Venous Thromboembolism Treatment in Cancer Patients: Update of the Role of Direct Oral Anticoagulants in this Scenario

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Tratamento do Tromboembolismo Venoso em Pacientes com Câncer: Atualização quanto ao Papel dos Anticoagulantes Orais Diretos nesse Cenário

Tratamiento de Tromboembolismo Venoso en Pacientes con Cáncer: Actualización sobre el Papel de los Anticoagulantes Orales Directos en este Escenario

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INTRODUCTION

Cancer is widely known for increasing the risk of thromboembolic complications. This risk is associated to the patients' own characteristics, its comorbidities and clinical conditions, in addition to factors related to the tumor and the moment of the treatment. The prescription of anticoagulant therapy must consider the hemorrhage risk and recurrence of deep venous thrombosis (DVT).

To validate the use of new direct oral anticoagulants (DOACS) in patients with cancer-associated thrombosis (CAT) clinical trials were conducted. However, the risks must be taken into account in order to provide more proper and safety therapy for each patient. These therapeutic alternatives should be disclosed in the services of oncology, facilitating its utilization and more benefit for the patients.

The estimates is that 20% of the patients with active cancer will develop thrombosis in the course of their treatment[1]. In addition, this population in special presents a risk of recurrence of DVT of nearly 3 times compared to the population without cancer[2]. Because most of the times these are patients debilitated either by the disease itself or as result of the own treatment they underwent during their clinical evolution, they are two-fold more prone to hemorrhage events during the anticoagulant therapies[1,3].

The absolute risk of developing thromboembolic complications depends on the type of tumor, staging or extension of the cancer or treatment with antineoplastic agents. Oncologic patients, the estimates say, who developed DVT present 94% odds of dying until six months after the episode of DVT. DVT consequently is considered a negative predictive marker of survival of oncologic patients[4,5].

For each year of 2018-2019, the preview is 324,580 new cases among men and 310,300 in women in Brazil. It is likely to anticipate a significant number of thromboembolic events in oncologic patients based in these information[6].

This event may occur at any moment of the clinical evolution of the patient either preceding the cancer diagnosis when it appears as the first signal or symptom of cancer or during the hospitalization and treatment stages. This risk diminishes during the period of remission of the disease. Nevertheless, in metastasis, the risk of DVT increases significantly and can be a first sign of the relapse of the disease when the patient is in clinical control[1].

In this scenario, while prescribing an anticoagulant treatment for the patient with CAT, it is necessary to individualize this patient and evaluate according to four clinical-epidemiological aspects: *i)* factors inherent to the background of the patient in what concerns comorbidities, presence of varicose veins, history of DVT or thrombophilia ; *ii)* characteristics of the patient's tumor, the type and histologic degree of the tumor, its staging and the moment the cancer diagnosis occurs; *iii)* treatment applied: chemotherapies, antiangiogenic venous catheters, surgeries, radiotherapies, blood transfusion, immobility and hospitalization; *iv)* biomarkers: hematologic, D-Dimer, reactive C protein, P-selectin, activity of the tissue factors and prothrombin fragment 1+2[1]. Based in the evaluation of the patient in these four aspects and in the evaluation of the hemorrhagic risk and patient concurrence with the prescribed therapy the anticoagulant treatment will be initiated. This treatment must be

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evaluated considering its dynamic in the clinical evolution of the patient in oncologic treatment who is subject to multiple complications and changes of the clinical status.

DEVELOPMENT

What to prescribe for the patient with cancer-associated to thrombosis?

The evaluation of the patient with cancer associated to thrombotic event must consider the clinical epidemiologic factors described formerly and match the patient's clinical conditions, possible interventions it comes to undergo and share with the patient its decision, respecting its desire.

Since DOACS approval, studies of clinical practice with observational cohorts have been conducted describing the experiences of these drugs in the population with cancer[7]. The main focus lies in the efficacy translated as recurrence of thrombosis in the population. Another important factor is the interaction drug-drug with chemotherapic agents that may changes the pharmacodynamics of DOACS increasing the hemorrhagic or thrombotic risk. In that line, the concomitant use of some drugs that are potent inhibitors or inducers must be avoided[8].

