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Athina-Maria Aloizou

Vasileios Siokas

Alexios-Fotios A. Mentis

Metaxia Dastamani

Maria Sokratous

See next page for additional authors

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Recommended Citation

Aloizou AM, Siokas V, Mentis AFA, Dastamani M, Sokratous M, Xiromerisiou G, Mitsias PD, Hadjigeorgiou GM, and Dardiotis E. Advancements in the Treatment of Cerebrovascular Complications of Cancer. Curr Treat Options Neurol 2020; 22(6).

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Authors

Athina-Maria Aloizou, Vasileios Siokas, Alexios-Fotios A. Mentis, Metaxia Dastamani, Maria Sokratous, Georgia Xiromerisiou, Panayiotis Mitsias, Georgios M. Hadjigeorgiou, and Efthimios Dardiotis

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Curr Treat Options Neurol (2020) 22: 16
DOI 10.1007/s11940-020-00624-6

Cerebrovascular Disorders (Dara G. Jamieson, Section Editor)

Advancements in the Treatment of Cerebrovascular Complications of Cancer

Athina-Maria Aloizou, MD[1]
Vasileios Siokas, MD, PhD[1]
Alexios-Fotios A. Mentis, MD, MPH, PgCert[2,3]
Metaxia Dastamani, MD, MSc[1]
Maria Sokratous, MD, MSc[1]
Georgia Xiromerisiou, MD, PhD[1]
Panayiotis D. Mitsias, MD, PhD[4,5]
Georgios M. Hadjigeorgiou, MD, PhD[1,6]
Efthimios Dardiotis, MD, PhD[1,*]

Address
[*,1]Department of Neurology, Stroke Unit, University Hospital of Larissa, University of Thessaly, 41221, Larissa, Greece
Email: ebsdar@gmail.com
[2]Department of Microbiology, University Hospital of Larissa, University of Thessaly, Larissa, Greece
[3]Public Health Laboratories, Hellenic Pasteur Institute, Athens, Greece
[4]Department of Neurology, School of Medicine, University of Crete, 71003, Heraklion, Greece
[5]Department of Neurology & Comprehensive Stroke Center, Henry Ford Hospital, Detroit, MI, USA
[6]Department of Neurology, Medical School, University of Cyprus, Nicosia, Cyprus

Published online: 30 April 2020
© Springer Science+Business Media, LLC, part of Springer Nature 2020

Athina-Maria Aloizou and Vasileios Siokas contributed equally to this work.
This article is part of the Topical Collection on *Cerebrovascular Disorders*

Keywords Cancer · Cancer-associated thrombosis · Stroke · Thrombolysis · Anticoagulation treatment

Abstract

Purpose of review To present the new guidelines and therapeutic options regarding cerebrovascular complications of cancer, mainly ischemic stroke, cerebral venous thrombosis (CVT), and leptomeningeal carcinomatosis (LMC).

Recent findings A temporal trend study (2019) revealed that clinicians are still reluctant to apply thrombolysis to cancer patients, although two new studies (2018) reported no increased mortality. Several clinical trials on direct oral anticoagulants (DOACs) showed their superiority or, at least, non-inferiority compared with low molecular weight heparins in the treatment of venous thromboembolism (VTE) (2018–2019). These trials helped in formulating the new guidelines that are being published and the decisions made for cancer-associated thrombosis (CAT) as a whole. A new DOAC antidote was also officially released (US 2018, Europe 2019).
Summary Thrombolysis is safe in a malignancy setting, thus cancer per se should not be considered a contraindication for thrombolysis. Clinical trials assessing the newest DOACs for cancer-associated arterial thrombosis are scarce; however, based on data from VTE studies, the newest DOACs seem to be safe for CAT in patients that are not in high risk of bleeding or suffering from certain malignancies. The treatment should not be ceased after 6 months, but rather continued as long as the cancer remains active. Decompressive craniectomy should maintain its place in patients with CVST in risk of herniation. Last, the future also holds much promise on the role of novel compounds to be used in LMC.

