Glucocorticoids in clinical oncology

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■ Glucocorticoids have been used in clinical oncology for more than three decades. Their anti-inflammatory action plays a major role in their clinical applications in oncology. The incidence and severity of side effects depend on the total dose and the duration of therapy, but optimal dosages for these drugs have not been determined. Little is known about other risk factors for toxicity. Prednisone and dexamethasone, the two most commonly used drugs, are well absorbed orally and share quantitatively similar pharmacokinetic values. No definite relationship is known between the glucocorticoid blood level (total and unbound concentration) and therapeutic effect. Glucocorticoids play a major role in the treatment of lymphoproliferative disorders and breast cancer, and they often succeed in palliating common symptoms in advanced cancer.

□ INDEX TERMS: GLUCOCORTICOIDS; GLUCOCORTICOIDS, SYNTHETIC; PREDNISONE; DEXAMETHASONE; NEOPLASMS; PALLIATIVE TREATMENT
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THE CLINICAL VALUE of glucocorticoid drugs (GCs) has been established by 30 years of experience in cancer management. However, their role in oncology is based largely on early uncontrolled trials and experience from empirical use. The value of corticosteroid drugs in treating tumors began to be revealed in 1943, when they were found to have a lympholytic effect in mice.[1,2] Shortly thereafter, they were shown to cause regression of lymphoid tumors in humans,[3,4] and in the late 1940s they were introduced into clinical practice. Immediately upon becoming available for general clinical use in 1948, adrenocorticotropic hormone was tested in cancer patients. Dramatic symptomatic improvements were reported in several small studies in solid tumors.[5]

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Today, GCs are used in treating a variety of oncological disorders (*Table 1*). This review explores the rationale for their current use in clinical oncology.

CLINICAL PHARMACOLOGY

GC receptors are present in every cell type except nonnucleated red blood cells.[6] GCs have a proven direct antitumor effect, especially against lymphoproliferative tumors and steroid-responsive breast cancer.[6–9] Their beneficial effect in patients with primary or secondary brain tumors is believed to result primarily from reduction of cerebral edema. Leukemic cells do not preferentially accumulate prednisolone,[10] but they are more sensitive to the cytolytic effects of GCs than normal cells.

GCs are also effective in alleviating pain associated with bony metastasis. Focal metastatic bony lesions produce prostaglandins, which cause focal osteolysis and lower the peripheral pain threshold by sensitizing free nerve endings.[11] GCs inhibit the synthesis and

TABLE 1
USES OF GLUCOCORTICOIDS IN CLINICAL ONCOLOGY

- Management of primary disease
  - Hematologica malignancy
    - Acute lymphoblastic leukemia
    - Chronic lymphocytic leukemia
    - Hodgkin's disease
    - Non-Hodgkin's lymphoma
    - Multiple Myeloma
  - Solid tumors
    - Breast
    - Prostate
- Management of secondary disease manifestations
  - Neurologic
    - Cerebral metastases
    - Cerebral edema
    - Epidural metastases (with or without spinal cord compression)
    - Plexopathy (brachial, lumbar, sacral)
    - Carcinomatous meningitis
  - Respiratory
    - Lymphangitis carcinomatosa
    - Stridor (tracheal or bronchial obstruction)
    - Superior vena cava syndrome
  - Musculoskeletal
    - Bone metastases
    - Metastatic arthralgia
    - Hypertrophic pulmonary Osteoarthropathy
  - Metabolic
    - Hypercalcemia
    - Adrenal failure
    - Carcinoid syndrome
  - Gastrointestinal
    - Large bowel obstruction
    - Fungating rectal tumors
    - Liver metastases
  - Symptom treatment
    - Fever
    - Anorexia
    - Mood
    - Weakness
    - Cough
    - Itching
  - Miscellaneous
    - Lymphedema
    - Tumor masses (retroperitoneal, pelvic, mediastinal)
- Management of iatrogenic disease
  - Chemotherapy
    - Pulmonary toxicity
    - Antiemetic prophylaxis
    - Chemotherapy-related extravasation
  - Radiation therapy
    - Radiation plexopathy
    - Tissue injury
    - Pulmonary toxicity

release of prostaglandins and are thought to relieve the pain of nerve compression and infiltration by reducing perineural edema.[12,13]

