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THE EFFECTS OF CANCER'S METASTATIC STATUS AND CHEMOTHERAPY ON TOTALLY IMPLANTABLE VENOUS ACCESS PORT PATENCY AND PORT-RELATED VENOUS THROMBOEMBOLIC EVENTS

KANSERİN METASTATİK DURUMUNUN VE KEMOTERAPİNİN TAMAMEN İMPLANTE EDİLEBİLİR VENÖZ ERİŞİM PORTU AÇIKLIĞI VE PORT İLİŞKİLİ VENÖZ TROMBOEMBOLİK OLAYLAR ÜZERİNE ETKİSİ

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ABSTRACT

Objective: Totally implantable venous access port (TIVAP) is of great importance as a vascular access route in the treatment of cancer patients. In this study, we retrospectively researched the effects of cancer types, metastases, chemotherapeutic drugs, and intervention sites on port patency and TIVAP-related venous thromboembolism (VTE).

Method: Demographics, cancer types, metastases, vascular access sites, chemotherapy drugs, TIVAP patency and TIVAP related complications were evaluated in 297 patients who had TIVAP implanted and 37 patients who underwent removal in our clinic between 2017-2021.

Results: TIVAP implanted 297 patients were followed-up for a mean 17.7±16.6 months. TIVAPs were removed in 37 patients due to infection 14 (4.7%), occlusion 8 (2.7%), VTE 9 (3%), malposition 1 (0.3%), and treatment completion 10 (3.3%). TIVAPs of 270 (90.9%) patients were found to be usable for an average of 18.5±17.1 months. Complications of VTE, occlusion, infection and malposition developed in a total of 71 (23.9%) patients. In the comparison of development of these complications according to the presence of metastasis in patients, it was found to be that they were significantly higher in metastatic patients (47-27.9%/24-18.6%, $p<0.05$). There was a significant positive correlation between taxanes, methotrexate, etoposide and vinorelbine and the rate of VTE development compared to other chemotherapy drugs($p<0.05$). The rate of TIVAP associated VTE was found to be significantly higher in elderly patients, patients with metastatic cancer and patients with lung cancer ($p<0.05$). No significant difference was present in TIVAP patency, complications and TIVAP-related VTE, in terms of venous access site and side.

Conclusion: Primary cancer, metastases, and chemotherapy are important factors for the development of systemic or TIVAP-related VTE. More multicenter studies are needed for the prevention and treatment of VTE in certain types of cancer and chemotherapy regimens that increase the risk of TIVAP-associated VTE.

Key Words: Totally Implantable Venous Access Port, Venous Thromboembolism, Cancer

ÖZ

Amaç: Tamamen implante edilebilir venöz erişim portu (TIVAP), kanser hastalarının tedavisinde damar giriş yolu olarak büyük önem taşımaktadır. Bu çalışmada, kanser türlerinin, metastazların, kemoterapötik ilaçların ve girişim bölgelerinin, TIVAP açıklığı ve TIVAP ilişkili venöz tromboembolizm (VTE) üzerindeki etkilerini retrospektif olarak araştırdık.

Yöntem: 2017-2021 yılları arasında kliniğimizde TIVAP takılan 297 hasta ve çıkarma işlemi uygulanan 37 hastanın demografik özellikleri, kanser türleri, metastazları, damar girişim bölgeleri, kemoterapi ilaçları, TIVAP patensleri ve TIVAP'a bağlı komplikasyonları değerlendirildi.