A systematic review of the literature describing all the observational studies about this topic reported that the majority of the studies used rivaroxaban and low molecular weight heparin (LMWH)[9]. The durations of the treatments with DOACS were longer when compared to LMWH, which can reflect the preferences of the patients for oral agents and cost. Almost all the studies reflect the low rates of recurrence in the groups treated with DOACS compared to those who used LMWH. For severe and less important bleeding, heterogeneous data were found. Observational studies, it is noticed, present biases that limit some interferences about the data described[10].

The patients reported efficacy and safety of the oral anticoagulants as the most important and prefer its administration orally in comparison to injections[7]. Therefore, the utilization of DOACS as therapeutic option allows more commodity for the treatment and extended adherence of the patients.

At this moment, only rivaroxaban and edoxaban present studies pertinent to the population of oncologic patients. The differences of the mechanism of action of dabigatran, which is one direct inhibitor of thrombin, do not allow inferences or comparisons with other anticoagulant as mechanism of action anti-Xa.

From the individual evaluation of the patient and shared decision, specific DOACS, edoxaban and rivaroxaban for the patients with CAT are suggested. However, for those patients with acute thrombosis and high hemorrhage risk, LMWH is recommended, including the patients with intact luminal gastrointestinal tumors, without having submitted to resection, and those tumors of the genitourinary tract, nephrostomies, active duodenal ulcers, esophagitis or colitis[7].

Another important issue to reflect upon are those patients with extremes of weight and accentuated reduction of renal depuration, where caution is mandatory either for prescription of LMWH or DOACS.

DOACS in patients with cancer

Select-D trial was a study whose objective was the evaluation of an oral inhibitor of factor anti-Xa, in case rivaroxaban as therapeutic alternative for the treatment of thrombosis in oncologic patients. Several sites enrolled patients with active cancer who had PE (pulmonary thromboembolism) and DVT. To one of the study arms, patients were assigned for treatment with dalteparin, 200 UI/Kg, daily during one month and, next, the dose was adjusted to 150 UI/Kg for the following months. In another arm, patients treated with rivaroxaban 15 mg daily, twice a day for 21 days were assigned; and, next, the dose was adjusted to 20 mg once a day. The primary outcome was the recurrence of thrombosis during six months of follow up[11].

The safety was evaluated per major bleeding and clinically relevant non- significant bleeding. The study was conducted with a sample of 400 patients. The ratio of recurrence of thrombosis in six months in the arm of dalteparin was 11% and in the arm of rivaroxaban, 4%. The cumulative rate of bleeding and major bleeding was higher than 4% for dalteparin and 6% for rivaroxaban. The study concluded that rivaroxaban was associated to a relatively low recurrence of DVT, however, with the increase of bleeding in the arm of rivaroxaban[11].

Another study designed specifically to evaluate anticoagulation in patients with cancer was *Hokusai-cancer*, whose drug, edoxaban a direct inhibitor of the factor of coagulation activated Xa, was compared to dalteparin. The proposal was treatment from six to until 12 months. In the arm edoxaban, it was initiated anticoagulation with dalteparin subcutaneous, dose of 200 UI/kg, once a day for five days; next, edoxaban, dose of 60 mg/day. The arm dalteparin was initiated with the dose of 200 UI/kg per day and, next, the dose was reduced to 150 UI/kg per day until the end of the treatment. The primary outcome as the endpoint formed by recurrence of thrombosis or hemorrhage during the 12 months of treatment. The study evaluated the cases of low weight, *clearence* of creatinine between 30-50 mL/min[12].

The anticoagulant therapy of choice in the oncologic patient must be individualized and dynamic because at any moment, changes in the patient's clinical evolution

may occur both in terms of complications, procedures, interventions or changes in the therapeutic plan, needing the revaluation of the patient. The drug-drug interaction, renal and liver functions, platelets counting and other hematimetric indexes, the risk of major or recurrence of thrombosis must be considered (Table 1).

