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Review Article

Emerging Therapies in Cytogenetically Normal Acute Myeloid Leukemia

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Abstract

Acute Myeloid Leukemia (AML) is a clinically and biologically heterogeneous clonal disorder of hematopoietic progenitor cells that results in disturbed cellular growth, proliferation, and differentiation. Since the first published description of leukemia in 1827, continued advances in molecular biology have been paramount in deciphering the pathogenesis of disease. In AML, somatic mutations are often thought to contribute to leukemogenesis. Genetic variation in AML is measured using molecular karyotyping and has become the most important tool for risk stratification and defining prognosis. However, in approximately 40-50% of AML patients, no clonal chromosomal aberrations are detected. Such cases of cytogenetically normal AML (CN-AML) are currently categorized in the intermediate risk group, though much heterogeneity remains present within this group. Gene profiling by DNA analysis has further conferred prognostic significance in adult patients with CN-AML. The expansion of knowledge on the effects of genetic variation has provided new opportunities to develop a more personalized approach and tailoring treatment based on genetic characteristics. This review describes important genetic characteristics of CN-AML, and provides an overview of the therapeutic agents that are currently being investigated in the treatment of this disorder.

Keywords: Acute myeloid leukemia; Hematopoietic; Leukemia; DNA

Introduction

Acute myeloid leukemia (AML) is the second most common type of leukemia affecting adults and is responsible for the largest number of leukemia related deaths [1]. According to the American Cancer Society, the number of new cases of AML that will be diagnosed in 2015 is estimated to be 20,830, accounting for around 38% of all new cases of leukemias [2].

Over the last few decades, there has been an increase in the rates of remission and cure mainly due to the role of allogeneic stem cell transplantation (ASCT). Advances in the molecular testing of AML have led to the identification of a number of deregulated or mutated genes that are associated with favorable, intermediate or unfavorable prognoses resulting in improved AML risk stratification. However, the treatment outcomes remain variable. There remains a need to identify disease specific markers to allow for a more personalized, targeted therapeutic approach. At present, targeted therapy is primarily restricted to the application of all-trans retinoic acid (ATRA) in patients with acute promyelocytic leukemia (APL) with the t (15;17)/PML-RARA.

NPM1

Nucleophosmin 1 (NPM1) is one of the most abundant, multifunctional, phosphor proteins in the nucleolus. As NPM1 shuttles constantly from the nucleolus and cytoplasm, its serves as a histone chaperone, essential in facilitating ordered assembly of nucleosomes. In addition, it is thought to be a major contributor in the processes of DNA replication, recombination, transcription, and repair [3].

NPM1 interacts with the tumor suppressor p14ARF and p53, influencing cellular apoptotic responses [3]. Abnormalities in the NPM1 gene, via translocation or heterozygous deletion in the N-terminal region, have been associated with numerous malignancies, including ALCL, MDS, and APML [4]. Mutations specifically in exon 12 cause abnormalities in biogenesis and transport of ribosomes, DNA repair, genomic stability, endoribonuclease activity, and apoptosis. Such aberrations are detectable in 45-62% of CN-AML, with the incidence of NPM1 mutation increasing with age until the age of 60 years [5,6].

Accounting for approximately 75-80% of cases, mutation A is a duplication of a 4 based sequence TCTG at position 956 to 959 of the NPM1 sequenced gene [7]. This duplication results in a slightly longer protein with a different C-terminal amino acid sequence. Consequences of this change promote aberrant cytoplasmic localization of the NPM1 leukemic mutants through generation of new leucine rich nuclear export signal motifs. In addition, there is also a loss of the two tryptophan residues 288 and 290 which prevents the correct folding of the C-terminal domain and thus prevents nucleolar localization [8].

Targeted therapies for mutated NPM1 have been discussed including interfering with the mutant NPM1 trafficking system, disrupting the nucleolar integrity by interfering with residual wild type NPM1 and evaluating the benefit of epigenetic drugs such as 5-azacytidine that act on differentiation and apoptosis.

