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REVIEW ARTICLE

Angiogenesis Inhibitor Induced Thromboembolism in Cancer Patients

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Abstract

Therapy with Angiogenesis Inhibitors (AIs) is a newer targeted approach in treating cancers. It gained popularity in the past decade because of better outcomes and fewer side effects when compared to conventional chemotherapeutic agents. These agents act by inhibiting the VEGF pathway and inhibit vasculogenesis, thus shutting off the nutrient supply to the continuously multiplying tumor cells. Growth of blood vessels is a dynamic process in the human body which is required for the various other processes throughout the human life. Thus, apart from their effects on tumor cells, AIs have a unique side effects profile which is quite different from the side effects of traditional chemotherapeutic agents. Thromboembolic Events (TES), both arterial and venous, are part of AIs side effects, which may be life threatening at times and should be diagnosed as soon as possible in patients who are on AI therapy. They need to be taken care of expeditiously to prevent more serious side effects. This review aims to enumerate the risk of TEs with each AI and the current recommendations to be followed in patients with history of TEs or in patients with TEs while on AI therapy. These recommendations will help to prevent more catastrophic events from occurring in these patients.

Keywords

Thromboembolism, Angiogenesis inhibitor, Cancer, Targeted therapy, Side effect

Introduction

With greater advancements in the understanding of the basic pathogenesis of cancer development as well as the molecular basis of the cancer cells, novel approaches in the treatment of various cancers are continuously being developed. In recent years there has been more focus in the development of targeted therapies compared to conventional chemotherapy. Targeted agents are providing better outcomes in patients with cancer and with fewer side effects when compared to conventional agents.

Angiogenesis Inhibitors (AIs) are one of the classes of targeted therapy being used in the treatment of various cancers. Adverse effects profile of AIs is completely different when compared to traditional chemotherapeutic agents owing to their different mechanism of action on tumor cells. Due to more promising results with AIs, an increasing number of oncologists are utilizing these agents in treatment regimens for cancer patients. However, there is an increase in the number of patients being seen by their respective primary care physicians to manage the side effect profile of these agents. Thus, it has become necessary for primary care physicians to be familiar with these agents as well as with the adverse effect profile of these agents.

Methods

A systematic search of Pub med and the NIH website was performed to identify all the United States Food and Drug Administration (FDA) approved AIs as well as to identify all the data regarding the risk factors, incidence, severity and recommendations for thromboembolic events associated with these agents.

Angiogenesis *in vivo*-brief overview

Human cells essentially derive all of their nutrition from Blood Vessels (BVs), with each cell being at least 100-200 µm in proximity to the nearby BV, allowing them to receive their nutrition via diffusion. This distance is usually the ideal average diffusion range for most of the BVs. Whenever a cell happens to grow beyond this distance range from the nearby BV, it will

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Table 1: Conditions resulting from aberrations in angiogenesis.

Due to inadequate angiogenesis or vessel regression		Due to excessive or abnormal angiogenesis	
Alzheimer`s disease	Crohn`s disease	Cancer	Primary pulmonary hypertension
Amyotropic lateral sclerosis	Diabetic neuropathy	Kaposi's sarcoma	Hemangiomas
Pre-eclampsia	Gastric or oral ulcerations	Psoriasis	Arthritis
Impaired bone fracture and healing	Osteoporosis	Digeorge`s syndrome	Synovitis
Hair loss	Neonatal respiratory distress	Inflammatory bowel disease	Osteomyelitis

Table 2: Factors involved in angiogenesis.

Pro-angiogenic agents		Anti-angiogenic agents
Vascular endothelial growth factor	Fibroblast growth factor	Angiopoietin II
Angiopoietin I	Insulin-like growth factor	Angiostatin
Platelet-derived growth factor	Placental growth factor	Endostatin
Epidermal growth factor	Tumor necrosis factor α & β	Fumagillin
Hepatocyte growth factor	Platelet-activating factor	Thrombospondin 1 & 2
		Transforming growth factor β
		Interferon α, β, γ

result in the growth of new BVs for maintenance of its nutrition [1]. Thus, angiogenesis is one of the most vital processes in the human body.

The most essential process for establishment of human life is angiogenesis, as it is required for the implantation of the embryo during establishment of pregnancy as well as throughout the period of embryogenesis and fetal growth until term for meeting the ever increasing demand for nutrition of the developing fetus. Later following birth of a baby, it continues throughout life as a dynamic process required for growth and maturation of the human body and also for the maintenance of homeostasis between various processes in the human body.