GCs are also useful as a "co-analgesic" for treatment of pain associated with large tumor masses within a relatively confined space, eg, the pelvis. By reducing edema, GCs reduce the total tumor mass, depressurizing the neighboring veins and lymphatic vessels.[12]

GCs are often effective in reducing bone resorption due to multiple myeloma, lymphoma, and breast cancer. In malignancy-related hypercalcemia, increased osteoclastic activity leads to increased net flux of calcium from the skeleton into the extracellular fluid.[14] GCs counteract this, presumably through direct oncolytic effects and by interfering with tumor-induced production of osteoclast-stimulating products (osteoclast-activity factor and prostaglandins).[15,16] GCs are ineffective in reversing hypercalcemia mediated by excessive parathyroid hormone.[16]

Prednisone, prednisolone, dexamethasone: pharmacokinetics

Prednisone is a pro-drug which is extensively and rapidly converted to prednisolone in first-pass metabolism by the liver. Both prednisone and prednisolone are rapidly absorbed after oral administration.[17,18] Approximately 80% of prednisone is absorbed and converted to prednisolone.[18] Food delays the peaking of both prednisone and prednisolone levels without affecting overall bioavailability. The plasma half-life of prednisone is slightly longer than that of prednisolone (*Table 2*).[20]

Two protein fractions, transcortin (corticosteroid-binding globulin) and albumin, account for GC binding. Normally, more than 90% of prednisolone is reversibly bound to plasma protein. Patients with hypoalbuminemia (serum albumin <2.5 gm/dL) experience more side effects than others, due to the increased fraction of physiologically active, unbound, free steroid.[21]

Dexamethasone is also well absorbed (about 80% of oral dose), highly metabolized, and has pharmacokinetic values that are quantitatively similar to those of prednisolone.[22,23] The plasma half-life of dexamethasone is around 3 hours.[22] The drug clearance and half-life do not appear to be dose-dependent over a 40-fold dose range.[23,24]

Drug interactions

Pharmacokinetic interactions with hepatic microsomal enzyme-inducing agents (such as barbiturates, phenytoin, and rifampin) and with other GCs leads to accelerated clearance of GCs.[18,20] Consequently, the dosages of corticosteroid drugs need to be increased during concurrent administration.[25–27]

Oral contraceptive pills increase transcortin levels and so decrease both clearance and volume of distribu-

TABLE 2
GLUCOCORTICOID EQUIVALENCIES

Glucocorticoid	Relative anti-inflammatory potency	Relative mineralocorticoid potency	Half-life Plasma (minutes)	Half-life Biological* (hours)	Route of administration	Approximate equivalent anti-inflammatory dose (mg)	Average cost per dose
Short-acting							
Cortisone	0.8	2	30	8-12	PO/IM	25	$0.41
Hydrocortisone	1	2	80-112	8-12	PO	20	2.35
					IM/IV		0.67
Intermediate-acting							
Prednisone	4	1	200-230	18-36	PO	5	0.06
Prednisolone	4	1	115-212	18-36	PO	5	0.08
					IV/IM		1.39
Methylprednisolone	5	0	78-188	18-36	PO	4	0.38
					IV		0.20
Triamcinolone	5	0	200+	18-36	PO	4	0.97
					IM		0.54
Long-acting							
Dexamethasone	25-30	0	110-210	36-54	PO	0.75	0.43
					IV		2.96
Betamethasone	25	0	300+	36-54	PO	0.6-0.75	0.76
					IV		0.70

Modified from *Drug Facts and Comparisons*.[19]
PO = orally; IV = intravenously; IM = intramuscularly.
*Biological half-life = duration of action.

tion of prednisolone.[28] GCs antagonize the hypoprothrombinemic effects of oral anticoagulants; therefore, their use may require increasing the amount of oral anticoagulants taken.[29] Due to their vascular effects, concomitant GC administration with anticoagulants may increase the risk of hemorrhage in some patients.[30] Concomitant use of GCs with antidiabetic drugs can alter diabetic control, due to the intrinsic hyperglycemic activity of GCs. GCs may enhance the potassium wasting effect of amphotericin-B.[31,32] Similarly, use of GCs with a loop diuretic (furosemide) may result in excessive potassium loss via the renal tubules, leading to significant hypokalemia.

