

New Strategies in Acute Myelogenous Leukemia: Leukemogenesis and Personalized Medicine

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Abstract

Recent advances in molecular technology have unraveled the complexity of leukemogenesis and provided the opportunity to design more personalized and pathophysiology-targeted therapeutic strategies. Despite the use of intensive chemotherapy, relapse remains the most common cause for therapeutic failure in acute myelogenous leukemia (AML). The interactions between leukemia stem cells (LSC) and marrow microenvironment appear to be critical in promoting therapeutic resistance through progressive acquisition of genetic and epigenetic changes within leukemia cells and immune evasion, resulting in leukemia cell survival. With advances in genomic sequencing efforts, epigenetic and phenotypic characterization, personalized therapeutic strategies aimed at critical leukemia survival mechanisms may be feasible in the near future. Here, we review select novel approaches to therapy of AML such as targeting LSC, altering leukemia/marrow microenvironment interactions, inhibiting DNA repair or cell cycle checkpoints, and augmenting immune-based anti-leukemia activity.

Background

Acute myelogenous leukemias (AML) are a heterogeneous group of disorders that differ in their genotypic, phenotypic, and epigenetic characteristics, and in their net responses to anti-leukemic interventions. Despite the achievement of complete remission (CR) in substantial proportions of AML subgroups, relapse occurs in the majority and remains the most common reason for treatment failure.

Contrary to what might be expected for such a diverse group of diseases, the AML genome on average contains only 13 gene mutations, and the vast majority of AML patients carry at least one pathogenic mutation affecting biologically relevant pathways, with unique patterns of mutual exclusivity and cooperation (1). Nonetheless, clonal complexity evolves from diagnosis through treatment and disease progression, at least in part due to selective pressure from chemotherapy (2, 3).

The ability to measure minimal residual disease (MRD) seems critical to determining optimal post-induction strategies that can eventually lead to disease eradication. Several AML subtypes have well-defined molecular aberrations and/or gene mutations, e.g., NPM-1 or FLT-3, that permit the use of high-sensitivity molecular detection of the leukemic burden by reverse transcriptase quantitative (qRT)-PCR (4-8). Alternatively, in AMLs lacking such specific molecular hallmarks, qRT-PCR for WT1, a zinc-finger transcription factor that is preferentially overexpressed in AML patients, may provide valuable information regarding MRD status. Several studies, including the recent European LeukemiaNet study, have found that the magnitude of WT1 log reduction following induction chemotherapy is an independent predictor of relapse (5, 9).

Flow cytometry provides an alternative method for detection of MRD based on the presence of aberrant cell surface marker expression. Detection of MRD by flow cytometry correlates with relapse (5). Additionally, flow cytometry holds the promise to track residual leukemia stem cells (LSCs). Although to date there is a limited consensus regarding LSC phenotypes, there are discrete markers reported to facilitate the isolation and identification of LSCs, including CD34, CD38, CD44, CD47, CD96, CD32, CD25, CD133, CD90, CD117, CD123, TIM3, CLL-1, and ALDH1 (10, 11). As a case in point, Gerber et al. (12), used flow cytometry to assess aldehyde dehydrogenase (ALDH) expression in CD34+ cells, and identified a population of CD34+CD38- cells with intermediate ALDH activity that was 89% leukemic by fluorescence in situ hybridization (FISH), reproducibly generated AML upon transplantation into mice, and was highly predictive of relapse.

If we are to combat AML more effectively, we must develop strategies that take into account the multiple factors contributing to leukemia pathogenesis and pathophysiology, including the LSC, its interaction with its surrounding bone marrow (BM) microenvironment, and the development of net drug resistance over time. In this review, we discuss selected approaches that address aspects of both the leukemic clone and its supportive milieu.

On the Horizon

Targeting leukemia stem cells and marrow microenvironment

Leukemia stem cell directed therapies. LSCs share many properties with normal hematopoietic stem cells (HSCs) such as self-renewal, quiescence, and resistance to traditional cell-cycle dependent chemotherapeutic agents (13). An ability to target LSCs offers a possibility of eradicating AML at its roots. Such eradication, however, requires the ability to exploit

differences between LSCs and HSCs in terms of dependence on specific survival pathways, alterations in the genetic, epigenetic and metabolic landscapes, and immunophenotypes. As new drugs are developed to selectively target the abnormalities responsible for leukemia initiation and perpetuation, there may be an opportunity to eradicate LSC clones before acquisition of additional mutations renders them resistant to therapy (Table 1).

