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An Assessment of the Use of Enoxaparin/Warfarin vs. Enoxaparin/Rivaroxaban in Patients with Gynecologic Cancer Co and Venous Thromboembolism

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Introduction

Venous thromboembolism (VTE), which consists of deep venous thrombosis and pulmonary embolism, is a frequent complication of cancer and its treatments. The presence of neoplasia increases about four to eight times the risk of thromboembolic events when compared to the general population. Cancer patients have several risk factors and pathogenic mechanisms that increase the likelihood of developing VTE. Changes in coagulation mechanisms are related to the progression of the disease, influencing the prognosis and survival [1-4].

The prothrombotic properties of tumor cells, surgical interventions and aggressive chemotherapy contribute to a high incidence of VTE [4]. Among the treatments for VTE, low molecular weight heparin is the best (golden standard) and safer option for anticoagulation during chemotherapy in patients who developed VTE in the course of their oncological treatment. However, it brings the patient the burden to undergo the daily injections. Because of this, after the end of chemotherapy, enoxaparin is replaced by warfarin, an oral anticoagulant that presents a series of limitations, dietary restrictions, drug interactions that make its adjustment to the optimal therapeutic range difficult. With the advent of new oral anticoagulants, there was an opportunity to use new drugs to treat patients with neoplasms and VTE, such as rivaroxaban, an oral anticoagulant that directly inhibits the factor Xa and provides rapid onset of anticoagulation [5-9].

However, the management of anticoagulation in cancer patients is challenging as the risk of recurrent VTE increases during the oncologic treatment, as well as hemorrhagic events. In this context, it is necessary to evaluate the new oral anticoagulants as anticoagulant therapy in cancer patients and their impact on patient survival.

The aim of the present study is to evaluate the efficacy and safety of rivaroxaban compared to warfarin in the anticoagulant therapy of patients with gynecological neoplasia and in the treatment of venous thromboembolism, as well as its impact on the survival of these patients.

Methodology

This article consists of a cohort study in which women with gynecological cancer enrolled in the Hospital of Cancer II (HC II) of the National Cancer Institute of Brazil José Alencar Gomes da Silva (INCA) and diagnosed with deep vein thrombosis or confirmed pulmonary embolism were selected. Patients were treated with enoxaparin and warfarin or with enoxaparin and rivaroxaban. They were identified through the consultation of the hospital's pharmacy anticoagulant delivery records, in the period from January 2013 to December 2015. Patients younger than 18 years old and those with difficulties in understanding were excluded. Hemorrhagic events characterized by the presence of bleeding in any body area of the patient during treatment with oral anticoagulant, classified as mild, moderate or severe, were considered a safety outcome.

The drug's efficacy outcome was evaluated by the recurrence of thromboembolic event, which refers to the appearance of new thrombosis or pulmonary embolism during the administration of oral anticoagulants and the occurrence of death. Data were collected from physical and electronic medical records. Sociodemographic variables (date of birth, race/color/ethnicity, education, alcohol and tobacco consumption, tumor characteristics, cancer treatment and death) were extracted from the HC II Hospital Cancer Registry database and those with information losses of less than 20% were included in the analyses.

A descriptive study of the population was performed by using the mean (standard deviation) for continuous variables and the distribution of absolute and relative frequencies for categorical variables. In order to compare the incidence of adverse effects between the VTE treatment groups (rivaroxaban or warfarin), a logistic regression was performed, from which the odds ratio (OR) was obtained. Furthermore, the Kaplan-Meier method was applied for the overall survival analysis. The occurrence of death was considered an event and the patients who did not die were censored in the last hospital consultation. To identify factors associating the thromboembolic treatment and overall survival, a Cox regression was performed. The data were analyzed using the SPSS statistical package, version 20.0. This study was approved

by INCA's Research Ethics Committee in the 22nd October 2015, under the CAAE number: 47709515.0.0000.5274.

Results

The study included 311 women with gynecological neoplasms and venous thromboembolism. Of these, 180 were treated with enoxaparin and warfarin, while 131 received enoxaparin and rivaroxaban. Regarding the sociodemographic characteristics of the study's population, it was observed that the mean age of the total study population was 53.24 years, most patients had no partner (56.6%), did not work (63.3%) and were not smokers (59.2%). Education and alcohol consumption showed statistically significant differences between the treatment groups, demonstrating a lower level of education (79.4%) and a higher frequency of non-ethanolic patients (90.6%) in the group of patients treated with warfarin (Table 1).

