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Impact of Dexamethasone on Metabolic Profile and Survival in Glioblastoma

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Abstract

Background: Although patients with glioblastoma require corticosteroids, such as dexamethasone, for symptom control, they could worsen prognosis. However, it is not clear whether personalized corticosteroid doses have this effect. We have examined the effects of different doses of dexamethasone on the metabolic profile and prognosis of patients with glioblastoma.

Methods: Patients diagnosed with glioblastoma from 2013 to 2016 were included. We recorded changes in glycemia, glycosylated hemoglobin, insulin, Insulin-like Growth Factor 1 (IGF-1), triglycerides, and total cholesterol and correlated these changes with dexamethasone dose, Progression-Free Survival (PFS), and Overall Survival (OS).

Results: Among the 32 evaluable patients, the median daily dose of dexamethasone during radiotherapy and concomitant temozolomide was 1.4 mg/day (range=0, 8.3 mg/day). The median cumulative dose of dexamethasone was 250 mg (range=0 to 2,648 mg). Neither dexamethasone during concomitant therapy nor median cumulative dose >250 mg was associated with PFS or OS. Total cholesterol increase at progression relative to baseline levels (+20.5 mg/dL, p=0.04) was associated with cumulative dexamethasone dose >250 mg (p=0.01). Only hyperglycemia was identified as an independent marker of shorter PFS (HR, 3.7; 95% CI=1.3, 10.8; p=0.02) and OS (HR, 8.4; 95% CI=2.6, 27.1; p<0.001).

Conclusion: Personalized doses of dexamethasone are not associated with worse outcome. The interrelation between dexamethasone, cholesterol, and outcome merits further investigation.

Keywords: Dexamethasone; Glioblastoma; Glycemic profile; Lipid profile; Survival

Key Points

- First prospective study of dexamethasone impact on metabolic profile in glioblastoma
- Personalized doses of dexamethasone do not influence survival in glioblastoma
- Novel findings on the relationship between cholesterol and survival in glioblastoma

Importance of the Study

Glioblastoma is the most aggressive tumor of the brain. Dexamethasone, the corticosteroid most widely used for control of symptoms and treatment-related adverse effects, has been linked to worse prognosis. Our findings in this prospective study of glioblastoma patients indicate that personalized doses of dexamethasone do not produce changes in metabolic parameters of patients, with the exception of a correlation between cumulative dexamethasone dose and cholesterol levels. In line with other studies, hyperglycemia was linked to shorter progression-free and overall survival.

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In contrast, neither dexamethasone during concomitant therapy nor median cumulative dose >250 mg was associated with patient outcome. We suggest that treatment with dexamethasone in patients with glioblastoma should be customized according to the needs of the patient, independently of the extent of resection. The relationship between cholesterol and dexamethasone merits further investigation.

Introduction

Glioblastoma Multiforme (GBM) is the most frequent and most aggressive tumor of the CNS. Standard treatment consists of maximal surgical resection followed by radiotherapy with concomitant and adjuvant temozolomide [1,2], but prognosis is poor, with survival rates of <5% at five years [3-6]. The major prognostic factors are age, extent of resection, and methylation of the promoter of O^6-Methylguanine-DNA-methyltransferase (MGMT) [7]. Control of symptoms and of treatment-related adverse events, both at diagnosis and throughout treatment, relies mainly on corticosteroids, primarily Dexamethasone (DXM) [8,9]. DXM, a potent anti-inflammatory, is highly active against cerebral edema and can lead to clinical benefit in GBM. However, recent reports indicate that the use of DXM may be a double-edged sword, conferring benefit through its anti-inflammatory properties but also leading to poor prognosis by suppressing immune systems [10,11]. A meta-analysis of three databases of GBM patients found that DXM was negatively correlated with survival [10]. However, the retrospective nature of the meta-analysis makes it difficult to draw definite conclusions [12].