Both, insufficient and excessive angiogenesis, can be responsible for multiple disease processes in the human body. Some important conditions caused by aberrations in angiogenesis are listed in Table 1 [2].

Angiogenesis regulation

Angiogenesis is regulated by both pro- and anti-angiogenic molecules (Table 2) [3]. Vascular Endothelial Growth Factor (VEGF) gene expression is the major rate limiting step in the process of angiogenesis. Oxygen tension, in turn is the major contributor for the expression of the VEGF gene through Hypoxia Inducible Factor-1 (HIF-1) [4,5].

Other cytokines which are responsible for the up regulation of VEGF gene expression are Epidermal Growth Factor (EGF), Transforming Growth Factor - α & β (TGF - α & β), Insulin - Like Growth Factor-1 (IGF-1), Fibroblast Growth Factor (FGF), and Platelet-Derived Growth Factor (PDGF). All are primarily limited to ischemic zones [5,6]. While these factors are essential for VEGF gene expression, angiopoietins play an essential role in regulation of endothelial cell survival and its interactions with other supporting cells [7]. Agents like angiostatin, endostatin, fumagillin and thrombospondin-1 and 2 are involved in the inhibition of VEGF expression [8].

VEGF family, VEGF pathway and cancer chemotherapy

Apart from the above mentioned cytokine signaling pathways, other signaling pathways involved in the process of angiogenesis are notch, Delta Like Ligand-4 (DLL-4), hedgehog and WNT pathways [9]. Among all the pathways, VEGF is a very important factor regulating both physiological and pathological vasculogenesis (angiogenesis and lymph angiogenesis).

The VEGF family consists of VEGF A to D, Placental Growth Factor (PLGF) and homologous sequences in parapoxvirus Orf viruses. VEGF-A (previously known as vascular permeability factor) is the dominant growth factor responsible for the angiogenesis. All of these act via specific tyrosine kinase receptors - VEGF Receptors (VEGFR). VEGFR-1 and VEGFR-2 are primarily found on endothelial cells and are associated with the development of BVs, whereas VEGFR-3 is primarily associated with lymph angiogenesis [10].

VEGFs are responsible for vascular hyper permeability, endothelial cell activation, proliferation, invasion and migration as well as their survival. All of these characteristics determine the angiogenic ability of a tumor which in turn primarily defines its basic characteristics like growth, progression, invasion and metastasis. Thus, targeting the angiogenic signaling molecules have shown promising results in controlling the tumor burden. Angiogenesis is targeted at various steps in its pathway. Current AIs in the market act via the following mechanisms,

1) Direct inhibition of VEGF by anti-VEGF Antibodies (ABs), anti VEGFR ABs and small molecule VEGFR inhibitors.

2) Inhibition of other ancillary cytokines stimulating VEGF gene expression - Epidermal Growth Factor (EGF) ABs and Epidermal Growth Factor Receptor (EGFR) inhibitors.

Table 3: Characteristics of angiogenesis inhibitors.

Drug name	Brand name	EGFR - I	TKI	VEGF - I	AI	Mode of administration
Afatinib	Gilotrif	✓	✓		✓	Oral
Axitinib	Inlyta		✓	✓	✓	Oral
Bevacizumab	Avastin			✓	✓	Intravenous, Intravitreal
Bosutinib	Bosulif		✓		✓	Oral
Cabozantinib	Cometriq		✓	✓	✓	Oral
Ceritinib	Zykadia		✓		✓	Oral
Cetuximab	Erbitux	✓			✓	Intravenous
Crizotinib	Xalkori		✓		✓	Oral
Dasatinib	Sprycel		✓		✓	Oral
Erlotinib	Tarceva	✓	✓		✓	Oral
Gefitinib	Iressa	✓	✓		✓	Oral
Ibrutinib	Imbruvica		✓		✓	Oral
Imatinib	Gleevec		✓		✓	Oral
Lapatinib	Tykerb	✓	✓		✓	Oral
Nilotinib	Tasigna		✓		✓	Oral
Panitumumab	Vectibix	✓			✓	Intravenous
Pazopanib	Votrient		✓	✓	✓	Oral
Ponatinib	Iclusig		✓		✓	Oral
Ramucirumab	Cyramza			✓	✓	Intravenous
Regorafenib	Stivarga		✓	✓	✓	Oral
Ruxolitinib	Jakafi		✓		✓	Oral
Sorafenib	Nexavar		✓	✓	✓	Oral
Sunitinib	Sutent		✓	✓	✓	Oral
Vandetanib	Caprelsa	✓	✓	✓	✓	Oral
Ziv-Aflibercept	Zaltrap			✓	✓	Intravenous

