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Leukemia (PH Wiernik, Section Editor)

Current and Future Molecular Targets for Acute Myeloid Leukemia Therapy

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Abbreviations *AML* Acute myeloid leukemia · *BCL-2* B-cell lymphoma gene 2 · *CAM* Chick egg chorioallantoic membrane · *EGFR* EGF receptor · *EMT* Epithelial–mesenchymal transition · *FAK* Focal adhesion kinase · *FGF* Basic fibroblast growth factor · *FLT3* FMS-like tyrosine kinase 3 · *IDH* Isocitrate dehydrogenase · *JAK-2* Janus kinase-2 · *NDAT* Nano-diamino-tetrac · *NF-κB* Nuclear factor kappa-light-chain-enhancer of activated B cells · *NPM* Nucleophosmin · *PEG* Polyethylene glycol · *PI3K* Phosphatidylinositol 3-kinase · *STAT* Signal transducer and activator of transcription · *Tetrac* Tetraiodothyroacetic acid · *TGFβ* Transforming growth factor β · *TK* Tyrosine kinase · *T4* L-Thyroxine

Opinion statement

Acute myeloid leukemia (AML) disease prognosis is poor and there is a high risk of chemo-resistant relapse for both young and old patients. Thus, there is a demand for alternative and target-specific drugs to improve the 5-year survival rate. Current treatment mainstays include chemotherapy, or mutation-specific targeting molecules including FLT3 inhibitors, IDH inhibitors, and monoclonal antibodies. Efforts to devise new, targeted therapy have included recent advances in methods for high-throughput genomic screening and the availability of computer-assisted techniques for the design of novel agents predicted to specifically inhibit mutant molecules involved in leukemogenesis. Crosstalk between the leukemia cells and the bone marrow microenvironment through cell surface molecules, such as the integrins αvβ3 and αvβ5, might influence drug response and AML progression.

This review article focuses on current AML treatment options, new AML targeted therapies, the role of integrins in AML progression, and a potential therapeutic agent—integrin αvβ3 antagonist.

Introduction

Acute myeloid leukemia (AML) is a multifaceted life-threatening hematological malignancy that affects the blood and lymphoid system of the body [1]. AML is heterogeneous in nature and is characterized by abnormal proliferation and absence of differentiation of immature and abnormal blast cells. In adults, AML is one of the most common types of leukemia and accounts for about 3.5% of all cancers [2]. The prevalence of AML cases is slightly more common in men compared to women, even though the average lifetime risk of acquiring AML in both genders is around one half of 1% [3]. According to the American Cancer Society's estimations for AML cases in the USA for 2019, there will be 21,450 new cases and 10,920 deaths from AML [3]. Among all the leukemia cases, 32% of cases in adults are due to AML [4].

The 5-year survival rate for adults suffering from AML is only about 24% [4], although recently there have been more selective and targeted immunotherapy options developed [5], which have slightly increased the 5-year survival rate. These new targeted treatments are either used as monotherapy or in combination with chemotherapy to achieve a better outcome. However, managing the side effects of these combinations of drugs can be challenging and needs more research on how to optimize the therapy for the best possible outcome, which is to ensure maximum efficacy with minimum adverse effects. Given the disease prognosis, heterogeneity, and mortality rates, the goal is to ensure and provide treatment options that are not only effective but also safe in the long run [6].

Recent clinical studies have demonstrated that heterodimeric cell surface molecules composed of α and β chains, called integrins and which can bind extracellular matrix (ECM) molecules, cell surface molecules, and variable soluble mediators [7, 8], have a role in AML progression and cessation. This has raised interest to develop therapeutic agents targeting integrin receptors. The β3 integrin (ITGB3) chain can form heterodimers only with the two α chains αIIb and αV, which play an important role in leukemogenesis and chemo-resistance in human AML.

Pathophysiology

AML is a heterogeneous disease with a complex and distinct pathogenesis that involves a wide array of molecular modifications, leading to disruption of cell growth and development. These molecular modifications comprise cellular processes like regulation of cell differentiation and proliferation, survival, self-renewal, DNA-repair, chromatin stability, cell-cycle checkpoint control, and cell distribution [9]. Molecular genetic alterations underlie the core of AML pathogenesis and disease progression, hence understanding these processes is vital to develop more disease-specific therapies.

