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Pharmacological cancer treatment and venous thromboembolism risk

Andrés J. Muñoz Martín[1]*, Sara Pérez Ramírez[1], Laura Ortega Morán[1], Magdalena Ruiz Zamorano[2], María Carmen Viñuela Benéitez[2], Inmaculada Aparicio Salcedo[1], Ignacio García Escobar[3], and José Manuel Soria Fernández[4]

[1]*Medical Oncology Department, Hospital General Universitario Gregorio Marañón, Calle Doctor Esquerdo 46, 28007 Madrid, Spain;*
[2]*Department of Medicine, Faculty of Medicine, Universidad Complutense, Av. Séneca 2, 28040 Madrid, Spain;*
[3]*Medical Oncology Department, Hospital General Universitario de Ciudad Real, Calle Obispo Rafael Torija s/n, 13005 Ciudad Real, Spain; and*
[4]*Genomic of Complex Disease Unit, Institut dinvestigació Sant Pau (IIB-SANT PAU), Joan Alcover, 7-2° 2ª, 08031 Barcelona, Spain*

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Risk factors for cancer-associated thrombosis are commonly divided into three categories: patient-, cancer-, and treatment-related factors. Currently, different types of drugs are used in cancer treatment. Chemotherapy has been identified as an independent risk factor for venous thromboembolism (VTE). However, it should be noted, that the risk of VTE is not consistent among all cytotoxic agents. In addition, different supportive care drugs, such as erythropoiesis stimulating agents or granulocyte colony stimulating factors, and hormonotherapy have been associated to an increased risk of VTE. Immunotherapy and molecular-targeted therapies have significantly changed the treatment of cancer over the past decade. The main subtypes include tyrosine-kinase inhibitors, monoclonal antibodies, small molecules, and immunomodulatory agents. The relationship between VTE and targeted therapies remains largely unknown.

Los factores de riesgo para la trombosis asociada al cáncer se suelen dividir en tres categorías: factores relacionados con el paciente, con el cáncer y con el tratamiento. En la actualidad, existen distintos tipos de fármacos que se emplean en el tratamiento del cáncer. La quimioterapia se ha determinado como un factor de riesgo independiente para el desarrollo de la tromboembolia venosa (TEV). No obstante, cabe destacar que el riesgo de padecer TEV no es coherente entre los agentes citotóxicos. Por otra parte, distintos fármacos de tratamiento paliativo, como los agentes estimulantes de la eritropoyesis o factores estimulantes de colonias de granulocitos, se han asociado a un aumento del riesgo de TEV. La inmunoterapia y los tratamientos dirigidos a dianas moleculares han supuesto un cambio significativo en el tratamiento del cáncer en la última década. En los principales subtipos se incluyen los inhibidores de las tirosina-cinasas, anticuerpos monoclonales, fármacos tradicionales y agentes inmunomoduladores. La relación entre la TEV y los tratamientos dirigidos sigue siendo en gran medida desconocida.

*Corresponding author. Tel: + 34-914269394, Fax: + 34-915737985, Email: andresmunmar@hotmail.com; ajmunoz.hgugm@salud.madrid.org

关键词
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免疫疗法；
支持性护理

癌症相关性血栓形成的风险因素通常分为三类：患者相关、癌症相关和治疗相关因素。当前，用于治疗癌症的药物多种多样。化学疗法已确定为静脉血栓栓塞（VTE）的独立风险因素。但必须注意，各种细胞毒性药物产生 VTE 的风险并不一致。另外，不同的支持性护理药物（如促红细胞生成刺激剂或粒细胞集落刺激因子）以及激素疗法可增加 VTE 风险。在过去的十年中，免疫疗法和分子靶向疗法已大大改变了癌症的治疗方法。主要亚型包括酪氨酸激酶抑制剂、单克隆抗体、小分子和免疫调节剂。VTE 和靶向疗法之间的关系在很大程度上仍然未知

Introduction

The close relationship between cancer and venous thromboembolism (VTE) has been known for more than a century.[1,2] Risk factors for cancer-associated thrombosis are commonly divided into three categories: patient-, treatment-, and cancer-related factors. Chemotherapy has been identified as an independent risk factor for VTE. Data suggest that chemotherapy is associated with a six-fold increase in the risk of VTE, reaching an estimated annual incidence of over 10% in tumours with high thrombogenic potential.[3] However, the risk of VTE is not consistent among all cytotoxic agents, as not only marked differences may be found among different types of drugs but also for drugs within the same therapeutic group.[4] Molecular-targeted therapies and immunotherapy have significantly changed the landscape of cancer treatment over the past decade. The main subtypes include tyrosine-kinase inhibitors (TKI), monoclonal antibodies (moAb), small molecules, and immunomodulatory agents. The relationship between VTE and targeted therapies remains largely unknown and, therefore, no clear recommendation has been made regarding thromboprophylaxis. In the last decade, due to there is a significant variation in VTE risk between individual cancer patient, partially driven by cancer treatment, the main guidelines have recommended VTE risk assessment at diagnosis and periodically throughout cancer evolution specially when starting new systemic antitumour therapy.

At present two questions arise for VTE and cancer therapy: do all drugs share the same venous thromboembolic risk? Should we draw a line between chemotherapy and other cancer therapies as immunotherapy or targeted therapy regarding VTE risk? In the other hand, pharmacological treatments for cancer affect risk of VTE not only directly but also acting over the cancer itself and possibly reducing tumour-induced risk of VTE when tumour response is achieved.

Venous thromboembolism risk associated to cancer treatments ranging from chemotherapy to supportive care is reviewed below.

