

## Angiogenesis in Leukemias: A Review

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### ABSTRACT

**Objectives:** This study aimed to investigate the influence of the angiogenic process on the development of leukemias.

**Methods:** A systematic review was performed based on 230 published manuscripts, 90 of which between 1995 and 2016, involving *in vitro* and *in vivo* experiments and reviews of the angiogenic process, types of leukemias and angiogenic factors involved in the origin of tumors. Searches were carried out in the Latin American and Caribbean Literature in Health Sciences (LILACS), Scientific electronic library online (SciELO), Scopus and Pubmed databases, among others. We excluded articles that did not report the relationship between angiogenesis and leukemias or angiogenic factors and leukemias.

**Results:** Evidence suggests that angiogenic factors such as FGF, HGF, TGF, TNF, HIF-1, MMPs, the c-Myc gene, endothelin and especially VEGF are strongly expressed in malignant cells and can lead, for example, to hematological malignancy. Regulation of miRNA expression, such as miR-17 and miR-20a, is also involved in the abnormal proliferation, differentiation and apoptosis of these cells.

**Conclusion:** Some angiogenic factors such as VEGF, MMPs and FGF act not only on initiation, but also on the progression, metastasis and apoptosis of solid tumor cells and leukemias, which may favor the development of a target-based therapy against angiogenesis in leukemias. As such, angiogenesis inhibitors aim to inhibit tumor growth and metastasis.

**Keywords:** Angiogenic factors; Leukemias; Tumor cells; Hematological malignancy

## INTRODUCTION

Tumor angiogenesis studies involving induction or interruption of the angiogenic process have become a hallmark in cancer research. Angiogenesis is the growth of new blood vessels from existing vessels. It is essential for the growth and survival of solid tumors. Its action occurs through the proliferation of blood vessels that penetrate the tumor, supplying it with nutrients and oxygen. The angiogenic process is a requirement for continuous tumor growth and metastasis.

It is important to underscore the influence of the angiogenic process on leukemias, a progressive neoplastic malignancy that affects the human hematopoietic system. Leukemia is the 11<sup>th</sup> most prevalent malignant disease worldwide. All forms of leukemia exhibit prognostic factors, determined by the use of

cytogenetics. In the present study, we define the appropriate treatment for a given patient. A number of angiogenesis induction factors have been investigated in leukemias, such as Vascular Endothelial Growth Factor (VEGF), Transforming Growth Factor (FGF), Hepatocyte Growth Factor (HGF), Growth Factor (HIF-1), Matrix Metalloproteinase (MMPs), the c-Myc gene, Endothelin (ET), Integrins (FF), Tumor Necrosis Factor (TNF) and Angiopoietin (PIGF), among others [1].

Some studies have demonstrated that the angiogenic process is regulated by the balance of angiogenic and anti-angiogenic cytokines, which can be induced through leukemia cells in the bone marrow. Research has shown that leukemia may be dependent on angiogenesis, which increases the likelihood of using anti-angiogenic drugs in the treatment of this disease. An important factor involved in tumor angiogenesis is the Vascular

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Endothelial Growth Factor (VEGF), which significantly increases vascular permeability. The fact that many leukemia cell lines and primary cells can synthesize and secrete may modulate the malignant biological behavior of leukemia cells.

Knowledge of angiogenic factors, such as VEGF, MMPs and FGF, has shown that they act not only on the initiation, but also in the progression, metastasis and apoptosis of solid tumor cells and leukemias. This study aimed to review the influence of the angiogenic process on leukemias, the main angiogenic factors expressed in leukemia cells and the possible prognostic and treatment strategies for patients with leukemia using angiogenic therapy [2].

## LITERATURE REVIEW

This is a descriptive quantitative study using a systematic review of the literature between April and June 2016. The main descriptors, searched in both Portuguese and English, were angiogenesis, leukemia, lymphoid, acute, chronic, myeloid, angiogenic factors, antileukemic therapy and the Boolean operators 'and' and 'or'.

**Table 1:** Principal angiogenic factors involved in leukemias.

Factors	Type of leukemia
VEGF	AML
	Hodgkin's Lymphoma (HL)
	Non-Hodgkin (NHL)
	Lymphoma (NHL)
Gene c-Myc	AML
MMP matrix	ALL and CLL
HIF-1	AML
FGF	ALM, CML and CLL

In 1997, Perez-Atayde, et al. first reported that angiogenesis occurred in the bone marrow in specific cases of ALL. Further research has also shown that in certain hematological parameters exhibiting malignancy accompanied by angiogenesis, there is a relationship with the prognosis of childhood ALL or a contribution to the development and progression of CLL cases. The angiogenic process is normally regulated by the balance of angiogenic and anti-angiogenic cytokines, which can be induced by leukemia cells in the bone marrow. Research has shown that leukemia may be dependent on angiogenesis, which increases the likelihood of anti-angiogenic drugs in the treatment of this disease [4].