Several pathways appear to promote LSC survival preferentially. NF- κ B, a transcription factor that promotes cell growth and inhibits apoptosis, is constitutively activated in LSCs (14). Parthenolide induces LSC apoptosis via NF- κ B inhibition and increase in reactive oxygen species (ROS), and decreases engraftment of LSCs but not HSCs in mice (15). The proteasome inhibitor Bortezomib produces an anti-NF- κ B effect by inhibiting the degradation of I κ B. Bortezomib given with traditional induction chemotherapy produced encouraging results (CR 65%; DFS and OS of 7.4 and 17.5 months) in newly diagnosed elderly AML patients (16). Whether or not this is a consequence of more effective LSC eradication will require further studies. The PI3K/AKT/mTOR pathway is frequently up-regulated in AML and plays a central role in multiple key survival processes within the cells such as in regulation of formation of reactive oxygen species (ROS), modulation of Bcl-2 family proteins, up-regulation of NF- κ B, and self-renewal of LSCs through Wnt/B-catenin pathway (17). PI3K/mTOR inhibitors were found to augment the effects of parthenolide on LSCs possibly through down-regulation of Nrf2, a transcription factor involved in activating the expression of antioxidant enzymes such as heme oxygenase (HMOX-1) (18). Thus, inhibition of PI3K/AKT/mTOR may sensitize LSCs to agents that induce oxidative stress by increasing that stress and thereby reducing LSC self-renewal. However, when given as single agents or in combination with chemotherapy, mTOR analogues or perifosine

demonstrated only modest clinical activity in AML, (19-21) likely due to mTORC1 but not mTORC2 inhibition. New PI3K/mTOR inhibitors are in clinical trials in AML (NCT01756118, NCT01396499).

LSCs reside in a hypoxic environment in the BM and depend heavily on oxidative phosphorylation, which is a pivotal function of mitochondrial proteins. This oxidative phosphorylation is critical to LSC maintenance and survival. As a case in point, LSCs upregulate specific Bcl-2 family members to evade apoptosis and promote survival and chemoresistance. Bcl-2 and Bcl-XL are highly expressed in LSC while Mcl-1 has a key role in maintenance of HSCs (22). This difference provides a therapeutic opportunity to sensitize LSC to chemotherapy via Bcl-2 inhibition (23). For instance, anti-Bcl2/BH3 mimetic ABT-737 preferentially inhibited LSC survival in preclinical studies; however, compensatory increases in Mcl-1 may limit its net activity (24). Dual inhibition of Bcl-2 and Mcl-1 promoted anti-leukemia activity (25, 26), but the clinical applicability of this approach could be challenged by potential hematologic toxicity.

Several phenotypic markers preferentially expressed on LSC may serve as therapeutic targets. Targeting surface antigens with monoclonal antibodies (mAb), immunotoxins, chimeric antigen receptor modified T cells (CAR T-cells) are in diverse stages of clinical testing. For instance, CD123 is preferentially expressed in CD34⁺CD38⁻ AML cell population (27) and pre-treatment of NOD/SCID with anti-CD123 mAb decreases AML cell engraftment (28). Two biologic agents targeting anti-CD123 are in clinical testing: mAb CSL362 (NCT01632852) and DT388IL3 (NCT00397579)(29). The LSC express CD47 that binds to signal-regulatory-protein-alpha (SIRP α) on macrophages and inhibits phagocytosis. The disruption of CD47-SIRP α

interaction using anti-CD47 Abs or SIRP α -Fc fusion protein decreases LSC engraftment in xenograft models and promotes macrophage-mediated phagocytosis of AML cells (30, 31).

Microenvironment: the LSC niche as a therapeutic target. Two distinct BM microenvironmental niches, osteoblastic and vascular, are required for maintenance of HSCs but also provide a sanctuary for leukemic cells to evade chemotherapy-induced death. In principal, both LSC and HSC are dependent on signals from their microenvironment, including stromally-produced cytokines, chemokines, and intracellular signals initiated by cellular adhesion; however, LSC are able to outcompete HSCs, hijacking the BM environment and creating their foster home through reversible changes in BM stromal cell function (32).