Venous thromboembolism and clinical trials

Some essential information about VTE in cancer patients receiving chemotherapy is seldom reported in randomized clinical trials: incidence of cancer-related venous and arterial thromboembolism (ATE), information with respect thrombosis location, the clinical significance of the event (symptomatic vs. incidental), prognosis, and possible relationship with other supportive treatments. Mandalà *et al*.[5] analysed a total of 28 randomized controlled clinical trials on first-line chemotherapy in advanced colorectal cancer to retrieve the reported VTEs. Overall, only 17.8% of clinical trials reported this type of toxicity despite most studies had been published in important medical journals after the inclusion of VTE as a non-haematological adverse event in the US National Cancer Institute Common Toxicity Criteria Guidelines (CTCAE). In three out of the five clinical trials that reported the occurrence of VTE events, the incidence remained below 1%, which is clearly underestimated. Furthermore, connecting each drug with a specific venous thromboembolic risk may result challenging as many studies evaluate simultaneously different combinations of antineoplastic agents. Moreover, the individual risk of each anticancer drug often overlaps with other well-known thromboembolic risk factors, such as central-venous catheters, etc.

Antiangiogenic monoclonal antibodies

Concerns have arisen regarding the risk of VTE and ATE with antiangiogenic moAb. To date, three of these anticancer drugs are available for their use in daily clinical practice: bevacizumab, aflibercept, and ramucirumab.

Bevacizumab was the first moAb targeting the vascular endothelial growth factor (VEGF) approved in cancer patients. Initially, this drug was associated with and increased risk of both VTE and ATE. Nonetheless, since the approval of bevacizumab, at least five meta-analyses[6-10] and several other randomized controlled trials have yielded new data that disprove this initial perception. In three meta-analyses[6-8] conducted in patients with a wide variety of advanced solid tumours, bevacizumab did not increase the occurrence of VTE (*Table 1*). Conversely, a more recent study investigating the association between bevacizumab and VTE in patients with castration-resistant prostate cancer (CRPC) reported a potential protective effect of this drug on venous thromboembolic risk [occurrence of grade $\geq$3 VTE in bevacizumab plus chemotherapy vs. placebo plus chemotherapy 4.4% and 7.1%, respectively with a hazard ratio (HR) of 0.6, 95% confidence interval (CI): 0.35-1.02; $P = 0.059$][11] based on the tumour control benefit resulting from bevacizumab therapy. On the other hand, bevacizumab was associated with a modest but significant two-fold increase of ATE.[6,9,10] The occurrence of ATE events was associated with age and previous medical history; however, bevacizumab was not formally

Table 1 Bevacizumab-associated venous and arterial thromboembolic risk: meta-analyses of randomized controlled trials

Meta-analysis	Year	Patients/number of studies	Tumour subtypes	VTE risk
VTE				
Scappaticci *et al.*[6]	2007	1745/5	mBC, mCRC, NSCLC	RR: 0.89, 95% CI: 0.66-1.20; $P = 0.44$
Nalluri *et al.*[7]	2008	7956/15	mBC, mCRC, NSCLC, RCC, PC, MS	RR: 1.33, 95% CI: 1.13-1.56; $P = 0.001$
				[a]RR: 1.10, 95% CI: 0.89-1.36; $P =$ NS
Hurwitz *et al.*[8]	2011	6055/10	mBC, mCRC, NSCLC, RCC, PC,	RR: 0.89, 95% CI: 0.66-1.20; $P = 0.44$
Meta-analysis	Year	Patients/number of studies	Tumour subtypes	ATE risk
ATE				
Scappaticci *et al.*[6]	2007	1745/5	mBC, mCRC, NSCLC	RR: 2.0, 95% CI: 1.05-3.75; $P = 0.031$
Ranpura *et al.*[9]	2010	12 611/20	Advanced solid tumours	RR: 1.44, 95% CI: 1.08-1.91; $P = 0.013$
Schutz *et al.*[10]	2011	13 026/20	mBC, mCRC, NSCLC, RCC, PC, MS	RR: 1.46, 95% CI: 1.11-1.93; $P = 0.007$

mBC, metastatic breast cancer; mCRC, metastatic colorectal carcinoma; MS, mesothelioma; NS, not significant; NSCLC, non-small-cell lung cancer; PC, pancreatic cancer; RCC, renal cell carcinoma; RR, risk ratio.
[a]Exposure-adjusted VTE RR.

contraindicated in this subset of patients as clinical benefit was found to be consistent in all the subgroups examined including elderly patients and patients with previous ATE. Furthermore, no dose-effect relationship between bevacizumab and ATE was reported with a relative risk (RR) of 1.52 vs. 1.5 for bevacizumab at 2.5 and 5.0 mg/kg/week, respectively.[9]

Aflibercept is a recombinant fusion protein that binds to circulating VEGFs thereby inhibiting the activity of VEGF-A, VEGF-B, and placental growth factor. It is been approved for use in combination with FOLFIRI for metastatic colorectal cancer that is resistant to or has progressed following treatment with an oxaliplatin-containing regimen. As previously reported with bevacizumab, the addition of aflibercept to concurrent chemotherapy did not increase the risk of VTE (occurrence of Grade 3-4 VTE aflibercept 6.1% vs. placebo 6.4%, RR: 0.95, 95% CI, 0.71-1.28).[12] Even though aflibercept displays a stronger inhibition of the VEGF pathway, the incidence of VTE remains similar to patients treated with bevacizumab. Several studies[13] have reported a trend towards an increased risk of ATE. Most events peaked in early treatment cycles and decreased sharply following initial presentation.[14] In a meta-analysis of anti-VEGF class adverse events, the ATE incidence was low and a non-significant difference of ATE was observed (aflibercpet 1.7% vs. placebo 1.0%; RR: 1.69, 95% CI, 0.85-3.34).[12]