Bulgular: TIVAP takılan 297 hasta ortalama 17.7±16.6 ay takip edildi. Enfeksiyon 14 (4.7%), okluzyon 8 (2.7%), VTE 9 (3%), malpoziasyon 1 (0.3%) ve tedavi tamamlanması 10 (3.3%) nedenleri ile toplam 37 hastada TIVAP çıkarıldı. 270 (90.9%) hastanın TIVAP'ı ortalama 18.5±17.1 ay süre ile kullanılabilir durumda saptandı. Toplam 71 (23.9%) hastada VTE, okluzyon, enfeksiyon ve malpozisyon komplikasyonları gelişti. Hastalarda metastaz varlığına göre bu komplikasyonların gelişimi karşılaştırıldığında, metastatik hastalarda anlamlı olarak yüksek saptandı (47-%27.9/24-%18.6, $p<0.05$). Özellikle taksanlar, metotreksat, etoposid ve vinorelbin ile VTE gelişme oranı arasında diğer kemoterapi ilaçlarına kıyasla anlamlı bir pozitif korelasyon saptandı ($p<0.05$). İleri yaş hastalarda, metastatik kanseri olanlarda ve akciğer kanseri hastalarında TIVAP ile ilişkili VTE oranı anlamlı yüksek saptandı ($p<0.05$). TIVAP açıklığı, komplikasyonları ve TIVAP ile ilişkili VTE'de venöz giriş yeri ve tarafı açısından anlamlı fark yoktu.

Sonuç: Primer kanser, metastazlar ve uygulanan kemoterapi, sistemik veya TIVAP ile ilişkili VTE gelişimi için önemli faktörlerdir. TIVAP ile ilişkili VTE riskini artıran belirli kanser türlerinde, kemoterapi rejimlerinde VTE'nin önlenmesi ve tedavisi için daha fazla çok merkezli çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Tamamen İmplante Edilebilir Venöz Erişim Portu, Venöz Tromboembolizm, Kanser

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INTRODUCTION

Totally implantable venous access port (TIVAP) are widely used in cancer patients for the administration of chemotherapy because of the advantages like being less visible, more acceptable for the patients, requiring less special care, and lower risk of complications, which have markedly improved the patients' quality of life. The use of TIVAP also reduces health care costs by allowing patients to receive chemotherapy at home [1]. Despite this, TIVAP are associated with venous thromboembolism (VTE) with a documented frequency of 0-13.6%, which varies between centers, depending on patient population, diagnostic method, and technique used for catheterization [2]. Upper extremity deep vein thrombosis is seen in 2-6% of cancer patients with central venous catheters as the result of catheter insertion, venous stasis caused by indwelling catheters, and cancer-related hypercoagulability [3]. Catheter-related thrombosis is the reason for 11.4% of all removed TIVAP [4]. As it is known, VTE is a serious and common complication in active cancer patients with or without a central catheter, with an incidence of 4% to 20% [5]. Beyond the patient-related factors such as age, race, and comorbidities; primary cancer location, subtype, metastatic status, and administered systemic chemotherapy increase the risk of VTE [6]. While the highest rates of VTE were reported in hematologic malignancies (particularly lymphoma), primary brain (47%), pancreatic (19.2%), stomach (15.8%), and lung (13.9%) tumors; it is reported that systemic chemotherapy increases the risk for VTE 2-6 fold. Moreover, anticoagulation treatment is riskier in these patients than in those without cancer and/or not receiving chemotherapy due to the high risk of thrombosis and bleeding [7].

There is no consensus in the literature on routine prophylactic anticoagulant use in cancer patients with TIVAP. While low molecular weight heparin (LMWH) was recommended by the guidelines for the treatment and prevention of catheter-related thrombosis as standard until 2016, as the results of the Hokusai-VTE Cancer trial, SELECT-D and CARAVAGGIO trials, direct oral anticoagulants (DOAC) are increasingly recommended as alternatives [8-10].

In this study, the effects of primary cancer, metastases, accessed vein, access side, and administered systemic chemotherapy over the TIVAP patency and TIVAP-related VTE were evaluated.

