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Incidence and Frequency of Vascular Events in Oncology Patients in Qena University Hospital

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Abstract

Objective: To detect the incidence and frequency of vascular events as deep venous thrombosis (DVT), venous thromboembolism (VTE) and arterial thrombosis in cancer patients admitted to Qena University Hospital.

Patients and Methods: A retrospective study was conducted on 2500 cancer patients from July 2013 to January 2017 and patients were classified into two groups, the venous group and the arterial group according to patient clinical presentation. These patients with VTE were treated with injectable enoxaparin 1 mg/kg/day for 5-7 days, followed by warfarin 4-6 months or longer and in those with arterial thrombosis causing leg ischemia, trial surgical thrombectomy was done in 2 patients and 2 have undergone percutaneous transluminal angioplasty (PTA) and 1 has undergone surgical bypass but soon thrombosed on day 10th postoperative, about 6 patients have undergone major amputation, the remaining 4 patients with arterial thrombosis died within treatment course.

Results: Out of 2500 cancer patients admissions, 645 patients (representing 25.8% of total admissions) were found to have different vascular events. Age distribution was 5-60 years, 439 were females and 206 male (female to male ratio was 2:1). Fifty two patients had haematological tumors while 593 patients had solid organ tumors. Seventy five patients were found to have arterial event (about 11.6%), while 570 cancer patients (88.37%) had venous event (with significant difference, as p value less than 0.0001). Significant relation was found between incidence of vascular events and surgery followed by chemotherapy where p value was<0.0001 while with radiotherapy it was non-significant p value>0.0001 (0.161).

Conclusion: DVT/VTE occurs frequently in patients with malignancy. All cancer patients should be regularly assessed for risk of DVT/VTE as a routine procedure for hospital attendance. Acute arterial thrombosis although rare, in the presence of active malignancy carries a very bad prognosis.

Keywords: Malignancy; Venous; Arterial; Thrombosis

Introduction

It is well known since the 19th century that oncology patients have an increased risk for venous thromboembolism (VTE), compared with those without cancer [1]. Furthermore, the malignancy pro-thrombotic state may be increased by chemon, hormonal therapy and surgery [2-4]. Moreover, cancer associated thrombosis had a poor prognosis. It is the second leading cause of mortality in oncology patients [5]. In a previous epidemiological study, nearly 20% of new VTE cases are associated with underlying malignancy, whereas 26% of incident cases had idiopathic VTE [6,7]. The relative risk of VTE occurrence is approximately seven times higher in patients with active malignancy [8-14].

Some cancers are associated with a higher DVT incidence than others, these are pancreas, ovary, liver (primary), brain, lymphoid tissue and bone marrow (polycythaemia vera) malignancies [15,16]. However, as there is higher incidence of prostate and primary lung cancer , these cancers are the most frequently found among DVT patients 15-17 .The risk of VTE in oncology patients varies according to specific disease factors as location, type, and stage of malignancy [17,18].

Regarding arterial thrombosis, few cases in the literature were reported. In one study which included 311 patients with pancreatic cancer, only two patients (0.006%) developed arterial thrombosis [19]. In a second study, 192 patients presenting over a period of 1.5 year with critical limb ischaemia (CLI) were examined and investigated for occult malignancy markers [20]. Of them, 22 patients (11.5%) were confirmed to have an underlying malignancy. Ten presented with acute ischaemia and 12 had chronic ischaemia. The difference between the groups was not statistically significant.

We aim in this study to determine the incidence and frequency of vascular events in oncology patients. The association between cancer and VTE could be explained by the fact that tumor cells induce a hypercoagulability state thus promoting tumor growth and metastasis [21].The classic VTE treatments are vitamin K antagonists and low molecular weight heparins administration [22]. Further, anticoagulants could show antineoplastic effects, when given for prophylaxis in long-term [23]. Regarding arterial thrombosis, pathogenesis is complex and multifactorial in cancer patients and its treatment is variable [24].

