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Current state of non-hematologic cancer-associated thrombosis at a tertiary care hospital in India

*Mukul Aggarwal, Amrita Ramaswami, Manoranjan Mahapatra *, Seema Tyagi, Renu Saxena*

All India Institute of Medical Sciences, New Delhi, India

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ABSTRACT

Introduction: Cancer-associated thrombosis is a leading cause of morbidity and mortality in malignancy patients. Prophylactic anticoagulation is under-utilized and the cost of low-molecular-weight heparin (LMWH) and direct oral anticoagulants is a major barrier in developing countries.

Material and methods: A retrospective analysis was performed of all cancer-associated thrombosis patients attending the thrombosis clinic at a tertiary-level referral hospital based in North India between 2011 and 2015. Patient demographics and disease-related parameters were collected and analyzed.

Results: A total of 771 patients attended the thrombosis clinic during study period, of which 64 cases were malignancy-associated. Of these, 56% of the patients were female and 20% were bedridden. The median age was 48.5 years, adenocarcinoma (48%) being the most common histological subtype. Gynecological malignancies (30%) were the most common malignancies, followed by genitourinary (11%) malignancies. Most of the cases occurred during first year of diagnosis (51%), and only 14% occurred after 3 years. Most of the patients were on combined treatment. Almost 40% of the patients developed thrombosis within 30 days of surgical treatment. Lower limb thrombosis was the most commonly seen type (56%), while abdominal and pulmonary thrombosis were both seen in 5%. Patients were managed with LMWH and vitamin K antagonists (84.3%) and only 6.25% with LMWH alone. Direct oral anticoagulants were not commonly used during the study period.

Discussion: At the hospital studied, most of the cases occurred early in the disease course. Post-operative prophylaxis could have contributed towards reducing thrombosis in the peri-operative period. Early suspicion and prompt treatment can improve quality of life in such patients.

* **Corresponding author at:** Department of Hematology, All India Institute of Medical Sciences, New Delhi, India.
E-mail address: mrmahapatra@hotmail.com (M. Mahapatra).

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Introduction

Cancer-associated thrombosis (CAT) is a leading cause of morbidity and mortality in malignancy patients.[1,2] This association was first reported by Jean Basptiste Bouillaud in 1823.[3]

The risk of venous thromboembolism (VTE) is fourfold to sevenfold higher in patients with cancer than in those without cancer. It is estimated that about 20–30% of patients with cancer experience venous thrombosis at the annual incidence rate of 0.5%, compared to 0.1% in the general population. Overall, cancer patients constitute 15–20% of the patients diagnosed with VTE.[4–8] The incidence and mortality of VTE is seen in the initial period after diagnosis and increases with stage and distal metastasis.[8] The cumulative incidence of VTE in first year was 8% in the Vienna Cancer and Thrombosis study of 840 cancer patients.[9]

Prophylactic anticoagulation is under-utilized and the cost of low-molecular-weight heparin (LMWH) and direct oral anticoagulants (DOAC) is a major barrier in developing countries. The clinical profile of cancer-associated venous thromboembolism is continually changing, given the introduction of newer anti-cancer agents and better integration of cancer therapies, as well as the use of prophylactic anticoagulation and screening for VTE. The study aimed to understand the epidemiological and clinical profile of cancer-associated thrombosis at the institute and the treatment of thrombosis. The objectives were to investigate various types of malignancies associated with VTE, their treatment, presentation of VTE and its treatment.

Methods

A retrospective analysis was performed of all CAT patients, *i.e.*, cancer patients with deep vein thrombosis (DVT) and pulmonary embolism (PE) attending the thrombosis clinic from 2011 to 2015 at the hospital. This hospital is a tertiary care referral center located in northern India with multiple specialities and ultra-specialized departments. Patients of all ages with different types of malignancies are offered treatment in various departments; however, being a public sector hospital, access to treatment is limited at times due to long waiting periods and costs. The Hematology Department runs a weekly thrombosis clinic where all VTE patients are managed. The CAT patients referred from various other departments, such as surgical and medical oncology, gynecology, general surgery, urology, *etc.*, are also seen in this clinic. Patient demographics and disease-related parameters were collected from the clinical records and files and data was analyzed. The study was approved by the Institute Ethics Committee (IESC/T-486/30.09.2015).

The DVT was diagnosed by the Doppler ultrasound (USG) and the PE, by computed tomography with pulmonary angiography. Combined therapy for cancer was defined as two or more modalities of treatment (surgery, radiotherapy and chemotherapy), with or without hormonal therapy.

Descriptive statistics (including median, mean, range and interquartile range) were used to describe the central tendency and dispersion of variables. A p-value of less than 0.05 was considered statistically significant. All the statistical analysis was performed using the Statistical Package for Social Science Software (SPSS 21, IBM SPSS Statistics for Windows, version 21.0; IBM Corp., Armonk, NY, USA).