DXM has also been shown to affect the metabolic profile of patients. It can cause hyperglycemia, a marker of poor prognosis [11,13,14], which can lead to hyperinsulinemia. Hyperinsulinemia, in turn, has been shown to stimulate tumor growth through the activation of Insulin-like Growth Factor 1 (IGF-1) in colon and breast tumors [11]. However, no studies have examined the potential association between IGF-1 and tumor growth in GBM. Corticosteroids also increase lipolysis, leading to increased plasma levels of non-esterified fatty acids. These acids accumulate within muscle cells and reduce glucose uptake by interfering with insulin signaling [15]. Moreover, it has been suggested that GBM cells may rely on exogenous cholesterol for survival [16]. Nonetheless, the relationship between corticosteroids, lipid profile, and prognosis in GBM patients has not been well examined.

We have carried out a prospective study in order to shed further light on the impact of DXM on the prognosis of GBM patients. We have evaluated the glycemic and lipid profiles of GBM patients treated in our center and correlated our findings with DXM dose, Progression-Free Survival (PFS), and Overall Survival (OS).

Materials and Methods

Study design and population

This was a prospective observational study conducted at the University Hospital Dr. Josep Trueta (Girona, Spain) between November 2013 and June 2016, with follow-up concluding in July 2017. All patients aged ≥ 18 and <75 years diagnosed at our center with GBM (WHO grade IV astrocytoma [3]) and treated with the standard regimen of radiotherapy and temozolomide1 were eligible for inclusion. Patients without histological confirmation of GBM and those with other tumors were excluded. Hypo fractionated radiotherapy (40 Gy/15 fractions over 3 weeks [17] was allowed in some cases according to the criteria of the attending medical and radiation oncologists.

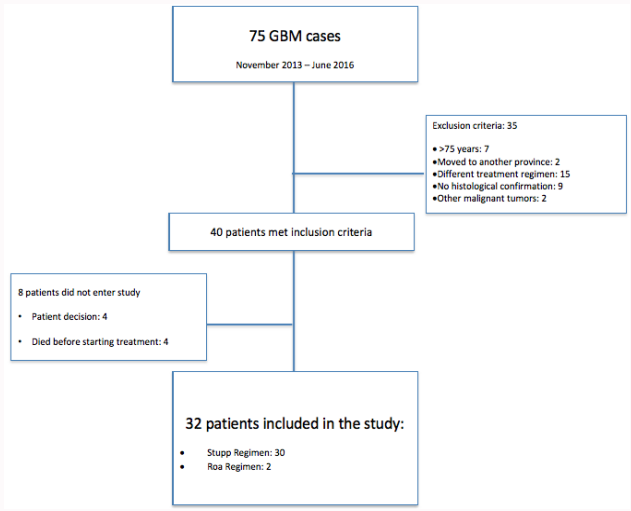

Figure 1: Chart showing flow of patients through the study.

Once the histological diagnosis of GBM was confirmed, a baseline blood sample was drawn. To ensure that baseline glucose values were measured prior to the initiation of DXM treatment, patients with a radiological image highly suspicious of GBM had an emergency room blood test (non-fasting glucose). Subsequently, a blood sample (fasting glucose) was drawn every three months until progression. The following metabolic parameters were measured in all blood samples: glucose, glycosylated Hemoglobin (Hb1Ac), insulin, IGF-1, total cholesterol, and triglycerides. Clinical and demographic characteristics were recorded for all patients, including episodes of hyperglycemia (fasting glucose ≥ 126 mg/dL), DXM daily doses during concomitant treatment, and cumulative dose of DXM (calculated from the beginning of concomitant treatment to disease progression) [18].

Clinical follow-up was performed at the start and at the conclusion of the concomitant treatment, every four weeks during adjuvant treatment, and subsequently every three months until progression. Disease progression was determined according to Response Assessment in Neuro-Oncology (RANO) criteria. Patients were censored at the last follow-up if progression or death did not occur [19].

Ethics statement

The trial was approved by the Ethics Committee of our center and conducted in compliance with the principles of Good Clinical Practice of the Declaration of Helsinki.

Statistical analyses

Patient baseline characteristics and metabolic profiles were summarized by absolute frequencies for categorical variables and by mean or median and range for continuous variables. Changes in metabolic parameters between baseline and disease progression were compared with a paired t-test or with the Wilcoxon signed-rank test when the assumption of normality was not fulfilled. A linear regression analysis was performed to evaluate changes in the metabolic parameters as a function of the cumulative dose of DXM.

