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Intermittent High-Dose Glucocorticoid Treatment Does Not Cause Adrenal Insufficiency in Patients with Diffuse Large B-Cell Lymphoma: A Prospective Study

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Glucocorticoids · Adrenal insufficiency · Diffuse large B-cell lymphoma

Abstract
Glucocorticoid (GC) treatment suppresses the hypothalamic-pituitary-adrenal axis and can cause GC-induced adrenal insufficiency. In this study, we investigated the incidence of GC-induced adrenal insufficiency in patients receiving intermittent short-term high-dose oral GC treatment for newly diagnosed diffuse large B-cell lymphoma. Cosyntropin stimulation test was used to assess adrenal function at study entry (baseline), at 2 months (before the 5th cycle), and 6 months from baseline (3 months after the last cycle). Ten patients were included (40% women). Mean age was 61 years. The mean (range) plasma morning cortisol was 407 (320–530) nmol/L at baseline, 373 (260–610) nmol/L at 2 months, and 372 (230–520) nmol/L at 6 months from baseline. All patients had normal response to cosyntropin stimulation at baseline as well as 2 and 6 months from baseline. Thus, none of the patients developed biochemically verified adrenal insufficiency. Therefore, short-term high-dose GC therapy, a commonly used adjuvant treatment in patients with malignant hematological diseases, does not seem to down-regulate the hypothalamic-pituitary-adrenal axis.

Introduction

Pharmacological glucocorticoid (GC) treatment suppresses the hypothalamic-pituitary-adrenal axis and may cause GC-induced adrenal insufficiency, also known as tertiary adrenal insufficiency [1, 2]. Long-term GC treatment and high doses of GCs are thought to increase this risk [2]. The diagnosis of adrenal insufficiency is biochemically verified by a confirmatory dynamic test such as the cosyntropin stimulation test [3].

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GCs are commonly used in high doses as an adjuvant treatment to chemotherapy for treatment of various malignant diseases. Previous studies have shown that 20–67% of patients with hematological malignancies have suppressed adrenal function after such GC treatment [4–7], whereas according to a meta-analysis, including data from 20 patients with hematological malignancies, the weighted risk of GC-induced adrenal insufficiency was 60% [2]. More recent studies have investigated adrenal function after intermittent high-dose GC treatment and shown that 20–30% of the patients develop adrenal insufficiency after the 3rd (9 weeks from baseline) or 5th (15 weeks from baseline) treatment cycle [6, 7]. Given that GC-induced adrenal insufficiency may cause deterioration of the patient's health and possibly lead to death, it is important to know if intermittent high-dose GC treatment causes adrenal insufficiency.

Materials and Methods

This was a prospective pilot study. Patients (>18 years old) with newly diagnosed diffuse large B-cell lymphoma, who were planned to receive short-term high-dose GC therapy as part of chemo-immunotherapy, were included. The patients were recruited at the Department of Hematology and Coagulation at Sahlgrenska University Hospital between March 1, 2018 and January 20, 2020. Patients using any forms of GCs (e.g., oral, inhalation, nasal spray, injections, or ointment) before the study start were excluded. In addition, all patients with adrenal metastasis or previous history of adrenal insufficiency were excluded from participation.

All patients were planned for 6 cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) with either 14- or 21-day intervals (denoted as R-CHOP-14 and R-CHOP-21, respectively). The prednisone dose was 50 mg/m^2 per day on day 1–5 during each cycle. Thus, the interval between prednisone treatment was 9 days for R-CHOP-14 and 16 days for R-CHOP-21. Cosyntropin stimulation test was used to assess adrenal function at study entry (baseline), 2 months from baseline (before the 5th cycle), and 6 months from baseline (3 months after the last cycle). The cosyntropin stimulation test is a dynamic test where 250 μg of synthetic adrenocorticotropic hormone (SYNACTHEN®) is administrated intravenously. Plasma cortisol concentrations were measured before as well as 30 and 60 min after the injection. All the cosyntropin stimulation tests were done between 8 and 9:00 a.m. after overnight fast. Plasma adrenocorticotropic hormone (ACTH) concentration was also measured before the injection. Morning plasma cortisol (between 8 and 9:00 a.m.) >280 nmol/L and peak plasma cortisol 30 or 60 min after injection of cosyntropin >450 nmol/L were defined as normal adrenal function [8–10]. Plasma cortisol concentrations were determined by radioimmunoassay (Roche Cobas, Cortisol-II). The coefficient of variation was 7% at 100 nmol/L and 5% at both 570 and 990 nmol/L. Plasma ACTH was measured by electrochemiluminescence assays, with a reference interval of 1.6–14 pmol/L.