Results

Demographic characteristics of the study group

A total of 771 patients attended **thrombosis** clinic during study period, of which 64 were malignancy-associated. Three quarters of the patients were in the age group of 40 to 59 years, with the median age 48.5 years and male-to-female ratio of 1:1.28. The majority comprised outpatients (80%) at the diagnosis of CAT. Eight out of the thirteen bedridden patients had a malignancy affecting the central nervous system (**Table 1**).

Tumor characteristics of the study group

Gynaecological malignancies (n = 20, 30.3%) were the most common malignancies, followed by genitourinary (n = 11, 16.7%) and central nervous system (CNS) (n = 9, 13.6%). Adenocarcinoma (n = 31, 48%) and squamous cell carcinoma (n = 10, 16%) were the most common histological subtypes (**Table 1**).

Details of venous thromboembolism of the study group

Most of the cases occurred during first year of diagnosis (n = 33, 51%) and only 9 patients (14%) had VTE after 3 years. The CAT preceded the diagnosis of cancer in 3 patients and occurred in remission in 2 patients. More than 90% of the patients (n = 59, 92%) had an active cancer at the diagnosis of VTE. Of these 59 patients, 51 had **VTE** at the primary presentation and 8, at relapse. The most common thrombosis sites were the lower limbs (n = 56, 86%). The DVT with concurrent PE was seen in 4 out of 64 patients and one patient had an isolated PE.

Cancer treatment characteristics of the study group

Most of the patients were on combined treatment, followed by isolated surgical and chemotherapy-based regimens. Hormonal therapy was used in breast, gynecological and genitourinary cancers as part of combined therapy. Forty patients (62.5%) of **VTE** patients had undergone surgery for their treatment. Sixteen of these 40 patients (40%) developed **VTE** early in the post-operative period, usually within 30 days before discharge from the hospital. Neurosurgeries (n = 9) and abdominopelvic surgeries (n = 5) were mostly associated with early **VTE**, while other events occurred with miscellaneous procedures.

Treatment of VTE in the study group

Most of the patients were managed with LMWH and vitamin K antagonists (VKA) (84.3%) and only 6.3% with LMWH alone. Unfractionated heparin (in patients with deranged renal function) and fondaparinux (physician preference) were each used in 3 patients (**Table 2**). The DOAC were not commonly used/

Table 1 – Clinical profile of the patients (total *n* = 64).

Site of malignancy	*n* (%)
Breast[a]	5 (7.6%)
Gynecological cancers:	20 (30.3%)
Ovary[a]	11
Endometrium	1
Cervix	8
Colorectal:	7 (10.6%)
Stomach	2
Periampullary carcinoma	2
Rectum	1
Colon	2
Hepatobiliary:	2 (3.0%)
Lung	2 (3.0%)
Genitourinary:	11 (16.7%)
Renal cell carcinoma	1
Urinary bladder	4
Prostate	4
Penis	2
Central nervous system	9 (13.6%)
Hematologic	4 (6.1%)
Miscellaneous:	6 (9.1%)
Thymic carcinoma	1
Unknown primary	1
Germ cell tumor	2
Head & neck tumors	2
Temporal relation of VTE to malignancy	
Preceded the diagnosis	3 (4.7)
Active cancer	59 (92%) - 51 at primary presentation, 8 at relapse
During remission	2 (3.1)
Time to DVT after first diagnosis of cancer	*n* (%)
Less than 1 year	33 (51%)
1 – 3 years	19 (30%)
More than 3 years	9 (14%)
VTE preceded the diagnosis of cancer in 3 patients.	
Treatment for malignancy[b]	*N* (%)
Surgery ± hormonal therapy	19 (33.3%)
Chemotherapy ± hormonal therapy	12 (21.1%)
Radiotherapy ± hormonal therapy	3 (5.2%)
Hormonal therapy only	0 (0%)
Combination therapy (two or more of the above-mentioned therapies ± hormonal therapy)	23 (40.4%)
TOTAL	57

[a] Two patients had both carcinoma breast and carcinoma ovary, sequentially. Hence, the total number of events is 66.
[b] Seven patients had not received any form of therapy for cancer at the time of VTE diagnosis.

Table 2 – Characteristics of thrombosis for the patients studied.

Site of venous thrombosis	*n* (%)
Lower limb	56 (86%)
Upper limb	2 (3%)
Abdominal veins (splanchnic veins, renal veins, inferior vena cava[a])	5 (8%)
Cerebral veins	0
Other sites	2 (3%)
Agent used for treatment of VTE	*n* (%)
Low molecular weight heparin only	4 (6.3%)
Unfractionated heparin only	1 (1.6%)
Low molecular weight heparin + oral vitamin K antagonist	54 (84.3%)
Unfractionated Heparin + oral vitamin K antagonist	2 (3.1%)
Fondaparinux + oral vitamin K antagonist	3 (4.7%)
Total	64

[a] One patient had right lower limb DVT extending up to IVC.

available during the study period. All CAT patients were advised to undergo long-term anticoagulation treatment.