METHOD

After the approval of the institutional ethics committee on health sciences a total of 297 cancer patients who had TIVAP implanted in our cardiovascular surgery clinic between 2017 and 2021 were included in our study. These patients were researched retrospectively for the diagnosis of primary cancer, metastasis, the accessed vein, the access side, the chemotherapeutic agents used, port patency and port-related complications. Patients who received therapeutic or prophylactic anticoagulants before the TIVAP was implanted were excluded from the study. Also, thromboprophylaxis was not administered to the TIVAP implanted patients unless a VTE complication occurred. All implantation procedures were performed in the interventional catheterization laboratory. The same brand of single lumen TIVAP (Bard Power Port Implantable Port, Bard Access Systems Inc. 605 North 5600 West Salt Lake City, UT 84116 USA) was implanted in all patients. The venous accesses were made under ultrasonography guidance (SonoSite M-Turbo ultrasound system, SonoSite Ltd.European Headquarters Alexander House, 40A Wilbury Way, Hitchin, Herts SG4 0AP, United Kingdom). Catheter tip position (just above the vena cava superior – right atrium junction) was confirmed by fluoroscopy. Two surgeons, also the authors of this article, performed all implantation procedures. The oncology department staff performed the flushing, locking, and maintenance of the TIVAP with saline and heparinized saline according to the institutional protocols. TIVAP-related VTE diagnoses were made via Doppler ultrasonography and computerized tomography. TIVAP, which were requested to be removed by oncologists due to occlusion, infection, or no longer needed, were also removed in our clinic too. Patient demographics, primary cancers, metastases, administered chemotherapy, accessed veins, access sides, and developed VTE complications were collected from the institutional electronic database and archives of the oncology and cardiovascular surgery departments.

Ethical Consideration

This study was performed with the approval of Muğla Sıtkı Koçman University, Health Sciences Ethics Committee. (Application No: 220003)

Statistical Analysis

The data obtained from the study were analyzed with SSPS software (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0 Armonk, NY, US IBM Corp.). Kolmogorov-Smirnov test examined whether the quantitative variables were suitable for normal distribution. Differences between nominal variables were tested with the chi-square test. Whether the TIVAP patency differed statistically according to different groups was examined with the Mann-Whitney U-test since the variable did not fit the normal distribution. The generalized linear models was used to measure the between TIVAP and non-TIVAP patients in terms of certain variables. Correlations not conforming to normal distribution were analyzed with Spearman's correlation. Descriptive statistics were shown as mean±standard deviation; qualitative variables were expressed as frequency (%). Values of $p < 0.05$ were considered statistically significant.

RESULTS

A total of 297 cancer patients who had TIVAP implanted were included in the study. The mean age of the patients was 59.46±10.91(18-86). TIVAPs were removed in 37 patients due to infection 14(4.7%), occlusion 8(2.7%), VTE 9(3%), malposition1(0.3%), and treatment completion 10(27.0%). TIVAP was re-implanted in 27 patients in order to continue the treatment. Demographic data of the patients, implantation sites and sides, types of developed VTE, primary cancer distribution and metastases of the patients were expressed in Table 1.

Table 1. Demographic data of the patients, implantation sites and sides, types of developed VTE, primary cancer distribution and metastases, removal reasons of the patients

Variables		n	%
Gender	Male	164	55.2
	Female	133	44.8
Access Side	Right	267	89.9
	Left	30	10.1
Accessed Veins in Implantation	Subclavian vein	76	25.6
	Jugular vein	221	74.4
Primary Cancers of the TIVAP Implanted Patients	Colon Carcinoma	133	44.8
	Stomach Carcinoma	30	10.1
	Breast Carcinoma	50	16.8
	Pancreatic Carcinoma	19	6.4
	Laryngeal Carcinoma	6	2.0
	Ovarian Carcinoma	7	2.4
	Esophageal Carcinoma	6	2.0
	Lung Carcinoma	12	4.0
	Prostate Carcinoma	3	1.0
	Liver Carcinoma	2	0.7
	Bladder Carcinoma	3	1.0
	Others	26	8.8

Metastasis	Metastatic	168	56.6
	Non-metastatic	129	43.4
Complication	Occlusion	8	2.7
	Infection	14	4.7
	Malposition	1	0.3
	VTE	**48**	**16.2**
	DVT	21	7.1
	PE	10	3.4
	JVT	12	4.0
	SVT	7	2.4
	AVT	5	1.7
	PVT	3	1.0
	VCST	1	0.3
	SPVT	1	0.3
Completion of treatment		10	3.4
Reasons for TIVAP Removal (n=37)*	Occlusion	8	21.6
	Infection	14	37.8
	Malposition	1	2.7
	VTE	9	24.3
	Completion of treatment	10	27.0

