investigators noted a greater than 50% reduction in tumor mass in 5 of 16 patients, and found that responding patients benefited clinically with less pain, improved performance status, and increased hemoglobin.

Norfolk and Child performed a similar study in 17 patients with relapsed or refractory disease. Patients in this study received prednisolone, 60 mg/m\(^2\)/d for 5 days, followed by a 9-day rest.[10] Fourteen patients completed six cycles of treatment, and 10 had more than a 25% reduction in serum paraprotein or a 50% reduction in urinary light-chain excretion. An overall improvement in quality of life was also noted. Notably, two of the nonresponders demonstrated an improvement in performance status. Median survival for the group was more than 19 months.

In 1991, the Eastern Cooperative Oncology Group reported a pilot study of high-dose, pulsed dexamethasone in patients with relapsed or refractory disease.[11] Patients received dexamethasone, 40 mg/d, 4 days a week for 8 weeks. Of 32 patients enrolled, 13 (40%) achieved objective responses and 28.5% showed improvement in pain or performance status. The study also reported significant toxicity, with 19 patients experiencing side effects assessed as at least grade 2. Median survival was 19 weeks, and the authors suggested that less frequent administration at longer intervals should be considered.

Alexanian also reported on the use of intermittent, high-dose dexamethasone, noting a 27% response rate in patients who did not respond to their prior treatment.[12] The Southwest Oncology Group reported a trial of alternate-day administration of corticosteroids (oral prednisone, 100 mg every other day for 2 weeks, then 50 mg every other day for 10 weeks) in 121 patients with relapsed or refractory myeloma. They measured glucocorticoid receptors from patient samples and found an
improved response, but no change in overall survival among patients with a moderate number of receptors, compared with patients with a low number of receptors. They reported a 10% partial response rate (defined as a 50% to 75% decrease in M-protein), although 81 patients maintained stable disease while enrolled in the study.

Prednisone, as used in this study, was well tolerated and appeared to be associated with response and median survival rates (12 months) similar to those reported with other drug schedules used in myeloma.

Non-Hodgkin’s Lymphoma

In 1996, Newcom reported on the outcome of two patients with refractory, poorly differentiated lymphocytic lymphoma who had been treated with continuous corticosteroids (prednisone, 60 to 100 mg/d).[13] Both patients improved within 3 weeks of the initiation of single-agent prednisone, and both reportedly experienced regression of nodes and organomegaly as well as an improvement in function. However, the patients died 14 and 15 months after initiation of therapy with prednisone.

Breast Cancer

have been used in the primary treatment of breast cancer in elderly women after failure of front-line hormonal therapy.[18] Minton et al followed 91 women aged 65 years and older in whom disease progressed following initial hormonal therapy with estrogens, tamoxifen (Nolvadex), or androgens.[14] A treatment-free period of 1 month was recommended to control for a withdrawal response. The majority of patients received prednisolone, 15 mg daily, and 10 patients received hydrocortisone acetate, 75 mg daily. Objective responses were noted in 13 patients (14%). Another 19 (21%) achieved stable disease for at least 6 months. There was no correlation with any prior response to endocrine therapy, and toxicity was felt to be acceptable. Unfortunately, the authors did not report a clinical benefit as subjectively reported by the patients.

Mercer and colleagues reported a prospective randomized trial of aminoglutethimide (Cytadren, 125 mg twice daily) vs hydrocortisone (20 mg twice daily) in advanced breast cancer.[15] All patients were postmenopausal and had experienced disease progression on tamoxifen. Of 61 patients entered into the trial, 56 were included in the analysis. Three patients who received aminoglutethimide achieved a partial response (11%), while one partial and five complete responses (21%) were reported in the hydrocortisone group. Although this difference was not statistically significant, it does serve as evidence that corticosteroids have activity in breast cancer. The authors did not report on clinical benefit.