Table 1: Sociodemographic characteristics of the study population

Variable	Total (311) N (%)	Warfarin (180) N (%)	Rivaroxaban (131) N (%)	p- value*
Average (SD)	53.24 (±13.2)	53.84 (±12.6)	52.14 (±14.2)	0.304
Marital Status				
With partner	133 (42.8)	80 (44.4)	53 (40.5)	0.492
Without partner	176 (56.6)	99 (55.0)	77 (58.8)	
Without information	2 (0.6)	1 (0.6)	1 (0.8)	
Education (Years of Study)				
0 to 7 years of study	203 (65.3)	143 (79.4)	60 (45.8)	< 0.001
≥ 8 years of study	76 (24.4)	37 (20.6)	39 (29.8)	
Without information	32 (10.3)	0 (0)	32 (24.4)	
Occupation				
Worker	113 (36.3)	63 (35.0)	50 (38.2)	0,591
hosewife	197 (63.3)	116 (64.4)	81 (61.8)	
Not informed	1 (0.3)	1 (0.6)	-	
Alcohol Consumption				
Yes/former consumer	23 (7.4)	11 (6.1)	12 (9.2)	0.068
No	244 (78.5)	163 (90.6)	81 (61.8)	
Without information	44 (14.1)	6 (3.3)	38 (29.0)	
Tobacco Consumption				
Yes/former smoker	83 (26.7)	54 (30.0)	29 (22.1)	0.980
No	184 (59.2)	120 (66.7)	64 (48.9)	
Without information	44 (14.1)	6 (3.3)	38 (29.0)	

* Analysis performed with known values;

In bold are the variables that presented a statistically significant difference between the groups (p< 0.05).

Regarding the clinical and cancer treatment characteristics, the most frequent gynecological neoplasm was of the cervix (49.5%), followed by endometrium (28.0%), ovary (15.8%) and vulva and vagina (2.3%). Advanced staging III and IV totaled more than 50% of the cases when compared to the initial staging I and II. Only 1.9% of patients did not receive cancer treatment, while 92.6% had some type of treatment and the combination of radiotherapy and chemotherapy was the most frequent modality (36.7%). Of the patients surveyed, 61.4% had already died (Table 2).

Table 2: Clinical and treatment characteristics of the study's population

Variable	Total (311) N (%)	Warfarin (180) N (%)	Rivaroxaban (131) N (%)	p- value*
Topography				
Cervix	154 (49.5)	98 (54.4)	56 (42.7)	0.323
Endometrium	87 (28.0)	54 (30.0)	33 (25.2)	
Ovary	49 (15.8)	24 (13.3)	25 (19.1)	
Vulva and vagina	7 (2.3)	4 (2.2)	3 (2.3)	
Without information	14 (4.5)	0 (0)	14 (10.7)	
Staging				
I	56 (18.0)	36 (20.0)	20 (15.3)	< 0.001
II	73 (23.5)	57 (31.7)	16 (12.2)	
III	113 (36.3)	69 (38.3)	44 (33.6)	
IV	45 (14.5)	14 (7.8)	31 (23.7)	
Without information	24 (7.7)	4 (2.2)	20 (15.3)	
Cancer Treatment				
Yes	288 (92.6)	180 (100)	108 (82.4)	0.002
No	6 (1.9)	-	6 (4.6)	
Without information	17 (5.5)	-	17 (13.0)	
Frequent Treatment				
Surgery	34 (10.9)	23 (12.8)	11 (8.4)	0,.031
Radiotherapy (Rxt)	23 (7.4)	15 (8.3)	8 (6.1)	
Chemotherapy (Qt)	17 (5.5)	8 (4.4)	9 (6.9)	
Surgery + Rxt	19 (6.1)	16 (8.9)	3 (2.3)	
Surgery + Qt	51 (16.4)	33 (18.3)	18 (13.7)	
Surgery + Rxt + Qt	12 (3.9)	8 (4.4)	4 (3.1)	
Rxt + Qt	114 (36.7)	75 (41.74)	39 (29.8)	
Others	4 (1.3)	2 (1.1)	2 (1.5)	
Did not treat	6 (1.9)	-	6 (4.6)	
Without information	31 (10.0)	-	31 (23.7)	
Treatment Modality				
Isolated Treatment	74 (23.8)	46 (25.6)	28 (21.4)	
Combined Treatment	200 (64.3)	134 (74.4)	66 (50.4)	
Did not treat	6 (1.9)	-	6 (4.6)	
Without information	31 (10.0)	-	31 (23.7)	
Death				
Yes	191 (61.4)	116 (64.4)	75 (57.3)	0.198
No	120 (38.6)	64 (35.6)	56 (42.7)	

*Non-white = Black, brown, yellow and indigenous; ** Analysis performed with known values;
In bold are the variables that presented a statistically significant difference between the groups ($p< 0.05$).
b- Chi-square test performed.