NPM1 has also been shown to act as a measurement of minimal residual disease and has potential to be used as an early marker for relapse before overt hematological relapse can be documented,

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allowing for earlier initiation of treatment [9].

A small molecular inhibitor, NSC348884, which disrupts the wild type and mutant NPM1 dimer formation, was found to have efficient cytotoxicity on several different cancer lines by up regulating p53 in a dose-dependent manner and inducing apoptosis. Furthermore, NSC348884 synergized with doxorubicin cytotoxicity on cancer cell viability [10]. It has since been shown that down regulation of mutant NPM1 also induces differentiation and apoptosis, while sensitizing AML cells to ATRA and Cytarabine [11]. In contrast, normal CD34 progenitor cells not carrying NPM1 mutation are relatively unaffected.

Development of drugs targeting the abnormal traffic of the NPM1 mutant is hampered by several hurdles. NPM1 mutations are always heterozygous, suggesting that a certain amount of wild type NPM1 may be necessary for leukemic survival. An alternative possibility is that NPM1 mutations hinder the function of residual wild-type NPM1 encoded by the normal allele [12]. Experimental evidence has demonstrated that complete deletion of the NPM1 gene in knockout mice leads to unrestricted centrosome duplications, genomic instability, and ultimate death [5].

CEBPA

The CCAAT/enhancer binging protein alpha (CEBPA) is a transcription factor important in regulating differentiation of myeloid progenitor cells.

Two significant types of mutations in the CEBPA gene have been identified in 15% CN-AML cases and subsequently lead to the failure of granulocyte differentiation. In-frame mutations in the C-terminal region lead to decreased DNA- binding or dimerization activity [13]. Nonsense mutations affecting the N-terminal region of the molecule result in an abbreviated isoform with dominant negative properties [14].

Approximately one-third of CEBPA-mutated AML patients carry a monoallelic CEBPA mutation (moCEBPA). The remaining two-third of cases are biallelic CEBPA gene mutations (biCEBPA) and usually harbor an N-terminal mutation on one allele and a C-terminal mutation on the second allele. The CEBPA (biCEBPA) genotype appears to be associated with improved overall survival after intensive chemotherapy [15]. Patients, on the other hand, carrying a monoallelic CEBPA mutation (moCEBPA), show no different outcome compared to patients with wild type CEBPA, and these mutations are frequently associated with mutated NPM1 or FLT3-ITD [16].

Targeted therapies for mutated CEBPA have remained elusive. However, more recently, re-activation of the CEBPA signature in a CEBPA dysfunctional subset of patients has prompted the search for small molecules with the ability to reverse the low expression of the CEBPA signature. In a cohort of 525 patients, histone deacetylase inhibitors have been shown to reactivate expression of the CEBPA signature and promote granulocytic differentiation in the aforementioned CEBPA dysfunctional subset of patients, primarily harboring biCEBPA [17].

Finally, pharmacologic restoration of function via DNA hypomethylation has given promise to the use of azacitidine or decitabine in reactivating silenced tumor suppressor genes by epigenetic event. Further exploration in identifying biomarkers of hypomethylation action is necessary in advancing an era of personalized medicine in CN-AML [18].

FLT3

FMS-like receptor tyrosine kinase 3 (FLT3) is a class III receptor tyrosine kinase (RTK) and exists in two forms: glycosylated membrane bound and un-glycosylated non-membrane bound. While the human FLT3 gene is located on chromosome 13 and contains 34 exons, the receptor is expressed on hematopoietic stem cells, the brain, placenta, and liver and particularly of a high proportion of AML and B-ALL. Its associated ligand plays a role in enhancing cellular proliferation and reducing apoptosis. Several unique mutations of FLT3 gene have been discovered; the most studied being an internal tandem duplication (ITD) in the juxtamembrane (JM) domain coding sequence.FLT3-ITD is formed when a JM fragment is duplicated in a direct head-to-tail orientation, sometimes with additional nucleotides inserted. The transcripts preserve the frame and produce a functional kinase with an elongated JM region [19]. Another well described gene aberration, FLT3-TKD, involves point mutations leading to single amino acid substitutions that occur within the activation loop of the tyrosine kinase domain [20]. There is less of a clear pattern with FLT3/TKD mutations, which are reported to occur in approximately 7% of patients, and seem to be more common in cytogenetically favorable risk AML [21].

