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Research Article

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Managing cancer associated thrombosis (cat): a dedicated service may help

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Summary

Cancer is single most important risk factor for developing thromboembolism (VTE). Cancer patients are at increased risk of bleeding due to various reasons [1]. Low molecular weight heparin (LMWH) remained the standard of care for many years [2]. Direct acting oral anticoagulants (DOACs) are simpler to administer and equally effective and safe as compared to LMWH [2]. However, there are several concerns associated with DOACs in cancer patients. They are related to drug-to-drug interactions and risk of bleeding in gastrointestinal and urothelial malignancies [3]. Authors have comprehensively summarized the available evidence related to managing venous thromboembolism in cancer patients.

Keywords: Cancer, Thromboembolism, Chemotherapy, Systemic Anticancer Therapy, Rivaroxaban, Mucosal Toxicity, Tumour Necrosis

Methods

Authors systematically examined medical databases (MEDLINE, Embase) looking at current information to manage cancer related thrombosis and formulated practical summary guidelines.

Introduction

Thromboembolism consists of arterial and venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE) [3]. VTE is a significant cause of morbidity and mortality in cancer patients. The incidence is higher when cancer is active especially during chemotherapy. Overall incidence of thrombosis in cancer patients is around 20% depending on type and burden of the cancer [4]. While on treatment, these patients have high risk of recurrent thrombosis and bleeding. Therefore comprehensive management of cancer associated thrombosis is complex and challenging. Drug-to-drug interactions remain a concern while on systemic anticancer therapy [4]. Managing these patients in a dedicated cancer associated service may improve patient satisfaction.

Treatment Recommendations

Aim of treatment should be to improve quality of life by preventing recurrent thrombosis and decreasing the risk of bleeding [5]. LMWH is more effective than warfarin without increase in bleeding [5]. Recently DOACs are found non-inferior to LMWH in safety and efficacy. Among DOACs, apixaban, edoxaban and rivaroxaban may be used in cancer patients [4]. There is not enough evidence for using dabigatrin in cancer patients [3] (Figure 1)
DOACs or LMWH may be the initial treatment for acute thrombosis. Treatment should be individualised based on patient characteristics and personal choices [3].

Generally, anticoagulation should be continued until cancer remains active or patient remains on systemic chemotherapy [6]. On-going reatment should be assessed on regular basis; i.e. every three months or sooner if clinical condition changes. Discontinuation of anticoagulation should be considered after 6 months if cancer is in remission [7].

LMWH is preferred when there is high risk of bleeding, significant drug-to-drug interactions, extremes of body weight, malabsorption, vomiting, diarrhoea, heavy burden of cancer, extent of thrombosis, previous gastrointestinal surgery and history of uterine or GI bleeding [4] (Figure 2).

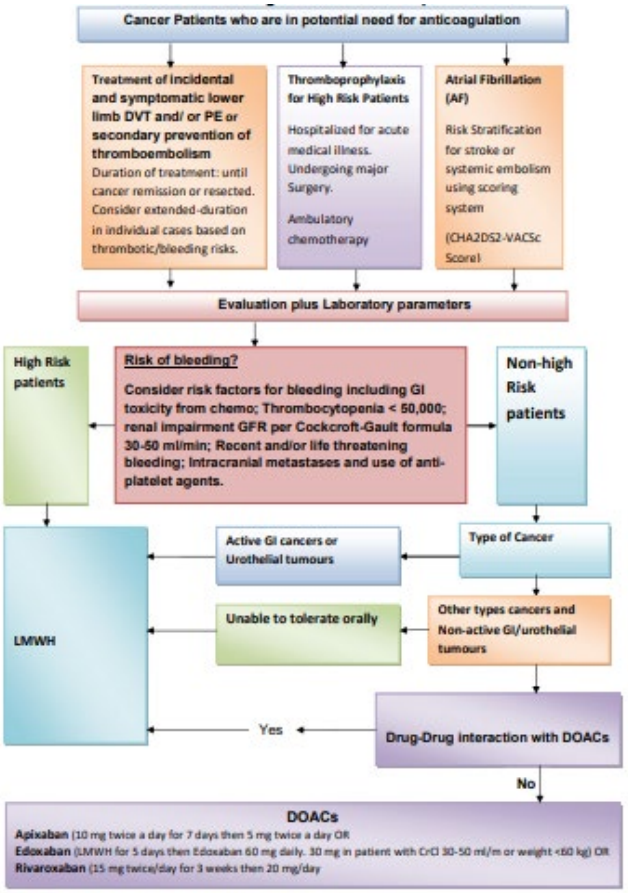

Figure 1: Initiation of antocoagulation in cancer patients.

