Chapter 21

Glucocorticoid Effect in Cancer Patients

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Abstract

The use of glucocorticoids is very varied in the context of cancer patients and includes the treatment of symptoms related to cancer, but also the management of the most common side effects of antitumor treatments or adverse events related to the immune system. There is a quantity of experimental evidence demonstrating that cancer cells are immunogenic. However, the effective activation of anticancer T cell responses closely depends on an efficient antigen presentation carried out by professional antigen-presenting cells such as dendritic cells (DCs). The classic strategies to improve the medical management of inflammation are aimed at exacerbating the host's immune response. Although successful in treating a number of diseases, these drugs have limited efficacy and variable responses can lead to unpredictable results. The ideal therapy should reduce inflammation without inducing immunosuppression and remains a challenge for healthcare personnel.

Key words Adjuvant analgesics, Anti-inflammatory, Apoptosis, Cancer patient, Chemotherapy, Glucocorticoid effect, Immune response

1 Introduction

Thanks to their anti-inflammatory, anti-edema, and anti-allergy properties, glucocorticoids (GC) are among the most widely prescribed drugs in patients with cancer. The indications for GC use are very wide and varied in the context of cancer and include the symptomatic management of cancer-related symptoms (compression, pain, edema, altered general state) but also prevention or treatment of common side effects of anticancer therapies (nausea, allergies, etc.) or immune-related adverse events (irAE).

The classic strategies to improve the medical management of inflammation are aimed at exacerbating the host's immune response with aminosalicylates, antibiotics, corticosteroids, thiopurines, methotrexate, and biological antitumor necrosis factor (TNF) agents. Although successful in treating a number of diseases, these drugs have limited efficacy and variable responses can lead to

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unpredictable results. The ideal therapy should reduce inflammation without inducing immunosuppression and remains a challenge for healthcare personnel [1].

However, severe even life-threatening side effects can arise from prolonged exposure to synthetic GC, as well as from elevated production of endogenous glucocorticoids, as seen in the rare endocrine cancers known as Cushing's disease. Common side effects include osteoporosis, hypertension, mood disorders, muscle and skin atrophy, and increased susceptibility to infection. Although these side effects are often said to limit the clinical utility of GCs, prolonged treatment with GCs is far from uncommon, particularly among the elderly. Since the discovery of GCs by Philip Hench and others in the 1940s, the uncoupling of their desirable anti-inflammatory or immuno-suppressive effects from their harmful side effects has been pursued with little success [2].

The involvement of GC in protumoral processes, particularly tumor proliferation, cell adhesion, or epithelial–mesenchymal transition, remains controversial. It has been suggested that the use of GC may render tumors resistant or less susceptible to apoptosis after anticancer therapy.

Some cancer types, such as hematologic malignancies, can be effectively treated with GC, whereas responses of epithelial cancers to GC treatment vary, even within cancer subtypes. GCs may have ancillary antitumor effects due to their cytotoxic actions on cancer cells; however, GC can also promote cancer progression, colonization of distant metastatic sites, and metastasis [3].

Indeed, GC treatment was found to downregulate basal and chemotherapy-induced expression of apoptotic effects in human cervical and lung carcinoma cells [4]. Variations in effects have also been observed within tumors, with variable effects shown in breast cancer depending on histologic subtype or tumor microenvironment. For example, some results indicate that the activation of the GC receptor increases heterogeneity and metastasis, which suggests that caution is needed when using GC to treat patients with breast cancer who have developed cancer-related complications [5].

Evidence indicates too that GCs induce apoptosis in hematological cells, thus supporting their use as chemotherapeutic agents for leukemias, lymphomas, and myeloma. GCs are a therapeutic component in their own right in chemotherapy protocols for hemopathic malignancies and have been shown to be very efficacious in association with cytotoxic chemotherapy for the treatment of acute lymphoblastic leukemia, chronic lymphocytic leukemia, Hodgkin and non-Hodgkin lymphoma, as well as multiple myeloma [6]. The mechanisms by which GCs could induce tumor cell apoptosis are still incompletely understood but appear to be multiple and interrelated.

Immune checkpoint inhibitors (ICIs) have revolutionized the management of advanced non-small cell lung cancer. With the intention of generating an antitumor immune response, ICIs can also lead to inflammatory side effects involving a wide variety of organs in the body, termed immune-related adverse events. Although no prospective clinical trial exists to guide recommendations for optimal and more specific immunosuppressive treatments rather than corticosteroids, further studies may lead to a more mechanistic-based approach towards these toxicities in the future. In relation to current practice, adherence to the recent published guidelines is recommend, which emphasize the importance of early recognition and administration of temporary immunosuppressive therapy with corticosteroids in most cases, depending on the organ system involved and the severity of toxicity. Recognition of these toxicities is increasingly important as the use of these agents expands within different indications for patients with lung cancers and to other tumor types [7].

