Cancer-Associated Thrombosis

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Venous thromboembolism (VTE) is a common complication among patients suffering from malignancies, leading to increased mortality. Novel randomized trials have added valuable information regarding cancer-associated thrombosis (CAT) management using direct oral anticoagulants (DOACs).

Keywords: cancer-associated thrombosis ; venous thromboembolism ; direct oral anticoagulants ; recommendations

1. Introduction

Venous thromboembolism (VTE) is a common complication among patients suffering from malignancies, while the risk of VTE varies during the progression of the disease [1]. Different mechanisms and risk factors have been related to cancer-associated thrombosis (CAT) and could be differentiated into patient, tumor, and treatment related [2][3]. Regarding patients suffering from CAT, the risk of fatal pulmonary embolism as well as bleeding is expected to be significantly higher compared to that among the general population [4]. Thus, CAT patients represent a special group, concurrently presenting a high risk for life-threatening thrombotic and bleeding events. Chemotherapy may be an additional significant VTE-associated mortality risk factor [5]. The estimated incidence of VTE in patients under chemotherapy is 9%, while the associated VTE mortality presents a 47-fold increase compared to that among the overall population [5].

In 2016, the revised American Community of Chest Physicians (ACCP) guidelines recommended the use of low molecular weight heparin (LMWH) over vitamin K antagonists (VKA) or direct oral anticoagulants (DOACs) in patients suffering from CAT [6]. In recent years, novel studies and randomized controlled trials (RCTs) have added further information regarding CAT management, and newer data have been included in the more recent recommendations.

2. Current Recommendations on CAT Management

As the experience in DOACs' application expands, their use increases in the daily clinical practice and includes different patient populations. In 2018, the International Society of Thrombosis and Hemostasis (ISTH) guidance recommended the use of DOACs, including only edoxaban and rivaroxaban, inflow bleeding risk CAT patients without pharmaceutical contraindications [7]. Patients suffering from gastrointestinal cancer, with or without mucosal abnormalities, were excluded due to the associated higher bleeding risk [7]. Specifically, the ISTH guidelines separated the CAT population into two groups, according to the primary malignancy-related bleeding risk. Patients with low bleeding risk were driven to be treated with rivaroxaban or edoxaban, while in the remaining population, LMWHs were preferred [7].

A year later, the American Society of Clinical Oncology (ASCO) guidelines recommended that CAT patients could be managed with LMWH, unfractionated heparin (UFH), fondaparinux, or rivaroxaban in the acute phase [8]. Except the UFH, the remaining pharmaceutical factors were also proposed for long-term management, while the recommendation was similar for patients needing extended anticoagulation [8]. In 2019, the European Society of Cardiology recommendations suggested the use of edoxaban as an alternative to LMWH in gastrointestinal cancer patients, while rivaroxaban should be considered in patients without gastrointestinal malignancies [9][10]. An analogous strategy was also suggested by the International Initiative on Thrombosis and Cancer (ITAC) guidelines regarding acute, long-term, and extended anticoagulation in CAT [11].

The latest recommendations in CAT were published in 2021 by the American Society of Hematology (ASH) and European Society for Vascular Surgery (ESVS) [12][13]. In the ASH recommendations, the use of DOACs is recommended as thromboprophylaxis in ambulatory patients with cancer and high thrombotic risk due to systemic therapy [12]. The recommendation includes only rivaroxaban and apixaban and relies on a moderate level of evidence, while the application of DOACs is not proposed in low or moderate VTE risk ambulatory patients [12]. DOACs (including apixaban, edoxaban, and rivaroxaban) are suggested as an alternative to LMWH during the initial 7-day phase, as standard treatment for three to six months, and an option for long-term treatment of more than six months [12].

The ESVS, using a meta-analytic approach of the currently available RCTs, suggested LMWHs as the standard of treatment in CAT, while a switch to DOACs is recommended only for the extended phase in high thrombotic risk patients [13]. As previously mentioned, the group of gastrointestinal and genitourinary malignancy patients are considered of high hemorrhagic risk [13]. In the remaining CAT cases and with a careful patient selection, an approved DOAC may be used as an initial, long-term, and extended treatment option [13].

Despite the differences recorded between the strategies suggested by the societies, it should be acknowledged that DOACs seem to find their role as thromboprophylaxis and VTE treatment in CAT patients (**Table 1**). However, the comparison of the currently available recommendations is hampered by the different approach used by the societies for the conduct of recommendations and systems applied to report the level of evidence (**Table 1**). It is of note that through these recent years, the level of evidence tends to rise, as more data are available.

Table 1. Current recommendations suggest direct oral anticoagulants (DOACs) as a safe and effective alternative in patients with CAT. While LMWHs are preferred in the initial phase, DOACs' application is expanded in the principal and extended treatment phase in high thrombotic risk patients with an associated low bleeding risk.

