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New agents for AML and MDS

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Abstract

The heterogeneity of acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) has led to a multiplicity of treatments, from cytotoxic agents to signal transduction modulators, cell cycle inhibitors, and epigenetic therapies. While some have shown promising initial results, the outlook for AML patients, particularly older and relapsed patients, as well as patients whose cells exhibit certain adverse chromosomal abnormalities or mutant oncoproteins, continues to be grim. Combination chemotherapy using new agents that act at a number of different levels may provide the greatest potential for successful future therapies. A select number of new agents, approaches, and combinations are reviewed here.

Keywords

AML; MDS; FLT3 inhibitors; FTI; clofarabine; HDAC; DNMT; mTOR; parthenolide; PIM kinase

Introduction

The past several years have brought exciting new treatments strategies for acute myeloid leukemia (AML) and the myelodysplastic syndromes (MDS). This review discusses a selective number of novel and relatively new agents, provides insights into why they may or may not be effective, and proposes some future possibilities for these agents. The agents covered fall into 7 major categories: cytotoxic agents, tyrosine kinase inhibitors, agents directed against novel targets, other signaling inhibitors, epigenetic agents, transcription factor targets, and new combination strategies (Table 1).

Cytotoxic Agents

Fludarabine phosphate, cladribine, clofarabine, and laromustine are among the large number of new cytotoxic agents that have been introduced for the treatment of AML. The purine analog clofarabine was approved in 2004 by the US Food and Drug Administration for the treatment of relapsed or refractory pediatric acute lymphoblastic leukemia (ALL) and is being studied in AML. It has significant single-agent activity in high-risk and elderly AML patients, producing a 40%-55% overall response rate (ORR) in this patient population.¹ Its ultimate role, however, may be in combination chemotherapy with such other agents as ara-C, which yields response rates greater than 50% in patients older than 60 years.²

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However, the high response rates observed with clofarabine come with a cost. As with most other cytotoxic regimens, clofarabine alone and in combination is associated with significant morbidity and mortality. Induction mortality with clofarabine and other cytotoxic agents ranges from 10% to 30%.³ Such considerations serve as a strong impetus for the development of more targeted therapies that are potentially capable of sparing normal host tissues while retaining activity against leukemic cells.

Laromustine is an alkylating agent similar in several respects to cyclophosphamide that has shown significant activity in AML and MDS. In a trial involving patients over the age of 60 with high-risk untreated AML or MDS, an overall response rate of 32% was obtained, with response rates of 50% and 40% in patients with de novo AML or high-risk MDS respectively.⁴ Toxicity was relatively modest. Trials are currently underway in AML evaluating regimens combining laromustine and ara-C, although initial reports indicate that the toxicity of this regimen may be substantial.

Tyrosine Kinase Inhibitors

FLT3 inhibitors are tyrosine kinase inhibitors that prevent essential proteins from binding to DNA by interfering with abnormal FLT3 function. FLT3 is mutated in approximately 33% of AML patients.⁵ FLT3 mutations can be either internal tandem duplications (ITD) or point mutations, and both carry an adverse prognosis.⁵ Numerous FLT3 inhibitors, including CEP-701 (lestaurtinib), PKC412 (midostaurin), KW-2449, and sorafenib, have shown unequivocal biologic effects in clinical trials, but objective responses in leukemia are relatively rare.^{6,7} Therefore, these agents may be most effective in combination, for example, with daunorubicin. A key question regarding FLT3 inhibitors is what downstream pathways, for example, AKT, ERK, or PIM, relieve the leukemic cells of their “addiction” to FLT3. Pharmacokinetic and pharmacodynamic factors, such as the lack of sustained inactivation, may represent a critical determinant of antileukemic activity in the case of FLT3 inhibitors.