There is some evidence that several antiangiogenic drugs, such as those targeting VEGF and its receptors, are able to treat patients with cancer. However, inhibition of VEGF is not as effective as previously thought. Thus, it is imperative to develop more effective targets for the treatment of patients with leukemia. A number of angiogenesis induction factors have

During the initial manuscript screening period, we found two hundred and thirty articles. Of these, eighty nine original national and international articles published between 1995 and 2016 were selected. We included clinical trials involving *in vitro* and *in vivo* experiments (case-control, cohort) and reviews of the angiogenesis process, types of leukemia and angiogenic factors related to the origin of tumors. The searches were carried out in the following databases: Latin American and Caribbean Literature in Health Sciences (LILACS), Scientific electronic library online (Scielo), specializing in biomedical sciences and life sciences (Medline), Scopus, Pubmed and Drugdex Medications. The manuscripts that did not report the relationship between angiogenesis and leukemias or angiogenic factors and leukemias were rejected [3].

### Angiogenic factors in the development of leukemias

According to the data obtained in this review, the main angiogenic factors involved in leukemias are VEGF, the c-Myc gene, MMP matrix, HIF-1 and FGF (Table 1).

been investigated in leukemias, such as VEGF, FGF, HGF, TGF, TNF, Ang, Hypoxia 1 Induction Factor (HIF-1), MMPs, the c-Myc gene, Endothelin (ET), Integrins and Placental Growth Factor (PIGF), among others. The combination of these factors with their receptors can promote vascular endothelium cell division and induce the formation of new vessels, which provides favorable conditions for the occurrence and progression of tumors. Additionally, the relationship between angiogenic factors in leukemia has demonstrated their role in modulating proliferation, differentiation and apoptosis events.

### The role of Vascular Endothelial Growth Factor (VEGF) in leukemias

VEGF is the best-characterized pro-angiogenic factor to date and its first purification occurred from the *in vitro* culture of follicle-starved bovine cells.

After its mitogenic activity was detected in vascular endothelial cells, VEGF was considered not only a highly specific mitogenic coagent in endothelial cells, but also a factor promoting vascular permeability.

VEGF can act efficiently and specifically on vascular endothelial cells and promote regeneration, in addition to increasing vascular permeability through three Receptor Tyrosine Kinases (RTKs): VEGFR-1 (or the VEGFR-1 receptor) is also expressed in other cell types, including Hematopoietic Stem Cells (HSCs), vascular smooth muscle cells, monocytes and leukemia cells (VEGFR-2), while VEGFR-3 (or KDR) is predominantly expressed in the vascular endothelium. However, the VEGFR-2 receptor is expressed mainly in Endothelial Progenitor Cells (EPCs) and megakaryocytes [5].

The regulation of lymphatic vessel formation (lymphangiogenesis) depends on the binding of homologues to VEGF, VEGF-C, VEGF-D and VEGFR-3 receptors, which is largely restricted to lymphatic endothelial cells. In addition, high VEGF-D receptor expression was detected in both Hodgkin's (LH) and Non-Hodgkin's Lymphomas (NHL) and in Reed-Sternberg (RS) cells with a large number of tumor microvessels, suggesting a role in angiogenesis. Induction of tumor angiogenesis as well as disruption of the angiogenic process have become a hallmark in cancer research. As an inhibitor of tumor angiogenesis, VEGF can significantly increase vascular permeability. Many leukemia cell lines and primary cells can synthesize and secrete this factor, which modulates the malignant biological behavior of leukemic cells by positive feedback loops: paracrine and autocrine signaling [6].

VEGF secreted by leukemia cells interacts with endothelial cell receptors, which start to produce growth factors, such as the Granulocyte Colony Stimulating Factor (G-CSF), increasing leukemia cell proliferation and resistance to drugs or acting on the surface receptors of autologous cells to increase autologous proliferation activity. The functional interaction between the VEGF-A receptor and the Formyl Peptide Receptor (FPRL1) mediated by Connective Tissue Growth Factor (CTGF) secretion has been demonstrated by some researchers. CTGF directly activates the FPRL1 signals, leading to an increase in intracellular  $Ca^{2+}$  levels and the kinase signal controlled by phosphorylated extracellular signaling (ERK).