Patients and Methods

This retrospective study was performed on 2500 known cases of cancer who had been admitted in Qena University Hospital from July 2013 to January 2017. Out of 2500 patients, 645 patients with malignancy associated vascular events were recruited in the study. Inclusion criteria were malignancy with clinical picture of venous or arterial thrombosis. Biopsy proven malignancy was required for all patients. Patients' data included their age, sex, underlying diseases such as chronic lung disease, congestive heart failure (CHF) and inactivity (defined as being bedridden for at least three days) , oral contraceptive pills (OCP) consumption, hormone replacement therapy (HRT), and previous history of DVT or arterial occlusion, site of tumor, pathology of cancers were recorded. Routine baseline investigations including complete blood picture, liver & renal functions, ECG and X-rays were done on all patients.

Diagnosis of VTE/DVT was based on history, physical examination and diagnostic ultrasonography, cerebral venous thrombosis was confirmed via magnetic resonance venography while arterial thrombosis was diagnosed clinically, duplex ultrasound and CT angiography in some cases. Regarding cerebral vascular events, CT brain was done in some cases and CT abdomen in cases of portal vein thrombosis. Methods of cancer treatment whether chemo, radiotherapy alone or combined or surgical were all recorded. Code of ethics was achieved and all patients' informations were kept confidential. Treatment protocol of patients diagnosed with VTE/DVT included Inj. Enoxaparin 1 mg/Kg body weight subcutaneously twice daily for 5-7 days. Warfarin was started at the same time then continued for 4-6 months and longer periods, depending upon the non-resolution of the thrombus confirmed by duplex ultrasound and activity of underlying malignancy.

While those with arterial thrombosis causing leg ischemia, trial surgical thrombectomies were done in 2 patients and 2 have undergone PTA and 1 has undergone surgical bypass but soon thrombosed on the 10th day postoperative, about 6 patients have undergone major amputation, the remaining 4 patients with arterial thrombosis died within treatment course. Those with mesenteric vascular occlusion (MVO), laparotomy was done and resection of gangrenous loops and anastomosis of viable loops of intestine was achieved with poor outcome due to advanced cancer process where 2 patients complaining of MVO died. Regarding cerebral vascular stroke, neuro consultation was done with bad prognosis as 17 patients from 20 died.

According to the patients' number who had venous and arterial thrombosis, we calculated the incidence and frequency of VTE/DVT and arterial thrombosis and measured the correlation between the VTE/DVT and arterial thrombosis and patients' variables as well as the tumour type and site and method of cancer treatment.

Data were analyzed by SPSS (v.16, SPSS Inc., Chicago, IL, USA). Independent variables for each group were collected with descriptive analysis. Intergroup comparisons of demographic data, pathologic pictures, cancer location, and treatment modalities were performed with Chi square test. Fisher's test was used for finding the correlation between risk factors and DVT/VTE and arterial thrombosis. In all tests, P value<0.0001 was considered as statistically significant level.

Results

From 2500 cancer patient's admissions from July 2013 to January 2017, 645 patients (25.8% of total admissions) had malignancy with vascular events, VTE/DVT in 570 patients (about 88.37%) and arterial events in 75 patients (about 11.6%). Patients' age distribution was 5-60 years, with mean age of 35 years. Gender distribution was 206 male patients 439 female patients (female to male ratio is about 2:1).Primary cancer location and associated vascular events are shown in Tables 1-3.

Tumor type	Venous event	Arterial event
Solid organ tumors		
1. Breast cancer	82	12
2. Pelvic malignancy (rectum, urinary bladder & gynecological)	158	10
3. Brain Tumors		
4. Head &neck		
5. Lung cancer	50	3
6. Hepatocellular	44	4
7. Upper GIT	84	6
8. Renal malignancies	100	26
Haematological malignancies		
1. Non-hodgkin's lymphoma	26	3
2. Multiple Myeloma	6	7
3. Chronic Myeloid Leukemia	15	2
4. Myelofibrosis	5	2

Table 1: Shows cancer site and associated vascular events.