When assessing the incidence of complications during thromboembolic treatment, there was no statistically significant difference between the groups of patients who received warfarin and rivaroxaban ($p=0.552$ for bleeding and $p=0.982$ for recurrence. From the patients who were treated with warfarin, 35 (19.4%) presented bleeding and 18 (10.0%) were diagnosed with a new thromboembolic event; and among the patients treated with rivaroxaban, 22 (16.8%) presented bleeding and 13 (9.9%) presented new VTE. Although there were 16 (45.7%) cases of mild bleeding in the warfarin group compared to five (22.7%) in the rivaroxaban group, no statistically significant differences were observed in the subgroups on this outcome (table 3).

Table 3: Incidence of complications with medications

Variable	Total (311) N (%)	Warfarin (180) N (%)	Rivaroxaban (131) N (%)	p- value*
Bleeding				
Yes	57 (18.3)	35 (19.4)	22 (16.8)	0.551
No	254 (81.7)	145 (80.6)	109 (83.2)	
Type of bleeding[a]				
Mild	21 (36.8)	16 (45.7)	5 (22.7)	0.180
Moderate	24 (42.1)	12 (34.3)	12 (54.5)	
Severe	12 (21.1)	7 (20.0)	5 (22.7)	
Rethrombosis				
Yes	31 (10.0)	18 (10.0)	13 (9.9)	0.982
No	280 (90.0)	162 (90.0)	118 (90.1)	

Notes: * Chi-square test performed.
[a] *Fisher's exact test performed.

After the logistic regression, it was evidenced that the patients who received warfarin presented 20% greater chance of bleeding and 1% of recurrence. However, these results were also not statistically significant (Table 4).

Table 4: Logistic Regression

Treatment	Bleeding			Rethrombosis		
	OR	CI 95%	p-value	OR	CI 95%	p-value
Rivaroxaban	1.00	-	-	1.00	-	-
Warfarin	1.20	0.66 – 2.15	0.551	1.01	0.48 – 2.14	0.982

Regarding the patients' survival, the group treated with rivaroxaban exhibited a median survival time of 41.13 months, while the group treated with warfarin presented 50.86 months (table 5), with no statistically significant difference (p=0.266) (Figure 1). Similarly, the risk of death showed no statistical difference between the use of rivaroxaban compared to warfarin (p=0.267) (Table 5).

Table 5: Median survival in patients treated with rivaroxaban and warfarin

Treatment	N	Median (months)	CI 95%
Rivaroxaban	131	41.13	29.09 – 53.18
Warfarin	180	50.86	41.50 – 60.22

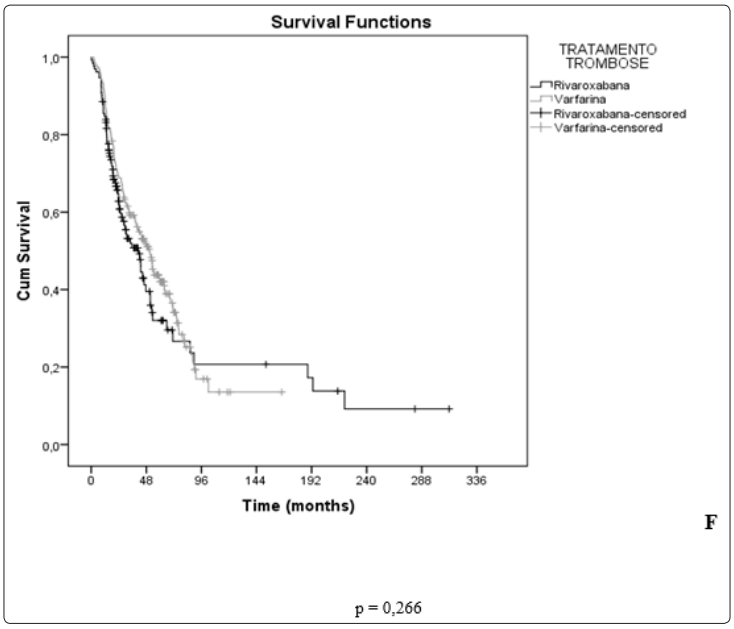

Figure 1: Survival curve of patients treated with rivaroxaban and warfarin

Discussion

The prevalence of venous thromboembolism is high in the population of cancer patients. Cancer is a strong and independent risk factor to VTE. It is estimated that it is responsible for about 18% of the total number of VTE cases. Its occurrence in cancer patients is related to a worse prognosis [10].