Recently, many cytogenetic abnormalities were identified in the different subtypes of leukemia. Genetic abnormalities are present in more than 80% of AML patients and acute lymphoblastic leukemia patients, and most of them are recurrent [10]. Moreover, the heterogeneity of acute leukemia is related not only to clinical outcome but also to heterogeneity in the response to chemotherapies.

For example, acute promyelocytic leukemia (APL) patients with t(15;17) and (q22;q21) are responsive to all-*trans*-retinoic acid (ATRA) treatment, but APL patients with t(11;17) and (q23;q21) are resistant to ATRA [11].

Evasion from programmed cell death

The evasion of apoptosis by cancer cells is one of the most important processes by which they develop malignancy (Fig. 1). Usually, cancer cells proliferate and attain increased cell survival probability due to the activation of protein tyrosine kinase, which in turn activates the phosphatidylinositol 3-kinase (PI3K) signaling [12]. PI3K signaling activates AKT serine/threonine kinase, which in turn helps to release the BCL-2 pro-survival molecule by phosphorylating BAD proteins [13]. In AML, survival rates and clinical response rates can be predicted by observing the expression of the BCL-2 pro-survival molecule and hence it is an important molecular target for AML treatment [14, 15].

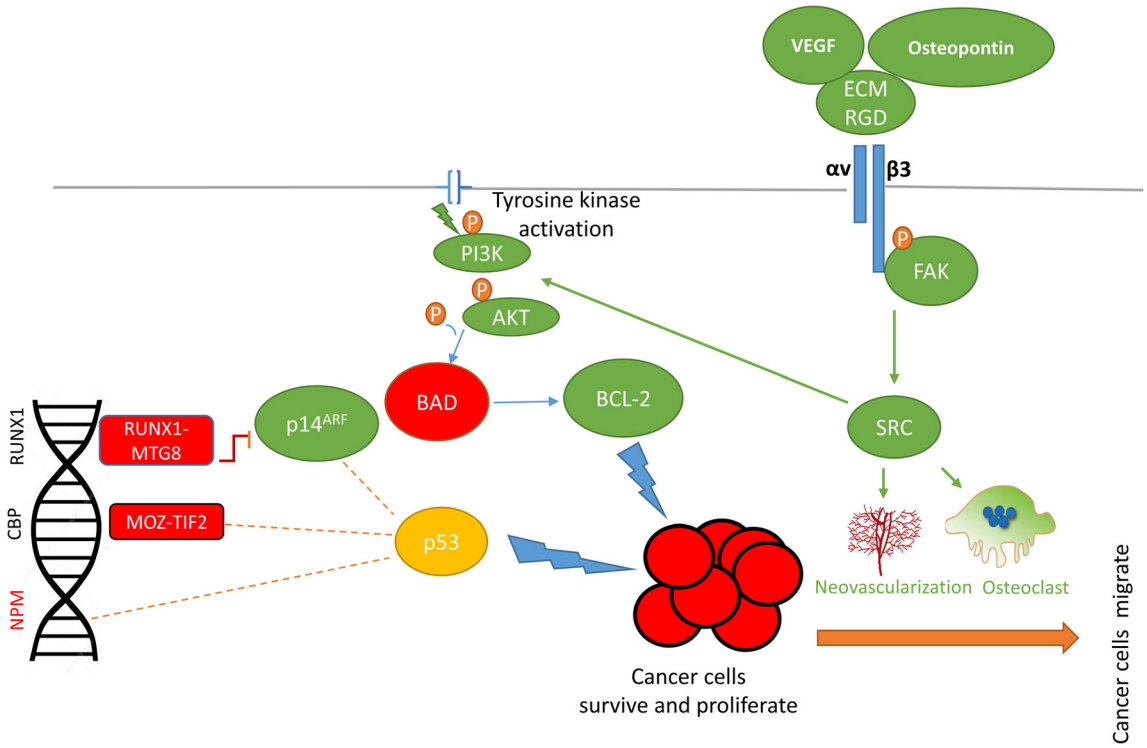

Fig. 1. Cancer cells' evasion from apoptosis and metastasis. Auto-activation of tyrosine kinases by different mutations associated with activation of phosphatidylinositol 3-kinase (PI3K) signaling. PI3K signaling activates AKT serine/threonine kinase, which in turn helps to release the BCL-2 pro-survival molecule by phosphorylating BAD proteins. Another important mechanism is the destabilization of p53 protein, which can occur by different mechanisms including suppression of $p14^{ARF}$ expression by the RUNX1–MTG8 fusion protein, binding of the MOZ–TIF2 fusion protein to core binding protein (CBP), or mutation of nucleophosmin (NPM) protein that is important for the cytoplasmic localization of p53. On the other hand, integrin αvβ3 binds a wide range of extracellular matrix molecules with an Arg-Gly-Asp (RGD) motif, including VEGF and osteopontin. Upon binding, the cytoplasmic tail initiates a signaling cascade, including the activation of Src kinases via phosphorylation of focal adhesion kinase (FAK). These signaling pathways are involved in cell survival, proliferation, osteoclast-mediated bone resorption, and neovascularization, which are important for tumor metastasis.