*TIVAP: Totally implantable venous access port, VTE: Venous thromboembolism, DVT: Deep vein thrombosis PE: Pulmonary embolism JVT: Jugular vein thrombosis, SVT: Subclavian vein thrombosis, AVT: Axillary vein thrombosis, PVT: portal vein thrombosis, VCST: Vena cava superior thrombosis, SPVT: splenik vein thrombosis. *In our study, occlusion in 4 patients and infection in 1 patient were detected at the same time with vte.*

Complications of VTE, occlusion, infection and malposition developed in a mean follow-up of 17.7±16.6 months in 71 patients. In the comparison of these complications according to the presence of metastasis, it was found to be that they were significantly higher in metastatic patients (47-24 p<0.05).

In the comparison of each complication separetely, especially the rate of VTE was found to be significantly higher in metastatic patients compared to the non-metastatic group (20.8%-10.1% p<0.05) (Table 2).

TIVAPs were removed in 12(7.1%) metastatic and 15(11.6%) non-metastatic patients due to VTE, occlusion, infection and malposition (Table 2).

Table 2. The relationship between the metastatic status of the patients and VTE, occlusion, infection and removed TIVAPs (except for those removed due to treatment termination)

Relationship		**Met.**	**N-met.**	**p**
VTE	n	35	13	**0.009***
	%	20.8	10.1	
Occlusion	n	6	2	0.245
	%	3.5	2.9	
Infection	n	5	9	0.091
	%	2.9	6.9	
Removed TIVAPs (except for those removed due to treatment termination)	n	12	15	0.223
	%	7.1	11.6	

*Met: Metastatic, N-met: Non metastatic, VTE: Venous thromboembolism, TIVAP: Totally implantable venous access port, *p<0.05*

When the subclavian vein and jugular vein were compared as the venous access site, although the VTE and infection rate were found to be high in subclavian vein access, they were not statistically significant (22.3%-14% / 5.2%-4.5% respectively, p>0.05) (Table 3). In the evaluation of TIVAP patency; including 10 patients who wanted their TIVAP removed, although they were usable, due to treatment termination, the TIVAPs of 270(90.9%) patients were found to be usable for an average of 18.5±17.1 months. There was no statistical difference in terms of the venous access site, side, the metastatic status of the cancer, and the chemotherapeutic agents used in patients who required TIVAP removal due to VTE, infection, occlusion, and malposition.

Table 3. The relationship between the accessed vein and VTE, occlusion, infection and removed TIVAPs (except for those removed due to treatment termination).

Relationship		**SV**	**JV**	**p**
VTE	n	17	31	0.066
	%	22.3	14.0	
Occlusion	n	1	7	0.349
	%	1.3	3.1	
Infection	n	4	10	0.501
	%	5.2	4.5	
Removed TIVAPs (except for those removed due to treatment termination)	n	6	21	0.819
	%	7.8	9.5	

SV: Subclavian vein, JV: Jugular vein, VTE: Venous thromboembolism, TIVAP: Totally implantable venous access port

When evaluated in terms of the chemotherapeutic drugs used, a significant positive correlation was found between the VTE rate and especially taxanes, methotrexate, etoposide and vinorelbine compared to other drugs(p<0.05). No significant correlation was found in terms of occlusion and infection(p>0.05) (Table 4).

In our study, 12 patients with jugular vein thrombosis (JVT), 7 patients with subclavian vein thrombosis (SVT), 5 patients with axillary vein thrombosis (AVT) and 1 patient with superior vena cava thrombosis (VCST) were accepted as TIVAP-related VTE. In these 19(6.3%) patients, the possible effects of age, the accessed vein, the access side, metastases, cancer types, and the chemotherapeutic drugs used on TIVAP-related VTE were evaluated (Table 5).