Interactions between CXCL12 (stromal cell derived factor alpha-1) and its receptor CXCR4 on leukemia cells contribute to LSC homing to the microenvironment. CXCR4 expression is increased on AML cells, particularly in FLT3-mutated AML, and is associated with poor outcome (33). Anti-CXCR4 mAb given to NOD/SCID mice engrafted by human AML decreased the numbers of AML cells in blood, BM, and spleen, but did not affect homing of HSCs (34). CXCR4 inhibitors are currently in clinical studies in AML (NCT01120457, NCT01352650, NCT01160354). Plerixafor, a small molecule antagonist of CXCR4, mobilizes AML cells into peripheral blood where they are more sensitive to chemotherapy. Plerixafor in combination with chemotherapy produced complete remission in 46% of relapsed/refractory AML patients, and correlative studies demonstrated two-fold increased mobilization of leukemia cells into peripheral blood (35). Adhesion of LSCs to the BM microenvironment promotes survival, self-renewal and resistance to therapy. Interaction between VLA-4 on the surface of leukemia cells and fibronectin on stromal cells activates pro-survival pathways and contributes to MRD

persistence (36). Another adhesion molecule, CD44, promotes LSC homing to microenvironmental niches by mediating cell-cell and cell-extracellular matrix interactions through binding to hyaluronan (37).

Leukemia progression may promote hypoxia in the BM niche, leading to overexpression of HIF-1a which promotes leukemia cell quiescence as well as recruitment and retention of leukemia cells through activation of CXCL12-CXCR4 signaling (38). Targeting HIF-1a transcription factor and its downstream target CIAX is now amenable to pharmacologic inhibition. The hypoxia-activated pro-drug PR-104 demonstrated clinical activity in AML patients but produced prolonged myelosuppression at higher doses (39). Nonetheless, since HSCs and LSCs use overlapping pathways of microenvironmental protection, it will be important to examine the safety and selectivity of these novel agents.

Novel treatments based on improved understanding of AML biology

Epigenetic therapies. Global epigenetic modulators such as DNA methyltransferase (DNMT) or histone deacetylase (HDAC) inhibitors are associated with reduction but not eradication of LSCs (40). The identification of recurring unique mutations in epigenetic mediators and overall epigenetic profiles opens the possibility of developing more effective inhibitors. Mutations such as IDH1/IDH2 or DNMT3 appear to be leukemia-initiating and may contribute to initial LSC expansion (41, 42). IDH mutations lead to production of 2-hydroxyglutarate which inhibits histone and DNA methyltransferases, resulting in increased DNA methylation and blocked cellular differentiation (43). Small molecule inhibitors of IDH2 (AG-6780, AG-221) reduce 2-HG levels, increase differentiation, and produce survival benefit in xenograft models (44, 45). AG-221 is currently in phase I testing (NCT01915498). The presence

of DNMT3 mutations may be associated with an increased response to hypomethylating agents, as reported in a small number of AML patients treated with decitabine (46). DNMT3 mutations occur early in leukemogenesis (41), raising the possibility that DNMT3 inhibitors could be used selectively, not only in initial therapy, but also as maintenance or to target MRD following chemotherapy in DNMT3-mutated leukemias.

Increasing the DNA-damaging efficacy of chemotherapy. Cytarabine remains the single most effective drug for therapy of AML and there are ongoing efforts to identify strategies to enhance its activity. CPX-351 is a liposomal encapsulation of cytarabine and daunorubicin at a 5:1 molar concentration ratio that provides optimal synergistic activity (45). A randomized Phase II study of CPX-351 versus 7+3 in older adults with newly diagnosed AML resulted in improved CR rates (66.7% versus 51.2%) with survival advantage noted in patients with secondary AML (12 .1 vs 6.1 months), leading to a Phase III study in this population (NCT01696084)(47).

