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Original Research

Associations of anticoagulant use with outcome in newly diagnosed glioblastoma

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Abstract ***Background:*** To test the hypothesis that despite bleeding risk, anticoagulants improve the outcome in glioblastoma because of reduced incidence of venous thromboembolic events and modulation of angiogenesis, infiltration and invasion.
Methods: We assessed survival associations of anticoagulant use from baseline up to the start of temozolomide chemoradiotherapy (TMZ/RT) (period I) and from there to the start of maintenance TMZ chemotherapy (period II) by pooling data of three randomised clinical trials in newly diagnosed glioblastoma including 1273 patients. Progression-free survival (PFS) and overall survival (OS) were compared between patients with anticoagulant use versus no use; therapeutic versus prophylactic versus no use; different durations of anticoagulant use versus no use; anticoagulant use versus use of anti-platelet agents versus neither anticoagulant nor anti-platelet agent use. Cox regression models were stratified by trial and adjusted for baseline prognostic factors.

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Results: Anticoagulant use was documented in 75 patients (5.9%) in period I and in 104 patients (10.2%) in period II. Anticoagulant use during period II, but not period I, was associated with inferior OS than no use on multivariate analysis ($p = 0.001$, hazard ratio [HR] = 1.52, 95% confidence interval [CI]: 1.18–1.95). No decrease in OS became apparent when only patients with prophylactic anticoagulant use were considered. No survival association was established for anti-platelet agent use.
Conclusions: Anticoagulant use was not associated with improved OS. Anticoagulants may not exert relevant anti-tumour properties in glioblastoma.

1. Introduction

Venous thromboembolic events (VTEs) are an important complication of glioblastoma [1,2]. Yet, there is no information on their contribution and treatment to morbidity and mortality. Prevention and treatment of VTE in glioblastoma have remained insufficiently studied. There is increased interest in anticoagulants as modifiers of tumour biology which improve outcome. Low-molecular-weight heparin (LMWH) may influence cancer cell adhesion, proliferation, invasion and angiogenesis, in part through coagulation-independent pathways [3–8]. Cohort studies and a Cochrane review have suggested a potential improvement in the outcome in cancer patients treated with anticoagulants [9–12]. Several limitations, however, exist and introduce bias in the interpretation of these results: studies were published more than 15 years ago; patient numbers per study were small; survival was not the primary end-point and cancer types, staging, performance status, clinical status, schedule of chemotherapy, dose and type of anticoagulant and treatment duration varied. Prevention of VTE by LMWH has been evaluated in three studies enrolling patients with World Health Organisation (WHO) 2007 grade III or IV gliomas [13–15], without firm conclusions on modulation of survival. These observations encouraged the evaluation of an association with the outcome of anticoagulant use in the newly diagnosed glioblastoma.

2. Materials and methods

2.1. Patients

To assess associations of anticoagulant use during initial treatment of patients with the newly diagnosed glioblastoma and the outcome, we analysed data from a pooled cohort of patients randomised in three contemporary clinical trials: CENTRIC (cilengitide, temozolomide, and radiation therapy in treating patients with newly diagnosed glioblastoma and methylated gene promoter status) (n = 545) [16], CORE (cilengitide, temozolomide, and radiation therapy in treating patients with newly diagnosed glioblastoma and unmethylated gene promoter status) (n = 265) [17] and avastin in glioblastoma (AVAglio) (n = 463) [18]. All patients from CENTRIC and CORE were included because cilengitide was interpreted to be inactive therapeutically and not to affect the risk of VTE. The control arm only of AVAglio was included to avoid a confounding effect of bevacizumab for progression-free survival (PFS) and incidence of VTE (Fig. 1). Investigations were approved by local institutional review boards. Informed consent was obtained from each patient. For each trial, data sets were received with anonymised individual patient information including the date of randomisation, PFS, OS and the baseline covariates age, gender, WHO performance status, extent of resection, steroid use, Mini-Mental State Examination (MMSE), O^6-methylguanine DNA methyltransferase (*MGMT*) promoter methylation status and details on anticoagulant and anti-platelet agent use.

2.2. Statistical analysis

In this prospective retrospective analysis, we hypothesised that anticoagulant use would be associated with longer OS. We thus set out to compare the outcome of patients with and without anticoagulant exposure. Before the analysis, it was decided that the primary hypothesis would correspond to (i) the OS comparison of any anticoagulant use versus no use. Anticoagulant use was evaluated at baseline, corresponding to the time from randomisation into the trial, including the two weeks before, to the date of the first dose of concomitant temozolomide chemoradiotherapy (TMZ/RT) (period I), and during initial treatment, defined as the time interval from the first dose of TMZ/RT until the first dose of maintenance TMZ (period II). A patient was considered taking anticoagulants when at least one dose was taken at any time during the respective periods. Anticoagulant therapy was defined as the use of LMWH, unfractionated heparin, vitamin K antagonists or factor Xa inhibitors. PFS was investigated as an additional time-to-event end-point. Further planned analyses included the comparison of PFS and