1.1 Definitions

Immune-related adverse events (irAEs) are a unique spectrum of side effects of ICIs that resemble autoimmune responses. irAEs affect almost every organ of the body and are most commonly observed in the skin, gastrointestinal tract, lung, and endocrine, musculoskeletal, and other systems [8].

Biological antitumor necrosis factor agents. Tumor necrosis factor (TNF) plays a central role in the pathogenesis of several inflammatory conditions, including rheumatoid arthritis (RA). TNF is made intracellularly, mainly by activated macrophages. The precursor TNF is converted to soluble TNF after proteolysis by the TNF-converting enzyme. This soluble TNF then oligomerizes and forms the biologically active homotrimer TNF. There are two types of TNF, which are very closely related, TNF-alpha and TNF-beta. The activities of both TNFs are mediated through binding to the TNF receptors I and II (TNFRI and TNFRII), which are present on almost all cell types (except erythrocytes) [9–11].

Immune checkpoint inhibitors (ICIs) are novel therapeutic agents increasingly used in cancer therapy. Tumor cells can evade destruction by the immune system by triggering immune checkpoint receptors, such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1), or programmed death-ligand 1 (PD-L1), that are expressed on T cells and whose engagement inhibits T-lymphocyte function [10]. Immune checkpoint inhibitors are monoclonal antibodies that prevent this immunosuppression by blocking the engagement of these checkpoint molecules, thereby reinvigorating the antitumor immune response [12].

Dendritic cells (DCs) are antigen-presenting cells derived from bone marrow precursors and form a widely distributed cellular system throughout the body. DCs exert immune surveillance for exogenous and endogenous antigens and the later activation of naive T lymphocytes, giving rise to various immunological responses. Different growth factors and cytokines can modulate the differentiation and function of DCs, GM-CSF, M-CSF, Flt3, and TGF-β, resulting in a large variety of DCs with different functional abilities. Functionally, the cDCs may be divided into two states: immature and mature. Immature DCs are specialist in uptaking and processing antigens; in contrast, mature DCs are professional in antigen presentation. It has been observed that immature cDCs can induce immune tolerance, while mature cDCs may induce Th2 or Th1 immune responses. It is worth noting that different subpopulations of DCs have the ability to secrete different cytokine patterns, resulting in the induction of different immunological responses. Furthermore, DCs are involved in the pathophysiology of several diseases such as contact hypersensitivity, autoimmune diseases, or cancer, but they can also be used as therapeutic tools in these conditions [13].

2 Effect of Glucocorticoids (GC) on the Immune Response

Paul Ehrlich at the beginning of the twentieth century presented his immune surveillance theory for cancer. According to Ehrlich, tumor cells appeared spontaneously in the body and were eliminated by the immune system, thus defending the idea of an immune system with anticancer capabilities. In fact, it seems that the efficacy of classical treatments also lies largely in the activation of immune responses after the release of immunostimulatory molecules from necrotic cells [14, 15].

Actually, there is a quantity of experimental evidence demonstrating that cancer cells are immunogenic. However, the effective activation of anticancer T cell responses closely depends on an efficient antigen presentation carried out by professional antigen-presenting cells such as dendritic cells (DCs) [16].

A mathematical model based on a system of ordinary differential equations was developed for the characterization of the regulation of antitumor immune activity.

These mathematical simulations indicated that GC treatment can suppress the antitumor immune response in a dose-dependent manner. The model simulations were in line with previous experimental observations of the inhibitory effects of GCs on T, natural killer (NK) cells, and DCs. Thus, the results of this study could be useful in predicting clinical outcomes in patients receiving GC therapy [17].

NK cells play a crucial role in antitumor immunity because of their innate ability to differentiate between malignant versus normal cells. But these NK cells are severely affected during the period immediately following cancer surgeries. Therefore, an opportunity arises in the aftermath of cancer surgery for residual cancer cells, including distant metastases, to gain a foothold in the absence of NK cell surveillance. In the sense of GC therapy predicting clinical outcomes, it is interesting to know that the release of sympathetic stress-related factors (e.g., cortisol, prostaglandins, catecholamines), anti-inflammatory cytokines (e.g., IL-6, TGF-β), and myeloid derived suppressor cells mediates NK cell dysfunction. Thus, peri-operative therapies to mitigate NK cell suppression in the post-operative period could improve curative outcomes following cancer surgery [18].

Another study investigated the effects of tolerogenic GC-treated DCs on NK and T cell antitumor responses in CD8+ T cells. The effects caused by GC-treated DCs were compared to the responses to immunogenic, CpG-activated DCs. The immunization with CpG and peptide-treated DCs protected against tumor growth by activation of NK cell response. Also, immunogenic DCs induced the expansion of cytotoxic CD8+OT-1 cells. In contrast, the peptide and GC-treated DCs increased the numbers of immature Mac-1+CD27- NK cells as well as Foxp3+ and IL-10 secreting CD8+OT-1 cells with suppressive properties. In conclusion, the generation of tolerogenic DCs is one of many immunosuppressive mechanisms that can be induced by GC [19].