The VEGF-2 receptor plays an important role in VEGF-induced angiogenesis and the binding between this factor and the Flt-1 receptor can activate MAPKs, kinase C (PKC), RAS proteins or induce vascular endothelial cell proliferation. To date, it has been shown that VEGF is the only growth factor for angiogenesis, while others such as FGF and PDGF may act, with less specificity, in numerous cell types concomitant with vascular endothelial cells. This factor can regulate the development of hematopoietic stem cells, remodel the extracellular matrix and regenerate inflammatory cytokines [7].

Activation of VEGFR-2 also plays a necessary role in mediating VEGF-dependent angiogenesis and inducing vascular permeability. VEGF-A receptors (VEGFR-1 and VEGFR-2) act on pathological angiogenesis, including tumor angiogenesis. The VEGF-C and D factors, together with their VEGFR-3 receptor,

can regulate angiogenesis during the embryonic process, in addition to regulating lymphangiogenesis. VEGF is closely related to MMPs, through the complexity of this factor as a mediator of MMP-9 expression. In other studies, this relationship contributed to tumor angiogenesis and metastasis and showed a partial association with increased VEGF secretion. This combination of VEGF and MMPs has been used in clinical trials and is considered a possible therapeutic target. Evidence suggests that it is also involved in the proliferation, abnormal differentiation and prognosis of AML. The positive regulation of these pro-angiogenic cytokines in microvessel density, marrow and plasma also reinforces this theory [8].

Representative cytokines, VEGFs and their receptors are expressed in the white cells (blasts) of AML, osteoblast niches and peripheral circulation. In this respect, a therapeutic approach focused on antiangiogenic action has become increasingly effective and promising through the use of immunomodulators, such as anti-VEGF monoclonal antibodies, VEGFR and histone inhibitors. As such, therapy using antiangiogenic factors based on inhibiting the physiological function of VEGF has become the hotspot of oncoterapies. For example, ilorasertib (or ABT-348) is a novel inhibitor of aurora kinases, which may inhibit the action of VEGF, PDGF and receptor tyrosine kinase families.

Glucosamine 3B1 heparin sulfate can promote angiogenesis and cell proliferation by inducing VEGF in AML cells. This has contributed positively to the progression of AML and these activities are associated with induced VEGF expression. The compound genoside (Rg3) is used not only as antiangiogenic dormancy in anticancer therapy, but also exhibits an antileukemic effect, due to its antiangiogenic activity in the inhibition of the PI3K, Akt and ERK1 pathways that regulate HIF-1 $\alpha$  and VEGF expression. Histone Deacetylase (HDAC) also acts to inhibit tumor angiogenesis by down-regulating angiogenic factors.

The Valproic Acid-induced antiangiogenic mechanism (VPA) is associated with the suppression of VEGF and its receptor. In addition, the combined use of histone deacetylase and the VPA inhibitor, All-Trans-Retinoic Acid (ATRA), deoxyribonucleic acid polymerase- $\alpha$  and cytarabine inhibitor (Ara-C) is currently considered the most viable treatment for AML, with promising anti-proliferative effects and modulation in the release of angiogenic mediators of endothelial cells. Another example is foretinib, which consists of a multiple inhibitor kinase and when subjected to clinical trials, has inhibited VEGFR-2 activity. Its activity may also inhibit VEGF-A, VEGF-C and angiopoietin-2, reducing the expression of VEGFR-2 and VEGFR-3 as well as TIE-2 activation. However, although VEGF receptors have a potential delay mechanism for AML, cediranib (AZD2171), an endothelial tyrosine kinase inhibitor, acts against VEGF receptors and on KDR and FLT-1 factor responses, but cannot be confirmed in other groups [9].

Understanding the components of the cellular complex of bone marrow may lead to the discovery of new extrinsic factors responsible for the onset and progression of leukemia. Activation of endothelial cells by VEGF-A favors the profusion of large numbers of leukemia cells, in addition to increasing

adherence of endothelial cells in leukemia. The development of drugs targeting vascular niche activation could be an effective therapy in combination with other chemotherapeutic agents. On the other hand, high VEGF-C expression is associated with chemoresistance and indicates an adverse prognosis in AML. VEGF-C induces Cyclooxygenase 2 (COX-2) expression, thereby promoting resistance to chemotherapy. In addition, ET1 induces COX-2 mRNA expression. The regulation between VEGF-C/COX-2 and ET-1 represents a potential target for improving resistance to chemotherapy in AML patients [10].

