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# Clinical trials with anti-angiogenic agents in hematological malignancies

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## Abstract

New blood vessel formation (angiogenesis) is not only essential for the growth of solid tumors but there is also emerging evidence that progression of hematological malignancies like multiple myeloma, acute leukemias, and myeloproliferative neoplasms, also depends on new blood vessel formation. Anti-angiogenic strategies have become an important therapeutic modality for solid tumors. Several anti-angiogenic agents targeting angiogenesis-related pathways like monoclonal antibodies, receptor tyrosine kinase inhibitors, immunomodulatory drugs, and proteasome inhibitors have been entered clinical trials or have been already approved for the treatment of hematological malignancies as well and in some instances these pathways have emerged as promising therapeutic targets. This review summarizes recent advances in the basic understanding of the role of angiogenesis in hematological malignancies and clinical trials with novel therapeutic approaches targeting angiogenesis.

## Introduction

The hypothesis of tumor angiogenesis in malignancies was raised by Judah Folkman: To grow over a certain size of a few millimetres in diameter solid tumors need blood supply from surrounding vessel [ 1]. Up to 2-3 $mm^3$ solid tumors can grow without blood vessel supply. Nutrition and oxygen is provided via diffusion from the surrounding tissue. Above this size, diffusion becomes insufficient due to the negative surface/volume ratio. Based on a balance between angiogenic and anti-angiogenic growth factors, a tumor of this size can stay dormant for a very long time period until the so-called angiogenic switch occurs [ 2]. Tumor blood vessels are generated by various mechanisms, such as expansion of the host vascular network by budding of endothelial sprouts (sprouting angiogenesis), cooption of the existing vascular network, remodeling and expansion of vessels by the insertion of interstitial tissue columns into the lumen of preexisting vessels (intussusceptive angiogenesis) and homing of endothelial cell precursors (EPC; CEP) from the bone marrow or peripheral blood into the endothelial lining of neovessels (vasculogenesis) [ 3].

Tight control of angiogenesis is maintained by a balance of endogenous anti-angiogenic and pro-angiogenic factors [ 4]. VEGF has a key, rate-limiting role in promoting tumor angiogenesis and exerts its effects by binding to one of three tyrosine kinase receptors: VEGF receptor-1 (VEGFR-1; fms-like tyrosine kinase-1, Flt-1), VEGFR-2 (human kinase domain region, KDR/murine fetal

liver kinase-1, Flk-1) and VEGFR-3 (Flt-4). VEGFR-1 (ligands include VEGF-A, -B and placental growth factor [PIGF]) and VEGFR-2 (ligands include VEGF-A, -C and -D) are predominantly expressed on vascular endothelial cells, and activation of VEGFR-2 appears to be both, necessary and sufficient, to mediate VEGF-dependent angiogenesis and induction of vascular permeability [ 4, 5]. Both receptor tyrosine kinases are expressed in all adult endothelial cells, except for the brain endothelial cells. VEGFR-1 is also expressed on hematopoietic stem cells, vascular smooth muscle cells, monocytes, and leukemic cells [ 6, 7], while VEGFR-2 is expressed on endothelial progenitor cells and megakaryocytes [ 8, 9]. VEGFR-3, largely restricted to lymphatic endothelial cells, binds the VEGF homologues VEGF-C and VEGF-D and may play an important role in the regulation of lymphangiogenesis. Thus, VEGF and VEGFR represent significant anti-cancer therapy targets, which elegantly bypass potential tumor-related treatment barriers [ 4].

A further important pathway in angiogenesis is the recently identified Delta-Notch pathway, and particularly the ligand Delta-like 4 (Dll4), was identified as a new target in tumor angiogenesis [ 10]. Dll4 is highly expressed by vascular endothelial cells and induced by VEGF [ 11]. It interacts with Notch cell surface receptors to act as a negative feedback inhibitor downstream of VEGF signaling to restrain the sprouting and branching of new blood vessels [ 10, 12]. Inhibition of Dll4-Notch signaling induces an increase in vessel density but these blood vessels are abnormal and not perfused [ 13]. Therefore intratumour hypoxia is increased and leads to induction of transcription of proangiogenic genes regulated by Hypoxia inducible factor-1 (HIF-1) [ 10, 14]. Disruption of Dll4 signaling by overexpression or inhibition of Dll4 may impair angiogenesis and blockade of Dll4-Notch signaling results in an increased density of nonfunctional vasculature and is associated with a reduction in the growth of human tumor xenografts [ 13, 14]. Further, certain xenografts that are resistant to anti-VEGF therapy are reported to be sensitive to anti-Dll4 and combination treatment with anti-VEGF and anti-Dll4 has additive inhibitory effects on tumor growth [ 13– 15].

