VEGF targeted therapy in acute myeloid leukemia

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Accepted 28 September 2010

Abstract

The cooperation of two classes of mutations in hematopoietic cells is hypothesized in a multistep pathogenesis model of acute myeloid leukemia (AML). Class I mutations confer a proliferative and/or survival advantage, whereas Class II mutations block hematopoietic differentiation and impair apoptosis in AML cells. In addition to these two classes of mutations, a relevant role for angiogenesis in the pathophysiology of AML has been recently proposed. The recognition that the vascular endothelial growth factor (VEGF) pathway is a key regulator of angiogenesis has led to the development of several VEGF-targeted approaches. These include neutralizing antibodies, VEGF traps or selective tyrosine kinase inhibitors for VEGFRs. Other drugs that indirectly affect VEGF

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doi:10.1016/j.critrevonc.2010.09.009

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pathway, such as statins or arsenic trioxide, also have been shown to possess antiangiogenic activity in leukemias. The benefits of these VEGF targeted agents and their current stage of development as novel anti-angiogenic therapies in AML are discussed in this review.

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Keywords: AML; VEGF; Tyrosine kinase inhibitors; Arsenic trioxide; Statins

1. Introduction

Acute myeloid leukemia (AML) is a clonal disorder which is the consequence of acquired somatic mutation that occurs in a hematopoietic progenitor. The molecular pathogeny of AML is to some extent dependent on the age of the population under consideration. In children and younger adults, balanced chromosomal translocations are relatively common, while in older patients AML is characterized by a more common picture of chromosomal losses and gains, often in the context of a complex karyotype. Evidence to date suggests that karyotype identifies biologically distinct subsets of disease and is highly predictive of response to therapy and overall survival [1].

The generation of chimeric fusion proteins, through chromosomal translocations, which lead to a block in differentiation and contribute to the biological characteristics of different subsets of leukemia, is generally believed to be a primary event in the pathogenesis of AML. Nevertheless, over the last few years it has become apparent that mutations in genes encoding components of the signal transduction pathways are frequent in AML; these include activating mutations of FLT3, RAS, KIT, and SHP2. Therefore a multistep pathogenesis model of AML has been hypothesized [2] where AML is the consequence of a cooperation between two broad classes of mutations: Class I mutations, that confer a proliferative and/or survival advantage to hematopoietic cells by constitutively activating tyrosine kinases or their downstream effectors, and Class II mutations that primarily impair hematopoietic differentiation and may provide a selective advantage for these cells as well by impairing subsequent apoptosis. Regardless of the timing or order of acquisition of mutations, individuals with both Class I and Class II mutations have a clinical phenotype of AML characterized by a proliferative and/or survival advantage to cells and by impaired hematopoietic differentiation.

Among the Class I mutations, activating mutations in hematopoietic receptor tyrosine kinases (RTKs) are frequent events in AML and are associated with poor prognosis [3–5]. Mutation of the FLT3 gene encoding Fms-like tyrosine kinase 3 is one of the most common genetic lesions identified in AML thus far, being detected in almost one third of cases. The majority are length mutations (internal tandem duplications, FLT3/ITDs) involving the juxtamembrane region of the receptor, which contains the inhibitory signal for the tyrosine kinase. Alternative and less frequent mutations (approximately 4–7% of AML cases) are localized in the activation loop of FLT3 (FLT3/ALMs), which normally blocks access of ATP and substrate to the kinase domain. These mutations are also referred to as FLT3 tyrosine kinase domain mutations (FLT3/TKD). Although both types of mutation lead to constitutive activation of the receptor, FLT3/ITDs and FLT3/TKD promote different downstream effectors and different biological responses [6,7]. These mutations cause FLT3/WT and FLT3/ITD–TKD to behave in different ways. In these sense, it has been shown that several receptor tyrosine kinase inhibitors have different activity against wild type and mutated FLT3. These inhibitors usually bind to FLT3/ITD with increased affinity, probably due to differences in conformation between FLT3/WT and FLT3/ITD receptors; accessibility to drug may be influenced by differences in cellular localization; or levels of ligand necessary to stimulate phosphorylation of FLT3/WT in vitro may be higher than physiologic levels.

FLT3 mediates proliferation and anti-apoptotic effects through several signalling pathways, including the Ras/MAPK, JAK/STAT and PI3K/Akt pathways [6,8,9]. Nevertheless, studies in our lab have demonstrated that the inhibition of mutated FLT3 receptor does not prevent the constitutive activation of ERK, Akt or STAT in some primary AML blasts that hold the FLT3 mutation, suggesting that additional cytogenetic alterations, such as the Ras or JAK mutations, which activate ERK and Akt, might be necessary to induce the abnormal signal transduction found in these cells [10].

In addition to these two classes of mutations, it has been proposed the relevant role of angiogenesis in the pathophysiology of AML. A balance between pro-angiogenic and antiangiogenic growth factors and cytokines tightly controls angiogenesis [11,13]. Although the role of angiogenesis in the growth of solid tumors has been studied extensively, investigation of the importance of this process in hematologic malignancies has been recognized only recently. Earliest studies revealed that bone marrow infiltrated by AML blasts exhibits an increased microvessel density compared to normal bone marrow [12,14], and microvessel density decreased in response to induction therapy [14].

One of the most specific and critical regulators of angiogenesis is vascular endothelial growth factor (VEGF), which regulates endothelial proliferation, permeability, and survival. In mammals, VEGF family consists of five glycoproteins referred to as VEGFA, VEGFB, VEGFC, VEGFD (also known as FIGF) and placenta growth factor (PIGF, also known as PGF) [15]. The best characterized of the VEGF family members is VEGFA (commonly referred to as VEGF), which is expressed as various isoforms derived from alternative splicing that leads to mature 121-, 165-, 189- and 206-amino-acid proteins. VEGF165 is the predom-
invariant isoform and is commonly overexpressed in a variety of human tumors [16]. Three structurally similar type III receptor tyrosine kinases, designated VEGFR1 (also known as Flt-1), VEGFR2 (also known as KDR) and VEGFR3 (also known as FLT4) are activated upon binding of VEGF ligands. Leukemia cells commonly express one or both of the major VEGF receptor tyrosine kinases, the c-fms-like tyrosine kinase (Flt-1) and the kinase domain receptor (KDR) and can produce and secrete VEGF [17].

