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RECENT ADVANCES IN VASCULAR TARGETING AGENTS AS ANTICANCER DRUGS

Moses Muyaba [a]*, Yuanyuan Liu [a], Wenbo Si [a], Minhang Xin [a],Fan Meng [a], Qidong You [b], Hua Xiang [a,b]

[a] Department of Medicinal Chemistry, School of Pharmacy, China Pharmaceutical University, 24 Tong Jia Xiang Road, Nanjing 210009, Jiangsu, P. R. China.

[b]Jiangsu Key Laboratory of Drug Design and Optimization, China Pharmaceutical University, 24 Tong Jia Xiang Road, Nanjing 210009, Jiangsu, P. R. China.

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***Correspondence for Author**
Hua Xiang
Department of Medicinal Chemistry, School of Pharmacy, China Pharmaceutical University, 24 Tong Jia Xiang Road, Nanjing 210009, Jiangsu, P. R. China.

ABSTRACT

The tumor vasculature is an important target for anticancer therapy because the blood vessels deliver oxygen and nutrients to whole-body, as well as provide a route for tumor development and metastatic spread. The vascular targeting agents (VTAs) are promising strategy targeting the tumor vasculature. In recent years, the increased knowledge of tumor vascular system and its molecular mechanism has led to the clinical studies or approval of a lot of new VTAs. Although beneficial for cancer patients, their limited efficacy remains a challenging problem and new therapeutic strategies are being explored. This review highlights the recent advances of VTAs including their structures, biological mechanism and clinical status.

KEYWORDS: anticancer drugs; tumor vasculature and vascular targeting agents.

INTRODUCTION

Based on the statistics of the World Cancer Report 2014, an estimated 14 million new cancer cases occurred all over the world in 2012 and the figure is projected to rise to 22 million annually within the next two decades.[1] Cancer is the leading cause of death in the world.[2] Early in 1971, Dr. Folkman proposed a concept that solid tumor growth is angiogenesis-dependent.[3] In 1982, Dr. Denekamp described the antivascular approaches which target the established tumor blood vessels.[4] Blood vessels provide avenues to deliver essential oxygen

and nutrients and to eliminate waste products of metabolism, as well as to offer convenient routes for tumor growth and metastasis. The tumor vasculature has become an important target for anticancer/antitumor therapy and brought about a vigorous field of new anticancer therapeutics over the past decade.[5]

VTAs, also known as angiogenic inhibitors (AIs), prevent the development and progression of tumor neovascularization and exhibit preventive and chronic effects.[6] The increased knowledge of the tumor vascular system and its molecular mechanism has led to the clinical studies and/or approval of a lot of new VTAs. Although beneficial as anticancer agents, their limited efficacy remains a major challenge. New principles and strategies aimed at improving the outcome of cancer treatment are being explored.

This article focuses on the recent progress of VTAs which have been approved or undergoing clinical trials. Besides describing the connection between tumor angiogenesis and tumor growth briefly, it highlights the structural features of small molecular drugs, the biological mechanism, clinical status and the insufficiency if any.

ANGIOGENESIS AND TUMOR

Angiogenesis is a normal and vital process in cell growth and development. However, it is also a fundamental event of tumor progression and metastasis. Angiogenesis depends on the coordinated regulation of multiple factors. In the initial stage of cancer, tumor cells absorb nutrients and oxygen for growth and proliferation from the surrounding tissues mainly by diffusion. Vessels are not imperative in this period. Tumors cannot exceed 1-2 mm^3 in an avascular state. Angiogenesis is involved for the purpose of obtaining sufficient oxygen and nutrients and discarding wastes. Hypoxia and other oncogenic-inducing factors activate the angiogenic switch which propagates angiogenesis.[7, 8] New vessels rapidly proliferate to increase blood supply and to accelerate tumor growth exponentially. [9] Tumor will enter the vascular period.

Several modes of vessel formation have been identified in normal tissues such as sprouting angiogenesis, vasculogenesis and intussusception. Besides these, tumor cells can use vessel co-option, vascular mimicry or endothelial cells derived from putative cancer stem-like cells to form tumor blood vessels.[10]Multiple pathophysiological steps are required in the blood vessel formation process [11]: These are 1. pericyte detachment and blood vessel dilation; 2. basement membrane and extracellular matrix (ECM) degradation; 3. onset of new blood-

vessel sprout lumen through endothelial cell conglutination guided by pericytes; 4. fusion of blood-vessel sprouts and formation of new blood vessels.

Each step in tumor angiogenesis is regulated by a variety of angiogenic factors such as angiopoietin (Ang), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), transforming growth factor (TGF), epidermal growth factor (EGF) and insulin-like growth factor (IGF).[12] Usually, signal transduction, activators of transcription 3 (STAT3) and hypoxia inducible factor (HIF) are activated under hypoxic conditions in the core of tumors. Phosphorylated STAT3 and HIF bind VEGF promoter region simultaneously, up-regulate transcription of VEGF and promote angiogenesis which is important for tumor cell survival.[13, 14]

Tumor blood vessels are different from normal vasculature because of altered morphology, blood flow and permeability.[15, 16] Vascular endothelial cells in normal tissues are integral, orderly and connected tightly with normal cell morphology. These cells are usually quiescent. When tumor endothelial cells proliferate at a very fast rate, the tumor vasculature becomes disorganized, tortuous, thin-walled and highly permeable with the no pericytes and abnormalities in the basement membrane. The blood flow is frequently sluggish or even in a reversed direction.