KW-2449 is an orally active, potent FLT3 inhibitor that also inhibits other tyrosine kinases, including FGFR and TRK. It also inhibits aurora kinases, particularly aurora kinase A, and is a potent inhibitor of BCR/ABL, including drug-contact site/ATP binding region mutants such as T315I. However, a recent phase I study suggested that a lack of sustained FLT3 inhibition with current schedules may limit its activity in FLT3-associated AML.⁸ Conversely, investigators have found that transient potent BCR/ABL inhibition is sufficient to achieve irreversible apoptosis in chronic myeloid leukemia cells.⁹

Novel Targets

PIM kinase is a serine threonine kinase that is a potential target for the treatment of hematopoietic malignancies. The PIM kinase family actually consists of 3 PIM kinases—Pim1, PIM2, and PIM3, which act downstream of many other oncogenes that have been implicated in leukemogenesis and lymphomagenesis, including FLT3, STAT5, and BCR/ABL. The prototype PIM kinase inhibitor K00135, a imidazo[1,2-b]pyridazine, has shown marked antileukemic activity in vitro.¹⁰ A number of PIM1 and pan-PIM1 kinases are expected to enter the clinic in the course of the next year. While it is conceivable that some PIM kinases may demonstrate some single-agent activity, the ultimate role of PIM kinase inhibitors may ultimately be in conjunction with other agents, either conventional cytotoxic or possibly other targeted agents.

Parthenolide and its analogs represent another interesting and potentially promising class of compounds. Parthenolide is a sesquiterpene lactone, an active ingredient of the herbal medicine Feverfew. It is a potent inhibitor of NFκB, upon which leukemic and other malignant hematopoietic cells depend. In preclinical studies, parthenolide selectively targeted leukemia

stem cells.^{11,12} Parthenolide's clinical counterpart, LC-1, has been shown to potentiate fludarabine lethality in chronic lymphocytic leukemia (CLL) cells.¹³ Clinical trials of LC-1 have recently been initiated in AML and are planned for CLL.

mTOR, the mammalian target of rapamycin, is involved in multiple critical cellular processes, including glucose and protein homeostasis. mTOR represents an important downstream component of the PI3K/AKT pathway and is involved in the regulation of diverse processes relevant to leukemia cells, including survival, proliferation, and protein synthesis, among others. Significantly, mTOR inhibition has been shown to target leukemia stem cells.¹⁴ RAD001 (everolimus) and numerous other mTOR inhibitors are currently being investigated in leukemia and other hematologic malignancies. Recent studies suggest they may be particularly effective in patients with NPM1 mutations.¹⁵ Combination trials of mTOR inhibitors with cytotoxic chemotherapy and other targeted agents are also underway. A number of reports indicate that inhibition of mTOR leads to a feedback response through an IGF1 receptor-related process, potentially leading to activation of Ras-Raf-MEK-ERK and possibly AKT itself.¹⁶ Thus, combinations of mTOR inhibitors with upstream inhibitors including those of IGF1 are being pursued and deserve attention in AML.¹⁷ mTOR has also been shown to reverse multidrug resistance phenotypes,¹⁸ a phenomenon that provides an additional rationale for incorporating mTOR inhibitors into the therapeutic armamentarium in leukemia.

Other Signaling Inhibitors

Farnesyltransferase inhibitors (FTI) represent a class of antitumor agents that block the oncogenic activity of Ras by interfering with Ras farnesylation, which is necessary for Ras membrane translocation and activity. While it is tempting to postulate that FTIs would be particularly effective in cells transformed by Ras mutations, whether or not this is the case remains to be determined. For example, Ras mutations are present in 10%-20% of AML patients,¹⁹ yet the relationship between Ras mutation status and response is not entirely clear. This raises the possibility that other Ras-farnesyl transferase targets may be involved in the activity of FTIs, eg, Rho proteins.

FTIs have shown activity in 5%-10% of patients 70 years and older, but this was not associated with an increase in overall survival.^{20,21} This was not sufficient for FDA approval. Nevertheless, there is still a great deal of interest in combining FTIs with cytotoxic chemotherapy, such as high-dose ara-C and idarubicin, and other targeted agents, both in the relapsed as well as maintenance setting.