As for other receptor tyrosine kinases, VEGF binding to the receptor leads to receptor homodimerization or heterodimerization and subsequent autophosphorylation on certain tyrosine residues, which in turn triggers intracellular signaling cascade mediated by several effectors, which are able to recognize and dock at phosphorylated tyrosine residues of the activated receptors. These interactions are mediated by Src homology 2 (SH2), phosphotyrosine-binding, and other domains of the signaling proteins [18].

There is now much evidence that VEGFR2 is the major mediator of VEGF-driven responses in endothelial cells and it is considered to be a crucial signal transducer in both physiologic and pathologic angiogenesis. VEGFR2 signaling pathways are relatively well understood. In human VEGFR2 the major autophosphorylation site following VEGF binding is Y1175, that serves as a docking site for phospholipase C-gamma, which indirectly mediates activation of the mitogen activated protein kinase pathway and thus regulates cell proliferation. In addition, Y1175 is a binding site for other adaptor molecule, such as Src homology 2 (SH2) domain-containing protein containing adaptor protein B (Shb) [19].

Interaction between Shb and phosphorylated Y1175 of VEGFR2 is required for VEGF-dependent activation of phosphatidylinositol 3-kinase/Akt antiapoptotic pathway [20]. A second major autophosphorylation site in human VEGFR2 is Y1214, which is involved in activation of Cdc42 and p38 mitogen-activated protein kinase [21].

Autocrine and paracrine growth stimulation with VEGF results in a mitogenic response within hematologic malignancies and specifically promotes self-renewal of leukemia progenitors [17,22,23]. The pivotal role for autocrine VEGF loops in hematologic malignancies is confirmed by the co-expression of both VEGF and VEGF receptors in leukemia, lymphoma and multiple myeloma coupled with its direct effects on tumor cell survival migration, and proliferation [24]. Moreover, it has been shown that there is autocrine activation in the expression of VEGF and other proangiogenic molecules such as tissue factor in AML blasts [25].

2. VEGF-targeted approaches for AML

Prognostic variables in myeloid malignancies are critical tools for estimating survival expectation and stratifying patients according to optimal treatment approaches. Although the prognostic significance of angiogenic markers remains largely conflicting, measurements of microvessel density, VEGF and VEGFR1 overexpression have demonstrated correlation with lower remission rate and reduced overall survival in AML patients [14,26].

Recognition of the VEGF pathway as a key regulator of angiogenesis in hematologic malignancies has led to the development of several VEGF-targeted approaches. These include neutralizing antibodies to VEGF or VEGF receptors, soluble VEGF receptors or tyrosine kinase inhibitors (TKIs) with selectivity for VEGFR receptors (Fig. 1). Other drugs that indirectly affect VEGF pathway, such as statins or arsenic trioxide, have also been shown to possess antiangiogenic activity in AML (Fig. 2). The benefits of these VEGF targeted agents and their current stage of development as novel anti-angiogenic therapies in AML will be detailed below.

2.1. Neutralizing antibodies

Bevacizumab (rhuMAb VEGF, Avastin, Genentech, Inc) is a recombinant humanized monoclonal antibody (MAb) that targets VEGF-A isof orm and blocks its binding to the VEGF receptors [27]. Bevacizumab has been approved as a treatment for several solid tumors, including metastatic colorectal cancer, nonsquamous cell lung cancer, metastatic breast cancer, metastatic renal cell cancer, prostate cancer, and glioblastoma [28]. A recent study performed in nine patients with relapsed or refractory AML not fit to intensive chemotherapy showed that bevacizumab treatment was well tolerated with a favourable safety profile. Monotherapy with bevacizumab significantly caused decrease of VEGF expression without significant change in VEGFR2 expression and phosphorylation in bone marrow of these AML patients. However, none of the patients had a clinical response [29]. Nevertheless, the combination of bevacizumab and chemotherapeutic agents, such as 1-b-D-arabinofuranosylcytosine (ara-C) and mitoxantrone in a phase II clinical trial in AML patients resulted in enhanced antitumor activity compared to either agent alone. The overall response rate was 48%, including complete responses (33%) and partial responses (14.5%). Serum VEGF levels decreased within 2 h after bevacizumab treatment, and reduced the bone marrow microvessel density over the course of 7 days. These results support the use of bevacizumab in combined therapy in AML patients that are resistant to traditional treatment approaches [30].

Aflibercept (VEGF Trap) is a recombinant protein consisting of domain 2 from VEGFR1 fused to domain 3 from VEGFR2, attached to the hinge region of the Fc(a) domain of human immunoglobulin (Ig) G1. VEGF Trap is a circulating antagonist that prevents VEGF receptor binding which binds VEGF-A more tightly than monoclonal antibodies. VEGF Trap has a relatively long half-life, of approximately two weeks. Phase I clinical trials have evaluated the safety, pharmacokinetics, and pharmacodynamics of VEGF Trap in advanced solid tumors. VEGF blockade and partial responses were observed [31]. Currently, a multi-center phase II study of VEGF Trap as a single agent in AML is undertaken.
Monoclonal antibodies with high affinity for human VEGFR2 have also been generated, such as IMC-1121 which blocked VEGF/KDR interaction with an IC₅₀ of approximately 1 nM. This anti-KDR antibody strongly inhibited VEGF-induced migration of human leukemia cells in vitro, and when administered in vivo, significantly prolonged survival of mice inoculated with human leukemia cells [32]. The effect of IMC-1121 is now being evaluated in a phase II study...
Table 1