Lenalidomide (Revlimid®) is a clinically active immunomodulatory agent in patients with CLL, and its anti-CLL effect is mediated by changing micro-environmental elements, which implies modulating several factors related to angiogenesis and disrupting endothelial cells. As a result, the leukemic environment becomes highly enriched for lymphangiogenic stimuli, and VEGFR-3 inhibition restores NK cell function. Blocking VEGFR-3 modulates the function of these cells, providing possible advanced therapeutic approaches using immune cells against myeloid leukemia. Understanding the functional characterization of lymphocyte factors in bone marrow and AML may also represent a potential target in disrupting stem cell transplantation, as well as enhancing immune cell function by modulating the tumor microenvironment.

### The c-Myc gene: An important angiogenic factor involved in leukemias

The c-Myc gene is a member of the Myc proto-oncogene family, a pleiotropic regulation transcript. It may induce genome instability and directly or indirectly affect the occurrence and progression of tumors, thereby playing an important role in programmed cell proliferation and death. Its specific DNA sequence is responsible for the transcription of the Leucine Zipper and Helix loop. This gene heterodimerizes with the corresponding MAX protein and stimulates the transcription of a number of genes, including ODC, ECA39, eIF4E, CDC25, CAD, CDK4, eIF4G1, hTERT and CCND1. In recent years, the c-Myc gene has also been found to act as an important factor in tumor angiogenesis due to its relation to VEGF expression. The binding region of this gene (271bp) promotes VEGF expression. After a mutagenesis process, this region may favor greater VEGF expression under hypoxic conditions through co-participation of c-Myc and subsequently promote angiogenesis and tumorigenesis.

Some studies also report that tumor angiogenesis can be promoted by miRNAs, which induce c-Myc and IL-1 $\beta$  activation, representing the effect of this gene as an inducer of angiogenesis initiation. Furthermore, this gene is highly expressed in HL-60 cell lines (human promyelocytic leukemia cells) and related to the proliferation and differentiation of leukemia cells. The c-Myc gene may be uniquely activated by amplifying the rearrangement of other genes, its level of expression is related to the state of cell growth and it is highly expressed at the undifferentiated stage. The gene is a promising target in the development of therapies because of its oncogenic activities, since it is hyperexpressed in most human cancers. Attempted c-Myc binding in certain genes

that inhibit the action of small molecules was tested and some of these genes were found to be effective at disrupting interactions of proteins essential to DNA.

Studies show that increased c-Myc expression plays an important role in leukomogenesis. In cases of AML, this gene is responsible for directly controlling the expression of the *EZH2* gene, which participates in the recruitment of DNA methyltransferase enzymes (DNMTs) and locates the methylation point in DNA. During the differentiation of AML cells, simultaneous induction occurs in the reduction of c-Myc and *EZH2* levels. Some variations in *EZH2*, present in AML, depend mainly on the transcriptional control of c-Myc. Tumor-Associated Macrophages (TAM) may also express the c-Myc gene, regulating its' *in vivo* pro-tumor and phenotypic activities. The role of c-Myc in TAM can therefore control tumor growth, indicating that this gene has become an ideal target in genetic therapies to combat tumors and leukemias.

## DISCUSSION

### Involvement of Matrix Metalloproteinases (MMPs) in hematological malignancies

Matrix metalloproteinases (MMPs) are a series of finger-dependent zinc proteinases with high homology. There are three common domains in MMPs: Pro-peptide, catalytic and hemopexin as the C-terminal domain. According to the specific characteristics of amino acid sequences and substrates, MMPs can be classified into four main types: Collagenase (MMP-1, MMP-8, MMP-13, MMP-18), gelatinase (MMP-2, MMP-9), stromelysins (MMP-3, MMP-10 and MMP-11), and matrilysins (MMP-7, MMP-26). MMPs can degrade the extracellular central matrix, which may be an important signal in the initiation of angiogenesis, invasion and tumor metastasis.

Some studies have reported that MMP expression is related to the metastatic potential of several human tumors and plays an essential role during the development of LEUCO-diapedese and Disseminated Intravascular Coagulation (DIC). Important transcription factors, such as Plasminogen Activator type 1 (PAI-1), are involved in MPP modulation. Transcription factors PEA3, NF $\kappa$ B, transducers and Transcription Activators (TSAT), as well as other factors involved in regulating MPP expression can also regulate VEGF transcription levels. Understanding the invasive properties of tumor cells in humans reveals an association with the low expression of Tissue Metalloproteinase Inhibitors (TIMPs), including TIMP-1, 2, 3 and 4. In addition, TIMP expression levels may directly affect the activity level of MMPs. The various MMPs and TIMPs can be released by primary AML cells and affect the behavior of leukemia cells.