EGFR-I: Endothelial Growth Factor Receptor Inhibitors; TKI: Tyrosine Kinase Inhibitors; VEGF-I: Vascular Endothelial Growth Factor Inhibitors; AI: Angiogenesis Inhibitors; ✓: Yes.

Additional drugs which also act by inhibiting other molecules related to angiogenesis such as PDGF and HIF1s, and drugs targeting antiangiogenic agents *in vivo* are still in clinical trials.

Many of the AIs approved by the FDA may be used either alone or in conjunction with other chemotherapeutic agents in various solid tumors as well as hematologic malignancies for much better results with the therapy (Table 3 and Table 4). Most common adverse effects of AIs include fatigue, hypertension, proteinuria, abdominal pain and change in bowel habits, stomatitis, impaired wound healing and electrolyte disturbances. More serious adverse effects with the usage of AIs which result in changes in dose or complete discontinuation of treatment with AIs include grade 3 and 4 hypertension, severe (grades ≥ 3) Thromboembolic Events (TEs), hemorrhage, gastrointestinal perforation, cardiac impairment and neutropenia [11].

Angiogenesis inhibitor associated thromboembolism

Endothelial cells play a critical role in the regulation of vascular homeostasis by various mechanisms, one of which is the maintenance of local balance between pro-coagulant and anticoagulant molecules. Any stimulus which disturbs the normal structure of endothelium will also result in a deranged balance between pro- and anti-coagulant molecules locally which in turn leads to either increased clotting or increased bleeding [12]. Cancer patients have an increased predisposition for endothelial disruption due to various local and systemic inflammatory stimuli produced by either the cancer cell themselves of which are derived from the host cells as a secondary response to the underlying neoplastic process. These stimuli include release of cytokines like TNF, Interleukin-β (IL-β) or antiangiogenic factors as well as increased expression of tissue factor. Endothelial cell damage leads to the activation of hemostatic mechanisms in the body.

Other risk factors also contribute to the pro-coagulant states in cancer patients. These may be divided into 3 broad categories - Patient related, cancer related or therapy related. Patient related factors may include all the factors which are implicated for increased risk of coagulation as in normal patients like advanced age, underlying comorbidities, family history of coagulation disorders and level of activity. Cancer related factors depend on type of cancer and stage of cancer. Treatment related factors include type of agent, duration of treatment, and long term hospitalizations for treatments.

Therapy with AIs increases the risk of thrombosis in already hyper coagulable patients secondary to cancer. Various mechanisms responsible for increased incidence of thrombosis in cancer patients with AI therapy include, a) Resistance to activated protein C, b) High levels of C-Reactive Protein (CRP), factor VIII, and Von Willebrand Factor (VWF) [13,14]. Another mechanism of thromboses in patients on AIs is due to diminished regenerative capacity of endothelial cells secondary to

Table 4: FDA approved indications of angiogenesis inhibitors.

