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RESEARCH ARTICLE

Chemoprophylaxis after Oncological Resections

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Abstract:

Background National societies recommend extended-duration VTE chemoprophylaxis for up to 4 weeks following major oncologic resections with the literature demonstrating an incidence of approximately 2% for symptomatic VTE. Despite this, patients are not routinely discharged on VTE chemoprophylaxis at our institution.

Methods A retrospective chart review was performed for major abdominal oncologic resections, including esophagectomy, at an academic community cancer center between 2015 and 2020. The primary outcome was clinically evident VTE events within 30 days of discharge. Exclusion criteria included in-hospital mortality, in-hospital VTE, or discharge on anti-coagulation. Comparisons were performed using Fisher's Exact and Mann-Whitney test.

Results After exclusion criteria were applied, 458 patients were identified. A total of 6 (1.3%) patients developed symptomatic VTEs, 5 (1.1%) PEs and 3 (0.7%) DVTs. No procedural interventions were required. On average, patients re-presented 14.3 (±8.4) days after discharge. There were no mortalities within 30 days of discharge. Intraoperatively, estimated blood loss in VTE group was decreased (150 vs 88 mL, p=0.01), while length of inpatient hospitalization (6.5 vs 10 days, p=0.05) was increased. Type of operation demonstrated an increased proportion of esophagectomy (9.6% vs 16.7%, p=0.57), palliative bypass (8.1% vs 33.3%, p=0.08) and small bowel resection (7.9% vs 33.3%, p=0.08) in the VTE group.

Conclusion The percentage of symptomatic VTEs in our patients was not higher then reported averages despite no patient receiving chemoprophylaxis. Questions remain as to which subset of patients would benefit from chemoprophylaxis after major abdominal oncologic resection. Further investigation into long term effects of asymptomatic DVT should be undertaken.

Keywords: VTE prophylaxis, Oncologic resection, DVT

Introduction

Venous thromboembolism (VTE), comprised of lower extremity deep vein thrombosis (LE DVT) and pulmonary embolism (PE), is commonly cited as a leading cause of preventable deaths in cancer patients (1,2). Cancer patients are reported to be at even higher risk in the post-surgical period compared to non-cancer patients undergoing similar operations (3-5). The overall rate of VTE in the postoperative oncologic patient has been reported to be between 1.3-2% (6,7).

In response to this risk, the American Society of Hematology, CHEST, and the American Society of Surgical Oncology (SSO) guidelines recommend extended-duration (3-4 weeks) VTE chemoprophylaxis for patients undergoing major abdominal and pelvic oncologic operations (8-10). Although these recommendations are widely promulgated and come from prominent societies, only a small percentage (1.5% to 13.0%) of post-operative cancer patients in the United States are discharged with a prescription for extended-duration VTE chemoprophylaxis (11-13).

The current recommendations rely on evidence from studies whose subjects are majority cancer patients who underwent major thoracic, abdominal or pelvic operations (14-21). However, the design and data reported in these studies make clinical interpretation difficult. While all these trials demonstrated a reduction of asymptomatic DVTs on ultrasound with extended-duration VTE chemoprophylaxis, the clinical impact of identifying an asymptomatic DVT is uncertain (9, 22). The location of the DVT, proximal or distal, has been suggested to impact the long term consequences with some evidence that distal asymptomatic DVT's may be self-limited without treatment (23-25). Additionally, and most importantly, studies do not demonstrate a statistically significant reduction in outcomes of mortality, PE or symptomatic DVT when patients receive chemoprophylaxis (6, 14-21).

Based on the poor national compliance and uncertain evidence supporting the guidelines, we wanted to see if our population of patients, who are not routinely prescribed extended duration VTE prophylaxis, are negatively affected. We decided to conduct a retrospective review on post-oncologic resection patients at our academic community cancer center to investigate the number of VTEs events. Our hypothesis was that our VTE rates of post major oncologic surgical patients without chemoprophylaxis would be the same as the 1.3-2% cited in literature.