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>Phase of development in solid tumors</th>
<th>Phase of development in AML</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>VEGF ligand</td>
<td>Approved for colorectal, nonsquamous cell lung, breast, renal cell, prostate cancers, and glioblastoma, phase II/phase III for other cancers</td>
<td>Phase II</td>
<td>Mukherji et al. [28]; Karp et al. [30]</td>
</tr>
<tr>
<td>Aflibercept (VEGF Trap)</td>
<td>VEGF ligand</td>
<td>Phase I for advanced solid tumors</td>
<td>Phase II</td>
<td>Lockhart et al. [31]</td>
</tr>
<tr>
<td>IMC-1121</td>
<td>VEGF receptor, extracellular domain</td>
<td>Phase II for advanced solid tumors</td>
<td>In vitro studies</td>
<td>Zhu et al. [32]</td>
</tr>
<tr>
<td>Sunitinib (SU11248)</td>
<td>VEGFR1, 2, 3, PDGFR, KIT, FLT3, CSF-1R, RET</td>
<td>Approved for kidney cancer and GIST, phase II or III for other cancers</td>
<td>Phase I</td>
<td>Vroling et al. [34]; Heinrich et al. [35]; Fiedler et al. [37]</td>
</tr>
<tr>
<td>Semaxinib (SU5416)</td>
<td>VEGFR1, 2, KIT, FLT3</td>
<td>Phase I or II</td>
<td>Phase II</td>
<td>Fiedler et al. [45]; O’Farrell et al. [46]; Salzberg et al. [47]</td>
</tr>
<tr>
<td>SU5614</td>
<td>VEGFR1, 2, KIT, FLT3</td>
<td>In vitro studies</td>
<td>Phase II</td>
<td>Aleskog et al. [51]; Arseni et al. [52]; von Bubnoff et al. [53]</td>
</tr>
<tr>
<td>Sorafenib (BAY43-9006)</td>
<td>VEGFR-2, -3, PDGFR, Raf, KIT</td>
<td>Approved for kidney and liver cancer, phase II or III for other cancers</td>
<td>Phase I</td>
<td>Llovet et al. [57]; Delmonte et al. [58]; Zhang et al. [59]; Safaian et al. [60]; Metzelde et al. [61]</td>
</tr>
<tr>
<td>Lestaurtinib (CEP701)</td>
<td>VEGFR2, FLT3, KIT, FMS, PDGFR-β</td>
<td>Phase I</td>
<td>Phase III</td>
<td>Chan et al. [64]; Knapper et al. [65, 66]</td>
</tr>
<tr>
<td>Midostaurin (PKC412)</td>
<td>PKC, VEGFR2, PDGFR, FLT3</td>
<td>Phase II</td>
<td>Phase III</td>
<td>Millward et al. [69]; Stone et al. [70]</td>
</tr>
<tr>
<td>Axitinib (AG-013736)</td>
<td>VEGFR1, 2, 3, PDGFR, KIT, FLT3</td>
<td>Phases II and III</td>
<td>Phase II</td>
<td>Kelly and Rixe [77]; Giles et al. [78]; Giles et al. [79]</td>
</tr>
<tr>
<td>Cediranib (AZD2171)</td>
<td>VEGFR1, 2, 3, PDGFR-β, KIT</td>
<td>Phase II/phase III</td>
<td>Phase I</td>
<td>Lindsay et al. [84]; Fiedler et al. [85]</td>
</tr>
<tr>
<td>Vatalanib (PTK787/ZK 222584)</td>
<td>VEGFR1, 2, 3, PDGFR, KIT, FMS</td>
<td>Phase II or III</td>
<td>Phase I</td>
<td>Roboz et al. [95]; Joensuu et al. [91]; George et al. [94]; Sharma et al. [92]</td>
</tr>
<tr>
<td>Vandetanib</td>
<td>VEGFR2, EGFR, RET, KIT, FLT3</td>
<td>Phase II or III</td>
<td>In vitro studies</td>
<td>Morabito et al. [100]; Nishioka et al. [40]; Jia et al. [101]; Xiong et al. [105]; Baselga et al. [106]; Martinelli et al. [107]; Reardon et al. [108]</td>
</tr>
<tr>
<td>AEE788</td>
<td>VEGFR1, 2, EGFR</td>
<td>Phase I</td>
<td>In vitro studies</td>
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in advanced solid tumors, but has not yet been tested for the treatment of AML.

2.2. Receptor tyrosine kinase inhibitors

In the last few years many VEGF receptor tyrosine kinase inhibitors have been developed and tested in solid tumors. Currently, most of them are being evaluated in open clinical trials for AML treatments (Table 1).

2.2.1. Sunitinib (SU11248 or SU01248)

Sunitinib is an orally active inhibitor of at least eight RTKs including all VEGFRs (VEGFR1, VEGFR2 and VEGFR3), platelet-derived growth factor receptors (PDGFRα and PDGFRβ), cKIT, FLT3/WT, and colony-stimulating factor-1 receptor (CSF-1R), and is effective at low concentrations (nM) [33]. Sunitinib inhibits angiogenesis by blocking signaling through VEGFR1, VEGFR2, and PDGFRβ. Renal cell cancers that have metastasized or spread from the primary tumor, exhibit extensive vascularity, and sunitinib shows efficacy in the treatment of these tumors. Currently, sunitinib has been approved for the treatment of advanced kidney cancer [34] and tumors that are resistant to imatinib, such as gastrointestinal tumors [35].

In vitro AML studies demonstrated that sunitinib significantly decreased VEGF production and potently inhibited the FLT3/ITD phosphorylation [36]. These authors reported that signaling downstream of both FLT3/WT and FLT3/ITD resulted in VEGF production. They claimed the novel finding that FLT3 signaling leads to secretion of VEGF in vitro, most notably in FLT3/ITD cell lines, since FLT3 ligand was additioned to RS4:11 and OC1-AML5 cell lines (which expressed low levels of VEGF) and they observed that VEGF production was increased by 3- to 4-fold in each cell line. In their experiments, sunitinib inhibited the VEGF expression levels induced by the addition of FLT3 ligand. In addition, sunitinib inhibited VEGF production in MV4:11 cell line (FLT3/ITD) in a dose-dependent manner with an IC50 of approximately 10 nM. Thus, the authors suggested that sunitinib inhibits VEGF production due to inhibition of FLT3 signaling.