3 The Role of MicroRNA in Glucocorticoid Action

MicroRNAs (miRNAs) are short RNA species, generally 19–22 nucleotides in length, which mediate post-transcriptional down-regulation of protein expression [20].

Although individual miRNAs exert relatively little effect on cortisol biosynthesis, coordinated changes of miRNA abundance may have a more striking impact, for example, in the context of hypoxia or adenocarcinoma [21, 22]. Local GC availability can also be regulated via effects of miRNAs [23].

GCs regulate many aspects of neuronal development and function, having particularly important roles in adaptation to stress. Since pathophysiological point of view, prolonged exposure to stress or elevated GC levels can cause long-lasting reprogramming of neuronal GC responses, which can result in neuropsychiatric disorders such as depression in later life. Such reprogramming at critical developmental stages in utero may contribute to the trans-generational effects of antenatal GC exposure [24, 25]. It has been suggested that miRNA-mediated fine-tuning may contribute to preventing consequences such as GC-induced atrophy of the adrenal glands [26].

Various miRNAs have been implicated in the positive or negative regulation of inflammatory and immune responses, and these mechanisms may be subject to GC modulation. The best characterized example is miR-155, which is generated from the B-cell integrating pool of the precursor transcript [27]. Elevated levels of miR-155 have been described in many types of cancer, leading to its identification as one of the first oncogenic miRNAs (oncomirs).

In experiments with mice, those lacking miR-155 were resistant to synovial inflammation and bone erosion [28]. Dexamethasone GC inhibited lipopolysaccharide (LPS)-induced expression of miR-155 in primary macrophages and macrophage cell lines [29] spleen and liver cells from LPS-injected mice [29, 30] and T lymphocytes from sepsis patients [31].

The regulatory impact of a new miRNA on cancer growth and migration is currently being discussed. The new emerging miRNA-338-3p can regulate the response of cancer cells to chemotherapy and radiotherapy. It appears that miRNA-338-3p has a dual role in cancer chemotherapy, acting as a tumor-promoting or tumor-suppressing factor. The experiments reveal the antitumor activity of miRNA-338-3p in cancer. Therefore, increasing the expression of miRNA-338-3p is important in effective cancer therapy. Long noncoding RNAs, circular RNAs, and hypoxia are possible upstream mediators of miRNA-338-3p in cancer. Antitumor agents including baicalin and arbutin can promote miRNA-338-3p expression to suppress cancer progression [32].

However, successful therapeutic manipulation of miRNA expression is likely to be highly tumor-type specific and mimic viral infection, such as Toll-like receptor 9 (TLR9) ligands. Such agonists render plasmacytoid dendritic cells resistant to GC-induced apoptosis [33].

In summary, as miRNAs exert such pervasive effects on biological processes, it is not surprising that they touch on GC action at several points. Their touch is often light, in the sense that individual miRNAs alter expression of their targets only modestly. Nevertheless, one miRNA can hit several targets, and one target may be hit by several different miRNAs. Therefore, coherent and coordinated changes of miRNA abundance can affect complex biological processes quite profoundly [34].

4 Glucocorticoids and Apoptosis

Clinically, GCs are used for allergies, autoimmunity, and chronic inflammation, because they have strong anti-inflammatory effects and induce the apoptosis of lymphocytes. Past studies have reported the positive and negative effects of GC on the immune system. These opposing properties of GC may regulate the immune balance between the responsiveness to antigens and excessive inflammation in steady-state and stress conditions.

Glucocorticoid receptor (GR) acts as a transcription factor and represses the expression of inflammatory cytokines, chemokines, and prostaglandins by binding to its motif, to GC response element, or to other transcription factors. In mice, GR suppresses the antigen-stimulated inflammation mediated by macrophages, dendritic cells, and epithelial cells and impairs cytotoxic immune responses by downregulating interferon-γ production and inhibiting the development of type-1 helper T cells, CD8+ T cells, and NK. These immune inhibitory effects prevent lethality by excessive inflammation but at the same time increase the susceptibility to infection and cancer. Consistently, stress-induced GCs strongly suppress cell-mediated immunity and cause viral infection and tumor development. They may also enhance the development of pathogenic helper T cells and cause tissue damage through neural and intestinal inflammation [35].

New findings show that GR antagonism enhances tumor cell apoptosis due to cytotoxic agents under physiological GC concentrations in mice. Thus, GR antagonism will help guide the clinical development of relacorilant in combination with cytotoxic agents for the treatment of solid tumors. Anti-proliferative agents, including, but not limited to, paclitaxel, consistently cause tumor cell apoptosis in vitro. Resistance to such therapies is, unfortunately, the norm in clinical practice in patients with solid tumors. The data presented in some studies expand our understanding of the pro-apoptotic effects of GR antagonists described in ovarian and breast cancer cells [36, 37]. Relacorilant improved the activity of diverse cytotoxic agents, and the most pronounced benefits were seen in combination with microtubule-targeted agents [38].