GCs can enhance the hepatic metabolism and increase renal excretion of isoniazid, decreasing its antitubercular effectiveness.[25] Little information is available about drug interactions between GCs and nonsteroidal anti-inflammatory drugs. However, as both have potential ulcerogenic effects on the gastric mucosa, concurrent administration may increase the incidence or severity of gastrointestinal ulceration and hemorrhage.

Drug selection

The choice of GCs in the practice of clinical oncology is arbitrary. Among the available GCs, no agent possesses any property that would lead the clinician to prefer it over the rest. Except for the difference in milligram-per-milligram anti-inflammatory potency (*Table 2*), there appears to be little difference between them in terms of pharmacologic activity.

Cortisone, prednisone, prednisolone, and dexamethasone are probably the four most commonly used GC drugs. Except in adrenal insufficiency, hydrocortisone is unsuitable for long-term therapy because of its mineralocorticoid effects. Dexamethasone is favored for treating raised intracranial pressure and spinal cord compression because of its minimal salt-retaining properties and relative potency compared with other GCs. Prednisone and dexamethasone appear to be the main agents used in oncological practice in North America, although an objective basis for this practice is lacking. Hydrocortisone and prednisolone are preferred in patients with hepatic insufficiency. Triamcinolone may cause severe muscle wasting, anorexia, and depression, especially at higher doses,[33] and should be avoided.

DISEASE-SPECIFIC INDICATIONS

Acute lymphoblastic leukemia

In acute lymphoblastic leukemia, the agent chosen for combination chemotherapy should have cytolytic action selective for lymphoblasts. Its action should be cell-cycle-nonspecific and relatively nontoxic to normal marrow elements. Prednisone fulfills these requirements and is an essential component of both induction and maintenance chemotherapy of acute lymphoblastic leukemia.[34-37]

Several important observations were made with

regard to treatment of acute lymphoblastic leukemia during the early "single-drug" era. As a single agent, prednisone in daily therapy (which is superior to an intermittent or every-other-day schedule in inducing remission) produces a complete remission in 45% to 65% of previously untreated patients.[38] The reinduction rate falls to about 25% in relapsed disease retreated with prednisone.[39] Used as a single agent, GCs are better at inducing than maintaining remission.[38,39]

Several agents other than prednisone (vincristine, L-asparaginase, and anthracyclines) are also selectively toxic to lymphoblasts. In modern therapy in the induction phase, prednisone (40 to 100 mg/m^2/day) is combined with vincristine and a third agent, either L-asparaginase or an anthracycline.[34] Such combination regimens induce complete remission in approximately 90% of children and in 60% to 80% of adults.[34,35] Curiously, even though GCs enter the spinal fluid with relative ease after oral administration, they are not effective in treating meningeal leukemia.[40] Hydrocortisone has been used intrathecally in combination with methotrexate and cytarabine in treating meningeal acute lymphoblastic leukemia and lymphoma.[41] It is not known whether GCs in combination with cytotoxic drugs offer any advantage over a cytotoxic drug alone.

Chronic lymphocytic leukemia

GCs reduce the tumor burden in chronic lymphocytic leukemia by causing lysis of the lymphoid tissue. Virtually all patients given prednisone 50 to 100 mg daily show prompt symptomatic improvement associated with rapid reduction in the size of the liver, spleen, and lymph nodes.[42,43] When given without an alkylating agent, GCs induce transient paradoxical leukemic lymphocytosis due to compartmental shift of lymphocytes from tissues to blood.[42,44] This is not seen when an alkylator is used with prednisone.