Sunitinib was investigated against AML in a phase I clinical trials. Overall, a single dose of sunitinib was well tolerated.
at doses from 50 mg to 300 mg. At molecular levels, downstream effects of sunitinib in AML patients, such as inhibition of STAT5 and ERK kinases, probably are due to the inhibition of receptors such as VEGFR. Moreover, 100% of FLT3/ITD patients had partial responses compared with 20% of FLT3/WT patients. However, the responses in both types of patients were of short duration [37,38]. The effect of combined treatment with sunitinib plus traditional antileukemic agents (cytarabine or daunorubicin) on the proliferation and survival of AML cells were analyzed. Sunitinib was shown to have additive inhibitory effects in AML FLT3/ITD cell survival when combined with cytarabine or daunorubicin. In contrast, the effects of these combinations were not different than those seen when each agent was administered separately in AML FLT3/WT [39]. Furthermore, it has been shown recently that the blockade of MEK/ERK signaling potentiated the ability of sunitinib to inhibit the growth and to induce apoptosis in AML cell lines [40]. So far, the overall data seem suggest that sunitinib therapy could improve treatment results exclusively in AML patients harbouring FLT3/ITD mutation.

2.2.2. Semaxinib (SU5416)

SU5416 is a potent inhibitor (IC50 0.1 μM) of VEGFR1, VEGFR2 and cKIT phosphorylation [41]. Thereafter, it was shown that also inhibited cellular phosphorylation of both wild-type FLT3 and FLT3/ITD mutants (IC50 0.1–0.25 μM) [42]. Semaxinib inhibits VEGF-dependent endothelial cell proliferation in vitro and in animal models, due to the inhibition of the phosphorylation of its VEGFR2 receptor. Moreover, it produces a dose-dependent inhibition of tumor growth in a variety of xenograft models, including malignant melanoma, glioma, fibrosarcoma, and carcinomas of the lung, breast, prostate and skin [43].

In vitro studies in blasts from AML patients have shown a parallel downregulation of the expression of VEGF and key signal transduction intermediates, such as STAT5 and Akt, after treatment with semaxinib [44]. These authors showed that semaxinib decreased VEGF levels in AML blast from 72% of patients analyzed. Moreover, patients with higher levels of VEGF suffered a stronger inhibition and higher clinical response rate than patients that expressed low levels of VEGF.

A multicenter phase II study with semaxinib was carried out in 43 patients with refractory AML using a dose of 145 mg/m². The results showed that patients with AML blasts expressing high levels of VEGF mRNA had a significantly higher response rate and reduction of bone marrow microvesSEL density than patients with low VEGF expression [45]. Semaxinib monotherapy was investigated in various multicenter phase II studies in refractory AML patients; however semaxinib had modest clinical activity [46]. Overall median survival was 12 weeks with grade 3 or 4 leukemia-specific adverse effects, probably due to the drug formulation [48], which is currently a major issue in the development of this drug.

2.2.3. SU5614

Compared to SU5416, the molecular structure of SU5614 was modified by a chloride substitution at the C-5 position of indolin-2-one. This compound was designed as a selective inhibitor of VEGFR1 and VEGFR2 activity at submicromolar levels [49]. In vitro studies showed that SU5416 was a potent inhibitor of the VEGF-induced endothelial cell sprouting. In AML cells this inhibitor induced growth arrest and apoptosis; however there was no correlation between VEGFR expression and sensitivity to the growth inhibitory activity of SU5614. The inhibitory effect was dependent on the expression of the receptor kinase c-KIT [50]. However, this compound efficiently inhibited the VEGF-induced capillary sprouting of endothelial cells in a dose-dependent manner. These authors suggested that SU5614 had a dual mode of action in the treatment of AML, inhibiting c-KIT in AML cells and VEGFR2 in endothelial cells. In this way, SU5614 blocks two signalling pathways which are critical for the molecular phenotype of AML.

Combinations of SU5614 with cytotoxic agents (etoposide and amsacrine) showed better effect compared with the monotherapy [51]. Moreover, other study performed in peripheral blood and bone marrow cells demonstrated the efficacy of SU5416 at eliminating leukemic stem cells in AML patients. However, the data also pointed to a considerable toxicity to normal hematopoietic stem cells, which should be taken into account in the management of patients with compromised normal hematopoiesis [52].

2.2.4. Sorafenib (BAY43-9006)

BAY43-9006 or sorafenib, a novel bi-aryl urea, was initially developed as a specific inhibitor of C-Raf and B-Raf. Subsequent studies revealed that this compound also inhibits several other important tyrosine kinases involved in tumor progression, including VEGFR2, VEGFR3, PDGF-β, and c-KIT [54]. The IC50 values for VEGFR2, VEGFR3, FLT3, c-KIT and PDGFRβ were 90, 20, 32.6, 68 and 57 nmol/L, respectively.

The mechanism of action of sorafenib is being widely studied. It initially inhibited tumor cell proliferation by targeting the MAPK pathway at the level of Raf kinase in various tumor cell lines, including those harboring mutant Ras or B-Raf [55]. Recent works reported that sorafenib also induced marked mitochondrial damage manifested by cytochrome c and apoptosis-inducing factor release into the cytosol, caspase activation, and apoptosis in several tumor cells, including human leukemia cells [56]. It has been shown that sorafenib inhibits tumor-cell proliferation and tumor angiogenesis and increases the rate of apoptosis in a wide range of tumor models [55]. The inhibition of tumor growth and stabilization of tumor was correlated with a decrease of tumor angiogenesis, which was due to inhibition of VEGF-mediated endothelial cell. Currently, it is undergoing phase II/III clinical evaluation in advanced solid tumors, including hepatocellular carcinoma [57].
In addition to the inhibition of VEGFR2 and VEGFR3, sorafenib also interacts with FLT3/ITD at an IC\textsubscript{50} of 2 nM, whereas the IC\textsubscript{50} for FLT3/WT cells was 3000 nM. A phase I trial to evaluate the safety and the efficacy of two different schedules of sorafenib in 20 AML patients was reported. The authors concluded that this inhibitor was safe in AML [58]. Thereafter, sorafenib was tested in other clinical study on 16 patients with AML, and was found to be particularly active in six of the seven FLT3/ITD positive patients. However, treatment duration was short (21–70 days) and no durable responses were reported [59]. Notably, a complete molecular remission has recently been reported in a patient relapsing after stem cell transplantation (SCT) [60]. In addition, other authors have shown that sorafenib-monotherapy prior or post allo-SCT had remarkable clinical activity in FLT3/ITD-positive AML [61]. All these recent studies suggest that sorafenib deserves further evaluation in prospective clinical trials.