Introduction

The umbrella term "cerebrovascular complications of cancer" encompasses a wide spectrum of clinical entities that arise from vascular dysfunction in the central nervous system (CNS), mainly the brain, and are the direct or indirect result of an underlying malignancy. Among those, stroke, either hemorrhagic or ischemic, is the commonest, with other entities, such as cerebral venous thrombosis (CVT) and leptomeningeal carcinomatosis (LMC), also affecting many cancer patients as well [1, 2].

The management of cancer patients has always been a challenging task for many clinicians, including neurologists and neuro-oncologists, either in terms of the cancer itself and its direct complications, or in terms of other comorbidities that require treatment. Clinical trials involving the treatment of cerebrovascular complications in cancer patients are scarce so that in the majority of cases healthcare professionals act empirically, based on their own experience and on knowledge extrapolated from handling other types of patients in slightly different clinical settings [3]. The challenge in handling these patients lies in the fact that cancer patients have higher complication and recurrence rates, especially in regard to thromboembolic events; higher risk of drug-drug interactions when on chemotherapy regimens; and reduced drug efficiency or clearance when the absorption routes have been affected, e.g., in chemotherapy-induced endothelial damage, or in hepatic or renal failure [4].

According to several studies, around 15% of cancer patients suffer from a concomitant cerebrovascular disease (CVD) [1, 5]; therefore, the number of patients in need of intervention is large, and the probability that clinicians will have face such patients at some point is also high.

In the present review, we aim to provide an overview of the most recent advances in the treatment of cancer-associated cerebrovascular complications, focusing primarily on those reported during the last few years and the clinical entities of cancer-associated thrombosis (CAT) and cancer-associated ischemic stroke (IS).

Advancements in the treatment of CVD in cancer patients

Thrombolysis for acute ischemic stroke

About 1 in 10 to 20 hospitalized IS patients have a concurrent malignancy [6•, 7]. Cancer has been consistently linked to venous thromboembolic (VTE)

events (contributing principally through hypercoagulability, based on Virchow's triad); nonetheless, cancer has also been recognized as a predisposing factor for arterial thromboembolism as well, with IS being one of its most serious manifestations [3]. The risk for cancer-associated thrombosis (CAT) varies according to cancer type. Cancers strongly associated with VTE and hypercoagulability state, such as lung and pancreatic cancer, are associated with the highest incidence rates for stroke as well [8]. Other factors related to cancer, such as chemotherapy, radiotherapy, tumor emboli, and infections, also add to the increased incidence of IS [1].

Studies involving patients with cancer seem to agree that thrombolysis is relatively safe for the treatment of acute IS in this setting. A small-scale retrospective study by Masrur et al. (2011) revealed that rates of mortality or intracranial hemorrhage (ICH) for patients with cancer who underwent thrombolysis [either intravenous (IV) with rtPA (recombinant tissue plasminogen activator), or intra-arterial therapy, or a combination of both] for IS were not higher than those of non-cancer patients [9]. After adjusting for confounders, Murthy et al. (2013) found no difference in the discharge and in-hospital mortality rates of cancer and non-cancer IS patients treated with IV thrombolysis or endovascular (EV) treatment. There was no difference in the symptomatic ICH rate either [5]. In another small retrospective observational case-control study, Geraldes et al. (2017) compared cancer and non-cancer IS patients, to whom rtPA was administrated and found no significant differences in the complication and hemorrhage (intracranial or systemic) rates between the two groups, agreeing with the results of the aforementioned reports [10]. Weeda and Bohm (2018) reported no difference regarding in-hospital mortality between the two IV thrombolysis cohorts (i.e., on patients with cancer and without cancer, respectively), but they found a slightly higher rate of intracerebral hemorrhage in patients with cancer (odds ratio 1.60, confidence interval 1.17–2.17) [11]. Additionally, Selvik et al. (2018) reported no adverse effects in their cancer-IS patient cohort [12]. Overall, the available data indicates that cancer should not be considered a contraindication for IV thrombolysis, even though cancer patients may carry more contraindications than non-cancer ones [1, 3]. Finally, the American Heart Association/American Stroke Association has not included cancer in the absolute contraindications for IV thrombolysis [13]; per the 2019 recommendations, for cancer patients with a reasonable life expectancy and no contraindications, IV rTPA may have benefits, but in those with GI malignancies or recent bleedings, IV rTPA is not recommended. The stated absolute and relative exclusion criteria for rtPA, however, include entities more frequently encountered in malignancy patients, such as recent intracranial surgery and thrombocytopenia (platelet count $< 100{,}000/mm^3$). In the presence of relative exclusion criteria (warnings), the careful weighing of risks and benefits is advised, and IV thrombolysis may be attempted after cautious consideration [14].