Thus, the optimal clinical application for a GR antagonist would necessarily avoid the use of corticosteroids. For example, paclitaxel formulated with albumin and without cremophor does not require co-administration of corticosteroids and is thus a rational first choice for combination with relacorilant. Additionally, the benefit of relacorilant combined with a diverse set of cytotoxic agents identified further expands the number of potential corticosteroid-sparing regimens with relacorilant [38].

In this way, the aim of a recent study was to identify the effect of ionizing radiation on the structure of prednisolone and cancer cells. Prednisolone is a GC used for the treatment of liver disease and cancer. A new derivative of prednisolone was created by irradiation (prednisolone IR) and its anticancer properties were investigated in liver cancer cells. IR prednisolone promoted apoptosis and arrested the cell cycle at the G0/G1 stage in Huh7 cells. IR prednisolone also altered the mitochondrial membrane potential and activated caspase-associated proteins, thereby activating the intrinsic apoptotic signaling pathway. In conclusion, IR prednisolone promoted anticancer effects in liver cancer cells through activation of apoptosis. This study showed that IR prednisolone may be a potential anticancer agent against liver cancer, although specific molecules have not yet been identified [39].

5 Impact of Glucocorticoid Use on Cancer-Related Symptoms

Cancer remains the leading cause of death worldwide and also carries significant morbidity. Pain resulting, directly or indirectly, from abnormal growth of malignant cells in normal tissue, is the most common and feared symptom associated with cancer [40]. It is estimated that one-third of cancer patients undergoing active treatment, and two-thirds of those with advanced disease, experience pain that requires treatment with analgesic drugs [41].

In addition, the recommendations of the World Health Organization (WHO) and the European Association for Palliative Care for the treatment of pain indicate and establish the adjuvant analgesics that should be used in each step of the WHO analgesic scale, GC being one of the adjuvant analgesics, according to treatment guidelines [42].

In oncology, GCs have long been used to help control cancer-related symptoms, especially those related to inflammation and/or edema caused by the tumor, with most patients receiving GCs followed up in oncology, at some point in their cancer treatment [43].

Due to their anti-inflammatory mechanism of action, corticosteroids are said to provide effective analgesia for pain associated with inflammation and in the treatment of cancer-related complications such as brain metastases and spinal cord compression [41], especially in bone metastases [44, 45], and are also widely used in cancer patients in the palliative phase of the disease [46]. Dexamethasone is often the corticosteroid of choice for specialized palliative care teams [47], as it has a more even tissue distribution and better penetration of the blood–brain barrier [48], and its minimal mineralocorticoid means that dexamethasone causes less retention of liquids, and its long biological half-life of 36–54 h allows once-daily dosing [47].

However, some studies and meta-analyses have shown that the efficacy is lower than expected and should be considered in perspective with the potential adverse effects of this treatment [49].

Recently, a meta-analysis on the use of GC for pain management in adult cancer patients has been carried out, and the authors concluded that more trials are needed, and with a larger number of participants, to evaluate the safety and the effectiveness of corticosteroids for the treatment of cancer pain in adults and to establish an ideal dose, duration of treatment, and route of administration. More randomized controlled clinical trials are indicated, and with adequate statistical power, having pain as the primary outcome and being measured with a standardized and universally accepted tool, using a single GC drug (e.g., dexamethasone, which is the GC most used in this type of patients), at a dose and with a predetermined

route of administration, for a short period of time. Likewise, it would be recommended that long-term toxicity be documented during a long follow-up period [50].

Another symptom related to cancer is dyspnea, which has a multifactorial origin and appears in 70% of these patients when they reach the final phase of life and whose treatment with GC can be effective [43]. Currently, and depending on the origin of dyspnea, GCs have several arguments in favor of their use, for example, when dyspnea appears in patients who, due to tumor progression, suffer from bronchospasm, pleural effusion, or superior vena cava syndrome [51], since GCs have an anti-inflammatory component that includes immune infiltration of the wall of the airways, increased proinflammatory cytokines in lung tumors (such as IL-8, IL-6, and C-reactive protein), or increased peripheral activation of neutrophils, which may explain its ability to attenuate dyspnea in view of the high inflammatory response of these patients [52, 53].

However, as dyspnea is known to be multifactorial in cancer patients, GCs may be more effective in some cases, such as lymphangitis carcinomatosa or airway obstruction by tumor, but less so in other circumstances [49].