Incorporation of cytarabine into DNA activates Chk1, a serine/threonine kinase which stabilizes stalled replication fork, induces S phase arrest, and diminishes cytarabine toxicity. Depletion of Chk1 either by siRNA (48) or selective Chk1 inhibitor SCH900776 (MK8776) (49) can overcome S-phase checkpoint activation and enhance cytarabine cytotoxicity in AML. In a phase I study, SCH900776 given with timed sequential cytarabine produced CR in 33% of patients with relapsed/refractory AML, and increased H2Ax phosphorylation in marrow blasts consistent with unrepaired DNA damage (50). A randomized phase II study comparing cytarabine plus MK8776 to cytarabine alone is ongoing in patients with relapsed or refractory AML (NCT01870596). Several other cell cycle checkpoint inhibitors have shown preclinical or

clinical activity in AML (Fig. 1). WEE-1 kinase is an essential G2/M as well as G1/S checkpoint kinase that phosphorylates CDK1, thereby delaying cell cycle progression, providing time to repair DNA damage and complete cell division. Inhibition of WEE-1 kinase by siRNA or pharmacologically with WEE-1 inhibitor MK1775 resulted in potentiation of ara-C cytotoxicity in AML cells (48). A study of WEE-1 kinase inhibitor in combination with cytarabine in AML is planned. Aurora kinases and Polo-like kinases (Plk) also play important roles in cell cycle progression. Aurora B kinase has a predominant role in mitosis and its inhibition by AZD1152 produced 25% response rate in poor-risk AML (51) and 45% response rate in older AML patients when given with low dose cytarabine (LDAC) (52). Plk inhibition leads to a disruption in spindle assembly causing a mitotic arrest and subsequent apoptosis. A randomized phase II study of volasertib, a Plk1 inhibitor, plus LDAC versus LDAC alone in older AML patients showed improvement in response rate and survival with the combination versus LDAC alone (31% vs 13%; OS 8 vs 5.2 months) (53), leading to Breakthrough Therapy designation and initiation of a phase III randomized study of the same regimens in AML patients older than 65 (NCT01721876).

Aberrant or impaired repair of DNA double-strand breaks (DSB) is common feature of AML and MDS (54, 55). Inhibition of poly(ADP)ribose polymerases (PARP), a family of enzymes involved in base excision repair and other nuclear processes, may lead to an increase in single strand breaks (SSBs) which form DSBs upon encountering a replication fork which cannot be repaired in cells with a defective DSB repair background (defective BRCA, ATM, or Fanconi Anemia proteins). PARP inhibitors demonstrate single agent anti-leukemia activity in preclinical studies (56, 57) and potentiate the cytotoxic effects of diverse classes of DNA damaging agents

in multiple tumor cell types, including AML (58, 59). Clinical trials are exploring activity of veliparib (ABT-888) with temozolomide (NCT01139970) or topotecan plus carboplatin (NCT00588991) in refractory AML.

Immunomodulation. Multiple mechanisms contribute to the dysfunction of effector T cells in AML, including 1) wide tissue expression of leukemia antigens; 2) the ability of AML cells to lose antigen/MHC expression limiting effective T cell response; 3) expression of negative co-stimulatory ligands by tumor cells; 4) expansion of regulatory T cells (Tregs) and myeloid derived suppressor cells (MDSC); and 5) deletional peripheral T cell tolerance (60-62).

Recent attention has focused on blocking negative regulatory signals in order to activate T cell-mediated anti-tumor immunity (Table 2). CTLA-4 and PD-1, members of CD28 family, are the key inhibitory receptors that limit T cell activation. CTLA-4 is expressed on activated T cells and Tregs and binds CD80/CD86 ligands on antigen presenting cells (APCs). On effector T cells, CTLA-4 is able to outcompete CD28 for access to the immune synapse, thereby limiting co-stimulation (61, 63). The anti-CTLA-4 inhibitory mAb Ipilimumab was approved by FDA after clinical studies in advanced melanoma demonstrated remarkable activity (64). CTLA-4 blockade by mAb enhances AML specific T cell responses *in vitro* (65), and CTLA-4 polymorphism has been associated with AML relapse (66). Ipilimumab is now being evaluated in patients with relapsed MDS/AML (NCT01757639) or following allogeneic stem cell transplantation (NCT01822509).

