Cancer-associated thrombosis in some African populations: A growing concern

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ABSTRACT
The burden of cancer is gradually increasing in developing countries in Africa. This has accounted for significant rates of morbidity and mortality. The development of thrombosis in cancer patients impacts significantly on the outcome of care. Cancer-associated thrombosis may occur due to the stage of cancer, its organ site, treatment modality among other reasons. Some reports of studies of the management of patients with deep venous thrombosis (DVT) from African centers have identified malignancy as a significant risk factor for DVT. However, there are no reported studies in cancer patient groups to evaluate the prevalence, risk factors, and efficacy of prophylactic measures in Africa. This review focuses on the epidemiology, pathophysiology, risk indicators, and reports of thrombosis affecting cancer patients in Africa. The aim is to increase awareness and draw the attention of clinicians and oncologist in cancer management in Africa to the need for a robust multicenter research, establishing evidence-based interventions, and guidelines for improved patient outcome.

Key Words: Africa, cancer-associated thrombosis, deep venous thrombosis, risk assessment

Introduction
The connection between cancer and thrombosis had been established over 140 years ago by Trousseau. Since then, there have been many studies to provide significant evidence to attest to this patient with cancer are at increased risk of deep venous thrombosis (DVT). This could be as a result of aggressive antitumor therapy, surgery, use of central venous catheters or other access lines, or the etiology of cancer. Cancer-associated thrombosis is underdiagnosed in patients with malignancies in Africa thus; morbidity and mortality due to venous thromboembolism (VTE) may be high. There is a growing pool of data and research in this area of medicine in many parts of the developed world. However, from Africa, there appears to be a paucity of research and data in this area. Some oncologists do not appreciate the link between cancer, its treatment, the risk of thrombosis and the need for thromboprophylaxis in patients at-risk. According to the Frontline survey, 50% of surgical cancer and 95% of medical cancer patients did not receive appropriate thromboprophylaxis. This paper reviews reports of venous thrombosis as it affects cancer patients, with a bid to shed light on the severity of cancer-associated thrombosis in Africa.

Epidemiology of Cancer-associated Thrombosis
The incidence of venous thrombosis differs according to race, in studies from America, it has been shown that African-Americans have over 5-fold greater incidence than Asian-ancestry populations, and an intermediate
risk for European and Hispanic populations. The overall incidence of VTE is 30–60% higher in blacks than in whites. This holds true across age groups and for both men and women. This however is thought to be influenced by some genetic factors and environmental factors. In developed countries, there is research, improved diagnostic equipment and apparently more awareness compared to developing countries. Although cancer is one of the strongest risk factors, the rate of VTE in black and white hospitalized patients with cancer has been reported to be similar.

The cancer patient is at a greater risk of VTE compared to the general population; they are thought to be in an acquired thrombophilic state. They make up to 15–20% of patients diagnosed with VTE and VTE is the second leading cause of mortality in cancer patients. Overall, the incidence of clinically important thrombosis ranges from 5% to 60% in various malignancies. Autopsy data find evidence of VTE in as many as 50% of cancer patients, but this does not define clinically significant events.

Sometimes, VTE in cancer patients may be without clinical signs and symptoms; the detection of asymptomatic VTE is becoming more frequent with computerized tomography scans performed for cancer staging and they have a negative clinical impact on prognosis of cancer patients, which is similar to symptomatic VTE.

For those who survive an episode of VTE, postthrombotic complications may have a significant impact on the quality of life. The incidence of VTE in cancer patients in Africa may increase over time from contributing effects of improved awareness, heightened index of clinical suspicion among clinicians and oncologists, improved diagnostic capabilities for VTE as well as the use of novel anticancer therapeutic agents that promote VTE.

Pathophysiology and Risk Indicators

The bidirectional association between cancer and venous thrombosis has been known for almost two centuries, and this association has been widely studied; VTE is the clinically overt sign of up-regulation of the coagulation cascade in cancer. There is evidence that the activation of hemostasis in malignant disease contributes to tumor growth and progression by stimulation of intracellular signaling pathways. Cancer cells utilize hemostatic constituents for their growth progression, and this involves multiple pathways. Cancer cells have a growth advantage with reduced sensitivity to programmed cell death-apoptosis. They also develop functions of increased motility and cellular adhesion. It has been well established that the essential factors of hemostasis (e.g. coagulation, fibrinolytic proteins, and platelets), apart from their pro-coagulant effects, directly play a role in these processes. However, fibrin formation itself is essential as a supportive scaffold for angiogenesis that ensures the tumor's oxygen supply.

The risk factors for VTE in cancer patients have been grouped into patient-related (older age, female sex, race, comorbidities, lower performance status), cancer-related (site, advanced stage, histology, period after diagnosis), treatment-related factors (major surgery, hospitalization, hormonal therapy, chemotherapy, transfusions, etc.), and candidate biomarkers of the risk of thrombosis have been identified and validated.

