Anticoagulation in patients with brain cancer: an international registry

Subcommittee: Hemostasis & Malignancy

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Description Abstract

BACKGROUND

Patients with malignancy are at risk of developing cardiovascular complications which warrant anticoagulation, including venous thromboembolism (VTE) and atrial fibrillation (AF), with the former being especially prevalent in brain cancer [1]. Anticoagulation in cancer patients is associated with an increased bleeding risk, particularly ICH [2]. This increased risk of ICH with anticoagulation has been demonstrated in patients with high-grade glioma [3], but is yet to be confirmed in patients with metastatic brain cancer [4]. Over the past decade and a half, low-molecular-weight heparin (LMWH) has been the standard anticoagulant in cancer patients with VTE, and accordingly most of the above data relates to LMWH treatment. Direct oral anticoagulants (DOACS) have recently become an alternative for treatment of cancer-associated thrombosis, but limited data exists regarding the safety of DOACs in patients with brain cancer. Two recent retrospective studies conducted by our groups have shown similar rates of ICH with LMWH and DOACs in patients with metastatic brain cancer. Rates of ICH in patients with primary brain tumors treated with DOACs (0 of 20 patients; 0%) were remarkably low, compared with LMWH (17 of 47 patients; 36.2%) in one of these cohorts, while the other demonstrated similar ICH rates, albeit with an even smaller sample [5-7].

KNOWLEDGE GAPS:

1. **ICH rate with DOACs in patients with brain cancer.**
   Larger samples needed to achieve sufficient power to exclude an increased rate of ICH with DOACs for the following reasons: While the above data on DOACs in metastatic brain tumors are somewhat reassuring [5,6], the 95% CIs are broad (e.g. HR 0.57; 95% CI 0.12-2.87 for *major* ICH with DOAC vs. LMWH), and do not exclude an increased rate of bleeding; ICH rates differed between these studies, suggesting differences in patient populations; Only 93 patients receiving DOACs were included, overall (31 with primary brain cancer; 62 with metastatic brain cancer). Data on DOACs and ICH are especially lacking for primary brain cancer. Conflicting rates of ICH with DOACs. Number of DOAC-treated patients and ICH is low in two retrospective studies.
2. **Predictors of ICH in patients with brain cancer receiving anticoagulation are needed.**
   This is especially relevant for patients with AF whose bleeding risk might exceed the risk of thrombosis. The PANWARDS score [8] was not developed for cancer patients, but has been assessed in this setting with conflicting results. A high PANWARDS score was associated with ICH in patients with high-grade glioma [3] receiving LMWH, but not in patients with metastatic brain cancer receiving either LMWH or DOAC [5,6]. In one study, several clinical predictors (e.g. antiangiogenic therapy) did not predict ICH in glioma patients, but larger samples are needed.
3. **Management and outcomes of anticoagulation-related ICH.**
   Data on anticoagulation-related ICH and management is scarce and outcomes appear to be poor [9]: Outcomes of interest (in addition to overall survival) include rates of restarting anticoagulation, thrombosis-related outcomes, recurrent ICH, disruption of cancer-treatment and functional status.

4. **Validation and implementation of clinically relevant definitions of ICH.**
   Current definitions of major bleeding (at all sites) include a wide range of clinical severity and recently attempts have been made to address this issue [10,11]. Anticoagulation-associated major ICH is associated with decreased overall survival [3], however the definition of major ICH in this setting may vary. Ideally, clinical (e.g. clinical severity) and radiological definitions (e.g. volume cutoffs) should be measured against clinical outcomes.

STUDY AIMS:

By studying patients with primary and metastatic brain cancer receiving anticoagulation we aim to address the above knowledge gaps, as follows:

1. Determine whether DOACs (vs. LMWH) are associated with increased rates of ICH
2. Identify clinical and radiological variables associated with ICH
3. Develop a cancer-specific risk assessment model for anticoagulation-associated ICH
4. Assess management of anticoagulation-related ICH and associated outcomes
5. Evaluate clinical and radiological definitions of ICH severity

CLINICAL IMPLICATIONS:

Patients with brain tumors with an indication for anticoagulation are common. The landmark randomized controlled trials of DOACs vs LMWH included few patients with brain cancer, at most. Randomized trials of DOACs vs LMWH in this patient population are currently not expected, but DOAC use is expected to increase in cancer patients. A well-powered and well-designed observational study could indicate whether DOACs are an acceptable option in patients with primary and metastatic brain cancer. An ICH risk assessment model specific to this setting could inform decisions on anticoagulation, especially when the thrombotic risk is not high. Data on clinical outcomes after ICH and association with various definitions of ICH severity will indicate the health burden in this setting and enable design of clinically relevant management studies.