PD-1 is expressed on the surface of activated T cells, B cells, NK cells and monocytes in response to inflammation and binds two ligands: PD-L1 and PD-L2. PD-L1 is expressed on hematopoietic and non-hematopoietic cells and is over-expressed on multiple tumors, including

AML blasts, while PD-L2 is mainly restricted to APCs (61, 67, 68). Leukemia-specific T cell immunity and survival upon AML challenge was increased in PD-1 knockout mice or in wild type mice upon PD-L1 blockade using mAb (69). PD-1 expression is increased on peripheral blood T cells in leukemia patients compared to healthy donors (70). PD-1/PD-L1 pathway blockade has shown promising activity in solid tumors (71, 72) and is now investigated in clinical trials in AML in combination with a dendritic cell based vaccine (NCT01096602). Additional non-CD28/B7 family T cell inhibitory receptors such as LAG-3 and TIM3 have also been identified as potential therapeutic targets.

Immunosuppressive Tregs are defined by their expression of FoxP3 transcription factor and have been implicated as major contributors to the defective immune response in AML. AML patients have a greater Treg frequency at diagnosis relative to normals, their Tregs more potently suppress the effector T cells, and those with greater numbers of Tregs appear to have a relatively poor clinical outcome (62, 73, 74). In mice, Tregs accumulate at leukemia sites and impede the activity of cytotoxic lymphocytes (CTL) whereas their removal, alone or in combination with PD-L1 blockade, results in increased frequency of CTL at tumor sites and improves the efficacy of adoptive therapy (75, 76). Clinical studies are investigating if responses to tumor vaccines can be augmented in AML patients following Treg depletion using metronomic cyclophosphamide or/and anti-IL2 receptor (CD25) antibodies (NCT01513109, NCT01842139), or if immunomodulatory drugs such as pomalidomide may reduce Tregs following induction chemotherapy (NCT02029950).

Conclusion

The therapeutic armamentarium for AML is evolving as we increase our basic understanding of the diverse factors that play into leukemogenesis and leukemia cell biology. Given the complex interactions between AML cells and the many components of their environment, it is reasonable to surmise that the future of AML therapy lies in the combination of molecularly selective agents with traditional cytotoxics and/or with each other throughout induction and post-induction therapies. Such multi-directed approaches have the potential to overcome AML cell resistance by targeting crucial leukemic cell pathways and critical cellular and humoral components of the BM microenvironment, thereby preventing AML clonal expansion and survival. The successful introduction of diverse molecularly targeted agents into the clinic will require standardization of molecular tests, development of predictive biomarkers of response, proper timing, and integration with current therapies.

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Table 1. Select agents targeting leukemia stem cell and microenvironment

Molecular Target	Targeting Agent	Study in AML
<i>Leukemia Stem Cell</i>		
Survival pathways		
NF-κB	Parthenolide, bortezomib	Preclinical, phase I-III
PI3K/Akt/mTOR	BKM120, CAL-101, MK-2206, perifosine, GSK21110183, sirolimus, temsirolimus, deferolimus, everolimus, BEZ235, OSI-207	Preclinical, phase I-II
Self-renewal pathways		
Wnt/β-catenin	CWP232291, PRI-724	Phase I-II
Hedgehog	PF-04449913, LDE225	Phase I-II
Mitochondrial targets		
Bcl-2	Oblimersen sodium, obatoclax, ABT-737, ABT-199	Preclinical, Phase I-III
Mitochondrial translation	Tigecycline	Preclinical, Phase I
Cell surface antigen		
CD123	CSL362, SL-401 (IL-3-diphtheria toxin), *CAR T cells, MGD006 (*DART CD123, CD3)	Preclinical, Phase I-II
CLL-1	mAB, nanoparticle-daunorubicin	Preclinical
CD25	Basiliximab, Daclizumab, denileukin diftitox immunotoxin	Preclinical, Phase I-II
CD47	mAb, SIRPα Fc fusion protein	Preclinical

CD33	Gemtuzumab ozogamicin, SGN-CD33A, 225- Aclintuzumab, AMG-330 (CD3, CD33 *BITE Ab), *CAR T cells	Preclinical, Phase I-III
Bone marrow microenvironment		
Adhesion, homing		
CXCR4/SDF-1	BMS-936564, BL-8040, plerixafor; NOX-A12 (SDF-1)	Preclinical, phase I-II
VLA-4	natalizumab	Preclinical
CD44	mAb	Preclinical
MUC1-C	peptide inhibitor GO-203	Preclinical
Hypoxia		
HIF-1a	ehinomycin	Preclinical
VEGF	bevacizumab, lenalidomide, sunitinib, sorafenib	Preclinical, Phase I-III
Hypoxia-activated prodrugs	PR-104, TH-302	Preclinical, Phase I

