

# The importance of antiangiogenic effect in multiple myeloma treatment

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## Abstract

Angiogenesis plays a significant role in oncogenesis, and thus it has become an attractive target for cancer treatment. It is the formation of new blood vessels that occurs physiologically as well as under pathological conditions, and may influence cancer proliferation and survival. The current therapeutic approach in oncology includes conventional chemotherapy in combination with biologically-based treatment in various perspectives, targeting not only the malignant cells, but also its microenvironment. Target treatment might be less toxic than conventional chemotherapy. In multiple myeloma, there is a close connection between bone marrow stroma, myeloma cell growth and their ability to survive. It has been reported in many clinical observations that the more advanced the multiple myeloma, the more increased the angiogenesis, and this might correlate with the treatment response. There are several angiogenesis inhibitors already registered or in clinical trials in cancer treatment. Despite the continuous research on the development of prognostic factors and introduction of new agents in the treatment, multiple myeloma still remains an incurable and debilitating disease. Some antiangiogenic agents have already been introduced in multiple myeloma treatment, but there is still a need to search for new antiangiogenic drugs and the exploitation of angiogenesis in a clinical approach.

**Key words:** multiple myeloma, angiogenesis, treatment, angiogenesis inhibitors

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## Introduction

Angiogenesis is the formation of new blood vessels, occurring physiologically in various stages of human life. Under pathological conditions, it plays a significant role in the inflammation process, and proliferation and metastasis of most malignant neoplasms. Recent studies have shown a role of angiogenesis and angiogenic factors in the development and course of hematological malignancies.<sup>1</sup>

Multiple myeloma (MM) is a hematological disorder, derived from B lymphocytes that are in the final stage of differentiation. This accounts for approx. 10% of hematologic malignancies. The essence of multiple myeloma is clonal proliferation of plasma cells in the bone marrow, monoclonal protein production and release of cytokines responsible for the destruction of bone tissue. Symptoms of multiple myeloma depend mainly on the stage of the disease.<sup>2</sup> Despite the continuous research on the development of prognostic factors and introduction of new agents in the treatment, multiple myeloma still remains an incurable and debilitating disease.<sup>3</sup>

The field of neovascularization was first evaluated in solid tumors. In 1997, Folkman et al. observed an increased amount of microvessels in the bone marrow of children with acute lymphoblastic leukemia.<sup>4</sup> Angiogenesis is a multifactorial process, associated with the formation of new blood vessels on the basis of the existing vascular network.<sup>5</sup> It begins with an increase of permeability and widening the lumen of blood vessels. Subsequently, endothelial sprouts are formed, and this process is regulated by several proangiogenic and antiangiogenic factors.<sup>6,7</sup> In fact, the process of pathologic angiogenesis associated with cancer activity differs from physiological blood vessel formation. The new blood vessel network is chaotic and might be associated with blood flow alteration and increased permeability of the vessels. The proangiogenic growth factors are produced mainly by endothelial cells, but also mast cells and pericytes. In the case of cancer, the “angiogenic switch” is induced. Cancer cells have the potential to produce

proangiogenic cytokines, but also to stimulate the environment. Under normal conditions, there is a balance between proangiogenic and antiangiogenic factors. When it is switched, there is an increased angiogenesis potential. Several factors associated with angiogenesis may provide autocrine and paracrine effects to cancer cells. Importantly, the “angiogenic switch” may occur at any stage of cancer, but it is dependent on the cancer type and its interaction with the microenvironment.<sup>8</sup>

## Angiogenesis in multiple myeloma

In multiple myeloma, inducement of proangiogenic and proinflammatory cytokine production is associated with the interaction of myeloma cells and the bone marrow stroma that includes fibroblasts, stromal cells, and also osteoblasts and osteoclasts, monocytes, macrophages, mast cells, and T lymphocytes. In general, in MM there is a tight connection between bone marrow stroma, myeloma cell growth and their ability to survive. The MM cells directly produce some proangiogenic molecules, such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), hepatocyte growth factor (HGF), interleukin-8 (IL-8), osteopontin (OPN), metalloproteinases and angiopoietin-1 (Ang-1), but can also stimulate other cells of the bone marrow microenvironment to secrete different growth factors, and finally endothelial cells to originate the angiogenic process.<sup>5</sup> The involvement of selected genes associated with angiogenesis in MM disease is described in Table 1.

