

Effect of Cumulative Dexamethasone Dose during Concomitant Chemoradiation on Lymphopenia in Patients with Newly Diagnosed Glioblastoma

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Background Lymphopenia frequently occurs after concomitant chemoradiation (CCRT) in patients with glioblastoma (GBM) and is associated with worse overall survival (OS). A few studies have tried to identify risk factors for lymphopenia; however, the results were not clear. We aimed to identify potential risk factors for lymphopenia, focusing on the use of dexamethasone to control cerebral edema in patients with GBM.

Methods The electronic medical records of 186 patients with newly diagnosed GBM treated at our institution between 2009 and 2017 were retrospectively examined. Acute lymphopenia was defined as total lymphocyte count less than 1,000 cells/ μ L at 4 weeks after completion of CCRT. Multivariate logistic regression analysis was used to identify independent risk factors for lymphopenia, and Cox regression analysis was used to identify independent risk factors for OS.

Results Of the 125 eligible patients, 40 patients (32.0%) developed acute lymphopenia. Female sex and median daily dexamethasone dose ≥ 2 mg after initiation of CCRT were independent risk factors for acute lymphopenia on multivariate analysis. Acute lymphopenia, extent of surgical resection, and performance status were associated with OS; however, dexamethasone use itself was not an independent risk factor for poor OS.

Conclusion Female sex, median daily dexamethasone dose ≥ 2 mg after initiation of CCRT until 4 weeks after completion of CCRT may be associated with acute lymphopenia. However, dexamethasone use itself did not affect OS in patients newly diagnosed with GBM. These results should be validated by further prospective studies controlling for other confounding factors.

Key Words Glioblastoma; Lymphopenia; Lymphocyte count; Dexamethasone; Glucocorticoid; Chemoradiotherapy.

INTRODUCTION

Lymphopenia, defined as a reduction in total lymphocyte count (TLC), frequently occurs after concomitant chemoradiation (CCRT) for glioblastoma (GBM), and it was recently suggested as a novel biomarker associated with overall survival (OS) in newly diagnosed GBM [1-6]. As lymphocytes play a major role in the immune response to eliminate malig-

nant cells, an insufficient number of circulating lymphocytes could weaken the immune system's control of GBM progression [7-10].

Several clinical factors have been suggested as contributors to lymphopenia including sex, age, irradiated brain volume, chemotherapy, and the use of dexamethasone [11-18]. Radiotherapy (RT) was found to be significantly associated with lymphopenia in GBM patients [10,11,14-16,18,19]. Dexamethasone, which is a commonly prescribed drug for controlling brain edema and improving performance of GBM patients, is also known for its potent immunosuppressive effects [20-22]. However, its effect on inducing lymphopenia in GBM patients remains controversial [11,14,15,17]. Three previous studies

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did not find an association between the use of dexamethasone and acute lymphopenia [11,14,15], but another study showed that increased use of dexamethasone during CCRT was an independent risk factor for acute lymphopenia after CCRT [17]. As numerous immunotherapeutic agents are being developed for GBM, it is critical to minimize iatrogenic lymphopenia to maintain sufficient immunity to fight against cancer cells [10,23].

In this context, we attempted to elucidate the clinical factors associated with lymphopenia following CCRT in patients with newly diagnosed GBM focusing specifically on the use of dexamethasone. We examined the overall cumulative dose of dexamethasone from initiation of CCRT to 4 weeks after completion of CCRT to facilitate a more accurate evaluation of this association.

MATERIALS AND METHODS

Patient selection

Our study was approved by the Institutional Review Board of Seoul St. Mary's Hospital (KC19RESI0168). The need for informed consent was waived due to the retrospective nature of our study. The electronic medical records (EMR) of 186 patients with newly diagnosed GBM who were treated at our institution between August 2009 and December 2017 were retrospectively examined. The eligibility criteria were as follows: 1) newly diagnosed GBM confirmed by craniotomy or stereotactic biopsy, 2) completion of CCRT at our institution, 3) accessible baseline and follow-up complete blood count (CBC). The exclusion criteria were as follows: 1) prior history of diagnosed malignancies, chemotherapy, or radiation due to other medical illnesses, 2) evidence of acute infection or autoimmune disease at the time of blood sampling.

Clinical variables and treatment protocols

Patient characteristics included sex, age, performance status, extent of resection (EOR), pathologic findings, radiation dosage and fraction, radiation volume, radiation modalities, dose of dexamethasone used, and CBC. Performance status at baseline was measured using the Eastern Cooperative Oncology Group (ECOG) performance score. EOR was measured by comparing radiologic findings on MRI at baseline and within 48 hours after surgery. Resection of 90% or more of the tumor volume was considered gross total resection (GTR) and <90% was considered non-GTR [24]. Isocitrate dehydrogenase 1 (IDH1) mutation was evaluated by immunohistochemistry or direct sequencing.