In summary, Angiogenesis is a complex process that relies on the coordination of many different activities. Endothelial cells, pericytes, fibroblasts, growth factors and ECM components interact with each other to influence endothelial cell migration, proliferation, tube formation and vessel stabilization.[17] Over the past decade, the increased understanding of tumor vasculature has made it possible to restrain tumor progression by inhibiting tumor angiogenesis.

VASCULAR TARGETING AGENTS

VTAs work by blocking tumor cells from making new blood vessels. They achieve their anti-angiogenic effect mainly by inhibiting specific tyrosine kinases which are involved in tumor neovascularization. They therefore have a preventive effect, require long term therapy and are more effective when given in the early stage of the disease before the tumor is well established or after surgery to prevent recurrence.[18]The effects of VTAs are tumor-cell necrosis and secondary tumor-cell death though these results are quiet slow.[3]As mentioned before, Angiogenesis is a very complex multi-step process. All aspects and regulatory factors

in this process are likely to be the potential targets of VTAs.[19, 20]By their different mechanisms of action, VTAs can be divided into: (a) VTAs associated with VEGF/VEGFR signal pathway; (b) VTAs associated with FGF/FGFR signal pathway; (c) VTAs associated with PDGF/PDGFR signal pathway; (d) VTAs directly inhibiting endothelial cell proliferation; (e) Matrix metalloproteinase inhibitors; (f) VTAs interfering with endothelial cell adhesion; (g) VTAs associated with unknown mechanisms.

VTAs associated with VEGF/VEGFR signal pathway

VEGFs are major regulators among the blood vessel growth-stimulating factors, and the inhibition of VEGFR kinase has been one of the most powerful clinical strategies in cancer treatment.[21] Six known members of the VEGF family have been discovered: VEGF-A, -B, -C, -D, and -E and the placental growth factor (PLGF). Biological effects are mediated by VEGFs signaling through VEGF receptors (VEGFRs) known as members of receptor tyrosine kinases (RTKs). So far, three VEGFRs have been found. These are VEGFR-1 (fms-like tyrosine kinase receptor, Flt-1), VEGFR-2 (kinase insert domain containing receptor, Flk-1/KDR) and VEGFR-3 (Flt-4).[22, 23] VEGFR-1 and -2 are expressed on vascular endothelium and up-regulated in angiogenesis. The angiogenic effects mainly depend on VEGF-A which binds to and activates VEGFR-2 on vascular endothelium resulting in mitogenic, chemotactic and prosurvival signal upregulation.[24] Inhibition of VEGF/VEGFR signal pathway suppresses angiogenesis, which has become an important strategy in the treatment of solid tumors. Several kinds of drugs targeting the VEGF/VEGFR signal have been approved, and more drugs are in clinical studies. Their structures range from biological macromolecules to diverse small chemical molecules.

Neutralizing antibodies

Bevacizumab (Avastin ®, Genentech) is one of the recombinant humanized monoclonal antibodies and the first FDA-approved angiogenesis inhibitor. It specifically binds to and neutralizes all human VEGF-A isoforms and bioactive proteolytic fragments to suppress angiogenesis. Bevacizumab significantly prolongs overall survival of metastatic colorectal cancer patients, non-small cell lung cancer (NSCLC) patients, and glioblastoma multiforme patients.[25] It has also been confirmed to be effective against lung and breast cancer.[26]

Aflibercept (Zaltrap®, Sanofi-Aventis), known as VEGF-Trap, contains the extracellular domain 2 of VEGFR-1 and extracellular domain 3 of VEGFR-2 linked to the Fc portion of human IgG1.[27] Similar to Bevacizumab, Aflibercept has a conspicuous effect on preexisting

or newly formed vessels. It functions as a decoy VEGFR and inhibits VEGF signaling by selectively binding to VEGF-A, -B and PLGF.[28] Aflibercept significantly improved survival in previously treated metastatic colorectal cancer patients and was approved by FDA in August 2012.[29]

Ramucirumab (IMC-1121B; ImClone Systems/Eli Lilly), is a fully human mAb that binds to human VEGFR-2 thus blocking VEGF from binding and inhibiting angiogenesis. It is currently in Phase III studies for patients with breast cancer and hepatocellular carcinoma.[30] Ramucirumab is also in its phase III trial as an agent for the treatement of colorectal, prostate, liver, and ovarian cancers.[31, 32] In September 2013, its phase III breast cancer trial failed due to poor progression-free survival among patients [33, 34] In 2014, it was approved by FDA for gastric cancer and non-small cell lung.[35]

IMC-18F1, another fully humanized IgG1 antibody which binds to VEGFR-1, has been associated with inhibition of cancer growth in multiple stages. The preliminary results from its phase I trial have exhibited its favorable safety profile.[36] IMC-1C11, a chimeric anti-KDR antibody, blocks VEGF-KDR interaction, blocks VEGFR activation and restrains VEGFR-induced endothelial cell proliferation. The Phase I Study showed that IMC-1C11 is both safe and well tolerated.[37]

Small molecular VEGFR inhibitors

Great effort has been made in recent years to design and synthesize small molecular VEGFR inhibitors as cancer drugs besides neutralizing antibodies. Sorafenib (**1**, BAY43-9006, Nexavar® Bayer/Onyx) (Fig. (**1**) was the first approved oral VEGFR inhibitor. It is a multiple inhibitor of tyrosine kinase receptors, including VEGFR-1, -2, -3, PDGFR, FGFR, stem cell factor receptor (kit), Flt-3, *etc*.[38] Sorafenib was approved by FDA in 2005 for the treatment of advanced kidney cancer and in 2013 for the treatment of progressive differentiated thyroid carcinoma(DTC).[39] E7080 (**2**) (Fig. (**1**) is an analogue of Sorafenib and also an oral inhibitor of multiple RTKs such as VEGFR, FGFR and PDGFR.[40] New research shows that E7080 does not markedly suppress tumor cell proliferation but inhibits their migration and invasion.[41] E7080 is in phase I/II clinical trial for patients with liver cancer and phase III trial for patients with thyroid cancer.[43, 44, 45]