Design and methodology

DESIGN

Multicenter retrospective cohort study of consecutive patients with primary or metastatic brain cancer receiving therapeutic-dose anticoagulation (DOACs or LMWH) for any indication. All patients will be required to have at least two neuroimaging studies (computed tomography or magnetic resonance imaging) from index day until the end of 12-month follow-up, unless death occurs first.

Study index will be defined as the first day of concurrent anticoagulation and diagnosed brain cancer, and patients will be followed for 12 months. Patients who develop an anticoagulation-related ICH during the study period will be followed for an additional 90 days post ICH.

Each center will use a locally-adapted screening strategy based upon diagnostic codes and prescription records to identify consecutive potential patients. Electronic medical records (EMRs) will be reviewed manually to ensure eligibility. Granular data will be extracted from the EMRs of each patient in the final cohort. The written reports of all neuroimaging studies during the study period (i.e. 12 months, and the 90-day post-ICH period) will be reviewed for each case. Imaging studies reporting any type of ICH or intracranial presence of blood products during follow-up will be read centrally by a neuroradiologist blinded for type of anticoagulant and clinical data. A neuroradiologist will perform the following: confirm ICH presence of hemorrhage; assess ICH-related outcomes (e.g. bleeding volume, number of bleeds). In

line with prior studies, major ICH will be defined as spontaneous ICH, those that measured ≥ 10 mL in volume, required surgical intervention, or were associated with clinical symptoms, focal neurologic deficits or changes in cognitive function [3,4]. A second neuroradiologist will perform a second reading of a random sample of ~40 images. In case of disagreement on classification of major ICH in more than 10%, all ICH images will be double-read, and a third reviewer (i.e. referee) will be used in cases of disagreement.

Demographics and variables related to cancer, anticoagulation (including the underlying thrombotic disorder) and ICH risk (e.g. PANWARDS score) will be documented at index. Where possible, susceptibility weighted imaging (SWI) data from the MRI studies at baseline will be documented. Data on anticoagulation will be collected throughout follow up. In patients with post-index ICH, the following variables will be recorded at the time of ICH: radiological and clinical characteristics of the ICH [10,11]; acute management of ICH (e.g. hemostatic factors, surgery); anticoagulation status immediately prior to ICH and concomitant antiplatelet therapy.

STATISTICAL ANALYSIS

The primary endpoint (objectives #1-3) will be defined as the incidence of major ICH during 12-months follow-up. The secondary endpoints include any ICH, VTE, and ischemic stroke or systemic arterial thromboembolism. All analyses will be performed separately for patients with primary brain tumors and metastatic brain cancer. For the primary objective (#1), the study exposure is the type of anticoagulation (DOAC vs. LMWH). The cumulative incidence of major ICH and any ICH (and the other secondary endpoints) will be compared between anticoagulation groups, using the Fine and Gray model, with death as competing risk. Hazard ratios with corresponding 95% CIs for ICH will be calculated. This analysis will be repeated with anticoagulation as a time-dependent covariate, taking into account changes in or discontinuation of anticoagulation occurring before end of follow-up. For objectives #2-3, associations between baseline variables and major ICH (and any ICH) at 12 months will be evaluated using multivariate analysis. Subsequently, a risk-assessment model aimed at detecting major or any ICH at 12 months will be built. For objectives #4-5, management of management of anticoagulation-related ICH will be reported descriptively. Associations between management (e.g. restarting anticoagulation) and clinical outcomes at 90 days post-ICH will be assessed. Clinical outcomes include rates of restarting anticoagulation, thrombosis-related outcomes, recurrent ICH, disruption of cancer-treatment and functional status. Clinical and radiological definitions of ICH severity will be associated with clinical outcomes at 90 days post-ICH, to assess clinical relevance.

SAMPLE SIZE CONSIDERATIONS

The sample size was calculated for the primary objective (#1), and separately for the two cancer groups (i.e. primary and metastatic), based on estimates from prior retrospective cohort studies. The 12-month incidence of the primary outcome (major ICH) varied between studies, and the more conservative estimates were selected (i.e. higher rate of major ICH with LMWH). Taking the rate of major ICH and the clinical impact of major ICH into account, we considered a difference of ≥5% in the rate of major ICH between the LMWH and DOAC group to be clinically significant. Based upon prior studies and expected prescription practice, a 2:1 ratio between the LMWH and DOAC group was used. All calculations aimed for an 80% power (β=0.2) at a two-sided significance level of 0.05.