Discussion

A strong association between cancer and thrombosis has been demonstrated consistently in experimental and clinical studies. Of the 771 cases of venous thromboembolism, 64 cases (8.3%) were associated with malignancy in this study. This percentage is lower than that of the studies by Heit et al. and Imberti et al., who had reported that about 20% of the VTE occurred in cancer patients.[4,5] In the study by Khorana et al.,[10] it was reported that approximately 78% of VTE events in cancer occurred in the outpatient setting. A similar incidence rate was reported in outpatients by Spencer et al.[11] In a current study, 51 of 64 patients (80%) were outpatients.

In a study by Khorana and colleagues,[12] pancreas (8.1%), ovary (5.6%), kidney (5.6%), lung (5.1%), stomach (4.9%) and brain (4.7%) were identified to be most frequently associated with the CAT. In the current analysis, gynecological and CNS cancers constituted 30% and 14% of the cases, respectively. Ovarian carcinoma was the single largest contributor to the total of cases. It is important to remember that the type of cancer varies with the types of malignancy treated at a particular institute and therefore, there are bound to be referral and selection bias in such an analysis.

The risk of CAT is at its highest in the first few months of the diagnosis of malignancy.[8,13] Chew et al. showed the CAT rate per patient year in the first year after diagnosis of cancer as 3.3, which dropped to 0.8 in second year.[6] In present study, the majority of VTE events (51 %) occurred within one year of the diagnosis of malignancy. Cancer diagnosed with VTE, or within one year of VTE, is associated with an advanced stage and poor prognosis.[14]

Patients receiving therapy for cancer, whether surgery or chemotherapy, have a 2-fold to 3-fold increase in the risk of VTE, as compared with cancer patients not receiving chemotherapy.[15–17] In the current study, 40.3% had received combination therapy. Hormonal therapies for gynecological and breast malignancies, abdominopelvic surgeries and the treatment of bedridden neurological patients with malignancies are known treatment-related risk factors present in this study cohort. As cancer treatment usually involves multiple disciplines, it is difficult to assess the contribution of individual therapy and direct comparisons between treatment modalities are unavailable. In a Chinese retrospective study

involving gynecological cancers by Ye et al., 35.1% of thrombotic events occurred in the post-operative period.[18] In present analysis, the rate of post- operative VTE was comparable (40%).

Guidelines suggest the use of specific DOACs (apixaban, rivaroxaban or edoxaban) for acute CAT, low risk of bleeding and no drug–drug interactions with current systemic therapy. The LMWHs constitute an acceptable alternative. The LMWHs are preferred for CAT with high risk of bleeding, including patients with luminal gastrointestinal or genitourinary tract cancers, or patients with active gastrointestinal mucosal abnormalities, such as duodenal ulcers etc. Specific DOACs are acceptable alternatives.[19–21] The DOACs have better efficacy in preventing the recurrence of VTE than LMWH, but have higher bleeding rates.[21,22]

In the current study, most patients (84.3%) were initially given an LMWH and then switched to the VKA. This is a common option in resource-poor settings where the LMWH prophylaxis or treatment and DOACs are beyond the financial reach of many patients. Also, at the time of the study, the DOACs had not been recommended for CAT. Real-world treatment of CAT is variable. The LMWH and unfractionated heparin (UFH) were the most common initial inpatient CAT treatments (35.2% and 27.4%, respectively), followed by DOACs (9.6%). Most DOAC patients remained on DOACs from inpatient to outpatient settings (71.4%), while 24.1%, 43.5% and 0.1% of patients treated with LMWH, warfarin or UFH, respectively, remained on the same therapy after discharge.[23] Use of the VKA causes concern in CAT due to poor nutrition, drug interactions and the need for invasive diagnostic or therapeutic procedures. At present, with generic versions of the DOACs available on the market and various insurance/government schemes to procure the cancer therapy, the use of the DOACs is likely to increase in the CAT management.

This study has some limitations, the most important being the retrospective nature of the study. This carried referral and information biases, as with any other retrospective analysis. Only patients who were referred to the outpatient thrombosis clinic were included in the study. Patients who could not visit the clinic due to inpatient mortality, or who had been lost to follow-up, were not available for evaluation and hence, the study may not represent the actual burden of the CAT at the Institute. Furthermore, the data on stage, metastasis, comorbidities, recurrence of thrombosis and mortality were not available for all the patients. A prospective study that includes outpatient and inpatient data and a longer follow-up can provide important insights on these aspects.

Conclusions

In the hospital studied, most of the cases occurred early in the disease course and surgical treatment is commonly associated with thrombosis. Postoperative prophylaxis could contribute to reducing thrombosis in the perioperative period. The LMWH and VKA are still the principal therapeutic agents used in resource-poor settings.

Conflicts of interest

None.

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