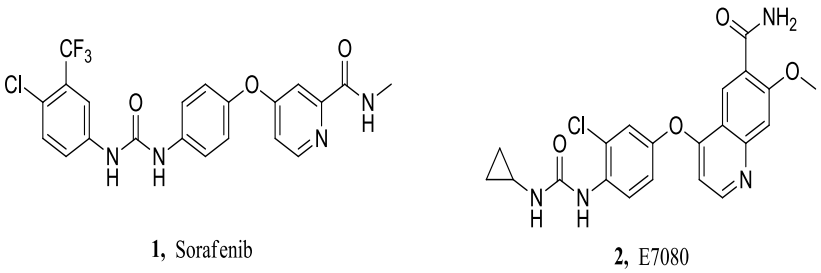


Fig. (1). Sorafenib and its analogue.

Sunitinib (**3**, SU-11248, Sutent®, Pfizer) (Fig. (**2**) an oral VEGFR inhibitor, inhibits at least eight RTKs including VEGFR-1 -2 -3, PDGFRa and PDGFRb, Kit, Flt-3 and colony-stimulating factor-1 receptor (CSF-1R).[42]It was approved for marketing by FDA in 2006 for the treatment of gastrointestinal stromal tumor and metastatic renal cell carcinoma. New findings suggest that Sunitinib increases the sensitivity of endothelial cells to radiation therapy thus it can be combined with radiation therapy for better results.[46] Sunitinib analogues SU6668 (**4**), SU-14813 (**5**), TKI-258 (**6**) and BIBF 1120 (**7**) are also multi-target RTK inhibitors (Fig. (**2**). SU6668 is in phase II clinical trial for breast cancer, liver cancer and other solid tumors. SU-14813 and TKI-258 have well-finished phase I clinical trial for malignant tumor treatment.[47, 48] Phase II clinical trials of BIBF 1120 on patients with relapse ovarian cancer after chemotherapy revealed that the agent has a good safety profile and potential improvement in progression-free survival.[49] Its phase III clinical trial is ongoing.

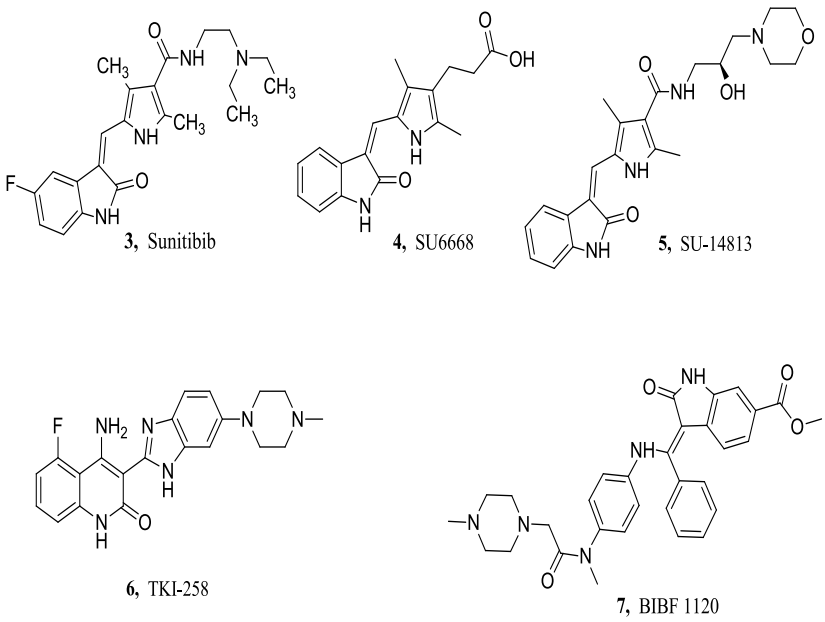
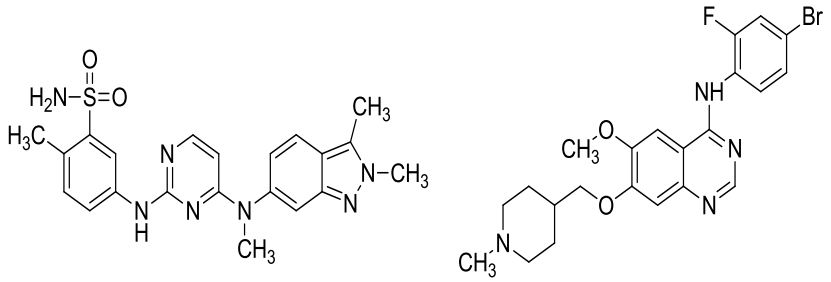


Fig. (2). Sunitinib and its analogues.