The clinical characteristics are presented as mean ± standard deviation, median (range), or number (%). Repeated measures ANOVA was used to investigate significant difference between measurements (morning cortisol, peak cortisol, plasma sodium, plasma ACTH, systolic blood pressure, body mass index) at baseline, 2 months, and 6 months from baseline. The study was approved by the Regional Research Ethics Committee in Gothenburg, Sweden (reference number 750-17, approved October 23, 2017). All patients gave written informed consent prior to participation.

Results

Ten patients, 4 women and 6 men, with a mean age of 61 years (range 40–78 years), were included in the study (Table 1). Six patients had no medications. Three patients were being treated for hypertension and two for diabetes. Eight patients were planned for R-CHOP-14 and 2 patients for R-CHOP-21. One patient had 2 cycles of R-CHOP-14 and was then converted to R-CHOP-21. In three cases, the patient received 4 cycles of R-CHOP-14 and received thereafter 2 cycles of only rituximab due to limited disease. The mean prednisone dose used was 95 mg/day (range 75–100 mg/day) (Table 1).

All patients had normal morning plasma cortisol and normal response to cosyntropin stimulation at baseline. During follow-up, all patients had adequate response to cosyntropin stimulation, both at 2 months from baseline (before 5th cycle) as well as at 6 months from baseline (3 months after last cycle) (Fig. 1, 2). One patient had morning cortisol of 260 nmol/L at 2 months and 2 patients had plasma morning cortisol of 230 and 240 nmol/L at 6 months. All these patients had adequate responses to cosyntropin stimulation test. There was no statistically significant difference in morning cortisol, peak cortisol, or plasma ACTH between baseline, 2 months, and 6 months ($p = 0.607$, $p = 0.247$, and $p = 0.198$, respectively; Table 2). At baseline, 2 months, and 6 months, plasma sodium concentration, systolic blood pressure, and body mass index were not significantly different ($p = 0.780$, $p = 0.206$, and $p = 0.059$, respectively).

Discussion

Our study indicates that short-term high-dose oral GC therapy does not down-regulate the hypothalamic-pituitary-adrenal axis in patients with diffuse large B-cell lymphoma, results that are in contrast with two previous studies. These studies, by Owattanapanich et al. [6] and by Manosroi et al. [7] showed transient

Table 1. Information on type of treatment and time from baseline to cosyntropin stimulation test

	Type of chemotherapy	Prednisone dose	Weeks from baseline to 5th cycle	Weeks from baseline to last visit
Patient 1	R-CHOP-14	75 mg	10	28
Patient 2	R-CHOP-14	100 mg	8	24
Patient 3	R-CHOP-14 × 2 and R-CHOP-21 × 4	75 mg	12	28
Patient 4	R-CHOP-14	100 mg	8	24
Patient 5	R-CHOP-14	100 mg	9	23
Patient 6	R-CHOP-21	100 mg	12	30
Patient 7	R-CHOP-14 × 4 and R × 2	100 mg	8	25
Patient 8	R-CHOP-14	100 mg	8	NA
Patient 9	R-CHOP-21 × 4 and R × 2	100 mg	12	NA
Patient 10	R-CHOP-14 × 4 and R × 2	100 mg	8	23
Mean± SD		95±10.5	9.5±1.8	25.6±2.7

R-CHOP-14, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone with 14-day intervals; R-CHOP-21, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone with 21-day intervals; R, rituximab therapy; NA, not applicable; SD, standard deviation.