PFS was calculated from surgery to progression, and OS was calculated from surgery to death from any cause. Univariate analyses for PFS and OS were performed including patient baseline metabolic parameters, episodes of hyperglycemia, DMX dose during

Table 1: Baseline characteristics of the study population.

Characteristic		N=32 n (%)
Age, yrs	Mean (range)	59.7 (47-72)
Sex	Male	21 (65.6)
	Female	11 (34.4)
Extent of resection	≤ 5%	1 (3.1)
	6% to 33%	8 (25.0)
	34% to 67%	11 (31.3)
	68% to 95%	9 (28.1)
	96% to 100%	1 (3.1)
	Biopsy only	1 (3.1)
	Unknown	1 (3.1)
KPS	90% to 100%	22 (68.7)
	70% to 80%	8 (25.1)
	≤ 60%	2 (6.2)
MMSE score	30-27	17 (53.1)
	≤ 26	15 (46.9)
MGMT methylation status	Methylated	14 (43.8)
	Unmethylated	17 (53.1)
	Unknown	1 (3.1)
IDH	Wild-type	28 (87.5)
	Mutated	0 (0)
	Unknown	4 (12.5)
Diabetes Mellitus	Yes	6 (18.8)
	No	26 (81.2)
Dyslipidemia	Yes	6 (18.8)
	No	26 (81.2)
Treatment regimen	Standard	2 (6.2)
	Hypofractionated RT+TMZ	30 (93.8)

MMSE: Mini Mental State Examination; IDH: Isocitrate Dehydrogenase; TMZ: Temozolomide

concomitant treatment, and cumulative DXM dose [18]. Cut-offs for glycemia, HbA1c, total cholesterol, and triglycerides were based on prior published reports [18,20,21] cut-offs for insulin and IGF-1 were the median values. Results of the analyses were expressed as Hazard Ratios (HR) with their corresponding 95% Confidence Intervals (CI). Significance was set at $p \leq 0.05$. All statistical analyses were performed using SPSS version 22 (IBM).

Results

Patient characteristics

Figure 1 shows the flow of patients through the study. During the study period, 75 patients were diagnosed with GBM in our center, but only 40 met the inclusion criteria. Eight patients withdrew from the study (four due to death; four due to patient decision). The remaining 32 patients were included in the analyses.

Only seven patients (21.9%) were >65 years of age. Six (18.8%) had a medical history of Diabetes Mellitus type 2 (DM2) and six (18.8%) dyslipidemia; three of these patients had both DM2 and dyslipidemia. Thirty patients (93.8%) received the standard treatment, [1] while two (6.2%) received hypo fractionated radiotherapy plus temozolomide [17]. All 32 patients started adjuvant temozolomide, but only 14 (43.8%) completed all six cycles. During follow-up, six patients (18.8%) had at least one episode of hyperglycemia (Table 1).

DXM dose

At diagnosis, all patients received DXM for symptom control. The initial dose was 12 mg/day in 31 patients and 16 mg/day in the remaining patient. After surgery, all patients received tapering doses of DXM.

During concomitant treatment, 25 patients (78.1%) required DXM. Of the remaining seven patients, six received DXM during adjuvant treatment and follow-up, while one did not require corticosteroids at any time until progression. The median dose of DXM during concomitant treatment was 1.4 mg/day (range: 0, 8.3 mg/day), while only seven patients received doses of >4 mg/day. The median cumulative dose of DXM was 250 mg (range: 0, 2648 mg).

Metabolic parameters and cumulative DXM dose

Table 2 shows the changes in metabolic parameters from baseline to progression. Only glycemia (mean decrease of 12.8 mg/dL; p=0.01) and total cholesterol (mean increase of 20.5 mg/dL; p=0.04) showed significant changes. The linear regression analysis showed an association between change in total cholesterol and DXM dose (p=0.01), where patients who received a cumulative dose of DXM >250 mg had the greatest increase (45.3 mg/dL). The change in glycemia was not associated with cumulative DXM dose (p=0.8) (Table 2).