With respect to clinical use, the number of molecules in the extracellular matrix, including types IV, V, collagens XI and laminin, are also digested by MMPs related to angiogenesis and tumor metastasis, such as MMP-1, which acts as a negative regulatory factor in angiogenesis and development and MMP-13, which promotes VEGF secretion and induces *in vivo* tumor angiogenesis. MMP-3, MMP-10 and MMP-11 can activate tumor cells. Because of the lack of a hemopexin domain, matrilysins



(MMP-7 and MMP-26) can be considered MMPs and MMP-7 not only plays an important role in the degradation of extracellular matrix proteins, but also participates in the activation, degradation, abscess and other biochemical processes of non-extracellular matrix proteins, essential for the development of tumor angiogenesis. MMPs are generally hyperexpressed in tumors and overexpression of gelatinases, including MMP-2 and MMP-9, is always accompanied by tumor growth, metastasis and angiogenesis [11].

Some studies have been conducted on the functions of MMP-2 and MMP-9 in hematologic malignancies. Plasma MMP-9 contributes to the clinical evolution of patients with CLL and as such, can be used in the prognosis of this type of leukemia. In patients with Myelodysplastic Syndrome (MDS), MMPs are a useful diagnostic tool and may be a possible target in the treatment of the disease. LMA cells generally secrete high levels of several MMPs (MMP-2 and MMP-9, TIMP1 and VEGF). Moreover, the proteolytic release of VEGF from the tumor matrix by MMP-9 plays an important role in modulating leukemia cell proliferation. The HIF-1 factor may be closely related to VEGF and MMP-9 expression. VEGF can significantly reduce MMP-9 production in leukemia and type B cells.

Blocking MMPs can completely inhibit VEGF production and significantly reduce vasculature volume. A number of studies have confirmed that MMP-2 activation is dependent on the TIMP-2 inhibitor, since, when TIMP-2 concentration increases, it combines with TIMP-1 and activates MMP-2, which may trigger the tumor activation event. Due to their role in the development of leukemias, specific MMP inhibitors may be constituents of anticancer therapy. Special attention should be given to MMPs as an anti-leukemic strategy because of the importance of developing new therapies. MMPs directly and indirectly influence the development of VEGF-mediated vasculature.

### Relationship between VEGF and HIF-1 in hematological malignancy

Hypoxia-Induced Factor 1 (HIF-1) is the central regulator of the response to changes in oxygen concentration and plays a key role in physiological and pathological processes in humans. It is capable of forming a heterodimer with the Aryl Hydrocarbon Receptor Nuclear Translocator (ARNT) and binds to the Hypoxia Responsive Element (HRE) of human erythropoietin. This factor activates the expression of numerous genes in response to hypoxia. In hypoxia, the HIF-1 factor becomes stable and may interact with the CBP / P300 co-stimulation auxiliary factor to regulate oncogene activity. This factor influences the regulation of a variety of genes that act on the anaerobic glucose metabolism, in addition to promoting angiogenesis in tissues subject to ischemia by increasing VEGF expression.

The HIF-1 factor can be regulated by the Inhibitory PAS protein domain (IPAS), exhibiting pro-apoptotic activity through other proteins that interact with members of the Bcl-2 family. In aerobic conditions, proline residues present in HIF-1 $\alpha$  undergo hydroxylation, which promotes proteosomal ubiquitination and degradation by the enzyme ubiquitin ligase (E3). Under hypoxic

conditions, the HIF complex increases the transcription of genes such as the VHL tumor suppressor gene, responsible for increasing the supply of O<sub>2</sub> and nutrients *via* angiogenesis [12].

Not only does HIF-1 stimulate the production of angiopoietins (ang), but it also regulates the expression level of Ang receptors. This factor also plays an important role in the extracellular matrix metabolism and displays other effects after activation, such as promoting adaptive changes in the cellular metabolism and stimulating renal cells in the production of erythropoietin, which acts as the main regulator in the induction of angiogenesis in malignant tumors. HIF-1 also influences the growth and development of tumor cells by increasing the expressiveness of target genes, including VEGF expression. A remarkable feature of the hematopoietic niche is the low oxygen level at which hypoxia is required for the long-term maintenance of hematopoietic stem/progenitor cells. It is known that hypoxia causes intrinsic metabolic changes in solid tumors and modifications in the tumor microenvironment, such as the stimulation of angiogenesis by HIF-1 activation.