Despite the relative safety of IV thrombolysis in cancer-related stroke, lower rates of rtPA administration were reported in patients with cancer compared with non-cancer patients [12], revealing thus a trend in clinical practice, where healthcare professionals are more reluctant to proceed with this treatment in patients with cancer. Chatterjee et al. (2019) studied the rates of IV thrombolysis and endovascular (EV) treatment in cancer and non-cancer IS patients between 1998 and 2015. The rates of IV thrombolysis increased in both cohorts

during the above period, from 0.02% in non-cancer patients and 0.01% in cancer patients in 1998, to 7.22% and 4.91% respectively in 2015. Although both groups received IV thrombolysis very rarely in 1998, the treated percentage of the malignancy cohort in 2015 remained considerably smaller than that of non-cancer patients. In contrast, the rates of EV treatments were similar, but still quite low, in both cohorts (1.90% and 1.88%) [6•]. Taken together, these findings indicate that despite the overall increase in rtPA administration in the setting of an underlying malignancy, healthcare professionals are reluctant to use this disability-saving treatment, despite the existing evidence for its safety.

Intravenous rtPA has been established as one of the two main standard treatments of IS [15]. Endovascular thrombectomy (EVT) is the other one and is an effective alternative to the IV option [16]. In regard to its safety in the setting of an underlying malignancy, Murthy et al. (2013) showed that EVT had the same complication rates between cancer and non-cancer patients [5]. Merkler et al. (2014) also described two cases of lung cancer patients with left middle cerebral artery occlusions that were treated with EVT. Both patients had an exceptional neurological recovery following the intervention, and they experienced no complications. The authors recommended that this treatment option should be considered in patients with a good premorbid functional status and large vessel occlusions [16]. Furthermore, Navi et al. (2018) reported that, unlike the IV option, EV thrombolysis was performed at a similar rate in cancer and non-cancer cases [3]; this is a finding replicated in the study by Chatterjee et al. (2019) [6•]. In the latter, the overall percentages of cancer and non-cancer IS patients who received EV therapy tended to increase with the percentages being similar in both groups [6•].

Combining the above, it appears that when the endovascular option is considered, healthcare professionals are less reluctant to administer it in a patient with active malignancy. This absence of reluctance is important, as cancer patients tend to often have contraindications for rtPA, such as recent surgery and thrombocytopenia [14], and the endovascular approach has been shown to be a safe and effective treatment option for cancer patients, based on the aforementioned studies. Therefore, it is encouraging to see that clinicians go forward with EVT even in malignancy cases. All in all, although studies with larger groups are still needed, highlighting the safety of both procedures is of paramount importance, so that IS patients are given the appropriate treatment whether they have a concurrent malignancy or not. As in IS patients without cancer, rtPA is usually the first choice, if it can be administered within 4.5 h of symptom onset. EVT is considered in patients with large vessel occlusion, whether they have or have not received IV thrombolysis; EVT can be effective in a much more prolonged therapeutic window (up to 24 h from symptoms onset as long as there is significant volume of viable tissue and small infarct core). Per the European Stroke Organization, the combination of the two options is recommended for patients who have indications for both treatments [17]. Guidelines specifically addressing patients with cancer-related IS are not available; therefore, the recommendations in the literature are usually made by extrapolating data from guidelines in the general setting of IS, and reports on the safety of the proposed treatment options in malignancy settings.

