Impact of lymphopenia on survival for elderly patients with glioblastoma: A secondary analysis of the CCTG CE.6 (EORTC 26062-22061, TROG08.02) randomized clinical trial

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Abstract

Background. Lymphopenia may lead to worse outcomes for glioblastoma patients. This study is a secondary analysis of the CCTG CE.6 trial evaluating the impact of chemotherapy and radiation on lymphopenia, and effects of lymphopenia on overall survival (OS).

Methods. CCTG CE.6 randomized elderly glioblastoma patients (≥ 65 years) to short-course radiation alone (RT) or short-course radiation with temozolomide (RT + TMZ). Lymphopenia (mild-moderate: grade 1–2; severe: grade 3–4) was defined per CTCAE v3.0, and measured at baseline, 1 week and 4 weeks post-RT. Preselected key factors for analysis included age, sex, ECOG, resection extent, MGMT methylation, Mini-Mental State Examination, and steroid use. Multinomial logistic regression and multivariable Cox regression models were used to identify lymphopenia-associated factors and association with survival.

Results. Five hundred and sixty-two patients were analyzed (281 RT vs 281 RT+TMZ). At baseline, both arms had similar rates of mild-moderate (21.4% vs 21.4%) and severe (3.2% vs 2.9%) lymphopenia. However, at 4 weeks post-RT, RT+TMZ was more likely to develop lymphopenia (mild-moderate: 27.9% vs 18.2%; severe: 9.3% vs 1.8%; p<0.001). Developing any lymphopenia post-RT was associated with baseline lymphopenia (*P* < .001). Baseline lymphopenia (hazard ratio [HR] 1.3) was associated with worse OS (HR: 1.30, 95% confidence interval [CI] 1.05–1.62; *P* = .02), regardless of MGMT status.

Conclusions. Development of post-RT lymphopenia is associated with addition of TMZ and baseline lymphopenia and not with RT alone in patients treated with short-course radiation. However, regardless of MGMT status, only

baseline lymphopenia is associated with worse OS, which may be considered as a prognostic biomarker for elderly glioblastoma patients.

Key Points

- This is a secondary analysis of the CCTG CE.6 trial evaluating the impact of lymphopenia.
- Development of lymphopenia is not associated with RT alone.
- Baseline lymphopenia is associated with worse OS.

Importance of the Study

This is a secondary analysis of CCTG CE.6 trial evaluating the impact of lymphopenia with overall survival in elderly patients with glioblastoma. The study demonstrated that the hypofractionated radiation treatment regimen used in the trial did not lead to development of lymphopenia. Rather, development of post-radiation lymphopenia was associated with addition of TMZ and baseline lymphopenia. Regardless of MGMT status, only baseline lymphopenia is associated with worse OS, which may be considered as a prognostic biomarker for elderly glioblastoma patients. This is the first study evaluated the incidence of treatment developed lymphopenia with hypofractionated radiation with and without temozolomide, as well as the impact of lymphopenia on overall survival of elderly patients with newly diagnosed glioblastoma based on prospectively collected data.

Advancing the treatment paradigm for elderly glioblastoma patients has been a complex balancing act between maximizing survival and aggressiveness of care. Compared to best supportive care, adjuvant radiation therapy (RT) with conventional fractionation (standard course) was shown to nearly double median survival times (16.9 weeks vs 29.1 weeks) without compromising quality of life (QOL).[1] Additional studies explored hypofractionation, with various shortened treatment schedules showing no difference compared to outcomes with conventional fractionation.[2,3] Temozolomide alone was found to be comparable for survival to standard course alone[4] and hypofractionated radiation alone.[5]

Canadian Cancer Trials Group (CCTG) CE.6 (EORTC 26062-22061, TROG08.02) was a multi-institutional, open-label randomized Phase III clinical trial investigating the benefits of adding temozolomide to hypofractionated (short course) RT for elderly (age ≥ 65 years) patients with newly diagnosed glioblastoma.[6] The authors reported both an overall survival (OS) and progression-free survival (PFS) benefit, with a more pronounced effect in patients with methylated O^6-methylguanine-DNA methyltransferase (MGMT) status. There is concern, however, that the addition of temozolomide to radiation may lead to increased incidence and severity of lymphopenia after concurrent treatment has been completed.

