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Original Article

Retrospective Study of The Corticosteroids Administration in GBM patients as Prognostic Factor in The Disease

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ABSTRACT

Purpose: Discussing the clinical relation between corticosteroids usage in GBM patients and quality of life as well as the disease progression free survival according to the recorded data from the joined hospitals.
Patients and Methods: Retrospective analysis of 66 adult patients diagnosed with GBM by surgery or imaging criteria. In order to assess the relation between corticosteroid dependence and the survival, patients were recruited into two groups (arms) according to dependency. Arm (A) was steroid dependant (34 patients) and arm (B) was steroid non-dependent (32 patients).
Results: Corticosteroids dependency was statistically significant correlated to both OS (median 2.5 in arm (A) vs. 13.1 months in the arm (B), $p < 0.001$), and PFS (median 2.3 in arm (A) vs. 9.4 months in arm (B), $p = 0.035$). Also steroid dependency was independent prognostic factor by doing the COX regression analysis.
Conclusion: Dependence on corticosteroids during course of treatment is identified as a poor prognostic factor.

Keywords
Corticosteroids,
GBM,
Glioblastoma multiform,
Dexamethasone,
Prognostic Factor.

INTRODUCTION

According to Globocan web site incidence of CNS tumors in Egypt was estimated by 6.6/100 000. In a study that included 1618 cases of CNS tumors among Egyptians in delta region, Gliomas were of the highest frequency 35.2 %. Glioblastoma represented 38.3% of gliomas [1].In another study performed in Ain Shams University hospitals a total number of registered newly diagnosed patients received during the study period were 943 cases. CNS tumors accounted for 53 newly diagnosed cases (5.6%) and it was ranked as the fourth common cancer in both sexes. Glioblastoma Multiforme was the most common pathology occurring in about 43.3% of the presented cases [2].

Exposure to ionising irradiation has been associated with increased risk of development of glioma, while association with the use of cell phones could not be confirmed in epidemiological studies. Rare hereditary syndromes carry an increased risk for glioma: Cowden-, Turcot-, Lynch-, Li-Fraumeni syndrome and neurofibromatosis type 1 [3].

GBM is the most aggressive diffuse glioma of astrocytic cell line and classified as grade IV in WHO Classification[4]. GBM remains an incurable disease with a median survival of 15 months [5].

Treatment is complex and initially consists of maximal-safe surgical resection followed by radiation therapy (RT) with concurrent temozolomide (TMZ) chemotherapy followed by six cycles of maintenance TMZ [6].

Steroids were introduced into the care of brain cancer patients nearly 60 years ago based on their powerful effects on tumor-induced edema. Ingraham pioneered the use of cortisone to treat postoperative cerebral edema in neurosurgical patients in 1952, and Kofman first used prednisone for peritumoral edema from

brain metastases in 1957. More than 50 years ago, it was demonstrated that dexamethasone effectively alleviated cerebral edema due to brain tumors [7].

Edema results from the flow of fluid into the extracellular space of the brain parenchyma through an incompetent blood–brain barrier (BBB) [8]. Dexamethasone is most commonly used by neuro-oncologists owing to its comparably minimal mineralocorticoid activity, possible lower risk of infection and occurrence of cognitive impairment. It has been suggested that corticosteroids produce their anti-edema effect by reducing the permeability of tumor capillaries[9].

Corticosteroids are commonly used perioperatively to control cerebral oedema and are frequently continued throughout subsequent treatment, especially during radiotherapy, to get control of its side effects. The effects of corticosteroids such as Dexamethasone (DEX) on cell growth in glioma models and on patient survival have remained controversial.

There is experimental and clinical evidence that corticosteroids have direct effects on tumor cell proliferation and apoptosis. Data from in vitro experiments suggest a variable inhibitory effect of dexamethasone on the proliferation of glioma cells. Dexamethasone and other glucocorticoid hormones have shown to decrease proliferation of embryonic neural stem cells with associated long-term effects on brain development. Dexamethasone, specifically through the glucocorticoid receptor, has an inhibitory effect on proliferation, but not differentiation of neural progenitor cells in the process of neurogenesis [10].