Another difficult clinical problem is the treatment of cancer-associated stroke in patients harboring intracranial lesions. Most available studies consist only of case reports; there are no available randomized, controlled clinical trials

addressing this clinical setting. Etgen et al. (2014) summarized the cases reported until 2014 and reported their own case where a patient with IS and coexisting large frontal meningioma fully recovered after thrombolysis. The authors concluded that thrombolysis may be considered for IS patients with extra-axial tumors with benign features (e.g., meningioma) but is not advisable in the presence of an intra-axial primary or metastatic neoplasm due to the high risk for hemorrhage [18]. As Fugate and Rabinstein (2015) discussed, CNS structural lesions are considered a relative contraindication for rtPA, because the available reports mostly refer to "successfully" thrombolysed patients or patients with intracranial lesions that received IV rtPA for reasons other than IS, and who did not present an ICH [19]. Although publication bias cannot be excluded, these findings may imply that thrombolysis may be relatively safe in some patients with intracranial lesions. Finally, according to a population-based study of thrombolysed patients by Murthy et al. (2015), the in-hospital mortality, ICH, and home discharge rates were similar between patients with and without brain tumors [20]. Patients with malignant brain tumors, however, had comparatively higher rates of ICH and in-hospital mortality [20]. Intraparenchymal tumor location was also associated with higher in-hospital mortality and lower home discharge rates as well. The authors suggested that after careful consideration, thrombolysis may be a safe treatment for IS patients harboring intracranial tumors, especially benignones [20], similar to previous reports [15].

The mere presence of cancer does not constitute an absolute reason for patients to be excluded from thrombolytic treatment. However, the overall prognosis of cancer-related IS is rather unfavorable despite the offered interventions. Recurrence rates of IS in the malignancy setting are significantly higher [21], and mortality rates are also high. Cutting et al. (2017) reported that half of cancer-related IS patients, excluding brain malignancies, died within 3 months, despite acute phase treatments [22], highlighting thus the difficulty in managing the many comorbid conditions of these patients. Cancer, as a multifaceted disease, significantly worsens the condition and prognosis of IS patients and makes emergency administration of reperfusion therapies a critical element in their management so that quality of life is preserved at the best possible level.

Anticoagulation therapy for cancer-associated thrombosis

Cancer has been repeatedly proven to be a risk factor for thrombosis [1], especially concerning VTE, with pulmonary embolism (PE) and deep vein thrombosis (DVT) consisting the main and most serious complications in patients with cancer [23]. As mentioned previously, malignancy is now also recognized as a factor that predisposes to arterial thrombosis as well [3]; therefore, in terms of cerebral complications, cancer can lead to stroke and cerebral venous occlusion. Anticoagulation agents have been a cornerstone in treating and preventing these two maladies; however, the data on patients with cancer are scarce while most of the decisions for anticoagulation treatment for cancer-associated arterial thrombosis are based on studies performed in the setting of VTE [3]. Regarding the cost effectiveness of these drug classes, the data on cancer patients is also scarce. Recent studies suggest that DOACs are the most cost-effective option. Li et al. (2019) compared dalteparin to edoxaban and rivaroxaban in a CAT setting and reported that the DOACs are more cost

effective than the LMWH [24], while Sarigiannidis et al. (2019) analyzed the anticoagulant classes for cancer patients in the Greek health system and reported that DOACs are more cost effective for low-risk patients, and LMWH remain the best option for high-risk patients [25]. It is evident that more studies on the matter, with large patient cohorts, are needed in order to reach an accurate conclusion; nonetheless, the available literature on DOACs for cancer patients seems to be encouraging.

Trials and studies on drug safety and efficacy

The three main groups of anticoagulants, vitamin K antagonists (VKA), low molecular weight heparins (LMWH) and the direct oral anticoagulants (DOACs), have been compared in terms of safety and efficacy in several studies [26]. The evidence indicating that low molecular weight heparins are more effective than vitamin K antagonists is now well-established, given that data from clinical trials, such as the CLOT and CATCH studies, proving the superiority of LWMH in this context have been available for more than a decade [27, 28]. Additionally, LMWH carry some inherent benefits, such as their adequate absorption despite gastrointestinal (GI) disturbances, which are frequent in cancer patients, and the smaller rates of drug-drug interactions [23]. That being said, an extended discussion on the aforementioned studies exceeds the aim of this review.

