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Glucocorticoids as an adjunct to oncologic treatment in solid malignancies – Not an innocent bystander

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ABSTRACT

Glucocorticoids are steroidal hormones which exert their action via genomic and non-genomic mechanisms. In the clinical setting, glucocorticoids are utilized for their anti-inflammatory, anti-allergenic and immunomodulatory effects and for their well-established, pro-apoptotic effects on hematological malignancies. In the treatment of solid tumors, glucocorticoids serve primarily for alleviation of tumor- and treatment-related symptoms and in most cases are not considered to have a direct effect on tumor growth and spread. However, significant pre-clinical data suggest that glucocorticoids have diverse effects on tumor progression, both pro- and anti- tumorigenic. In contrast, the clinical data regarding the pro- and anti-tumorigenic effects of glucocorticoids on solid tumors is scarce, and summarized in this review. The following review presents the suggested glucocorticoids mechanism of action and the effects of glucocorticoids on tumor cells, on the tumor microenvironment and on tumor response to cytotoxic therapy, in the pre-clinical and clinical settings.

1. Introduction

Endogenous glucocorticoids are steroidal hormones essential to sustaining human life. Synthetic glucocorticoids have been utilized for medicinal purposes for over 70 years (Kadmiel and Cidlowski, 2013), first prescribed for the treatment of rheumatoid arthritis. Glucocorticoids were first used for the treatment of cancer as part of the treatment protocol of leukemia. They were later used for the treatment of many hematological malignancies due to their ability to mediate apoptosis in leukemia, lymphoma and myeloma cells (Greenstein et al., 2002; Frankfurt and Rosen, 2004).

Glucocorticoids play a key role as co-medication in the treatment of solid tumors, both in the curative and palliative settings. Synthetic glucocorticoids, such as dexamethasone, hydrocortisone and prednisone, are mostly aimed at alleviation of tumor- and treatment-related symptoms (Table 1), including edema secondary to brain metastases (Ryken et al., 2010), spinal cord compression (Sørensen et al., 1994; George et al., 2015) and superior vena cava syndrome (Rowell and Gleeson, 2001); treatment of anorexia, dyspnea, fatigue and pain (Dans et al., 2016; Yavuzsen et al., 2005; Lin et al., 2012; Hui et al., 2016; Yennurajalingam and Bruera, 2014; Wooldridge et al., 2001; Mercadante et al., 2007); prophylaxis of treatment-related nausea and vomiting (Aapro and Alberts, 1981; Chu et al., 2014; Ioannidis et al., 2000; Italian Group For Antiemetic Research, 2004); drug related hypersensitivity (Markman et al., 1999; Bookman et al., 1997) and vessel permeability/fluid retention (Markman, 2003; Piccart et al., 1997; Burris, 1996). Most recently, glucocorticoids have been established as a crucial component in the management of immune-related adverse events induced by immunotherapy (Merck, 2018; Squibb, 2016; Villadolid and Amin, 2015).

The purpose of this review is to examine the pre-clinical and clinical data on possible pro- and anti-tumorigenic effects of glucocorticoids. Specifically, we focus on effects that may be universal, affecting several or all solid tumor cell types. The specific effects of glucocorticoids on hormone-dependent cancer cells, such as prostate cancer (Narayanan et al., 2016; Ndibe et al., 2015) and breast cancer (Mitre-Aguilar et al., 2015), mediated by the effect of glucocorticoids on cellular hormone receptors, as well as the dramatic effect of glucocorticoids in the treatment of hematologic malignancies (Greenstein et al., 2002; Frankfurt and Rosen, 2004) are beyond our scope and have been reviewed elsewhere.

2. Review methodology

The presented data was collected using an electronic search of the PubMed database, with the keywords ‘glucocorticoid’, ‘solid tumors’, ‘cancer’, and ‘tumor growth’. A specific search was made regarding each cell type comprising the tumor and tumor micro-environment (i.e.

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Table 1
Medical indications of using synthetic glucocorticoids in oncologic patients.

Indication	1 dose-cyclic	1–5 days cyclic	Limited to symptom resolution	Continues treatment	Grade of recommendation and reference*
Treatment-related adverse events					
Hypersensitivity	+				A Bookman et al. (1997)
Vessel permeability/fluid retention		+			A Piccart et al. (1997); Burris (1996)
Emesis		+			A Ioannidis et al. (2000); Italian Group For Antiemetic Research (2004)
Immune-related adverse events			+		NA** (Villadolid and Amin (2015)
Anti-edema effect in case of tumor growth and/or location					
Brain metastases			+		B Ryken et al. (2010)
Spinal cord compression			+		B Sørensen et al. (1994); George et al. (2015)
Superior vena cava syndrome			+		C Rowell and Gleeson (2001)
Cancer-related symptoms					
Fatigue				+	C Yennurajalingam and Bruera (2014)
Dyspnea				+	C Lin et al. (2012); Hui et al. (2016)
Anorexia				+	C Yavuzsen et al. (2005)
Pain				+	B Wooldridge et al. (2001); Mercadante et al. (2007)

* Adopted from the Oxford Center for Evidence Based Medicine-Grade of Recommendation; Grade A-consistent level 1 studies; Grade B-consistent level 2 or 3 studies or extrapolations from level 1 studies; Grade C-level 4 studies or extrapolations from level 2 or 3 studies; Grade D- level 5 evidence or troublingly inconsistent or inconclusive studies of any level. For further information see www.cebm.net/blog/2009/06/11/oxford-centre-evidence-based-medicine-levels-evidence-march-2009.