In a recent study of Pitter et al they analyzed data from three large independent datasets which were further supported with a recent correlative retrospective analysis of 73 patients with glioblastoma by Shields et al [11]. Showing that DEX use during radiotherapy with concurrent TMZ correlated with reduced overall survival and progression-free survival. They couldn't exclude that detrimental effects of steroids other than direct interference with radiotherapy contributed to the overall inferior outcome of patients exposed to steroids. So steroids can contribute to morbidity and mortality through their direct toxicity, including steroid myopathy, impaired immune function, adrenal insufficiency, and bowel perforation [12].

To support the direct detrimental effect of corticosteroids interfering with the activity of radiotherapy, Pitter et al. reported that pretreatment with DEX decreased the survival benefit offered by radiotherapy in murine gliomas. In these tumours, DEX decreased proliferation and the expression of many cell cycle-related genes. Expression of these genes inversely correlated with survival in The Cancer Genome Atlas (TCGA) glioblastoma patient dataset**.** Specifically, the p21 protein is induced by DEX in glioma cells, slows cell cycle progression and may confer cytoprotection [12].

AIM OF THE WORK

In this study we aim at discussing the clinical relation between corticosteroids usage in GBM patients and quality of life as well as the disease progression free survival according to the recorded data from the joined hospitals.

PATIENTS AND METHODS

Type of study:
A retrospective descriptive analytical study.

Patients and data collection:
66 adult patients diagnosed with GBM by surgery or imaging criteria.

Definition of survival
Date of surgery was considered as the time of diagnosis.
Progression free survival was calculated from the date of surgery to the date of disease progression at the primary location or other sites of the brain.

Overall survival was calculated from the date of surgery to date of death due to any cause or to the date of data analysis.
Date of data analysis was April 2017.

Corticosteroids dependence is defined as the failure to withdraw the corticosteroids after initiating it as part of those patient treatment (with radiotherapy and TMZ) as relapse of the increased intra-cranial tension symptoms occur.

Non-dependence: is defined by the opposite of dependence, in which corticosteroids can be successfully withdrawn from the patients without recurrence of the ICT symptoms.
In order to assess the relation between corticosteroid dependence and the survival, patients were recruited into two groups (arms) according to dependency. **Arm (A) steroid dependence (34 patients) and Arm (B) steroid non-dependence (32 patients).**

Recorded toxicity was assessed by CTC version 4.0 according to patient's files[13].

Statistical methods:
Data were analyzed using statistical program for social science (SPSS) version 20. Quantitative data were expressed as mean ± standard deviation (SD), median and range (minimum – maximum). Qualitative data were expressed as frequency and percentage.

RESULTS

Corticosteroids dependency was statistically significant correlated to both OS (median 2.5 in the corticosteroids dependant group vs. 13.1 months in the non-corticosteroids dependant group, $p < 0.001$), and PFS (median 2.3 in the corticosteroids dependant group vs. 9.4 months in the non-corticosteroid dependant group, $p = 0.035$). See table 3 & 4.