Lymphopenia has been observed in glioblastoma patients receiving standard of care (SOC) chemoradiation, with up to 40% developing grade 3 or higher adverse events.[7] Temozolomide has demonstrated a dose-dependent toxicity for lymphopenia in glioblastoma.[8] Glioblastoma patients are also oftentimes exposed to steroids, which also exhibit a dose-dependent association with lymphopenia.[9] Lymphopenia, particularly with a severe reduction in lymphocyte counts, has been associated with worse survival outcomes, with a hazard ratio (HR) of 1.8 for malignant gliomas receiving SOC, resulting in a median OS difference of 16 versus 18 months.[10] Elderly patients who are predisposed to being immunocompromised[11] may be at higher risk for this phenomenon.

To date, there has not been an analysis of prospectively collected data to compare incidence and severity of treatment-related lymphopenia (TRL) between the treatment arms of radiation alone (RT) versus radiation with temozolomide (RT + TMZ). Based on these considerations, we performed a secondary analysis of CCTG CE.6 to investigate the impact of concurrent chemoradiation versus RT alone on the incidence and severity of lymphopenia in this patient population and the potential association with survival outcomes.

Methods

This study was approved by the Institutional Review Board at Thomas Jefferson University (Philadelphia, PA, USA). The original study was registered on ClinicalTrials.gov (Identifier: NCT00482677).
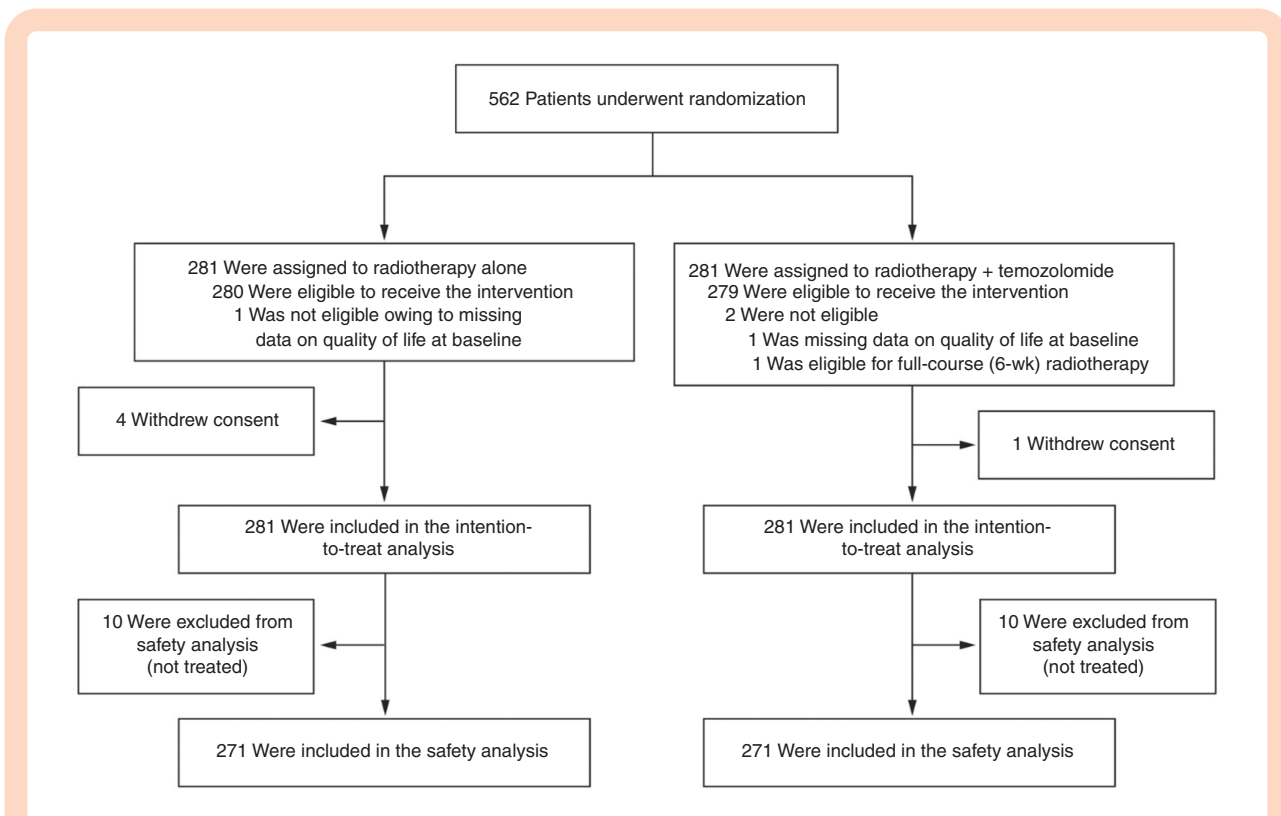
Figure 1. CONSORT diagram from CCTG CE.6.