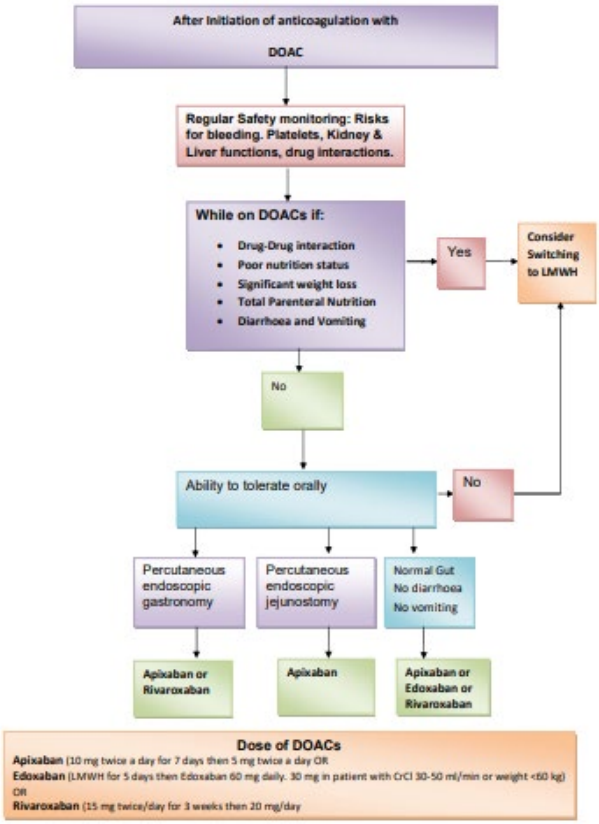

Figure 2: On-going anticoagulation treatment in cancer patients.

Incidental VTE

The incidental thrombosis found on routine imaging in cancer patients should be managed in the similar way as of symptomatic cancer associated thrombosis [6].

Upper Extremity and Catheter Related Thrombosis

Available evidence is limited in these patients therefore anticoagulant choice for thrombosis associated with central line, including peripherally inserted central catheter (PICC), should be individualised [7].

Risk of Bleeding

Identifying patients at high risk of bleeding is crucial to tailor anticoagulation. Major bleeding (MB) and clinically relevant non major bleeding (CRNMB) is relatively higher in cancer patients receiving DOACs than with LMWH, especially in gastrointestinal and genitourinary malignancies [6].

Features consistent with high risk of bleeding are drug-to-drug interactions, gastrointestinal (GI) and uro-epithelial tumours, treatment related mucosal toxicity and tumour necrosis, previous history of GI bleeding, angiodysplasia, oesophageal varices and portal hypertension [4].

Thrombocytopenia

Thrombocytopenia due to chemotherapy increases risk of bleeding. Clinical judgement is required to decide dose modification or temporary break from anticoagulation until platelet count recovers to <50,000/ml [7]. DOACs should be avoided in these patients where platelets are frequently fluctuating due to chemotherapy cycles [8].

In patients with platelet counts less than 50,000/ml, LMWH may be given at 50% dose or at prophylactic dose and sometime it is given under cover of platelet transfusion especially during first month of VTE event [4].

Primary or Secondary Brain Cancers

There is limited evidence in such patients but LMWH can be considered for initial use in CAT with high risk of intracranial lesions like glioma [4,6].

Hepatic Impairment

Patients with significant liver impairment are at high risk of bleeding when treated with DOACs [9]. Therefore none of the DOACs are recommended for patients with liver disease with Child-Pugh Class C. Rivaroxaban is contraindicated in patients with moderate to severe hepatic impairment [10]. Apixaban should be used with caution in patients with liver impairment at Child-Pugh Class A/B. Similarly edoxaban exhibit comparable metabolism in patients with Child-pugh class A/B [10] (Figure 3).

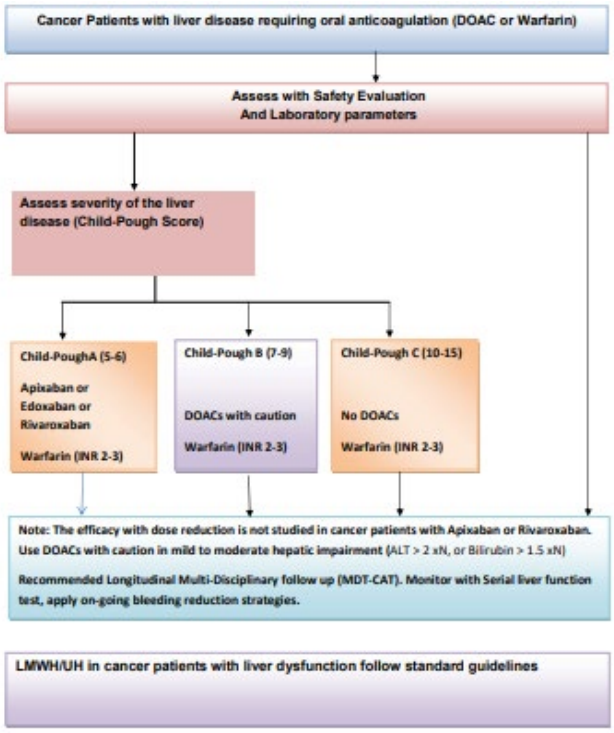

Figure 3: Liver impairment in cancer patients and oral anticoagulation.