Methods

Approval to conduct the study was obtained from our Institutional Review Board. Data were extracted from the Electronic Health Records (EHR) using procedure codes for all major oncologic abdominal or pelvic operations at our academic community cancer center between 2015 to 2020. Patients were included if they underwent a major abdominal or pelvic surgery for malignancy, including retroperitoneal resections, abdominothoracic esophagectomies, or hyperthermic intraperitoneal chemotherapy (HIPEC), with either a surgical oncologist or thoracic surgeon. Patients who had an initial biopsy with malignancy were included even if there was no residual disease found by pathology in the surgical specimen.

Patients were excluded if they did not have a malignancy (no confirmatory pathology available), died during hospitalization, had a minor procedure (<24 hour stay, diagnostic laparoscopy or laparotomy with biopsy only), had an in-hospital VTE, or were admitted or discharged on therapeutic anti-coagulation.

The primary outcome was VTE (LE DVT or PE) within 30 days of discharge and diagnosed on admission to the Emergency Department or to the hospital. Secondary outcomes were post discharge death and major bleeding events. Demographic information and co-morbidities determined according to the Elixhauser algorithm (REF) were extracted from the EHR. Charts were subsequently reviewed for patients' preoperative and surgical characteristics.

Major bleeding was defined as causing death, a fall in hemoglobin concentration by 2g/dL, requiring ≥2 units of blood, requiring surgical or medical intervention, or occurring in a critical area or organ (intracranial, intraspinal, intraocular, retroperitoneal, pericardial) (17, 20).

Continuous variables were compared between patients with and without outcomes using Mann-Whitney tests and categorical variables using Fisher's exact test.

Results

A total of 1325 patients were identified after our initial screen and narrowed to those performed by a surgical oncologist or thoracic surgeon. After exclusion criteria, 458 patients met inclusion criteria and were reviewed for the study (see Figure 1). Patients' surgical and postoperative characteristics are described in Table 1.

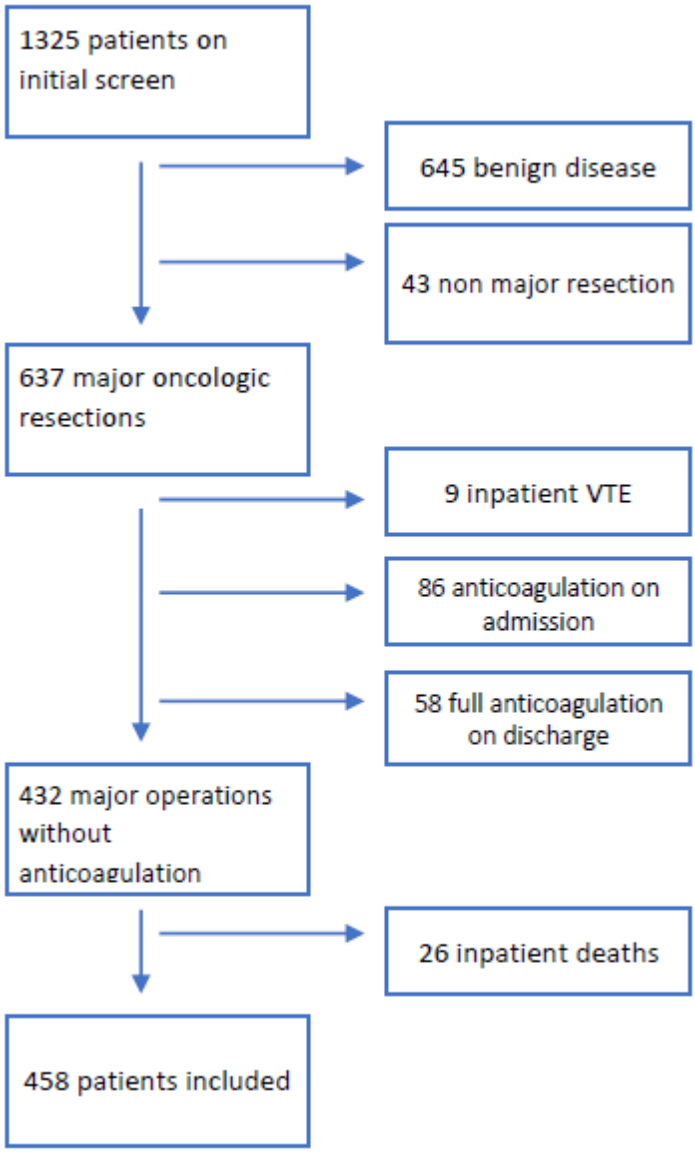

Figure 1: Flow chart of patients inclusion and exclusion

Table 1. Demographic characteristics of all patients

		All patients (n=458)
Age, mean (SD)		65.2 (12.3)
Sex (M), n(%)		251 (54.8)
Race, n(%)	White	317 (69.2)
	African American	107 (23.4)
	Asian	16 (3.5)
	Other	18 (3.9)