This review summarizes the role of pathological angiogenesis in hematological malignancies focusing on multiple myelomas (MM), acute leukemias, and myeloproliferative neoplasms (MPN) and its therapeutic intervention with novel agents within clinical trials or already approved.

## Pathophysiology of angiogenesis in hematological malignancies

Many studies suggest a role for angiogenesis not only in the pathogenesis of solid tumors but also in hematological malignancies like acute and chronic leukemia, lymphoma, myelodysplastic syndromes, myeloproliferative neoplasms, and multiple myeloma [ 16– 21]. We and others reported an increased microvessel density and VEGF expression in the bone marrow of patients with myeloproliferative neoplasms and lymphoma [ 17, 20]. Thereby, the extent of angiogenesis in the bone marrow often correlated with disease burden, progonosis, and treatment outcome [ 22, 23]. In the neoplastic bone marrow there is an imbalance of the cells, cytokines and growth factors maintaining physiological angiogenesis in the normal bone marrow. The bone marrow tumor cells upregulates several factors, including interleukin-6, granulocyte-macrophage colony-stimulating factor and VEGF, have autocrine and paracrine effects acting on multiple cell types, thereby stimulating angiogenesis and leading to increased vascularity [ 7, 24]. The role for VEGF in hematogical malignancies has been extensively studied since its isolation from the leukemia cell line HL- 60 in 1989 [ 25]. Apparently, this growth factor is expressed in many other leukemic cell lines [ 7, 26] and a subset of leukemic cells also expresses VEGFR-2 which allows VEGF to act as autocrine growth factor in leukemia [ 26, 27]. In addition to that, isolated blast cells from leukemia patients also produce VEGF [ 26] and the cellular level of VEGF in acute myeloid leukemia (AML) patients has been identified as independent prognostic risk factor [ 28]. VEGF from leukemic blasts contributes to disease progression, either as positive regulator

for proliferation and apoptosis protection for the blast itself or by activating the surrounding stroma cells with subsequent induction of bone marrow angiogenesis.

Regarding the Notch pathway, Notch signals are oncogenic in hematogical malignancies in many cellular contexts [ 29]. Activating Notch-mutations have been shown to be present in at least 50% of human T-cell acute lymphoblastic leukaemia (T-ALL) cases and have been proved to play a unifying role in the pathogenesis of T-ALL [ 30]. An important role of Notch has been proposed in cell survival in several B-cell malignancies such as Hodgkin's disease [ 31, 32] and in two B-cell non-Hodgkin lymphoma entities, chronic lymphocytic leukaemia (CLL) [ 33– 35] and in MM [ 36, 37].

## Multiple myeloma

MM was the first hematological malignancy, in which increased angiogenesis rate was detected [ 21, 38]. MM is characterized by proliferation of malignant plasma cells that accumulate in the bone marrow and often produce a monoclonal immunoglobulin. New vessel formation in the bone marrow seems to play an important role in the pathogenesis of MM [ 39, 40]. Increased bone marrow microvessel density (MVD) in patients with MM appears to be also an important prognostic factor [ 41]. Malignant plasma cells can secrete various cytokines, including VEGF, basic fibroblast growth factor (bFGF), and hepatocyte growth factor (HGF), all known for their pro-angiogenic activity [ 42]. It has been shown that MM cells are capable of secreting VEGF in response to Interleukin-6 (IL-6) stimulation; in response to that VEGF stimulation microvascular endothelial cells and bone marrow stromal cells secrete in turn IL-6, a potent growth factor for malignant plasma cells, thus closing a paracrine loop [ 43]. Specifically, increased microvessel density (MVD) in the BM of MM patients has been correlated with disease progression and poor prognosis [ 21, 23]. Moreover, VEGF also exerts direct effects on MM cell migration, proliferation, survival, and drug resistance. VEGF triggered effects in MM cells are predominantly mediated via VEGFR 1 and in endothelial cells, predominantly via VEGF R2 [ 44]. Rajkumar et al. showed a gradual increase of bone marrow angiogenesis along the disease spectrum from monoclonal gammopathy of undetermined significance (MGUS) to smoldering MM, newly diagnosed MM and relapsed MM [ 45], though the expression levels of VEGF, bFGF, and their receptors were similar among MGUS, smoldering MM, and newly diagnosed MM [ 46], rising the hypothesis that MVD increase in plasma cell neoplasias could be rather a function of chronology.