Recently, attention has focused on identification of molecular signatures that might predict response to the FTI tipifarnib in AML. A 2-gene classifier, RasGRP1 and APTX, appears to predict for response and enhanced survival in a subset of patients with AML. RasGRP1 is a guanine nucleotide exchange factor that activates Ras, and APTX is involved in DNA excision repair. Ninety-two percent of patients who have a RasGRP1/APTX expression ratio greater than 2 responded to tipifarnib.²¹ This phenomenon may be analogous to the case of patients with EGFR mutations in lung cancer, who show a high response rate to EGFR inhibitors. Single-agent tipifarnib in high-risk MDS patients achieves responses comparable to those of standard epigenetic therapies, including hypomethylating agents, and for this reason, FTIs deserve further investigation in AML and MDS.

Epigenetic Agents

Histone deacetylase (HDAC) inhibitors represent prototypical epigenetic agents. They promote open chromatin structure and either enhance or downregulate gene expression. HDAC inhibitors are categorized as class I nuclear HDAC inhibitors, pan-HDAC inhibitors (which inhibit both class I nuclear and class II non-nuclear HDACs), and isoform-specific inhibitors,

such as HDAC6 inhibitors, which function as a tubulin deacetylase. The HDAC inhibitor vorinostat has been approved for use in cutaneous T-cell lymphoma,²² and there is emerging evidence that HDAC inhibitors, including both pan-HDAC inhibitors and class I HDAC inhibitors, have single-agent activity in leukemia.^{23,24}

A key question regarding the optimal utilization of HDAC inhibitors in AML/MDS is understanding the mechanism by which they exert their antileukemic effects. HDAC inhibitors are highly pleiotropic in their actions and act through multiple mechanisms (Table 2). For example, they can act at the level of chromatin structure, promoting reexpression of genes that are responsible for cell death or differentiation. They can also lead to downregulation of pro-survival genes, antagonize the actions of corepressors, and acetylate a variety of other proteins, including transcription factors. Acetylation of transcription factors has multiple effects on gene expression, including indirect epigenetic effects through modulation of the function of transcription factors themselves rather than solely modifying chromatin structure. HDAC inhibitors acetylate a wide variety of other proteins, including chaperone proteins, DNA repair proteins, and Ku70. These diverse actions can collaborate to either promote or inhibit cell death in human leukemia cells. The challenge will be how best to combine HDAC inhibitors and other targeted agents.

DNA methyltransferase (DNMT) inhibitors represent another prototypical epigenetic class of agents. DNMT inhibitors can reverse the methylation of CpG-rich promoter regions and induce reexpression of silenced genes implicated in differentiation and/or cell death.²⁵ Two DNMT inhibitors, azacitidine and deoxycytidine, are active in high-risk MDS,²⁶ and azacitidine has improved survival in high-risk patients.²⁷ However, it is still not entirely clear whether these agents act primarily through epigenetic or cytotoxic mechanisms, or possibly a combination of the two.

Significant interest has focused on combinations of HDAC and DNMT inhibitors in view of their multiple modes of action, as well as accumulating evidence that simultaneous hypomethylation of DNA and acetylation of histones can result in synergistic reexpression of silenced genes. Combinations of these agents have shown significant activity in patients with high-risk MDS and poor prognosis AML. These combinations include vorinostat and azacitidine, decitabine and valproic acid, azacitidine and MGCD0103, and three-agent combinations involving azacitidine, valproic acid, and all-trans retinoic acid.²⁸⁻³⁴ Nevertheless, a number of caveats and questions remain regarding the DNMT/HDAC inhibitor strategy. Notably, this combination therapy has had the greatest success in high-risk MDS/AML but is less effective in multiply treated, refractory patients. Numerous questions persist related to the further development of this strategy. For example, what is the optimal DNMT inhibitor to use in combination with HDAC inhibitors? What is the optimal type of HDAC inhibitor—class I, pan-HDAC, or HDAC-specific inhibitors? What are the optimal sequences and schedules? Are the mechanisms by which these regimens exert their antileukemic effects truly epigenetic? In fact, it would be surprising if the mechanisms were solely epigenetic in nature, as both HDAC inhibitors and DNMT inhibitors also act as cytotoxic agents. In this context, data are emerging suggesting that interference with DNA methyltransferase function can disrupt DNA repair complexes. As a result, it is conceivable that DNMT/HDAC inhibitor strategies may involve interactions at the DNA damage level as well as changes in the genetic background.