BMI, mean (SD)		29.3 (6.9)
Coronary Artery Disease, n(%)		65 (14.2)
Congestive Heart Failure, n(%)		32 (7.0)
Chronic Lung Disease, n(%)		121 (26.4)
Coagulopathy, n(%)		40 (8.7)
Diabetes Mellitus, n(%)		122 (26.6)
Hypertension, n(%)		288 (62.9)
Liver disease, n(%)		148 (32.3)
Elixhauser Comorbidity Count, mean (SD)		5.5 (3.6)
Open Surgical Approach, n(%)		380 (84.1)
Emergency Surgery, n(%)		13 (2.8)
Operative Time (minutes), median (range)		193 (39-872)
Surgery, n(%)	Pancreatectomy	128 (27.9)
	Gastrectomy	74 (16.2)
	Hepatectomy	47 (10.3)
	Esophagectomy	45 (9.8)
	Palliative bypass	39 (8.5)
	Small bowel resection	38 (8.3)
	Colectomy	37 (8.1)
	Other	50 (10.9)
Received Neoadjuvant Treatment, n(%)		153 (33.4)
Stage, n(%)	1	98 (21.4)
	2	108 (23.6)
	3	116 (25.3)
	4	107 (23.4)
Tumor Stage, n(%)	1	60 (13.1)
	2	103 (22.5)
	3	128 (27.9)
	4	59 (12.9)
Length of Stay (day), median (range)		6.5 (1.1-169)

Received In Hospital VTE prophylaxis, n(%)		453 (98.9)
Length of In Hospital VTE prophylaxis, median (range)		5 (1-156)
Discharge disposition, n(%)	Home	408 (89.1)
	Rehab/Long Term	41 (9.0)
	Hospice	9 (2.0)
<30d Readmission, n(%)		111 (24.2)

SD=standard deviation; M=male; BMI= body mass index

Primary outcome

Of the 458 patients, 6 (1.3%) patients with VTE events were identified. Out of those 6 patients, there were 5 (1.1%) PEs and 3 (0.7%) DVTs. The median time between discharge and re-admission was 14.3 days (± 8.4) and the median re-admission length of stay was 6 days (range 1-44 days). No VTE patients required interventional procedures. Individual VTE details are presented in Table 2. All of the VTE patients were otherwise healthy, had uncomplicated primary hospitalizations and were on VTE prophylaxis throughout their initial hospitalization.

Table 2. Details of patients readmitted with VTE

Age	Sex	Diagnosis	Surgery	Stage	Surgical Time (min)	EBL	Inpatient VTE ppx (d)	Readmit Reason	PE	DVT	Time to VTE (d)	Readmit LOS (d)	Intervention
56	F	GE junction adenocarcinoma	MI Ivor Lewis Esophagectomy	ypT1aN0M0	221	100	8	PO intolerance	Y (central)	N	12	14	Heparin GTT-> Enoxaparin
63	F	Pancreatic adenocarcinoma	Robotic-> Open Distal Pancreatectomy	pT2N1M0	166	75	5	Shortness of breath	Y (seg)	Y (iliac)	20	1	Enoxaparin
65	M	Esophageal adenocarcinoma	Open LOA, SBR, Aborted Esophagectomy	cT1N0M0	418	4000	9	Shortness of breath	Y (central)	Y (CFV, Fem, TP, PT)	20	6	ICU, Enoxaparin
71	F	Breast lobular carcinoma	Open GJ Bypass	No specimen M1*	87	10	5	Shortness of breath	Y (central)	N	2	44	Heparin GTT-> Hematemesis -> IVC filter
74	M	CLL	Open SBR	No specimen	59	250	9	Ureteral stone	N	Y (CFV)	24	6	Abixaban
80	F	Cholangio-carcinoma	Open GJ Bypass	No specimen M1*	130	75	15	Fall with sacral fractures	Y (seg)	N	8	3	Enoxaparin