## Acute leukemias

The first demonstration that leukemia progression might be accompanied by an increase of bone marrow vascularization was provided by Judah Folkman's group [ 47]. In their studies, it was demonstrated that the bone marrow of acute lymphoblastic leukemia (ALL) patients had increased blood vessel content, compared to normal counterparts. Moreover, it was also shown that urine and peripheral blood samples from ALL patients contained elevated levels of pro-angiogenic growth factors, namely bFGF and VEGF, which correlated with the increase of bone marrow angiogenesis [ 48]. The existence of an "angiogenesis switch", first proposed for solid tumors [ 49], was therefore suggested to apply to hematological malignancies as well. "Angiogenesis switch" in leukemia is documented by increased bone marrow MVD, increased expression of HIF-1, multiple pro-angiogenic factors (VEGF, bFGF, angiopoietin-2), soluble VEGFR, and decreased expression of endogenous angiogenesis inhibitors, such as thrombospondin-1 [ 50, 51].
In a recent study by Norén-Nyström et al. [ 52] MVD, analyzed on 185 bone marrow biopsies, was higher in T-ALL compared to B-ALL. In the B-ALL group, cases with t(12;21) were characterized by a low MVD, while patients with hyperdiploid leukemia showed a high MVD. Similarly, in previously untreated acute myeloid leukemia (AML), increased levels of plasma VEGF correlate with reduced survival and lower remission rates [ 53]. In addition to that, isolated blast cells from leukemia patients also produce VEGF and the cellular level of VEGF in

AML patients has been identified as independent prognostic risk factor [ 28]. In a reccent study [ 54] dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) was used as a non-invasive technique to measure bone marrow angiogenesis in AML. DCE-MRI was performed beforte treatment and on day 7 after induction chemotherapy. Thereby, bone marrow angiogenesis with remission, rate overall and disease-free survival.

### Myeloproliferative neoplasms

The available data on angiogenesis and expression of VEGF and its receptors in the bone marrow of patients with *BCR-ABL1*- negative myeloproliferative neoplasms (MPN) suggest that MVD is increased, especially in primary myelofibrosis (PMF), and that increased angiogenesis might inversely correlate with survival [ 55– 58]. In a recent study, we found a significantly increased MVD and VEGF expression in MPN compared to controls especially in cases with high *JAK2-V617F* mutant allele burdens [ 17]. The identification of an acquired somatic mutation in the *JAK2* gene, resulting in a valine to phenylalanine substitution at position 617 ( *JAK2-V617F* ), has provided new insights into the pathogenesis of *BCR-ABL1*- negative MPN, being present in most patients with polycythaemia vera (PV) and in about 50% of patients with essential thrombocythemia (ET) and PMF [ 59, 60]. In another study by Alonci et al. in patients with MPN, serum levels of VEGF and VEGFR-2 was examined. In MPN, VEGF levels were higher compared to controls, wheresas VEGFR-2 levels was reduced in ET but not in PV and PMF [ 61].

## Anti-angiogenic therapies in hematological malignancies

Anti-angiogenic therapies are mostly based on inhibiting the binding of VEGF to VEGFR by neutralizing antibodies to the ligand or to the receptor, soluble receptors, small molecule inhibitors or are directed against the tyrosine kinase activity of the VEGF receptors (Figure 1 ). The first anti-angiogenic agent to be approved in solid tumors was bevacizumab (Avastin™ , Genentech), a humanized anti-VEGF monoclonal antibody. Administration of bevacizumab, in combination with cytotoxic chemotherapy, conferred benefits to patients with metastatic colorectal cancer, non-squamous, non-small cell lung cancer and metastatic breast cancer [ 62–64]. Additionally, two small-molecule inhibitors targeting VEGFRs and other kinases, sorafenib (Nexavar™ , Bayer and Onyx pharmaceuticals) and sunitinib (Sutent™ , Pfizer), have been approved based on their efficacy in treating renal cell- and hepatocellular carcinoma [ 65, 66]. A growing list of anti-angiogenics is now available, either in various stages of clinical development or as components of standard clinical regimens. The major classes of anti-angiogenic therapy include: (1) direct anti-VEGF acting molecules (anti-VEGF antibodies, *VEGF* -antisense nucleotides); (2) immunomodulatory drugs (IMIDs) with antiangiogenic properties; (3) receptor tyrosine kinase inhibitors, targeting VEGFR signaling as well as receptors of other (pro-angiogenic) factors; (4) anti-endothelial approach of metronomic therapy and (5) other new compounds, targeting signaling downstream to pro-angiogenic growth factors, such as mammalian target of rapamycin (mTOR) inhibitors, histone deacetylases' (HDAC) inhibitors and proteasome inhibitors. Figure 1

Therapeutic strategies to target the VEGF/VEGF receptor system. VEGF, vascular endothelial growth factor.

