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ORIGINAL ARTICLE

Contribution of low-molecular weight heparin addition to concomitant chemo-radiotherapy in the treatment of glioblastoma multiforme

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Summary

Purpose: *Glioblastoma multiforme (GBM) is the most common brain tumor in adults and has a very aggressive course. Median survival is as short as 2 years with standard treatment (chemoradiotherapy followed by adjuvant temozolomide). The purpose of this study was to determine the contribution of low molecular weight heparin (LMWH) addition to concomitant chemoradiotherapy in the treatment of GBM.*

Methods: *All patients with newly diagnosed GBM between March 2004-May 2009 were evaluated. After surgical intervention (total, subtotal resection or only biopsy) all of them were treated with concomitant chemoradiotherapy (2 Gy daily, 5 days a week, 30 fractions, total tumor dose 60 Gy; and 75 mg/m^2 temozolomide, 7 days a week), followed by adjuvant temozolomide (6 cycles, 150-200 mg/m^2, 5 days every 28 days), with or without LMWH (4000 IU/day, 7 days a week, concomitant with radiotherapy) because of risk of thrombosis. The primary endpoint was the determination of progression-free survival (PFS) and overall survival (OS); secondary endpoints were 1- and 2-year OS survival.*

Results: *30 patients (13 patients in the group non receiving LMWH (LMWH-) and 17 patients in the group receiving LMWH (LMWH+)) were included in the study. Median age was 54 years (range 24-75). Median PFS was 57 and 38 weeks in LMWH+ and LMWH- groups, respectively (p=0.068). Median OS was 69 and 44 weeks (p=0.095), 1-year OS survival 84.6 and 41.2% (p=0.016), and 2-year OS survival 38.5 and 5.9% in LMWH+ and LMWH-, respectively (p=0.061). No significant difference was noted between the two groups for grade 3-4 toxicity (p>0.05).*

Conclusion: *Better PFS, OS and 2-year OS survival were obtained in present study with the addition of LMWH to concomitant chemoradiation for GBM but without statistical significance. One-year OS survival was statistically significant favoring the LMWH group. The addition of LMWH did not increase temozolomide toxicity.*

Key words: enoxaparin, glioblastoma multiforme, low molecular weight heparin, temozolomide

Introduction

GBM is the most common type of primary brain tumors in adults and represents approximately 60% of all brain tumors. Based on a significant survival advantage provided by use of concomitant chemo-radiotherapy and adjuvant chemotherapy with temozolomide demonstrated in a recent phase III study [1], this therapeutic approach is recently considered as standard of care for newly diagnosed GBM. In GBM patients survival is still lower than 2 years despite of all treatment modalities including surgical resection, radiation therapy and chemotherapy. In cancer patients, thromboembolic complications are included in the main causes of death. Anticoagulant treatment, especially LMWH, has been demonstrated to improve the survival in cancer patients not only owing to decrease of thromboembolic events, but also to raised possibility of antineoplastic activity in different cancer types [2].

The purpose of this study was to see for any difference between GBM patients that were administered

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LMWH due to increased risk of thrombosis and those who were not.

Methods

Patients diagnosed with GBM who applied to the Radiation Oncology Department or Medical Oncology Department of Dicle University Faculty of Medicine between March 2004 and May 2009 were included in the study.

Inclusion/exclusion criteria

The eligibility requirements included patients ≥ 18 years with histologically confirmed GBM based on WHO classification. Patients were not eligible if they had previously received treatment (chemoradiotherapy) for the disease but did not complete it.

Data collection

Data were collected retrospectively from the patient files. Patient age, gender, past surgical procedures, localization, presence of epilepsy and deep venous thrombosis and ECOG performance status (PS) were recorded. The process starting from the diagnosis to progression and to death was recorded in weeks.

Treatment

All patients received conventional fractionated external radiotherapy (2D), 5 days a week (from Monday to Friday), 2 Gy daily, for a total tumor dose of 60 Gy in 30 fractions in 6 weeks. Special thermoplastic masks were used for each patient to maintain immobilization. Simulix Oldef HP model simulator (Nucletron) was used to perform conventional simulation. For the treatment of patients, 6 MV photon was used with Alcyon II model Co60 (General Electric) radioactive source teletherapy or Saturn 43 F model Linear Accelerator (General Electric). For target volume determination, treatment zone was established by adding 2-3 cm safety margin to the volume including tumor and peripheral edema which were contrasted taking preoperative cranial MRI images as reference. Irradiation was performed by the isocentric technique using parallel-opposed bilateral fields.