EBL= Estimated Blood Loss; VTE=Venous Thromboembolism; ppx=Chemoprophylaxis; PE=Pulmonary Embolism; DVT=Deep Vein Thrombosis; LOS=Length of Stay; GE=Gastroesophageal; MI=Minimally Invasive; GTT=Infusion; Seg=segmental; LOA=Lysis of Adhesion; SBR= Small Bowel Resection; CFV= Common Femoral Vein; Fem= Femoral; TP= Tibial Peroneal; PT= Posterior Tibial; ICU= Intensive Care Unit; GJ=Gastrojejunal; IVC= Inferior Vena Cava; CLL= Chronic Lymphocytic Leukemia; *M1- biopsy specimen confirming metastatic cancer

Secondary outcomes

No patient died within 30 days of discharge. One patient (0.2%) was readmitted for major bleeding; 66 year old male who underwent an open gastrojejunal bypass for recurrent, metastatic pancreatic adenocarcinoma. He was readmitted with melena, transfused multiple units of packed red blood cells, underwent an esophagogastroduodenoscopy and mesenteric arteriography without identification of source, and eventually self-resolved.

Patient demographics

Patient characteristics were compared between those with and without VTE (Table 3). We did not find any statistical differences between the two groups when comparing age, sex, race and other patient demographics.

Table 3. Comparing demographic and patient characteristics of VTE and non-VTE patients

		non-VTE (n=452)	VTE (n=6)	p value
Age, mean (SD)		65 (12)	68 (8.6)	0.55
Sex (M), n(%)		203 (44.9)	2 (33.3)	0.69
Race, n(%)	White	312 (69.0)	5 (83.3)	1.00
	African American	106 (23.5)	1 (16.7)	
	Asian	16 (3.5)	0	
	Other	18 (4.0)	0	
Body Mass Index, mean (SD)		29 (6.9)	31 (7.1)	0.50
ASA, n(%)	2	70 (15.5)	1 (16.7)	1.00
	3	325 (71.9)	5 (83.3)	
	4	57 (12.6)	0	
Elixhauser Comorbidity Count, mean (SD)		5.4 (3.7)	6.2 (2.2)	0.63
Cardiac Arrythmia, n(%)		105 (23.2)	1 (16.7)	1.00
Coronary Artery Disease, n(%)		64 (14.2)	1 (16.7)	1.00
Congestive Heart Failure, n(%)		32 (7.1)	0	
Chronic Lung Disease, n(%)		120 (26.5)	1 (16.7)	1.00
Coagulopathy, n(%)		40 (8.8)	0	
Diabetes Mellitus, n(%)		120 (26.5)	2 (33.3)	0.66
Hypertension, n(%)		284 (62.8)	4 (66.7)	1.00

Pulmonary Circulation Disorder, n(%)	21 (4.6)	1 (16.7)	0.26
Renal Failure, n(%)	41 (9.1)	0	

SD= standard deviation; DVT=Deep Vein Thrombus; PE=Pulmonary Embolism; M=male; ASA=American Society of Anesthesiology Physical Status Classification System

Operative and post-operative characteristics

In examining surgical and postoperative factors (Table 4), there were 2 variables with statistically significant differences between non-VTE and VTE groups. Estimated blood loss was lower in the VTE group (150 vs 88 mL, p=0.01) whereas the length of inpatient hospitalization (6.5 vs 10 days, p=0.05) was higher in the VTE group. The type of operation, although not statistically significant, demonstrated an increased proportion of esophagectomy (9.6% vs 16.7%, p=0.57), palliative bypass (8.1% vs 33.3%, p=0.08) and small bowel resection (7.9% vs 33.3%, p=0.08) in the VTE group. There were no other statistically significant differences seen in other categories including receiving neoadjuvant treatment, type of cancer, oncologic stage, or positive margins.