GCs are also an element used in the treatment of symptomatic cerebral edema (nausea, vomiting, and headache) and are recommended to reduce intracranial pressure related to the progression of a primary brain tumor or intracerebral metastasis [54]. Dexamethasone is the treatment of choice to relieve the symptoms of brain tumor progression with signs of intracranial hypertension and/or neurological deficits [55]. The reason for choosing dexamethasone is due to its limited mineralocorticoid effects and the lower risk of a rebound effect after discontinuation.

The treatment of leptomeningeal metastases and their symptoms is generally more complex and may require therapy with intrathecal administration of GC. In addition, treatment with GC has been shown to be effective and is among the main therapeutic options (along with surgery and radiotherapy) for the treatment of symptoms related to spinal cord compression, especially during spinal cord metastases. Spinal cord metastases occurs in numerous cancers such as breast or lung; in these cases, prompt attention is needed to restore neurological function, relieve pain, and prevent permanent damage [56].

Likewise, GCs appear in clinical guidelines and are currently used systemically in the management and treatment of digestive occlusive symptoms of tumor origin or cause, with the main objective of restoring or improving said occlusive symptoms [57]. This intestinal obstruction can be mechanical or functional, with extrinsic mechanics being representative of a higher percentage of cases.

Said occlusive digestive symptoms may be the result of compression of the digestive tract lumen, by a tumor or primary cancerous mass, by a metastasis (mesenteric or epiploic), by radiation-induced fibrosis secondary to radiotherapy, or by adhesions: abdominal and/or pelvic [58]. Malignant intestinal obstruction is estimated to occur in 10–28% of colorectal cancers and 5–42% of ovarian cancers; in general, it is estimated that it occurs in 2% of all patients in advanced phase of the disease [59].

There is a systematic review on the use of corticosteroids in the management of cancer patients with symptoms of intestinal obstruction, in which several randomized clinical trials with double blind and placebo were analyzed and in which the authors concluded that that there is a tendency towards evidence that GC in a dose range of 6–16 mg of dexamethasone administered intravenously can achieve resolution of intestinal obstruction, presenting an extremely low incidence of side effects in all included studies [60].

At the same time that GCs are used to manage the impact of the symptoms of the disease on the quality of life of cancer patients, they are also used to help control the secondary effects of antitumor treatments, such as chemotherapy, immunotherapy, and radiotherapy, with nausea and vomiting standing out among these symptoms [61].

To control these symptoms, and together with GCs (which are the drugs used for this function for the longest time), 5HT3 or NK1 receptor antagonists are associated depending on the emetic response of the chemotherapy protocol. Chemotherapy is known to induce the production of inflammatory mediators, such as eicosanoids, which may explain the efficacy of GC treatment in preventing such nausea and vomiting [62].

In addition to nausea and vomiting, there are certain chemotherapy agents (bleomycin, gemcitabine) or targeted therapies, EGFR (erlotinib, gefitinib), mTOR or MEK inhibitors, or even HER2 monoclonal antibodies (especially trastuzumab and deruxtecan, which are known to cause disease interstitial lung), which can cause respiratory and pulmonary toxicity [63]. Parallel to the interruption of the drug implicated in said toxicity, the use of GC is recommended in the clinical guidelines, since they can help resolve dyspneic symptoms and even improve the pulmonary radiographic presentation [64].

GCs, in addition to being used in the symptoms of cancer patients described above, also have favorable side effects regarding the general condition of cancer patients, due to their orexigenic or appetite-stimulating effect [65] and to having a positive impact on the characteristic asthenia of this type of fragile patients [53]. In general, several studies carried out with cancer patients with advanced and palliative cancer have shown an improvement in the quality of patients receiving treatment with GC, compared to patients receiving placebo [53, 66].

However, and despite the evidence that indicates the benefit of the use of GC in this type of patient, it must also be considered that, like any drug, GC can cause certain clinical side effects in patients (candidiasis oral administration, severe proximal myopathy, insomnia, etc.), which can cause patients to show certain reluctance and difficulties in the use of GCs, even outweighing the possible potential benefits [49]. For all these reasons, even in patients with advanced cancer and palliative patients, GCs should be used with the minimum effective dose and with the shortest possible duration [67].

6 Future Perspectives

Acquired GC resistance emerges over time because the underlying disease process finds mechanisms to evade GC-induced apoptosis [68]. The mechanisms underpinning acquired GC resistance are nevertheless divergent and often cell-type specific, which contributes to the heterogeneity in GC responsiveness observed in patients [69, 70].

Given the extensive number of factors that can contribute to GC resistance, GC resistance is clearly not governed by one single mechanism, but by several mechanisms acting consecutively or alternating to achieve full-blown resistance. Interpatient variability in the underlying mechanisms is also to be expected, as both the GC dose and the duration of GC therapy are often different between patients, in turn affecting the moment of onset and the degree of GC resistance. Frontline technologies such as single cell RNA-sequencing will further help dissecting the gradual emergence and inherent heterogeneity of GC resistance [71].