O⁶-methylguanine-DNA methyltransferase (MGMT) gene methylation status was evaluated by polymerase chain reaction.

We used navigation and intraoperative monitoring in all

surgeries and we also performed awake surgery or 5-aminolevulinic acid fluorescence-guided surgery, for achieving maximal safe resection, when indicated. CCRT was started within 28 days of surgical resection if possible, considering wound healing, the patient's condition, and RT schedules [25]. Radiation was administered at a dosage of either 5,940 cGy for 33 fractions or 6,000 cGy for 30 fractions, regardless of age. RT was conducted with either three-dimensional conformal RT (3DRT) or intensity-modulated RT (IMRT). Temozolomide (TMZ) dosages were 75 mg/m² during CCRT and 150–200 mg/m² for adjuvant therapy. We used dexamethasone, considering the patient's neurologic status, general condition, and radiologic findings after surgery to control brain edema and improve patient performance. Other steroids including prednisolone were not prescribed.

TLC and dexamethasone

We collected results of blood tests, including white blood cell count and the composition of neutrophils and lymphocytes, at baseline and 4 weeks after completion of CCRT. TLC were calculated from these data for the analysis.

We also reviewed prescribed dexamethasone doses using EMR from initiation of CCRT until 4 weeks after the completion of CCRT, which was the same day blood samples were collected for calculating TLC. We estimated the cumulative dexamethasone dose from the EMR. Median dexamethasone dose prescribed during this period was calculated by dividing the cumulative dexamethasone dose (mg) by the days from initiation of CCRT to 4 weeks after the completion of CCRT. For example, if a patient took a cumulative dexamethasone dose of 200 mg over 80 days from initiation of CCRT to 4 weeks after completion of, the median daily dexamethasone dose was 2.5 mg. In our study, the median period from initiation of CCRT until 4 weeks after completion of CCRT was 78.3 (range 65–98) days.

Statistical analysis

Lymphopenia was defined as TLC <1,000 cells/ μ L at 4 weeks after completion of CCRT, based on previous reports. The primary endpoint in our study was OS. OS was calculated using the time interval from date of initial surgery to death. Dates of death were obtained from the Korea Central Cancer Registry database. Patients who were confirmed alive on July 30, 2019 were censored. The median follow-up period was 26.1 (range 4–117) months.

All clinical variables were characterized with descriptive statistics. Differences between groups in which dexamethasone was and was not used were compared with Fisher's exact test or the chi-squared test. A test of normality was performed for continuous variables. Univariate and multivariate analyses

were conducted using the Cox proportional regression model. The hazard ratio (HR) and 95% confidence intervals (CIs) were calculated. Multivariate analysis was performed using the variables with p -values <0.2 , and p -values <0.05 were considered statistically significant. Statistical analysis was performed using R Statistical Software (Version 3.4.4; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient characteristics

We included 125 patients who met our eligibility criteria. Of them, 89 patients who did not take any dexamethasone were assigned to the “not used group” and 36 patients who

took dexamethasone were assigned to the “used group.” Baseline patient characteristics are shown in Table 1. The “used group” had poor ECOG performance score at baseline and had more patients who underwent non-GTR, while other clinical variables including sex, age, IDH1 mutation status, presence of MGMT promoter methylation, median planning treatment volume (PTV), median TLC at baseline and at 4 weeks after completion of CCRT, and proportion of lymphopenia were not significantly different. The median daily dexamethasone dose (mg) in the “used group” was 1.9 (range 0.1–8.3) mg/day. Eighteen of 36 patients (50%) took a median dexamethasone dose less than 2.0 mg/day, 12 patients (33.3%) from 2.0 to 4.0 mg/day, and 6 patients (16.6%) more than 4 mg/day.

