INTRODUCTION

For more than four decades, corticosteroids (CS) remained essential in clinical oncology, and they still play an important role in the daily treatment of cancer patients. They may be used alone or in combination with other treatments, either as a chemotherapeutic agent or more often as a supportive care medication, commonly to decrease inflammation. Despite decades of work, most of the clinical indications and prescriptions of CS are empirical. The overview presented here focuses on CS such as prednisone and dexamethasone, which are the main glucocorticoids currently used in oncology, in part for their minimal mineralocorticoid activity. Careful administration is required, and long-term side-effects must be considered.

CS have been largely used in lymphoproliferative diseases such as Hodgkin and non-Hodgkin lymphomas, acute lymphoblastic leukemia, and multiple myeloma, and are still included in several chemotherapy regimens targeting these malignancies.[1-4] Preclinical studies showed that the antitumor effects of CS are achieved mainly by inducing apoptosis in lymphatic tissues. The current standard treatment for multiple myeloma illustrates such CS-based regimens: It combines the use of dexamethasone and a novel agent, bortezomib for induction, followed by high-dose therapy with autologous stem cell transplantation. When stem cell transplantation is not possible, the standard therapy includes a combination of prednisone and melphalan plus a novel agent such as thalidomide[5] or bortezomib.[6] In both clinical scenarios, CS are the cornerstone of multiple myeloma treatment. Of importance, CS are such effective antineoplastic agents in lymphoma that they should be withheld before any imaging or diagnostic consideration, including positron emission tomography/computed tomography (CT) imaging or CT scan-guided biopsy, unless their antiinflammatory property is required to decrease a symptomatic cerebral edema or mass effect, for instance.

Contrary to lymphatic tissues, the effects of CS on solid tumors are far more complex, ranging from cell survival to cell death. Indeed, CS were shown to confer apoptosis resistance to various anticancer agents in some solid tumors cells, such as in breast cancer. Moreover, concomitant administration of dexamethasone with paclitaxel contributes to breast cancer cell survival via inhibition of mitogen-activated protein kinase phosphatase-1 expression and activation.[7] The reduction of paclitaxel-induced apoptosis by CS involves alteration of NF-κB activity, a well-known survival pathway.[8] Opposite to this effect, dexamethasone pretreatment in...
breast cancer xenografts significantly increased antitumor activity of carboplatin, gemcitabine, and adriamycin through an enhanced drug uptake in the tumor leading to a significant decrease in cell proliferation and tumor volume, and an increase in apoptosis. This shows that dexamethasone may exhibit both antiproliferative and antiapoptotic activity in breast cancer cell lines. Of note, CS receptors were observed in all stages from normal breast tissue to breast cancer. Similarly, increased resistance and faster tumor growth post-CS was observed in mouse xenografts and in primary cells isolated from surgically resected brain, lung, bladder, colorectal, and prostate cancer tissues. Effects of CS on cancer cells appear to be tumor type and time course specific, and most of their targets are not yet fully understood. Globally, it should be noted that most of the data supporting the benefits of CS were derived from retrospective studies.[9] Therefore, a need exists to perform new randomized trials assessing the clinical effects of CS in a broad range of solid tumors.