The increased angiogenesis in MM was first described by Vacca et al., who conducted in vitro research and revealed increased activity of isolated plasma cells from active myeloma patient cells to produce the proangiogenic factors, in comparison with plasma cells derived from patients with monoclonal gammopathy of undetermined significance (MGUS) or inactive MM.<sup>9</sup> This observation was followed by continuous research that showed increased bone marrow

**Table 1.** Involvement of selected genes and proteins associated with angiogenesis in MM disease<sup>5,16,17,19</sup>

Gene and protein name	Impact on angiogenesis	Expression by MM cells
VEGF	proangiogenic	expressed
HGF	proangiogenic	aberrantly expressed
ANG	proangiogenic	aberrantly expressed
IL-8	proangiogenic	upregulated (vs normal plasma cells)
ANGPT1	proangiogenic	upregulated (vs normal plasma cells)
MMP-9	proangiogenic	expressed
TSP-1	antiangiogenic	expressed (potential prognosis factor)
ADAMTS9	antiangiogenic	aberrantly expressed
LAMA5	antiangiogenic	downregulated (vs normal plasma cells)

VEGF – vascular endothelial growth factor; HGF – hepatocyte growth factor; ANG – angiogenin; IL-8 – interleukin-8; ANGPT1 – angiopoietin-1; MMP-9 – matrix metalloproteinase-9; TSP-1 – thrombospondin-1; ADAMTS9 – a disintegrin and metalloproteinase with thrombospondin motifs 9; LAMA5 – laminin alpha 5.