Ramucirumab is a fully humanized monoclonal antibody of the IgG1 class that binds to the vascular endothelial growth factor receptor-2 (VEGFR-2) thus preventing the binding of the VEGF ligand. Once more, this drug did not increase the risk of VTE.[15-18] It is worth noting that in all four studies, the incidence of VTE was lower in the ramucirumab treatment arm (*Table 2*). The risk of ATE was uneven among the main clinical trials with no significant increase of grade $\geq$3 events reported (*Table 2*). A meta-analysis of individual patient was presented in the European Society of Medical Oncology (ESMO) Congress 2017.[19] It analysed 4996 patients from six different Phase 3 placebo-controlled clinical trials including different neoplasms (gastric/gastro-oesophageal junction, non-small-cell lung, and metastatic colorectal cancers). Ramucirumab was not associated to an increased risk of VTE all grades (RR: 0.7, 95% CI: 0.5-1.1) and Grade 3-4 VTE (RR: 0.7, 95% CI: 0.4-1.2). Similar results were described for ATE events, ATE all-grade (RR: 0.8, 95% CI: 0.5-1.3) and Grade 3-4 ATE (RR: 0.9, 95% CI: 0.5-1.7).

Non-antiangiogenic monoclonal antibodies

To date, no randomized controlled clinical trials have explored the incidence of VTE or ATE in cancer patients treated with non-antiangiogenic moAb. Nonetheless, an important number of these targeted drugs have been recently approved for the treatment of different neoplasms.

The anti-epidermal growth factor receptor (EGFR) agents cetuximab and panitumumab are associated with a significant increase in the risk of VTE in patients with advanced solid tumours specially in colorectal and head and neck malignancies.[20] In a meta-analysis including 13 studies, the RR of VTE in patients assigned to anti-EGFR agents (cetuximab and panitumumab) vs. controls was 1.32 (95% CI: 1.07-1.63; $P = 0.01$) suggesting a 32% higher risk of developing VTE with anti-EGFR agents compared with controls. Most of the events were classified as high grade according CTCAE with a RR of 1.36 in grade 3-4 events. Additionally, five randomized Phase II and III clinical trials were available to calculate the risk of ATE resulting in a non-significant RR of 1.34 (95% CI: 0.94-1.9; $P = 0.11$) in the anti-EGFR vs. the control arm. It should be highlighted that the risk of VTE increases when anti-EGFR agents are combined with irinotecan- or cisplatin-based chemotherapy and in patients with clinically advanced malignancies vs. those with complete tumour resection.[21,22]

Table 2 Randomized, controlled trials on venous and arterial thromboembolic risk associated with ramucirumab

Randomized controlled trials	Regimen (N)	VTE (any grade)	VTE (grade ≥ 3)
VTE			
REGARD (2nd line GADC, EGJ-ADC), Fuchs *et al.*[15]	RM (236)	4%	1%
	Placebo (115)	7%	4%
RAIBOW (2nd line GADC, EGJ-ADC), Wilke *et al.*[18]	RM + paclitaxel (327)	4%	2.4%
	placebo + paclitaxel (329)	5.5%	3.3%
REVEL (2nd line NSCLC), Garon *et al.*[16]	RM + Docetaxel (627)	3%	2%
	Placebo + Docetaxel (618)	6%	3%
ROSE/TRIO-12 (1st line mBC), Mackey *et al.*[17]	RM + Docetaxel (752)	2.4%	1.3%*
	Placebo + Docetaxel (382)	4.2%	2.1%*
Randomized controlled trials	Regimen (*N*)	ATE (any grade)	ATE (grade ≥ 3)
ATE			
REGARD (2nd line GADC, EGJ-ADC), Fuchs *et al.*[15]	RM (236)	2%	1%
	Placebo (115)	0%	0%
RAIBOW (2nd line GADC, EGJ-ADC), Wilke *et al.*[18]	RM + paclitaxel (327)	1.5%	0.9%
	placebo + paclitaxel (329)	1.8%	0.9%
REVEL (2nd line NSCLC), Garon *et al.*[16]	RM + Docetaxel (627)	2%	1%
	Placebo + Docetaxel (618)	2%	1%
ROSE/TRIO-12 (1st line mBC), Mackey *et al.*[17]	RM + Docetaxel (752)	1.1%	0.7%
	Placebo + Docetaxel (382)	1.3%	0.3%

ATE, arterial thromboembolism; EGJ-ADC, oesophago-gastric junction adenocarcinomas; GADC, gastric adenocarcinomas; mBC, metastatic breast cancer; *N*, number of patients; NSCLC, non-small-cell lung cancer; RM, ramucirumab; VTE, venous thromboembolism.
*$P < 0.05$.

Necitumumab is a recombinant human IgG1 monoclonal antibody that is designed to block the ligand-binding site of EGFR. Necitumumab, in combination with gemcitabine and cisplatin, is approved for the firstline treatment of patients with metastatic squamous non small-cell lung cancer (NSCLC) and it is the first biologic approved in this tumour subtype. Necitumumab plus chemotherapy was associated with increased VTE risk compared to chemotherapy alone in the two randomized Phase III studies, SQUIRE trial (RR: 1.699, 95% CI 1.09-2.65) and INSPIRE trial (RR: 1.58, 95% CI 0.99-2.52).[23,24]

The clinical use of anti-epidermal growth factor receptor-2 (HER2) moAb (trastuzumab, pertuzumab, and TDM-1) in breast and gastric cancer treatment does not increase the risk of VTE. Neither do the different classes of antibodies approved for the treatment of haematological malignancies, such as rituximab, alentuzumab, and the conjugate 90Y-ibritumomab tiuxetan.