*CAR (Chimeric Antigen Receptor) T cells; BITE Ab (Bispecific T cell Engager Ab); DART (Dual Affinity Retargeting Molecule)

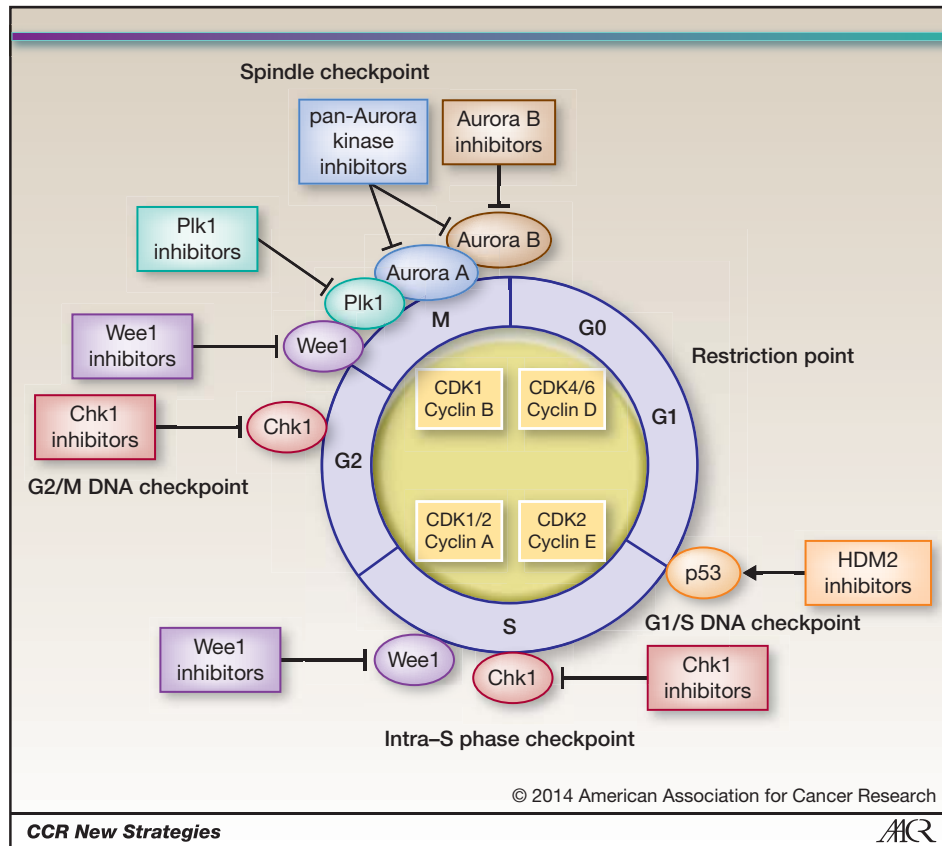
Table 2. Select Immunotherapeutic Strategies		
Target	Agent	Mechanisms/Studies in AML
<i>Inhibitory pathways</i>		
<i>CD28/B7 family receptors</i>		
CTLA-4 (Cytotoxic T lymphocyte antigen-4)	Ipilimumab*	CTLA-4 blockade enhances AML-specific T cell responses; CTLA-4 polymorphism associated with relapse (65, 66). *Clinical study in relapsed AML and after alloHSCT.
PD-1 / PD-L1 (Programmed death-1)	Nivolumab, MK-3475*, CT-011*, MEDI0680, BMS-936559, MEDI4736, MPDL3280A	PD-L1 is expressed on AML blasts ; PD-1 expression increased on circulating T cells in leukemia patients; leukemia -specific T cell immunity and survival upon AML challenge increased in PD-1 knockout mice or upon PD-L1 blockade (61, 69, 70). *Clinical study of CT-011 and vaccine; and MK-3475 in MDS.
<i>non-CD28/B7 family receptors</i>		
LAG-3 (Lymphocyte activation gene-3)	BMS-986016, IMP321	No studies in AML.
TIM-3/ galectin-9 (T cell immunoglobulin domain and mucin domain 3)	mAb, TIM-3 fusion protein	Galectin-9 is expressed on AML cells; co-expression of TIM-3 and PD-1 identifies exhausted T cells in mice with advanced AML and increases during AML progression; combined blockade of TIM-3/ PD-L1 had an additive effect in improving survival of AML-bearing mice (77).
<i>Inhibitory enzymes</i>		
IDO (Indoleamine 2,3-dioxygenase)	INCB024360*, indoximod, NLG919	IDO overexpressed in AML cells, predicts poor prognosis, depletes tryptophan, thus, limiting T cell proliferation and stimulating Tregs accumulation. (78-80) *Clinical study in MDS.
Targeting T regs	CD25 (Basiliximab*, Daclizumab, denileukin diftitox immunotoxin); Metronomic cyclophosphamide ; Immunomodulatory drugs (Pomalidomide*, Lenalidomide*, Thalidomide); Fludarabine	*Several clinical studies of anti-CD25 plus vaccine and chemotherapy plus immunomodulatory drugs ongoing in AML.
Targeting NK cells		
KIR(Killer-cell immunoglobulin-like receptors)	*Anti-KIR Ab (IPH2101, lirilumab)	*Phase I, II clinical studies-maintenance in older AML patients (81).