FLT3-ITD is mutated in 30-40% of patients with AML and consequently has become one of the most studied mutations in CN-AML [22]. Unfortunately, it is associated with a higher WBC, LDH, peripheral blood and bone marrow blast count at presentation but more importantly, an inferior disease free survival in patients younger than 60 compared to patients with FLT3-Wild Type (WT) [23]. The ratio of WT to mutant FLT3 as well as its location may also have prognostic significance with higher proportion of FLT3 transcripts being associated with poorer prognosis.

In a study of 91 patients (55 FLT3-WT and 36 FLTs-ITD), a group of patients received supportive care and/or experimental therapies while the remaining received induction chemotherapy, followed by allogeneic SCT. Advanced age was associated with shorter overall survival (OS) and intensive therapy was associated with improved OS. FLT3-ITD was associated with shorter OS compared to FLT3-WT [24].

There is evidence that persistent low levels of FLT3-ITD can be associated with increased likelihood of relapse in patients with otherwise good prognosis [25]. A retrospective analysis of patients with CN-AML in the first clinical remission with FLT3-ITD indicated increased relapse incidence and decreased leukemia free survival (LFS) compared with FLT3-WT. The increase in relapse incidence was observed independent of other variables such as stem cell source or donor type. This effect does not appear to be related to lower GVHD incidence or higher use of *in vivo* T-cell depletion, confirming the negative influence of this mutation in allogeneic-HSCT. The adverse impact of FLT3-ITD on transplantation does not seem to preclude indication of the procedure if they have identical sibling. A two-year LFS of 58% and relapse incidence of 30% was far better than outcomes following chemotherapy, with a 2.5month median survival [26].

FLT3 is an important target for therapy of different types of leukemia. Several small molecule kinase inhibitors with activity against FLT3 are currently under clinical investigation in patients with AML as single agents and in combination with intensive chemotherapy, e.g. midostaurin (PKC412), lestaurtinib (CEP-701), sunitinib (SU11248) and sorafenib (BAY 43–9006) [27]. However, these agents only induce partial remission and development of resistance has been reported. Potent and novel dual FLT3/PDGFR combination tyrosine kinase inhibitors are still being screened and under investigation for their efficacy in AML [28].

In a large international phase III study, Midostaurin, a semi-synthetic derivative of staurosporine, is being evaluated in conjunction with both induction (Daunorubicin/Cytarabine) and consolidation (High-Dose Cytarabine) chemotherapy in newly diagnosed patients < 60 Years of Age With FLT3 Mutated Acute Myeloid Leukemia (AML). Prior phase II clinical trials have shown that midostaurin has significant activity in both patients with FLT3-mutatnt and wild-type, as reflected by a decrease of peripheral blasts count by 50% [29].

The TKI lestaurtinib has demonstrated biologic activity and measurable clinical response in patients with relapsed or refractory FLT3 mutated AML. Unfortunately, responses remained short lived and in combination with cytarabine and Idarubicin in young patients, it failed to increase survival [30].

Sunitinib, a well-known, small-molecule, multi-targeted receptor tyrosine kinase inhibitor has been approved for both renal cell carcinoma and imatinib resistant gastrointestinal stromal tumor. In a phase I/II clinical study, the use of sunitinib in combination with standard induction and consolidation therapy, specifically in elderly patients with AML with activating FLT3 mutations was evaluated. The CR rate in AML with FLT3-ITD was 53% (8/15) and was 71% (5/7) in those with FLT3 -TKD. 13 patients how attained a CR received repetitive cycles of high-dose Cytarabine consolidation therapy, and seven proceeded to single-agent sunitinib maintenance therapy (median duration, 11 months; range, 1 – 24 months). Within this study, median survival was 18.8 months, median relapse-free survival 11 months, and two patients are in sustained CR [31].