Another important protein that is linked to cell-cycle regulation and apoptosis is p53 protein (Fig. 1). Patients with AML experience adverse reactions in response to chemotherapy treatment due to p53 protein mutations [16]. Leukemogenic signaling causes alterations in p53 regulation, which compromise the function of this protein in AML. Destabilization of p53 protein occurs due to the suppression of $p14^{ARF}$ expression by the RUNX1–MTG8 fusion protein. Furthermore, p53 transcriptional activity is debilitated indirectly due to binding of the MOZ–TIF2 fusion protein to core binding protein (CBP) [17]. The stability of p53 protein is regulated by the nucleophosmin protein (NPM), but unfortunately, about 35% of newly diagnosed AML cases are due to mutations within the NPM coding region that is linked with cytoplasmic localization of this protein [18].

Leukemia cell propagation

Leukemia cells' dissemination from the bone marrow to other cells and tissues has not been clearly understood until recently; however, it can be assumed that there is a role for RUNX1 fusion protein in regulating expression of cell surface proteins [19]. In AML, high levels of selectin expression on the surface of the leukemic cells is a detrimental predictive marker that is increased by the secretion of other cytokines and tumor necrosis factors. This can lead to increased expression of adhesion proteins like selectins, integrins, and cadherin on vascular endothelium, augmenting leukemic cell adhesion. Monoclonal antibodies like anti-CD33 could be a possible therapeutic option because it can interfere with leukemic cell adhesions with cell surface proteins, diminishing cancer cell growth and proliferation [20].

The process of invasion and metastasis depends mainly on degradation of the ECM. Integrins, a family of cell adhesion molecules, are involved in a wide range of cell–ECM and cell–cell interactions. Integrin $\alpha v\beta 3$ binds a wide range of ECM molecules with an Arg-Gly-Asp (RGD) motif, including vascular endothelial growth factor (VEGF), fibronectin, fibrinogen, vitronectin, osteopontin, and laminin [21]. Upon binding, the cytoplasmic tail initiates a signaling cascade, including the activation of Src kinases (a family of non-receptor tyrosine kinases) via phosphorylation of focal adhesion kinase (FAK) [22]. Activation of Src kinases enhances activation of different signaling pathways including PI3K/AKT and mitogen-activated protein kinases (MAPK) [23]. Therefore, the $\alpha v\beta 3$ signaling pathway plays an important role not only in cell proliferation but also in osteoclast-mediated bone resorption and neovascularization, which are important for tumor metastasis (Fig. 1).

Conventional AML therapies

Treatment of AML is dependent on the subtype of AML present and may be different than treatment used in other forms of leukemia. In addition, prognostic factors including patient age, overall health status, and presence of genetic or chromosomal abnormalities are important in determining which treatment will lead to the safest and most effective outcome for each patient. The following are some of the cornerstones used in current treatment of AML [10, 24].