Table 1. Characteristics of patients with newly diagnosed glioblastoma who completed CCRT according to dexamethasone use

Variables	Dexamethasone not used (n=89)	Dexamethasone used (n=36)	Total (n=125)	p -value
Sex				0.268
Female	38 (42.7)	20 (55.6)	58 (46.4)	
Male	51 (57.3)	16 (44.4)	67 (53.6)	
Age at diagnosis (yr)	59.0 (20–79)	59.0 (30–79)	59.0 (20–79)	0.667
Age ≥ 65 yr	29 (32.6)	9 (25.0)	38 (30.4)	0.535
ECOG at baseline				0.053
0–1	59 (66.3)	17 (47.2)	76 (60.8)	
2–3	30 (33.7)	19 (52.8)	49 (38.2)	
Extent of resection				<0.001
GTR	70 (78.7)	15 (41.7)	85 (68.0)	
Non-GTR	19 (21.3)	21 (58.3)	40 (32.0)	
IDH1 mutation				0.252
Yes	5 (5.6)	0 (0.0)	5 (4.0)	
No	40 (44.9)	20 (55.6)	60 (48.0)	
Unknown	44 (49.4)	16 (44.4)	60 (48.0)	
MGMT methylation				0.391
Yes	35 (39.3)	15 (41.7)	50 (40.0)	
No	35 (39.3)	4 (11.1)	52 (41.6)	
Unknown	19 (21.3)	17 (47.2)	23 (18.4)	
RT technique				0.352
IMRT	23 (25.8)	13 (36.1)	36 (28.8)	
3DRT	66 (74.2)	23 (63.9)	89 (71.2)	
PTV (cm ³)	210.3 (14.7–691.4)	280.7 (12.9–568.4)	214.1 (12.9–691.4)	0.541
Daily dexamethasone dose (mg)	0.0 (0.0–0.0)	1.9 (0.1–8.3)	-	
<2 mg/day	-	18 (50.0)	-	
2–4 mg/day	-	12 (33.3)	-	
>4 mg/day	-	6 (16.7)	-	
TLC at baseline (cells/ μ L)	1,601 (256–4,950)	1,569 (548–4,410)	1,583 (256–4,950)	0.883
TLC 4 weeks after completion of CCRT (cells/ μ L)	1,330 (471–4,632)	1,078 (240–2,187)	1,300 (240–4,632)	0.113
TLC $<1,000$ cells/ μ L 4 weeks after completion of CCRT	24 (27.0)	16 (44.4)	40 (32.0)	0.092

Data are presented as number (%) or median (range). CCRT, concomitant chemoradiation; ECOG, Eastern Cooperative Oncology Group; GTR, gross total resection; IDH, isocitrate dehydrogenase; IMRT, intensity-modulated radiation therapy; 3DRT, three-dimensional conformal radiation therapy; PTV, planning treatment volume; TLC, total lymphocyte count

Table 2. Univariate and multivariate Cox regression for overall survival

Parameters	Univariate analysis		Multivariate analysis*	
	Hazard ratio (95% CI)	<i>p</i> -value	Hazard ratio (95% CI)	<i>p</i> -value
Sex (male vs. female)	0.74 (0.48–1.14)	0.177	0.99 (0.62–1.61)	0.997
Age ≥65 yr (vs. <65 yr)	1.16 (0.73–1.87)	0.525	-	-
ECOG 0 or 1 (vs. 2 or 3)	0.41 (0.26–0.64)	<0.001	0.46 (0.28–0.76)	0.002
Incomplete resection (vs. complete resection)	2.19 (1.39–3.46)	0.001	1.62 (0.96–2.66)	0.007
Dexamethasone used (vs. not used)	2.15 (1.34–3.46)	0.002	1.36 (0.78–2.37)	0.274
Median dose of dexamethasone ≥2 mg/day (vs. <2 mg/day)	1.90 (1.06–3.40)	0.031	1.23 (0.42–1.64)	0.598
Lymphopenia (vs. no lymphopenia)	1.99 (1.28–3.09)	0.002	2.08 (1.33v3.25)	0.001

*Multivariate analysis was performed on the variables with *p*-values <0.2. CCRT, concomitant chemoradiation; ECOG, Eastern Cooperative Oncology Group; CI, confidence interval

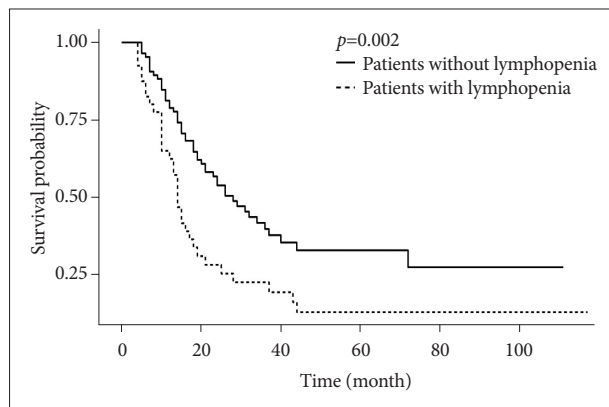


Fig. 1. Kaplan-Meier survival curves of overall survival for patients with lymphopenia vs. without lymphopenia.