References

1. Sales-Ca-Campos H, Basso PJ, Alves VB et al (2015) Classical and recent advances in the treatment of inflammatory bowel diseases. Braz J Med Biol Res 48(2):96–107
2. Clark AR, Bervisi MG (2012) Maps and legends: the quest for dissociated ligands of the glucocorticoid receptor. Pharmacol Ther 134:54–67
3. Zhidkova EM, Lylova ES, Savinkova AV et al (2020) A brief overview of the paradoxical role of glucocorticoids in breast cancer. Breast Cancer 14:117822342097466
4. Herr I, Ucur E, Herzer K et al (2003) Glucocorticoid cotreatment induces apoptosis resistance toward cancer therapy in carcinomas. Cancer Res 63:3112–3120
5. Obradovic M, Hamelin B, Manevski NR et al (2019) Glucocorticoids promote breast cancer metastasis. Nature 567(7749):540
6. Pufall M (2015) Glucocorticoids and cancer. Exp Biol Med 872:315–333
7. Wills B, Brahmer J, Naidoo J (2018) Treatment of complications from immune checkpoint inhibition in patients with lung cancer. Curr Treat Options Oncol 19:46
8. Bramer JR, Lacchetti C, Atkins MB et al (2018) Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 36(17):1714–1768

9. Feldmann M, Maini R (2001) Anti-TNF alpha therapy of rheumatoid arthritis: what have we learned? Annu Rev Immunol 19:163–196
10. Gottlieb A (2007) Tumor necrosis factor blockade: mechanism of action. J Investig Dermatol 12(1):1–4
11. Roach D, Bean A, Demangel C, France M, Briscoe H, Britton W (2002) TNF regulates chemokine induction essential for cell recruitment, granuloma formation, and clearance of mycobacterial infection. Immunology 168(9): 4620–4627
12. Pardoll K (2012) The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 12:252–264
13. Castell-Rodríguez A, Piñón-Zárate G, Herrera-Enríquez M, Jarquín-Yáñez K, Medina-Solares I (2017) Dendritic cells: location, function, and clinical implications. In: Biology of myelomonocytic cells, 3rd edn. Anirban Gosh
14. Arce F, Kochan G, Breckpot K, Stephenson H, Escors D (2012) Selective activation of intracellular signalling pathways in dendritic cells for cancer immunotherapy. Anti Cancer Agents Med Chem 12:29–39
15. Ghiringhelli F, Bruchard M, Apetoh L (2013) Immune effects of 5-fluorouracil: ambivalence matters. Oncoimmunology 2(3):e23139
16. Gato T, Liechtenstein T, Blanco-Luquín I, Zudaire M, Kochan G, Escors D (2015) Dentritic cells in cancer immunotherapy. An Sist Sanit Navar 38(2):279–287
17. Yakimchuk K (2019) Mathematical modeling of immune modulation by glucocorticoids. Biosystems 187:104066
18. Angka L, Khan S, Kilgour M, Xu R, Kennedy M, Auer R (2017) Dysfunctional natural killer cells in the aftermath of cancer surgery. Int J Mol Sci 18(8):1787
19. Chen L, Hasni M, Jondal M, Yakimchuk K (2017) Modification of anti-tumor immunity by tolerogenic dendritic cells. Autoimmunity 50(6):370–376
20. Filipowicz W, Bhattacharyya S, Sonenberg N (2008) Mechanisms of post-transcriptional regulation by microRNAs: are the answers in sight? Nat Rev Genet 9:102–114
21. Robertson S, Diver LA, Alvarez-Madrazo S et al (2017) Regulation of corticosteroidogenic genes by microRNAs. Int J Endocrinol 2017: 1–11
22. Nusrin S, Tong S, Chaturvedi G, Wu R, Giesy J, Kong R (2014) Regulation of CYP11B1 and CYP11B2 steroidogenic genes by hypoxia-inducible miR-10b in H295R cells. Mar Pollut Bull 85:344–351
23. Han Y, Staab-Weijnitz C, Xiong G, Maser E (2013) Identification of microRNAs as a potential novel regulatory mechanism in HSD11B1 expression. J Steroid Biochem Mol Biol 133:129–139
24. de Kloet E, Fitzsimons C, Datson N, Meijer O, Vreugdenhil E (2009) Glucocorticoid signaling and stress-related limbic susceptibility pathway: about receptors, transcription machinery and microRNA. J Brain Res 13(1293): 129–141
25. Moisiadis V, Matthews S (2014) Glucocorticoids and fetal programming part 2: mechanisms. Nat Rev Endocrinol 10(7):403–411
26. Pentkowski N, Bouquin S, Maestas-Olguin C, Villasenor Z, Clark B (2008) Characterization of the vulnerability to repeated stress in Fischer 344 rats: possible involvement of microRNA-mediated down-regulation of the glucocorticoid receptor. Eur J Neurosci 27(9): 2250–2261
27. Vigorito E, Kohlhaas S, Lu D, Leyland R (2013) An ancient regulator of the immune system. Immunol Rev J 253:146–157
28. Kurowska-Stolarska M, Alivernini S, Ballantine L et al (2011) MicroRNA-155 as a proinflammatory regulator in clinical and experimental arthritis. Proc Natl Acad Sci U S A 108:11193–11198
29. Zheng Y, Xiong S, Jiang P et al (2012) Glucocorticoids inhibit lipopolysaccharide-mediated inflammatory response by downregulating microRNA-155. Free Radic Biol Med J 52: 1307–1317
30. Wang Z, Liang Y, Tang H et al (2013) Dexamethasone down-regulates the expression of microRNA-155 in the livers of septic mice. PLoS One 8:e80547
31. Chen Y, Wang G, Liu Z, Wang S, Wang Y (2016) Glucocorticoids regulate the proliferation of T cells via miRNA-155 in septic shock. Exp Ther Med 12:3723–3728
32. Mirzaei S, Zarrabi A, Asnaf S, Hashemi F, Zabolian A (2021) The role of microRNA-338-3p in cancer: growth, invasion, chemoresistance, and mediators. Life Sci 268:119005
33. Guiducci C, Gong M, Xu Z et al (2010) TLR recognition of self-nucleic acids hampers glucocorticoid activity in lupus. Nature 465:937–941
34. Clayton S, Jones S, Kurowska-Stolarska M, Clark A (2018) The role of microRNAs in glucocorticoid action. J Biol Chem 293(6): 1865–1874

