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Original Research Article

Neutrophilia as a biomarker for overall survival in newly diagnosed high-grade glioma patients undergoing chemoradiation

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ABSTRACT

Objective: To study the prognostic value of neutrophil disorders in a retrospective cohort of high-grade glioma patients receiving definitive concurrent temozolomide and radiation.
Materials and methods: Clinical records of consecutive patients treated in our Institution between January 2005 and December 2010 with concurrent temozolomide (75 mg/m^2 daily) and radiation were collected. The prognostic value of pretreatment neutrophilia on survival, defined as a neutrophil count exceeding 7 G/L, was examined.
Results: We identified 164 patients, all treated with concurrent temozolomide-based chemoradiotherapy. Initial surgery was achieved in most (75%), with resection > 90% in 55 patients (34%). Total 151 patients (92%) had glioblastoma, and 13 patients (8%) had WHO grade III glioma. Eighty-two patients (50%) displayed pretreatment neutrophilia. Neutrophilia was not associated with concurrent or adjuvant temodal discontinuation ($p > 0.3$). The 2-year actuarial overall survival was 45%. Steroid consumption, i.e. 60 mg or more of daily prednisolone, increased pretreatment neutrophil count ($p = 0.005$). In univariate analysis, neutrophilia was associated with worse overall survival ($p = 0.019$), as well as age $\geq$ 65 years ($p = 0.009$), surgical resection < 90% ($p = 0.003$) and prednisolone consumption $\geq$ 60 mg/day ($p = 0.016$). In multivariate analysis, neutrophilia ($p = 0.013$), age $\geq$ 65 ($p = 0.001$), and surgical tumor resection < 90% ($p = 0.010$) independently decreased overall survival, while, steroid consumption was not ($p = 0.088$).
Conclusion: In high-grade gliomas treated with concurrent temozolomide and radiation, pretreatment neutrophilia may be a significant prognosis factor for overall survival. In addition with previously available markers, this independent cost-effective biomarker could help identifying patients with worsened prognosis.

Introduction

Glioblastoma is the most common primary brain tumor in adults. Since 2005, standard treatment for glioblastoma patients is maximal safe surgical resection followed by combined radiotherapy and temozolomide chemotherapy [1]. Phase III studies with an addition of targeted antiangiogenic therapies failed to show benefits in overall survival compared to the Stupp protocol [2,3].

Age, performance status (PS), extent of resection, Mini Mental State Examination (MMSE), and O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status have demonstrated their prognostic impact on patients outcome [4]. The MGMT DNA repair enzyme antagonizes the genotoxic effects of alkylating agents. Its low expression is associated with favorable outcome in patients with glioblastoma undergoing alkylating agent based chemotherapy [5]. Still, prognostic markers to guide individual concomitant and maintenance therapy are mandatory.

In addition to cancer cells, stromal cells, blood vessels and infiltrating inflammatory cells are major components of the tumor microenvironment [6]. As additional markers, prognostic value of

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neutrophil-to-lymphocyte ratio (NLR) > 4 in peripheral blood had previously been described in glioblastoma as an accessible and cost-effective marker of systemic inflammatory responses [7–9]. Still, NLR reflects either neutrophilia, lymphopenia or both. In gliomas, high level of CD4(+) tumour-infiltrating lymphocytes (TILs) combined with low CD8(+) TILs has been associated with poor prognosis in glioblastoma patients [10]. Neutrophils are the most abundant circulating leukocytes, and stand as early immune defense. As leukocytes influence the function and phenotype of CD8+ T cells, neutrophils could represent a potential prognosis biomarker in patients with high-grade gliomas [11]. Recently, tumor-associated neutrophilia has been associated with poor clinical outcome in several human cancers [12–14].

In the current study, prognostic significance of pretreatment systemic neutrophilia was retrospectively examined in a single center cohort of consecutive high-grade (III and IV) glioma adult patients treated with concurrent temozolomide and radiotherapy.

Materials and methods

Patients and tumors

We examined clinical records of all consecutive patients registered in our institution between January 2005 and December 2010. We excluded patients with pretreatment immune disorder, patients with grade I or II gliomas at diagnosis, and patients treated with hypofractionated chemoradiation. All patients had been referred to a multidisciplinary neuro-oncology tumor board prior treatment initiation. Explorations at diagnosis included both computed tomography (CT) and a brain magnetic-resonance imaging (MRI) with at least T2, FLAIR, T1 and T1 enhanced gadolinium sequences.

