COMMENTARY

blood advances

TO THE EDITOR:

DOACs for VTE in patients with brain cancer and brain metastases: choices, choices, choices

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Giustozzi et al[1] recently published a systematic review and meta-analysis that investigated intracranial hemorrhage (ICH) in patients with primary or metastatic brain cancer managed with or without anticoagulants. The analysis included 30 retrospective studies and concluded that (1) the rate of ICH and major ICH is higher in patients with metastatic brain cancer than in those with primary brain cancer (all ICH, 13% vs 6.4%; major ICH, 15.4% vs 3.9%), (2) anticoagulation is associated with an increased risk of ICH and major ICH in patients with primary brain cancer but not in those with metastatic brain cancer, and (3) the risk of ICH is a third lower in patients treated with a direct oral anticoagulant (DOAC) than in those treated with low-molecular-weight heparin (LMWH).

Here, we offer some further thoughts on the third conclusion. In the trials of DOACs versus LMWH for cancer-associated venous thromboembolism (VTE), there were very low numbers of patients with primary brain cancers: none in the Caravaggio trial[2] and 8 of 300 patients (2.7%) in the ADAM-VTE trial[3] (both apixaban), and 3 of 406 patients (0.7%) in SELECT-D[4] (rivaroxaban). Conversely, the Hokusai VTE cancer trial of edoxaban vs dalteparin included 74 patients with brain cancer or metastases.[5] In this group, there were major bleeding events in 2 of 31 patients (6.5%) treated with edoxaban vs 3 of 43 patients (7.0%) treated with dalteparin, which is a nonsignificant difference, although the trial was not powered for the analysis of this subgroup. Therefore, we are also reliant on retrospective studies, studies that are highly susceptible to confounding, bias, and erroneous findings, from which to draw conclusions.

Giustozzi et al include 4 retrospective studies in which patients who were treated with a DOAC were compared with those who were treated with LMWH,[6-9] and 1 study in which patients were compared with those treated with warfarin.[10] Of these 5 studies, 3 were rated as good quality and 2 as poor (studies summarized in Table 1). In the analysis of Giustozzi et al, supplemental Figure 4 is a forest plot demonstrating that the only study to show a statistically significant difference between DOAC and LMWH is that by Carney et al,[6] one of the studies rated as poor quality. This study retrospectively compared outcomes of 41 patients taking a DOAC (primary brain cancer, 20; metastatic brain cancer, 21) and 141 patients taking enoxaparin (primary brain cancer, 47; metastatic brain cancer, 84). In the primary brain cancer group, the incidence of major ICH was 0 of 20 patients in the DOAC group and 8 of 47 patients (18.2%) in the enoxaparin group. This is reported as statistically significant (Fisher's exact test, $P = .049$). In the metastatic group, the difference in the rates of major ICH were nonsignificant: 11.1% in the DOAC group and 17.8% in the enoxaparin group ($P = .38$). The study groups were reported as well matched in terms of sex, age, cancer diagnosis, and the time from cancer diagnosis to initiation of anticoagulation, but with higher rates of hypertension, aspirin use, and chronic kidney disease in the DOAC group. These results must be treated with caution. The large effect size in the primary brain cancer group in favor of DOAC vs enoxaparin is somewhat implausible with drugs that have a similar mechanism of action. This was a retrospective study, and the patients were not randomized to therapy. Therefore, there is a high risk

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Table 1. Retrospective studies including patients treated with DOACs included in the study by Giustozzi et al

First author, year	Quality*	Apixaban	Dabigatran	Edoxaban	Rivaroxaban	Total DOAC	LMWH	Warfarin
Carney et al, 2019[6]	Poor	20	5	0	16	41	131	–
Primary	–	15	0	0	5	20	47	–
Metastatic	–	5	5	0	11	21	84	–
De Melo Jr et al, 2020[10]	Poor	2	0	0	19	21	4	29
Leader et al, 2020[7]	Good	–	–	–	–	–	–	–
Metastatic	–	11	5	8	17	41	55	–
Lee et al, 2021[8]	Good	13	1	5	38	57	56	–
Dubinski et al, 2022[9]	Good	0	0	8	6	14	32	–
Total		46	11	21	96	174	278	29

*As assessed by Giustozzi et al.

of selection bias, with clinicians perhaps more likely to choose enoxaparin for patients who were deemed less fit and at higher risk of bleeding. Furthermore, the duration of anticoagulant exposure was much longer for patients treated with DOAC than that for those receiving enoxaparin (14 months vs 5 months). Can this longer exposure be explained by the conclusion that enoxaparin is more likely to cause bleeding and thus stopped sooner, or are there other explanations? Given that median survival in glioma is about 14 months,[11] we could speculate that if the time on treatment is related to survival, the DOAC group would survive far longer than the enoxaparin group. Were they fitter and more likely to live longer? Did they have less aggressive disease and not need early treatment? Were patients with more aggressive disease who needed more expeditious treatment, such as surgery, radiotherapy, or chemotherapy, more likely to be given enoxaparin? Temozolomide, a key DNA-alkylating agent used in the treatment of glioma, can cause severe thrombocytopenia, increasing the risk of bleeding[12]; were patients who were given this drug more likely to be given enoxaparin rather than a DOAC? Finally, were patients on enoxaparin treated earlier in time, before the advent of DOACs, and as such, did they receive different anticancer care? None of these questions can be satisfactorily answered, but the difference in the time on treatment is indicative that these 2 groups are not well matched. Dedicated randomized