Table 1. Patient demographics, disease characteristics and treatment given

Age	Mean ±SD	52.80 ± 12.62	
	Range	25 – 75	
		No. 66	**%**
Sex	Female	21	31.8%
	Male	45	68.2%
Performance status	1	26	39.4%
	2	18	27.3%
	3	8	12.1%
	4	14	21.2%
Fits	No	52	78.8%
	Yes	14	21.2%
Site	One Lobe	24	36.4%
	Bi Lobe	36	54.5%
	More than two	6	9.1%
Surgery	None	10	15.2%
	Biopsy	38	57.6%
	Debulking	8	12.1%
	Maximal resection	10	15.2%
Progression	No	42	63.6%
	Yes	24	36.4%
Life status	Died	61	92.4%
	Alive	5	7.6%
Radiotherapy	No	18	27.3%
	Yes	48	72.7%
Radiotherapy doses	No	18	27.3%
	45 GY	9	13.6%
	60 GY	39	59.1%
Technique of RTH	No	18	27.3%
	Hypo fraction	9	13.6%
	Standard	39	59.1%
Concomitant TMZ	No	25	37.9%
	Yes	41	62.1%
Adjuvant TMZ	No	32	48.5%
	Yes	34	51.5%
2nd line	No	62	93.9%
	Yes	4	6.1%
Type of second line	No	61	92.5%
	TMZ dose-intense therapy	2	3 %
	TMZ + Bev.	1	1.5%
	CCNU + Bev.	1	1.5%
	CVP	1	1.5%
Beyond 2nd line	No	65	98.5%
	Yes	1	1.5%

Table 2. Corticosteroids dependence

		No.	**%**
Dependence	Arm A (dependent)	34	51.5%
	Arm B (non dependent)	32	48.5%

Table 3. Comparison between median PFS in arm A and arm B

	PFS (months)		**95% CI**		**Log rank test**	
	Median	**SE**	**Lower**	**Upper**	**X^2**	**P-value**
Arm A (dependent)	2.3	0.163	1.145	3.528	5.244	0.022
Arm B (non dependent)	9.4	1.306	6.441	11.559		

Table 4. Comparison between median OS in arm A and arm B

	OS (months)		**95% CI**		**Log rank test**	
	Median	**SE**	**Lower**	**Upper**	**X^2**	**P-value**
Arm A (dependent)	2.5	0.656	1.214	3.786	63.012	<0.001
Arm B (non dependent)	13.1	1.905	9.365	16.835		

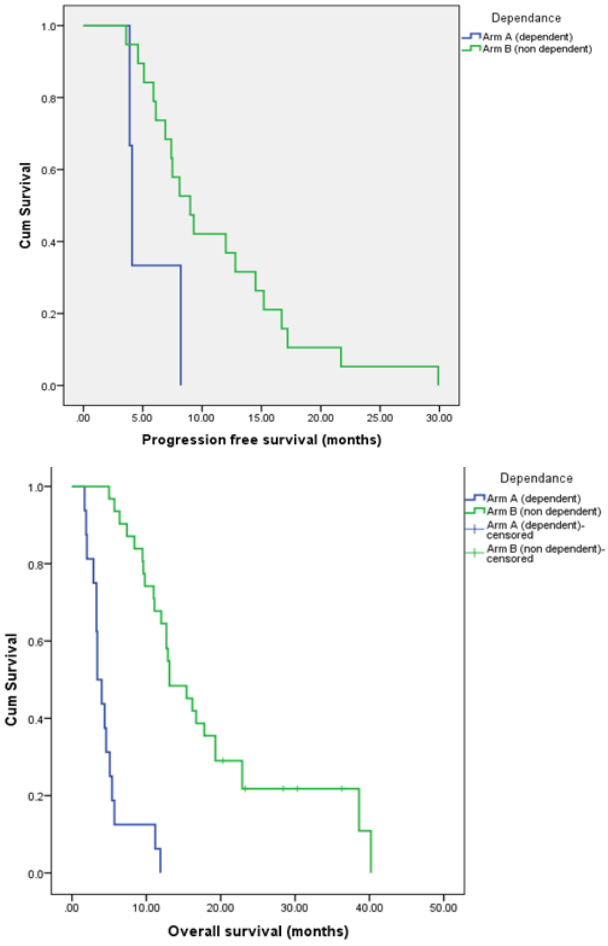

Figure 1. Kaplan-Mier curves for PFS and OS in Arm A and Arm B

DISCUSSION

The administration of steroids to control neurological morbidity associated with brain tumors has been established as a standard of care decades ago. Except for primary CNS lymphoma where steroids are given as therapeutic agent owing to their direct cytotoxic effects, control of edema associated with brain tumors has been proposed to be the reason behind improvement of the disease symptoms.