TIVAP-related VTE was found to be significantly higher especially in metastatic patients and patients with lung cancer. In addition, the mean age of the TIVAP-related VTE group was significantly higher (64.6±9.6- 59.2±10.9 p<0.05). Despite this, no significant difference was found in terms of access site and side (p>0.05) (Table 5). When evaluated in terms of chemotherapeutic agents, TIVAP-related VTE was found to be higher in patients taking taxanes, etoposide, biphosphonates and vinorelbine, but it was not statistically significant (p>0.05) (Table 5).

VTE developed in 48(16.2%) patients, TIVAPs were removed due to VTE in 9(18.7%) patients and re-implanted for continuation of treatment. Although 39(81.3%) patients had VTE, TIVAP continued to be used with LMWH treatment. LMWH was started in all patients who developed VTE. However, DOACs were started in 14(29.1%) patients due to non-compliance with injectable LMWH treatment.

Table 4. The relationship between the most commonly administered chemotherapeutic agents and VTE, occlusion, infection and TIVAP patency

Correlation	VTE		Oclusion		Infection		TIVAP Patency	
	r	p	r	p	r	p	r	p
Pyrimidine Antagonists	0.009	0.88	0.075	0.19	-0.03	0.61	-0.08	0.69
Tamoxifen	0.017	0.77	-0.145	**0.01***	-0.01	0.76	0.22	0.27
Taxanes	0.134	**0.02***	-0.02	0.71	0.01	0.80	0.22	0.28
Biphosphonates	0.107	0.06	0.010	0.86	0.01	0.82	-0.36	0.06
Methotrexate	0.132	**0.02***	-0.152	**0.009***	0.05	0.37	-	-
Etoposide	0.149	**0.01***	0.043	0.45	0.06	0.31	-	-
Vinorelbine	0.147	**0.01***	-0.074	0.21	0.02	0.63	0.06	0.76
Platinum Based Agents	0.06	0.292	-0.023	0.69	-0.06	0.05	-0.11	0.57
Anthracyclines	0.026	0.66	-0.24	**0.00***	0.05	0.36	0.033	0.90
EGFR	-0.04	0.45	-0.05	0.32	-0.03	0.60	-0.09	0.65
Aromatase Inhibitors	-0.001	0.98	-0.09	0.08	0.01	0.86	0.08	0.67

VTE: Venous thromboembolism EGFR: Endothelial growth factor receptor *tyrosine kinase inhibitor, TIVAP: Totally implantable venous access port, * p<0.05*

Table 5. The effect of the mean age of the patients, access side and accessed vein, primary cancers, metastatic status of the patients and chemotherapeutic agents TIVAP-releated VTE

Variables		TIVAP-releated VTE n:19**	Non- TIVAP-releated VTE n:278	p
Age		64.6±9.6	59.2±10.9	**0.038***
Accessed Veins in Implantation	Subclavian	4 (21.1%)	72 (25.8%)	**0.013*,a**
	Jugular	15 (78.9%)	206 (74.1%)	
Access Side	Right	17 (89.5%)	250 (89.9%)	0.318[a]
	Left	2 (10.5%)	28 (10.1%)	
Primary Cancers of the TIVAP Implanted Patients	Colon Carcinoma	8 (42%)	125 (45.1%)	**0.002*,a**
	Stomach Carcinoma	2 (10.5%)	28 (10.1%)	
	Breast Carcinoma	3 (15.8%)	47 (17%)	
	Pancreatic Carcinoma	-	19 (6.9%)	
	Laryngeal Carcinoma	-	6 (2.2%)	
	Ovarian Carcinoma	-	7 (2.5%)	
	Esophageal Carcinoma	-	6 (2.2%)	
	Lung Carcinoma	5 (26.3%)	7 (2.5%)	
	Prostate Carcinoma	-	3 (1.1%)	
	Liver Carcinoma	-	2 (0.7%)	
	Bladder Carcinoma	-	3 (1.1%)	
	Others	1 (5.3%)	25 (9%)	
Metastasis	Metastatic	16 (84.2%)	152 (54.7%)	**p<0.001*,a**
	Non-metastatic	3 (15.8%)	126 (45.3%)	
Chemotherapeutic Agents	Pyrimidine Antagonists	14 (73.7%)	225 (80.9%)	0.955[a]
	Tamoxifen	1 (5.3%)	15 (5.4%)	0.689 [a]
	Taxanes	11 (57.9%)	83 (29.9%)	0.208[a]
	Biphosphonates	4 (21.1%)	29 (10.4%)	0.058[a]
	Methotrexate	1 (5.3%)	0 (0%)	1.000[a]
	Etoposide	5 (26.3%)	10 (3.6%)	0.063[a]
	Vinorelbine	4 (21,1%)	15 (5.4%)	0.361[a]
	Platinum Based Agents	18 (94.7%)	226 (81.3%)	0.077[a]
	Anthracyclines	6 (31.6%)	67 (24.1%)	0.482[a]
	EGFR	5 (26.3%)	63 (22.7%)	0.330[a]
	Aromatase Inhibitors	2 (10.5%)	23 (8.3%)	0.340[a]