Over the last years, one of the main questions that have emerged is whether DOACs are better or, at least, as safe and efficient as LMWH in patients with cancer. The DOACs approved until now in the US include direct inhibitors of factor Xa (rivaroxaban, apixaban, and edoxaban), and a direct thrombin inhibitor (dabigatran) [29]. These are oral agents, in contrast to LMWH which are injectable, cause pain or discomfort to most patients, and can also lead to several dermatological complications [30]. Additionally, DOACs are not associated with risk for heparin-induced thrombocytopenia, which is a severe and potential lethal side effect of LMWH. When compared with VKA, DOACs also have significant advantages, including the following: no need to regularly monitor therapeutic levels, the much fewer dietary restrictions, and fewer drug-drug interactions, something of importance in patients under multidrug regimens [29].

DOACs have now replaced VKA as the standard of care for the treatment of VTE in non-cancer patients, based on the results of numerous studies which included a small subset of individuals with malignancies as well. Van es et al. (2014) meta-analyzed the subset of patients with cancer from six relevant phase III clinical trials, and reported significantly lower rates of VTE events for DOACs, with similar risks of bleeding complications for the two drug groups [31]. Posch et al. (2015) also conducted their own meta-analysis on the six clinical trials, and they found a trend towards DOACs' superiority, which however did not reach the statistical significance threshold [32]. Therefore, the question in need for an answer is whether DOACs can replace LMWH.

In terms of safety and efficacy, several recent clinical trials compared LMWH and DOACs in patients with cancer, and most have been elegantly reviewed in several publications. Below, we will give a brief description of these clinical trials, outline the most recently published results, and mention the ongoing trials the results of which are anticipated in the near future. A summary of the

included studies can be found in Table 1, while the ongoing included studies can be found in Table 2.

The randomized open-label CANVAS study (NCT02744092), the results of which are unpublished as of yet, aims to compare a DOAC (the specific DOAC was left up to the discretion of each investigator on a case by case basis) and LMWH with or without transition to VKA in patients with cancer and VTE. This study is different from the rest that have been published so far, whose design has included a specific DOAC, and its results are expected with much interest.

The HOKUSAI-VTE, a randomized, open-label, non-inferiority trial involved a large number of patients and compared edoxaban to dalteparin after 5 days of LMWH treatment for acute VTE events. The investigators showed that both regimens were equally effective in preventing VTE occurrences and that the overall survival was similar in both cohorts, albeit with a higher ratio of bleeding complications in the edoxaban group, especially heightened in GI malignancies [33•].

Rivaroxaban was compared with dalteparin in the prospective, randomized, open-label SELECT-D trial, in which rivaroxaban was shown to be more

Table 1. Studies examining the safety and efficiency of DOACs compared with LMWH

Author, year	Trial name	Substance comparison	Results
Raskob et al., 2018	HOKUSAI-VTE	Edoxaban vs. dalteparin	• Similar efficiency in VTE prevention • Similar overall survival • Higher hemorrhagic complications ratio for edoxaban, especially in GI malignancies
Young et al., 2018	SELECT-D	Rivaroxaban vs. dalteparin	• Lower VTE recurrence rates with rivaroxaban • Similar survival and major bleeding rates • Higher non-major bleeding rates for rivaroxaban, especially in GI malignancies
Prins et al., 2014	EINSTEIN	Rivaroxaban vs. enoxaparin	• Similar efficiency in VTE recurrence prevention • Similar bleeding rates
Mantha et al., 2017	–	Rivaroxaban, compared results to EINSTEIN studies	• Similar recurrence and bleeding rates
Khorana et al., 2019	CASSINI/CALLISTO	Rivaroxaban in VTE prophylaxis	• No significant effect in VTE prevention in 3 months • Significant effect in the whole-intervention period
McBane et al., 2019	ADAM-VTE	Apixaban vs. dalteparin	• Lower VTE recurrence rates with apixaban • Similar survival and bleeding rates
Carrier et al., 2019	AVERT	Apixaban vs. placebo in patients with medium/high VTE risk and about to have chemotherapy	• Lower VTE rates and higher bleeding rates with apixaban