2.2.5. Lestaurtinib (CEP-701)

Lestaurtinib is an orally bioavailable indolocabazole alkaloid compound that is synthetically derived from the bacterial fermentation product K-252a. It is a potent FLT3 inhibitor with an IC\textsubscript{50} of 3 nM [62]. This inhibitor also displays low nanomolar inhibition of VEGFR2 (IC\textsubscript{50} = 65 nM). However, it is not a potent inhibitor of other tyrosine kinase receptors: IC\textsubscript{50} greater than 500 nM against c-KIT, FMS and PDGFR-\textbeta. Although lestaurtinib inhibits VEGFR2, its cytotoxic effect was due to the inhibition of FLT3 phosphorylation, since lestaurtinib produced a phosphorylation-dependent reduction in cell growth and survival of AML cells that express FLT3 [62].

Lestaurtinib was initially tested in phase II study in patients with refractory or relapsed or poor-risk AML [63,65]. The results were positive; the cytotoxic response required at least an 80% inhibition of FLT3 autophosphorylation. The dose of lestaurtinib necessary to reach this threshold varied between patients [65] and was likely to be higher in AML patients with FLT3/WT [66].

In vitro, lestaurtinib showed a synergic effect with standard chemotherapy, simultaneously or immediately given after chemotherapy [67]. AML patients in first relapse showing activating mutations of FLT3 were randomized to receive open-label chemotherapy alone or chemotherapy followed by lestaurtinib. Half of these patients achieved complete remission [80]. Lestaurtinib is one of the most efficient tyrosine kinase inhibitors in AML and have now reached phase III clinical trials.

2.2.6. Midostaurin (PKC412)

Midostaurin was identified as an inhibitor of PKC and other molecular targets, including VEGFR2 (86 nM), VEGFR1 (900 nM), PDGFR\textalpha, PDGFR\textbeta (IC\textsubscript{50} = 80 nM), c-KIT (IC\textsubscript{50} = 500 nM), FLT3 (IC\textsubscript{50} < 10 nM). Midostaurin was an inhibitor of angiogenesis, though the inhibition of VEGFR2 phosphorylation. The effects of midostaurin in specifically blocking the VEGF-induced angiogenic process was comparable to that observed with a monoclonal antibody that inhibit the activity of VEGF or sequestered VEGF with excess amounts of soluble extracellular domain of VEGFR1 in vivo. Thus, through the inhibition of VEGF, this compound caused inhibition of endothelial cell proliferation, migration capillary formation and tumor vascularisation. Moreover, midostaurin showed broad antiproliferative activity against various tumor cell lines, including those that were resistant to several other chemotherapeutic agents [68].

A phase II clinical trial was undertaken in advanced AML patients. Three-daily oral doses of 75 mg reduced peripheral and bone marrow blasts counts in the majority of the patients. However, these benefits were short-lived, lasting only 2–3 months [70].

Some in vitro studies were carried out to compare the efficacy of midostaurin and lestaurtinib in AML cells. The results showed that the cytotoxic effects of midostaurin was more limited, probably due to the inhibition by lestaurtinib of other cellular targets upstream of STAT5 [65,71]. Nevertheless, phases I and II clinical trials of lestaurtinib and PKC412 monotherapy in similar patient AML groups have demonstrated very similar rates and degrees of clinical response [63,70].

As the observed reductions in blast number produced by midostaurin were of relatively short duration, it was thought that the combination of midostaurin with other agents, such as a HDAC inhibitor, a HSP90 inhibitor, rapamycin with chemotherapy could achieve a better response. All these studies showed a positive effect of the combined therapy with midostaurin [65,72–74]. New diagnosed AML patients were treated with midostaurin concurrently with induction therapy (daunorubicin and cytarabine). Complete remission was achieved in 71% patients [75]. Midostaurin is now being investigated in a phase III trial in AML combined with chemotherapy.

2.2.7. Axitinib (AG-013736)

Axitinib is an orally available potent small molecule inhibitor of VEGFR1 and VEGFR2 phosphorylation, with an IC\textsubscript{50} of 1.2 and 0.25 nM, respectively. VEGFR3, cKIT, PDGFR-\textbeta and PDGFR-\textalpha were also inhibited by axitinib to a significant degree (IC\textsubscript{50} values of 0.29, 1.7, 1.6 and 5 nM, respectively). However, it has little activity against other type III receptors such as FLT3 (IC\textsubscript{50} > 1000 nM) [76]. In in vitro and in clinical studies, axitinib inhibited VEGF-mediated endothelial cell survival, tube formation, and downstream signaling through endothelial nitric oxide synthase, Akt and ERK pathways. It also produced consistent and dose-dependent antitumor efficacy that was associated with blocking VEGFR2 phosphorylation, vascular permeability, angiogenesis, and concomitant induction of tumor cell apoptosis in solid tumors [76]. Axitinib is currently in phases I–III development in a range of solid tumors. In phase II studies, axitinib showed activity in a wide range of tumor types, including advanced renal cell carcinoma, thy-
roid cancer, malignant melanoma, pancreatic, breast, lung and colorectal carcinomas. Ongoing phase III studies in pancreatic and metastatic renal cell carcinoma will ultimately define the therapeutic role of this targeted agent [77].

A first phase II study evaluated the effects of axitinib in eight elderly patients with poor prognosis AML. This inhibitor was generally well tolerated and two patients had stable disease of significant duration [78]. Thereafter, the same authors conducted a phase II clinical trial in six poor prognosis elderly AML patients to determine the overall response rate of axitinib. Moreover, pharmacokinetic analyses and the effects of this inhibitor on bone marrow cells and expression of angiogenic factors were evaluated. The results showed that monotherapy with axitinib had minimal clinical activity, probably due to lower VEGFR1 and VEGFR2 expression or the presence of other activating mutations in this elderly population [79]. As the results were not satisfactory, these data would not support the use of axitinib as induction therapy in patients with AML.