Transcription Factor Targets

Core binding factors (CBF) are heterodimeric transcription factors that are composed of a non-DNA-binding CBF β chain and a DNA-binding CBF α chain (RUNX1, RUNX2, RUNX3). Core binding factors are frequently targeted by translocations in leukemia, such as *AML1-ETO*. The

interaction between RUNX1 and CBF β can be disrupted by peptide inhibitors, culminating in cell death.³⁵ Small molecule peptide antagonists are currently being developed that inhibit proliferation and promote apoptosis in human leukemia cells. This strategy is analogous to peptide targeting of BCL-6 in non-Hodgkin's lymphoma or MLL-ENL9 in mixed lineage leukemias.

New Combination Strategies

Combination chemotherapy using novel agents that act at a variety of levels—signal transduction modulators, cell cycle modulators, epigenetic therapies—may provide the greatest potential for future approaches to leukemia and MDS. One such concept is HDAC and proteasome inhibition acting through a combination of factors, including inhibition of NF κ B, induction of aggresome dysfunction, and endoplasmic reticulum stress.³⁶ This concept has shown preliminary activity in multiple myeloma, and a trial is now underway in this disease with vorinostat and bortezomib.³⁷ A trial of bortezomib and vorinostat is also underway in MDS and AML.³⁸

The proteasome/HDAC inhibitor approach has also shown preclinical activity in primary AML cells. A phase I trial of belinostat, a pan-HDAC inhibitor, and bortezomib in patients with refractory AML or high-risk MDS is planned for fall of 2009.

Conclusion

A new paradigm is clearly needed in the therapy of acute leukemia and MDS. Salvage cytotoxic chemotherapy does not provide cures in most patients, and as a result, alternative approaches are necessary. A new generation of epigenetic agents, including histone methyltransferase inhibitors, histone demethylases, and histone acetylases, are currently being developed. For the immediate future, targeted therapy is now focusing on transcription factors, chromatin remodeling, signal transduction, and targeting of leukemia stem cells. In the future, it is possible that combination strategies incorporating more than one of these approaches will be necessary to meet the challenge of improving response to treatment in refractory AML/MDS. For example, numerous combination concepts can be envisioned involving a) more conventional cytotoxic agents; b) signal transduction modulators; and c) agents that target leukemia stem cells or developmental pathways. It is likely that the validity of such new approaches can be tested in the years to come.

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Table 1
New agents in AML and MDS

Category	Agents
Cytotoxic agents	Fludarabine Cladribine Clofarabine Laromustine
Tyrosine kinase inhibitors	FLT 3 inhibitors: CEP-701 (lestaurtinib) PKC412 (midostaurin) KW-2449 Sorafenib
Novel targets	PIM kinase: K00135 Parthenolide mTOR inhibitors
Other signaling inhibitors	Farnesyltransferase inhibitor: Tipifarnib
Epigenetic agents	DNA methyltransferase inhibitor: Azacitidine Deoxycytidine Histone deacetylase inhibitors: Belinostat Vorinostat
Transcription factor targets	Core binding factor
New combination strategies	HDAC and DNMT inhibitors: Azacitidine and vorinostat Azacitidine and MS-275 (entinostat) Decitabine and valproic acid Azacitidine and MGCD0103 3-agent combos: Azacitidine-valproic acid-all-trans retinoic acid HDAC and proteasome inhibition: Vorinostat and bortezomib Belinostat and bortezomib

Table 2
Multiple determinants of HDAC inhibitor-mediated lethality

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- Reactive oxygen species generation
 - Bid activation
 - Downregulation of antiapoptotic genes (BCL-XL, XIAP)
 - Upregulation of proapoptotic genes (BAX, BAK, BIM)
 - Induction of death receptors (DR4, DR5), FAS, TRAIL
 - Proteasome inhibition
 - Induction of p21^{CIP1}
 - Interference with Hsp90 function
 - Acetylation of Ku70; release of BAX
 - Disruption of G₂ and mitotic checkpoints
 - Activation of stress-related kinase (JNK)
 - Inactivation of cytoprotective pathways (Raf/MEK/ERK, AKT, BCR/ABL)
 - NF-κB activation/acetylation
 - Ceramide generation
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