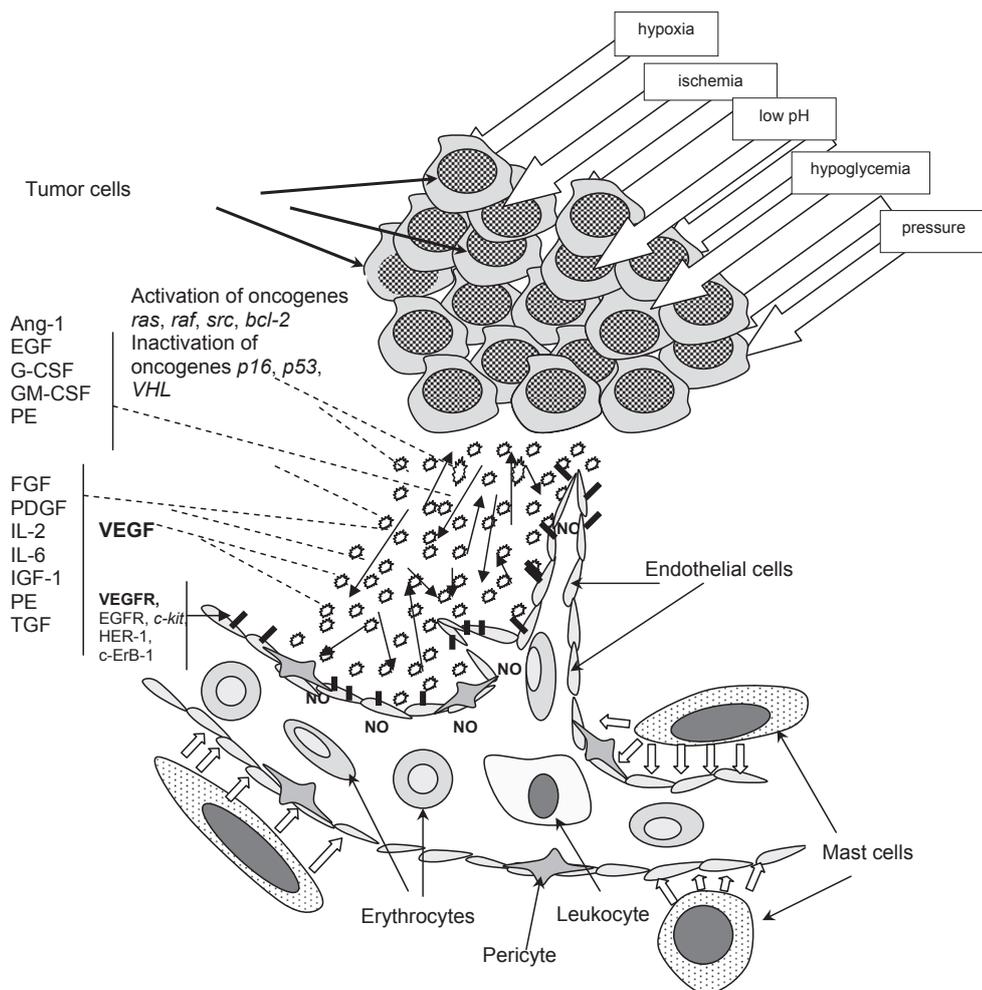


Fig. 1. Regulatory factors and mechanisms for angiogenesis in multiple myeloma<sup>18</sup>

VEGFR – vascular endothelial growth factor; PDGF – platelet-derived growth factor; FGF – fibroblast growth factor; EGFR – epidermal growth factor receptor; HER – human epidermal growth factor receptor; IGF-1 – insulin-like growth factor; Ang-1 – angiopoietin-1; EGF – epidermal growth factor; G-CSF – granulocyte colony-stimulating factor; GM-CSF – granulocyte-macrophage colony-stimulating factor; PE – plasma endostatin

angiogenesis in patients with advanced MM. It has been revealed that bone marrow microvessel density (MVD) assessed in histopathological samples was substantially higher in these patients than in health controls. In a study by Rajkumar et al., angiogenesis was assessed in bone marrow from 400 patients with multiple myeloma, MGUS and primary amyloidosis. It was found that the degree of angiogenesis is lower in patients with MGUS, and significantly increased in patients with multiple myeloma.<sup>10</sup> The greater intensity of blood vessel formation, the higher the proliferation of plasma cells seems to be, so it could indicate that angiogenesis might be associated with progression of the disease.<sup>10</sup> The assessment of bone marrow MVD might be an independent prognostic factor at the moment of diagnosis as well as in the response assessment.<sup>11–13</sup>

Several studies have been conducted on the relationship between the levels of angiogenic factors in the blood and MVD. The increased levels of proangiogenic molecules might also be associated with the treatment and prognosis.<sup>14,15</sup> The proangiogenic factors differ in respect of the activity. VEGF-A has the highest proangiogenic potential, and it is the main factor in angiogenesis and vasculogenesis. When the release of VEGF-A is inhibited, a regression of existing and formation of new blood vessels might be observed. A study conducted by Mileschkin et al. has

shown that VEGF levels decreased significantly in MM patients who responded to thalidomide therapy.<sup>16</sup> On the other hand, the research by Cibeira et al. has not confirmed any correlation between VEGF level and response rate.<sup>17</sup>

Apart from releasing and stimulating angiogenic factors, the MM cells might also influence new blood vessel formation by direct interaction with matrix cells and fibronectin (Fig. 1).<sup>18</sup> Endothelial cells located in the bone marrow microenvironment may also produce angiogenic factors that act in a dual way (autocrine and paracrine) on both MM and endothelial cells. Thus, there is a mutual stimulation between endothelial cells and malignant plasma cells.<sup>19</sup>

## Angiogenesis inhibitors in cancer treatment

The current therapeutic approach in oncology includes conventional chemotherapy in combination with biologically-based treatment in various perspectives, targeting not only the malignant cells but also its microenvironment, so new therapeutic targets are available nowadays. Angiogenesis seems to be a key factor in malignant tumor growth and survival, so there are some antiangiogenic agents already registered and others being investigated in