Chemotherapy

According to the American Cancer Society, intravenous chemotherapy is the mainstay treatment for most patients affected by AML due to its usefulness in reaching all areas of the body, that is, where leukemia has also reached. The two chemotherapy drugs most often used are a combination of cytarabine plus daunorubicin, or cytarabine plus idarubicin [25]. The standard induction regimen of these drugs for adult patients is a continuous infusion of cytarabine for 7 days, plus daunorubicin or idarubicin injections for the first 3 days, also commonly referred to as the 7 + 3 regimen [3, 26–28]. Cytarabine's main mechanism of action involves cytotoxicity on the dividing cells specifically in the S-phase. Cytarabine also gets metabolized to cytarabine-triphosphate (Ara-CTP), which ultimately inhibits DNA strand elongation and repair by incorporating into tumor cellular DNA [29]. The anthracyclines, daunorubicin and idarubicin, work via similar mechanisms by incorporating themselves between DNA base pairs, causing a DNA helix conformational change. This transformation in shape inhibits DNA and RNA polymerases, thereby interfering with strand elongation and protein synthesis of the tumor cells [30]. Table 1 shows a list of currently approved chemotherapies for AML and investigational drugs in the pipeline.

Typically, chemotherapy is given in two phases for adults under the age of 60. The first, called induction, is a short but intense treatment used to

Table 1. Investigation chemotherapies and currently approved chemotherapies for AML

Drug name (active ingredient)	Status or date of FDA approval	Manufacturer
(crenolanib)	Investigational drug	Arog Pharmaceuticals
(lestaurtinib)	Investigational drug	Cephalon
(quizartinib)	Investigational drug	Astellas Pharmaceuticals
Venclexta (venetoclax)	November 2018	AbbVie Inc. and Genentech Inc.
Xospata (gilteritinib)	November 2018	Astellas Pharma
Tibsovo (ivosidenib)	July 2018	Agios Pharmaceuticals
Mylotarg (gemtuzumab ozogamicin)	September 2017	Pfizer
Idhifa (enasidenib)	August 2017	Celgene Corp
Vyxeos (cytarabine/daunorubicin)	August 2017	Celator Pharmaceuticals
Rydapt (midostaurin)	April 2017	Novartis Pharmaceuticals
Dacogen (decitabine)	May 2006	Otsuka Pharmaceutical
Sutent (sunitinib)	January 2006	CP Pharmaceuticals
Nexavar (sorafenib)	December 2005	Bayer Healthcare Pharmaceuticals
Vidaza (azacitidine)	May 2004	Celgene Corp
Cytosar-U (cytarabine)	December 1998	Teva Pharmaceuticals
Etopophos (etoposide)	February 1997	Bristol-Myers Squibb
Idamycin PFS (idarubicin)	February 1997	Pharmacia and Upjohn Co
Fludara (fludarabine)	April 1991	Genzyme Corp

completely eliminate the leukemic myoblasts from the bloodstream and reduce the number of myoblasts in the bone marrow to below the normal 5% threshold [31]. When induction has been completed after approximately 1 week and the patient has had the chance to recover, the second phase, known as consolidation or post-remission therapy, is initiated. Consolidation is given in cycles and is used to eliminate the small number of leukemic cells that are known to be still present in the patient, although not necessarily detectable. A subsequent phase known as maintenance or post-consolidation is given months to years after the completion of phase II for a APL, but is rarely utilized for most other types of AML [3, 32].

New AML-targeted therapies

Despite using the combination of cytosine arabinoside (Ara-C) and anthracycline as the main pillar of AML treatment for almost 40 years, this regimen is associated with a high relapse rate. Different new agents have been developed to improve survival and decrease the relapse rate [33]. A summary of new trials against AML is given in Table 2.

FMS-related tyrosine kinase 3

FMS-related tyrosine kinase 3 (FLT3) is one of the most frequent mutations in AML, and it represents about 25–30% of mutations in AML patients [34•]. Different generations of FLT3 inhibitors have been developed. The first-generation FLT3 inhibitors include sorafenib (multikinase inhibitor) [35], sunitinib [36], lestaurtinib (a bioavailable indolocarbazole alkaloid compound derived from the bacterial) [37], and midostaurin (a small-molecule tyrosine kinase inhibitor (TKI) approved by the US FDA in 2017) [38, 39]. Second-generation FLT3 inhibitors include quizartinib (a selective and highly potent second-generation class III receptor TKI even in a low dose, 1 mg/kg) [40] and crenolanib (a selective inhibitor of FLT3/wild type mutations (WT), FLT3/internal tandem duplication mutations (ITD), FLT3-tyrosine kinase domain mutations (TKD), platelet-derived growth factor receptor mutations (PDGFRα/β), stem cell factor receptor gene mutations (KIT), and FLT3/aspartic acid codon 835 mutations (D835)) [41].