Pazopanib (**8**, GW-786034, Votrient®, Glaxo Smith Kline) (Fig. (**3**), an oral angiogenesis inhibitor targeting VEGFR, PDGFR and Kit, has been approved for patients with advanced renal cell carcinoma by FDA.[50] It is simultaneously on Phase II clinical studies for ovarian cancer, urothelial cancer and recurrent glioblastoma.[51, 52] Vandetanib (**9**, ZD6474, Zactima, Caprelsa®, AstraZeneca) (Fig. (**3**), an orally available small molecular inhibitor, is a reversible VEGFR-2 antagonist and also inhibits EGFR.[53] In April 2011, Vandetanib was approved by FDA and became the first agent for late-stage and medullary metastatic thyroid cancer in adult patients who are ineligible for surgery.



8, Pazopanib **9,** Vandetanib

Fig. (3). Pazopanib and Vandetanib.

Recently there are several VEGFR inhibitors that have been developed.[54] Cabozantinib (**10**, Cometriq®, Bristol-Myers Squibb) for the treatment of progressive medullary thyroid cancer and Axitinib (**11**, Inlyta ® Pfizer) for Renal Cell Carcinoma got approved by FDA in Nov and Jan 2012 respectively.[55,56] But unfortunately, Brivanib (**12**, BMS-58-2664) and Motesanib (**13**, AMG-706) were ceased for advanced hepatocellular carcinoma and for advanced non-small-cell lung carcinoma (NSCLC) respectively due to their disappointing Phase III results.[57, 58]

Apart from VEGFR inhibitors cited above, Vatalanib (**14**, PTK-787/ ZK222584) Cediranib (**15**, AZD -2171) and Telatinib (**16**, BAY57-9352) are undergoing l phase III trials.[59-61] CP-547632 (**17**), OSI-930 (**18**), BIBF-1000 (**19**), Linifanib (**20**, ABT-869 / AL-39324 / RG3635) are in phase II [62-65] (Fig. (**4**).

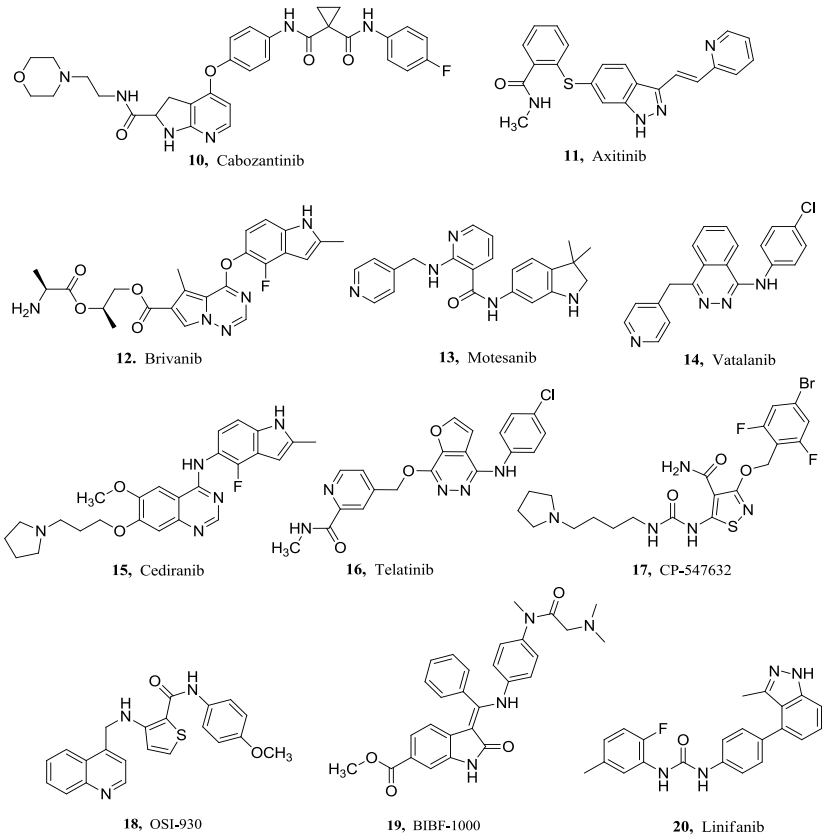


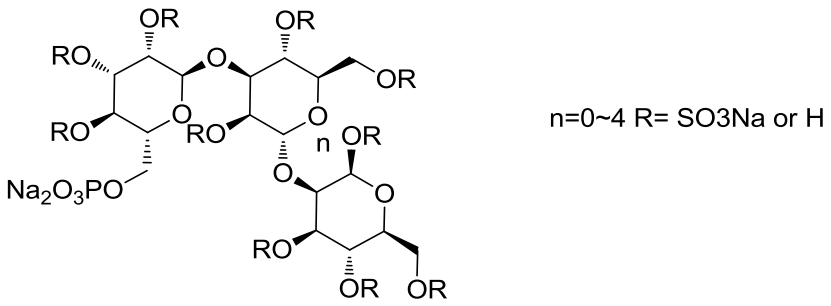
Fig. (4). Others VEGFR inhibitors on trials.

VTAs with FGF/FGFR signal pathway

FGFs are a family of heparin-binding growth factors which contain 22 known members and participate in diverse processes including embryonic development, tissue regeneration and wound healing.[66] FGFs exhibit their angiogenic activity by interacting with various endothelial cell-surface receptors including FGFRs, integrins and heparin sulphate proteoglycans (HSPGs).[67] The combination of FGFs with FGFRs is mediated by HSPGs.[68] As co-receptor of FGFR, HSPGs are composed of a core protein and one or more heparin-sulfate glycosaminoglycan (HSGAG) chains. FGFs exist as inactive dimers in matrix until they interact with HSPG fragments as diffusible complexes and reach the cell surface.[69] The active FGF dimers lead to FGFR dimerization and transphosphorylation. The signal transduction pathways are activated and then endothelial cell proliferation and migration are accelerated to form new blood vessels at last.[70, 71]

PI-88 (**21**) (Fig. (**5**) is a heparin sulphate simulant which is a mixture of highly sulfonated mannan oligosaccharides. PI-88 binds to FGF-1, -2 and VEGF with high affinity and restrains these ligands from combining with their corresponding receptors. Moreover, PI-88 inhibits the activity of heparanase so as not to prompt cellular proliferation by degrading the

heparan sulphate of ECM.[72] PI-88 is in phase III clinical trial as an adjuvant therapy for hepatocellular carcinoma after surgical resection.[73]



21 PI-88

Fig. (5). PI-88.