**Table 2.** Selected angiogenesis inhibitors in cancer treatment<sup>19</sup>

Drug	Signaling pathway	Molecular target	Indication (registered or in clinical trial)
Thalidomide	RTKs	VEGFR	multiple myeloma
Bevacizumab	RTKs	VEGFR-A	non-small lung cancer breast cancer glioblastoma colorectal cancer renal cell carcinoma
Aflibercept	RTKs	VEGFR-1 and -2	
Sunitinib	RTKs	VEGFR PDGFR c-kit FLT-3 CSF-1R	gist renal cell carcinoma breast cancer
Crizotinib	RTKs	c-Met HGFR	lung cancer breast cancer
Sofarenib	RTKs	Raf-kinase (B-Raf, C-Raf) VEGFR-2 and -3 PDGFR- $\beta$ c-kit	colon cancer pancreatic cancer breast cancer
Semaxanib	RTKs	VEGFR	colorectal cancer (clinical development stopped due to severe thromboembolic adverse events)
Erlotinib	RTKs	EGFR/HER-1	nscl pancreatic cancer
Imatinib	RTKs	PDGFR c-kit	antiangiogenic inhibition in vitro

RTKs – receptor tyrosine kinases; VEGFR – vascular endothelial growth factor; PDGFR – Platelet-derived growth factor receptors; HGFR – hepatocyte growth factor receptor; CSF-1R – Colony stimulating factor 1 receptor; EGFR – epidermal growth factor receptor; HER – human epidermal growth factor receptor.

clinical trials. It has been reported in animal models that target therapy might be less toxic than conventional chemotherapy. Angiogenesis is a complex pathway, involving a number of factors, so there is a possibility to inhibit it on different levels.<sup>18</sup> It is crucial to distinguish between agents that impact angiogenesis and vascular targets. Antiangiogenic drugs mainly affect new vessel growth and formation in cancer tissue. Vascular targeting agents may destroy the existing vasculature of the tumor. The actions of both kinds of agents may synergize. There are several molecules of interest as potential therapeutic targets that have a regulatory or signaling function involved in angiogenesis, such as growth factors (e.g., VEGF, fibroblast growth factor – FGF, epidermal growth factor – EGF), transcription factors like hypoxia-inducible factor (HIF), and receptor tyrosine kinases. The same applies to molecules involved in phosphatidylinositol-4,5-bisphosphate-3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) signaling.

Bevacizumab is the humanized monoclonal antibody VEGF, and is approved in combination with chemotherapy for the treatment of some cancers (non-small lung cancer, breast cancer, glioblastoma, colorectal cancer, and renal cell carcinoma). This acts by inhibition of VEGF receptors, thereby also interfering with the autocrine and paracrine mechanisms of malignant cell survival mediated by VEGFR-1 and VEGFR-2. Bevacizumab is also in clinical trials in metastatic breast cancer and colorectal cancer.<sup>20</sup>

The most important agents with antiangiogenic potential in clinical trials or already registered in cancer treatment are presented in Table 2.

## Angiogenesis inhibitors in MM

As angiogenesis seems to be strongly associated with MM development and prognosis, there have been increasing efforts to search for treatment with antiangiogenic potential. There are some drugs already registered in MM treatment that have demonstrated an antiangiogenic effect. These drugs might be administered alone or along with chemotherapy.

## Immunomodulatory drugs

Thalidomide was the first agent introduced to MM treatment because of its potential antiangiogenic action. The drug was synthesized in the early 1950s and prescribed because of its sedative effect; finally it was withdrawn due to serious teratogenic side effects. In the 1990s, a study of rabbit model corneal neovascularization induced in response to bFGF demonstrated the antiangiogenic activity of thalidomide.<sup>21</sup> Afterwards, the clinical efficacy of thalidomide in MM patients was reported. Singhal et al.