Several mechanisms can explain the efficacy of FLT3 inhibitors besides blocking of FLT3 phosphorylation, including (1) secretion of interleukin (IL)-15 by FLT3/ITD-mutated leukemic cells [42], (2) maintaining the low blast level in bone marrow by enhancing $CD3^+/CD8^+$ cell invasion in the bone marrow with high expression of IL-12 [43], and (3) downregulation of apoptosis regulatory proteins' expression (e.g., Mcl-1 and Bcl-2) by blocking Src kinase-mediated STAT3 phosphorylation [44, 45].

The different FLT3 inhibitors such as lestaurtinib have been used in clinical trials involving patients with refractory AML, showing a great ability to induce rapid clearance of blasts from peripheral and bone marrow without associated normal cell toxicity. Combined therapy of FLT3 inhibitors with conventional chemotherapy was associated with ~90% complete remission [46–49].

Table 2. Summary of new AML therapies

Drug name	Current phase	Target	Drug classification	Route of administration
ACT-GRO-777	II	Nucleolin	NME	IV
Actimab-A	I/II	CD33	Biologic	N/A
Alvocidib	II	Cyclin dependent kinase (CDK)	NME	IV
Annamycin	I/II	Topoisomerase II (DNA gyrase)	NME	IV
APR-246	I/II	p53	NME	IV
ARGX-110	I/II	CD70	Biologic	IV
ASLAN003	II	Dihydroorotate dehydrogenase (DHODH)	NME	PO
AST-VAC1	II	Immune system/telomerase	Biologic	IV
AT9283	I/II	Aurora kinase/BCR-ABL fusion protein/JAK/STAT	NME	PO
ATIR101	III	Immune system/P-gp	Biologic	IV
AZD2811	I/II	Aurora kinase	NME	IV
Beleodaq	II	Histone deacetylase (HDAC)	NME	IV
BI 836858	I/II	Cluster of differentiation 33 (CD33)	Biologic	IV
BL-8040	IIb	Chemokine (C-X-C motif) Receptor 4 (CXCR4)	NME	SQ
BST-236	II	DNA polymerase/DNA synthesis	Non-NME	IV
BVD523	I/II	MAPK3/ERK1	NME	PO
Ceplene	III	Histamine H2 receptor (HRH2)	NME	SQ
Cloretazine	II	DNA	NME	IV
CNDO-109	I/II	Lymphocytes	Biologic	N/A
Crenolanib	III	FLT3/PDGFR	NME	PO
CX-01	IIb	CXCL12/SDF-1	NME	IV
DFP-10917	II	DNA	NME	IV
Diflucan	I/II	Cytochrome p450	NME	IV, PO
Dilanubicel	IIb	Stem cells/other cell therapies	Biologic	IV
Elzonris	I/II	IL-3 (Interleukin-3) Receptor/CD123	Biologic	IV
Entospletinib	II	Spleen tyrosine kinase (syk)	NME	PO
Estybon	I/II	PI3K/AKT pathway Polo-like kinase 1 (Plk1)	NME	IV
FF-10101	I/II	FMS-like tyrosine kinase 3 (FLT3)	NME	PO
FT-2102	I/II	Isocitrate dehydrogenase (IDH)	NME	PO
Gilteritinib	NDA	ALK Axl receptor tyrosine kinase/FLT3	NME	PO
Glasdegib	NDA	Hedgehog signaling pathway	NME	PO
GMI-1271	I/II	Selectins	NME	IV, PO
GO-203-2c	I/II	Mucin 1 (MUC-1)	NME	IV
Guadecitabine	III	DNA methyltransferase (DNMT)	NME	SQ
HDM201	II	Apoptosis (cell death)/Mdm2	NME	PO
Iclusig	II	BCR-ABL Fusion Protein/FGFR/FLT3 RET/(VEGFR)	NME	PO

Table 2. (Continued)