35. Shimba A, Ikuta K (2020) Control of immunity by glucocorticoids in health and disease. Semin Immunopathol 42(6):669–680
36. Skor M, Wonder E, Kocherginsky M et al (2013) Glucocorticoid receptor antagonism as a novel therapy for triple-negative breast cancer. Clin Cancer Res 19:6163–6172
37. Moran T, Gray S, Mikosz C, Conzen S (2000) The glucocorticoid receptor mediates a survival signal in human mammary epithelial cells. Cancer Res 60:267–272
38. Greenstein A, Hunt H (2021) Glucocorticoid receptor antagonism promotes apoptosis in solid tumor cells. Oncotarget 12(13): 1243–1255
39. Ramadhani F, Kang S, Kawala R, Chung B, Bai H, Kang B (2021) γ irradiated prednisolone promotes apoptosis of liver cancer cells via activation of intrinsic apoptosis signaling pathway. Mol Med Rep 23:425
40. van den Beuken-van Everdingen MH, Hochstenbach LM, Joosten EA, Tjan-Heijnen VC, Janssen DJ (2016) Update on prevalence of pain in patients with cancer: systematic review and meta-analysis. J Pain Symptom Manag 51(6):1070–1090
41. Foley KM (2011) How well is cancer pain treated? Palliat Med 25(5):398–401
42. Fallon M, Hanks G, Cherny N (2006) Principles of control of cancer pain. BMJ 332:1022–1024
43. Haywood A, Good P, Khan S, Leupp A, Jenkins-Marsh S, Rickett K, Hardy JR (2015) Corticosteroids for the management of cancer-related pain in adults. Cochrane Database Syst Rev 2015:CD010756
44. Chouahnia K, Luu M, Baba-Hamed N, Des Guetz G (2009) Bone metastases pain in the elderly. Rev Med Suisse 5:1126, 1128, 1130
45. Chow E, Meyer RM, Ding K, Nabid A, Chabot P, Wong P, Ahmed S, Kuk J, Dar AR, Mahmud A et al (2015) Dexamethasone in the prophylaxis of radiation-induced pain flare after palliative radiotherapy for bone metastases: a double-blind, randomized placebo-controlled, phase 3 trial. Lancet Oncol 16:1463–1472
46. Barghi K, Edmonds KP, Ajayi TA, Atayee RS (2018) Prescribing trends of palliative care team's use of dexamethasone for cancer-related pain. J Pain Palliat Care Pharmacother 32(1): 37–43
47. Bordag N, Klie S, Jurchott K, Vierheller J, Schiewe H, Albrecht V, Tonn JC, Schwartz C, Schichor C, Selbig J (2015) Glucocorticoid (dexamethasone)-induced metabolome changes in healthy males suggest prediction of response and side effects. Sci Rep 5:15954
48. Moricke A, Zimmermann M, Valsecchi MG, Stanulla M, Biondi A, Mann G, Locatelli F, Cazzaniga G, Niggli F, Aricò M (2016) Dexamethasone vs prednisone in induction treatment of pediatric ALL: results of the randomized trial AIEOP-BFM ALL 2000. Blood 127(17):2101–2112
49. Kalfeist L, Galland L, Ledys F, Ghiringhelli F, Limagne E, Ladoire S (2022) Impact of glucocorticoid use in oncology in the immunotherapy era. Cell 11:770
50. Zimmerman M, Drings P (1984) Guidelines for therapy of pain in cancer patients. In: Pain in the cancer patient. Recent results in cancer research, vol 89. Springer, Berlin/Heidelberg, pp 1–12
51. Lin RJ, Adelman RD, Mehta SS (2012) Dyspnea in palliative care: expanding the role of corticosteroids. J Palliat Med 15:834–837
52. Hui D, Kilgore K, Frisbee-Hume S, Park M, Tsao A, Delgado Guay M, Lu C, William W, Pisters K, Eapen G et al (2016) Dexamethasone for dyspnea in cancer patients: a pilot double-blind, randomized, controlled trial. J Pain Symptom Manage 52:8–16.e1
53. Paulsen O, Klepstad P, Rosland JH, Aass N, Albert E, Fayers P, Kaasa S (2014) Efficacy of methylprednisolone on pain, fatigue, and appetite loss in patients with advanced cancer using opioids: a randomized, placebo-controlled, double-blind trial. J Clin Oncol 32(29): 3221–3228
54. Ryken TC, McDermott M, Robinson PD, Ammirati M, Andrews DW, Asher AL, Burri SH, Cobbs CS, Gaspar LE, Kondziolka D et al (2010) The role of steroids in the management of brain metastases: a systematic review and evidence-based clinical practice guideline. J Neuro-Oncol 96:103–114
55. Roth P, Happold C, Weller M (2015) Corticosteroid use in neuro-oncology: an update. Neurooncol Pract 2:6–12
56. Sodji Q, Kaminski J, Willey C, Kim N, Mourad W, Vender J, Dasher B (2017) Management of metastatic spinal cord compression. South Med J 110:586–593
57. Laval G, Marcelin-Benazech B, Guirimand F, Chauvenet L, Copel L, Durand A, Francois E, Gabolde M, Mariani P, Rebischung C et al (2014) Recommendations for bowel obstruction with peritoneal carcinomatosis. J Pain Symptom Manag 48:75–91
58. Ferguson HJ, Ferguson CI, Speakman J, Ismail T (2015) Management of intestinal obstruction in advanced malignancy. Ann Med Surg 4(3):264–270