Vascular endothelial growth factor receptor tyrosine-kinase inhibitors

Several multitargeted VEGFR TKI agents have been approved for the treatment of solid tumours including sunitinib, sorafenib, pazopanib, vandetanib, and axitinib.

A meta-analysis[25] comprising 17 different Phase II and III clinical trials and involving a total of 7441 patients reported no significant overall increase in the risk of VTE with VEGFR TKIs. The RR of all grade and high-grade VTE for TKIs vs. no TKIs was 1.10 (95% CI: 0.73-1.66; $P = 0.64$) and 0.85 (95% CI: 0.58-1.25; $P = 0.41$), respectively. Furthermore, no differences were noted after stratified analysis for the underlying malignancy, age or trial design. A second meta-analysis[26] found that the use of VEGFR TKIs did not significantly increase this risk when compared to controls (RR: 0.912, 95% CI: 0.617-1.348; $P = 0.643$) and reported a 3% global incidence of VTE. Once more, no differences were observed in subgroup analyses based on the VEGRF TKI agent administered or based on tumour type. To sum up, according to both meta-analyses, TKIs did not increase significantly venous thromboembolic risk in cancer patients.

A meta-analysis including more than 10 255 patients selected from Phase II and III trials was conducted to determine the risk of ATE.[27] The incidence of ATE associated with the use of sunitinib and sorafenib was 1.4%, (95% CI: 1.2-1.6%) with a RR of ATE compared with controls of 3.03 (95% CI: 1.25-7.37%). No noticeable differences were found regarding tumour type. In another meta-analysis[28] including 9711 patients from 19 randomized clinical trials, the reported incidence of ATE was 1.5% (95% CI: 1.0-2.3%). Treatment with VEGFR TKIs significantly increased the risk of developing ATE when compared with controls [odds ratio (OR): 2.26, 95% CI: 1.38-3.68; $P = 0.001$]. The most common event reported for ATE was cardiac ischaemia (67.4%). In subgroup analyses, the OR was not significantly influenced by the underlying malignancy, VEGFR TKI agent administered, treatment regimen, or trial phase. In summary, both meta-analyses noted a significant increase of ATE though the incidence rate remained below 2%.

A most recent study analysing arterial thromboembolic risk and cardiovascular toxicity from the use of either sunitinib or sorafenib was published in October 2015.[29] Using

the Surveillance, Epidemiology and End Results (SEER) cancer registries, the study analysed 670 patients who were at least 66 years old, diagnosed with renal cell carcinoma (RCC) and treated with either sunitinib or sorafenib from 2000 to 2009. Congestive heart failure, cardiomyopathy (CHF/CM), acute myocardial infarction (AMI), stroke, and cardiovascular deaths were considered possible cardiovascular adverse events. A total of 171 cardiovascular events were registered among patients who received either sunitinib or sorafenib, which represents an overall incidence of 25.5%. The incidence rates for CHF/CM, AMI and stroke were 0.87, 0.14, and 0.14 per 1000 person-days, respectively. These results were compared to those obtained from 788 patients diagnosed with RCC between 2000 and 2009 who did not receive TKIs. After adjustments for baseline characteristics, the risk of any cardiovascular event among those who received sunitinib or sorafenib was higher than the risk for the comparison group with an HR of 1.38 (95% CI: 1.02–1.87%). The study concluded that the clinical use of VEGFR-TKIs in the elderly increased the risk of cardiovascular events.

Non-antiangiogenic tyrosine-kinase inhibitors and new molecules

Erlotinib and gefitinib are EGFR TKIs approved for the treatment of lung and pancreatic cancer. At least one meta-analysis has explored the risk of thrombotic events (TEs) with anti-EGFR drugs, showing that, overall, they do not significantly increase the risk of VTE (RR: 1.16, 95% CI: 0.61–2.18%; $P = 0.65$) or ATE (RR: 1.34, 95% CI: 0.94–1.9%; $P = 0.11$) in contrast to the data presented previously with EGFR moAb.[20]

Afatinib is another TKI that irreversible binds to ErbB family receptors and is indicated in patients with metastatic NSCLC with EGFR mutations. No increase in the risk of TEs have been noted in any of the studies conducted with this agent (estimated incidence rate $< 1\%$).[30,31]

Crizotinib is a selective TKI of ALK, MET, and its oncogenic variants (ALK fusion events and selective ALK mutated). It has been approved in patients with ALK-positive metastatic NSCLC. Recent studies have reported a higher risk of TEs in ALK-positive lung adenocarcinomas than in other lung cancer subtypes (EGFR and KRAS mutated).[32–34] In the two articles published in the *New England Journal of Medicine* (*NEJM*) regarding the use of crizotinib in first[35] and second[36] line treatments, no significant increase in the risk of venous or arterial TEs was highlighted. Nonetheless, and according to the data compiled in the appendix of both studies, while the overall incidence of pulmonary embolism (PE) was higher among patients receiving second-line treatment with crizotinib compared to those with chemotherapy (5% vs. 2%),[36] the opposite was observed in the first-line setting where PE was reported in 6% of the patients receiving crizotinib and in 7% of the patients managed with chemotherapy.[35]