TIVAP: Totally implantable venous access port, VTE: Venous thromboembolism, EGFR: Endothelial growth factor receptor *tyrosine kinase inhibitor, *p<0.05 [a]: p-values calculated based on age-adjustment, **In our study, 19 patients with jugular vein thrombosis (JVT), subclavian vein thrombosis (SVT), axillary vein thrombosis (AVT) and superior vena cava thrombosis (VCST) were accepted as TIVAP-releated VTE.*

DISCUSSION

The increases in the cancer patients' counts and the advances in the continuous systemic chemotherapy regimens in recent years brought out the increase in TIVAP use as a safe and comfortable device. Since 1982 when Niederhuber et al. described the TIVAP, many studies have been made on its advantages and safety [11,12]. However, the increasing use of TIVAP in these patients predisposed to VTE due to cancer has revealed TIVAP-related VTE as a problem that causes severe morbidity and worsens the patients` life quality [13]. As a type of central venous catheter, TIVAP is exposed to blood for months to years. Their artificial structure activates the contact pathway, which is part of the host defense mechanism and may promote inflammation and thrombosis [14,15]. When the risk factors of TIVAP-related VTE were examined, the following points draw attention: VTE risk increases with age in both adult women and men [16]. The type and the metastases of the underlying malignancy, chemotherapy, radiotherapy to the thorax, critical illness, systemic or catheter-related infection, thrombophilia, and hereditary or acquired hypercoagulability increase the risk of TIVAP-related VTE [17]. A recent meta-analysis by Jiang et al. showed that TIVAP-related VTE risk is lower than peripherally inserted central catheters (PICC) and Hickman catheters. They also supported previous data that TIVAP-related VTE is more common in patients who access upper extremity veins [13,18]. In their study, Piran et al. determined that the metastatic status of cancer is a strong risk factor for TIVAP-related VTE, consistent with the previous studies [19].

In our study, we determined the complications of VTE, infection, occlusion and malposition more in the metastatic patient group in the follow-ups after TIVAP implantation. Especially the development of VTE was statistically significant($p<0.05$). Although the rates of VTE and infection were higher in TIVAPs with subclavian vein access, it was not significant($p>0.05$). In addition, in our study, the mean age was found significantly higher (64.6 ± 9.6-59.2 ± 10.9 $p<0.05$) in 19(6.3%) VTE patients, who have JVT, SVT, AVT, and VCST (TIVAP-related VTE). In this group, we found the TIVAP-related VTE rate significantly higher, in metastatic patients and lung cancer patients($p<0.05$). However, there was no difference in this group in terms of the venous access site and side($p>0.05$).