Table 2. Ongoing trials of DOACs' administration in cancer patients

Trial number	Study name	Subject
NCT02744092	CANVAS	DOACs vs. LMWH ± warfarin in VTE
NCT02742623	COSIMO	Transition to rivaroxaban from LMWH/VKA in CAT
NCT02583191	CONKO-011	Safety and efficacy of rivaroxaban in VTE
NCT02746185	CASTA-DIVA	Safety and efficacy of rivaroxaban in CAT
NCT03139487	PRIORITY	Rivaroxaban vs. dalteparin in VTE for upper GI, hepatobiliary, or pancreatic cancer patients
NCT03045406	CARAVAGGIO	Apixaban vs. dalteparin in CAT
NCT02585713	–	Apixaban vs. dalteparin in VTE
NCT02581176	CAP	Safety and efficacy of apixaban in VTE

efficient in lowering VTE recurrence, with the rates of survival and major bleeding not significantly different between the groups, but with the rates of clinically relevant non-major bleeding being higher in the rivaroxaban group. As expected, and similar to the HOKUSAI-VTE trial, bleeding complications were also more frequent in patients with GI cancers, who were excluded from the study in its latter phases, following a protocol revision [34•]. In their own study, Mantha et al. (2017) also described the potency and safety of rivaroxaban, with recurrence and bleeding rates similar to the percentages reported in the EINSTEIN studies [35]. These two earlier EINSTEIN studies on PE and DVT compared rivaroxaban to enoxaparin followed by VKA administration, and their findings showed similar efficacy regarding VTE recurrence, with clinically relevant bleeding rates also comparable between the two groups [36]. However, the recently published CASSINI/CALLISTO trial assessed the efficacy and safety of rivaroxaban in high-VTE-risk ambulatory cancer patients without history of a VTE occurrence. It reported no significant effect in the prevention of VTE in the 3-month-surveillance window of the study, but found a significant difference when examining the whole intervention (first administration to 2 days after the last dose) period [37].

More studies on rivaroxaban are currently being conducted, including (a) the prospective COSIMO trial that will follow patients that switched from LMWH or VKA to rivaroxaban for the treatment or prevention of CAT (NCT02742623) [38]; (b) the CONKO-011 (NCT02583191) and the CASTA-DIVA (NCT02746185) trials, which will assess the overall safety and efficacy of rivaroxaban in German VTE and French CAT patients respectively; and (c) the PRIORITY randomized, open-label, phase II trial (NCT03139487), comparing rivaroxaban to dalteparin in patients with acute VTE events and upper GI, hepatobiliary, or pancreatic cancer. The completion and results of the latter study are eagerly anticipated because of the potential clinical interest, given that other studies, such as the SELECT-D on rivaroxaban and HOKUSAI on edoxaban reported higher bleeding rates in patients with GI malignancies, and higher rates of bleeds involving the GI tract as well. Therefore, the safety of DOACs in these patients needs to be further investigated.

Apixaban was compared with dalteparin in the ADAM-VTE trial on VTE patients with underlying cancer. Apixaban significantly lowered VTE recurrence in comparison to the LMWH, while bleeding and survival rates between the two study arms were described as similar [39•]. Carrier et al. (2019) published the results of the AVERT study on medium-to-high-risk VTE ambulatory cancer patients who were to start chemotherapy, confirming that apixaban was successful in significantly reducing VTE rates, combined, nonetheless, with an elevated risk of bleeding when compared with placebo [40]. The ongoing, randomized, open-label, non-inferiority phase III CARAVAGGIO trial (NCT03045406) will compare apixaban to dalteparin in a larger number of CAT patients, further aiming to confirm its efficacy and safety [41], similarly to another ongoing trial (NCT02585713). Finally, the single-arm, phase IV CAP trial on apixaban's efficacy is currently under way (NCT02581176).