No evident relationship has been established between imatinib,[37,38] lapatinib,[39,40] and VTE/ATE. Everolimus is a selective inhibitor of the mammalian target of rapamycin with recognized antitumour activity in advanced breast cancer, pancreatic neuroendocrine tumours, and RCC. An increased procoagulant state has been described in renal transplant recipients receiving immunosuppressive therapy with everolimus. The impairment of fibrinolysis, thrombin activation, and increased endothelial cell reactivity are deemed responsible for this increased thrombotic risk.[41] In the Phase III trial BOLERO-2,[42] in which women with hormone-receptor-positive, HER2 negative advanced breast cancer received everolimus in combination with exemestane vs. exemestane alone, no increase of TEs was noted (no Grade 3–4 TEs reported). Similarly, no Grade 3–4 TEs were described in the RADIANT-3 study,[43] a Phase III double-blind clinical trial, conducted to determine whether everolimus, as compared with placebo, would prolong progression-free survival among patients with advanced pancreatic neuroendocrine tumours. Finally, no increase in venous or arterial thromboembolic risk was noted in the RECORD-1[44] clinical trial of everolimus for metastatic RCC. Considering these findings, it can be concluded that treatment with everolimus does not increase the risk of TEs in patients with different types of advanced neoplasms.

Palbociclib is an inhibitor of cyclin-dependent kinases (CDK) 4 and 6 that blocks cell progression from the G1 into the S phase of the cell cycle. This drug is indicated for use in combination with letrozole for first-line treatment of postmenopausal women with oestrogen receptor positive, HER2 negative metastatic breast cancer. In Phase II PALOMA-1/TRIO-18 trial,[45] which granted accelerated approval of palbociclib, a higher incidence of PE was observed in patients who received this drug compared with those treated with placebo (5% vs. 0%). On the other hand, in the Phase III PALOMA-3 trial[46] of palbociclib and fulvestrant vs. palbociclib alone after progression on endocrine therapy, the incidence of TEs in women allocated to combination therapy was 2% in contrast to 0% among patients receiving monotherapy. The PALOMA-2 randomized trial showed similar results with a VTE incidence of 0.9% in the palbociclib-letrozole arm vs. 1.4% in the placebo-letrozole arm.[47] Two other CDK inhibitors have been approved by Food and Drug Administration (FDA), ribociclib, and abemaciclib. The MONARCH-2 trial[48] described an increased VTE incidence of VTE for the combination of abemaciclib plus fulvestrant compared to placebo plus fulvestrant (5.0% vs. 0.9%). In the MONARCH-3 trial,[49] similar findings were observed with an increased rate of VTE related to abemaciclib [abemaciclib-non-steroidal aromatase inhibitor (AI) 4.9% vs. placebo-non-steroidal AI 0.6%]. In addition, two deaths were related to VTE events in the abemaciclib arm and no deaths were considered attributable to VTE in the placebo arm. Finally, the MONALEESA study[50] reported a similar incidence of VTE with ribociclib-letrozole compared to placebo-letrozole (0.6% vs. 0%). Considering all these results together, some authors have suggested VTE could be considered a class effect of CDK inhibition. However, the physiopathology of VTE observed in patients treated with CDK inhibitors and the differences in VTE rates described among different drugs cannot be explained with the current data. Several Phase II and III clinical trials are evaluating the combination of abemaciclib or palbociclib plus tamoxifen in premenopausal women (NCT02747004

and NCT02668666), these combinations should be assessed carefully regarding the VTE risk.

So far, no increase in TEs has been reported with BRAF and MEK inhibitors in monotherapy (dabrafenib,[51] vemurafenib,[52] and trametinib[53]) in single clinical trials. However, a recent systematic review and meta-analysis published in August 2019 described a significant increase in the risk of PE in melanoma patients treated with the combination of BRAF and MEK inhibitors compared to BRAF inhibitors monotherapy (RR: 4.36, 95% CI: 1.23–15.44; $P = 0.02$). Five randomized clinical trials including 2317 patients, that received vemurafenib, dabrafenib, encorafenib, trametinib, binimetinib, and cobinimetinib, were analysed. The risk of PE was higher for patients with a mean follow-up time longer than 15 months (RR: 7.70, 95% CI: 1.40–42.12; $P = 0.02$). The mechanism of PE caused by this combination is not completed understood. The authors suggest the inhibition of the nitric oxide pathway as the main hypothesis of PE occurrence.

Classic cytostatic agents

Chemotherapy has been identified as an independent risk factor for TEs in cancer patients.[54] Although the mechanisms underlying the procoagulant effect are not fully understood, a prominent role can be attributed to endothelial damage. Data suggest that chemotherapy is associated with a six-fold increase in TEs.[3] However, it should be noted that the risk of VTE is not consistent among all cytostatic agents, as not only marked differences may be found between different types of drugs but also among drugs within the same category. Among chemotherapeutic agents, cisplatin has been associated with the highest risk of TEs. Cisplatin is classified as an alkylating agent and was the first of the so-called platinum salts approved for cancer treatment in 1970. From a physiopathological point of view, cisplatin can induce endothelial damage and platelet activation. In addition, renal impairment has been proposed as a surrogate marker of the endothelial injury prompted by this drug. Numerous case series and many retrospective studies have provided evidence of the thrombogenic potential of this cytostatic agent. In a recent retrospective study conducted by Moore *et al.*[55] In 47 clinical trials, which included 932 patients with solid malignancies treated with cisplatin-based chemotherapy, 18% of patients experienced a TE event and most of these events (88%) occurred within the first 3 months of starting cisplatin. Hence, ambulatory thromboprophylaxis should be considered for patients with low-bleeding risk who receive cisplatin-based chemotherapy. Other meta-analyses have focused on evaluating the incidence and risks of TEs associated with cisplatin-based chemotherapy. In this regard, the meta-analysis published in 2012 by Seng *et al.*[56] revealed that patients receiving cisplatin-based chemotherapy had a 1.67-fold increased likelihood of experiencing a TEs (95% CI: 1.25–2.33%, $P = 0.01$) with the highest risk observed in patients receiving weekly doses of cisplatin $>30\,mg/m^2$. Recently and for the first time, risk assessment scores for VTE in cancer patients are considering the specific value of individual chemotherapeutic agents. The PROTECHT score[57] (PROphylaxis of ThromboEmbolism during ChemoTherapy) is a modified Khorana risk assessment score that adds platinum or gemcitabine-based chemotherapy to the predictive values already included in the Khorana score. Therefore, in the Protecht predictive score, treatment with cisplatin, carboplatin, or gemcitabine adds one point and the combination of the previous drugs two points to the Khorana score.[58] This modified risk assessment score may improve the ability to identify patients at high risk for VTE however it has not been validated.