On the other hand, Levi stated in his study that cancer increases the risk of thrombosis 4 times; if the patient receives chemotherapy, the relative risk increases to 6.5, which would mean that the annual thrombosis incidence of cancer patients is about 0.5% [20]. Previous clinical and preclinical studies have demonstrated the increased VTE risk mediated by the most commonly used chemotherapy. For example, doxorubicin increases the venous thrombosis risk by up to 16.0% by harming the endothelium, down-regulating the protein C anticoagulant pathway, increasing tissue factor procoagulant activity, and activating platelets [21]. Cyclophosphamide and its metabolites cause microemboli, which lead to ischemic myocardial damage by stimulating the activation and release of platelet factor 4 and aggravating monocyte adhesion to endothelium [22]. Cisplatin harms endothelium and causes hypercoagulation and platelet aggregation by activating the arachidonic acid pathway that forms inflammatory and thrombogenic molecules [23]. 5-fluorouracil damages the endothelium and provokes severe vessel leakage and subsequent thrombus formation [24]. In our study, a significant positive correlation was found between the VTE rate and especially taxanes, methotrexate, etoposide and vinorelbine compared to other chemotherapy drugs($p<0.05$). We did not find a significant correlation in terms of occlusion and infection ($p>0.05$) In addition, TIVAP-related VTE rates were found to be higher in patients taking taxanes, etoposide, biphosphonates and vinorelbine, but it was not statistically significant ($p>0.05$). The inability to obtain statistically significant results with the other agents was attributed to the limited number of patients.

In treating cancer-related VTE, LMWH is preferred over VKA and used as a gold standard treatment, based on the previous studies [25,26]. However, the injectable use of LMWH results in patients not complying with VTE treatments. Completion rates of 6-month VTE treatment were 61% with oral anticoagulants and 37% with LMWH [27]. In the NCCN 2020, ESC 2020, and ASCO 2020 guidelines, which were updated after the studies on the use of DOAC, particularly in cancer patients (SELECT-D, HOSUKAI-VTE Cancer, ADAM-VTE, CARAVAGGIO); use of DOAC are strongly recommended in cancer-related VTE alternatively, in patients other than the ones who have gastrointestinal cancers [28-30]. However, in the ESVS 2021 guideline, LMWH stil remains the IA recommendation for cancer-related VTE, and DOAC is given as the IIaA recommendation in patients other than those with gastrointestinal and/or genitourinary cancers [31]. For TIVAP-related VTE in cancer patients, the CHEST and ACCP guidelines recommend continued anticoagulation as long as the central venous catheter remains in place and removal of the catheter when the catheter is no longer functional or necessary [32]. In this study, VTE developed in 48(16.2%) patients, TIVAPs were removed in 9(18.7%) patients due to VTE and a new one re-implanted for the continuation of the treatment. Although 39(81.3%) patients had VTE, TIVAP continued to be used with LMWH treatment, according to the ESVS guideline. However, DOAC was started in 14(29.1%) patients due to inability to comply with injectable LMWH treatment in the first six months of follow-up. TIVAP were removed when they became infected, unfunctional and/or unneeded with the request of oncologists.

Limitations

Our study has some limitations. Firstly, this is a single-center study, and therefore, the limited number of patients led to inability to obtain statistically significant results in some parameters. Due to the sample size imbalance between the groups, additional studies with larger and balanced numbers of groups are needed to generalize the statistical inferences obtained. Second, the institutional electronic database and archives of the oncology and cardiovascular surgery departments were used for data collection. Anticancer drugs and radiotherapy protocols administered at other institutions, and imaging studies for TIVAP-related VTE may have been overlooked. Third, although the effect of metastases of patients'cancers on VTE has been evaluated, VTE risk differences resulting from cancer's subtypes have not been evaluated.

CONCLUSION

Primary cancer, metastases, and chemotherapy are important factors for the development of systemic or TIVAP-related VTE. Thromboprophylaxis should be applied in certain types of cancer and chemotherapy regimens that increase the risk of TIVAP-related VTE. Multicenter studies with more significant numbers of patients are needed on the relationship between cancer-metastasis-chemotherapy-VTE and VTE treatment in cancer patients to form a consensus on the prevention and treatment of TIVAP-related VTE.

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