Table 2. Dosing, advantages, and disadvantages of anticoagulants used for VTE in patients with brain cancer

Drug	Dosing	Advantages	Disadvantages
Apixaban	10 mg bid for 5 d, then 5 mg bid thereafter	Lowest overall bleeding risk in meta-analysis for all DOAC indications Low renal clearance (~25%)	Very limited prospective evidence No licensed dose reduction for VTE Limited evidence of clinical benefit and limited availability of andexanet alfa
Dabigatran	LMWH for 5 d, then 150 mg bid thereafter. 110 mg bid for patients ≥80 y and those on verapamil 110 mg bid can be considered for patients aged 75-80 y, CrCl 30-50 ml/min and those at increased risk of bleeding	Lowest risk of ICH in meta-analysis (110 mg bid) of AF and VTE trials Licensed dose reduction (110 mg bid) Widespread availability of idarucizumab	Not well tolerated (large tablet) 80% renal clearance No prospective evidence in cancer-associated VTE and very little retrospective evidence Dose reduction to 110 mg bid based on pharmacokinetic data (was trialed in AF but not in VTE) Need to first give LMWH for 5 d
Edoxaban	LMWH for 5 d then 60 mg OD thereafter Reduce to 30 mg OD, if CrCl 15-50 ml/min, weight ≤60 kg, or on interacting medications (ciclosporin, dronedarone, erythromycin, ketoconazole)	Most prospective evidence of efficacy and safety OD dosing Licensed dose reduction (30 mg daily) Lactose free	No specific, licensed reversal agent Need to give 5 d LMWH first
Rivaroxaban	15 mg bid for 21 d, then 20 mg thereafter If CrCl 15-49 ml/min, consider 15 mg OD after initial 21 d	OD dosing Extended higher dosing intensity period	Very limited prospective evidence Dose reduction to 15 mg OD not trialed Should be taken with 600 kcal of food Limited evidence of clinical benefit and limited availability of andexanet alfa
LMWH	Weight-adjusted dosing depending on formulation as OD or bid (split dosing) Reduce dose by 25% after 1 mo (dalteparin only)	Familiarity Similar outcomes to edoxaban in prospective trial Parenteral administration Few drug interactions	Retrospective data suggest not as safe as DOAC Parenteral administration Incomplete reversal with protamine
VKA	Dosed as per INR, with usual target of 2.5 Target of 3.5 if breakthrough thrombosis has occurred with VKA or other anticoagulants	Availability of clinically meaningful monitoring of therapeutic effect Suitable for patients with poor renal function NEW LINE Rapidly reversible with PCC	Need for regular blood tests Many drug interactions Increased intracranial bleeding compared with DOACs

AF, atrial fibrillation; bid, twice daily; CrCl, creatinine clearance; INR, international normalized ratio; OD, once daily; VKA, vitamin K antagonist; PCC, prothrombin complex concentrate

controlled trials are very much needed in this space and should compare various dosing regimens of DOACs and LMWH.

Despite our observations of the problems with interpreting the data, we believe that in many patients, a DOAC is an appropriate option, but which DOAC should be used? In Table 2, we have summarized some of the benefits and drawbacks of individual DOACs.

The best prospective evidence exists for edoxaban in which 74 patients with brain cancer were included in a randomized controlled trial with comparable outcomes between edoxaban and dalteparin. Apixaban appears to be the safest DOAC overall for atrial fibrillation,[13] but notably, patients with brain cancers were excluded from the Caravaggio trial.[2] Dabigatran is associated with the best risk reduction of ICH compared with warfarin (warfarin, 60%; apixaban, 57%; edoxaban, 56%; rivaroxaban, 41%).[14] However, importantly the pathological mechanisms of ICH in patients with brain cancer are different than those of spontaneous ICH.[15] A drawback to dabigatran is its heavy reliance on renal excretion (~80%[16]), making it unsuitable for more patients than other DOACs and LMWH. Licensed dose reductions according to renal function are available for dabigatran, edoxaban, and rivaroxaban (the apixaban 2.5 mg twice daily dosage is for atrial fibrillation only and long-term secondary prevention of VTE), but only the dose reduction of edoxaban is supported by prospective clinical data in VTE.[5,17] A final consideration is the availability of reversal agents, with specific licensed reversal agents available for dabigatran (idarucizumab), and apixaban and rivaroxaban (andexanet alfa). Andexanet alfa is not licensed for edoxaban reversal, but prothrombin complex concentrates are widely used. It should be noted that andexanet alfa is costly and is not always available (not funded in England for ICH[18]). LMWH can be partially reversed with protamine sulfate, but the dosing is challenging, and protamine can itself be an anticoagulant when given in a higher dose than required to neutralize LMWH. Furthermore, no reversal agent for a DOAC has ever been proven to produce a survival benefit, but the availability of these drugs may be of some comfort to clinicians and patients, and can influence decision making.

In summary, differences in the outcomes between the 4 DOACs and LMWH are likely to be small. Therapy should be selected based on the pharmacokinetic profile of the drug in the context of individual patient physiology, concurrent medication, and patient values. Finally, whether anticoagulation should be given at all is an important consideration. It is generally accepted that untreated VTE has a high risk of mortality, but in patients who are at the end of life, anticoagulation may be futile and not in their best interests. Hematologists offering advice to colleagues should encourage this consideration.

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