Patient Selection

All eligible patients enrolled and randomized who received treatment in CCTG CE.6 from November 2007 to September 2013 were included in this analysis. See CONSORT diagram from the original study in Figure 1. Treatment details for each arm, for example, radiation therapy and temozolomide dosing, are included in the original publication for reference.[6] Patients who had evidence of disease progression or died prior to the time of 4 weeks after completion of RT, or missing hematology evaluation, were excluded from the analysis of week 4 lymphopenia's status on PFS and OS.

Radiation Treatment

Short-course radiation was delivered as 40.05 Gy in 15 fractions over 3 weeks. A single planning target volume (PTV) was derived from: (1) Gross tumor volume (GTV) defined as the contrast-enhancing volume on the postoperative planning magnetic resonance imaging (MRI) scan including surgical bed, (2) Clinical target volume (CTV) derived from GTV plus a 1.5-cm margin respecting anatomical boundaries, and (3) PTV CTV plus margin of 0.5 cm was applied. 3D planning techniques were utilized, while intensity-modulated radiation therapy was not permitted as specified per clinical trial protocol.

Temozolomide

Concurrent temozolomide was administered with radiotherapy at a dose of 75 mg per square meter of body-surface area per day for 21 consecutive days from day 1 until the final day of radiotherapy. Adjuvant temozolomide was administered at a dose of 150–200 mg per square meter per day for 5 consecutive days of a 28-day cycle for up to 12 cycles or until disease progression.

Lymphopenia Analysis

Lymphopenia was defined per Common Terminology Criteria for Adverse Events (CTCAE) v3.0 (US Department of Health and Human Services, National Institutes of Health, National Cancer Institute) by the following grouping of grades[12]:

1) Mild-moderate [Grade 1: $<$LLN $\times$ 0.8 – 10^9/L and Grade 2: $<$0.8 – 0.5 $\times$ 10^9/L]
2) Severe [Grade 3: $<$0.5 – 0.2 $\times$ 10^9/L and Grade 4: $<$0.2 $\times$ 10^9/L]

Lymphocyte counts were collected at baseline and post-radiation, including at 1 week and 4 weeks after completion.

Statistical Analysis

Preselected key baseline patient characteristics for the analysis included:

a) Age (65–70 years old; 71–75 years old; 76 years and older)
b) Sex (Male; Female)
c) ECOG Performance Status (0 or 1; 2)
d) Extent of resection (Biopsy only; partial or complete resection)
e) MGMT promoter methylation status (Methylated; Unmethylated)
f) Mini-Mental State Exam (0–30)
g) Steroid use at study randomization (Yes; No)
h) Assigned treatment arm (RT; RT+TMZ)

Chi-square test was used to assess association categorical variables; analysis of variance was used to test association of continuous factors with lymphopenia status; Kaplan–Meier curves were used to estimate distributions of the time to event outcomes. Landmark analysis was performed to study the association of week 4 lymphopenia's status on OS and PFS. Multinomial logistic regression models were used to identify factors associated with lymphopenia; and multivariable Cox regression models were then used to study effects of lymphopenia across time intervals on survival outcomes while adjusting baseline factors. All reported P values are 2 sided, and P value < .05 was considered statistically significant. Analyses were performed using SAS software (version 9.3; SAS Institute).