Prostate Cancer

Hormone therapy is well established in the treatment of prostate cancer. However, progressive disease after failure of hormone therapy is a difficult problem for patients in this setting. Tannock and colleagues from the Princess Margaret Hospital in Toronto have reported their experience with prednisone in the treatment of hormone-refractory disease.[16] In an informative study, these investigators prospectively treated 37 men with symptomatic bone metastases with 7.5 to 10 mg of prednisone daily. Pain scores were assessed by three different measures at monthly intervals.

An improvement in all three pain scales without an increase in opiate dosages was reported for a minimum of 1 month in 14 (38%) patients. Responses did not correlate with alkaline or acid phosphatase measures, but did appear to correlate with suppression of adrenal androgens. Although the median duration of response was only slightly more than 4 months, the investigators concluded that there was improvement in quality of life with little toxicity or expense. These investigators have now reported on the superiority of the combination of mitoxantrone (Novantrone) and prednisone as palliation for a similar group of patients; however, this therapy was not associated with a survival advantage.[17] Some patients will opt not to receive chemotherapy, although corticosteroids alone may be beneficial.

Sartor and colleagues assessed the effects of prednisone, 10 mg twice daily, on prostate-specific antigen (PSA) in 29 men with progressive, hormone-refractory prostate cancer.[18] Twenty-six of the
patients were symptomatic. PSA levels declined by at least 25% in 14 (48%) of the patients, and 23 of 26 reported an improvement in appetite, weight gain, or pain control. The median progression-free survival was 2 months; however, median overall survival was 12.8 months after initiation of therapy with prednisone. The duration of symptom control and any correlation with PSA measurements were not reported, but would be of interest as patients lived an average of 10 months beyond the development of progressive disease.

**Corticosteroids for Symptom Prevention**

**Nausea and Vomiting**

Many patients with advanced cancer receive treatment with chemotherapy or radiation therapy for palliation of symptoms. Corticosteroids can be used to prevent nausea related to chemotherapy and radiation therapy, and these preventive effects may be enhanced with concurrent use of other antiemetics.

In 1980, Rich et al reported the initial use of methylprednisolone as an antiemetic.[19] This was followed by reports of individual use based on "casual observations."[20] Aapro and Alberts showed positive results with the use of dexamethasone beginning the night before and continuing 48 hours after completion of chemotherapy with cisplatin (Platinol).[21] Cassileth et al performed a randomized, double-blind, crossover trial of premedication with oral dexamethasone as outpatient chemotherapy in patients with breast cancer.[22] They found that nausea and vomiting improved in patients who received chemotherapy cycles containing dexamethasone.

In a double-blind, placebo-controlled trial, Metz et al treated 27 women for prophylaxis of nausea and vomiting with 1 to 2 g of methylprednisolone in divided doses vs placebo.[23] These women received moderate- to high-dose therapy with cisplatin (50 to 118 mg/m²) for ovarian or cervical cancers. They reported total or major protection in 38.5% of cycles using methylprednisolone, compared with 25% in the placebo group (not a significant difference). Notably, half of the placebo patients (7 of 14), compared with only 1 of 13 methylprednisolone-treated patients, dropped out of the study ($P = .02$). This ultimately lowered the power of the study. Investigators were forced to conclude that methylprednisolone alone was not sufficient for prophylaxis against nausea associated with high-dose cisplatin.

Parry and Martin reported a randomized, single-blind study of intravenous (IV) dexamethasone (20 mg) vs placebo (0.9% saline) in patients receiving moderately emetogenic chemotherapy.[24] Significantly less nausea was seen in the treated group at 24 and 48 hours, with 63% of the treated group reporting no nausea, compared with 37% of the placebo group.

Markman et al conducted a randomized double-blind crossover trial that compared dexamethasone (20 mg IV, then 10 mg orally every 6 hours for 24 hours) with prochlorperazine (10 mg IV, then 10 mg orally every 6 hours for 24 hours) in patients being treated with non-cisplatin-containing chemotherapy.[25] They reported significantly less nausea and vomiting with less appetite suppression in patients receiving dexamethasone. Of 42 patients in the study, 29 achieved total antiemetic protection with dexamethasone, compared to 18 with prochlorperazine ($P < .001$).