2.2.8. Cediranib (AZD2171)

Cediranib, also known as AZD2171, is a highly, potent (subnanomolar IC\textsubscript{50}) and selective inhibitor of VEGF signaling, with activity versus all VEGFRs, and also has additional activity versus c-KIT and PDGFR\(\beta\). Excellent selectivity for KDR was evident, with IC\textsubscript{50} < 1 nmol/L, whereas the IC\textsubscript{50} values for VEGFR1/Flt-1, VEGFR3/Flt-4, c-KIT and PDGFR\(\beta\) were 5 nmol/L, ≤3 nmol/L, 2 nmol/L and 5 nmol/L, respectively [80]. Cediranib was found more potent against VEGF-induced HUVEC proliferation than other VEGFR TKIs that are currently under clinical trials, including vatalanib and sunitinib [81]. Cediranib promoted the reduction of tumor growth in a mouse model of spontaneous intestinal cancer [81] and blocked both ligand- and tumor cell-driven angiogenesis and lymphangiogenesis in vivo [82].

A first clinical study was carried out to determine the safety and tolerability, pharmacokinetic profile of cediranib and evaluation of its efficacy in patients with metastatic or advanced solid tumors refractory to standard treatments [83]. Once-daily oral at doses of 45 mg or less was generally well tolerated and its effects on tumor growth appeared to be dose-related. Thereafter, clinical studies have demonstrated that cediranib exhibit potential efficacy either as a monotherapy or in combination with chemotherapy, radiotherapy or other biological agents in many solid tumors, including lung, prostate, breast, renal, ovarian and colorectal cancers (reviewed in [84]. Cediranib is currently in phase II/phase III clinical development.

Despite its efficacy in solid tumors, cediranib had little evidence for in vitro cytotoxicity in 22 pediatric leukemia cell lines. More success was demonstrated in vivo when used against a panel of pediatric tumor xenograft models, suggesting a direct effect on tumor vasculature rather than tumor cells. Thus, this study do not support a therapeutically relevant effect for cediranib in the pediatric acute lymphocytic leukemia setting, most likely due to toxic effects of antiangiogenic strategies on the growth plate of growing children, a normal physiological role for the VEGF system [81]. On the contrary, this inhibitor clearly showed a cytotoxic effect in an AML cell line, Kasumi-1 [86]. In this way, a phase I clinical study has been recently carried out in thirty-five adult patients with AML refractory to induction chemotherapy or in relapse following first or subsequent induction treatments, or elderly patients with de novo or secondary AML. Dose- and time-dependent reductions in VEGFR2 were observed after treatment with cediranib. Also, they found that there was a positive correlation between cediranib exposure and the change in plasma VEGF levels. After cediranib treatment, 19% of AML patients experienced an objective response and bone marrow blasts were reduced in the majority of patients. Taken together, cediranib monotherapy demonstrated a modest clinical activity in AML patients [87].

2.2.9. Vatalanib (PTK787/ZK 222584)

Vatalanib is an oral angiogenesis inhibitor targeting VEGFRs tyrosine kinases, including VEGFR1, VEGFR2, VEGFR3, PDGFR and c-KIT. It is slightly more potent against VEGFR2 (IC\textsubscript{50} = 0.037 \(\mu\)M) than against VEGFR1 (IC\textsubscript{50} = 0.077 \(\mu\)M). It also inhibits VEGFR3 and PDGFR at higher concentrations (IC\textsubscript{50} = 0.66 \(\mu\)M; IC\textsubscript{50} = 0.58 \(\mu\)M, respectively). It has some additional activity against c-KIT and c-FMS (IC\textsubscript{50} = 0.73 \(\mu\)M; IC\textsubscript{50} = 1.4 \(\mu\)M) [88]. In preclinical models, vatalanib caused a significant decrease in vessel permeability, reduction in tumor vessel density and repression of tumor growth with high efficacy, though the inhibition of VEGFRs [88–90]. Phases I and II clinical studies have evaluated the biological activity of vatalanib in several advanced solid tumors known to overexpress VEGF and its receptors, such as metastatic gastrointestinal tumors, renal cell carcinoma and prostate cancer [91–94].

In a recent phase I study of vatalanib for the treatment of primary refractory or relapsed AML, 5 out of 17 patients treated with induction chemotherapy and vatalanib achieved complete remission [95]. Furthermore, an in vitro study showed that the combined treatment with amsacrine and vatalanib might lower the dosage of chemotherapy necessary to achieve equal levels of AML cells death [96]. In addition, our group showed that combined treatment with vatalanib plus a chemotherapeutic (idarubicin) in four AML cell lines and freshly isolated AML blasts had a potent inhibitory effect on the cell proliferation, apoptosis and angiogenesis [97].

2.2.10. Vandetanib (ZD6474)

Vandetanib is a selective inhibitor of VEGFR, epidermal growth factor receptor (EGFR) and the RET [98]. This compound has a potent activity versus the phosphorylation of VEGFR2/KDR (IC\textsubscript{50} = 40 nM) and some additional activity versus VEGFR3 (IC\textsubscript{50} = 110 nM), EGFR (IC\textsubscript{50} = 500 nM) and VEGFR1 (IC\textsubscript{50} = 1600 nM) [99]. The potent activity of vandetanib against VEGFR2 turned into an inhibition of VEGF signalling in endothelial cells. In vitro studies...
demonstrated the ability of vandetanib to inhibit tumor-induced neovascularization and growth of human tumor xenograft models, despite their histological origins (breast, lung, prostate, colon, ovary, and vulva) [99]. Moreover, in vivo analysis showed that vandetanib reversed the effects induced by VEGF in rats, but does not significantly alter the effects promoted by bFGF. These data supported the selective action of vandetanib in VEGF signal.

Phase I trials have shown that vandetanib is well tolerated as a single agent at daily doses <300 mg. Thereafter, vandetanib was evaluated in phase II clinical trials in several tumors types, including non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), breast cancer and multiple myeloma. Phase III clinical studies are currently being conducted in NSCLC (reviewed in [100]).

Two recent in vitro studies have shown the effects of vandetanib in several myeloid leukemia cell lines [40,101]. This compound induced growth arrest and apoptosis of EOL-1, MV4-11 and kasumi-1 cells (which harbour activating mutations in PDGFRα, FLT3 and c-KIT), by inhibiting the phosphorylation of these receptors and blocking their downstream effectors (ERK, Akt and STAT3). In addition, vandetanib treatment was active against freshly isolated AML blasts that had FLT3 mutations, supporting the use of vandetanib in AML that possess mutations in receptor tyrosine kinase genes [40].