In support of that direct detrimental effect interfering with the activity of radiotherapy, Pitter et al. report that pretreatment with dexamethasone decreased the survival benefit afforded by radio-therapy in murine gliomas (glioma bearing mice). In these tumours, corticosteroids decreased proliferation and the expression of many cell cycle-related genes. Expression of these genes inversely correlated with survival in the TCGA glioblastoma patient dataset. These genes are primarily known or predicted to be involved in proliferation, either via cell mitotic assembly, cycle checkpoints, DNA damage response and ATM signaling [12]. Specifically, the p21 protein - cell cycle inhibitor - is induced by corticosteroids in glioma cells, slows cell cycle progression and may confer cytoprotection.

In the current retrospective study, data were gathered from 66 patients with glioblastoma in whom corticosteroids administration was recorded. Corticosteroid dependency was more common in elder patients and those patients who presented with poor performance status. Patients with tumor of more than one lobe presentation were associated with corticosteroid dependency. Corticosteroids dependency was statistically significant correlated to both OS (median 4.1in the corticosteroids dependant group vs. 13.1 months in the non-corticosteroids dependant group, $p < 0.001$), and PFS (median 3.8 in the corticosteroids dependant group vs. 9.4 months in the non-corticosteroid dependant group, $p = 0.035$). Also Multi-variate analysis was performed for all the factors affecting the survival in the study patients and we identified the administration of corticosteroids as poor prognostic factor for the disease outcome.

Our findings were further supported with a correlative retrospective analysis done by Shields et al. of 73 patients with glioblastoma showing that dexamethasone usage during radiotherapy with concurrent temozolomide was a poor prognostic indicator of both OS (median 12.7 vs. 22.5 months, $p =0.02$), and PFS (median 6.0 vs. 8.8 months, $p =0.002$) in the whole cohort [11].

Another correlative result of a recent retrospective analysis done by K. Pitter and his colleges for a three large independent datasets, the first was 622 patients treated at Memorial Sloan Kettering Cancer Center (MSKCC) Patients not on DEX at the start of radiotherapy had a median survival of 20.6 months whereas patients on DEX had a survival time of 12.9 months ($P > 0.0001$).

Second group, was 573 patients from the pivotal EORTC NCIC trial, Patients with baseline steroids had a lower median progression-free survival (5.3 versus 6.4, $P > 0.0001$) and a lower median overall survival (12 versus 17 months, P50.0001, HR = 1.56) and higher doses of steroids were a negative prognostic factor in patients treated with radiotherapy alone more than in patients treated with TMZ/RTàTMZ.

Third group was 832 glioblastoma patients enrolled in the German Glioma Network (GGN) the progression-free survival and overall survival were inferior in steroid-exposed patients in all patients pooled.

They also did a Multi-variate analysis of the data in the three groups and they identified the use of corticosteroids early in the disease course, during radiotherapy without or with alkylating chemotherapy, as an independent predictor of poor outcome [12].

These results might support the molecular background of determinate effect of steroid on radiotherapy of gliomas, but we should keep in our mind that others factors such as age and performance status of the patient are proved to be independent prognostic factors for both PFS and OS and those factors may indirectly co-related with steroid dependence so Further studies are warranted to more precisely establish interactions between corticosteroids and these cell types and how these might influence the disease course.

CONCLUSION

There is experimental and clinical evidence that corticosteroids have direct effects on tumor cell proliferation and apoptosis. Data from in vitro experiments suggest a variable, time dependent inhibitory effect of dexamethasone on the proliferation of glioma cells.

Our results came consistent with the studies done recently; more usage of corticosteroids during course of treatment is a poor prognostic factor in the disease.

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