Vascular event	Number of patients	Percentage to total cases suffered vascular events
Deep venous thrombosis (DVT)	326	50.54%
Portal venous thrombosis	52	8%
Jugular venous thrombosis	10	1.5%
Splenic venous thrombosis	10	1.5%
Superficial thrombo- phlebitis	182	28.21%

Peripheral vascular disease	12	1.8%
Mesenteric vascular ischemia	02	0.31%
Acute limb ischemia	15	2.32%
Carotid artery occlusion	05	0.77%
Cerebral ischemia	10	1.5%
Pontine ischemia	01	0.15%
Cerebrovascular hemorrhagic stroke	20	3.1%

Table 2: Shows number and percentage of vascular events to different cancer types.

	Venous event	Arterial event	Total	OR(95% CI)	P value
Patient related factors					
Sex				1.175(0.774-1.782)	>0.0001 (0.409)
Male	133	18	151		
Female	437	57	494		
Age, y				0.904(0.697- 1.171)	>0.0001 (0.459)
5-19	44	3	47		
20-39	177	19	196		
40-60	349	53	402		
Underlying disease	397	34	431		<0.0001
OCP consumption	27	5	32		<0.0001
HRT	53	2	55		<0.0001
Physical inactivity	237	19	256		<0.0001
Previous vascular event	199	11	210		<0.0001
Cancer related factors					
Site of cancer				1.02(0.963-1.092)	<0.0001
Breast	82	12	94		
Pelvic	158	10	168		
Brain	50	3	53		
Head&Neck	44	4	48		
Lung	84	6	90		
Hepatic	13	9	22		
Upper GIT	69	10	79		
Renal	18	7	25		
Non- hodgkin's lymphoma	26	3	29		
Multiple Myeloma	6	7	13		
Chronic Myeloid Leukemia	15	2	17		

Myelofibrosis	5	2	7		
Pathology				1.03(0.944-1.13)	<0.0001
Small cell carcinoma	299	15	314		
Adenocarcinoma	113	13	126		
Squamous cell carcinoma	47	5	52		
Leukemia	13	7	20		
Lymphoma	11	8	19		
Sarcoma	20	3	23		
Breast carcinoma	60	22	82		
Others	7	2	9		
Treatment related factors					
Surgery followed by Chemotherapy	495	68	563		<0.0001
Radiotherapy	490	50	540		>0.0001 (0.161)

[a]Data are presented as numbers

[b]Abbreviations: OR: Odds ratio,OCP: Oral contraceptive pills, HRT: Hormonal replacement therapy

Table 3: Shows the frequency of vascular events based on patients' variables, cancer factors and treatment modalities.

Vascular events either venous or arterial were prevalent among female patients more than males (p value>0.0001) and more common in the age group (40-60Y) than other age groups with non-significant difference either (p value>0.0001).

Patients with pelvic malignancy had the highest frequency of vascular venous events and regarding tumor pathology, small cell carcinoma was the commonest pathology while vascular arterial events was high in breast cancer patients and regarding pathology, breast carcinoma was the commonest with significant difference (p value<0.0001).

Regarding modalities of treatment, either chemo, radiotherapy and surgery were associated with increased risk of vascular events, however surgery and chemotherapy had stronger association with vascular events (mainly venous) than radiotherapy with significant difference (p value<0.0001).

Regarding death rate of oncology patients due to vascular events, 20 cases representing 3% of total patients died most of them were due to pulmonary embolism (PE) and pelvic organ tumours patients representing the highest death rate as 17 patients of death from total deaths (20) due to vascular events rather than cancer type (with non-significant importance).