Results

Patient Characteristics

There was a total of 562 patients, of which 281 were in the RT alone arm and 281 received RT+TMZ. Of these, 74 patients (41 from RT and 33 from RT+TMZ) were excluded from survival analysis due to early progression or death, resulting in 488 patients (240 RT and 248 RT+TMZ). Patients who had early progression or death were more likely to have worse ECOG performance status (P = .02), biopsy only (P < .001), steroid use (P = .04), and lower Mini-Mental State Examination (MMSE) (P = .06).

Additional demographic and patient-related information can be found in Table 1.

Lymphopenia Incidence and Severity

At baseline, lymphopenia rates were virtually identical between treatment arms, with approximately 75.6% of patients with normal lymphocyte counts, 21.4% with mild-moderate lymphopenia, and 3% with severe lymphopenia (Table 2). At 1-week post-RT, there was a small numerical increase in mild-moderate lymphopenia for patients on RT+TMZ (15.4% vs 10.7%), however, this was not statistically significant (P = .25). At 4 weeks post-RT, there was a significant increase for both incidence and severity of lymphopenia for patients who received RT+TMZ versus RT, with 37.2% versus 20%, of which

Table 1. Patient Characteristics

Tab	Early P/D	Non-Early P/D	P-values
Age (years)	n (%)	n (%)	.10
65–70	27 (36.5)	138 (28.3)	
71–75	22 (29.7)	209 (42.8)	
76 and older	25 (33.8)	141 (28.9)	
Sex			.83
Female	28 (37.8)	191 (39.1)	
Male	46 (62.2)	297 (60.9)	
ECOG Performance			.02
≤2	49 (66.2)	383 (78.5)	
2	25 (33.8)	105 (21.5)	
Extent of Resection			<.01
Biopsy only	35 (47.3)	131 (26.8)	
Partial or complete	39 (52.7)	357 (73.2)	
Treatment Arm			.32
RT	41 (55.4)	240 (49.2)	
RT+TMZ	33 (44.6)	248 (50.8)	
Steroids Use			.04
Yes	63 (85.1)	360 (73.8)	
No	11 (14.9)	128 (26.2)	
Lymphopenia (BL or 1W)			.82
Grade ≥ 1	26 (35.1)	178 (36.5)	
Grade 0	48 (64.9)	310 (63.5)	
MGMT methylation status			.33
Methylated	18 (24.3)	147 (30.1)	
Un methylated	23 (31.1)	166 (34.0)	
Unknown	33 (44.6)	175 (35.9)	
MMSE	Mean (STD)	Mean (STD)	.06
	24.4 (5.6)	25.7 (4.4)	

BL, baseline; 1W, lymphocyte count 1-week post-RT; P/D, progression or death; STD, standard deviation.

9.3% versus 1.8% were Grade 3 or higher, respectively (P < .0001). The rate of lymphopenia at 4 weeks post-RT is significantly higher than 1 week post-RT in the RT-TMZ group, but not in the RT alone group.

At 4 weeks post-RT, factors associated with developing lymphopenia included treatment arm RT+TMZ (OR 2.15; 95% CI 1.38–3.33; P = .0007) and lymphopenia present at baseline (OR 5.12; 95% CI 3.30–7.94; P < .0001). These factors were also associated with developing severe lymphopenia, with RT+TMZ (OR 7.64; 95% CI 2.79–20.94; P < .0001) and baseline lymphopenia (OR 9.01; 95% CI –3.80–21.38; P < .0001), as well as biopsy only patients (OR 2.56; 95% CI 1.16–5.65; P = .02). Age, sex, ECOG, MGMT status, steroid use at baseline, and MMSE were not found to be associated with lymphopenia at 4 weeks post-RT in multivariable analysis.