VTAs associated with PDGF/PDGFR signal pathway

The ligands of PDGF family contains five dimeric isoforms (PDGF-AA, -BB, -CC, -DD, and -AB), each activating two cognate RTKs of PDGF receptor-α (PDGFR-α) and -β (PDGFR-β) [74, 75]

PDGF/PDGFR pathway plays a significant role in vascularization. The secretion of PDGF-B and stimulation of PDGFR-β associated with vascular smooth muscle cells (vSMC) or pericytes are crucial events in the process of stabilizing the newly formed vasculature and promoting endothelial cell survival.[76] The inhibition of both VEGFR and PDGFR has been reported to show potent anti-angiogenic activity in vivo and may be more effective in antiangiogenic therapy than inhibition of either alone.[77] Many drugs such as Sorafenib and Pazopanib targeting the VEGF/VEGFR signaling pathway inhibit PDGF pathway simultaneously.

VTAs directly inhibiting endothelial cell proliferation

Now that vascular endothelial cell proliferation is the basis of angiogenesis, the inhibition of endothelial cell proliferation could be a strategy for arresting tumor growth directly.

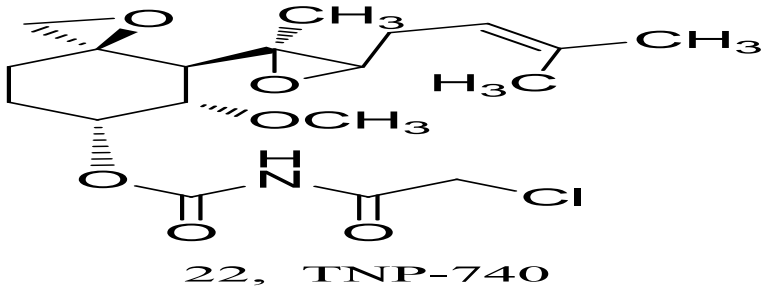
Angiostatin and Endostatin

Angiostatin and endostatin are endogenous inhibitors of endothelial cells, and have been found to inhibit endothelial cell proliferation, migration, invasion and vascular morphogenesis.[78, 79] Angiostatin and endostatin bind to integrin receptor and other receptors on endothelial cells, and reveal antitumor effect via a variety of pathways.[80] Endostatin also

stabilizes the adhesions of cell-cell and cell-matrix, and reinforces their junctions to prevent cancer from migrating during angiogenesis.[81] They are effective for treatment of a variety of tumors such as lung and breast cancers, and exhibit less toxicity and side effects.[78, 79]

There were two main disadvantages identified when these two endogenous inhibitors were used as anticancer drugs. Firstly, the optimum dose for antitumor activity was in a narrow range of concentration and secondly, they had a very short half-life of only 1-2 hours.[82] One of recombinant human endostatins was constructed by conjugating endostatin to Fc domain of IgG, and its half-life was extended to more than a week. Meanwhile, the optimum antitumor dose of Fc-endostatin is lower than that of endostatin.[83]

Endostar ® (Simcere), a modified and recombinant human endostatin, has been approved as first-line chemotherapy in patients with advanced NSCLC in China.[84] TNP-470 (**22**, AGM-1470) (Fig. (**6**), a semi synthetic analogue of Fumagillin secreted from *Aspergillus fumigatus*, is reported to inhibit tumor growth and metastasis by suppressing angiogenisis. It was found to be effective for the treatment of prostate cancer, breast cancer and other solid tumors with low toxicity.[85, 86]



22, TNP-740

Fig. (6). TNP-470.

Metronomic chemotherapy

Certain conventional cytotoxic agents function as antiangiogenic drugs when administered at a comparatively low but continuous non-toxic dose or at regular intervals with no prolonged disruption.[87] This is called low-dose metronomic chemotherapy. Metronomic regimens have potent antitumor effects with less toxicity compared with corresponding maximum tolerated dose (MTD) of conventional cytotoxic drugs.[88] Various types of cytotoxic drugs have anti-angiogenic effects, for instance, Cyclophosphamide, Docetaxel, Vinblastine and the like.[89] Preclinical studies of metronomic chemotherapy have shown that tumor cell apoptosis is preceded by the death of tumor endothelial cells in chemotherapy-resistant tumor models,

which indicates that endothelial cells are a primary target of metronomic chemotherapy.[90] Expression of the endogenous angiogenesis inhibitor Thrombospondin-1 increased significantly during the metronomic Cyclophosphamide treatment in several preclinical studies.[91] Tumor-induced immune tolerance can also be reduced by administration of metronomic Cyclophosphamide.[92] One animal research experiment shows that Cyclophosphamide at a MTD dose followed by Cyclophosphamide treatment on a metronomic schedule gives antitumor activity superior to either used individually.[93] Metronomic chemotherapies combined with other antiangiogenic agents are also reasonably helpful for anti-cancer treatment. In a phase II clinical trial, co-administration of metronomic Cyclophosphamide and Bevacizumab exhibited better antitumor activity than either one.[94]