Table 4. Comparing operative and post operative course characteristics between VTE and non-VTE patients

			non-VTE (n=452)	VTE (n=6)	p
Surgery	Open Surgical Approach, n(%)		375 (81.9)	5 (83.3)	1.00
	Emergency Surgery, n(%)		13 (2.8)	0	1.00
	Received Neoadjuvant Treatment, n(%)		150 (32.8)	3 (50)	0.41
	Cancer Location, n(%)	Pancreatic	111 (24.4)	1 (16.7)	1
		Gastric	114 (24.9)	1 (16.7)	1
		Colorectal	48 (10.5)	0	
		Duodenal	29 (6.3)	0	
		Small bowel	24 (5.2)	0	
		Bile duct	19 (4.1)	1 (16.7)	0.24
		Other	107 (23.7)	3 (50.0)	0.15
	Surgery, n(%)	Pancreatectomy	127 (27.7)	1 (16.7)	1
		Gastrectomy	74 (16.2)	0	
		Hepatectomy	47 (10.3)	0	
		Esophagectomy	44 (9.6)	1 (16.7)	0.57
		Palliative bypass	37 (8.1)	2 (33.3)	0.08

		SBR	36 (7.9)	2 (33.3)	0.08
		Colectomy	37 (8.1)	0	
		Other	50 (11.1)	0	
	Surgical Time (min), median (range)		193 (39-911)	148 (59-418)	0.39
	Estimated Blood Loss, median (range)		150 (3-3500)	88 (10-4000)	0.01
	Received Transfusion, n(%)		40 (8.7)	1 (16.7)	0.43
Pathology	Cancer Stage, n(%)	1	96 (21)	2 (33.3)	0.41
		2	107 (23.4)	1 (16.7)	1.00
		3	116 (25.3)	0	
		4	105 (22.9)	2 (33.3)	1.00
	No Residual Disease, n(%)		12 (2.6)	0	
	Positive Margins, n(%)		62 (13.5)	1 (16.7)	0.59
	Positive Lymph Nodes, n(%)		151 (33.0)	1 (16.7)	0.67
Postoperative Course	Length of Stay (d), median (range)		6.5 (1.1-169)	10 (6.2-21)	0.05
	Received In Hospital Chemoprophylaxis, n(%)		447 (97.6)	6 (100)	1.00
	Length In Hospital Chemoprophylaxis (d), median (range)		5 (1-156)	5 (2-14)	0.77
	Days Before Readmission*, median (range)		8 (0-30)	16 (2-24)	0.48
	Discharge Disposition, n(%)	Home	403 (88.0)	5 (83.3)	0.50
		Rehab/Nursing	40 (8.7)	1 (16.7)	0.43
		Hospice	9 (2.0)	0	

SBR= Small bowel resection; d=day; Readmission*- 105 patients for non-VTE patients (n=105)

Discussion

VTE, comprised of DVT and PE, is a well-known cause of postoperative oncologic morbidity and mortality with an often cited 2-fold increase in DVT and 3-fold increase in PE compared to similar nononcologic resections (5). As a result, many prominent societies recommend extended-duration VTE chemoprophylaxis following major oncologic resection, but with poor reported national compliance (8-10). Studies have theorized the underlying reasons for poor compliance are primarily insurance coverage of medication, limited anti-coagulation injection education, and physician prescribing patterns (11-13). However, the exact reason for the very low national compliance rate is unclear. In light of these published

findings, we investigated our own outcomes of symptomatic, post-oncologic resection VTE in patients who did not receive extended-duration prophylaxis and found 1.3% incidence of events which is in line with prior published rates (1.3-2%) (6,7).

Alignment with current literature

In trials which reported symptomatic VTEs, there was no statistical difference between the control (0.6%, range: 0-1.7%) and extended-duration VTE chemoprophylaxis (0.1%, range: 0-0.4%) regimens (14, 16-20). We wanted to confirm these results and see if our patient population was experiencing more complications from VTE's. Our outcomes demonstrated that our patients were not experiencing worse outcomes despite the lack of chemoprophylaxis.