In a similar study, 25 women with stage II breast cancer treated with intravenous CMF (cyclophosphamide [Cytoxan, Neosar]/methotrexate/ fluorouracil) received nausea prophylaxis with dexamethasone (24 mg in 5 divided doses), metoclopramide (1 mg/kg IV in a single dose), or a combination of the two drugs vs placebo. Dexamethasone, with or without metoclopramide, provided 45.7% to 50% complete protection from emesis (respectively), and was more effective than placebo (12.5%) or metoclopramide (20.8%) alone. Metoclopramide was not significantly better than placebo, and did not improve the efficacy of dexamethasone.

Dexamethasone has also been used in the prevention of radiation-induced emesis. In a placebo-controlled trial, the National Cancer Institute of Canada studied 154 patients who received fractionated radiotherapy to fields that included the upper abdomen for at least five fractions and treated them with 2 mg of oral dexamethasone three times daily.[26] Patients were followed for
control of emesis as well as quality of life. Total prevention of emesis was reported in 54 (72%) of 75 patients receiving dexamethasone vs 37 (49%) of 75 patients receiving placebo ($P = .025$). Using the European Organization for Research and Treatment of Cancer (EORTC) quality-of-life instrument (QLQ-C30+1), patients receiving dexamethasone reported significantly less nausea, vomiting, and loss of appetite, but more insomnia. Global quality-of-life scores were not significantly different.

The authors concluded that dexamethasone at this dosage and with the schedule described above is effective as emesis prophylaxis for patients receiving radiation therapy who are at moderate to high risk of developing emesis. They cautioned against prolonged use of dexamethasone and suggested that future studies should also incorporate 5-HT3-receptor antagonists.

Most clinicians now use 5-HT3-receptor antagonists for nausea and emesis prophylaxis with highly emetogenic chemotherapy. Several studies have suggested the superiority of ondansetron (Zofran) in combination with dexamethasone over ondansetron alone.[27-30] It is interesting to note that ondansetron and dexamethasone appear to be superior to metoclopramide, dexamethasone, and diphenhydramine when used with cisplatin chemotherapy regimens,[31] yet ondansetron alone may be less effective than dexamethasone and metoclopramide in women treated with CMF.[32] Ondansetron and dexamethasone have been reported to display similar efficacy in controlling emesis, although dexamethasone may have proven superior for preventing delayed symptoms.[33]

Similarly, granisetron (Kytril) was as effective as dexamethasone in one study, although the combination was significantly superior to either drug alone.[34] Again, dexamethasone appeared to offer some protection against delayed symptoms. In a subsequent randomized, double-blind placebo controlled study in patients receiving cisplatin chemotherapy, dexamethasone appeared to be as effective as dexamethasone plus granisetron in preventing delayed nausea and vomiting.[35]

Thus, there is sufficient evidence to suggest that dexamethasone as a single agent is as effective as 5-HT3-receptor antagonists and is probably superior for delayed nausea and vomiting. The combination likely represents our most efficacious treatment for the prevention of nausea and vomiting in patients receiving chemotherapy.

**Hypersensitivity**

Corticosteroids have become standard premedications for regimens containing the taxanes. Hypersensitivity reactions from paclitaxel (Taxol) and docetaxel (Taxotere) can be prevented effectively with corticosteroids administered prior to initiating chemotherapy. Initial regimens with paclitaxel incorporated oral dexamethasone the night before and the day of chemotherapy. Paclitaxel can be delivered safely with 10 mg of intravenous dexamethasone 30 to 45 minutes prior to treatment.