2.2.11. AEE788

AEE788 is a novel synthesized, oral small-molecule TKI of both EGFR and VEGFR [102]. At the enzyme level, AEE788 inhibit EGFR and VEGFRs in the nM range (IC50s: EGFR 2 nM, VEGFR2 77 nM, and VEGFR1 59 nM).

In vivo and in vitro studies showed that AEE788 strongly inhibited phosphorylation of MAPK and Akt through the inhibition of VEGFR2. The dual inhibition of EGFR and VEGFR phosphorylation by AEE788 reduced the growth, and induced apoptosis of hepatocellular carcinoma cells. Moreover, in a subcutaneous xenograft model, AEE788 decreased tumor growth by reducing proliferation and vascularisation [103]. In others in vitro studies, AEE788 profoundly blocked the interaction of renal cell carcinoma (RCC) cells with endothelium and extracellular matrix and reduced tumor growth [104]. This drug is being evaluated in phase I studies in patients with advanced solid tumors [105–107] and with recurrent glioblastoma [108].

Recently, we have analyzed the effects of AEE788 in the cell survival of three AML cell lines: THP-1, MOLM-13 and MV4-11, as well as AML blasts. Moreover, we analyzed the activation VEGF/VEGFRs loop, FLT3 and their downstream effectors. AEE788 abrogated VEGFRs activation and many survival signaling pathways, including Akt, ERK, STAT5 and NF-κB. This compound also acted as a FLT3 and had an antiproliferative and proapoptotic activity in AML-derived cell lines that endogenously expressed an activated FLT3 receptor. Taken together, our results suggested that AEE788 might represent a new promising therapy for the treatment of AML patients [109].

2.3. Statins

Statins are 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors, blocking the mevalonate pathway and its downstream products such as cholesterol. Lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, cerivastatin, pitavastatin and rosuvastatin are currently commercially available (Fig. 3). These drugs decrease hepatic cholesterol production, which leads to increased LDL receptor turnover,
enhanced hepatic LDL-cholesterol uptake, and ultimately decreased plasma LDL-cholesterol levels. The lowering of serum cholesterol levels is therefore thought to be the primary mechanism underlying the therapeutic benefits of statin therapy in cardiovascular disease.

Moreover, by inhibiting HMG-CoA reductase, statins can also inhibit the synthesis of isoprenoids, which are important lipid attachments for intracellular signaling molecules, such as Rho GTPase family (Rho, Rac and Cdc42). Each member of the Rho GTPase family serves specific functions in terms of cell shape, motility, secretion and proliferation. The pleiotropic effects of statins might due to the wide range of Rho GTPase proteins functions. Thus, Rho is associated with stress fiber formation, cytoskeletal regulation, cell cycle regulation, signal transduction, proliferation and migration, and eNOS and NO regulation; Rac1 is involved in cytoskeletal regulation, superoxide production, oncogenesis, Map3K activation and Pak activation and finally Cdc42 is related to cytoskeletal regulation and signal transduction (reviewed in [110]). Statins might affect vascular function through the modulation of these signaling proteins that depend on post-translational modification with isoprenoid. Indeed, several studies suggest that statins might be involved in immunomodulation [111], neuroprotection [112] and cellular senescence [113].

Recently, there is emerging interest in their use as anti-neoplastic agents, due to their antiproliferative, anti-invasive and proapoptotic effects (reviewed in [114]). Moreover, it is possible that statins may modulate angiogenesis in a therapeutic manner, enhancing endothelial functions. It has been shown that statins possess dose-dependent effects on angiogenesis. Statins reduced tumor growth and inhibited VEGFR2 expression at high (micromolar) concentrations, while enhanced angiogenesis at low (nanomolar) concentrations [115]. Several studies have reported that statins decrease VEGF synthesis in different cell types, including tumor cells [115–117].

In vitro, statins induce apoptosis in both primary and tumor cells derived from patients with a variety of malignancies [116]. Recently, several studies have suggested the possible use of statins in therapy for AML [118,119]. The first studies that supported the therapeutic potential of statins in the treatment of AML were performed with lovastatin and simvastatin. In vitro studies in AML cell lines showed that lovastatin induced a differentiation response and cytotoxicity at physiological concentrations of this agent [120,121] and in a short term [122]. Moreover, the combination of lovastatin with other agents such as tyrosine kinase inhibitors might potentiate their cytotoxic effects [118]. Regarding in vivo studies, high dose of lovastatin suppressed blast cell growth in an elderly patient with AML [119].

On the other hand, it has been shown that simvastatin has great antiproliferative effect on AML blasts in vitro and that the combined treatment with simvastatin plus ARA-C significantly enhanced the antiproliferative effect of each drug [123]. The combination of simvastatin with farnesyltransferase inhibitors was also beneficial in the treatment of AML, although this treatment caused differential responses depending on the AML CD34 (+) and CD34 (−) subfractions [124].

Pravastatin was tested in a phase I study in which it was combined with idarubicin and high-dose cytarabine. Rhabdomyolysis is a prominent and severe effect of these drugs. Thus, the application of very high doses of statins has to be taken into consideration. This work showed tolerable toxicity at very high doses of pravastatin. High response rates for both newly diagnosed patients with poor prognosis and for salvage patients were demonstrated. Moreover, the addition of pravastatin to conventional chemotherapy blocked the cholesterol increase, which is usually produced in AML blasts after chemotherapy. The authors encourage future phase II studies [125].

In an effort to find effective therapies for the treatment of acute promyelocytic leukemia (APL), statins have been tested to overcome the development of ATRA resistance by APL cells. Recently, it was evaluated the antileukemic spectrum of various statins for chemotherapeutic use in ATRA resistant APL. In this study it was found that fluvastatin enhanced the differentiation induced by ATRA and consequently enhanced the cytotoxic effect of ATRA in APL cells [126]. Thereafter another study revealed that simvastatin had an unique mechanism that causes apoptosis via mitochondrial dysfunction, followed by the caspase-9-related cascade, and thus it might be useful solely for the anti-leukemic therapy in APL [127]. Most of these works described above have been performed in AML cell lines or blasts, thus supporting the need for further evaluation of statins in clinical trials for the treatment of AML.