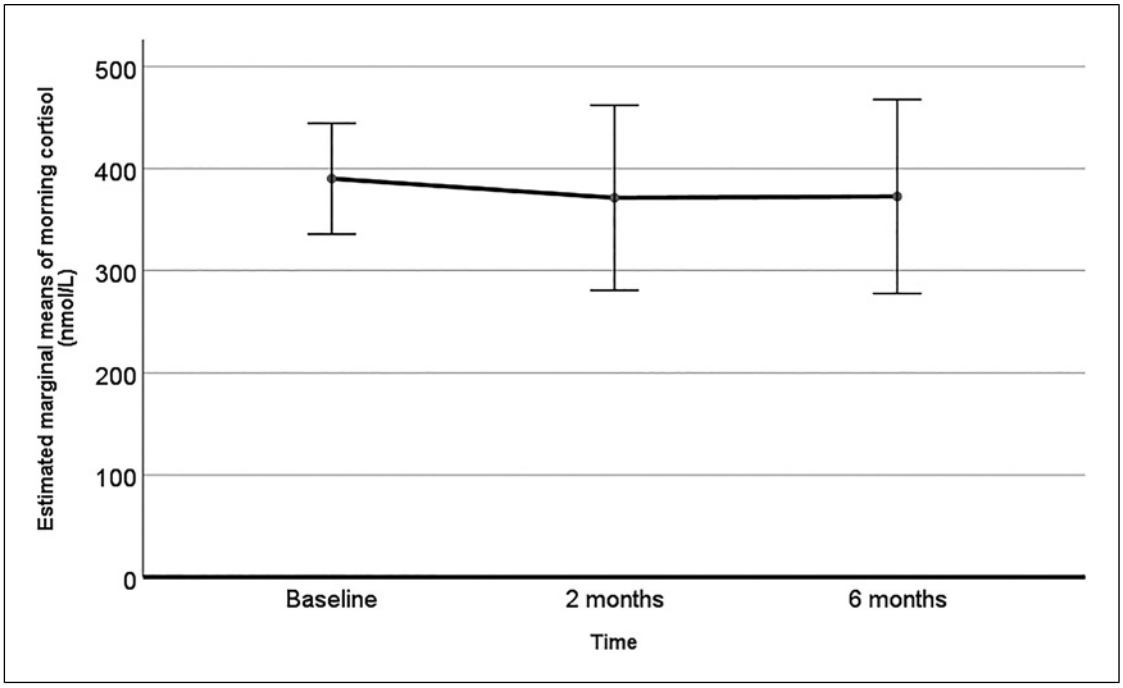

Fig. 1. Estimated marginal means of morning plasma cortisol (nmol/L) at baseline, 2 months, and 6 months from baseline. Error bars are 95% confidence interval.

adrenal insufficiency during R-CHOP-21 therapy in a significant subset of the patients. Owattanapanich et al. [6] included 10 patients with diffuse large B-cell lymphoma receiving R-CHOP-21. Adrenal function was assessed with a low-dose (1 μg) cosyntropin stimulation before every cycle. Three of 10 patients were considered to have adrenal insufficiency with the highest incidence after the 5th cycle. The adrenal function recovered 3–5 weeks after the last cycle in all patients [6]. In the study of Manosroi et al. [7], 15 patients with diffuse