Survival

Median PFS was 8 months (95% CI=4.5, 11.4), and median OS was 18.8 months (95% CI=15.2, 22.4). Disease progression was the cause of death in all patients. Episodes of hyperglycemia were associated with shorter PFS (HR =3.7; 95% CI=1.3, 10.8; p=0.02) and shorter OS (HR=8.4; 95% CI=2.6, 27.1; p<0.001) (Table 3 and 4).

DXM >4 mg/day during concomitant treatment was not associated with PFS (HR = 0.8; 95% CI=0.3, 2.0; p=0.59) or OS (HR=1.2; 95% CI=0.4, 3.3; p=0.76). Cumulative DXM dose >250 mg was not associated with PFS (HR=1.1; 95% CI=0.5, 2.4; p=0.86) or OS (HR=1.9; 95% CI=0.8, 4.8; p=0.15) (Table 3 and 4).

Discussion

Although DXM has been linked to poor prognosis in GBM, perhaps through its possible impact on the metabolic profile of patients, the relationship between different metabolic parameters and DXM dose has not been well explored. We have carried out a prospective study to examine the potential relationship between metabolic parameters, DXM dose, and outcome in a series of 32 GBM patients treated at a single center. Our findings indicate a significant increase in total cholesterol as a function of the cumulative DXM dose >250 mg (p=0.01) but no other associations between metabolic parameters and DXM dose. Somewhat unexpectedly, there was no association between DXM dose-either daily or cumulative-and PFS or OS.

In contrast to these results, previous studies had found an association between DXM and survival [8,20,21]. Retrospective analyses 10 of three independent cohorts of 573, 622, and 832 patients identified corticosteroid use during radiotherapy as a marker of shorter survival. However, the median DXM dose was only reported for one of the three cohorts: 12 mg/day for biopsied patients and 6 mg/day for resected patients. An earlier retrospective analysis had

Table 2: Changes in metabolic parameters from baseline to progression and their association with cumulative dexamethasone dose.

Parameter	Mean (range) at baseline	Mean (range) at progression	Change	*p*[a]	Association with DXM >250[b]		
					β	95% CI	*P*[a]
Glycemia	122.0 mg/dL (76–236)	109.2 mg/dL (71.0–308.0)	-12.8 mg/dL	0.01	5.5	38.8, 49.8	0.8
HbA1c	5.91% (4.9–9.7%)	5.93% (4.6–9.5%)	+0.02%	0.08	0.4	-0.3,1	0.29
Insulin	13.3 mcUI/mL (3.5–60.5)	11.7 mcUI/mL (2.8–29.4)	-1.6 mcUI/mL	0.8	-10.4	-30.0, 9.1	0.28
IGF-1	176.0 ng/mL (31–348)	166.3 ng/mL (85.5–297.8)	-9.7 ng/mL	0.7	9.1	-50.5, 68.7	0.75
Total cholesterol	198.6 mg/dL (134–274)	219.6 mg/dL (131.0–342.0)	+20.5 mg/dL	0.04	45.3	9.9, 80.8	**0.01**
Triglycerides	116.8 mg/dL (41–225)	130.5 mg/dL (42.0–368.0)	+13.7 mg/dL	0.2	18.2	-26.4, 62.8	0.41

HbA1C: glycosylated hemoglobin; IGF-1: insulin growth factor 1; β: coefficient
[a]Significant values are shown in bold.
[b]Results of the linear regression analysis for an association between the changes in metabolic parameters and cumulative dexamethasone dose >250 mg.

Table 3: Univariate analysis of progression-free survival (PFS) according to baseline metabolic parameters and dexamethasone (DXM) dose.