Drug name	FDA approval year	Prescribing considerations for TE risk	Indications
1. Afatinib	2013	No	• Metastatic NSCLC with EGFR exon mutations
2. Axitinib	2012	Yes	• Advanced Renal Cell Carcinoma (RCC) after failure of one prior systemic therapy
3. Bevacizumab	2004	Yes	• First or second line treatment for mCRC as a combination agent with 5 Fluorouracil (5 FU) • Progression of glioblastoma on prior other therapy • As a combination agent for • Persistent, recurrent, or metastatic carcinoma of the cervix • Unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer • Metastatic RCC • Recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer
4. Bosutinib	2012	No	• Philadelphia Chromosome Positive (Ph+) Chronic Myelogenous Leukemia (CML)
5. Cabozantinib	2012	Yes	• Progressive, metastatic Medullary Thyroid Cancer (MTC)
6. Ceritinib	2014	No	• Metastatic NSCLC, Anaplastic Lymphoma Kinase (ALK) positive
7. Cetuximab	2004	No	• EGFR expressing wild type K RAS mCRC • Squamous cell carcinoma of the head and neck
8. Crizotinib	2011	No	• Anaplastic Lymphoma Kinase (ALK) positive metastatic NSCLC
9. Dasatinib	2006	No	• Newly diagnosed chronic phase Ph+ CML • Ph+ CML chronic, accelerated, or myeloid or lymphoid blast phase with resistance or intolerance to prior therapy including imatinib • Ph+ ALL with resistance or intolerance to prior therapy
10. Erlotinib	2004	Yes	• NSCLC with EGFR exon mutations • Progressive locally advanced or metastatic NSCLC • Locally advanced, unresectable or metastatic pancreatic cancer
11. Gefitinib	2015	No	• Metastatic NSCLC with EGFR exon mutations
12. Ibrutini b	2013	No	• Mantle Cell Lymphoma (MCL) • Unresponsive Chronic Lymphocytic Leukemia (CLL) • CLL with 17p deletion • Waldenström's Macroglobulinemia Lymphoma (MCL)
13. Imatinib	2001	No	• Newly diagnosed chronic phase Ph+ CML • Blast crisis, accelerated phase, or chronic phase and relapsed or refractory Ph+ CML • Newly diagnosed Ph+ ALL in pediatric patients • Myelodysplastic/myeloproliferative diseases with PDGFR gene re arrangements, in adult patients • Aggressive systemic mastocytosis without or unknown c Kit mutation • Hypereosinophilic syndrome and/or chronic eosinophilic leukemia • Dermatofibrosarcoma protuberans unresectable, recurrent and/or metastatic • Malignant gastrointestinal stromal tumors Kit (CD117) positive unresectable and/or metastatic • Adjuvant treatment for Kit (CD117) positive Gastrointestinal Stromal Tumor (GIST) after complete gross resection

14. Lapatinib	2007	No	• Advanced or metastatic breast cancer with over expression of Human Epidermal Growth Factor Receptor 2 (HER2)
15. Nilotinib	2007	Yes	• Newly diagnosed chronic phase and resistant or intolerant chronic and accelerated phases of Ph+ CML
16. Panitumumab	2006	Yes	• Wild type KRAS mCRC
17. Pazopanib	2009	Yes	• Advanced RCC • Advanced Soft Tissue Sarcomas (STS)
18. Ponatinib	2012	Yes	• T315I positive CML (chronic phase, accelerated phase, or blast phase) or T315Ipositive Ph+ ALL • Chronic phase, accelerated phase, or blast phase CML or Ph+ ALL for whom no other TKI therapy is indicated
19. Ramucirumab	2014	Yes	• Progressive advanced or metastatic, gastric or gastro esophageal junction adenocarcinoma • Progressive metastatic NSCLC • Progressive mCRC
20. Regorafenib	2012	Yes	• Resistant or progressive mCRC • Progressive locally advanced, unresectable or metastatic GIST
21. Ruxolitinib	2011	No	• Intermediate or high risk myelofibrosis, including primary myelofibrosis, postpolycythemia including primary myelofibrosis, postpolycythemia vera myelofibrosis and postessential vera myelofibrosis and postessential thrombocythemia myelofibrosis • Polycythemia vera in patients with inadequate response to or who are intolerant of hydroxyurea
22. Sorafenib	2005	Yes	• Unresectable Hepato Cellular Carcinoma (HCC) • Advanced RCC • Radioactive iodine treatment refractive locally recurrent or metastatic, progressive, DTC
23. Sunitinib	2006	No	• Progressive GIST or GIST in patients intolerant to imatinib • Advanced RCC • Unresectable locally advanced or metastatic, progressive, well differentiated pancreatic neuroendocrine tumors
24. Vandetanib	2011	Yes	• Symptomatic or progressive, unresectable locally advanced or metastatic MTC
25. Ziv Aflibercept	2012	Yes	• Resistant or progressive mCRC

inhibition of the VEGF pathway which plays a role in the endothelial cell proliferation survival and maintenance of vascular integrity [15]. Disinhibition of pro-coagulant pathways due to inhibition of the VEGF pathway which results in reduction of Nitric Oxide (NO) and Prostacyclin (PGI2) was also considered as one of the mechanisms predisposing to increased Thromboembolic Events (TEs) in patients on AIs. Increased blood viscosity due to over production of hepatic erythropoietin secondary to VEGF inhibition also contributes to increased risk of thrombosis during therapy with AIs [16-18].