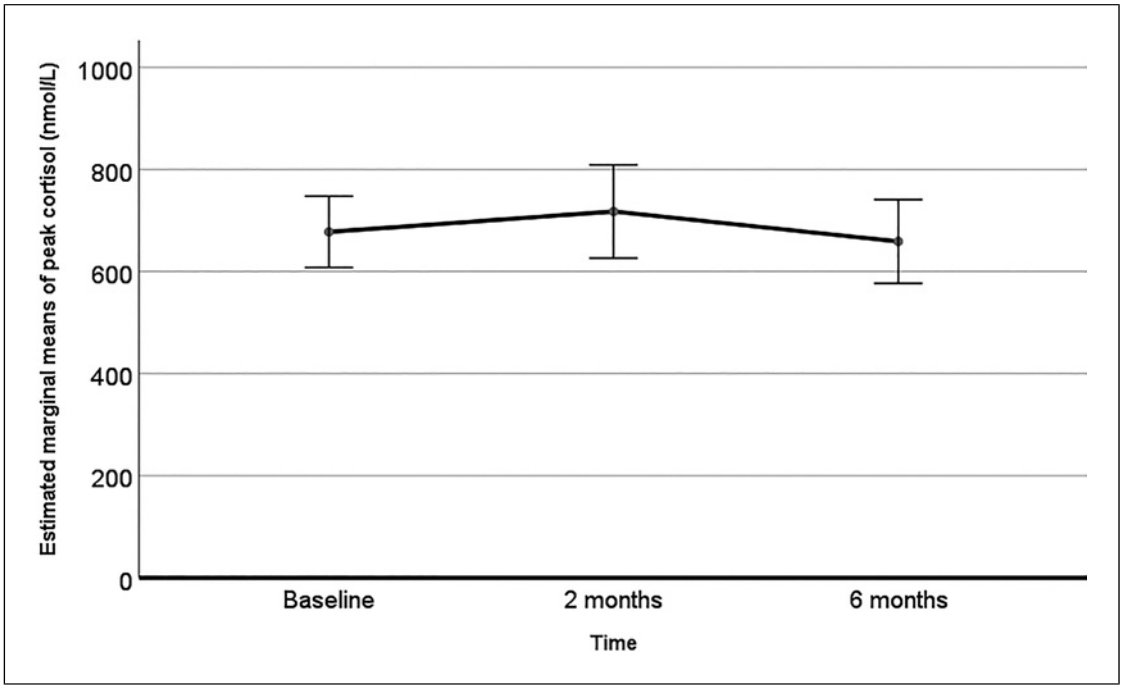

Fig. 2. Estimated marginal means of peak plasma cortisol (nmol/L) at baseline, 2 months, and 6 months from baseline. Error bars are 95% confidence interval.

large B-cell lymphoma were included and three of them developed adrenal insufficiency after the 5th cycle, defined as peak cortisol <400 nmol/L (<14.5 μg/dL) following a low-dose (5 μg) cosyntropin stimulation.

There are several potential explanations for the different findings in the current study in relation to the above-mentioned studies. Our study had a different design, with shorter intervals between the R-CHOP cycles (14 days for most of the patients in our study but 21 days in previous studies), a high-dose (250 μg) synthetic ACTH was used to evaluate the hypothalamic-pituitary-adrenal function and the definition of adrenal insufficiency was different. Previously, low-dose cosyntropin stimulation test was considered to offer better diagnostic accuracy than the high-dose test in diagnosing secondary adrenal insufficiency [11, 12]. However, a meta-analysis based on 30 studies, showed that the diagnostic accuracy does not differ between the high- and low-dose cosyntropin stimulation test [13]. Importantly, however, several studies have shown a risk of false-positive results with the low-dose cosyntropin stimulation test, i.e., being diagnosed with adrenal insufficiency without actually having it, rising from technical problems in connection with dilution of the synthetic ACTH, and that the peak cortisol cutoff value has been set too high [14, 15]. For instance, adrenal insufficiency was defined as peak cortisol <497 nmol/L (<18 μg/dL) after a low-dose cosyntropin stimulation test in the study by Owattanapanich et al. [6]. This is a high cutoff value and could therefore cause false-positive results [15]. The peak cortisol cutoff value had been set lower (450 nmol/L [<16.3 μg/dL] as in our study), only 2 patients with marginally low cortisol (386 and 440 nmol/L, respectively) would have met the criteria of adrenal insufficiency.

Our results are in line with a previous study on patients receiving IV methylprednisolone as a pulse treatment for Graves' ophthalmopathy. Twelve patients were included and treated with methylprednisolone weekly for 12 weeks. None of the patient had adrenal insufficiency on high-dose cosyntropin stimulation test before the final pulse infusion [16].