Primary brain tumors: A 12-month major ICH rate of 18% in patients treated with LMWH was assumed [3,5]. In order to detect a difference of ≥5% in the major ICH rate between the LMWH and DOAC group, 1720 subjects would be required, which was considered prohibitive given the rarity of these tumors. Therefore, we used a pragmatic difference of 7.5% to calculate a sample size of *705 subjects (235 DOAC-treated; 470 LMWH-treated)*.
Brain metastases: An average 12-month major ICH rate of 15% in patients treated with LMWH was assumed [4-6]. In order to detect a difference of ≥5% in the major ICH rate between the LMWH and DOAC group, 1452 subjects would be required, which was considered feasible given the frequency of brain metastases and the high VTE rates associated with common tumors frequently accompanied by brain metastases (e.g. lung cancer). Therefore, the sample size was set at *1452 subjects (484 DOAC-treated; 968 LMWH-treated)*.

Study population

SETTING AND SAMPLE

The cohort includes subjects treated as inpatients or outpatients in the hemato-oncology or oncology departments at the study centers between January 1st, 2014 and January 1st, 2020. Adult patients will be eligible if the following inclusion criteria are met (irrespective or what comes first): 1) active high-grade glioma or confirmed presence of brain metastases; 2) anticoagulation therapy prescribed at therapeutic doses in the presence of active brain cancer, for any indication and any duration. Patients were excluded from study participation in case of ICH occurring before initiation of anticoagulation, neurosurgery within 4 weeks prior study index, or lack of follow-up data.

PARTICIPATING INSTITUTIONS

This project is proposed by 3 centers (Rabin Medical Center, Petah Tikva, Israel; AMC, Amsterdam, the Netherlands; BIDMC, Boston, USA). Additional centers will be recruited via the ISTH SSC and through local and international networking (including neuro-oncology working groups since a neuro-oncologist is in the study team). We calculated the minimum number of centers needed by considering the number of patients recruited in the pilot studies to date [5,6], together with a longer study period. The assumption is that the DOAC cohort will be the limiting factor. This is a conservative estimate and less centers may be needed due to increasing rates of DOAC use.
Therefore, a minimum of ***13 additional centers*** is needed (16 in total), meaning that ***each*** center would have to include ***30 DOAC-treated*** patients with ***metastatic brain cancer*** and ***15*** with ***primary brain cancer*** (as well as 60 and 30 LMWH-treated patients respectively). Considering the multinational make-up of the study team, we expect to meet this number of centers.

Expected timeline:
From set-up to publication of all related articles we anticipate a maximum of ***30 months, in total***:

1. PROJECT SET UP: ***3 months*** needed for adaptation of the existing REDCap project, setting up the radiology review system and adjusting screening strategies to identify consecutive patients.
2. LAUNCH: ***on September 1st 2020***. We anticipate that *6 months* will be needed until the full set of study centers is recruited and has local institutional/ethical approval
3. DURATION: ***March 1st – Sep 1st 2021*** (*6 months*) for data extraction and review of imaging
4. FINALIZATION/ANALYSIS: ***Sep 1st 2021 – Mar 1st 2022*** (*6 months*) for refinement of data and all statistical analyses (obj. #1-5)
5. REPORTING: ***March 1st – Dec 1st 2022*** (*9 months*) to write the 3 planned manuscripts (see below)

Expected outcomes: The following publications are intended as original articles:

1. Risk of ICH with DOACs in patients with brain cancer, compared to LMWH (*aim #1*)
2. Predictors of anticoagulation-associated ICH in patients with brain cancer (*aims #2-3*)
3. Clinical outcomes after anticoagulation-related ICH, and associations with management and ICH severity (*aims #4-5*)

Description of project set/up and management, needed infrastructure and resources

1. PROJECT SET UP
    a. The ***ISTH REDCap server*** would be needed to host this study, The existing project (created for the pilot studies) can be seamlessly copied into this environment.
    b. ***Technical support and data sharing capabilities*** would be needed to enable central review of ICH-qualifying MRI/CT studies in patients with ICH. This means the uploading of approximately 390 imaging studies (i.e. ~ 18% of all patients). If not feasible, funding for shipping of hardcopies of the imaging studies would be needed.
2. LAUNCH: The ***ISTH networking capabilities*** needed to increase awareness and participation
3. DURATION: ***Funding for radiologists performing central review*** may be needed. 390 ICH cases at only 50$ per case would cost 19,500$ for single review. Financial support (e.g. 50-100$) per case to increase participation is prohibitively costly.
4. FINALIZATION/ANALYSIS: Analyses will be performed in-house at the leading centers.

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