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Review Article

The Role of Glucocorticoids in the Treatment of Non-Hodgkin Lymphoma

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Abstract

First line chemotherapy for aggressive non-Hodgkin lymphoma (NHL) typically involves high doses of glucocorticoids (GCs) over several days. The most commonly used combination chemotherapy regimen for NHL includes cyclophosphamide, adriamycin, vincristine, and prednisone (CHOP) or given with rituximab (R-CHOP). The dose of prednisone used in the R-CHOP regimen varies in historical studies and in current clinical trials. There is a paucity of prospective data outlining the management of hyperglycemia during chemotherapy in diabetics or the risk of hyperglycemia or steroid-induced hyperglycemia during or following chemotherapy. Often, the adverse short and long-term effects of high doses of GCs are not reported in clinical trials. We will discuss the history of GC incorporation into combination chemotherapy for lymphoma, the potential implications of liberal GC use in this population, and the opportunities for further research.

Keywords: Glucocorticoid; Steroid; Non-Hodgkin lymphoma; Diabetes; Cancer; Hyperglycemia

Introduction

Glucocorticoids (GCs) are a class of steroid hormones produced in the adrenal cortex and are responsible for regulation of physiologic functions and stress related homeostasis in humans [1]. The most common endogenous GC is cortisol. Exogenously administered systemic GCs include dexamethasone, prednisolone, triamcinolone and prednisone. Synthetic steroids are made from cholic acid obtained from cattle or plants and further modified into oral, injectable or topical agents [2]. Clinicians use synthetic GCs for a variety of benign and malignant diseases [3-5]. GCs have been known to affect the volume, structure, and function of lymphoid tissue since 1944, when cortisone was found to cause tumor regression in a murine model [6]. Further studies confirmed this finding and now GCs are widely used in the treatment of hematologic malignancies [7]. GCs are effective when combined with chemotherapy, but are also effective for treatment of cancer-related nausea, pain, anorexia, and other chemotherapy-related side effects. In lymphomas, the use of GCs in combination with cytotoxic chemotherapy is particularly attractive because of non-overlapping toxicity. Although used in many therapeutic settings, GCs are associated with many adverse effects such as weight gain, immunosuppression, and osteoporosis. Moreover, at high doses GCs may result in insulin resistance causing overt diabetes in pre-diabetics or worsening underlying diabetes in those with mild disease.

What is the mechanism of action as a cancer therapeutic?

The ability of GCs to affect proliferation and apoptosis in malignant cells is predominantly initiated by mechanisms mediated by the binding of GCs to the GC receptor (GCR), an intracellular ligand-dependent transcription factor [8]. Once activated by their ligand, the GCR can act through transactivation or transrepression to mediate pro-apoptotic signaling pathways [9]. While GC-induced apoptosis is dependent on adequate levels of the GCR, the mechanism of GC-induced apoptosis is complex and involves multiple signaling pathways [10,11]. In hematologic malignancies, pathways involved in GC induced apoptosis include transactivation of Bim, a BH-3 only protein and apoptosis inducing member of the Bcl-2 family, and inhibition of the pro-survival transcription factors, AP-1 and NF-kB [12]. The transcriptional upregulation of Bim results in initiation of the intrinsic apoptotic pathway, via activation of Bax/Bak complexes, mitochondrial destabilization through mitochondrial outer membrane permiablization (MOMP), formation of the apoptosome and ultimately activation of Caspase 9 and the executioner caspase, Caspase 3 [13]. In solid tumors, such as breast and prostate cancer, the molecular mechanisms of GC induced apoptosis are less well-defined and the benefits of GCs as a cancer therapeutic are less clear [14].

The most commonly used initial steroid for NHL is prednisone, although dexamethasone is often used in other hematologic malignancies. While the superiority of prednisone versus dexamethasone has not been extensively studied in NHL, in pediatric acute lymphoblastic leukemia (ALL), dexamethasone results in lower incidences of relapse, particularly in the central nervous system, as compared to prednisone or prednisolone, but is associated with increased toxicity [15-17]. In adult ALL, dexamethasone is not superior to prednisolone and is associated with comparable toxicity [18].