One difficulty in comparing outcomes between the guideline-supporting trials and our study is the lack of data on the VTE patient's course or localization of VTE events. In our study, none of the patients required any procedural interventions and only two patients were started on a heparin infusion. In the other trials, no information on interventions required was reported making it difficult to determine the severity of the presenting events. Also, the studies do not characterize PEs which makes it difficult to interpret their significance as the morbidity, mortality risk and need for treatment vary greatly between central and subsegmental locations (26-30). Frequently fatal PEs are used in the argument for extended-duration VTE chemoprophylaxis (17, 31). In our cohort we had no incidence of fatal PEs and a lower than national reported rate of symptomatic PE (1.1%).

A strong reason to support extended-duration VTE chemoprophylaxis would be to decrease in mortality, however there were no post discharge mortalities, VTE related or otherwise, in our study. This is similar to the extended-duration VTE chemoprophylaxis trials, which also demonstrated no significant decrease in mortality with chemoprophylaxis (14, 15, 17-21).

The reason why a majority of patients nationwide are not prescribed chemoprophylaxis postoperatively is multifactorial including limited injection education, perceived cost, and physician judgement. The discomfort of self-injections and cost to the patient are the main reasons for patient non-compliance (32). Compliance with self-injections have been reported in orthopedic studies to be dependent on patients health insurance status or assistance at home (33). Cost analysis on extended duration VTE prophylaxis in both surgical and obstetrics literature demonstrates the cost to patient ranging from $10-$62, but limited data is present and cost widely varies based on insurance (34, 35). Additional published literature reports substantially higher costs with insurance where a patient can incur an out-of-pocket expense as high as $1,210 (35).

Despite the patient factors, physician judgement is reported as the biggest reason for lack of compliance with the recommendations (32, 11-13). While education has shown to improve prescribing practices, the lack of drastic outcome changes when extended chemoprophylaxis is not prescribed makes it difficult to convince providers to change their prescribing habits. In addition, while studies have not consistently demonstrated significant increased risk of major bleeding with chemoprophylaxis, the known risk of bleeding in cancer patients often gives pause for prescribing chemoprophylaxis (31). Our data contributes to literature that demonstrates no change in mortality for patients who do not receive extended duration chemoprophylaxis. We believe that the current literature does not

describe significant major deleterious short term or long term effects of not prescribing extended chemoprophylaxis.

Recommendations for clinical practice

Given the lack of evidence showing a reduction in clinically symptomatic VTE as well as the barriers to patient and physician compliance, we question the necessity of extended-duration VTE chemoprophylaxis. We therefore would recommend prescribing extended-duration prophylaxis on a case-by-case basis with detailed evaluation of the patient and their individual high-risk features. Perhaps further investigation should be undertaken to identify a more exclusive list of high-risk features for developing post operative VTE for patients undergoing major oncologic operations.

Another area that would help to determine the necessity of extended chemoprophylaxis would be investigating clinical significance of asymptomatic DVT in this patient population. Majority of the literature promoting extended duration chemoprophylaxis focus on the reduction of asymptomatic DVT. The trials cited by the guidelines clearly demonstrate a significant reduction in postoperative, asymptomatic DVTs with extended-duration VTE chemoprophylaxis (14-21), but currently literature is not conclusive for definitive long term complications due to these asymptomatic VTE's (22, 25).

Limitations

To determine a potential benefit to extended-duration VTE in high-risk subsets of our population, we compared the characteristics of those with and without VTE. However, the VTE events were so few in our study, that statistically significant conclusions are difficult to determine. Neoadjuvant treatment, gastric cancer, pancreatic cancer, or advanced stages of cancer have been previously linked to an increased risk of VTE, but that was not demonstrated in our study (36-38). Limited mobility after surgery is also discussed as a high risk feature, but this was not a factor collected in our data and therefore its effect could not be determined in our study. Further investigation with a larger sample size of patients would help to delineate these subsets of patients better.

Another limitation of this study is that some patients may have presented to an outside hospital. While our health care system is the largest in the state with an integrated health system and robust follow up data, it is possible that patients with symptomatic VTE's were missed. Despite this, it is likely that even with missed patients, our rate would still be lower than the 2% as reported in a large review by Agnelli 2006 (7).

Our study is a retrospective single center review and has inherent biases. As an institution, VTE prophylaxis is not prescribed, and the selection bias of patients may have effects on this study. However, we looked at numerous different operation types, oncologic cases and different surgeons included to help minimize these biases.

Disclosure

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