Table 2. Lymphopenia by Treatment Arms at Different Time Intervals

Treatment Arm	Lymphopenia at Baseline				
	Grade 0	Grades 1&2	Grades 3&4	Total	
RT	212 (75.4%)	60 (21.4%)	9 (3.2%)	281	
RT +TMZ	213 (75.8%)	60 (21.4%)	8 (2.9%)	281	
Treatment Arm	Lymphopenia at post-RT 1 week				
	Grade 0	Grades 1&2	Grades 3&4	Total	*P*-value
RT	238 (84.7%)	30 (10.7%)	13 (4.6%)	281	.25
RT +TMZ	224 (80.0%)	43 (15.4%)	13 (4.6%)	280	
Treatment Arm	Lymphopenia at post-RT 4 weeks				
	Grade 0	Grades 1&2	Grades 3&4	Total	*P*-value
RT	225 (80.1%)	51 (18.2%)	5 (1.8%)	281	<.0001
RT +TMZ	176 (62.9%)	78 (27.9%)	26 (9.3%)	280	

Impact on OS and PFS

OS was worse for patients who developed lymphopenia at 4 weeks post-RT (HR 1.29; 95% CI 1.04–1.60; *P* = .02) with median OS of 7.95 months versus 9.92 months (Figure 2) in landmark analysis. Comparison across lymphopenia severity did not yield statistically significant differences between mild-moderate versus severe lymphopenia (*P* = .07), with median of OS of 7.92 versus 8.08 months, respectively.

However, after adjusting for confounding factors on multivariable modeling, lymphopenia status at 4 weeks post-RT was no longer associated with OS (*P* = .49), including for severe lymphopenia (*P* = .58). Instead, baseline lymphopenia (HR 1.30; *P* = .02), males (HR 1.41), biopsy only (HR 1.59), and lower MMSE (HR 0.975), were significantly associated with worse OS (Table 3).

Similarly, 4-weeks post-RT lymphopenia was significantly associated with PFS on univariate (HR 1.25; *P* = .04), but not in multivariate analysis (*P* = .21). Baseline lymphopenia was marginally significant for worse PFS (HR 1.22; *P* = .06), while male patients (HR 1.27; *P* = .01), biopsy only (HR 1.33), and lower MMSE patients had significantly worse PFS.

On the other hand, patients with baseline lymphopenia have significantly worse OS (*P* = .0037, HR 1.341, 95% CI 1.099–1.637), and PFS (*P* = .0356, HR 1.235, 95% CI 1.013–1.506). This remains significant after adjusting for confounding factors on multivariable modeling (Figure 2).

MGMT Promoter Methylation Status Stratification

When stratifying survival analysis by MGMT promoter methylation status, baseline lymphopenia (HR 1.66; *P* = .02), males (HR 1.45; *P* = .04), steroid use at baseline (HR 1.84; *P* = .005) were significantly associated with worse OS in MGMT methylated patients. Baseline lymphopenia (HR 1.59; *P* = .004) and lower MMSE (HR 0.961; *P* = .05) were significantly associated with worse OS in MGMT unmethylated patients.

For PFS, MGMT methylated patients who were male (HR1.61; *P* = .01) and steroid use (1.86; *P* = .005), had worse outcomes. Baseline lymphopenia (HR 1.75; *P* = .003) and

worse ECOG (HR 1.65; *P* = .05) were associated with reduced PFS in MGMT unmethylated patients.

Discussion

Our study results confirm our hypothesis that the addition of concurrent TMZ to RT results in not only increased incidence of treatment-related lymphopenia, but also increased severity. However, surprisingly, the severity and incidence of 4 weeks post-RT lymphopenia did not impact OS or PFS, including on subgroup analysis by MGMT methylation status. Instead, lymphopenia present at baseline of both mild-moderate and severe grades was significantly associated with OS for both MGMT methylated and unmethylated patients.

Our study is unique as the largest reported for exploring lymphocyte counts in glioblastoma patients from a prospectively conducted investigation. With a 1:1 split between treatment arms and all patients receiving short-course RT by clinical trial design, this provides a well-controlled environment answering questions on how specific treatment modalities may contribute to the incidence and severity of lymphopenia, and more importantly the impact these events may have on survival outcomes. Although our results may appear discordant with prior reports of smaller studies in the GBM literature,[10,13] we believe that our finding on baseline lymphopenia as a prognostic factor may, in a way, is in agreement.[14–16] Previously reported literature has various definitions for baseline lymphopenia, ranging from lymphocyte counts of 800/μL to 1000/μL and 1500/μL.[10,17–19] Studies specifically addressing this question are limited, with one publication from the literature addressing lymphopenia in elderly GBM, however, this was a retrospective study of 72 patients, of which just 20 patients (30.56%) received short-course RT.[14] Thus, our study provides a unique prospective outlook on elderly GBM which typically has less aggressive RT and concurrent phase therapy.