showed a response to thalidomide monotherapy in a clinical phase II trial that included previously treated patients with refractory disease.<sup>22</sup> Partial response was achieved in almost 1/3 of patients and 14% achieved a complete or nearly complete remission.<sup>22</sup> That was the beginning of subsequent clinical studies and, in consequence, thalidomide was approved by the United States Federal Drug Administration (FDA) for the therapy of newly-diagnosed MM patients in combination with dexamethasone. The results of a phase III trial showed that the response rate in patients treated with thalidomide and dexamethasone was 63% in comparison to 41% in patients treated with dexamethasone in monotherapy.<sup>23</sup> The mechanism of the antiangiogenic effect associated with thalidomide is actually unknown. It has been observed that thalidomide might have important immunomodulatory effects associated with a decreasing synthesis of TNF- $\alpha$  and shifting the T cell population toward T helper. Thalidomide also decreases the expression of intercellular and vascular cell adhesion molecules (intercellular adhesion molecule 1 – ICAM-1 and vascular cell adhesion molecule – VCAM), and thus attenuates the interaction between stromal and malignant plasma cells.<sup>24</sup> In a study by Gupta et al., thalidomide and the newer immunomodulatory drugs like lenalidomide have been reported to significantly decrease the expression of proangiogenic factors, mainly VEGF and interleukin-6 (IL-6), in MM patients.<sup>25</sup> However, as has been reported in some other studies, the thalidomide action seems not always to be associated with a decrease of bone marrow angiogenesis and the levels of cytokines related to angiogenesis.<sup>17</sup> Moreover, in spite of high vascularity of extramedullary plasmocytoma, it has been observed that it does not respond to thalidomide treatment.<sup>26</sup>

Lenalidomide is derived from a modified thalidomide chemical structure and it also shows the immunomodulatory effects with lower rates of adverse events. In patients that were previously treated and had relapsed or refractory MM, lenalidomide in combination with dexamethasone showed a significant increase in the response rate, from 22.5% to 59.2%, in comparison to dexamethasone alone.<sup>27</sup> Lenalidomide was previously approved by the FDA for second-line therapy in MM and, further, in 2015 for newly diagnosed patients. The mechanisms of action mainly seen in MM may comprise induction of cell cycle arrest by an increase in expression of the cyclin-dependent kinase inhibitor p21 and decrease in expression of interferon regulatory factor 4, and also induction of apoptosis and attenuation of angiogenesis.<sup>28</sup>

Lu et al. conducted in vitro research and reported that lenalidomide may inhibit the formation of microvessels in a dose-dependent manner.<sup>29</sup> The inhibitory effect of lenalidomide may derive from the associations between cadherin 5,  $\beta$ -catenin and CD31. Moreover, lenalidomide was shown to attenuate PI3K–Akt pathway signaling induced by VEGF, which is known to modulate adherence junction formation.<sup>29</sup> In a Dredge et al.'s study, it was observed that

le antiangiogenic effect of lenalidomide might not be related to a decrease of endothelial cell proliferation, still the migration of endothelial cells is inhibited significantly.<sup>30</sup> The study has been extended and it has been reported that lenalidomide may inhibit the action of some proangiogenic molecules in an animal model.<sup>31</sup>

Pomalidomide is a novel anti-myeloma agent among the immunomodulatory class drugs. Preclinical studies have shown that pomalidomide is active against MM cell lines in cases of bortezomib and lenalidomide resistance, which has been confirmed in a number of further clinical trials with a relatively tolerable safety profile.<sup>32,33</sup> Aside from these mechanisms of actions, pomalidomide inhibits stromal cell adhesion in bone marrow and has been shown to significantly inhibit angiogenesis by targeting VEGF and hypoxia-inducible factor-1 $\alpha$  (HIF1- $\alpha$ ), a transcription factor regulating angiogenesis by induction of VEGF transcription.<sup>34</sup>

## Proteasome inhibitors

Bortezomib, a modified boronic acid dipeptide, is a selective inhibitor of nuclear factor- $\kappa$ B (NF $\kappa$ B) and has been approved for clinical use for the treatment of MM patients, but also shows activity in other hematological malignancies. It blocks very specifically the  $\beta$ -subunit of the 26S proteasome.<sup>35</sup> The anticancer activity of bortezomib might also be associated with angiogenesis inhibition. It has been previously reported that proteasome inhibitors have antiangiogenic potential in animal models.<sup>36</sup> Inhibition of NF $\kappa$ B mediated by bortezomib is supposed to be involved in targeting HIF-1 $\alpha$ -mediated VEGF expression.<sup>37</sup> Roccaro et al. examined the activity of bortezomib on the angiogenic phenotype of multiple myeloma patient-derived endothelial cells (MMEC). The authors reported that bortezomib induced a dose-dependent inhibition of VEGF and IL-6 production, and confirmed reverse transcriptase-PCR related to drug downregulation, IL-6, insulin-like growth factor-I (IGF-1), angiopoietin 1 (Ang1), and angiopoietin 2 (Ang2) transcription.<sup>38</sup>