2.4. Arsenic trioxide

Arsenic has been used for centuries to treat a wide variety of diseases. Arsenic trioxide (ATO) has been shown to have multiple biological effects, including depletion of cellular thiols, disruption of mitochondrial respiration, induction of apoptosis and antiproliferative activity [128]. Concretely, ATO induces apoptosis via changes in the mitochondrial membrane potential. This compound produces an increase of intracellular levels of hydrogen peroxide, lowering mitochondrial membrane potential and leading to cytochrome c release and subsequent caspase pathway activation. Moreover, ATO induces the expression of bax which down regulates the expression of bcl-2 family members and inhibits the NF-κB activation. This compound also promotes the recruitment of PML onto matrix-bound nuclear bodies for degradation, which contribute to the induction of apoptosis. In the other hand, its antiproliferative capacity is due to the growth arrest in the G1 phase of the cell cycle, inhibition of STAT3 activity and the induction of the cell differentiation through the induction of CD11b maturation marker (reviewed in [128]).
ATO may additionally affect tumor cell growth by inhibiting angiogenesis. In a mouse model with a solid tumor, ATO induced preferential vascular shutdown in tumor tissue, so that the central part of the tumor showed massive necrosis, whereas normal vasculature remained relatively unaffected [129]. Thereafter, treatment of leukemic cells with ATO has been shown to produce a down-regulation of VEGF expression, culminating in apoptosis. Moreover, the reciprocal stimulatory loop between leukemic cells and endothelial cells was blocked [130]. The antileukemic activity of ATO has been widely studied in the APL subtype of AML. It has been shown that ATO is useful for the treatment of resistant or relapsed cases of APL after treatment with ATRA [131]. The main mechanisms of action involved in the responsiveness of leukemic promyelocytes to ATO include activation of the apoptotic caspase cascade, induction of differentiation and reduction of microvascular density of bone marrow. Currently, ATO is being used as a single agent as initial therapy in APL. Single-agent ATO in untreated APL, showed a very high clinical and a reasonably good molecular remission rate [132]. In addition, several studies have shown the benefit of ATO in both the induction and the consolidation therapy in this AML subtype [133,134].

There is evidence that the effects of ATO are not restricted to events specific for APL. In vitro studies have demonstrated that ATO have antiproliferative and apoptotic effects on a variety of AML cell lines at doses that are achievable in vivo [135]. No responses were observed in a phase II trial with ATO monotherapy in patients with relapse/refractory AML, secondary leukemia, and AML in older adults [136]. However, several studies have suggested that the combination therapy with ATO and molecules capable of inhibiting tyrosine kinase proteins may lead to improved ATO efficacy against AML. In vitro studies in blasts from 25 patients with different subtypes of AML showed that combination of ATO with an inhibitor of MEK/ERK pathway greatly enhanced the apoptosis of these cells [137]. Other work demonstrated a synergistic growth-inhibitory effect for the combination of ATO and a chemical inhibitor of FLT3 phosphorylation in AML FLT3/ITD cell lines [138]. Clinical data have shown that the combination of ATO with low-dose cytarabine or ascorbic acid improved responses in AML elderly patients compared with either agent alone [139,140]. Overall studies suggest that ATO deserves further clinical study in the treatment of AML.

3. Conclusions

As multiple signal transduction pathways are activated in AML, just a molecular targeted therapy is unlikely to be curative if used alone. Although lately VEGF have brought up much attention in the pathology of AML, there is evidence that its only inhibition is not as effective as it was firstly thought. The responses are modest and transient. Thus, simultaneous inhibition of multiple targets is necessary in most patients. These targets would include FLT3, KIT and VEGF signalling. Inhibitors that block simultaneously the signalling induced by these molecules at lower concentrations have the possibility of being more effective in the treatment of AML, since they are capable of inhibiting both the angiogenesis and the cell proliferation. Moreover, it is important to note that the combination of these new therapies based on the inhibition of angiogenesis with cytotoxic agents that work independently on different cellular targets is turning out into an effective treatment for AML. In this way, lestaurtinib and midostaurin are the two multi-receptor tyrosine kinase inhibitors that are in phase III trials, and combined with chemotherapy have showed good results, achieving complete remissions.

The effects of many of the described inhibitors also depend on the specific cellular and molecular profile of each AML patient, such as the levels of VEGF/VEGFRs expression, or the positivity for the FLT3/ITD mutation, which should also be analyzed and taken into account prior to the administration of those compounds. Another relevant aspect to consider when developing new drugs should be not only their specificity in terms of angiogenesis, proliferation or tyrosine kinase inhibition, but also the adverse effects caused in AML patients, either given alone or in combination with standard chemotherapy, an aspect that has provoked the stopping of many clinical trials. Thus, special care should be further taken in the drug formulation.

Taken together, a plethora of new treatment approaches for AML patients has emerged in recent years. All of them have shown limited effectiveness, and, in a similar way to what happened with the ‘traditional treatments’ administered to AML patients, showed a number of adverse effects. Nevertheless, the knowledge continues increasing, and there are two lessons to learn from the experience to date: (1) that no single treatment is effective and safe enough and (2) that every single patient shows a cellular and molecular profile that physicians should seriously take into consideration. As there are still cases in which the remissions are partial or patients develop resistance to the treatment, others antiangiogenic drugs that block the interaction of VEGF with its receptors, or acting as tyrosine kinase inhibitors, or indirectly inhibiting VEGF, remains to be developed that deserve further evaluation in prospective clinical trials.

Conflict of interest

The authors reported no conflict of interest.

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Acknowledgement

This work was supported by grants from Junta de Andalucia (JA0030/2007), Spain.

References


[66] Knapper S, Mills IK, Gilkes AF, Austin SJ, Walsh V, Burnett AK. The effects of lestaurtinib (CEP701) and PKC412 on primary AML blasts: the induction of cytotoxicity varies with dependence on FLT3 signaling in both FLT3-mutated and wild-type cases. Blood 2006;108:3494–503.

[67] Levis M, Pham R, Smith BD, Small D. In vitro studies of a FLT3 inhibitor combined with chemotherapy: sequence of administration is important to achieve synergistic cytotoxic effects. Blood 2004;104:1145–50.


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