Lymphopenia rates reported previously in primary as par for hematologic toxicity, but not stratified by timepoints and not statistically analyzed for significance between
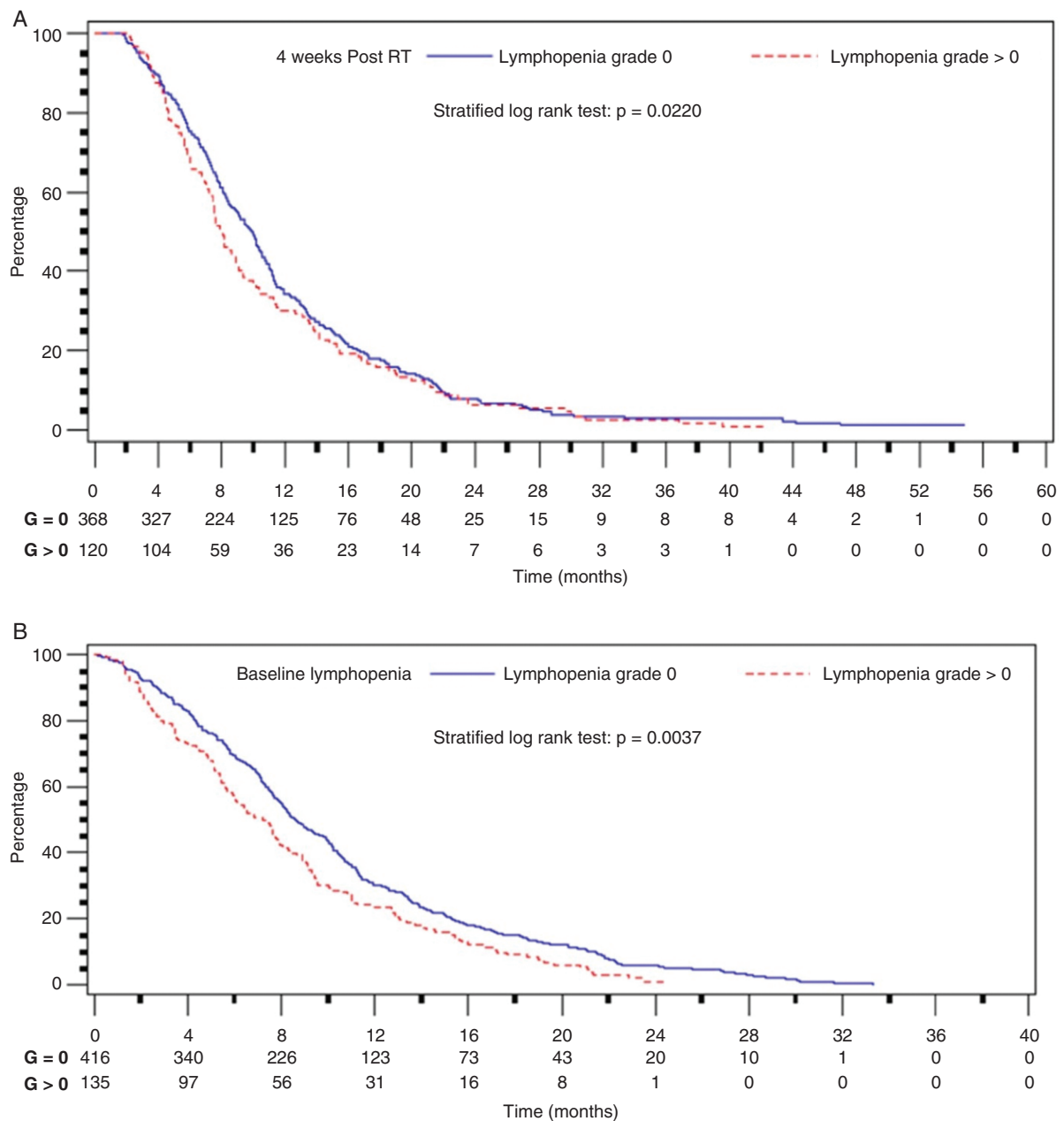
Figure 2. Kaplan–Meier survival curves. (A) Overall survival for 4 weeks post-RT lymphopenia. (B) Overall survival worse with baseline lymphopenia (Grade >0).