Drug name	Current phase	Target	Drug classification	Route of administration
Idasanutlin	III	Mdm2	NME	PO
Idhifa	Approved	Isocitrate dehydrogenase (IDH)	NME	PO
Imetelstat	II	Telomerase	NME	IV
IMG-7289	I/II	Lysine-specific demethylase-1 (LSD1)/KDM1A	NME	PO
INCB59872	I/II	Lysine-specific demethylase-1 (LSD1)/KDM1A	NME	PO
Indoximod	I/II	IDO (indoleamine 2,3-dioxygenase)/immune system	NME	PO
Lirilumab	II	Immune system/KIR (killer immunoglobulin-like receptors)	Biologic	IV

PO oral, *IV* intravenous, *SQ* subcutaneous, *N/A* not available

Recently, the FDA approved gilteritinib (ASP2215), a novel dual FLT3/AXL inhibitor, for the treatment of patients who have relapsed or have refractory AML with a FLT3 mutation [34•, 50]. It targets mainly the FLT3/ITD-positive leukemia cells, decreasing their colony-forming capacity [51] by blocking the phosphorylation of FLT3 and its downstream targets [51, 52]. Approval of gilteritinib was based on a clinical trial that included 252 adult patients with relapsed or refractory AML having a FLT3 ITD, D835, or I836 mutation [53]. Gilteritinib was well tolerated and the response rate was more than 50% in patients with FLT3 mutation at doses ≥80 mg/day. No major side effects were reported (less than 5% experienced neutropenia). Mild thrombocytopenia, muscle pain with increased creatine phosphokinase enzyme, diarrhea, nausea, headache, and vomiting were the most common associated side effects [53].

Isocitrate dehydrogenase (IDH)

IDH inhibitors (IDH-i) are used in patients with AML who have mutations in either *IDH1* or *IDH2* genes, causing abnormal maturation patterns in white blood cells, thus leading to leukemia [54]. Two targeted IDH-i, ivosidenib and enasidenib, work by blocking the proteins IDH1 and IDH2, respectively. This inhibition allows for the normal maturation and differentiation of what would have been leukemic white blood cells, thereby reducing immature blast counts and increasing the percentage of mature myoblasts [55, 56]. While quite efficacious, a safety concern with IDH-i is the possible side effect known as differentiation syndrome, brought on by the release of inflammatory cytokines from cancerous promyelocytes, sometimes referred to as the "cytokine storm". Differentiation syndrome is serious and potentially fatal, with complications ranging from hypoxemia, hypotension, and respiratory distress to renal and hepatic dysfunction, but may be reversed by stopping the offending agent [47].

Aurora kinases

Aurora kinases are a family of mitotic serine/threonine kinases that are essential for cytokinesis during cell division. Aurora A (AURKA), Aurora B (AURKB), and Aurora C (AURKC) kinases are important for both mitosis

(especially the process of chromosomal segregation) as well as for meiosis process [57]. Deletion of Aurora kinases leads to cell division arrest, while the overexpression of Aurora kinases has been associated with a number of cancers such as lung, colorectal, and melanoma. Recent studies have demonstrated that inhibition of Aurora kinases could potentiate the effect of chemotherapies, especially in AML [57, 58].

An Aurora kinase inhibitor was tested against different AML cell lines (NB4 and KG1) and also primary cells obtained from AML patients, and it was associated with increased apoptosis (~3-fold) [59]. Recently, different Aurora kinases inhibitors were tested in clinical trials including AURKA inhibitors (e.g., MLN8054, phase I [60]; ENMD-2076, phase II [61]; MLN8237, phase III [62, 63]) and AURKB inhibitors (e.g., AZD1152, phase II/III [64, 65]; PHA-680632, preclinical [66]).

Beta cell lymphoma-2 (BCL-2)

Venetoclax is a recently approved (November 2018) agent to treat AML based on its extensive response rates as a selective small-molecule inhibitor of beta cell lymphoma-2 (BCL-2) protein [67]. It is another alternative for newly diagnosed patients of age 75 years and older who are incapable of sustaining high-intensity induction chemotherapy. The BCL-2 protein is responsible for antagonizing cellular apoptosis and has been associated with chemotherapy resistance. Venetoclax's role in binding to BCL-2 with high affinity allows for inhibition of the anti-apoptotic protein and, ultimately, leukemic cell death. Prescribers should remain aware of the serious side effect profile of venetoclax, including the potential for tumor lysis syndrome, which may lead to renal failure, the need for dialysis, or death [68, 69].