Carfilzomib is a second-generation proteasome inhibitor, which has been approved by the FDA for clinical use in relapsed or refractory MM patients. In preclinical trials, carfilzomib demonstrated more potent antimyeloma activity than bortezomib.<sup>39</sup> It has got a similar antiangiogenic potential like bortezomib.

## Agents targeting VEGF

In the study by White et al. (AMBER trial), bevacizumab was administered in combination with bortezomib for the treatment of relapsed/refractory MM patients. There was no significant increase of progression free survival (PFS) when bevacizumab was given along with bortezomib vs

bortezomib in monotherapy.<sup>40</sup> Similar unsatisfactory observations have been reported about other VEGF receptor-targeted agents, such as semaxanib (SU5416), zactima (ZD6474), and pazopanib (GW786034).<sup>41–43</sup> Although anti-VEGF antibodies might suppress a pathway involved in malignant myeloma cell growth, there are other factors associated with the disease activity and progression that these agents might not add any clinical benefits to in the treatment.

## Novel antiangiogenic strategies

It has been suggested that modifications in multicellular eukaryotic messenger RNA (miRNA) expression may participate in the pathogenesis of most cancers in humans.<sup>44</sup> MicroRNAs are actually the class of non-coding RNAs (22-nucleotide) that operate in RNA silencing and post-transcriptional regulation of gene expression. They maintain biological events in various settings, such as cell growth, differentiation and apoptosis, but also metabolism of fat and viral infection. It has been observed that some miRNAs may be involved in controlling the production of angiogenic molecules, and therefore the angiogenesis process. Roccaro et al. have demonstrated that miR-15a and miR-16 are significantly diminished or lacking in relapsed/refractory MM patients. In vitro, as the regulators of MM pathogenesis, miR-15a and miR-16 attenuate the formation of capillaries and MM cell-associated endothelial cell growth. When pre-miR-15a and pre-miR-16 were transfected into malignant plasma cells, this contributed to significant inhibition of VEGF secretion. The authors have concluded that the field of regulation of VEGF by these miRNAs in MM patients' needs to be investigated.<sup>45</sup> Furthermore, Sun et al. conducted a study concerning the miR-15a and miR-16 expression levels and their association with the advanced stage of MM patients. The miRNAs were found to be downregulated in malignant plasma cells, and a correlation between downregulation and the MM stage was established. The results also confirmed the previous observations that miR-15a and miR-16 expression may inhibit the proangiogenic activity of malignant plasma cells.<sup>46</sup> Currently, there have been several reports that hypoxia is involved in miRNA expression in cancer. Another miRNA that is downregulated in MM is miR-199a-5p, and this has become an important issue of concern, as it directly targets HIF1- $\alpha$ , a transcription factor regulating angiogenesis, by induction of VEGF transcription.<sup>47</sup> A Raimondi et al.'s study has revealed that enforced expression of miR-199a-5p contributed to downregulation of HIF-1 $\alpha$  expression and, moreover, some other proangiogenic factors such as FGFb, VEGF-A and IL-8 in hypoxic malignant plasma cells in vitro.<sup>48</sup>

## Summary

Multiple myeloma is a unique hematological cancer wherein abnormal plasma cells, through interaction, subordinate the microenvironment for their own growth and expansion. MM might be a metastatic as well as a localized disease. Every single time it remodels the environment, destroying the bone structure and forcing angiogenesis, and thus provides a supply of substances essential to its survival. Awareness of these mechanisms may enable the development of a strategy for prolonged treatment based on specific inhibitors that could stabilize the treatment effect, and thus extend patients' survival. Research on the regulatory mechanisms of angiogenesis in MM according to their complexity and usefulness for treatment should be continued.

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