Symptoms or cytopenias are indications for GC treatment in patients with chronic lymphocytic leukemia. A suitable, safe regimen is a combination of chlorambucil and prednisone given daily until a clinical and hematologic response is seen—usually in 4 to 8 weeks.[42–44] Hematologic responses should be closely monitored during therapy. Chronic lymphocytic leukemia that resists treatment with alkylating agents is a specific indication for GC therapy, as is chronic lymphocytic leukemia associated with or presenting with autoimmune hemolytic anemia or thrombocytopenic purpura. In these situations, GCs should be given initially in high doses (prednisone 60 to 100 mg), with a rapid reduction in the dose once a stable response has been obtained. The role of GCs in managing variants of chronic lymphocytic leukemia such as hairy-cell leukemia and prolymphocytic leukemia is less well defined.[45]

Multiple myeloma

Alkylating agents, along with prednisone and radiotherapy, are the cornerstones of therapy for myeloma. Steroids used alone appear to have a modest antitumor effect in multiple myeloma; however, in 1969, Alexanian et al showed that adding prednisone to intermittent high-dose melphalan improves the response rate of previously untreated multiple myeloma from 35% to 73%.[46] The combination of alkylating agents (melphalan, cyclophosphamide, carmustine, or chlorambucil) with prednisone has remained the standard first-line therapy for most patients with multiple myeloma.

In 1984, Alexanian designed a new combination chemotherapy regimen for patients with resistant multiple myeloma. It incorporates intermittently administered, very high doses of dexamethasone (40 mg/day for 4 days) with a continuous 96-hour infusion of doxorubicin and vincristine called "VAD." VAD evoked a response rate of 70% in patients with resistant myeloma.[47,48] Subsequently, VAD was compared with high-dose intermittent dexamethasone used alone in relapsed and refractory multiple myeloma. In refractory disease, both regimens produced similar response rates. However, in disease relapses, the VAD regimen was superior, producing response rates of 65%, vs 21% with dexamethasone.[49]

Hodgkin's disease

In spite of extensive experience, the real place of GCs in combination chemotherapy of Hodgkin's disease has not been clarified. The most successful and widely employed combination program uses mechlorethamine, vincristine, procarbazine, and prednisone (MOPP). MOPP achieves complete remission in 80% of patients in advanced disease (stages III and IV).[50,51] In the original program, prednisone was given only during the first and fourth cycles of the six-cycle course. The British National Lymphoma Investigation Group prospectively compared MOPP with MOP (MOPP without prednisone) in stage IV Hodgkin's disease and found MOPP to be superior in achieving complete remission.[52] However, a retrospective analysis by the Stanford group did not confirm the importance of the GCs.[53]

Non-Hodgkin's lymphoma

GCs have a place in many combination chemotherapy regimens for aggressive non-Hodgkin's lymphoma; the commonly used combinations are summarized in *Table 3*. As a single agent, they are used in treating indolent, low grade, and good prognosis non-Hodgkin's lymphoma.

Breast and prostate cancer

The role of GCs as a single agent in metastatic breast cancer is controversial. Using high doses (equivalent to 100 to 400 mg/day of cortisone) in patients with metastatic disease, Stoll et al[61] reported a response rate of about 11%, while Talley et al[62] reported a response rate of about 22%. GCs seem particularly helpful in palliating advanced breast cancer in elderly women. Modest daily doses (15 mg) of prednisone controlled metastatic disease for about 12 months in 35% of 91 elderly women (age 65 and over).[63] Adding prednisone to a regimen of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) in metastatic breast cancer delays relapse and increases overall survival, as compared with CMF therapy alone.[64] This also allows larger doses of CMF to be given.[64]

The combined action of prednisone and CMF suggests that the actual action of GCs in breast cancer treatment may be to improve patient tolerance to cytotoxic drugs. The Ludwig Breast Cancer Study Group found that both adjuvant chemo-endocrine and endocrine therapy are superior to mastectomy alone in prolonging the disease-free interval in patients with operable stage II disease.[65] In endocrine therapy, low-dose prednisone (7.5 mg/day continuously) was combined with tamoxifen (10 mg twice a day orally).

Medical adrenalectomy with aminoglutethimide removes the adrenal source of estrogen and is a valuable second- or third-line hormonal treatment for relapsed advanced mammary cancer in postmenopausal women. Hydrocortisone used with aminoglutethimide physiologically replaces both GCs and mineralocorticoids.[66]

Aminoglutethimide combined with hydrocortisone is reported to effectively palliate pain in some patients with advanced hormone-resistant prostate cancer.[67] Apart from disseminated breast and prostate cancer, GCs have no other role in the treatment of solid tumors. Further controlled prospective studies to clarify the role of GCs in breast cancer seem justified.

