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Pharmacokinetic variability of anticoagulants in patients with cancer-associated thrombosis: Clinical consequences

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ABSTRACT

The use of anticoagulants in patients with cancer is challenging as several co-morbidities modifying pharmacokinetic (PK) parameters and significant drug-drug interactions with concomitant anti-neoplastic therapies may lead to PK variability resulting in increased risk of thrombosis or bleeding.

Data on the management of patients with cancer-associated thrombosis (CAT) in real life are scarce since patients with cancer presenting with significant comorbidities tend to be excluded from large trials.

This review is mostly based on case-reports and pharmacokinetics in an attempt to provide oncologists, with relevant orientation based on our best knowledge to date.

Overall, low-molecular-weight heparins (LMWH) are the preferred option for the long-term prophylaxis and treatment of CAT as their benefit-risk was shown superior to vitamin K antagonists (VKA). Direct oral anticoagulants (DOAC) may represent an alternative to LMWH provided that a favorable benefit-risk in patients with CAT is evidenced in the future. We recommend a systematic risk-assessment including body composition, multiple medication, and renal function. Moreover a systematic and early discussion between pharmacist and oncologist should optimize the benefit-risk ratio for each patient.

1. Thromboembolism in patients with cancer

1.1. Cancer-associated thrombosis (CAT): an underestimated health problem

Cancer is an independent risk factor for Venous Thromboembolism (VTE). Patients with cancer present up to a 7-fold higher risk to develop VTE as compared to non-cancer patients (Noble and Pasi, 2010) while anticoagulation therapy for cancer-associated thrombosis (CAT) is an independent risk factor for VTE recurrence and bleeding (Lee and Levine, 2003; Lee and Peterson, 2013; Timp et al., 2013). The use of central venous catheters (CVC), conventional cancer treatments such as surgery, radiotherapy, chemotherapy as well as targeted therapies such as anti-angiogenic agents, and even supportive care such as epoetins or blood transfusions further increase the risk of VTE recurrence in cancer patients (Nalluri et al., 2008; Chee et al., 2014; Kyrle, 2014; Douros et al., 2016).

The prevalence of CAT is underestimated (Cohen et al., 2008) while both thromboprophylaxis and CAT patient management remain insufficient (Brown, 2012; Khalil et al., 2015).

In addition to anticoagulant treatment, cancer patients receiving both multiple antineoplastic drugs and co-medications related to their numerous comorbidities are likely to experience pharmacokinetic drug-drug interactions that may alter the expected benefit of the overall therapy. The optimization of CAT management is therefore of major importance to ensure an efficient treatment to prevent VTE recurrence without increased bleeding risk.

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Table 1
International treatment guidelines for the long-term treatment and prevention of cancer-associated venous thromboembolism.

	Treatment		Thromboprophylaxis	
	Preferred anticoagulant	Recommendations	Preferred anticoagulant	Recommendations
ESMO (Mandala et al., 2011)	LMWH	At least 6 months	LMWH	Outpatients at high risk of thrombosis (pancreatic and lung cancer) receiving chemotherapy, hospitalized patients and patients undergoing major surgery
NCCN	LMWH	Indefinite duration while cancer is active, or at least 3 months	LMWH	*All inpatients with active cancer and patients undergoing surgery* On an individual basis for outpatients at high risk of VTE based on Khorana risk assessment score ≥ 3
ASCO (Lyman et al., 2015)	LMWH	At least 6 months	LMWH	*Recommended for hospitalized patients with acute medical illness or undergoing surgery. Not recommended for hospitalization for minor procedures or outpatients (except highly select high risk patients)*
ACCP (Kearon et al., 2012)	LMWH	3 to 6 months then VKA or LMWH indefinitely or until cancer resolution	LMWH	Prophylactic doses of LMWH in all outpatients with active cancer at risk of thrombosis receiving chemotherapy
ITAC-CME (Farge et al., 2016)	LMWH	3 to 6 months and beyond 6 months according to benefit-risk	LMWH	For patients undergoing surgery or hospitalized. Primary prophylaxis is not recommended routinely but has to be considered for outpatients with advanced pancreatic and lung cancer

ACCP, American College of Chest Physicians; ASCO, American Society of Clinical Oncology; DVT, deep-vein thrombosis; ITAC-CME, International Initiative on Thrombosis and Cancer; LMWH, low-molecular-weight heparin; NCCN, US national Comprehensive Cancer Network; PE, pulmonary embolism; VKA, vitamin K antagonist.