AIs, either given alone or in combination with conventional chemotherapeutic drugs have been shown to increase the risk of TEs, both on the arterial as well as venous sides. The most common presentations include peripheral vascular disease, ischemic heart disease, myocardial infarction, deep vein thrombosis, and pulmonary embolism. Less commonly, it may lead to cerebral ischemia, transient ischemic attack, intra-abdominal thrombosis, retinal vein thrombosis, and thrombotic microangiopathy [19].

Incidence of thrombotic events varies depending on various patient demographics like age of the patient, other comorbidities present, and previous history of TEs. They also vary depending on the type of cancer being treated, the total dose and duration of AI treatment, the concomitant use of the other chemotherapies, or the use of other drugs causing thromboembolism [20].

Thromboembolic Events with various Angiogenesis Inhibitors

The very first report highlighting the angiogenesis in tumor growth was published by Dr. Judah Folkman in NEJM, 1971 [21]. He emphasized the importance of angiogenesis in tumor growth and survival and hypothesized that, if the factor responsible (which was not yet determined at that time) for the tumor angiogenesis can be blocked, it will result in the death of the tumor. Actual interest of biopharmaceutical industry to exploit antiangiogenesis for treating tumors was started in the 1980`s, and they started creating new therapeutic compounds. Thirty three years after the famous publication

Table 5: CTCAE grading of thromboembolic events [41].

Adverse event	Thromboembolic event	
Grade 1	Venous thrombosis (e.g., superficial thrombosis)	
Grade 2	Venous thrombosis (e.g., uncomplicated deep vein thrombosis)	Medical intervention indicated
Grade 3	Thrombosis (e.g., uncomplicated pulmonary embolism [venous], non-embolic cardiac mural [arterial] thrombus)	Medical intervention indicated
Grade 4	Life-threatening (e.g., pulmonary embolism, cerebrovascular event, arterial insufficiency); hemodynamic or neurologic instability	Urgent intervention indicated
Grade 5	Death	

Table 6: Risk of arterial/venous thromboembolism with AI's and recommendations.

Drug name	Risk of ATE	Risk of VTE	Recommendations
Axitinib	✓	✓	Axitinib should be used with caution in patients who are at increased risk of thromboembolic events as well as in patients who have a prior history of these events [24].
Bevacizumab	✓	✓	Bevacizumab should be discontinued in all patients who experience a severe ATE and safety of its resumption has not been studied yet. Permanently discontinue Bevacizumab therapy in patients with life threatening (grade 4) VTE`s [28].
Cabozantinib	✓	✓	Should be discontinued in patients who experience acute MI as well as in patients who develop any other clinically significant arterial thrombotic complications [29].
Erlotinib	✓	✓	No specific recommendations [30].
Nilotinib	✓	Not reported	Patients who are being started on Nilotinib should be advised to seek immediate medical attention, should they develop any signs or symptoms of cardiovascular events. Before starting Nilotinib, patients cardiovascular status should be evaluated and cardiovascular risk factors should be monitored and managed regularly according to the standard guidelines [31].
Panitumumab	Not reported	✓	No specific recommendations [32].
Pazopanib	✓	✓	Pazopanib should be used with caution in patients with a history of ATE`s or who are at increased risk of ATE`s. All patients should be monitored for signs and symptoms VTE and PE during Pazopanib therapy [33].
Ponatinib	✓	✓	In patients suspected of developing ATE`s, it is recommended that the treatment should be discontinued and a benefit risk re consideration should guide the decision to restart the therapy with Ponatinib. In patients who develop serious VTE, dose modification or discontinuation of the drug should be considered [34].
Ramucirumab	✓	Not reported	It should be permanently discontinued in patients experiencing a severe ATE [35].
Regorafenib	✓	Not reported	It should be discontinued in patients who develop new or acute onset myocardial ischemia or infarction. Resumption of the treatment should be based upon consideration of potential benefits versus risks of further cardiac ischemia [36].
Sorafenib	✓	Not reported	Temporary or permanent discontinuation of sorafenib should be considered in case of development of cardiac ischemia or infarction in a patient [37].
Vandetanib	✓	Not reported	Vandetanib should be discontinued in patients who experience severe thrombotic events [38].
Ziv Aflibercept	✓	Not reported	Ziv aflibercept should be discontinued in patients experiencing an ATE [39].