Preliminary reports of treatment with weekly paclitaxel suggest that premedication with corticosteroids may be gradually tapered and possibly eliminated.[36] Docetaxel is associated with the development of pleural effusions that can be effectively prevented with oral dexamethasone administered 1 day before and 4 days after treatment.[37] Weekly docetaxel regimens have utilized three doses of dexamethasone.[38]

**Corticosteroids in Supportive Oncology**

**Brain Metastasis**

It is widely accepted standard practice to administer corticosteroids to patients with primary or metastatic brain tumors. It is interesting to note that in spite of this acceptance, there is little evidence establishing the optimal drug, dose, schedule, or duration of treatment. Corticosteroids are typically used as an adjunct to radiation or surgery, and there is evidence that patients without neurologic symptoms can be treated definitively without steroids.[39] An early report suggested improvement in neurologic function with prednisolone.[40] and another report suggested that 16 mg of dexamethasone daily was an acceptable schedule.[41]
In two double-blind, randomized trials of different doses of dexamethasone, 4 mg was found to be as effective as 16 mg with significantly fewer side effects.[42] There is evidence supporting the use of the corticosteroids in the initial treatment of brain metastases; however, patients without symptoms who receive timely definitive therapy may not require corticosteroids. The optimal dose has not been established, but there appear to be no data on dexamethasone dosages above 16 mg daily.

Epidural Metastasis

Corticosteroids are commonly used for the initial treatment of epidural metastasis causing compression of the spinal cord, and guidelines for treatment have been published.[43] The usefulness of corticosteroids in the treatment of epidural metastasis is strongly suggested from work done in animal models. Ushio et al performed elegant studies in a rat model demonstrating that high-dose dexamethasone results in transient improvement of weakness in animals that have been injected with tumor cells near the spine.[44,45] These effects were lost by the fourth day of treatment.

These findings were translated into the clinic using a protocol of high-dose dexamethasone (100 mg IV bolus, followed by 96 mg/d orally in divided doses) with immediate initiation of external-beam radiation therapy.[46] After the first day, 39 of 61 evaluable patients (64%) reported a reduction in pain. Although the contribution of dexamethasone to this response is clouded by the immediate use of radiation, the authors felt that this degree of immediate improvement was higher than in their previous experience. In addition, six patients had complete pain relief after use of dexamethasone alone. The same group later reported experiments suggesting a dose-response relationship in favor of high-dose dexamethasone in the treatment of epidural compression.[47]

The value of corticosteroid treatment of epidural metastatic spinal cord compression was further supported by a report from Sorensen and colleagues.[48] They performed a randomized, single-blind study of high-dose dexamethasone (96 mg IV, followed by 96 mg/d orally for 3 days, then tapered over 10 days) vs no corticosteroids in patients with confirmed cord compression who had been treated with radiation.

Of 57 eligible patients, 27 were treated with dexamethasone and 30 received no corticosteroids. Patients were stratified by primary tumor and ambulatory status. A significantly greater number of patients were ambulatory at 6 months in the dexamethasone group (59% vs 33%, \( P = .05 \)), although not at 1 year (30% vs 20%, \( P = .40 \)). Patients with breast cancer treated with dexamethasone appeared to derive the greatest benefit. Median survival was identical in both groups at 6 months.

The optimal initial dose of corticosteroids in metastatic spinal cord compression remains to be determined. Vecht et al reported a randomized, double-blind trial of intravenous dexamethasone with an initial high-dose (100 mg) vs low-dose (10 mg) bolus followed by 16 mg/d orally.[49] Eligible patients had to have an abnormal myelogram and were stratified according to histology (lymphoma or carcinoma). Of the 37 patients enrolled, 22 were treated with high-dose dexamethasone and 15 were treated in the low-dose arm. All patients received external-beam radiation therapy within 12 hours of therapy; however, pain scores for the group were significantly decreased at 3 hours.