Societies' recommendations	International Society of Thrombosis and Hemostasis (ISTH) 2018	In Itiative on Thrombosis and Cancer (ITAC/CME) 2019	European Society of Cardiology (ESC) 2019	American Society of Clinical Oncology (ASCO) 2020	American Society of Hematology (ASH) 2021	European Society for Vascular Surgery (ESVS) 2021
Anticoagulant choice	Use of specific DOACS (edoxaban, rivaroxaban) and LMWHs are the preferred pharmaceutical choices (Weak guidance) LMWHs are preferred in patients with high bleeding or DDI risk (weak guidance)	Initial phase (5–10 days): LMWH, rivaroxaban, or edoxaban following ≥5 days of parenteral anticoagulation (Grade 1B) Long-term (<6 months): LMWH or DOACs (edoxaban, rivaroxaban) (Grade1A) Extended therapy (>6 months): LMWH or DOACs (Grade 1A0	In patients with PE and cancer, LMWH should be considered for the first 6 months over VKAs. (Class IIa Level A) Rivaroxaban and edoxaban should be considered as alternatives to LMWHs in patients without gastrointestinal cancer (Class IIa Level C and Class IIa Level B, respectively)	Initial phase (5–10 days): LMWH, fondaparinux or rivaroxaban preferred (evidence quality: high; strength of recommendation: strong) Long-term (<6 months): LMWH, edoxaban or rivaroxaban (VKAs are acceptable alternatives for long-term therapy if LMWH/DOACs not available) (Evidence quality: High; Strength of recommendation: strong) Extended therapy (≥6 months): LMWH, edoxaban or rivaroxaban or VKAs (evidence quality: low; strength of recommendation: weak to moderate)	DOACs (rivaroxaban, apixaban) as prophylaxis in ambulatory high thrombotic risk cancer patients under systemic therapy (moderate evidence) Initial phase (<7 days): LMWHs or DOACs (apixaban, edoxaban, rivaroxaban) as alternative (very low evidence) Long-term (3–6 months): DOACS over LMWH (Low evidence) Extended therapy (>6 months): DOACS or LMWHs (very low evidence)	LMWHs as standard of treatment in initial and principal phase (Class I Level A) Extended therapy (>6 months): DOACs (Class I Level C) DOACs as an alternative in patients without GI or genitourinary cancer for initial, principal, and extended treatment (Class IIa Level A)
Societies' recommendations	**ISTH 2018**	**ITAC/CME 2019**	**ESC 2019**	**ASCO 2020**	**ASH 2021**	**ESVS 2021**
Duration of therapy	NR	LMWHs or DOACs should be used for a least 6 months, while extension should rely on individualized evaluation (Grade 1A)	Extended anticoagulation (>6 months) should be considered for an indefinite period or until cancer is cured (Class IIa Level B)	Extended therapy may be considered in active cancer (evidence quality: low; strength of recommendation: weak to moderate)	Extended anticoagulation (>6 months) should be considered for an indefinite period in active cancer (low evidence)	Extended anticoagulation (>6 months) should be considered for an indefinite period in active cancer (in text)
Societies' recommendations	**ISTH 2018**	**ITAC/CME 2019**	**ESC 2019**	**ASCO 2020**	**ASH 2021**	**ESVS 2021**

Aim & weighting the evidence	**To outline expert experience and the biological rational that may affect clinical decision** **The guidance statements are in accordance with the following premises:** **1. Average patient with cancer and VTE** **2. “we recommend” reflects a strong guidance with strong consensus among the panel** **3. ”We suggest” reflects a weak guidance with moderate consensus among the panel**	**To establish a global consensus for the treatment and prophylaxis of VTE in patients with cancer** **The GRADE approach was used by an expert panel to conduct a systematic review of the current literature. The level of evidence was characterized as high (A), moderate (B), low (C), and very low (D), while the level of recommendation was strong (grade 1), weak (grade 2), and characterized as best clinical practice (guidance)**	**To suggest optimal objectively validated management strategies for patients with suspected or confirmed PE.** **Conclusions based on the available scientific evidence, using the European Society of Cardiology grading system (A, B, or C indicates the level of current evidence).** **Depending on the strength of recommendation, each one is categorized as Class I, IIa/IIb, and III.**	**To provide updated recommendations about prophylaxis and treatment of VTE in patients with cancer** **A systematic review of RCTs reporting on VTE prophylaxis and treatment using PubMed and CENTRAL databases, executed by an expert commit using the “signals” approach**	**To support patients, clinicians, and others in decisions about treatment of VTE** **The Grading of Recommendations Assessments, Development and Evaluation (GRADE) approach was used by an expert panel**	**To assist clinicians in selecting the best management strategies to achieve optimal patient outcomes** **Revision and summary of the relevant peer reviewed published literature.** **Conclusions based on the available scientific evidence, using the European Society of Cardiology grading system (A, B, or C indicates the level of current evidence).** **Depending on the strength of recommendation, each one is categorized as Class I, IIa/IIb, and III.**

Footnotes: CAT: cancer-associated thrombosis; DOACs: direct oral anticoagulants.

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