TABLE 3
GLUCOCORTICOIDS IN COMBINATION CHEMOTHERAPY FOR LYMPHOMA

Abbreviation	Drug combination	References
CHOP	Cyclophosphamide, doxorubicin, vincristine, prednisone	54
BACOP	Bleomycin, doxorubicin, cyclophosphamide, vincristine, prednisone	55
ProMACE	Cyclophosphamide, adriamycin, VP-16, methotrexate, prednisone	56
COP-BLAM	Cyclophosphamide, vincristine, doxorubicin, prednisone, procarbazine, bleomycin	57
MACOP-B	Methotrexate, doxorubicin, cyclophosphamide, vincristine, bleomycin, prednisone	58
MVPP	Nitrogen mustard, vinblastine, procarbazine, prednisone	59
BCVPP	Carmustine, cyclophosphamide, vinblastine, procarbazine, prednisone	60
MOPP	Nitrogen mustard, vincristine, procarbazine, prednisone	50,51

GENERAL INDICATIONS

Neurological deficit

GCs are of vital and unquestioned value in treating brain and epidural metastases. Dexamethasone rapidly improves or stabilizes neurological deficit until definitive treatment (surgery or radiotherapy) is underway. GCs are also recommended during the perioperative period in patients undergoing brain or spinal cord surgery.

A starting dose of 16 mg/day (4 mg every 6 hours) of dexamethasone (or equivalent GC preparation) was first advocated over 25 years ago[68] and is still considered the standard initial treatment. Once the neurological deficit stabilizes and definitive therapy is started, the dose should be tapered. Dexamethasone treatment should not continue more than 14 to 21 days (including taper).[69] Patients showing progression in neurological deficit should have their dose escalated to a maximum of 100 mg/day (25 mg every 6 hours).[70] If a 5- to 7-day dexamethasone trial at 100 mg/day fails to bring about any neurological improvement, the dose should then be tapered to the lowest level that will maintain stable neurological function.

Patchell and Posner[71] selected the initial dose of dexamethasone in patients with epidural spinal metastases according to the degree of myelographic block. Patients with >80% block received 100 mg of dexamethasone intravenously followed by 24 mg/day

(6 mg every 6 hours). Patients with <80% spinal block received a standard regimen of 16 mg/day.[71,72] The high-dose regimen was superior in quick, substantial pain relief within 24 hours in 64%.[72] Similar data regarding pain control are unavailable for the standard-dose regimen. In most patients, GCs controlled symptoms quickly without affecting the overall neurological outcome.

Because of the potential for serious toxicity, long-term use of GCs is discouraged when the neurological deficit does not respond to GC therapy. Data related to side effects indicates that the total duration and amount of GCs, rather than the starting dose, are most important in initiating serious toxicities.[73]

Another indication for GC use is pain, often severe, from tumor- or radiation-induced plexopathy. In these situations GCs often reduce pain and ameliorate other neurological manifestations.[74] Dexamethasone is also commonly used for palliation in leptomeningeal carcinomatosis.[74,75]

Relief of respiratory symptoms

Lymphangitis carcinomatosa is a poorly defined entity which is often diagnosed on clinical grounds. There are anecdotal reports that dyspnea secondary to lymphangitis carcinomatosa can be ameliorated by GCs. Initially, prednisone should be used in high doses (60 to 100 mg/day). Upon subjective or objective improvement, the dose should be reduced rapidly to a minimum maintenance level. Unfortunately, the benefits of GCs may be short, lasting only for a few weeks. In the presence of a treatable malignancy such as breast cancer or lymphoma, chemotherapy should be given priority but should be used along with GCs in this life-threatening situation.[76]