Venous Thrombosis in Cancer Patients from African Reports

There have been reports of venous thrombosis from some centers in Africa as case reports, clinical experience of radiological diagnosis and treatment, postmortem findings of hospital deaths and risk groupings of hospitalized patients.

Early retrospective reports from Ibadan, Nigeria by Awotedu et al. in 1992, of pulmonary embolism in postmortem reports, showed a prevalence of 3.2% and cancer was one of the major predisposing factors. Another retrospective report of 989 autopsies 10 years after Awotedu et al.’s report, from the same center, recorded 2.9% as the prevalence of venous thrombosis in postmortem cases, and malignancy was the most common predisposing factor in 37.9% of the cases.

Apart from postmortem reports, some clinicians have reported their findings of predisposing factors and treatment of patients with thromboembolic diseases. Retrospective reports of management of sixty patients seen between 1986 and 1990 at the University College Hospital Ibadan did not include malignancy as a predisposing factor. However, a revisit to the subject in the same facility, 17 years later (2007–2012) reported an increase to 178 cases of DVT treated in the hematology department, and cancer patients made up to 12.2% of cases treated; prostate cancer patients were most affected. A report of the clinical and sonographic features of VTE as diagnosed in Cameroun by Kingue et al. showed neoplasia as one of the important risk factors in 22.2% of the patients evaluated.
Muleledhu et al. in Uganda carried out a prospective study of DVT following major abdominal surgery for 82 patients. They found that 5% had DVT postsurgery and cancer was the commonest risk factor.²⁹ Fall et al. also did a 3 year cross-sectional case–control study of patients admitted to emergency wards on account of DVT or PE, in various hospitals in Dakar, Senegal.³⁰ Their results showed that cancer was a risk for VTE in 3.81% of the 105 patients evaluated during the study. The patients in this study were drawn largely from medical units and not surgical units. Another retrospective review of 865 Doppler ultrasound scan of patients suspected to have DVT in a South African public hospital showed that of 685 of them were confirmed to have DVT, 4.1% of them were patients who had a concomitant diagnosis of cancer.³¹

From the reports from different countries in Africa [Table 1], there is evidence to confirm that thromboembolic disease is significant comorbidity in cancer patients, and it is associated with substantial mortality. It will be expedient for clinicians in oncology care in Africa to have more awareness of this condition and risk assess their cancer patients for this condition. A risk stratification model developed by Khorana utilizes the site of tumor and laboratory indices that can be evaluated in most hospitals in Africa–leukocyte counts, platelet count, hemoglobin level, D-dimer and others biomarkers like soluble P-selectin and tissue factor levels²²,²³ (which may not be routinely done in most of our hospitals). This model has been validated in many populations and has been used to predict cancer patients at high risk of VTE and thromboprophylaxis has been shown to be effective in reducing mortality.

Table 1: Studies from Africa on deep venous thrombosis

| Study            | Country | Design   | Population                                          | Number of cases | Number of cancer patients (%) |
|------------------|---------|----------|-----------------------------------------------------|-----------------|------------------------------|
| Awotedu et al.²⁶ | Nigeria | Retrospective | Postmortem findings of patients with PE               | 60              | -                            |
| Sotunmbi et al.²⁶| Nigeria | Retrospective | Records of postmortem reports of 989 hospital deaths | 29              | 11 (37.9)                   |
| Kotila et al.²⁷  | Nigeria | Retrospective | Review of treatment of DVT and PE                    | 178             | 22 (12.2)                   |
| Kingue et al.²⁶  | Cameroon| Retrospective | Sonological findings of suspected DVT                | 18              | 4 (22.2)                    |
| Muleledhu et al.²⁶| Uganda | Prospective | Evaluating incidence of DVT in 82 patients postmajor abdominal surgery | 4              | 4 (100)                    |
| Fall et al.²⁹    | Senegal | Prospective | Evaluating DVT in patients admitted for DVT in emergency wards | 105            | 4 (3.81)                   |
| Alsheiri         | South Africa | Retrospective | Sonological findings in suspected DVT | 685            | 4.1                         |

DVT - Deep venous thrombosis, PE - Pulmonary embolism

reiterate the need for more robust multicenter studies to test risk stratification models and their applicability in our setting. In most African communities where patients do out of pocket expenses for their treatment because of nonexisting cancer policies, subsidies on anticancer medications, health insurance schemes, thromboprophylaxis for at-risk cancer patients as well as early detection and treatment of cancer-related thrombosis could be a cost-effective strategy to reduce morbidity as well as improve the quality of life of these patients.

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Conflicts of interest
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