Guidelines and treatment of cancer-associated thrombosis

Recent studies reached the conclusion that DOACs are slightly more or at least as effective as LMWH in treating recurrent VTE, but are associated with higher bleeding risk (whether major or minor bleeding) [26, 29, 42]; these findings were replicated in a meta-analysis [43]. Because the above studies have only been recently completed and reported, their results are just starting to be included in the proposed guidelines for the treatment of CAT. Until now, these guidelines recommended LWMH as the first-line treatment for VTE and CAT [44], because of the proven efficacy and relative safety in clinical trials such as the DALTECAN [45]. In particular, the 2016 CHEST guidelines for VTE and cancer recommend the use of LMWH over VKA, followed by dabigatran, rivaroxaban, and apixaban as second-line alternative options [46]. Several other guidelines have also endorsed LMWH treatment for recurrent VTE, including the Anticoagulation Forum and the 2016 ISTH (International Society on Thrombosis and Hemostasis) Guidance Statement [47, 48]. LMWHs are also considered safe in thrombocytopenic patients, with a platelet count safety threshold of 50 × 109/L, and the recommendation is to administer platelet transfusions to maintain this level when anticoagulation therapy is needed; when transfusions are not possible in a patient with moderate thrombocytopenia, lower doses of LMWH are recommended instead [23, 49].

In light of the emerging shift towards DOACs, the National Comprehensive Cancer Network (NCCN) guidelines, last updated in February 2019, recommend (a) LMWH or unfractionated heparin for VTE prophylaxis, (b) LMWH for acute treatment, and (c) apixaban for patients having contraindications for LMWH (nccn.org, last accessed on December 10, 2019). A consensus of Italian experts supported DOACs as a valid alternative to LMWH; the latter however should be preferred in patients with GI malignancies [50]. This consensus is in accordance with the updated Canadian expert guidelines, which propose a risk stratification-based administration of DOACs in patients who are not at high risk for bleeding, or are not receiving medication(s) with severe drug interactions with DOACs, or present with GI cancers; all these categories should receive LMWH instead [51•]. Additionally, as of 2018, the ISTH endorses edoxaban and rivaroxaban in the setting of CAT as well [52]. Collectively, LMWH seem to be preferred in patients with GI cancers or mucosal disturbances such as ulcers, and those with high risk for bleeding [49].However, some groups are still

reserving the use of VKA for patients that remain stable under this form of treatment, or when DOACs and LMWH are either contraindicated or unavailable [40].

Another major issue is the duration of anticoagulation therapy. The Canadian consensus recommends re-evaluation every 3 months, taking into account factors such as cancer activity and treatments with thrombogenic potential [40], such as certain chemotherapy agents [1]. The DALTECAN study assessed dalteparin beyond the 6-month period, and found similar recurrence rates in the following 6 months, without an elevated bleeding risk [45]. The CancerDACUS study supports the continuation of anticoagulation therapy for as long as the malignancy is considered active, based on the high recurrence rates reported in patients that discontinued the treatment [53]; this is a practice endorsed by other scientific groups as well [44, 54, 55]. However, data from trials on the prevention of VTE events following the initial 6-month period of treatment are limited, while designing studies after that timeframe is rather difficult, since patients and doctors alike seem to have very particular desires regarding the continuation or not of their treatment, based on patients' fears and clinicians' experience.

Of note, the selection of appropriate treatment selection should be made for each patient individually, considering the specific health condition of every patient. LMWHs are mainly renally excreted and are relatively contraindicated in patients with a creatinine clearance of < 30 mL/min [56], like dabigatran, which is mostly renal-excreted too and therefore renal function, which may necessitate dose adjustment, should be considered when administering dabigatran [57]. Moreover, the hepatic metabolism of DOACs needs to be taken into account. Although DOACs present fewer drug interactions than VKA and do not seem to affect the activity of metabolic enzymes, they may interfere with chemotherapy agents. DOACs can interact with potent P-glycoprotein inhibitors, as P-gp substrates (for dabigatran this refers only to its prodrug), while CYP3A4/5 and CYP2J2 inhibitors can also increase the concentrations of both rivaroxaban and apixaban. Additional potential interactions with substances like rifampicin and macrolides should also be considered, according to the pharmaceutical instructions [4].

Concerning DOACs antidotes, which are crucial in the case of major bleedings, some agents have become available. Andexanet-alfa can quickly and efficiently reduce the activity of anti-Xa agents as a recombinant FXa protein [58], and it recently received its first global approval in the USA [59] and a conditional marketing authorization in Europe [60]. Furthermore, idarucizumab has been shown to promptly reverse the effect of dabigatran specifically [61], and PER977 has been shown to enhance hemostasis in patients taking edoxaban [62].