Carboplatin is an analogue of cisplatin with similar biochemical properties. Even though several studies have reported a significant increase of venous thromboembolic risk in patients receiving carboplatin-based chemotherapy, the rates of TEs seem to be higher with cisplatin.[59]

Oxaliplatin belongs to a new class of platinum compounds with a central atom of platinum surrounded by the group 1,2-diaminocyclohexane and a ligand represented by bidentate oxalate. It is one of the main drugs used for the treatment of gastrointestinal tumours. The global incidence of oxaliplatin associated VTE is around 2%.[60,61] In the PROTECHT study, oxaliplatin had the lowest incidence of VTE compared with cisplatin and carboplatin (incidence of thrombosis: cisplatin 7%, carboplatin 5.5%, and oxaliplatin 1.1%, respectively).[59] A clinical trial conducted in patients with advanced gastro-oesophageal cancer demonstrated a different thrombotic risk according to the platinum compound used. Significantly fewer TEs were reported with oxaliplatin compared with cisplatin (7.6% vs. 15.1%; $P = 0.0003$). Similar results were observed in VTE (6.5% vs. 12.2%; $P = 0.002$) and ATE (2.9% vs. 1.1; $P = 0.044$). After adjustments for potential risk factors, this difference remained highly significant in the multivariate analysis (HR 0.51; $P = 0.001$).[4]

Several chemotherapeutic agents of different therapeutic groups have been associated with an increase in VTE.

- In a retrospective study performed in patients with advanced solid malignancies, TEs occurred in 7.3% of the patients treated with fluorouracil. The risk was higher when chemotherapy was administered as a continuous infusion.[62]
- Another retrospective study conducted at Memorial Sloan Kettering Cancer Center including more than 2000 patients with metastatic non-haematological malignancies treated with systemic therapy, identified irinotecan as an independent risk factor for VTE (HR: 1.89, 95% CI: 1.29–3.59%; $P = 0.05$).[63] In addition, irinotecan-based chemotherapy used in colorectal cancer treatment has been associated with fatal vascular thromboembolic events.[64]
- The relationship between gemcitabine and thrombosis risk has been pointed out in multiple case reports, case series, and small studies. To our knowledge, the study that best examines the specific contribution of gemcitabine to the development of venous and arterial TEs is a meta-analysis published in 2013 including a total of 4845 patients from 19 randomized clinical trials (eight Phase II studies and 11 Phase III studies). The incidence of venous and arterial TEs in patients receiving gemcitabine was 2.1% and 2.2%,

respectively. Moreover, the ORs of gemcitabine associated VTE and ATE were 1.56 (95% CI: 0.86–2.83; $P = 0.15$) and 1.82 (95% CI: 0.89–3.75; $P = 0.10$), respectively. This study was the first to demonstrate that the use of gemcitabine tends to increase the risk of thrombosis.[65] The incidence of Grade 3–4 TEs in a study that examined the combination of carboplatin, gemcitabine, and bevacizumab in the treatment of advanced and irresectable or metastatic urothelial tumours was 20%.[66]

- Anthracyclines: a retrospective study that included >400 newly referred lymphoma patients considered anthracycline-based chemotherapy as a significant independent risk factor for VTE (OR: 3.47, $P = 0.003$).[67] In breast cancer patients, a 6% incidence rate of TEs has been reported with anthracycline-based regimens in the adjuvant setting,[68] TEs have also been related to the clinical use of liposomal anthraciclines[69,70] and epirrubicin[71] (oesophago-gastric cancer).
- Other cytostatic drugs that increase VTE risk are cyclophosphamide,[72] mitomycin-c,[73–75] and methotrexate.[76]

Occasional venous TEs have been notified with docetaxel and paclitaxel.[77] A wide range of chemotherapeutic agents used in the treatment of different types of neoplasms have not been associated with an increase in the risk of VTE. Among them pemetrexed, raltitrexed, bleomycin, temozolomide, and vinca alkaloids must be pointed out. No clear conclusion has been established with novel cytostatic agents such as nab-paclitaxel, but data suggest that the use of this agent does not significantly increase the risk of TEs.[78]

Palliative and supportive care

Blood transfusions

Anaemia is a frequent finding in cancer patients attributed to the underlying malignancy and exacerbated by myelotoxic chemotherapy. Though blood transfusions offer a rapid increase in haemoglobin levels, they are, however, not devoid of risks which include infection, transfusion-related reactions, fluid overload, and alloimmunization among others.[79] Besides the aforementioned, transfusions are associated with increased risk of VTE (OR: 1.60, 95% CI: 1.53–1.67) and ATE (OR: 1.53, 95% CI: 1.46–1.61) in hospitalized cancer patients.[80]

Erythropoiesis stimulating agents (ESAs)

ESAs represent an alternative to blood transfusions when there is no urgent need in rising haemoglobin levels. According to the American Society of Oncology (ASCO) and to the American Society of Hematology (ASH) guidelines, the higher the levels of haemoglobin, the higher the incidence of ESA-induced TEs.[81] Therefore, in patients treated with ESAs, the optimal target haemoglobin concentration should be around 11 g/dL. Higher haemoglobin levels have been associated with a significant increase of VTE.[81] Other reasons different from haemoglobin levels that could explain the thrombotic potential of ESAs are endothelial activation and increased platelet reactivity.