The utilization of an algorithm to guide the diagnosis and treatment of DVT in emergency rooms and outpatient units can facilitate proper prescription of anticoagulant therapy of the patient with CAT. In that line, the "Instituto Nacional de Câncer José Alencar Gomes da Silva (INCA)" developed an algorithm presented in Figure 1. An initial proper conduct can promote improved effectiveness and safety for the patient.

CONCLUSION

The risks of thrombosis and bleeding are high for the oncologic patient. The clinical conditions of each patient and the clinical moment as the patient is should always be evaluated.

The individualized therapeutic conduct minimized the risks of occurrence of thrombosis and hemorrhages. Patients with injuries in the genitourinary tract because of

Table 1. Clinical considerations during the choice of anticoagulant therapy for patients with cancer

DRUG	ACTION	CONSIDER
Direct oral anticoagulants	Good	Patients without gastrointestinal neoplasm Low risk of major bleeding Facility of the oncologic treatment Low interaction drug-drug
Direct oral anticoagulants	Avoid	Active gastrointestinal neoplasm History of previous gastrointestinal bleeding Weight extremes (<50Kg and >150Kg)
Heparins of low molecular weight	Good	TTherapies with nausea and extreme vomits Alterations of gastrointestinal absorption Drug-drug interactions with direct oral anticoagulants and antivitamin K Known risk of bleeding Recurring cancer associated to deep venous thrombosis during anticoagulation
Heparins of low molecular weight	Avoid	Aversion of the patient to parenteral therapy Renal insufficiency or fluctuation of renal status Weight extremes (<50Kg and >150Kg)
Antivitamin K	Good	Any condition demanding monitoring of anticoagulation (risks of bleeding or metabolic alterations or absorption) Advanced chronic renal insufficiency Weight extremes (<50Kg and >150Kg)
Antivitamin K	Avoid	Lack of control of anticoagulation-monitoring

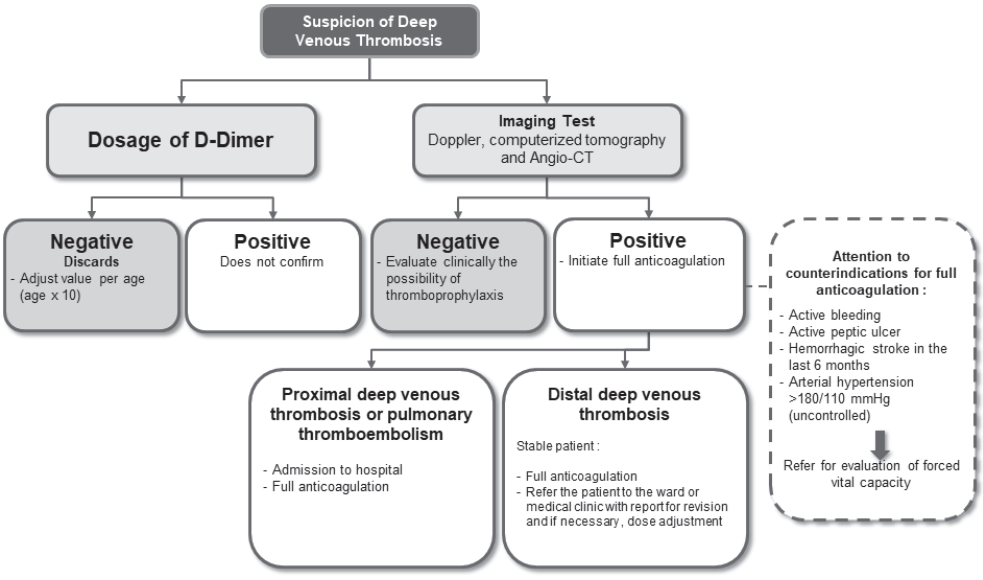

Figure 1. Algorithm for diagnosis and treatment of DVT of INCA

the great hemorrhage risks must be object of attention and finally, share the decision to be taken about anticoagulant therapy with the patient.

CONTRIBUTIONS

Marcos Jose Pereira Renni and Tatiana Abelin Saldanha Marinho participated of the conception and planning of the study, analysis and interpretation of the data, wording and critical review of the manuscript. Mirian Carvalho de Souza participated of the wording and critical review of the manuscript. All the authors approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There are no conflict of interests to declare.

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