Matrix metalloproteinase inhibitors

Matrix metalloproteinases (MMPs) are members of zinc-dependent endopeptidases. There are currently more than 20 human MMP members that can be divided into two groups based on their cellular localization, or into five main groups according to their structural and substrate specificity.[95] For a long time, MMPs have simply been assumed to have the ability to degrade ECM and promote tumor metastasis by preparing paths for tumor cells to migrate, invade and spread to distant secondary areas.[96] In fact, MMPs play an important role in tissue repair, angiogenesis and organogenesis by maintaining normal cellular environment via regulation of extracellular signaling networks.[97, 98] Not all of MMPs play a key role in promoting tumor activity as some subtypes have been found to have antitumor activity.[99]

MMP inhibitors (MMPIs) as anticancer drugs have been developed for more than 25 years. Batimastat (**23**) (Fig. (**7**) is a first broad-spectrum MMP inhibitor on clinical trial for the treatment of cancer.[100] Its phase III clinical trial was ceased due to its low bioavailability. Second-generation MMP inhibitors include Marimastat (**24**), Prinomastat (**25**), Neovastat (**26**), Tanomastat (**27**) and Rebimastat (**28**) [101-105] (Fig. (**7**). Unexpectedly second generation MMP inhibitors failed to show obvious improvements in cancer therapy in their phase III clinical trials. There may be two important reasons for the failure. Firstly, these MMP inhibitors with broad-spectrum antitumor activity lacked selectivity and caused severe side effects at therapeutic dosage. Secondly, they exhibited satisfactory effectiveness in animal experiments, but low bioavailability in humans.[106] In recent years, with more thorough understanding of subtypes and physiological activities of MMPs, selective MMP inhibitors have been developed for treatment of cancer. SB-3CT (**29**) (Fig. (**7**), a thirane derivative, is

one of the third-generation of selective MMP inhibitors with selective MMP-2/9 inhibitive activity.[107]

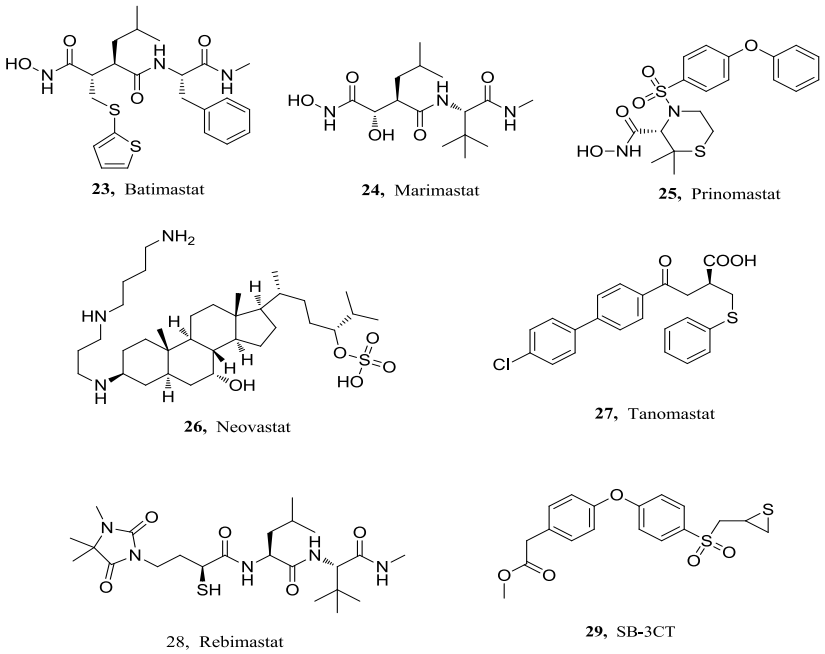


Fig. (7). Matrix metalloproteinase inhibitors.

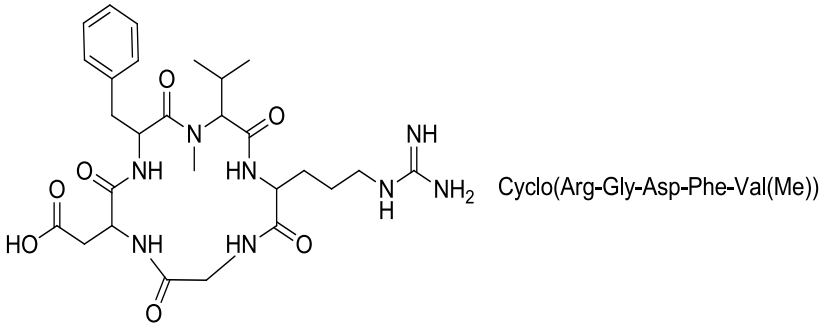
VTAs interfering with endothelial cell adhesion

Integrins are a family of glycosylated heterodimeric cell surface receptors which bind to components of the extracellular matrix (ECM) with adhesive functions, and provide traction for cell motility and invasion. They consist of non-covalently bound α- and β-subunits. One of 18 α-subunits and one of 8 β-subunits are paired to form 24 different integrins.[108] Integrins are mediate attachments between cell and surrounding tissues such as adjacent cells or ECM. They are important for cells to sense and integrate cues from the extracellular matrix by transducing signals for anchorage-dependent survival, growth, *etc.*[109] Meanwhile, they also have effects on cell shape, survival, proliferation, gene transcription and migration.[110] Integrins are now promising therapeutic targets since they are expressed in tumor cells and accelerate tumor proliferation and metastasis.[111, 112]