How does glucose metabolism occur in cancer cells?

In 1926, Otto Warburg postulated that in the presence of oxygen, malignant cells have increased glucose consumption as compared to non-malignant cells leading to increased lactic acid levels [19]. This observation helped to coin the term aerobic glycolysis. Indeed, for reasons that are still being elucidated, cancer cells show increased

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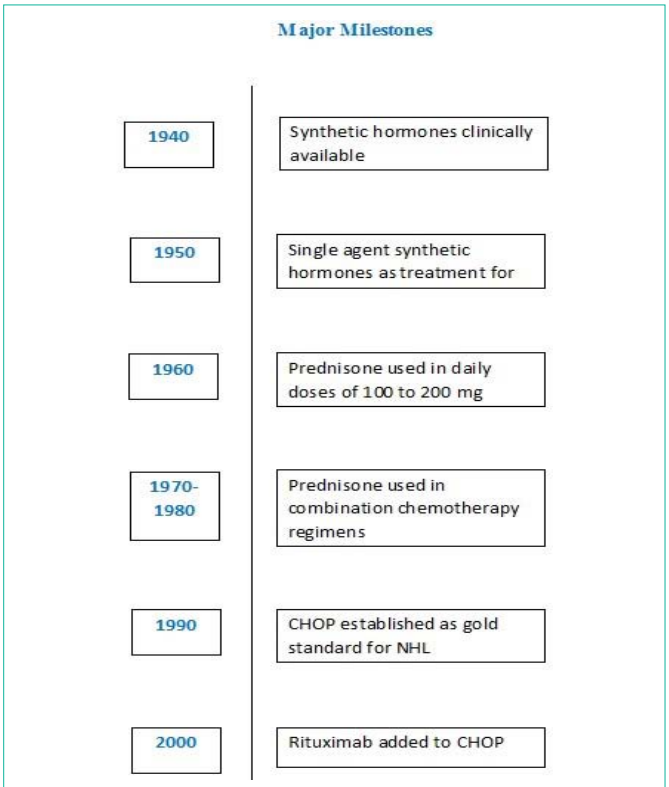

Figure 1: Significant events that led to the combination chemotherapy regimen used in NHL.

utilization of the glycolytic pathway [20]. Understanding this increased glucose metabolism provides a means for clinicians to utilize a technology developed to detect glucose utilization in cells, the positron emission tomography (PET) scan [21]. A PET scan is a nuclear medicine imaging procedure that uses a radiotracer, and in combination with a computed tomography (CT) scans produces images of targeted anatomical regions (CT), highlighting areas of increased glucose metabolism (PET). The most commonly used glucose analog radiotracer is 18-fluorodeoxyglucose (FDG), which was developed out of the need for a radiotracer with a longer half-life [22]. FDG, and other radiolabeled glucose derivatives, compete with glucose for energy utilization. However, when these radiolabeled analogs are processed, they become phosphorylated, like glucose, but cannot be further processed. This intermediate moiety is trapped in cells, providing a means for the potential detection of certain cancers like lymphomas [23]. The National Comprehensive Cancer Network (NCCN) recommends a PET-CT scan for initial staging of FDG-avid lymphomas. The scans can be more useful for identifying bone marrow infiltration than bone marrow biopsies in certain situations [24]. In 2014, the Lugano criteria were published and PET-CT scans were recommended for response assessment in FDG-avid lymphomas [25]. The results of interim PET scans are prognostic of survival in Hodgkin lymphoma [26].

How are glucocorticoids used in the treatment of lymphoma?