Discussion

Venous thromboembolism (VTE) is a critical cause of both morbidity and mortality in oncology patients [25]. Inspite of the fact that deep vein thrombosis (DVT) and pulmonary embolism (PE) are the most common vascular thrombotic complications, other vasculatures, such as the upper extremity and splanchnic veins could also be affected. A steady increase in the incidence of cancer-associated thrombosis during the past 2 decades is noted with increasing either age, cancer prevalence in the population, increase detection of incidental thrombosis and finally greater thrombogenicity of chemotherapeutic agents [18].

As a leading cause of death in oncology patients [26] thrombosis is associated with higher mortality risk, irrespective of cancer stage [27,28].

In our study, regarding the venous events, VTE and DVT are the most frequent events among cancer patients (representing 50.54% of total events) followed by other venous territories including portal (8%), jugular (1.5%) and splenic (1.5%) veins in addition to superficial thrombophlebitis in 182 patients representing 28.21% of total events. The location of the thrombus in other venous territories in our study was markedly different than other literatures as in the study by Sadaf et al. they concluded that out of 35 patients, 2 patients with polycythemia rubra vera had hepatic vein thrombosis and in 1 patient diagnosed as CML (chronic myeloid leukaemia) cerebral venous thrombosis, confirmed by MRV (magnetic resonance venogram) was found [29]. This is perhaps due to our big sample size.

Regarding arterial events, Schattner concluded that arterial thrombosis is a terminal event in pancreatic cancer patients [19]. In El-Sakka's study half of the cancer patients with arterial thrombosis died within six months [20] and this is comparable with our study as in our cancer patients associated with arterial thrombosis 4 patients with acute limb ischemia out of 15 patients(nearly one third) died within treatment course and this indicates the bad prognosis of cancer patients associated with arterial thrombosis while the rest 60 patients with arterial events survive during the follow up period and death happened due to the cancer process itself in many cases. Campbell discusses the dilemmas involved when making these difficult decisions and advises palliative care in advanced cases when acute limb ischaemia is just one part of a terminal illness [30].

Although the number of patients with arterial vascular events was low, our study suggested that conservative approach may be the most suitable. The severity of ischaemia caused by thrombosis may prove that anticoagulation or palliative treatment only is more appropriate.

Inspite of vascular events found more commonly in females over forty, the association between them and either sex or age was insignificant. Pelvic cancer patients had the highest rate of vascular venous events while breast cancer patients had the highest arterial event. Either event was identified more in some pathologic varieties such as small cell carcinoma, adenocarcinoma, and squamous cell carcinoma, in order. In addition, our study demonstrated the passive effect of inactivity, OCP and HRT and previous vascular events history on developing vascular events. Different treatment modalities whether surgery, chemotherapy and radiotherapy were associated with increased vascular events risk; however, they had stronger association with venous than arterial events. Prevalence of venous events (about 88.37%) was more than arterial (about 11.6%) and with more involvement of females than males and the prevalence of venous events per se was comparable to previous studies in Phlippine (0.45%), Netherland (1.23%) and United States (3.4%) [31-33] although our study had a smaller sample size than these studies. Also in these studies we should notify that they aimed to find the prevalence of VTE and DVT alone but in our study we searched for the arterial events as well. And as our patients were hospitalized for surgery, chemo or radiotherapy, or disease progression; so, they were not the representative of the total population of patients with cancer, which could explain the higher prevalence rate of vascular events especially venous ones in this study in accordance with the previous mentioned studies.

Although the risk of vascular events especially VTE increased with age, there was not any correlation between age and the prevalence of vascular events in our study. In many studies, age was an independent risk factor for VTE namely in hospitalized patients with cancer [2,34,35]; however, advanced age was not an important risk factor in some other retrospective studies [3,36,37]. This difference might be due to different sample size for estimation of this association or delayed cancer diagnosis in some of those studies. The increasing rate of vascular events especially VTE with age might be due to the increasing rate of risk factors such as hypertension, chronic renal disease, chronic liver disease, CHF, and inactivity with age or difference in pathologic type or location of cancer in different age groups.