During radiotherapy, all patients received concurrently temozolomide 75 mg/m^2, 7 days a week. Thirteen inpatients receiving radiotherapy were administered the LMWH enoxaparin for prophylactic purposes and were evaluated in the enoxaparin positive group. These patients were administered subcutaneous enoxaparin 4000 IU/day (including weekends) during radiotherapy. Following a 4-week interval, all patients were administered 6 cycles of adjuvant (as defined by Stupp et al.[1]) temozolomide (150 mg/m^2/day, 5 days every 28 days) in the first cycle and 200 mg/m^2/day, 5 days every 28 days from the second cycle onwards. Treatment-related toxicities were assessed according to the National Cancer Institute (NCI) system.

Statistical analysis

The primary endpoint of the study was PFS and OS and secondary endpoints were 1- and 2-year OS survival. Statistical analyses were carried out using SPSS 11.5 software. Fisher's exact test and the Independent Samples test were used for group comparisons. Survival analyses were done according to the Kaplan-Meier method with two-sided log rank statistics.

Results

A total of 30 patients were included in the study. Thirteen patients were in the LMWH- group and 17 in the LMWH+ group. Seven of these cases were female (23.3%) and 23 male (76.7%). Median age was 54 years (range 24-75). The most common symptom was headache (n=23; 76.6%). The most common localization was the frontal lobe (n=9; 30%) and the most common surgical procedure performed was subtotal excision (n=20; 66.7%). Statistical analysis showed no significant difference between the 2 groups in terms of age, gender, PS and the surgical procedure (p>0.05; Table 1).

Evaluation of survival results showed that median PFS was 38 weeks in the LMWM- group (95% CI, 12-112), while it was 57 weeks in the LMWH+ group (95% CI 22-113) (p=0.068; Figure 1). Median OS was 44 weeks in the LMWH- group (95% CI 13-128),

Table 1. Characteristics of patients with or without enoxaparin administration (n=17)

Characteristics	*Enoxaparin –*	*Enoxaparin +*	*p-value*
Age (years) median	55	53	NS
Gender			NS
Female	4	3	
Male	13	10	
ECOG performance status			NS
0-2	11	11	
3-4	6	2	
Surgery			NS
Biopsy	3	0	
Subtotal	10	10	
Total	4	3	

NS: non significant

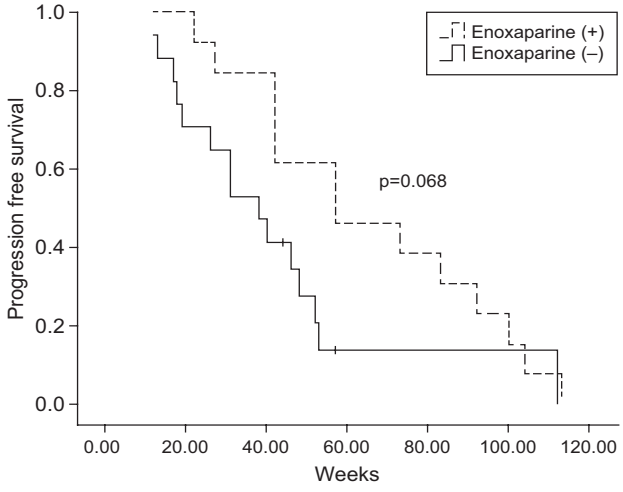

Figure 1. Kaplan-Meier estimates of progression-free survival according to treatment group.

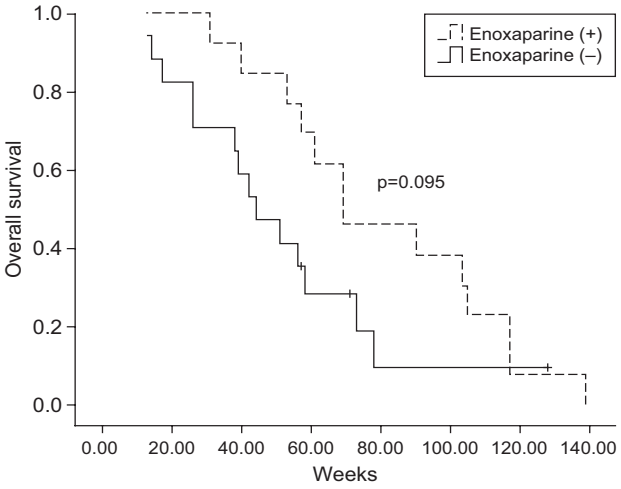

Figure 2. Kaplan-Meier estimates of overall survival according to treatment group.

while it was 69 weeks in the LMWH+ group (95% CI 31-139) (p=0.095; Figure 2). One-year survival was 41.2% (n=7) in the LMWH- group and 84.6% (n=11) in the LMWH+ group (p=0.016). Two-year survival was 5.9% (n=1) in the LMWH- group and 38.5% (n=5) in the LMWH+ group (p=0.061; Table 2).

As regards toxicity, grade 3-4 neutropenia developed in 3 patients in both groups. No toxic deaths occurred in any of the patients. No patient developed deep venous thrombosis. No bleeding was observed in either of the groups.