NF-κB inhibitors

NF-κB is an important transcription factor that plays a role for cell growth and apoptotic activity. The significant expression of NF-κB within leukemic cells is one of the promising targets for selective leukemic cell eradication [70].

Several studies are focused on targeting NF-κB, including using the proteasome inhibitor bortezomib, which enhances the anti-NF-κB effect by blocking the degradation of inhibitor of κB (IκB) [71, 72]. NF-κB can also be inhibited in leukemic cells by parthenolide (PTL), a naturally occurring sesquiterpene lactone, which occurs naturally in the plant feverfew (*Tanacetum parthenium*). PTL can stimulate the apoptotic pathways through inhibition of NF-κB, activation of p53, and the increase of reactive oxygen species, leading to decreased engraftment of leukemic cells into NOD/SCID mice [73]. In vitro studies were done to compare the effects of PTL against AML versus normal specimens, and the viability of AML CD34 cells was markedly suppressed by more than 70% in comparison to normal CD34 controls [74].

According to our preliminary data, both surface molecule CD44 and intracellular molecule NF-κB were broadly expressed in our AML patients in comparison to normal individuals (~25-fold). Our team designed a nano-encapsulating PTL to improve bioavailability and targeted delivery to leukemic cells. The preliminary data from 103 AML patients' bone marrow samples showed the correlation of high expression of NF-κB with a poor prognosis.

Also, our targeting strategy using nano-antiCD44 encapsulating PTL (7.5 μm) was associated with a significant ~50% decrease in the cell proliferation.

BMI-1 small molecule inhibitor (PTC-209)

BMI-1 (polycomb complex protein) is a transcription factor that is essential for the regulation of cell division, especially in highly dividing cells. Our previous work showed that BMI-1 was markedly increased in AML patients, especially FAB (M1, M5, and M7) [75]. Other studies have reported that the forced expression of BMI-1 led to a marked expansion of both multi-potential progenitors and hematopoietic stem cells (HSCs) in vivo [76, 77]. On the other hand, the absence of BMI-1 is associated with a marked defect in HSCs' self-renewal [78].

PTC-209 interferes with post-transcriptional regulation of BMI-1; however, the actual mechanism has not been clear until recently. In our previous study, we demonstrated the high expression of BMI-1 in AML cell lines, which confirms the role of BMI-1 in leukemogenesis and the possibility to be used as a new target for AML therapy. In vitro cell proliferation assay using different AML cell lines showed that the lowest concentration of anti-BMI-1 small molecule inhibitor PTC-209 (2 mM) decreased proliferation by about ~50–70% [75]. Kreso et al. have reported the effectiveness of PTC-209 against BMI-1 in human colorectal HCT116 and human fibrosarcoma HT1080 tumor cells [79].

The main obstacle for BMI-1 is that it is essential for both normal and leukemic cells' survival. So, BMI-1 might need to be selectively targeted to the leukemic cells in order to avoid damage to normal cells, which can be achieved by using targeted nano-encapsulation [80].

Monoclonal antibody

The novel agent gemtuzumab ozogamicin, an antibody–toxin conjugate that causes disintegration of DNA by binding at CD33 epitope and that can be given with or without chemotherapy, may also act as a low-intensity targeted agent for patients who are unable to tolerate high-intensity chemotherapy induction [54, 81]. This monoclonal antibody is administered via intravenous infusion and works by binding to CD33 protein present on most AML tumor cells. It functions as a signaling molecule that can enter malignant cells and destroy them during cell division. Safety issues arise because CD33 protein is also expressed on normal myeloid cells, causing potentially profound cytopenia as a serious side effect of the drug [81].

Thyrointegrin αvβ3 antagonist

The roles of thyroid hormones in cancer metastasis, cell proliferation, anti-apoptosis, and angiogenesis associated with cancer have been found to be interrelated based on pre-clinical studies [82••, 83–87] and clinical trials [88–91].

Integrins, transmembrane receptors that enable cell-ECM adhesion, are largely expressed by malignant cells and help in the dissemination of endothelial cells that are associated with cancer [92]. The extracellular domain of αvβ3 integrin has a thyroid hormone receptor for

tetraiodothyroacetic acid (tetrac), a deaminated analogue of thyroid hormone L-thyroxine (T4), which regulates cancer cell proliferation and the anti-apoptotic process of the cells [92–94]. The crosstalk between leukemia cells and the bone marrow microenvironment through integrins plays an important role in leukemic cell proliferation and engraftment. Some studies have reported the role of integrins in the modulation of drug response and the survival of AML [95, 96].