Parameter		Median PFS (months)	Hazard Ratio	95% CI	*p*[a]
Glycemia	≤ 113.5 mg/dL	11.3	1 (ref)		
	>113.5 mg/dL	7.9	1.6	0.7, 3.7	0.22
HbA1c	≤ 5.7%	9.8	1 (ref)		
	>5.7%	7.1	1.4	0.6, 3.1	0.38
Insulin	≤ 11.2 mcUI/mL	7.3	1 (ref)		
	>11.2 mcUI/ML	10.9	0.7	0.3, 1.6	0.37
IGF-1	≤ 154 ng/mL	11.3	1 (ref)		
	>154 ng/mL	7.3	1.0	0.4, 2.4	0.97
Total cholesterol	<200 mg/dL	7.9	1 (ref)		
	≥ 200 mg/dL	8	1.0	0.4, 2.2	0.94
Triglycerides	<150 mg/dL	9.8	1 (ref)		
	≥ 150 mg/dL	7.3	1.4	0.5, 3.6	0.55
DXM dose during concomitant treatment	≤ 4 mg/day	7.9	1 (ref)		
	>4 mg/day	9.2	0.8	0.3, 2.0	0.59
Cumulative DXM dose	≤ 250 mg	7.9	1 (ref)		
	>250 mg	8.0	1.1	0, 2.45	0.86
Hyperglycemia	No	13.1	1 (ref)		
	Yes	7.1	3.7	1.3, 10.8	**0.02**

HbA1C: glycosylated hemoglobin; IGF-1: insulin growth factor 1
[a]Significant values are shown in bold.
Cut-offs for glycemia, HbA1c, total cholesterol, triglycerides, and hyperglycemia were classified based on prior published reports; cut-offs for insulin and IGF-1 were their median values [18,20,21].

also reported that DXM use during concomitant therapy was an independent marker of shorter OS (HR 1.72, p=0.05). However, this study categorized patients as receiving or not receiving DXM without specifying the dose. In fact, the negative impact of DXM reported in these studies could be linked to higher doses [22]. Wong et al. [21] reported that patients receiving DXM>4.1 mg/day had shorter OS than those receiving ≤ 4.1 mg/day, while incremental doses up to 7.5 mg/day were associated with even poorer outcomes. In contrast, the median daily DXM dose in our patients was much lower (1.4 mg/day) and only seven patients received doses of >4 mg/day, which could account for the lack of correlation between DXM use and outcome. A recent small study found that a median cumulative dose of betamethasone >254 mg (equivalent to approximately 317 mg of DXM) was independently associated with shorter PFS, [23] but in our study cumulative doses of >250 mg were not associated with PFS or OS.

Interestingly, our patients showed an increase in total cholesterol of 20.5 mg/dL (p=0.04) from baseline to progression, which was significantly associated with cumulative DXM dose (p=0.01). The role of total cholesterol as a prognostic factor in GBM has not been extensively reported. An analysis of the Cancer Genome Atlas database [24] found that the synthesis of cholesterol had a differential prognostic impact according to the type of tumor. An increase in cholesterol synthesis was associated with shorter survival in sarcoma, acute myeloid leukemia, and melanoma, but with longer survival in gliomas. A recent study reported similar results [25]; leading the authors to hypothesize that proliferation of GBM cells might lead to uptake of cholesterol from blood and result in a decreased serum cholesterol level. Thus, rapidly growing GBM cells might absorb circulating LDL cholesterol at a higher rate, resulting in a lower serum cholesterol level. However, astrocytes synthesize most brain cholesterol from glucose-, glutamine-, or acetate-derived acetyl-CoA and supply cholesterol to neighboring cells [26], since serum cholesterol cannot be transported across the blood-brain barrier [27].

Table 4: Univariate analysis of overall survival (OS) according to baseline metabolic parameters and dexamethasone (DXM) dose.

Parameter		Median OS (months)	Hazard Ratio	95% CI	*p*[a]
Glycemia	≤ 113.5 mg/dL	19.9	1 (ref)		
	>113.5 mg/dL	17.6	1.8	0.7, 4.3	0.2
HbA1c	≤ 5.7%	16.9	1 (ref)		
	>5.7%	22.3	0.8	0.4, 2.0	0.68
Insulin	≤ 11.2 mcUI/mL	16.9	1 (ref)		
	>11.2 mcUI/ML	19.9	0.6	0.2, 1.4	0.22
IGF-1	≤ 154 ng/mL	19.9	1 (ref)		
	>154 ng/mL	14.2	1.6	0.6, 4.0	0.34
Total cholesterol	<200 mg/dL	19.2	1 (ref)		
	≥ 200 mg/dL	17.6	1.2	0.5, 2.8	0.73
Triglycerides	<150 mg/dL	18.8	1 (ref)		
	≥ 150 mg/dL	10.2	1.6	0.5, 4.9	0.42
DXM dose during concomitant treatment	≤ 4 mg/day	17.6	1 (ref)		
	>4 mg/day	19.2	1.2	0.4, 3.3	0.76
Cumulative DXM dose	≤ 250 mg	18.8	1 (ref)		
	>250 mg	16.9	1.9	0.8, 4.8	0.15
Hyperglycemia	No	22.3	1 (ref)		
	Yes	8.8	8.4	2.6, 27.1	**<0.001**