treatment arms.[6] We showed that baseline lymphopenia significantly increases the risk for developing treatment-related lymphopenia, including severe lymphopenia. Therefore, our analysis elucidated an additional facet on the importance of timepoint for lymphopenia, especially at baseline for elderly GBM patients, which had not been previously reported.

Baseline lymphopenia may represent several pretreatment concerns for patients. First, this may serve as a surrogate for poor reserve or immunocompromised patients. Second, this may represent a secondary lymphotoxic

effect from steroid exposure prior to trial randomization, which may indicate patients with more clinical symptoms, extensive disease burden, and/or unresectable disease. Analysis on patients enrolled on EORTC trials with breast, non-Hodgkin's lymphoma, and soft tissue sarcoma patients also showed pretreatment lymphocyte count less than 1000/mm^3 was associated with higher risk of death.[18] In GBM patients, pretreatment lymphopenia is associated with post radiation treatment lymphopenia,[19] which is consistent with our finding. However, caution should be given for GBM patients with pretreatment lymphopenia

Table 3. Multivariable Cox Proportional Hazards Model for 4 Weeks Post-RT on OS

Factors	HR (95% CI)	*P*-value
W4 Lymphopenia		.77
Grade 1 or 2	1.09 (0.83, 1.41)	.54
Grade 3 or 4	1.14 (0.71, 1.84)	.58
Grade 0	1	
Baseline Lymphopenia		
Grade 1+	1.30 (1.05, 1.62)	.02
Grade 0	1	
Sex		
Male	1.41 (1.16, 1.71)	.0004
Female	1	
Extent of Resection		
Biopsy only	1.59 (1.29, 1.96)	<.0001
Partial or complete resection	1	
Steroids use		
Yes	1.16 (0.93–1.44)	.18
No	1	
ECOG PS		
2	1.14 (0.89–1.45)	.31
0 or 1	1	
MMSE	0.976 (0.955–0.997)	.02

CI, confidence interval; HR, hazard ratio; OS, overall survival.

may be due to more extensive tumor and/or dependance of steroids, which may be associated with worse outcome. Although we controlled for steroid exposure at baseline, information regarding the length of exposure and dosing of steroids was not collected. Further study is needed to better understand the impact of steroids on GBM patients' treatment outcomes.

Radiation treatment plan dosimetry has been shown to predict the risk of lymphopenia, and V25 of brain tissue less than 56% with conventional fractionation regimen may reduce the risk of severe lymphopenia.[20] Despite the unavailability of detailed dosimetric data on radiation treatment plans in this study, our results show no significant lymphopenia attributable to radiation treatment alone. This may be due to the radiation target volume, and dose fractionation scheduled. Radiation volume is based on residual enhancing tumor and resection cavity, as well as encompassing FLAIR abnormalities. The hypofractionation radiation regimen used in the current trial may further reduce the risk of radiation induced lymphopenia. Based on the estimated probability of circulating lymphocytes through the radiation fields during treatment, the magnitude of radiation exposure and its impact is greatly reduced with hypofractionation.[7,21]

Our current analysis showed short-course RT alone does not lead to lymphophenia after treatment. Development of lymphopenia post-RT is associated with addition of TMZ and baseline lymphopenia. However, only baseline lymphopenia is associated with worse OS regardless of MGMT status. It may be useful to improve the predication of outcome based on current know risk factor, and help clinical treatment decision making. It may also be an stratification factor for clinical trial design. Further studies are warranted for validation.

Keywords

elderly | glioblastoma | lymphopenia | short-course radiotherapy | temozolomide

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