Considering that leukemia is not a "solid" tumor, the role of oxygen is poorly investigated. However, recent studies indicate that hypoxia influences the proliferation and differentiation of leukemia cells, as well as resistance to chemotherapy. However, the role of HIF proteins remains controversial, since they are either oncogenes or tumor suppressor genes, depending on the study and model. Other investigations show that HIF-1 promotes the development of angiogenesis and metastasis, and hypoxia may increase its concentration in primary AML cells. Similarly, low HIF-1 $\alpha$  expression and the release of several pro-angiogenic cytokines by leukemia cells can be induced by a decline in oxygen concentration.

A number of studies have reported that the HIF-1 factor may favor the differentiation of AML cells through an independent transcription mechanism, inhibiting the progression of this type of leukemia. Research has shown that HIF-1 suppression, through the expression of miR-17 and miR-20a, can paralyze the differentiation induced by this factor under hypoxia in AML cells. Moreover, miR-17 and miR-20 immediately inhibit the expression of p21 and STAT3. There is evidence that HIF-1 plays an important role in the survival of white blood cells and may be a driver in the chemoresistance mechanism.

### Relationship between Fibroblast Growth Factor (FGF) and leukemias

The Fibroblast Growth Factor (FGF) is involved in different development stages of an organism, such as tissue proliferation and differentiation. Its involvement in the angiogenic process and tissue repair is relevant in clinical studies. The FGF protein family contains at least 23 members, including acid FGF (aFGF or FGF1) and basic FGF (bFGF or FGF2), which are widely studied because of their varied functions. They bind to heparin, which increases their biological activity and protects them from proteolysis. Both FGF1 and FGF2 act on the same receptor; however, the affinity of FGF is about 30 to 100 times greater than that of bFGF.

FGF is a strong inducer of DNA synthesis in different cell types of mesoderm and neuroectoderm lines and also exhibits chemotaxis and mitogenic activities. A number of studies have demonstrated that bFGF can stimulate and regulate the proliferation and differentiation of several cell types derived from mesoderm and neuroectoderm, such as epithelial cells, myoblasts, osteoblasts and glial cells, which play an important role in embryogenesis and tissue healing, in addition to regulating VEGF expression. Considered a mitogenic factor of chemokines (proinflammatory cytokines) and vascular endothelial cells, bFGF is released extracellularly and can bind to different endothelial cell surface receptors, including TKR, Cell Adhesion Molecules (CAMs) and heparan sulfate proteoglycans, to activate its vasculogenic activity.

BFGF can also activate the P13K signaling pathway, inhibiting vascular endothelial cell apoptosis and promoting angiogenesis. Like a chemokine, bFGF can attract different cell types by chemotaxis and induce them to produce collagenases (proteolytic enzymes), thereby favoring the proliferation and migration of vascular endothelial cells and the degradation of extracellular matrix proteins to induce angiogenesis. Positive regulation of bFGF occurs in cases of AML, CML and CLL, largely resulting in poor prognosis. Mutations in the kinase domain are a common resistance mechanism in CML; however, the resistance mechanism in the absence of mutations has yet to be elucidated. A number of studies indicate that FGF2 promotes *in vitro* resistance to imatinib through the activation of mitogen-activated protein kinases by the FGF 3/RAS/c-RAS receptor. Furthermore, this factor is found at significantly lower levels in individuals taking ponatinib, suggesting that inhibition of FGF receptors may disrupt FGF-2-mediated resistance [13].

## CONCLUSION

Knowledge of angiogenic factors, such as VEGF, MMPs and FGF, has been shown to act not only on initiation, but also on the progression, metastasis and apoptosis of solid tumor cells and leukemias. In this respect, better understanding of the functions of these factors has indicated that they can favor targeted therapy based on the process of angiogenesis in leukemias. The development of tumor angiogenesis inhibitors to restrict growth and metastasis has become an effective new oncotherapy technique. In recent years, oncotherapy involving the combination of multiple targets has guided further research with antiangiogenic agents. Although studies remain confined to experiments and clinical trials without considering the real value in clinical practice, through the development of antiangiogenic agents, cancer therapies with antiangiogenic

compounds may open new avenues for the treatment of hematological diseases.

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