Renal Impairment

Clinicians should follow specific product monograph recommendations for dose adjustment for anticoagulants in patients with renal impairment [11,12] (Figure 4).

	Rivaroxaban	Edoxaban	Apixaban
eGFR > 90 ml/min	20 mg daily	60 mg daily	Use 5 mg BD, (Half dose if age <80 years, Weight <61 kg)
eGFR > 50-90 ml/min		30 mg daily	Use 5 mg BD, (Half dose if age <80 years, Weight <61 kg)
eGFR > 30-50 ml/min	Use with caution	30 mg daily	Use with caution
eGFR >15-30 ml/min	Consider alternate drug	Consider 30 mg daily but avoid if creatinine clearance less than 15 mL/minute.	Consider alternate drug
eGFR < 15 ml/min	avoid if creatinine clearance less than 15 mL/minute	avoid if creatinine clearance less than 15 mL/minute	avoid if creatinine clearance less than 15 mL/minute

LMWH/UH in cancer patients with renal impairment follow standard guidelines

Figure 4: Renal impairment in Cancer Patients and DOACs.

Use of Antiplatelet Agents

Concomitant use of antiplatelet agents should be assessed and discontinued, if appropriate, before starting treatment with anticoagulation [13]. It is recommended to discuss with relevant healthcare providers before making the decision [12].

Drug to Drug Interactions

Most of cancer patients are taking multiple drugs due to various reasons. Incidence of bleeding and mortality risks is higher in patients who are taking P-gp/CYP3A4 inhibitors concurrently with DOACs [15]. Blood levels of DOACs can be affected by various drugs due to their effect on p-glycoprotein or CYP3A4 enzyme system in liver [16]. Many anticancer drugs may inhibit or induce these pathways with potential fluctuation of drug levels in the blood leading to under or over treatment [9]. In these circumstances, its recommended to consider LMWH [3]. Given the complexity of therapeutic regimens, discussion with relevant oncologist or cancer associated thrombosis (CAT) specialist is warranted [3].

Other important factors to consider are patient preferences, body weight, history of bleeding, gastrointestinal surgery, chemotherapy induced vomiting, diarrhea, burden of cancer and extent of thrombosis [4].

Duration of VTE Treatment in Cancer Patients

Decision of continuation of anticoagulation beyond 6 months should be individualised [15]. There is insufficient evidence on safety and efficacy of anticoagulation for secondary prevention beyond twelve months [17]. Retrospective studies demonstrated elevated risk of thrombosis beyond twelve months in active cancer [15]. This supports long-term secondary prevention in cancer patients [13]. However duration and dosing of anticoagulation should be based on individual risk of recurrent thrombosis and bleeding [14]. Regular assessment is helpful to define cancer status and ongoing management [9]. Risk stratification and individualized approach is reasonable to gauge risk of bleeding and risk of recurrent thrombosis to define treatment beyond six months [15]. Given the complexity of managing cancer associated thrombosis, setting up a specialist team in this area is justified [3].

Risk Assessment of Thrombosis

High risk cancer patients undergoing chemotherapy with Khorana Risk Score 2 or more (KRS ≥2) should be considered for prophylaxis of thrombosis by offering them Apixaban, Riroxaban or LMHW in prophylactic dose for up to six months [18,19].

Discussion

Managing VTE in cancer patients is quite complex and arduous. Most of the recent guidelines recommend LMWH or DOACs in this setting. Recent evidence supports use of DOACs as reasonable option without increase in risk of bleeding. Moreover DOACs are attractive and convenient option for patients with better compliance. However, some questions remain unanswered. These need to be considered before choosing a favourable option. This dilemma rotates around concomitant drugs, cancer activity, brain involvment, central line thrombosis, extremes of body weight, diminished oral intake, compromised liver and kidney functions and gastrointestinal or urothelial cancers. Therefore a personalised approach should be considered for managing cancer associated thrombosis. Tackling these issues in multidisciplinary cancer associated clinic (CAT Clinic) seems a reasonable practical approach.

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