There was no difference detected with respect to reduction in pain or neurologic function. The authors recommended 10 mg of intravenous dexamethasone as initial therapy in the treatment of patients with epidural compression caused by metastatic disease. Other authors continue to recommend high-dose corticosteroids, particularly in patients with profound neurologic dysfunction.[50,51] There is also evidence that patients without neurologic dysfunction can proceed to radiation without receiving corticosteroids.[52]

**Corticosteroids for Palliative Care**

Physicians often use corticosteroids for the treatment of cancer patients facing the end of life. Moertel and colleagues from the Mayo Clinic reported the first controlled study of corticosteroids in terminally ill patients with cancer.[53] They randomized patients with advanced gastrointestinal
cancers to dexamethasone or placebo, and noted significant improvement in both strength and appetite among patients receiving dexamethasone.

Bruera and colleagues performed a randomized, double-blind crossover trial of methylprednisolone in terminally ill patients with cancer to determine the effects on pain, depression, appetite, and activity.[54] Included in the study were 40 patients with a variety of primary tumor sites who had "failed" multiple anticancer treatments. They received only opiate analgesics and had no contraindications to treatment with steroids.

These patients were randomized to methylprednisolone (16 mg orally twice daily) or placebo on days 1 to 5 followed by a 2-day rest, then crossed over on days 8 to 12, followed by another 2-day rest. After the 14-day double-blind phase was completed, all patients received 32 mg of methylprednisolone for 20 days. Notably, pain scores improved, appetite and activity increased, depression and analgesic use decreased, and patients requested methylprednisolone over placebo. No significant toxicity was noted, and the authors concluded that methylprednisolone improved the comfort level of patients with cancer.

Hanks et al looked at corticosteroid use in terminal cancer patients by performing a prospective study in patients admitted to an inpatient hospice unit.[55] Physicians prescribing steroids for patients in the unit noted the reason, and assessed them for response. Patients received prednisolone, 10 to 30 mg followed by 5 to 20 mg/d, or dexamethasone, 4 to 16 mg followed by 0.5 mg to 4 mg/d every other day. The most common uses included nerve compression, raised intracranial pressure, chemotherapy, airway obstruction, and nerve compression.

Of the 373 patients studied, 75 received corticosteroids for "nonspecific" uses. The most common side effects with either agent were thrush, fluid retention, and moon facies. The median duration of treatment was 4 to 8 weeks. Response rates greater than 30% were achieved when corticosteroids were used for nerve compression, chemotherapy, raised intracranial pressure, airway obstruction, metastatic arthralgias, and nonspecific reasons. The authors concluded that corticosteroids were valuable for symptom management, and overall, 40% of patients appeared to respond.

A retrospective review of the use of corticosteroids in terminally ill patients was reported by Needham et al.[56] Records of 100 consecutive patients admitted to hospice were reviewed for use of steroids, indications, and response, and 33 patients were found to have prior or present prescriptions for corticosteroids. Of those 33 patients, 20 had been taking corticosteroids for more than 1 month, and only 8 out of 28 (who were able to answer questions) reported benefits from the corticosteroids. Approximately, 15 patients did not know why they were taking corticosteroids, and 4 had severe side effects. Only 8 patients knew not to stop using steroids abruptly.

The authors suggest that the use of steroids should be accompanied by a clear goal and be monitored for response, and that the dose should be adjusted accordingly. They suggested that the drug should be stopped after 1 week if no response is noted, and if the patient improves, the corticosteroids should be adjusted to the lowest beneficial dose. In an accompanying editorial, Twycross suggests starting corticosteroids at a higher dose to prevent missing a beneficial effect, and then adjusting the dose as necessary.[57] He incisively notes, "If they are not working, stop them."

Pain

As previously discussed, pain relief is often achieved when corticosteroids are used for other indications. Corticosteroids are also used as adjuvants to opiate pain medications in many situations, mostly in the terminal phases of cancer. Their use for this indication is well documented in the medical literature, as reviewed by Watanabe and Bruera.[58] Again, drug, dose, route, and schedule are not standardized. Dexamethasone, prednisone, and prednisolone are commonly used for this indication.