Several meta-analyses[82–86] have examined the benefits and risks of ESAs. Overall, all studies reported an increase in the risk of thrombosis close to 50%. They also communicated negative data regarding mortality. These cases seemed to be restricted to patients not receiving chemotherapy. For this reason, ESAs are not recommended in this clinical setting (*Table 3*).

Although no direct comparative data exist regarding the risk of thrombosis between different ESAs, a similar risk among all erythropoietin agents has been suggested.[86]

The risk of experiencing TEs in patients receiving ESAs increases according to baseline haemoglobin levels (for haemoglobin < 10 g/dL, RR: 1.41, 95% CI: 1.06–1.99; for haemoglobin 10–12 g/d, RR: 1.64, 95% CI: 1.33–2.03; for haemoglobin > 12 g/dL, RR: 1.41, 95% CI: 1.15–1.80). Current recommendations proposed by the National Comprehensive Cancer Network (NCCN),[87] European Organization for Research and Treatment of Cancer (EORTC),[88] ASCO/ASH,[81] ESMO,[89] and Sociedad Española de Oncología Médica[90] on how to use ESAs suggest a haemoglobin target around 12 g/dL and avoid ESAs in patients not receiving chemotherapy.

Leaving aside the common risks arising from the use of ESAs in cancer patients, it has been noted that treatment with darbepoetin alfa in patients with chronic renal failure and anaemia increases the risk of cerebrovascular accidents (HR: 1.92, 95% CI: 1.38–2.68).

Despite the clear relationship that has been established between ESAs and thrombosis in cancer patients, no randomized clinical trial has yet evaluated the possible role of thromboprophylaxis in this context. To date, systemic prophylaxis with low-molecular-weight heparins or anti-platelet drugs (acetylsalicylic acid) is not generally recommended. However, it should be advised in those cases with low bleeding risk in which a considerable number of risk factors for thrombosis converge.

Granulocyte colony stimulating factors (G-CSF)

The use of G-CSF has been associated with an increase in the risk of VTE in patients with solid tumours (HR: 1.69, 95% CI: 1.09–2.64; $P = 0.02$).[63]

Corticosteroids

Corticosteroid treatment increases the risk of VTE.[91] A prospective observational cohort study conducted in the UK found a significant and independent increased risk of VTE and PE among oral corticosteroids users similar to that described with other commonly known risk factors such as oral contraceptives, obesity, surgery, varicose veins, etc.[91] This risk increases with extended treatment duration and elevated doses. A case–control study remarked a 1.2 to 2-fold increase in venous thromboembolic risk in patients receiving systemic corticosteroid therapy for >3 months.[92] The magnitude of the association between corticosteroid use and VTE depended on the administration form. Hence, the risk increased with cumulative doses so that it doubled with an equivalent dose of prednisolone of 1–2 g compared to doses below 10 mg. Also, patients who received corticosteroid treatment for the first time had a higher venous thromboembolic risk (RR: 3.06, 95% CI: 2.77–3.38) than

Table 3 Review of the main meta-analyses of safety of erythropoietin stimulating agents

Author	Year	Studies included	Global mortality	Mortality in studies with chemotherapy	Thrombotic risk
Bohlius *et al.*[82]	2006	Cancer patients *with/without anaemia, with/without chemotherapy* receiving ESAs.	HR: 1.08, 95% CI: 0.99-1.18; 42 studies, 8167 patients	RR: 1.02, 95% CI: 0.90-1.15; 30 studies, 6282 patients	RR: 1.67, 95% CI: 1.35-2.06; 35 studies, 6769 patients
Bennett *et al.*[83]	2008	Cancer patients receiving *chemotherapy* and darbopoetin alfa	HR: 1.10, 95% CI: 1.01-1.2; 51 studies, 13 611 patients		RR: 1.57, 95% CI: 1.31-1.87; 31 studies, 8172 patients
Ludwig *et al.*[84]	2009	Cancer patients with *chemotherapy-induced anaemia* treated with darbopoetin alfa	HR: 0.97, 95% CI: 0.85-1.1; 6 studies, 2211 patients		RR: 1.57, 95% CI: 1.10-2.26; 6 studies, 2122 patients
Glaspy *et al.*[85]	2010	Cancer patients *with/without anaemia, with/without chemotherapy* receiving ESAs.	HR: 1.16, 95% CI: 0.97-1.15; 60 studies, 15 323 patients	OR: 1.03, 95% CI: 0.93-1.13; 47 studies, 12 108 patients	RR: 1.48, 95% CI: 1.28-1.72; 44 studies, 13 196 patients
Tonia *et al.*[86]	2012	Cancer patients *with/without anaemia, with/without chemotherapy* receiving ESAs.	HR: 1.17, 95% CI: 1.06-1.29; 70 studies, 15 935 patients		RR: 1.52, 95% CI: 1.34-1.74; 57 studies, 15 498 patients

CI, confidence interval; ESAs, erythropoietin stimulating agents; HR, hazard ratio; OR, odds ratio; RR, relative risk.

those under chronic therapy. These findings were independent of potential confounding risk factors, such as the severity of the underlying disease or the risk of thrombosis secondary to the tumour itself. There is currently insufficient literature pertaining to the risk of VTE associated with corticosteroid therapy in patients with solid tumours to support thromboprophylaxis.