Acute upper-airway obstruction due to direct tumor growth into the lumen or from extrinsic compression is often seen with cancer of the thyroid, lung, or esophagus.[76] A rapidly growing mediastinal mass can cause significant tracheal compression. GCs, when used alone or in conjunction with radiotherapy, often achieve gratifying results in reducing respiratory distress from airway obstruction.[76] Symptom palliation can also be obtained by using prednisone or dexamethasone to combat chronic cough from advanced cancer. GCs combat cough by apparently reducing the size of mediastinal lymph nodes or tumor mass.[76–78]

Musculoskeletal pain

Pain due to bone metastases or metastatic arthralgia from a variety of solid tumors often responds to GC therapy.[78–80] Some bone metastases produce prostaglandins; in these cases GCs help control pain by interfering with prostaglandin production and secretion. Aspirin and nonsteroidal anti-inflammatory agents may act synergistically with GCs in managing bone pain.[79]

Obstruction and mass effects

Several types of malignancy are associated with superior vena cava syndrome.[81] The most prevalent among them is lung cancer, with small-cell undifferentiated carcinoma (oat-cell) being the most common subtype. Malignant lymphoma is second in frequency.[81,82] Other frequent malignant causes of superior vena cava syndrome are esophageal, colon, testicular, and breast cancers. It is well established that GCs achieve quick symptom control in this syndrome: even when used alone, they can produce dramatic results.

Lymphedema, with or without associated obstructing tumors, sometimes responds to GCs.[83] Lymphedema may cause considerable distress because of pain, paresthesia, disfigurement, or loss of mobility. If this is the case, steroids are worthy of a trial.[70,78,83]

Advanced colonic and ovarian cancer are often associated with large-bowel or ureteral obstruction. GCs can reduce peritumoral inflammation and edema and are used in palliative medical management of these complications.[74,78,83] For similar reasons, symptoms related to large masses in the mediastinum, pelvis, or retroperitoneum in advanced lymphomas or solid tumors respond well to GCs. Their use brings about improvement in subjective symptoms such as pain, dyspnea, fever, and cough. Liver metastases, particularly those associated with a friction rub (presumably secondary to capsule involvement), cause excruciating pain which responds dramatically to GCs.[74,78,84]

Metabolic complications of malignancy

Hypercalcemia is a common metabolic complication of hematologic malignancies such as multiple myeloma, lymphoma, leukemia, and some solid tumors.[16] GCs are specifically indicated in hypercalcemia associated with multiple myeloma, lymphoma, leukemia, and breast cancer (however, hypercalcemia due to primary hyperparathyroidism is refractory to GCs).[16,85] Initially, prednisone, 15 to 20 mg, is given orally every 6 hours. If hydrocortisone is preferred, it is given intravenously, 100 mg every 6 hours. The onset of action is slow and may take 5 to 7 days; therefore, GCs should be combined with other therapeutic measures such as intravenous rehydration, forced cal-

ciuresis by diuretics, calcitonin, and cytotoxic chemotherapy, as appropriate. Calcitonin combined with GCs is rapidly effective in treating hypercalcemia. GCs help to maintain the response to calcitonin by delaying the desensitization or "escape" phenomenon.[86]

Adrenal failure is uncommon in advanced metastatic disease, but the role of GCs in treating this condition is self-evident. Chronic adrenal insufficiency resulting from destructive lesions of the adrenal cortex requires cortisone acetate to be administered at 25 to 37.5 mg per day, or the equivalent in twice-daily doses. A common dose schedule is 25 mg on arising and 12.5 mg in the late afternoon. Fludrocortisone, 0.1 to 0.3 mg per day (usual adult dose), provides mineralocorticoid substitution. Therapy is guided by the patient's sense of well-being, alertness, appetite, weight, muscular strength, blood pressure, and freedom from orthostatic hypotension. GC use for symptomatic control in the carcinoid syndrome is reported but not well defined.[87]

PALLIATIVE CARE

The beneficial effects of GCs on subjective well-being are widely accepted in oncological and non-oncological practice. Controlled studies have confirmed symptomatic benefit in anorexia due to advanced gastrointestinal malignancy (however, no weight gain results).[78,88,89] GCs are effective antiemetic agents when used alone or in combination with other agents such as phenothiazines or butyrophenones. They can produce mild euphoria and a feeling of well-being, and can act as a nonspecific tonic for appetite stimulation.[88] Modest doses can produce rapid symptomatic improvement in critically ill, preterminal cancer patients by temporarily ameliorating fever, lethargy, weakness, and other nonspecific symptoms of advanced cancer.[88–90] Dosage varies widely; for relief of chronic symptoms a starting dose of prednisone, 10 mg to 30 mg a day, is recommended. To minimize toxicity, it is always advisable to taper steroids down to the minimal maintenance level.