Sorafenib, another multi-kinase inhibitor with activity against several oncogenic kinases, has *in-vitro* data as well as results from clinical trials that suggest it may be an effective drug in certain AML patients. The results of the randomized, placebo-controlled SORAML trial were recently released. Versus placebo as an add-on to standard induction and consolidation treatment in AML patient's ≤60 years, sorafenib treatment resulted in a significantly prolonged EFS and RFS, though at a cost of significantly higher risks for fever, bleeding events and HFS. Unfortunately, in 46 FLT3-ITD positive patients, no difference in EFS, but a trend for prolonged RFS and OS in favor of sorafenib was observed [32].

In the first of its kind, a phase I clinical trial, originally opened in 2010 and now having recently completed enrollment, the use of plerixafor, G-CSF and sorafenib to mobilize and kill leukemic cells, respectively, was tested. Eligible patients were 18 years or older and had relapsed or refractory FLT3-ITD AML. The participants received injections of plerixafor (240 mg/kg) and G-CSF (10 mg/kg) every other day on days 1–13 and oral sorafenib (400–600 mg) twice daily in 28-day cycles. The encouraging combination resulted in overall response rate for patients of 62%, with 28% complete remissions, and another 33% having partial remissions. Most common side effects included hyperleukocytosis, HFS, hypertension, and diarrhea; however there were no treatment-related deaths [33].

Quizartinib, a second generation, selective inhibitor of class III receptor tyrosine kinases, has achieved high response rates in difficult to treat cohort of patients. In the phase II ACE trial, two cohorts of patients were enrolled. In cohort 1 patient were 60 or older with the FLT3 mutation and had a recent first relapse or whom standard chemotherapy had failed. In cohort 2, patients were over the age of 18 and presenting with relapsed or refractory AML and had been given salvage chemotherapy after failure of prior treatment or relapse after a stem cell transplant. The majority of patients in both cohorts had the FLT3 mutation. In the older cohort 1, monotherapy with quizartinib, resulted in complete responses in more than 50% of elderly patients with FLT3 mutation–positive disease, allowing some patients to be bridged to stem cell transplant. Of note, slightly less than one-third of FLT3 mutation–negative patients attained a complete response as well [34].

In the FLT-3 positive cohort 2, quizartinib was given once daily at a starting dose of 90 mg/d in women and 135 mg/d in men in 28-day cycles until disease progression or unacceptable toxicity. The complete response rate was 46% in 100 patients with FLT3 mutation–positive disease and 32% in FLT3 mutation–negative patients [35]. Quizartinib permitted 37% of all patients to continue on to stem cell transplant. Amongst transplanted patients, median overall survival was 33.3 weeks, vs. 17.7 weeks for those who did not undergo transplant. Twenty-three patients (23 percent) are considered "long-term survivors" after having remained alive for more than 12 months.

Currently, a randomized comparative Phase 3 trial of quizartinib in relapsed/refractory AML patients with the FLT3-ITD mutation, titled QUANTUM-R is being conducted and actively recruiting participants [36].

IDH

IDH1/2(human cytosolic isocitrate dehydrogenase 1 and mitochondrial isocitrate dehydrogenase 2 upon discovery, were thought to cause loss of enzyme's normal ability to catalyze conversion of isocitrate to alpha-ketoglutarate [37]. However, investigators have uncovered a neomorphic gain-of-function, that leads to production of the oncometabolite (R)-2-hydroxyglutarate (2-HG), normally only found in trace amount in normal cells [38].

The discovery of 2-HG has provided a mechanism for how IDH mutations could initiate and drive multiple cancer types, serving as a potent oncogene [39].