** Based on guidelines, No trials or systemic reviews were found.

'tumor cells', 'endothelial cells', 'fibroblasts', etc.). Only peer-reviewed publications in English were considered. All cell line, animal and human studies, including pre-clinical and clinical, were considered and relevant studies were cited, irrespective of the year of publication. Furthermore, for every review paper found using this search method, we examined all the references, and relevant articles were referenced and cited.

3. Glucocorticoids mechanism of action

Synthetic glucocorticoids, like the natural glucocorticoid, cortisol, are cholesterol-derived steroidal hormones. Cortisol was the first glucocorticoid to be introduced to clinical medicine. Newer glucocorticoids, prednisone, methylprednisolone and the fluorinated glucocorticoids, dexamethasone and betamethasone, are more specific, having a greater glucocorticoid effect while exhibiting a lesser mineralocorticoid effect (Buttgereit et al., 2005). Glucocorticoids exert their action via genomic effects as well as rapid non-genomic effects. The genomic effects result in transcription modulation, both activation and repression of target genes. It is mediated by the cytosolic glucocorticoid receptor, which is a ligand-inducible transcription factor. The association of glucocorticoids to their receptor results in activation of the receptor and nuclear translocation of the complex. Gene activation (transactivation) is mediated by binding of the glucocorticoid-glucocorticoid receptor complex to a defined sequence in the promoter regions of the target genes, termed Glucocorticoid Responsive Elements (GRE) (Beato et al., 1989). The repression of gene transcription (transrepression) is mediated both via direct binding of the glucocorticoid- glucocorticoid receptor complex to negative GRE (Drouin et al., 1993; Meyer et al., 1997), as well as an indirect genomic effect, repressing gene transcription via antagonism of transcription factors activity, through protein-protein interaction (De Bosscher et al., 1997). Glucocorticoids have several non-genomic mechanisms of action which were classified by Stahn and Buttgereit (2008), Buttgereit and Scheffold (2002) into the following sub-categories:

(1) Direct interaction with cellular membranes resulting in intercalation of glucocorticoids into cellular and mitochondrial membranes altering cellular functions both by influencing cation transport via the plasma membrane and by increasing the proton leak of the mitochondria;
(2) Interaction via membrane-bound glucocorticoid receptors. The existence of such receptors has been demonstrated (Stahn et al., 2007), although their function is mostly unknown;
(3) Direct protein-protein interaction with signaling molecules that have a positive or negative effect on downstream signaling of the relevant partner. These molecules become activated following dissociation from the cytosolic glucocorticoid receptor which is induced by binding of glucocorticoids. Examples of known partners are the pro-inflammatory protein NFκB, and RAF1, a member of the mitogen-activated protein kinase (MAPK) signaling cascade (Wikström, 2003).

The genomic and non-genomic effects are both time- and dose-dependent. The non-genomic effects of glucocorticoids are faster than the genomic effects, taking effect within minutes to hours, while the genomic effects take hours to days (Cato et al., 2002). The rapidly occurring clinical effects, such as the anti-inflammatory, immunosuppressive, and anti-allergic effects, as well as some adverse events, are mediated via the non-genomic pathways (Schäcke et al., 2004, 2002). For a comprehensive review of genomic and non-genomic effects of glucocorticoids, see Stahn and Buttgereit (2008).

4. Pre-clinical data on effects of glucocorticoids on tumor cells and microenvironment

There are a significant amount of pre-clinical data regarding the effects of glucocorticoids on tumor growth and spread. Some of the data are contradictory, exerting both pro- as well as anti-tumorigenic effects (Table 2). These effects are dependent on glucocorticoids dosage, on tumor cell line and on the expression of glucocorticoid receptor in the tumor cell and supporting cells.

4.1. Glucocorticoid effect on tumor cells

4.1.1. Glucocorticoid-induced cytostatic effect

Glucocorticoids were shown to have a cytostatic effect on several solid tumor cell lines. This effect is mediated by a cell-cycle G1 arrest and was shown in hepatoma (Sánchez et al., 1993), mammary (Goya et al., 1993), thymic epithelial (Funakoshi et al., 2005), and melanoma (Osman et al., 1985) tumor cell lines. For example, the role of glucocorticoids on G1 arrest in hepatoma was studied using the BDS1 rat