HbA1C: glycosylated hemoglobin, IGF-1: insulin growth factor 1.
[a]Significant values are shown in bold. Cut-offs for glycemia, HbA1c, total cholesterol, triglycerides, and hyperglycemia were classified based on prior published reports; cut-offs for insulin and IGF-1 were their median values [18,20,21].

Taken together with these findings, our results lead us to suggest that the relationship between cumulative DXM dose and cholesterol and between cholesterol and outcome warrant further investigation in larger cohorts to more precisely determine the prognostic impact of cholesterol and the possible indirect effect of DXM through its modulation of cholesterol synthesis.

In line with previous reports, we found that hyperglycemia was associated both with shorter PFS (HR=3.7; p=0.02) and shorter OS (HR=8.4; p<0.001). Several theories have been posited to explain how hyperglycemia may worsen survival in GBM, including the Warburg effect, which postulates that cancer cells metabolize via aerobic glycolysis regardless of oxygen availability. Hyperglycemia by itself could thus promote tumor growth and survival, since GBM cells are dependent on glucose [28,29]. In fact, hyperglycemia has been associated with shorter PFS and OS in GBM patients, with glycemia values ranging from 113.5 to 180 mg/dL linked to poorer outcome [11,13,14,20]. In our series of patients, with a cut-off of ≥ 126 mg/dL, only six had hyperglycemia, yet it was still associated with poorer PFS and OS.

It is well known that excessive exposure to glucocorticoids can cause hyperglycemia. However, the only study performed in GBM found only a weak association between DXM, at a median dose of 4 mg/day, and glycemia levels [20]. In the present study, there was a significant decrease in glycemia levels between baseline and progression (p=0.01), although this change was not associated with cumulative DXM dose (p=0.80). In fact, the decrease may well have been due to the high baseline levels of glycemia in the non-fasting blood test taken in the emergency room before starting DXM. Moreover, the initially high doses of DXM (12 mg/day) administered before surgery were later tapered and adjusted to the needs of each patient, which could explain why glycemia levels did not rise during treatment and follow-up. Furthermore, glycemia levels fluctuate throughout the day, and hyperglycemia may go undetected if blood glucose is not measured daily or is not continuously monitored during a 24-h period. For this reason, HbA1c, which gives a three-month average plasma glucose concentration, would probably be a more reliable marker of a possible relation between blood glucose and survival. To the best of our knowledge, only one study has explored this potential relationship and found that HbA1c levels >6.9% were associated with shorter OS (HR 1.8, p=0.05) [30]. In the present study, only two patients had HbA1c values >6.9%, precluding any meaningful conclusions regarding the usefulness of HbA1c as a prognostic marker.

Hyperglycemia may also lead to hyperinsulinemia, which may facilitate tumor growth, [11] and stimulation of the IGF-1 receptor in GBM cell lines was shown to result in tumor proliferation [31]. However, in our patients, there were no significant changes in insulin or IGF-1 values during follow-up.

Our study has several limitations, including the small sample size, which may have affected statistical analyses and precluded drawing definite conclusions from our data. To the best of our knowledge, however, this is the first prospective study to evaluate the impact of DXM dose on the metabolic profile and outcome of patients with GBM. As such, it provides the first indications that when DXM doses are kept low and adjusted to the needs of each patient, there seems to be no impact on PFS or OS. A larger prospective study is warranted to further explore the prognostic impact of DXM and of cholesterol synthesis in GBM.

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