59. Tuca A, Guell E, Martinez-Losada E, Codorniu N (2012) Malignant bowel obstruction in advanced cancer patients: epidemiology, management, and factors influencing spontaneous resolution. Cancer Manag Res 4:159
60. Feuer DJ, Broadley KE (2000) Corticosteroids for the resolution of malignant bowel obstruction in advanced gynecological and gastrointestinal cancer. Cochrane Database Syst Rev 2000: CD001219
61. Grunberg SM (2007) Antiemetic activity of corticosteroids in patients receiving cancer chemotherapy: dosing, efficacy, and tolerability analysis. Ann Oncol 18:233–240
62. Gupta K, Walton R, Kataria SP (2021) Chemotherapy-induced nausea and vomiting: pathogenesis, recommendations, and new trends. Cancer Treat Res Common 26:100278
63. Tarantino P, Modi S, Tolaney SM, Cortes J, Hamilton EP, Kim S-B, Toi M, Andre F, Curigliano G (2021) Interstitial lung disease induced by anti-ERBB2 antibody-drug conjugates: a review. JAMA Oncol 7:1873–1881
64. Vahid B, Marik PE (2008) Pulmonary complications of novel antineoplastic agents for solid tumors. Chest 133:528–538
65. Miller S, McNutt L, McCann MA, McCorry N (2014) Use of corticosteroids for anorexia in palliative medicine: a systematic review. J Palliat Med 17:482–485
66. Yennurajalingam S, Bruera E (2014) Role of corticosteroids for fatigue in advanced incurable cancer: is it a "wonder drug" or "deal with the devil". Curr Opin Support Palliat Care 8: 346–351
67. Sturdza A, Millar BA, Bana N, Laperriere N, Pond G, Wong RKS, Bezjak A (2008) The use and toxicity of steroids in the management of patients with brain metastases. Support Care Cancer 16:1041–1048
68. Harding T, Baughn L, Kumar S et al (2019) The future of myeloma precision medicine: integrating the compendium of known drug resistance mechanisms with emerging tumor profiling technologies. Leukemia 33:283–883
69. Ramamoorthy S, Cidlowski J (2016) Corticosteroids: mechanisms of action in health and disease. Rheum Dis Clin N Am 42:15–31
70. Rasche L, Kortüm K, Raab M, Weinhold N (2019) The impact of tumor heterogeneity on diagnostics and novel therapeutic strategies in multiple myeloma. Int J Mol Sci 20:1–14
71. Clarisse D, Offner F, De Boscher K (2020) Latest perspectives on glucocorticoid-induced apoptosis and resistance in lymphoid malignancies. Biochim Biophys Acta Rev Cancer 1874(2):188430