We could not find an association between prevalence of vascular events and sex, but both were seen more frequently in females. There are converse findings in the literature regarding this for venous events; as many studies have declared higher percentage of VTE in males comparable to females, a newer combined study has found the reverse result and some studies have reported similar sex ratio [3,38-40].

For arterial events, we couldn't find many studies in the literature searching for the prevalence of them among cancer patients and their predominance in either sex. But there are two studies regarding arterial thrombosis in cancer patients. The first one searched at a series of 311 pancreatic adenocarcinoma patients, two (0.006%) of whom developed arterial thrombosis [19]. While in the second, 192 patients presenting over 18 months with critical limb ischaemia (CLI) were evaluated and scanned for markers of hidden malignancy [20]. Of them, 22 (11.5%) were confirmed to have an underlying malignancy. Ten presented with acute limb ischaemia and 12 had chronic limb ischaemia. The difference between the groups was not significant.

In our study, the vascular events prevalence was higher (89.76%) in patients with solid tumors than in those with hematologic malignancies (10.23%). Some other studies declared similar prevalence in patients with solid and hematologic tumors [41]. Our hematologic cancer patients were younger or had less underlying diseases and with small number (52 patients) in comparison with those with solid cancers. In the present study, vascular events prevalence showed difference based on site of tumor; the highest proportion of venous events cases was seen in the pelvic cancer followed by lung and breast, upper GIT, brain, head and neck, and finally renal cancers, consecutively. This finding is almost different from others; for example, in one study cancers of pancreas, other abdominal tumors, ovary, and kidney tumors had the highest risk of venous events namely DVT, consecutively [31]. In another study on hospitalized patients, the most prevalent tumors were pancreatic tumors, lymphoma, and brain malignancies [2]. While some studies showed that pancreatic cancer is associated with the highest prevalence of DVT [3,31], according to available studies, lung cancer has the high prevalence of DVT, especially during chemotherapy (7.3-24%). Although lung cancer does not have the highest prevalence among all cancers [40,41-43], it had the highest prevalence in some studies [32,33]. DVT prevalence increases with the tumor stage advancement, cancer chemotherapy, and non-small cell carcinoma [41]. In one study on Arabic cancer patients, the most common thrombosis-associated malignancies were breast, non-Hodgkin's lymphoma, and lung cancer consecutively and majority of DVT cases had developed in advanced stages of disease [31]. According to a large study on ambulatory high-risk cancer patients undergoing chemotherapy in the United States. Stomach, pancreas, and lung cancers were associated with very high risk of DVT (15.8%, 19.2%, and 13.9%, respectively) [44].

Regarding arterial events, the highest percentage was seen in breast, pelvic, upper GIT, hepatic, lung, head and neck and finally brain tumors. In different literatures, different types of malignancies were present and no deduction can be made to tumors most likely to present with arterial thrombosis. In El-Sakka's study the most common malignancy was lung cancer and it had recommended routine chest radiography in critical limb ischemia (CLI) patients [20].

The most common cancer in our study was pelvic malignancy cancer. As in our study pelvic malignancy included many organs' tumors (as rectum, urinary bladder & gynecological tumors) followed by breast cancer, which perhaps related to the common use of adjuvant therapy in those patients. In one study, breast cancer premenopausal patients are more likely to complain of arterial thrombosis if they have received both tamoxifen and chemotherapy compared with chemotherapy alone [45].

Some literatures report that some cancer patients could present with both arterial and venous thrombosis [46,47], but in our patients we didn't face such condition.

Conclusion

Since venous events prevalence rate was higher in cancer patients than arterial, a revised guideline to start early anticoagulation is seem necessary in hospitalized patients with cancer who are supposed to either undergo surgery or receive chemotherapy, especially in those with certain underlying diseases, cancer site, or pathologic findings. Arterial thrombosis in the presence of active malignancy carries a very bleak prognosis. The outcomes from surgery are poor. Careful

consideration of palliative care may be appropriate as arterial thrombosis is an agonal event in cancer patients.

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