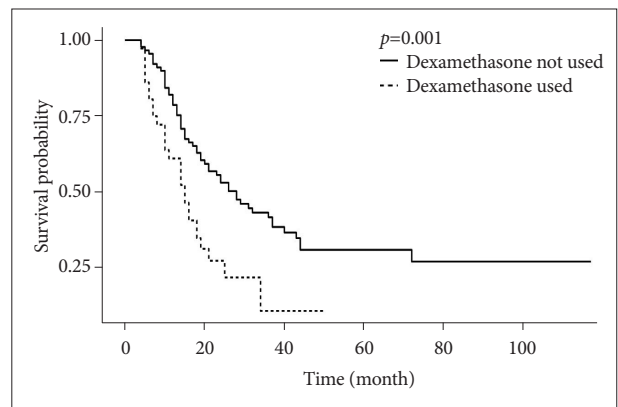


Fig. 2. Kaplan-Meier survival curves of overall survival for patients who took dexamethasone vs. did not take dexamethasone.

Lymphopenia and overall survival

Kaplan-Meier analysis and multivariate Cox regression analysis with previously identified prognostic factors were performed to evaluate the effect of lymphopenia and higher use of dexamethasone on OS (Table 2). The Kaplan-Meier curves showed that the median OS of patients with lymphopenia was shorter than that of patients without lymphopenia (14.0 months vs. 28.0 months, *p*=0.002) (Fig. 1) and the median OS of patients who took dexamethasone was shorter than that of patients who did not take dexamethasone (15.0 months vs. 28.0 months, *p*=0.001) (Fig. 2). On multivariate analysis, lymphopenia (<1,000 cells/μL) was independently associated with shorter survival (HR 2.08, *p*<0.001), while dexamethasone use alone and dexamethasone dose greater than 2 mg/day were not. Well-known prognostic factors, including non-GTR and an ECOG score of 2 or more, were significantly associated with shorter survival (HR: 1.62, *p*=0.007, and HR: 0.46, *p*=0.002).

Lymphopenia and risk factors

Multivariate logistic regression was performed to identify independent clinical factors associated with lymphopenia (Table 3). Female sex and dexamethasone dose greater than 2

mg per day were independently associated with lymphopenia (male vs. female, HR: 0.31, *p*=0.003, and HR: 2.85, *p*=0.032, respectively), while use of dexamethasone regardless of dose was not associated with lymphopenia (HR 1.45, *p*=0.238). Older age, non-GTR, PTV, RT modality, and baseline TLC count were not associated with lymphopenia.

DISCUSSION

In our study, we showed that lymphopenia was an independent prognostic factor in terms of OS as were already well-known parameters including EOR and performance status. We also found that female sex and median daily dexamethasone dose greater than 2 mg from initiation of CCRT to 4 weeks after completion of CCRT were independently associated with lymphopenia in patients with newly diagnosed GBM. However, dexamethasone dose less than 2 mg/day, EOR, baseline TLC, RT modality (IMRT vs. 3DRT), and PTV were not significantly associated with lymphopenia. In addition, the use of dexamethasone, regardless of dose, was not independently associated with OS.

Dexamethasone, as a synthetic glucocorticoids, bind to the glucocorticoid receptor, which is expressed in almost all im-

Table 3. Univariate and multivariate logistic regression for acute lymphopenia (TLC<1,000 cells/ μ L) 4 weeks after completion of CCRT

Parameters	Univariate analysis		Multivariate analysis*	
	Hazard ratio (95% CI)	<i>p</i> -value	Hazard ratio (95% CI)	<i>p</i> -value
Sex (male vs. female)	0.28 (0.12–0.61)	0.002	0.31 (0.14–0.71)	0.003
Age \geq 65 yr (vs. <65 yr)	0.68 (0.29–1.58)	0.369	-	-
ECOG 0 or 1 (vs. 2 or 3)	0.82 (0.38–1.76)	0.604	-	-
Incomplete resection (vs. complete resection)	1.99 (0.91–4.38)	0.087	1.14 (0.43–3.04)	0.798
IMRT (vs. 3DRT)	0.76 (0.32–1.77)	0.520	-	-
PTV \geq 250 cm ³ (vs. <250 cm ³)	1.66 (0.78–3.54)	0.190	1.70 (0.72–4.04)	0.228
Higher baseline TLC (1,000 cell/ μ L)	0.99 (0.94–1.03)	0.566	-	-
Use of dexamethasone (vs. not use)	2.17 (0.97–4.86)	0.060	1.45 (0.56–3.75)	0.238
Median dose of dexamethasone \geq 2 mg/day (vs. <2 mg/day)	3.21 (1.16–8.91)	0.025	2.85 (0.98–8.28)	0.032