In our review, we will focus on several molecules interfering with the VEGF/VEGFR system, which already have been approved or are currently evaluated in clinical trials for treatment of hematological malignancies (Table 1).

*Table 1*

Selection of clinical trials and approved anti-angiogenic therapies in hematological malignancies

| Drug | Target | Study entities | Approved for |
|---|---|---|---|
| Receptor tyrosine kinase inhibitors | | | |
| PTK787/ZK 222584 (Vatalanib®) | VEGFR1-3, PDGFRβ, c-Kit | AML, PMF, MDS, CML, DLBCL, MM | |
| SU5416 (Semaxinib) | VEGFR1-2, c-kit, Flt3 | AML, MDS, MM, MPN | |
| Sorafenib (Nexavar®) | VEGFR2-3, B-Raf, Faf-1, PDGFRβ | AML, ALL, MDS, CML, CLL, NHL, MM | Advanced renal cell carcinoma, HCC |
| Sunitinib (Sutent®) | VEGFR1-3, PDGFRα+β, c-kit, Flt3 | AML, MDS, CLL, Myeloma, NHL | Advanced renal cell carcinoma, GIST |
| PKC-412 (Midostaurin) | VEGFR2, PKC, PDGFR, Flt3, c-Kit | AML | |
| Cediranib (Recentin®) | VEGFR1-3, PDGFRβ, c-Kit | AML, MDS, CLL | |
| Proteasome inhibitors | | | |
| Bortezomib (Velcade®) | 26S proteasome, NF-κB | AML, ALL, MDS, CML, NHL, MCL | MM, MCL |
| Anti-VEGF strategies | | | |
| Bevacizumab (Avastin®) | VEGF-A | AML, MDS, CLL, CML, NHL, MM | Metastatic colorectal cancer, NSCLC, breast cancer |
| Immunomodulatory drugs | | | |
| Thalidomide | bFGF, VEGF, IL-6 | AML, MDS, MPN, CLL, NHL, MM | MM |
| Lenalidomide (Revlimid®) | bFGF, VEGF, IL-6 | AML, MDS, CLL, NHL | MM, 5q- MDS |

AML, acute myeloid leukemia; bFGF, basic fibroblast growth factor; DLBCL, diffuse large B-cell lymphoma; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; GIST, gastrointestinal stromal tumors; HCC, hepatocellular carcinoma; IL-6, Interleukin-6; NHL, non-Hodgkin lymphoma; NSCLC, non-small cell lung cancer; MCL, mantle cell lymphoma; MDS, myelodysplastic syndrome; MM, multiple myeloma; MPN, myeloproliferative neoplasm; PMF, primary myelofibrosis; VEGF, vascular endothelial growth factor.

### Anti-VEGF monoclonal antibodies

## Conclusions and future directions

Angiogenic and especially VEGF/VEGFR pathways are involved in the pathophysiology of hematological malignancies including multiple myeloma, acute and chronic leukemias, MPN and lymphomas. Although VEGF/VEGFR-related pathways seems to be the most relevant regulators of neoangiogenesis, vasculogenesis and recruitment of endothelial progenitor cells in such instances, but other pathways are important too. Further, VEGF/VEGFR interactions can stimulate proliferation, migration and survival of leukemia/lymphoma cells by autocrinous and

paracrinous loops. Novel agents, targeting VEGF, its receptors, and other angiogenic pathways, are in various stages of clinical development and investigation in hematological malignancies. As we know from the the treatment of solid tumors, combination therapies of different anti-angiogenic molecules with chemotherapy or irradiation increases treatment efficacy. Especially, as blocking VEGF activity has been shown to sensitize the vasculature and improve the delivery of cytotoxic drugs to tumor and endothelial cells. However, not all patients treated with anti-angiogenic therapies benefit from this kind of therapy and in most cases, the effect is transient. Therefore, there is an urgent need for biomarkers to identify patients likely to benefit from anti-angiogenic treatments, to select the optimal dose to minimize side effects, and to understand the mechanisms of resistance. Preclinical models suggest multiple mechanisms involved in acquired or primary resistance against anti-angiogenic therapies. Finally, also these "targeted therapies" has side effects profiles which must be considered carefully.

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# Declarations

## Authors' original submitted files for images

Below are the links to the authors' original submitted files for images.

Authors' original file for figure 1

Authors' original file for figure 2

## Competing interests

The authors declare that they have no competing interests.

## Authors' contributions

MM and KM selected publications for the review, drafted manuscript. Both authors read and approved the final manuscript.

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