CD200 / CD200R	mAb (anti-CD200)	CD200 is overexpressed in AML cells, correlates with poor prognosis, increases BM Tregs and directly inhibits the cytotoxic activity of NK cells (82, 83).
CD123/CD33/CD16	Triplebody (SPM2)	Increased patient's NK cell cytolytic activity against AML cells <i>ex vivo</i> (84).
CD16 X CD33	CD16xCD33 bispecific killer cell engager (BiKE)	Reversed MDSC (myeloid-derived suppressor cell) immunosuppression of NK cells and induced CD33+ MDS and MDSC target cell lysis <i>ex vivo</i> (85).

*Denotes therapeutics in clinical studies in AML and MDS.

Figure 1. Cell cycle checkpoint inhibitors in AML. Cell cycle is controlled by successive activation of cyclin-cyclin dependent kinases (CDKs). Cell cycle checkpoints serve to stop progression of the cell cycle in response to DNA damage, to allow time for DNA repair and to preserve genomic integrity. The p53-dependent G1/S checkpoint blocks initiation of DNA replication. p53 is frequently altered (mutations or losses) in patients with complex karyotype AML. Inhibitors of HDM2 (RG7112, RO5503781 and MK-8242) are in clinical studies in AML alone or in combination with cytarabine and have a potential to be effective in leukemia cells that retain wild-type p53. Tumors that are defective in p53 function rely on an intact S phase and G2 checkpoint. Depending on the type of genotoxic stress, either ataxia-telangiectasia mutated (ATM) protein kinase or ataxia-telangiectasia-related (ATR) protein kinase are activated leading to activation of Chk1 and Wee1 kinases that inactivate Cdk1 resulting in intra S phase and G2/M arrest, allowing time for DNA repair. Inhibition of Chk1 (MK8776) and Wee1 (MK1775) sensitizes leukemia cells to cytarabine cytotoxicity in preclinical studies and the combination of Chk1 inhibitor and cytarabine is in a phase II testing in AML. Synergistic activity has been described for Chk1 and Wee1 inhibition in leukemia cells. PLK1 and Aurora kinases are critical for centrosome maturation and proper formation of the mitotic spindle, and also play a role in chromosome segregation and cytokinesis. Plk1 inhibitor (volasertib) and Aurora B kinase inhibitor (AZD1152) have shown promising clinical activity in AML patients when given with low dose cytarabine. In addition, several pan CDK inhibitors (flavopiridol, dinaciclib) have been explored as a therapeutic strategy in AML. Flavopiridol in combination with cytarabine and mitoxantrone (FLAM) is in a phase III testing for newly diagnosed AML.

Figure 1:



Clinical Cancer Research

New Strategies in Acute Myelogenous Leukemia: Leukemogenesis and Personalized Medicine

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