Several integrin antagonists are undergoing clinical trials as anti-angiogenic agents for the treatment of cancer. Etaracizumab (Vitaxin, Abegrin ®, MEDI-522) is a humanized αvβ3 integrin monoclonal antibody. It blocks ligands such as vitronectin to bind to αvβ3 integrin and results in the inhibition of angiogenesis and metastasis. Its phase II clinical trial for malignant melanoma has been completed, but failed to be more effective than agent

Dacarbazine as a single agent.[113] Phase II clinical trial of Etaracizumab for prostate cancer and colon cancer are still ongoing.[114]

Intetumumab (CNTO 95), a monoclonal antibody, inhibits integrins and exhibits both antitumor and anti-angiogenic activities. [115] It has completed phase II clinical study of stage IV melanoma, and the results showed that Intetumumab is safe though it failed to improve overall survival significantly. [116] Another phase I clinical trial of Intetumumab is also in progress in combination with Docetaxel and Prednisone in metastatic hormone refractory prostate cancer patients. [117] Cilengitide (**30**, EMD 121974, NSC 707544) (Fig. (**8**), a cyclic Arg-Gly-Asp peptide, can specifically recognize the over-expressed integrin receptor αvβ3 and αvβ5 in tumor cells or tumor blood vessels. Cilengitide is the first integrin receptor antagonist in Phase III clinical trial for treatment of glial cell carcinoma [118] and was announced by Merck in 2013 not to meet its primary endpoint of prolonging overall survival.

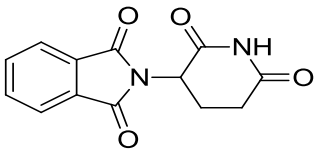


30, Cilengitide

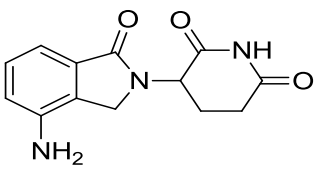
Fig. (8). Cilengitide

VTAs associated with unknown mechanism

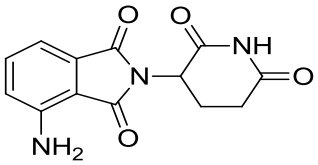
Thalidomide (**31**, Thalomid) (Fig. (**9**) is a synthetic glutamic acid derivative. In 1961, it was withdrawn due to the teratogenicity and neuropathy as a sedative drug typically used to cure morning sickness. In 1995, Thalidomide was found to have anti-angiogenic effect and used to treat cancer.[119] In 2006, Thalidomide was approved for treatment of multiple myeloma. A variety of Thalidomide analogues have been developed such as Lenalidomide (**32**, CC-5013, Revlimid ®, Celgene), Pomalidomide (**33**, CC-4047, Actimid ®, Celgene) and CPS49 (**34**) [120] (Fig. (**9**). In 2005, Lenalidomide was approved for treatment of fatal blood disease, myelodysplastic syndrome and multiple myeloma.[121]



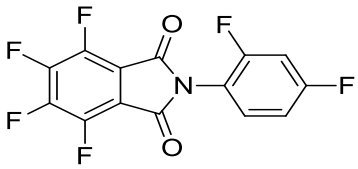
31, Thalidomide



32, Lenalidomide



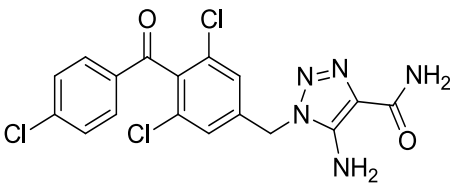
33, Pomalidomide



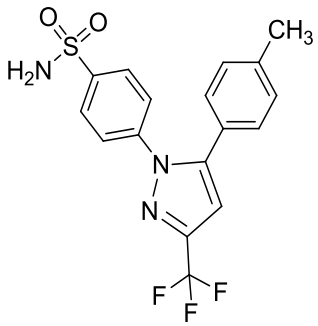
34, CPS49

Fig. (9). Thalidomide and its analogues.

Carboxyamidotriazole (**35**, CAI, NSC609974) (Fig. (**10**), one of calcium influx inhibitors with antiproliferative and antimetastatic activities, is used in the treatment of various cancers. Carboxyamidotriazole inhibits calcium uptake, blocks the release of arachidonic acid and activates nuclear factor-κB (NFκB) with largely unclear mechanisms.[122] But the phase III clinical trial showed that it did not provide a meaningful clinical benefit or an improvement in quality of life over placebo in advanced NSCLC.[123] In addition, selective cyclooxygenase-2 (COX-2) inhibitors, which were known to have anti-inflammatory, antipyretic and analgesic effects, also exert inhibition of tumor angiogenesis.[124] But in two phase III clinical trials, COX-2 inhibitor Celecoxib (**36**) (Fig. (**10**) failed to show any survival benefit for treatment of NSCLC.[125, 126] It has been reported that the combination of Celecoxib with chemotherapy drugs will increase the likelihood of cardiovascular adverse reactions seriously.[127]