Cortisone acetate and adrenocorticotropic hormone were first clinically available in 1948, with the initial published studies on its use in patients with lymphomas in 1949 [27]. Figure 1 describes the significant events that led to the combination chemotherapy regimen used in NHL. In the early 1950's, Rosenthal published the results of ten patients with lymphosarcoma and Hodgkin lymphoma treated with ACTH. The use of ACTH resulted in decreased organomegaly, adenopathy, hemolytic anemia, and improved appetite in some patients. The benefit, however, was only temporary [28]. Another study was then undertaken to evaluate the impact of "massive doses" of steroids defined as up to 500 milligrams of prednisone or prednisolone daily in patients with refractory lymphomas. Objective though transient remissions were obtained, but the complications of diabetes, infection, psychosis, and gastric ulceration or perforations were "forbidding" in their opinion. The authors concluded that "it is clear that massive steroid therapy can be justified only as a heroic measure to meet a desperate situation and then administration must be limited to a relatively brief period of time" [29]. In the early 1960's, Kofman, et al. sought to determine the most effective prednisolone dose and evaluated response to therapy based on Karnofsky performance status. Although, Kofman noted "when the impressive array of side effects due to corticosteroids is reviewed, it is surprising that corticosteroids have any role in clinical medicine". He documented tumor regressions in 28 patients out of the 53 treated. Further, this study found that patients that did not respond to 30 mg of prednisolone/day did respond to daily doses of 100 to 200 mg, but that none of patient's refractory to 100 to 200 mg responded to larger doses [30]. Currently, prednisone remains the most commonly used steroid in first-line combination regimens. Dexamethasone has been incorporated in salvage regimens such as combined with cytarabine and cisplatin (DHAP) or gemcitabine and cisplatin (GDP). Using rituximab as a backbone, the dose of dexamethasone in R-DHAP and R-GDP is 40 mg daily on days 1 through 4 [31,32]. Methylprednisolone is combined with etoposide, cisplatin, and cytarabine in (ESHAP). The dose of methylprednisolone used is 500 mg daily for 5 days [33]. Prednisone is considered an intermediate acting synthetic steroid while dexamethasone is considered long acting.

Later, GCs were used as part of chemotherapy combination regimens because the toxicity of GCs, such as prednisone, did not significantly overlap with that of other compounds, such as alkylating agents or anti-metabolites [7]. In 1993, Fisher published the definitive trial that established CHOP as the gold standard therapy for diffuse large B cell lymphoma. In this trial, prednisone 100 mg daily was given on days one through five of each chemotherapy cycle [34]. The prednisone dosing regimens have varied in many trials. Table 1 lists some of the major trials in lymphoma and the steroid dosing regimen used. None of the studies reported the incidence of hyperglycemia. The table also includes the total steroid dose of prednisone given each cycle. This does not include steroid dosing that may have been as pre-medications or for treatment of chemotherapy related side effects.

What are potential complications of steroids use during chemotherapy?

Toxicity from GCs used in combination with chemotherapy is often not reported in clinical trials. Common Terminology Criteria for Adverse Events version 4 (CTCAE v4.0) defines hyperglycemia in the fasting state only as the upper limit to 160 mg/dL; >160 – 250 mg/dL; >250 – 500 mg/dL and >500 mg; life threatening consequences for grade 1, 2, 3, and 4, respectively. Not only has a diagnosis of diabetes been associated with adverse outcomes in those with solid

Table 1: Prednisone dosing for major front-line lymphoma studies.

Author	Trial	N	Prednisone dosing schedule	Total prednisone equivalent doses based on BSA 2 m^2
[52]	GELA	399	40 mg/m^2 daily on days 1-5 each cycle	400 mg every 21 days
[53]	SWOG 8736	401	Prednisone 100 mg daily for days 1-5 each cycle	500 mg every 21 days
[54]	MInT	824	100 mg prednisone daily 1-5 each cycle (CHOP)	500 mg (CHOP) every 21 days
			40 mg/m^2 on days 1-84 (MACOP-B)	6,720 mg (MACOP-B) over 84 days
			50 mg prednisone d1-28 and alternating on days 29-84 (PMitCEBO)	2800 mg (PMitCEBO) over 84 days
[55]	US Intergroup	632	Prednisone 100 mg/m^2 daily on days 1-5	1000 mg
[56]	RICOVER-60	1222	Prednisone 100 mg days 1-5 each cycle	500 mg
[57]	Dose adjusted EPOCH	50	Prednisone 60 mg/m^2 BID on days 1-5 of each cycle	1200 mg