✓: Yes.

of Dr. Folkman, the first AI, bevacizumab, was approved by the FDA in 2004 for combination use with standard chemotherapy in patients with metastatic colon cancer. After approval of bevacizumab, many more AIs were approved by FDA in the past decade. There are many more in the FDA approval process waiting to appear in the market [22].

Afatinib, bosutinib, ceritinib, cetuximab, crizotinib, dasatinib, gefitinib, ibrutinib, imatinib, lapatinib, ruxolitinib and sunitinib have not been reported to have significant increase in TE`s with their use [23]. Remaining agents may result in various grades of TEs from simple superficial thromboses to severe life-threatening events and even death. Common Terminology Criteria for Adverse Events (CTCAE) grading of TEs is listed in Table 5. Table 6 describes the risks of ATE/VTE and recommendations for each of the following agents.

Axitinib: Axitinib is a small molecule Tyrosine Kinase Inhibitor (TKI) which was initially approved by the FDA in January 2012 for use as a second line treatment agent in patients with advanced Renal Cell Carcinoma (RCC), in patients who have failed one prior systematic therapy. It acts by inhibiting receptor tyrosine kinases which also includes VEGFR`s.

Axitinib use results in 2% arterial thromboembolic events of all grades with 1% of them being grade 3/4. These include Transient Ischemic Attacks (TIAs), Cerebrovascular Accidents (CVAs), Myocardial Infarction (MI) and retinal artery occlusions [24]. Incidence of all grade Venous Thromboembolic Events (VTEs) in patients receiving axitinib was reported around 3% in controlled clinical trials with most of them being grades 3/4. These include Pulmonary Embolism (PE), Deep Venous Thrombosis (DVT) retinal vein occlusion and retinal vein thrombosis. It has not been studied yet in patients who had an ATE within the previous 12 months or a VTE in the previous 6 months, prior to the start of axitinib therapy, hence caution should be used when administering this agent to these subsets of patients.

Bevacizumab: Bevacizumab (BV) is a recombinant, humanized monoclonal antibody, which specifically binds to VEGF and inhibits its action on endothelial receptors, thereby blocking angiogenesis. It was first approved by the FDA in 2004 for combination use with standard chemotherapy in patients with metastatic colon cancer. Later, it was approved for treatment in various other cancers either alone or in combination with other standard chemotherapeutic regimens. It has also been approved for the treatment of certain eye diseases.

BV usage results in 6% increased incidence of ATEs of any grade with 3% of them being grade 3/4. These events include cerebral infarction, TIAs, MI and angina. Major risk factors for occurrence of ATE in patients receiving BV in combination with other chemotherapeutic agents were observed to be history of previous ATE, diabetes and age ≥ 65 years.

Combination therapy with BV and chemotherapy did show increased risk of TE's in various studies. A meta-analysis performed by Ranpura, et al. published in 2010, concluded that relative risk of ATE was increased by 1.44 (95% CI, 1.08-1.91; p = 0.013) with combination therapy including BV and chemotherapy, when compared to standard anti-neoplastic therapy [25]. Another study performed by Schutz, et al. published in 2011, did show increased relative risk of ATE with BV-based therapy by 1.46 (95% CI 1.11-1.93, P = 0.007) when compared to the controls without BV-based therapy [26]. Similarly, another meta-analysis by Nalluri, et al. showed that the use of BV was also associated with an increased risk [with an RR of 1.33 (95% CI, 1.13-1.56; P < .001) compared with controls] of developing VTE in cancer patients [27].

Thus, BV should be discontinued in all patients who experience a severe ATE. Safety of its resumption has not been studied yet. Any grade VTE occurs with an incidence of 8-14% in patients receiving BV with 5-15% being grade 3/4. These include DVT, intraabdominal thrombosis and PEs. The risk of occurrence of these events still remains elevated (around 21%) with the continuation of BV therapy with the addition of anticoagulants following the initial event of VTE. Thus it is advised to permanently discontinue BV therapy in patients with life-threatening (grade 4) VTEs [28].

Cabozantinib: Cabozantinib is a small molecule TKI which inhibits the activity of multiple tyrosine kinases including MET proto-oncogene, Rearranged during Transfection (RET), VEGFR-1, 2, & 3, TIE-2. It was first approved by the FDA for the treatment of progressive, metastatic Medullary Thyroid Cancer (MTC) in 2012 and is currently undergoing clinical trials for the treatment of various other cancers. Treatment with cabozantinib results in increased incidence of any grade ATE (2%) as well as VTE (6%). It should be discontinued in patients who experience acute MI as well as in patients who develop any other clinically significant arterial thrombotic complications [29].