1.2. Clinical practice guidelines for the long-term treatment and prevention of CAT

According to the different international clinical guidelines, low-molecular-weight heparins (LMWH) are currently the preferred option for the treatment of CAT (Table 1) (Farge et al., 2016; Kearon et al., 2012; Khorana, 2007; Lyman et al., 2015) as they were shown superior to vitamin K antagonists (VKA) in preventing VTE recurrence (Posch et al., 2015). Despite the evidence (Akl et al., 2008; Laporte et al., 2012), there are substantial reports from observational studies of insufficient compliance with established treatment guidelines (Delate et al., 2012; Kahn et al., 2012; Sevestre et al., 2014; Spirk et al., 2011; Trujillo-Santos et al., 2010; Khorana et al., 2016) even though recent studies have shown that long-term LMWH were well accepted by patients with CAT (Cajfinger et al., 2016) and that physicians tended to underestimate patients' ability to accept long-term LMWH (Cimminiello and Anderson, 2012). There is no robust evidence of the efficacy of direct oral anticoagulants (DOAC) for the long-term treatment of CAT. DOAC were found non-inferior to VKA in a meta-analysis of data from limited-size sub-groups of patients with cancer in large trials (RR for recurrent VTE = 0.65 [95% CI: 0.38; 1.09] p = 0.10) (Posch et al., 2015). Randomized-control studies comparing directly DOAC and LMWH are ongoing while in the meantime guidelines recommend LMWH over DOACs for treatment of cancer-associated thrombosis in patients with no contraindications for use of anticoagulants (Lyman et al., 2015).

The usefulness of thromboprophylaxis is generally recognized by current practice guidelines for patients with cancer undergoing surgery or hospitalization for acute medical illness. However the benefit of long-term VTE prophylaxis in outpatients receiving antineoplastic treatment remains controversial (Frere and Farge, 2016). Updated American Society of Clinical Oncology (ASCO) Practice Guideline do not recommend routine thromboprophylaxis for cancer patients in the outpatient setting although it may be considered for selected high-risk patients (Lyman et al., 2015). Both the European Society of Medical Oncology (ESMO) and ASCO recommend low-molecular-weight heparins (LMWH) use in patients receiving chemotherapy for a solid tumor at high risk of thrombosis (Lyman et al., 2015; Mandala et al., 2011) while the National Comprehensive Cancer Network (NCCN) states that VTE prophylaxis is recommended for patients receiving chemotherapy with a Khorana VTE-risk score ≥3 (Khorana, 2013). The International Initiative on Thrombosis and Cancer (ITAC-CME) (Farge et al., 2016) recommends thromboprophylaxis in lung cancer and advanced pancreatic malignancy associated with low bleeding risk. Finally, the American College of Chest Physicians (ACCP) recommends the use of thromboprophylaxis in all outpatients with active cancer and a VTE risk factor, receiving chemotherapy (Kearon et al., 2012).

These differences in guidelines result from the scarcity of data on long-term thromboprophylaxis beyond 3 months in cancer outpatients. In the PROTECHT study, thromboprophylaxis with LMWH was associated with a significant VTE risk reduction of nearly 50% compared to placebo (Barni et al., 2011). In the SAVE-ONCO study, thromboprophylaxis with LMWH was associated with a significant VTE risk reduction of 64% without excess in clinically relevant or major bleeding (Agnelli et al., 2012). Despite this impressive relative risk-reduction observed in both trials, the absolute risk-reduction remains limited to about 2% of VTE events over 4 months, resulting in a number needed to treat to prevent one VTE event of 45 and 66 in the SAVE-ONCO and the PROTECHT study, respectively. A meta-analysis from the Cochrane database confirmed these results (Di Nisio et al., 2014). Considering lung cancer patients, prophylaxis decreases VTE occurrence, but survival benefit remains elusive (Fuentes et al., 2017). In the absence of definite clinical evidence and homogeneous recommendations, the use of VTE prophylaxis is left to physician's decision.