tumor malignancies, the presence of hyperglycemia during therapy has correlated with other grade III and IV non-hematologic toxicity in NHL [35-38]. A retrospective study found that the risk of steroid-induced diabetes in patients with lymphoma treated with CHOP was over 30%; independent risk factors included obesity and hemoglobin A1C >6% [39]. Further, diabetes or steroid induced hyperglycemia has been associated with poor outcomes in other hematologic malignancies such as multiple myeloma and ALL [40-43]. In acute myeloid leukemia (AML), hyperglycemia is associated with increased hospital mortality [44].

In multiple myeloma, the (IFM) 95-01 trial randomized 488 patients aged 65 to 75 years to melphalan-prednisone, dexamethasone alone, melphalan-dexamethasone, and dexamethasone-interferon alpha. Dexamethasone use was not recommended in elderly patients due to toxicity including severe diabetes, infection, hemorrhage, psychiatric complications, and DVT/PE [45]. Rajkumar, et al. published the results of low dose dexamethasone given 40 mg on days 1, 8, 15, and 22 of a 28-day cycle versus high dose dexamethasone 40 mg on days 1-4, 9-12, and 17-20 of a 28-day cycle in patients with multiple myeloma. The study showed improved overall survival and decreased incidence of deep vein thrombosis, infection, hyperglycemia, and grade 3 or 4 non-hematologic toxicity in the low dose dexamethasone arm [46].

How should hyperglycemia and/or diabetes be managed during or after chemotherapy?

From 1980 through 2014, the number of adults diagnosed with diabetes nearly quadrupled from 5.5 million to 21.9 million in the United States [47]. There is a paucity of data advising clinicians on how to manage GC-induced hyperglycemia during cancer therapy in the outpatient setting. The American Diabetes Association recommends a hemoglobin A1C target of less than 7% in most individuals and a target of less than 8% in those with comorbid conditions and/or limited life expectancies. The NCCN recommends that oral corticosteroids for supportive care should be used at the lowest possible dose for the shortest duration of time in patients over the age of 65, but does not have specific recommendations in the treatment setting [48]. It has been suggested that all patients should be screened for diabetes before initiating GC therapy and then routinely monitored during therapy. Treatment is then dependent on whether the patient has type 1 or 2 diabetes, the severity of the hyperglycemia, and the dose and duration of therapy. Often, oral hypoglycemic medications are not adequate and insulin is required [49]. Hershey, et al. (2014) reported that diabetes self- management significantly decreased while symptom severity significantly increased in patients over the age of 50 who were on chemotherapy for a minimum of eight weeks [50].

Discussion

NHL is often successfully treated with combination chemotherapy that includes high doses of GCs. While the use of GCs for treatment of NHL dates back several decades, their role in CHOP or CHOP-like chemotherapy remains anecdotal. The significant toxicity associated with liberal GC use has been described in ALL, AML, and multiple myeloma, but needs further evaluation in NHL. The complications of hyperglycemia or diabetes during chemotherapy, however, may have short and long-term impact. In the United States, the economic burden of diabetes and prediabetes are estimated to total $322 billion annually [51]. The goals of curative chemotherapy must be balanced with the potential long-term complications of uncontrolled glycemia. More prospective studies are required in NHL to identify the patients at risk for GC-induced complications, to manage potential short-term complications and to alleviate potential long-term complications. Currently, the role of GCs in the treatment of NHL is unclear because the optimal dose and optimal duration of GC use, and the risk of GC induced hyperglycemia or diabetes, are limited and require refined definitions.

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