Discussion

Glial tumors are the most common type of primary malignant brain neoplasms and constitute approximately 60% of all primary brain tumors [3]. For more than 3 decades, postoperative radiotherapy has been the standard treatment for newly diagnosed GBM. Pooled analysis of 6 randomized trials of postoperative radiotherapy vs. no radiotherapy showed significant survival benefit for radiotherapy [4,5]. However, the survival advantage after radiotherapy was short and OS remained poor with almost no long-term survivors. The addition of nitrosourea-based chemotherapy provided an additional modest benefit. A meta-analysis of 12 randomized trials of adjuvant chemotherapy for high-grade glioma showed a 35% 1-year survival rate for GBM, an absolute improvement of 6% [6]. In GBM patients, median survival is still approximately 1 year despite the usage of all treatment modalities including surgical resection, radiation therapy and chemotherapy [4,7-11].

About 5 years ago, a study conducted by EORTC and NCIC demonstrated that addition of temozolomide

Table 2. Survival results of patients with or without enoxaparin administration

Survival	*Enoxaparin –*	*Enoxaparin +*	*p-value*
Median PFS (weeks)	38	57	0.068
Median OS (weeks)	44	69	0.095
One-year OS survival, N (%)	7 (41.2)	11 (84.6)	0.016
Two-year OS survival, N (%)	1 (5.9)	5 (38.5)	0.061

PFS: progression free survival, OS: overall survival

to radiotherapy following surgery had positive impact on PFS and OS and that the treatment was well-tolerated [1]. After this study, addition of temozolomide to radiotherapy has become a standard in the adjuvant treatment of GBM. Later on, several studies obtained results supportive of these data [12-14]. Despite standard treatment of GBM, median survival data is still less than 2 years and the need for other treatment modalities is obvious.

There are several studies in the published literature reporting the antitumor activity of anticoagulant agents. These studies mostly focus on heparin, as an anticoagulant. In certain studies regression has been demonstrated in the primary tumor with these agents [15,16], while there are also those which showed reduced metastatic rates with these agents [17-19]. Several mechanisms have been suggested for the antitumor activity of heparin. Among these, the most convincing are prevention of tumor growth and metastasis by apoptosis induction and gene expression inhibition, blockade of angiogenesis by inhibition of growth factors to bind to their target receptors and inhibition of expression of growth factors and of fibrin formation, activity on immune system by macrophage activation, natural killer cell activation, increased tumor necrosis factor (TNF) and interferon (IFN), leukocyte activation and increased extravasation, inhibition of metastatic process by regulating the synthesis of the extracellular matrix proteins, inhibiting adhesion over sialyl Lewis and P-selectin and preventing the platelets to coat cellular surface [2]. In addition to heparin, LMWH has also been shown to possess antitumor activity in several studies [20,21]. In the literature, antineoplastic effect of anticoagulant agents was demonstrated for small cell lung cancer [16,22], malignant melanoma [20], pancreatic cancer [23] and colon cancer [24]. Antineoplastic activity of LMWH in high-grade glial tumors has been demonstrated *in vitro* [25], whereas an *in vivo* study with dalteparin reported decreased frequency of thromboembolic events but no contribution to survival (no direct comparison was made) [26]. We, therefore, investigated the addition of enoxaparin to standard treatment to clarify whether LMWH, the efficacy of which in *in vitro* studies was proven in GBM [22], is also effective *in vivo*.

In the present study there were no statistically significant differences between the 2 groups in terms of age, gender and the surgical procedure performed, although there were more patients with better PS in the group receiving enoxaparin (n=11; 84.6% vs. n=10; 58.8%; p>0.05). Despite the lack of a significant difference between the 2 groups in terms of PFS, a p-value at the margin of significance was obtained (p=0.068) favoring the enoxaparin group. For OS, a result also at the margin of statistical significance was obtained in favor of the enoxaparin group (p=0.095). One-year survival analysis showed a statistically significant difference in favor of the group receiving enoxaparin (84.6 vs. 41.2%, p=0.016), whereas there were no significant differences between the 2 groups in 2-year survival (38.5 vs. 5.9%, p=0.061), although the group receiving enoxaparin yielded better results. Also, no statistically significant differences were noted between the 2 groups in terms of toxicity, deep venous thrombosis and bleeding (p>0.05).

In conclusion, better PFS, OS and 2-year survival were obtained in the present study with addition of LMWH to their chemoradiotherapy, however without statistical difference. One-year survival was significantly better in LMWH+ group. Addition of enoxaparin to treatment did not increase toxicity. *In vitro* efficacy has been shown before and this is the first study in which *in vivo* efficacy has been shown. We believe that prospective studies and studies with higher number of patients will better clarify the data obtained in the present study.

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