Cancer Cachexia

Weight loss and anorexia are common problems in patients with advanced cancer. This topic was
reviewed by Bruera in this journal in 1992.[59] In Moertel’s study of dexamethasone vs placebo in advanced gastrointestinal cancer, an improvement in appetite was noted in the dexamethasone arm; however, treatment did not result in weight gain. Bruera reported improved appetite with methylprednisolone.[54] Willcox et al reported improvement in appetite without weight gain in cancer patients using prednisolone.[60] Unfortunately, these effects are short-lived, and other agents may be more efficacious.[61,62]

Two studies have investigated weight loss and anorexia by comparing corticosteroids to megesterol acetate, a commonly used appetite stimulant in patients with cancer cachexia. Lai et al compared oral administration of megesterol (40 mg four times daily), prednisolone (10 mg three times daily), and placebo (1 tablet three times daily) in 52 patients experiencing anorexia during external-beam radiation to the pelvis.[63] During the 21-day trial, megesterol proved significantly better than placebo, but not superior to prednisolone. Prednisolone did not significantly improve appetite over placebo, but was significantly better in preventing further loss of appetite. Performance status and well-being were said to have improved; however, this study could have benefited from blinding and altered dosing schedules.

Loprinzi and colleagues at the Mayo Clinic also tested this hypothesis by comparing dexamethasone (0.75 mg four times daily) with megesterol (800 mg daily) and fluoxymesterone (10 mg twice daily). Responses with dexamethasone were equivalent to those reported with megesterol, with the major differences occurring in side-effect profiles and cost. Trends were noted, however, suggesting the superiority of megesterol. Even though dexamethasone did not produce significantly greater side effects than megesterol, a higher rate of treatment discontinuation was seen with dexamethasone. Treatment with megesterol, however, resulted in a slightly higher rate of venous thrombosis.

The authors provided a stimulating discussion about whether or not cancer cachexia should be treated at all, and if so, at what cost. They point out that dexamethasone costs far less than a dollar a day, or up to 60-fold less than megesterol. Even if improved dosing were to have reduced costs, the cost analysis by Loprinzi et al did not include the excess cost of treating venous thrombosis. It is, therefore, important to assess the particular clinical situation before choosing one agent over the other. Dexamethasone may be the preferred agent for short-term use in terminally ill patients, for whom corticosteroids may provide other palliative benefits.

Hypercalcemia

corticosteroids have historically been used for the treatment of hypercalcemia, although their use in malignant hypercalcemia appears most beneficial in cancers responsive to corticosteroids, such as myeloma. With the development of bisphosphonates, corticosteroid use has become less important for the treatment of this complication. Initial symptomatic treatment, particularly in volume-depleted patients, includes the administration of normal saline.

Percival and colleagues conducted a comparative trial of saline and furosemide, with and without prednisolone (20 to 60 mg/d).[64] There was no difference in outcome between the groups, and the investigators concluded that corticosteroids were ineffective in the treatment of hypercalcemia related to solid tumors. This trial was limited in that it was apparently not a randomized trial, calcium levels were adjusted for albumin (rather than using a more precise measure), tumor types and corticosteroid dosages varied, and statistical methods were not detailed.

Another randomized trial of normal saline and furosemide, with and without methylprednisolone (25 mg po tid), was reported by Kristensen et al in 1992.[65] Thirty women with metastatic breast cancer were evenly divided between treatments, and significant decreases in ionized calcium were noted in each group, with the greatest differences seen in those receiving methylprednisolone. Furthermore, seven patients (47%) treated with methylprednisolone achieved normal ionized calcium levels, while none of the control group normalized.

Although there was no survival advantage for either arm, the data indicate that corticosteroids are effective in the treatment of hypercalcemia—at least in women with breast cancer—and may be useful adjuncts to bisphosphonates, which require several days of treatment to lower calcium levels. This trial was not weakened by design problems similar to those in the prior report, in that the
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patient population and treatment doses were similar, precise measures were utilized, and statistical methods were provided.