The pathophysiology of thrombosis associated with cancer is not fully understood. The state of hypercoagulability in cancer involves several complex interdependent mechanisms, including interaction between cancer cells, host cells and the coagulation system. Some tumor sites have a higher incidence than others and this is closely related to the tumor type. They are classified as high risk, intermediate risk and low risk [11-12].

Other factors corroborate to the occurrence of thromboembolism in these patients. They may be related to the patient him/herself and his/her co-morbidities, the presence of bio-markers in the course of his/her disease and also the time of treatment in which the patient is. In any case, the anticoagulation in these patients is difficult to handle and we must consider the factors associated with the individual, and thus decide which anticoagulant therapy is most appropriate for her/him. The purpose of anticoagulant treatment for VTE in cancer patients is the same as in other populations of patients with increased risk [10]. Generally, the treatment options for acute VTE were vitamin K antagonists (VKAs) with initial heparinization. In cancer patients low molecular weight heparin is often restricted in view of the difficulties resulting from interactions between the drugs and the therapeutic adjustment of the INR.

VKA treatment is associated with an increased risk of recurrence and bleeding when compared to patients without cancer. Cancer patients treated with AVK have approximately three times the risk of recurrence of VTE and a two to six times greater risk of bleeding [7,13,14].

With the advent of direct oral anticoagulants (DOACs) a new therapeutic perspective was opened in the anticoagulation of patients with neoplasms. The direct thrombin inhibitors (i.e., dabigatran) and the direct inhibitors of factor Xa (i.e., apixaban, rivaroxaban, and edoxaban) have the convenience of oral administration and a more predictable pharmacodynamics. Compared to AVK, they do not require laboratory monitoring and have lower drug-to-drug interaction [10].

Evidence from phase III clinical trials demonstrates that, during the primary treatment of venous thromboembolism (VTE) (i.e., the first three to six months after the event), direct oral anticoagulants (DOACs; dabigatran, rivaroxaban, apixaban, and edoxaban) are not inferior to therapy with vitamin K antagonists (AVK) to prevent recurrent, symptomatic VTE thrombosis and death by VTE [15].

Within this scenario our study proposal was to evaluate the efficacy and safety of rivaroxaban compared to warfarin. For institutional reasons all patients were initially treated with enoxaparin at full dose and subsequently migrated to oral therapy. Despite the discreet benefit of rivaroxaban, we cannot affirm it was superior to conventional oral anticoagulant therapy with warfarin in terms of efficacy and safety. However, we can confirm its non-inferiority to classical therapy with low molecular weight heparin and AVK.

Standard therapy with enoxaparin and warfarin faces a number of clinical and economic difficulties. Among the difficulties, we highlight the patients' adherence to parenteral therapy associated with the difficulty of maintaining the international normalized ratio (INR) within the therapeutic window. Numerous laboratory tests, dose adjustments, medical consultations and surveys to evaluate drug interactions are required. Often such interactions make it unfeasible to use warfarin as a therapeutic option.

It should be emphasized that drugs that strongly affect CYP3A4 enzyme and / or P-glycoprotein may alter the pharmacokinetics of DOACs and interfere with their metabolism and bioavailability. However, common agents based on platinum, antimetabolites, and monoclonal antibodies do not appear to interact significantly with DOACs. It is important to assess the potential for drug interactions when prescribing a concomitant DOAC to oncologic medications and, if necessary, to adjust the dose according to the drug [10].

In the institution from which the cases were evaluated, rivaroxaban has been used since the end of 2013 with great success and acceptance by the clinical staff and patients. Adverse events have been well conducted without a fatal event so far.

Conclusion

In this scenario, DOACs emerge as a promising therapeutic proposal. The International Society of Hemostasis and Thrombosis (ISTH) currently considers them as a therapeutic alternative for the treatment of cancer associated with thrombosis (CAT). When well used, that is, by individualizing the patient, the moment of clinical evolution and adjusting dose to the patient, the DOACs are undoubtedly a safe and effective anticoagulant therapy. They present themselves as a lower cost therapy, with a better adherence and with reduced complications, whether hemorrhagic or VTE recurrences. Further studies are underway and will likely confirm its use as first-line treatment in patients with CAT.

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