Other studies have demonstrated that the T4 receptor of αvβ3 integrin is associated with migration of malignant cells via various molecular mechanisms [97–99]. However, recently the T4 antagonism effects of tetrac at the αvβ3 integrin [92] were reported, making it a promising therapeutic agent in AML treatment. In addition, polyethylene glycol (PEG) can be covalently bonded to tetrac, which prolongs the action of tetrac molecules at the αvβ3 receptor. Studies have demonstrated that incorporation of tetrac with PEG has removed breast cancer xenografts that have already metastasized to bone [100, 101••], making it a potential therapeutic agent for AML patients.

There are various complex mechanisms by which thyroid hormones can lead to migration of the malignant cells including gene expression of matrix metalloproteinase (MMP), angiogenesis, microRNAs (miRs), epithelial–mesenchymal transition (EMT), transforming growth factor β (TGFβ), EGF receptor (EGFR), and tumor-associated macrophages [102].

Malignant cells' migration and engraftment have been linked with *MMP-2* and *MMP-9* gene expression [103–105], which have solubilizing activity of the ECM. Nano-diamino-tetrac (NDAT), a nano-pharmaceutical formulation of tetrac, can downregulate *MMP-2* and *MMP-9* gene expression, which verifies that NDAT has potential anticancer activity [94, 106]. On the other hand, thyroid hormone is associated with increased activity and gene expression of *MMP-2* and *MMP-9* [104].

The primary goal of the formulation for thyrointegrin αvβ3 antagonist is to ensure its components specifically target the extracellular domain of the αvβ3 integrin, sparing intracellular receptors and thereby reducing adverse effects. Because αvβ3 expression is substantial in tumor cells (especially in AML) compared to non-malignant cells, normal cells should be spared from the effects due to thyrointegrin αvβ3 antagonist. Blockade of thyrointegrin αvβ3 receptor leads to various anti-metastatic events, which include broad-spectrum anti-angiogenesis activities [107], reversal of resistance to chemotherapy and radiation therapy [108], upstream and downstream regulation of tumor suppressor genes, downstream regulation of tumor survival genes, PD-1/PDL-1 inhibition [109], and regulation of cancer stem cell signaling pathways.

Because the blockade of thyrointegrin αvβ3 receptor provides a unique way to block numerous pathways linked with cancer cell proliferations and differentiations, a logical step was to assess the efficacy and safety of this novel therapeutic agent for AML treatment. A macromolecule was made by covalently binding PEG with two bi-triazole tetrac molecules, called P-bi-TAT [110]. It augments the potency and broadens the anticancer properties of tetrac for the thyrointegrin αvβ3 target. P-bi-TAT obliterates the transcriptional makeup of the life-support structure of cancer cells, providing a unique and effective way of treating AML. P-bi-TAT has promising future aspects in AML treatment based on assessing its efficacy and safety profile in murine models [111]

Summary

Here, we have summarized current treatment options for AML and discussed potential targets for AML treatment that are hopeful for improved treatment outcomes and increased survival. After about four decades without any new approved pharmacologic agent for AML treatment, new classes of drugs were approved by the FDA in 2017, such as midostaurin and enasidinib (IDH2 inhibitors) and gemtuzumab ozogamicin (monoclonal antibody), which are used in combination with chemotherapy for AML treatment. Even so, the 5-year survival rate for AML patients has not significantly increased. There is a need for further well-designed clinical trials targeting other possible pathways by which AML progression and dissemination occurs. Targeting the αvβ3 integrin receptor is another promising target in treating AML. However, clinical trials in humans need to be carried out to ensure safety and efficacy of αvβ3 integrin receptor antagonists.

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Compliance with Ethical Standards

Conflict of Interest

Shaheedul A. Sami declares that he has no conflict of interest.
Noureldien H. E. Darwish declares that he has no conflict of interest.
Amanda N. M. Barile declares that she has no conflict of interest.
Shaker A. Mousa was issued a patent that is owned by NanoPharmaceuticals LLC, and he owns stock in NanoPharmaceuticals LLC, which is developing anticancer drugs.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

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