*Multivariate analysis was performed using the variables with *p*-values <0.2. CCRT, concomitant chemoradiation; ECOG, Eastern Cooperative Oncology Group; IMRT, intensity modulated radiation therapy; 3DRT, three-dimensional radiation therapy; PTV, planning treatment volume; TLC, total lymphocyte count; CI, confidence interval

immune cells [26]. Recent preclinical experiments using conditional glucocorticoid receptor-knockout mice as well as transgenic mice showed effects of glucocorticoid on immune and inflammatory responses [27–29]. In the thymus, glucocorticoid induced apoptosis of naïve T cell and resulted in regulation of T cell number and function during development [27,28]. In the periphery, glucocorticoid also promoted apoptosis of T cells in lymphoid organs and limited the migration activity of T cells to the site of inflammation [29].

Huang et al. [11] showed that acute severe lymphopenia was associated with higher brain volume receiving 25 Gy (V25Gy) [odds ratio (OR): 1.03, CI: 1.003–1.05], female sex (OR: 5.30, CI: 2.46–11.41), older age (OR: 1.05, CI: 1.02–1.09), and lower baseline TLC (OR: 0.92, CI: 0.87–0.98) in patients with high grade glioma who were treated with RT and TMZ chemotherapy. Rudra et al. [14] also found that higher brain volume receiving 25 Gy (OR: 1.048, CI: 1.022–1.074), older age (OR: 1.091 CI: 1.047–1.137), and female sex (OR: 2.901, CI: 1.391–6.047) were independently associated with acute severe lymphopenia in patients with GBM treated with CCRT. In addition, Lin et al. [15] found that older age (OR: 1.06, CI: 1.02–1.10), female sex (OR: 10.08, CI: 3.79–30.5), and TMZ use (OR: 72.3, CI: 7.8–679) were independently associated with lymphopenia after RT and/or TMZ in patients with high grade glioma. However, these three studies did not find that dexamethasone use was associated with lymphopenia. A recent study published by Hui et al. [17] calculated the cumulative exposure of dexamethasone during CCRT and showed that increased use of dexamethasone was independently associated with acute severe lymphopenia and OS. Chitadze et al. [13] showed that dexamethasone affects various immune cell parameters not including TLC in GBM patients. Based on our findings and previous reports, female sex seemed to be strongly associated with lymphopenia. Further investigation is needed to determine why females showed more

frequent lymphopenia than males.

In this study, we calculated the overall cumulative dose of dexamethasone from initiation of CCRT to 4 weeks after completion of CCRT (the day before starting the first round of adjuvant TMZ chemotherapy), which was also the same date blood samples were collected for calculating TLC. Most of the studies mentioned above included only baseline dose of dexamethasone and did not include overall cumulative dose from initiation of CCRT until blood sampling. We found that a median daily dexamethasone dose greater than 2 mg from initiation of CCRT until the start of the first round of adjuvant TMZ chemotherapy was independently associated with lymphopenia, while a dexamethasone dose less than 2 mg per day was not.

Our findings provide evidence that higher cumulative dexamethasone dose during CCRT in patients with newly diagnosed GBM could be a significant risk factor for developing lymphopenia. A large body of evidence from preclinical and clinical studies in other cancers supports the adverse effect of dexamethasone on patient immunity [20,30,31]. However, the use of dexamethasone itself was not independently associated with OS in our study. This may be due to other confounding factors and a larger prospective analysis considering various confounding factors is needed to further evaluate the potential relationship between dexamethasone use and lymphopenia.

Our study had several limitations. There is a possibility of selection bias due to its retrospective and non-randomized design. Molecular parameters, such as MGMT gene methylation, IDH1, and 1p19q co-deletion were not fully identified. More patients in the dexamethasone group underwent non-GTR surgery. Remaining microscopic and/or macroscopic tumor cells could also have induced immunosuppression. Further investigation of the immunosuppressive effect of remnant tumor cells is needed, although a higher dose of dexa-

methasone was independently associated with acute lymphopenia in our study.

In conclusion, use of dexamethasone itself after initiation of CCRT until 4 weeks after completion of CCRT was not associated with developing lymphopenia at 4 weeks after completion of CCRT. However, the median daily dexamethasone dose ≥ 2 mg was independently associated with lymphopenia. These results should be validated by further prospective studies.



Conflicts of Interest

The authors have no potential conflicts of interest.

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