Cerebral venous thrombosis treatment

In a recent case-control study, cerebral venous thrombosis (CVT) was shown to be 5 times more frequent in cancer patients, especially in those with hematological malignancies [63]. CVT is a frequent complication of local procedures and tumor-associated factors, but it can also appear in geographically remote areas in patients with intracerebral tumors [64].

CVT frequently manifests as stroke and is treated with anticoagulation therapy [65]; the European Stroke Organization guidelines (published in 2017, albeit not specifically for cancer patients) recommend LMWH to be used in the acute phase, while decompressive craniectomy is to be applied in the case of herniation [66]. Avanali et al. (2019) strongly recommend considering decompressive craniectomy as an early, life-saving measure during the first symptoms of herniation, because 4% of CVT patients develop hemorrhagic lesions and cerebral edema large enough to lead to this complication [67].

CVT occurs more frequently in patients with malignancies compared with the general population, but there is a significant paucity of data on therapeutic strategies. Given that anticoagulation therapy is the standard treatment of CVT, therapeutic decisions could be extrapolated from the data available from CVT and VTE trials.

Leptomeningeal carcinomatosis treatment

Leptomeningeal carcinomatosis (LMC) is an uncommon complication of cancer, mostly associated with lung cancer, breast cancer, melanoma [68], and late stages of the disease [69]. Due to the heterogeneity and relatively small numbers of patients, treatment guidelines and response criteria have been difficult to establish [70, 71].

The treatment of LMC is multifaceted and comprises of various options, including radiation therapy, surgery, systemic or intrathecal chemotherapy, and immunotherapy. Systemic chemotherapy usually has limited effect and is dependent on the drug's ability to cross the blood-brain barrier. However, because of the meningeal infiltration and the resulting tissue damage, some compounds can reach satisfactory cerebrospinal fluid levels when administered systematically [72, 73], thus aiding in increasing survival odds [74]. Additionally, targeted therapies for specific cancer types have shown promising results in ameliorating LMC [71]. Brastianos et al. (2018) recently presented encouraging results with pembrolizumab in LMC from solid tumors [75]. More of these specialized compounds are currently being tested in clinical trials, such as for the treatment of melanoma (NCT02939300). Intrathecal chemotherapy is another important aspect of non-nodular LMC treatment, although its efficacy over systemic treatment alone has not been proven [69, 76]. Traditionally used compounds for intrathecal treatment are methotrexate, cytarabine, and thiotepa [77–79]. The results of the DEPOSEIN clinical trial on intrathecal liposomal cytarabine on breast-cancer LMC are being expected as well (NCT01645839). Radiation therapy is usually symptom-directed, and it targets large volume lesions. Occasionally, whole-brain radiation may be administered [80]. Finally, regarding immunotherapy, several clinical trials are being currently conducted, including those on the intraventricular administration of I-131-labeled monoclonal antibody 3F8 (NCT00445965), and of I-131-labeled monoclonal antibody 8H9 [81].

Conclusions

The scientific community seems to be reaching a consensus regarding many previously unanswered questions that have arisen in recent years. However, the management of patients with cancer and cerebrovascular complications is a

complicated issue, and we expect that only large-scale clinical trials and new studies be conducted in order to enrich our existing knowledge and allow us to update the therapeutic protocols.

Regarding ischemic stroke, reperfusion therapies, both IV thrombolysis and endovascular thrombectomy, have been shown to be safe in malignancy settings, and cancer per se should not be considered a contraindication in proceeding with them. Trials on anticoagulants, notably the new DOACs, are still missing, especially concerning arterial thrombosis; however, by harnessing available data from existing VTE studies, it appears that DOACs are considered safe to be used in patients with cancer who are not in high risk for bleeding or are not suffering from GI malignancies. Treatment should not be stopped after 6 months, but rather continued for as long as the cancer is considered active. Finally, decompressive craniectomy should maintain its place in patients with CVT at risk of herniation. Last, the future also holds much promise on the role of novel compounds to be used in LMC.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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