Chemotherapy-Induced Lung Toxicity

Several chemotherapeutic agents are known to predispose patients to pulmonary toxicity, particularly bleomycin (Blenoxane). This may occur long after the chemotherapy was received, and in the case of bleomycin, can be activated by the administration of supplemental oxygen. Several reports suggest that symptoms of pulmonary toxicity as a result of treatment with bleomycin,[66-68] mitomycin (Mutamycin),[69] or gemcitabine (Gemzar)[70] can be improved with the use of corticosteroids.

Obstructive Renal Failure

Abdominal and pelvic cancers frequently cause ureteral obstruction. Flombaum et al reported two cases in which this complication was relieved with high-dose methylprednisolone (500 to 1,000 mg IV).[71] In each case, corticosteroid treatment resulted in improved in the output of urine.

Ascites

A provocative trial of triamcinolone for the treatment of malignant ascites was recently reported.[72] In this investigation, 15 prospectively enrolled patients were treated with large-volume paracentesis followed by the intraperitoneal instillation of triamcinolone hexacetonide (Aristospan), 10 mg/kg, and then by 10 mL of sterile normal saline flush.

The interval between treatment and subsequent paracentesis was 17.5 days, compared with pretreatment intervals averaging 9.5 days. Individual measures of general well-being, appearance, and distention improved significantly, as did mean symptom scores. Pre- and posttreatment paracentesis volumes were similar, and patients with low serum ascites-albumin gradients appeared to benefit most. This approach to palliation of this difficult problem deserves further study.

Superior Vena Cava Syndrome

Corticosteroids are occasionally used for initial symptomatic relief of superior vena cava obstruction related to malignancy, but few data exist regarding the efficacy of corticosteroids for this indication.[73]

Mucositis

Corticosteroids are common components of institutional "special" or "magic" mouthwashes for the treatment of oral mucositis. Rothwell and Spektor evaluated a cocktail of hydrocortisone, tetracycline, nystatin, and diphenhydramine, four times daily, in patients receiving radiation to the head and neck.[74] Treatment was administered in a blinded fashion to 12 randomized patients. The control group comprised 7 patients, and 5 received treatment. Results of clinical dental exams and symptom scores favored treatment with the cocktail. Although the trial was statistically underpowered to determine a difference, the data appear to suggest a benefit, and further investigation is warranted.

Leborgne et al took a slightly different approach, and performed a randomized double-blind trial of oral prednisone (40 mg/d) vs placebo in patients receiving radiation for head and neck malignancies.[75] No difference in the development of mucositis was detected, but a trend toward fewer treatment interruptions was noted. However, researchers did not specifically note whether treatment delays were due to neutropenia, emesis, mucositis, or other factors.

Thus, it is unclear whether the reduction in treatment delays was the result of corticosteroid-induced leukocytosis, improved nausea control, or effects on mucositis. The authors did not comment on the incidence of nausea in the study, but as previously discussed, corticosteroids may improve radiation-induced nausea. Thus, it would be helpful if future studies in this area also addressed potentially confounding symptoms.
Dyspnea/Lymphangitic Tumor Spread

Another oncologic scenario in which corticosteroids are occasionally used is the palliation of aggressive "inflammatory" tumor progression such as lymphangitic spread of tumor in the lungs.[76] This problem is commonly seen in patients with breast cancer, lung cancer, or relapsed lymphoma. Our experience suggests that corticosteroids produce a clinical benefit in this setting, whether they are used alone for comfort or as part of aggressive anticancer therapy.

Summary

Corticosteroids are useful agents in the treatment of patients with advanced, refractory cancer. Although few well-designed trials exist to definitively outline indications for treatment and dosages to be used, there is sufficient evidence to support their use in the palliation of symptoms related to advanced cancer. That said, responses may be brief, and consideration should be given to tapering them when efficacy is marginal or toxicity outweighs the benefit.

As with any cancer therapy, when the "art of medicine" leads us to a trial of corticosteroids, we should remember to provide an appropriate explanation to the patient and family, including a reasonable assessment of response and toxicity.

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