Erlotinib: Erlotinib is a reversible TKI which inhibits the kinase activity of EGFR. It was first approved by the FDA for use in patients with locally advanced or metastatic Non-Small Cell Lung Cancer (NSCLC), who has failed at least one other prior chemotherapy regimen. Though there are no reports yet suggesting increased incidence of ATEs or VTEs with erlotinib monotherapy, there are reports of increased incidence of these events with erlotinib in combination with other chemotherapeutic regimens. When erlotinib is used in combination with gemcitabine, increased incidence of DVT (4%), MI (2%) and CVAs (2%) were observed when compared to the use of placebo plus gemcitabine usage. Overall grade 3/4 thrombotic events occurred in 11% patients on erlotinib plus gemcitabine combination therapy when compared to gemcitabine plus placebo. There have been no significant studies performed to warrant any specific recommendations for the dose changes or for discontinuation of the drug [30].

Nilotinib: Nilotinib is a selective TKI which specifically targets BCR-ABL kinase by binding to ABL protein and acts by stabilizing the inactive conformation of the kinase domain. It was first approved by the FDA in 2007 for use in the treatment of adult patients with chronic and accelerated phases of Chronic Myelogenous Leukemia (CML) and accelerated resistance or intolerance to prior therapy which includes imatinib. Nilotinib is responsible for various ATEs which are dose dependent. Its use results in 9-15% of ATE`s, incidence varying with the dose of the drug (9% with 300 mg dose and 15% with 400 mg dose). Most of these events are ischemic heart disease, cerebral ischemia, peripheral arterial occlusions and ischemic cerebrovascular events [31].

Panitumumab: Panitumumab is a recombinant human IgG2 monoclonal antibody which specifically binds to the EGFR and competitively inhibits the binding of EGF and other ligands to it. It was originally approved by the FDA in 2006 for the treatment of patients with EGFR - expressing metastatic colorectal cancer with disease progression despite treatment with prior chemothera-

py regimens. Panitumumab monotherapy increases the incidence of PE by 1%. In combination with Oxaliplatin + Fluorouracil (5 FU) + Folinic Acid (FOLFOX) chemotherapy regimen, panitumumab increases the incidence of DVT`s by 5% [32].

Pazopanib: Pazopanib is a multi-targeted TKI which acts via inhibiting various cell surface receptors including VEGFR's 1-3, PDGFR's α & β and FGFR's 1 & 3 as well as many other receptor proteins. It was first approved in 2009 by the FDA for the use in the treatment of advanced or metastatic RCC. In patients with RCC receiving pazopanib, MI or ischemia occurred with an increased incidence of 2% along with an incidence of 0.3% cerebrovascular accidents and 1% TIA's. Fatal ATE's were reported in 0.3% of patients. In patients with STS, MI or ischemia and CVA`s occurred with an incidence of 2% and 0.4% respectively with no reported TIAs or fatal ATE`s. Pazopanib should be used with caution in patients with a history of ATEs or who are at increased risk of ATEs. There were no studies done for evaluation of risk of using pazopanib in patients with a history of ATE within 6 months prior to the start of pazopanib therapy, and thus it should be avoided in this subset of patients. Reported incidence for VTE`s were 1% in RCC patients and 5% in STS patients with no fatal PEs in RCC patients and 1% of fatal PEs in STS patients [33].

Ponatinib: Ponatinib is an orally available multi-targeted pan-BCR-ABL TKI first approved by FDA in 2012 for the treatment of adults with CML and Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL). In phase 1 and 2 clinical trials for ponatinib, arterial and venous TEs were reported in at least 27% of patients. Ponatinib is known to cause fatal and life threatening vascular occlusions, and these may be within 2 weeks of initiation of therapy. It can also result in recurrent and multi-site vascular occlusions. These vascular occlusive adverse events were seen more frequently with increasing age and in patients with a prior history of ischemia, hypertension, diabetes or hyperlipidemia. The risk of vascular adverse effects was particularly increased in patients who were sequentially treated with nilotinib and ponatinib.