Non-steroidal anti-inflammatory drugs

There are no specific studies of non-steroidal anti-inflammatory drugs (NSAIDs) and thrombosis in cancer patients. The only available information is based on population studies. Systematic review and meta-analysis[93] were conducted in 2014 including studies that reported ORs, RRs, HRs, or standardized incidence ratios for VTE among NSAIDs users compared with non-users. Six studies with 21 401 VTE were identified. The pooled risk ratio of VTE in NSAIDs users was 1.80 (95% CI: 1.28-2.52). Furthermore, the intake of COX-2 inhibitors was also responsible for an increased risk of VTE (RR: 1.99, 95% CI: 1.44-2.75).

Hormone therapy

Since the approval of tamoxifen by the US FDA multiple studies have concluded that tamoxifen therapy in breast cancer patients is an independent risk factor for the development of VTE.[94-97] Women treated with tamoxifen have a 1.5 to 7.1-fold increased risk of VTE compared to those treated with placebo or observation only.[94] In addition, AIs are also associated to VTE although its incidence falls below that of tamoxifen. However, not all the published studies have confirmed this finding. An observational cohort in a retrospective study from the UK described that therapy with AIs was not associated with VTE (HR: 0.8, 95% CI: 0.5-1.4; absolute rate 28.3 per 1000 person-years).[98] Several studies have compared tamoxifen with AIs for breast cancer treatment with similar results regarding to venous thromboembolic risk but a lower incidence of venous TEs in the AIs treatment arms (*Table 4*).[99-101] All these data were subsequently confirmed in a meta-analysis published in 2011 including seven studies and 30 023 women that compared AIs and tamoxifen as primary adjuvant endocrine therapy in postmenopausal women.[102] Longer duration of AI treatment was associated with a 45% decrease in the RR decrease of VTE in women who received an AI compared to those treated with tamoxifen (RR: 0.55, 95% CI: 0.46-0.64; $P < 0.001$). A second meta-analysis published in 2013 confirmed the significantly lower risk of TEs conferred by AIs compared to tamoxifen (OR 0.61, $P < 0.001$).[103]

Fulvestrant is a pure antioestrogen approved in breast cancer treatment. The prospectively combined analysis from studies 0020 and 0021[104] compared fulvestrant with anastrozole in the treatment of postmenopausal women with advanced breast cancer who had disease progression after receipt of previous endocrine treatment. The conjoint analysis of both studies showed that fulvestrant was not significantly different to anastrozole in terms of VTE incidence rate (anastrozole 4.5% vs. fulvestrant 3.5%, $P = 0.46$). Taken together, these data suggested that fulvestrant appeared to have a slightly lower risk of VTE that tamoxifen in women with hormone dependant advanced breast cancer.

Recently two new drugs with antiandrogenic activity have been approved for the treatment of CRPC: enzalutamide and abiraterone.

Table 4 Incidence of venous thromboembolism related to aromatase inhibitors compared with tamoxifen

Study	Number of patients	Drug	VTE results
ATAC[99]	9366	Anastrozole	Anastrozole 2.8% vs. tamoxifen 4.5% RR: 0.61, 95% CI: 0.47–0.80; $P = 0.004$
BIG 1-98[100]	8010	Letrozole	Letrozole 1.5% vs. tamoxifen 3.5% $P < 0.001$
TEAM[101]	9779	Exemestane	Exemestane 1% vs. Tamoxifen-exemestane 2% $P < 0.0001$

VTE, venous thromboembolism.

- Abiraterone inhibits androgen synthesis by blocking the enzyme cytochrome P450 17 alpha-hydroxylase (CYP 17). This enzyme plays a critical role in the synthesis of androgens in the adrenal glands, testes, and prostate.
- Enzalutamide is an androgen receptor inhibitor that acts on different steps in the androgen receptor signalling pathway. It has been shown to competitively inhibit androgen binding to androgen receptors and inhibit androgen receptor nuclear translocation.

None of the Phase III studies[105–108] that led to the approval of these drugs explicitly mention an increase in the VTE risk.

Immunotherapy

In the last decade, immune checkpoint inhibitors have been approved for different tumours. To date, no evidence coming from randomized clinical trials exists to prove the relationship between VTE with anti-cytotoxic T-lymphocyte-antigen-4 (CTLA4) agents (ipilimumab), anti-programmed death-1 (PD-1) agents (nivolumab and pembrolizumab), and anti-programmed death-ligand 1 (PD-L1) agents (atezolizumab, avelumab, and durvalumab). Recently, several clinical cases published have suggested that checkpoint inhibitors may induce systemic inflammation as main toxicity, possibly resulting in development of venous thromboembolism.[109] Other authors have reported ATE associated to anti-PD1 moAb.[110] The proposed physiopathology is accelerated atherosclerotic plaque development and inflammation in predisposed cancer patients. An interesting finding is that these events were observed in patients with cancer response to anti-PD1 therapy. The same authors have suggested it is likely these events could have been underestimated in clinical trials and not linked to checkpoint inhibitors. All this evidence suggests acute thrombosis could be considered a rare but potential fatal immune-related adverse event.

Conclusions

- In cancer patients, a thrombosis risk assessment should be conducted before starting any type of pharmacological systemic therapy (the risk of thrombosis varies significantly among the different agents).
- It would be desirable that clinical trials analysed in more detail the occurrence, clinical characteristics, and possible relationship of TEs with cancer treatments.
- VTE risk assessment scores should include variables related to pharmacological therapy.

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