Somatic IDH mutations have been identified in subgroups of patients across a broad range of solid and hematologic tumors, including but not limited to gliomas, chondrosarcoma, melanomas, prostate, colon, and lung cancers, lymphomas, and AML [40]. In patients with AML, IDH1 mutations are found in 4.4-9.3% of samples, and IDH2 mutations are found in 10.9%-16% of samples and are generally associated with normal cytogenetics [41]. Prognostic data for IDH are inconsistent, however most reports conclude either

a negative or no prognostic effect on overall survival for either mutation. Nonetheless, targeted inhibition of mutant IDH enzymes resulting in a reduction of 2-HG has the promise to deliver clinical benefit in patients with these mutations. AG-120 is a first in class, orally available, potent, reversible and selective inhibitor of IDH1 mutant enzyme. AG-221 serves as its twin, selectively inhibiting IDH2 mutations [42-45].

In a phase 1 trial of AG-120, out of 14 patients with relapsed and/or refractory AML, the medication was well tolerated and objective responses were seen in 50% of patients including four complete remissions with early evidence of durability [46].

AG-221 is also being assessed in a dose-escalation, phase 1 trial that now comprises 73 patients with advanced hematologic cancer, including 55 with relapsed/refractory AML and 5 with untreated AML. In 45 evaluable patients, the overall response rate was 56% including 15 complete response, 10 partial responses, and 17 patients with stable disease throughout the treatment period [47].

With safety data showing both drugs as being well tolerated and the majority of adverse events as either grade 1 or 2, both AG-120 and AG-221 have been granted Fast Track designation. A global, registration-enabling Phase 3 study is scheduled to begin in early 2016.

MLL

The MLL gene (mixed lineage leukemia) encodes a protein that plays a vital role in early development and hematopoiesis by working as a histone methyltransferase and transcriptional co-activator [48]. Among others it activates aberrant transcription DOT1L, which is considered a driver of leukemogenesis [49].

Partial tandem duplication of the myeloid/lymphoid or mixed lineage leukemia gene, (MLL-PTD), was the first molecular aberration associated with negative prognosis in CN-AML [50]. These duplications consist of an in-frame duplication of MLL exons. MLL-PTDs are named according to the fused exon 9 and exon 3. A few of these tandem duplications appear to be created by mispairing of Alu elements, which are recurring regions with high homology [51]. These intragenic MLL abnormalities, occurring primarily in CN-AML, are detected in about 5 to 10% of these patients and usually involve exon 5 to exon11 or, less commonly, exon 5 to exon12 [52]. MLL fusions involving AF9, AF10, and ENL account for the bulk of MLL rearranged AML. These resulting product recruit multiprotein complexes essential for transcriptional activation/elongation, such as that comprising the H3K79 methyltransferase DOT1L [53,54].

Placke et al, have recently demonstrated that AML cells driven by MLL-AF9 are remarkably dependent on the cell-cycle regulator CDK6, but not its functional homolog CDK4, and that the favored growth inhibition induced by CDK6 depletion is mediated through enhanced myeloid differentiation [55]. Translational implications are rapidly evolving, with a clinical phase I/IIb, open label trial of Palbociclib, an oral inhibitor of CDK4/CDK6, in MLL-rearranged acute leukemia currently pending [56].

Conclusion

CN-AML comprises the single largest subgroup of AML with patients having heterogeneous disease at the cytogenetic and molecular levels.

Key discoveries have been made since the turn of the century those have led to a better understanding of the molecular pathogenesis of AML as well as to an improvement in the risk stratification of this disorder. Clinical medicine is at the cusp of a new age in AML therapy, where treatment may become highly targeted and personalized.

Moreover, mutations such as NPM1, FLT3 or CEBPA have been found to not only provide significant prognostic information but have also helped guide physicians along certain algorithms involving post-remission care. It is imperative that mutation analysis should be part of the diagnostic work-up of every newly diagnosed AML patient.

We have only just started to unravel the vast genetic diversity of AML. Traditional cytotoxic chemotherapy used in induction as well as post remission regimens have and may continue to serve as the backbone for treatment. However, new small molecules with tolerable side effects are coming to the forefront and hopefully will soon result in improved outcomes of AML patients.

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