In neuro-oncology, CS are often used for the management of brain tumors (either primary or secondary), for neoplastic spinal cord compression, peripherally in brain surgery, as adjuvant chemotherapy, and with radiation therapy.[10] They provide transient relief from neurological symptoms caused by cerebral edema and increased intracranial pressure linked to cranial tumors, including cerebral metastases and gliomas.[11] They give temporary decompression of the spinal cord compressed by metastatic disease in the epidural space, likely by inducing both decreased edema production and increased edema reabsorption. This helps to avoid neurologic complications and alleviates back pain related to the epidural compression. They also may be effective in controlling pain in patients with carcinomatous meningitis. Although some physicians still prefer methylprednisolone, dexamethasone is mostly used in practice, partly due to its relatively low tendency to induce psychosis and its long biological half-life.[12] Dexamethasone is often administered at an empirical oral dose of 4 mg qid, whereas this dosing schedule is unnecessary given the 36-54 h half-life. Usually, dexamethasone induces improvement within 48 h or sooner, which is a sign that the focal neurologic symptoms are due to peritumoral edema.[13] Dose-effect studies in patients with cerebral metastases have shown that lower doses of dexamethasone may also be sufficient, between 4 and 16 mg/day, depending on the edema volume. If there is no improvement after CS administration, the neurologic symptoms are likely due to brain damage by the tumor and not to edema, implying a worse prognosis. In patients with significant central nervous system tumors, dexamethasone can be useful in controlling edema during radiation therapy, and should be maintained throughout the treatment, especially in patients treated for spinal cord compression.[14] Recent findings suggest that the currently used doses may be excessive, since 4 mg of dexamethasone per day appears sufficient to control edema during radiotherapy for brain metastases.[15] The dose can then usually be tapered down over the following 2-3 weeks depending on stability or improvement in neurological function.

Radiation pneumonitis or other pulmonar toxicietoies associated with chemotherapy compounds (mitomycin, bleomycin, busulfan, carmustine) may necessitate a short course of CS if the patient becomes symptomatic (i.e., dyspnea, cough, ...).[16] By reduction of peritumoral inflammation and edema, CS can partially control cancer-related obstructions and mass effects, including superior vena cava syndrome, lymphedema, liver metastases, masses in the pelvis, mediastinum, or retroperitoneum, and blockages of the large bowel or ureter.[17-19] Similarly, acute upper airway obstruction, resulting from direct tumor growth or by compression from thyroid, lung, and esophageal cancers, can be reduced by CS treatment, either alone or in combination with radiation.[20]

Corticosteroids are also effective in the treatment of several indirect effects of malignancies, and are widely used as general palliative therapy, to prevent nausea, vomiting, and hypersensitivity reactions induced by chemotherapeutic agents or radiotherapy.[21] While the precise mechanism is unknown, either 8-20 mg dexamethasone or 125-250 mg methylprednisolone can be employed to reduce vomiting episodes up to 70%. CS are extremely effective when used at low doses to enhance the antiemetic efficacy of serotonin receptor antagonists, such as granisetron or tropisetron.[22] They also produce rapid symptomatic improvements in critically ill patients, including relief of fever, sweats, lethargy, weakness, and other nonspecific effects of cancer. In the palliative setting, CS are also commonly used to stimulate appetite, alleviate pain or reduce fatigue, and may subsequently provide some improvements of quality-of-life.[23] Unfortunately, most of these effects are transient, and only short-term treatment is possible due to side-effects of high-doses. In addition, CS withdrawal can result in adrenocortical insufficiency. For these reasons, CS treatment is appropriate only for short periods.

Other uses for CS in cancer include a weak effect on hypercalcemia, a common complication of many malignancies,[24] often caused by increased bone resorption and renal calcium reabsorption. To reach efficacy in the treatment of hypercalcemia, high-doses of CS are required (i.e., 100 mg/d prednisolone). CS work best in cases of Vitamin D-mediated hypercalcemia, through inhibition of Vitamin D action on calcium metabolism. Pain from bone metastases or metastatic arthralgia from solid tumors often responds to CS treatment.
Finally, many considerable adverse effects and long-term complications of CS must be considered as they may cause significant (fatal) morbidity.[23] These include: Weight gain, hyperglycemia, myopathy,[26] osteoporosis,[27] lymphopenia, gastrointestinal perforation and hemorrhage, opportunistic infections,[28] depression, hypomania and mania, decline in memory and other cognitive alterations,[29] and skin and facial changes. Therefore, careful use of CS is required and the balance between risks and benefits should always be considered in clinical oncology.

REFERENCES


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