ATEs including fatal and life threatening events were observed in almost 20% patients. In patients suspected of developing ATEs, it is recommended that the treatment should be discontinued and a benefit-risk re-consideration should guide the decision to restart the therapy with ponatinib. VTEs were observed in 5% of the patients [34].

Ramucirumab: Ramucirumab is a recombinant monoclonal antibody which specifically binds to VEGFR-2 and blocks binding of VEGF ligands to the receptor. It was first approved by the FDA in 2014 for the usage in advanced or metastatic gastric or gastro-esophageal junction adenocarcinoma in patients with disease progression despite prior fluoropyrimidine or platinum-containing chemotherapy. Its use has been associated with 2% increase in ATEs which are serious and sometimes fatal. These events include MI, cardiac arrest, CVAs, and cerebral ischemia [35].

Regorafenib: Regorafenib is a multi-kinase inhibitor acting on various membrane-bound and intracellular kinases involved in the angiogenesis. It was first approved in 2012 by the FDA for use in patients with P(mCRC), who have disease progression despite prior treatment with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and anti-EGFR therapy (if KRAS wild type). Increased incidence (1%) of MI or ischemia was observed in patients treated with regorafenib [36].

Sorafenib: Sorafenib is a multikinase inhibitor which inhibits multiple intracellular and cell surface kinase receptors which are thought to be involved in tumor cell signaling, angiogenesis and apoptosis. It was first approved by the FDA for treatment of patients with advanced RCC. There was an increased risk of cardiac ischemia and infarction in patients treated with sorafenib, varying with the type of cancer [Hepatocellular Carcinoma (HCC) 3%, RCC 3% and differentiated thyroid carcinoma 2%]. Patients with unstable Coronary Artery Disease (CAD) or recent MI were not included in the studies performed [37].

Vandetanib: Vandetanib is a multikinase inhibitor which inhibits the activity of tyrosine kinases like EGFR, VEGF, Rearranged during Transfection (RET), Protein Tyrosine Kinase 6 (BRK), tyrosine kinase with immunoglobulin-like and EGF-like domains 2 (TIE-2). It was first approved by FDA in 2011 for the treatment of adult patients with late-stage (metastatic) MTC who are ineligible for surgical therapy and in whom the cancer is growing and causing symptoms. It results in an increased incidence of ischemic cerebrovascular events (1%) [38].

Ziv-aflibercept: Ziv-aflibercept, also known as VEGF-trap is a recombinant fusion protein which acts as a decoy receptor for VEGF-A, VEGF-B, and Placental Growth Factor (PlGF) and thus preventing the activation of VEGFR's by VEGF. It was first approved in 2012 for use in combination with FOLFIRI for treating metastatic colorectal cancer patients who are resistant to or have progressed on other oxaliplatin-based regimens. When used in combination with FOLFIRI regimen, ATE`s were increased by 3% as compared to FOLFIRI alone with 2% being grades 3-4. VTE's were increased by 9% by adding ziv-aflibercept to the FOLFIRI regimen [39].

Summary

Increased incidence of TEs are observed in most of the AIs, which is multifactorial as mentioned in the above review. There are no studies yet to recommend a generalized approach either for prevention or for treatment of these events specific to AIs. Recommendations are based on the rate and severity of occurrence of these events with individual drugs. There are no clinical

data yet regarding ATE preventive strategies to date. In terms of VTE, according to the National Comprehensive Cancer Network (NCCN) Practice Guidelines in Oncology, starting of aspirin or anticoagulant prophylaxis in patients with cancer depends on the presence or absence of risk factors for VTE and the use of Angiogenesis Inhibitors as such, was not indicated as a risk factor for VTE in cancer patients as per NCCN [40]. Nevertheless, there should be consideration given to the TE management in patients on AI therapy as mentioned in Table 6 as per the recommendations based on prescribing information of each individual AI. Though the therapy with AIs are initiated by oncologists, dealing with the adverse effects of AIs may be in the hands of primary care physicians. Thus, primary care physicians should be aware of the increase in the incidence of TEs with AIs as well as recommendations for drugs in this class. They should not only suspect an increased risk of TEs in patients, secondary to the cancer diagnosis, but also should think of compounded risk when the cancer patients are being treated with AIs and thus base their management decision. Hematologic events are a common reason for treatment discontinuation with AIs. Collaboration with oncologists, hematologist and primary care physicians is extremely important for the promising results of AI therapies.

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