IATROGENIC DISEASES

Several chemotherapeutic agents, such as mitomycin, bleomycin, busulfan, and carmustine, are associated with pulmonary toxicity.[91,92] Radiation pneumonitis is also a well-known dose-dependent complication of radiotherapy. High-dose GCs can effectively control or alleviate symptoms of pulmonary toxicity induced by mitomycin or mitomycin-containing chemotherapeutic regimens.[91] However, in pulmonary toxicity due to bleomycin, busulfan, and carmustine, the effect of GCs is less impressive.[92] As mentioned above, GCs are effective in combating pain and early neurological deficit from tumor-induced plexopathy;[74] they can be used similarly to treat iatrogenic radiation-induced plexopathies.

Nausea and vomiting associated with combination chemotherapy are common and troublesome. Cisplatin, mechlorethamine (nitrogen mustard), doxorubicin, and DTIC (dacarbazine) are the most potent emetogenic chemotherapeutic agents. While phenothiazines and butyrophenones are only partially successful in controlling nausea and vomiting,[93] high-dose dexamethasone and methylprednisolone have been used successfully as antiemetics in several studies.[94] At present, high-dose corticosteroids and metoclopramide are considered to be the most effective agents in antiemetic prophylaxis.[93] A prospective randomized study showed that a combined regimen including high-dose GCs (*Table 4*) is more effective in controlling the severity and duration of chemotherapy-induced nausea

TABLE 4
COMBINATION ANTIEMETIC TRIALS

Antiemetic agents	Dose and route	Results	References
Dexamethasone +metoclopramide vs	20 mg IV 2 mg/kg IV	60% no emesis	95
Dexamethasone +metoclopramide +diphenhydramine vs	20 mg IV 2 mg/kg IV 25 mg IV	60% no emesis	
Metoclopramide +prochlorperazine	2 mg/kg IV 10 mg/m^2 PO	39% no emesis	
Dexamethasone +chlorpromazine +metoclopramide vs	10 mg IV 25 mg IV 2 mg/kg IV	68% no emesis, 32%mild emesis	94*
Dexamethasone +prochlorperazine	8 mg IV 10 mg IV	30% mild emesis	
Dexamethasone +prochlorperazine +pentobarbital	10 mg PO 10 mg PO 100 mg PO	73% no emesis	97
Dexamethasone +metoclopramide +diphenhydramine +diazepam +thiethylperazine	20 mg IV 1 mg/kg IV 50 mg IV 5 mg IV 10 mg IV	3/12 1 vomiting episode 9/12 no emesis 11/12 sleep >2 hr	98

PO = orally; IV = intravenously
*This study was of pediatric patients.
Modified from Eyre HJ.[93]

TABLE 5
SIDE EFFECTS OF GLUCOCORTICOIDS

	Prednisolone (N = 146) n (%)	Dexamethasone (N = 109) n (%)
Candidiasis	38 (26)	40 (37)
Edema	30 (21)	20 (18)
Moon face	22 (15)	23 (21)
Dyspepsia	11 (8)	7 (6)
Psychic changes	2 (1)	9 (8)
Weight gain	7 (5)	4 (4)
Ecchymoses	4 (3)	5 (5)
Hyperactivity	–	5
Glycosuria/hyperglycemia	–	4
Insomnia	3 (2)	3
Hyperphagia	1 (1)	3 (3)
Myopathy	2 (1)	2 (2)
Myoclonic jerks	–	2 (2)
Cataract	–	2 (2)
Vomiting	1 (1)	–
Osteoporosis	1 (1)	–
Skin rash	–	1 (1)

Modified from Hanks GW.[89]

and vomiting than a regimen not including a GC.[99]