35, CAI



36, Celecoxib

Fig. (10). CAI and Celecoxib

Limitation and new opportunities for VTAs

Although anti-angiogenic antibodies and small molecules significantly prolong overall survival of cancer patients, there are still many limitations such as resistance and monotherapeutic ineffectivity. Intrinsic resistance and acquired resistance to VTAs are notably clinical problems.[128] Intrinsic resistance mainly occurs in tumor cells which obtain oxygen and nutrients from existing blood vessels in vasculature-rich organs like lungs, brain and colon.[129] Neovascularization is not necessary for tumors in these organs. Acquired resistance emerges as a result of crosstalks among signaling pathways which regulate the vasculature. For example, bFGF will be up-regulated within the tumor after treatment with anti-VEGFR antibody therapy.[130] It is possible that many induced growth factors such as PDGFR, EGFR and c-kit act in a synergistic manner to prompt tumor angiogenesis. Acquired resistance can also be obtained by gene mutations of tumor endothelial cells.[131] Angiogenesis has also been found to be a critical function for the expansion and metastasis of tumor and it is influenced by the tumor microenvironment.[132] VEGF signaling pathway has been identified to be the most prominent pro-angiogenic molecule which is the key component in both early and late phase angiogenesis. It is highly produced by tumor cells and its receptors can be found expressed on tumor and stromal cells. The high expression of VEGF is an independent factor predicting poor prognosis in different types of tumors.Therefore many components of the VEGF pathway have been major targets in cancer therapy.[133] FGFR pathway is also one of the signaling pathways that has been implicated in endometrial cancer. It has been shown to be mutated in a subject of endometrial tumors and inhibition of FGFR pathway with TKI leads to reduced cell growth and increased antitumor activity in endometrial tumor models. Based on such observation, agents targeting EGFR are being tested on patients with advanced, metastatic and recurrent endometrial cancer.[134]

To overcome resistance and improve the treatment outcome, combination therapy is promising good results. As discussed above, VTAs predominantly inhibit neovascularization and show greatest activity at the tumor periphery. A combination of Vascular disrupting agents (VDAs) which are highly effective at the tumor core with VTAs is likely to lead to higher efficacy as the two will have spartial cooperation and non overlapping toxicities.[135,136]

The rationale of such combination is supported by preclinical data. In a preclinical study, a combination of VDAs like fosbretabulin ,OXi4503 or vadimezan with bevacizumab showed a significantly enhanced tumor response in the treatment of human tumor xenografts.[137]

As some antiangiogenic agents act by normalizing the existing tumor vasculature which is abnormal in function and morphology, they will increase tumor oxygenation and lead to better 'normalization' window.[138] This vascular normalizing principle has been used as a strategy to improve the penetration of chemotherapeutics and overcome resistance. This process also increases sensitivity of tumor cells to radiation as oxygen is vital for the radiation-induced DNA damage.[139] In order to achieve increased drug penetration, distribution and radio-sensitivity as a result of vascular normalization, it is important to administer the VTA and the effecter chemotherapeutic agent in a precise sequence and timing. A study by Winkler et al. showed that the synergistic tumor growth inhibition obtained by combining anti-VEGFR-2 antibody DC101 and radiation therapy is observed in tumor-bearing mice only when radiation therapy is administered 4 to 6 hours after initiation of antibody therapy.[140]

In a 2012 clinical trial on patients with advanced head and neck cancer, a combination of Bevacizumab, erlotinib and chemo radiation found a 96% clinical complete response after concurrent chemo-radio therapy. Another preclinical study using Vandetanib and radio-therapy in EGFR positive and EGFR null human head and neck tumor xenografts showed that such a combination had enhanced anti- tumor activity.[141]

CONCLUSIONS AND FUTURE PERSPECTIVES

The use of VTAs is an important aspect for fighting against cancer. Vascular inhibitors have been developed for decades, and many significant advances have been made. On the other hand, the limited efficacy of these drugs remains a challenging problem. Besides, toxicity and resistance are still far from satisfaction.[10]

In recent years, several VTAs such as VEGF-neutralizing antibody Bevacizumab and many mult-targeted RTK inhibitions like Sorafenib, Sunitinib, Pazopanib, Cabozantinib and Axitinib have been approved. Their mechanisms have just revealed a small part and still need farther exploration. Many patients with metastaic tumor have either refractory or acquired resistance to VTAs. VTAs only induce delayed tumor growth but not long-term remission. Besides, clinical studies showed that VTAs combined with chemotherapeutic drugs may cause unpredictable toxicities and side effects.[142] Recent research indicates that VEGF inhibitors increase the risk of tumor metastasis in mouse models.

How will the therapeutic strategies targeting the tumor vasculature be improved from now on? One consideration is rational or optimized use of current VTAs which includes drug combination, dose regimen design, administration schedule and duration. A deeper understanding of different modes of tumor vascularization such as sprouting angiogenesis, vasculogenesis, intussusception, co-option and vascular mimicry is needed and this can be correlated with the different dosage regimen or administration schedule. Furthermore, an increased knowledge of VTAs mechanism of action is required for the proper design and administration of these drugs. On the other hand, combination therapy is a useful strategy and more potent to eradicate the residual tumor vessels than monotherapy.[143] Meanwhile, the recent research progress in tumor vasculature showed that vessel normalization will be a new therapeutic strategy for anticancer treatment. Since tumor vessels are abnormal in all aspects of structure and function [95], it is possible for tumor invasion and metastasis to become more aggravating due to the excessive vascular inhibition and blockade through VTAs. A genetic research concluded that a streamlined monolayer of phalanx endothelial cells has the activity of reducing tumor cell invasiveness, intravasation and metastasis by providing a more impenetrable barrier for intravasating tumor cells without accelerating tumor growth.[79] The finding offers a new prospective possibility of anticancer strategy targeting at tumor vasculature. More novel anticancer drugs including but not limited to VTAs will be developed to improve the effectiveness of cancer treatment in the future.

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