Treatment characteristics and follow-up

After prior surgical resection or biopsy, patients received concurrent radiotherapy. Prescribed doses were 60 Gy administered as 2-Gy fractions 5 days per week in patients with glioblastoma, or 59,4 Gy delivered by 1.8 Gy per fraction in patients with grade III gliomas. All patients had daily concomitant oral temozolomide (75 mg per square meter of body-surface area per day for a maximum of 49 days).

Radiotherapy was planned with a dedicated computed tomography (CT) and three-dimensional planning systems; conformal radiotherapy was delivered with linear accelerators with nominal energy of 6 MV or more. Radiotherapy was delivered by a 3D conformal technique.

The concurrent-therapy phase was followed by a 28-day treatment break. During the adjuvant part, patients received temozolomide (150 mg per square meter per day on days 1–5 during the first cycle and 200 mg per square meter per day during subsequent cycles if unacceptable toxic effects did not occur) [1].

Patients were assessed 6 weeks after the completion of treatment with physical examination and imaging studies and then with physical examination every 2–3 months until progression.

Complete blood count analysis

Complete blood count were obtained postoperatively in the week preceding the first chemoradiation for the current analysis. The daily steroid dose considered in the analysis was on the day of the drawing of the blood sample. Patients underwent systematic complete white blood cell counts (WBC) weekly during chemoradiation. Leukocytosis and neutrophilia assessing biological inflammation were defined as blood count over 10 G/L and 7 G/L, respectively. Anemia was defined as hemoglobin count below 13.0 g/dL. Thrombocytosis, lymphopenia, and monocytosis were defined as platelets count over 400 G/L, lymphocytes count below 1.0 G/L, and monocytes count over 1.0 G/L, respectively. We tested these parameters for statistical correlation with OS. The NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count, with 4 being the cutoff for positivity, in accordance with the previously published literature [9].

Statistical analysis

Differences in patient characteristics regarding pretreatment neutrophilia were compared with Fisher test, Student-t test, and by variance analysis. Survival times were defined as the time between the diagnosis and time of death for OS, estimated by the Kaplan Meier method. Patients were censored at the time of last follow-up visit. Survival curves were constructed using the Kaplan-Meier method and statistical comparisons were performed using the log-rank test for univariate analyses. Multivariate analyses were performed using the Cox proportional hazards model with variables with p value <0.1 in univariate analysis. Statistical analyses were performed using R (version 3.3.2).

Results

Patients and tumors

Among 164 patients, median age was 60 years (range: 19–83). Total 13 patients (8%) had grade III glioma, and 151 patients (92%) had glioblastoma.

On initial blood count, before the week of the initial chemoradiation part, median neutrophil count was 7.0 G/L (1.6–16.6). Leukocytosis and neutrophilia were found in 60 patients (37%) and 82 (50%) patients, respectively (Table 1A & Supplementary Fig. S1). Mean neutrophil count were comparable in patients with grade III gliomas or glioblastomas: 7.0 vs. 7.3 G/L, respectively ($p = 0.701$). Patients with daily prednisolone equivalent dose below 60 mg (6.7 G/L) had significantly lower neutrophil counts compared to patients with dose above 60 mg (8.5 G/L; $p = 0.005$) (Supplementary Fig. S2).

Radiotherapy and chemotherapy

All patients underwent a 3D-conformal brain irradiation to a median 60.0 Gy dose (range: 14–60) with concurrent temozolomide (75 mg/m^2 daily during chemoradiation). Median delay from surgery was 1.5 month (range: 0.1–13.3). Most of the patients received the planned treatment doses; adverse events leading to discontinuation of temozolomide involved 11 patients (7%) during chemoradiation phase, and 68 patients (41.5%) during maintenance phase. A total of 5 (3%) and 11 (7%) patients discontinued or stopped concomitant temodal therapy, independent from pretreatment neutrophilia ($p = 0.670$ and $p = 0.371$ respectively). Similar, 15 (11%) patients discontinued concomitant temodal therapy for toxicity, independently from neutrophilia ($p = 0.377$) (Table 1B).

Survival and disease control

145 patients (88%) died during the follow-up (median 28.7 months; range, 0.5–99.0). Estimated 1 and 2-years OS were 75% (95%CI: 68–82) and 45% (95%CI: 37–53), respectively.