The small sample size is the main limitation of our as well as for the aforementioned studies. Patients with newly diagnosed lymphoma are receiving a physically and psychologically demanding chemotherapy and participation in scientific studies with additional testing, and appointments can therefore be difficult. Consequently, the participation rate in the current study was low. However, even if it cannot be ruled out that intermittent short-term high-dose GC treatment may develop clinically significant adrenal insufficiency in

Table 2. BMI, blood pressure, and laboratory blood test results at baseline, 2 months, and 6 months from baseline

	Baseline (n = 10)	2 months from baseline (n = 10)	6 months from baseline (n = 8)*	p
BMI, kg/m^2				0.059
Mean±SD	25.8±5.1	24.7±5.1	25.4 (6.2)	
Median (range)	27.6 (16.8–32.4)	25.1 (16.5–32.4)	24.5 (16.9–35.1)	
Systolic blood pressure, mm Hg				0.206
Mean±SD	126±16.8	118±17.9	124±17.4	
Median (range)	125 (104–153)	121 (87–147)	123 (101–148)	
Plasma sodium				0.780
Mean±SD	139±3.9	139±2.5	NA	
Median (range)	139.5 (130–144)	139 (136–144)	NA	
Morning plasma cortisol, nmol/L				0.607
Mean±SD	407±68	373±96	372±113	
Median (range)	390 (320–530)	360 (260–610)	395 (230–520)	
Peak plasma cortisol, nmol/L after injection of cosyntropin				0.247
Mean±SD	703±95	738±127	659±98	
Median (range)	720 (530–860)	710 (570–970)	700 (490–730)	
Plasma ACTH, pmol/L				0.198
Mean±SD	7.3±3.9	6.2±4.5	8.1±3.4	
Median (range)	6.3 (2.5–16)	5.5 (2–18)	7.4 (5.2–16)	

Data are presented as mean ± standard deviation (SD), median (range), or number (%). Repeated measures ANOVA was used to identify changes in body max index, systolic blood pressure, plasma sodium, morning plasma cortisol, peak plasma cortisol, and ACTH concentration at baseline, 2 months, and 6 months from baseline. Plasma sodium was not measured 6 months from baseline. ACTH, adrenocorticotropic hormone; NA, not applicable; BMI, body mass index. *Two patients did not undergo the last cosyntropin stimulation test because of the coronavirus pandemic and were not included in repeated measures ANOVA analysis.

some patients, we did not observe this. These findings are important for all patients receiving GC as an adjuvant treatment to chemotherapy for malignant diseases. Nevertheless, the awareness of GC-induced adrenal insufficiency is essential and in case of symptoms and signs, it is critical to investigate and treat these patients appropriately.

In conclusion, this pilot study showed that short-term high-dose oral GC therapy, a commonly used treatment in patients with malignant hematological diseases, i.e., aggressive lymphomas does not seem to down-regulate the hypothalamic-pituitary-adrenal axis.

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Statement of Ethics

The study was approved by the Regional Research Ethics Committee in Gothenburg, Sweden (reference number 750-17, approved October 23, 2017). All patients gave written informed consent prior to participation.

Conflict of Interest Statement

G.J. has served as consultant for Shire, Ascendis Pharma, and AstraZeneca and has received lecture fees from Novo Nordisk, Shire, and Pfizer. M.J.E., H.L.K., R.B., P.T., C.L., and O.R. have no conflicts of interest to declare.

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Author Contributions

M.J.E., O.R., G.J., R.B., P.T. designed the study. O.R. supervised the study. M.J.E., H.L.K., and C.L. collected the data. M.J.E. performed the statistical analysis. M.J.E. and O.R. wrote the original draft of the manuscript. All authors reviewed and approved the final manuscript. G.J. obtained funding. O.R. and M.J.E. are guarantors.

Data Availability Statement

Data are not publicly available due to ethical reasons. Further inquiries can be directed to the corresponding author (margret.jona.einarsdottir@gu.se).

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