Doxorubicin and daunorubicin are vesicants. Barlock et al[100] demonstrated that local GCs given subcutaneously or intradermally are useful in reducing the initial tissue inflammation during doxorubicin extravasation. GCs are also used in the immediate management of generalized hypersensitivity reactions reported with the use of L-asparaginase, cisplatin, teniposide, and etoposide.[101]

GC SIDE EFFECTS

Weissman et al[73] found that the toxicity of GCs and the incidence and severity of side effects depends upon the dosage and total duration of therapy. Specifically, larger doses or longer duration of therapy are associated with greater toxicity. They reported a 76% incidence of toxicity in patients taking dexamethasone for more than 3 weeks, compared with 5% in patients taking it for less than 3 weeks. Likewise, the toxicity rate was 75% in patients receiving a total dose of dexamethasone greater than 400 mg, compared with 13% for total doses under 400 mg.[73]

The side effects of GCs are well described (*Table 5*), but no studies have compared individual agents in cancer therapy. Oropharyngeal candidiasis, fluid retention and weight gain, facial mooning, dyspepsia, and proximal myopathy are common side effects of GC therapy in cancer patients. There is marked variation among individuals in the incidence and severity of side effects, the reasons for which are not known.

Electrolyte abnormalities (hypokalemia, hypochloremic metabolic alkalosis) are less common with 16-alpha substituted compounds such as dexamethasone and triamcinolone. Proximal myopathy (often bilateral) is most common with triamcinolone.[33] No direct relationship between myopathy and the dose or duration of GC treatment is known.

Generalized osteoporosis affecting the dorsolumbar spine, femoral necks, and long bones is more common with prolonged administration of GCs. The incidence of osteoporosis among cancer patients is difficult to ascertain, but it is probably higher than in a normal population because of the additive effects of factors like advanced age, poor nutrition, and immobilization, which put cancer patients at increased risk.

Dyspepsia is a relatively common complaint in patients taking oral GCs, but a relationship to gastric ulceration has not been defined. As mentioned above, the concomitant use of GCs with other ulcerogenic drugs likely increases the incidence or severity of gastrointestinal ulceration and hemorrhage. Posner reported a 5.6% incidence of peptic ulcers among patients with brain metastases treated with GCs, and an overall GC complication rate of about 16%.[102]

Even small doses of GCs can lead to biochemical hypothalamic-pituitary-adrenal axis suppression,[103] but there is no uniform agreement about its severity or duration, or its significance for the possible development of adrenal failure. Despite the widespread use of GCs at supraphysiological doses, there are remarkably few documented cases of iatrogenic adrenal crisis.[104–106] It seems that the theoretical risk of this complication is greater than the practical risk. Therefore, the common practice of slowly tapering GC doses may simply expose the patient to the increased risk of prolonged therapy. Rapid tapering, especially after relatively short periods (less than a month) of therapy, should be tailored to control the disease and to prevent disease rebound.

Cancer patients are especially vulnerable to the immunosuppressive effects of GCs. Patients with advanced cancer are already immunodeficient—due to the primary disease and the concomitant administration of cytotoxic therapy—and are probably more prone to develop opportunistic infections, especially oral candidiasis, which is ubiquitous with long-term use of GCs in these patients. The increased incidence of insidious recrudescence of tuberculosis has been documented in immunocompromised patients.[107] Therefore, results of a purified protein derivative skin test and chest radiography should be considered before

putting cancer patients who are not terminally ill on long-term palliative steroid therapy.

CONCLUSION

GCs are valuable in medical oncology. Their judicious use plays an important part in the management of specific and nonspecific manifestations of various malignant disorders. They are important in the chemotherapy of lymphoproliferative disorders and breast cancer, and they are invaluable in controlling clinical complications common to many forms of cancer—eg, raised intracranial pressure and pulmonary lymphangitis carcinomatosa. In addition, by producing subjective improvement in appetite, a sense of well-being, and increased strength, GCs can effectively palliate far-advanced cancer. Prolonged use of GCs has the potential for serious side effects, and this must be taken into account in assessing the risk-benefit ratio. It is disappointing that, given the large number of reported indications for GCs, little scientific evaluation of their role in cancer management has been conducted.

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