Review

Azacitidine Use for Myeloid Neoplasms

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Abstract

Azacitidine and decitabine are hypomethylating agents frequently used interchangeably to treat myeloid neoplasms in different settings. Azacitidine is metabolized intracellularly into decitabine. Hypomethylating agents work by inhibiting DNA methyltransferases, causing demethylation of aberrantly methylated promoter regions of genes involved in the pathogenesis of myeloid neoplasms. Azacitidine was the first agent approved by the US Food and Drug Administration for treatment of myelodysplastic syndrome in 2004, after which, the use of azacitidine in other myeloid neoplasms increased significantly. It is a well tolerated agent and can be safely administered in the outpatient setting, which makes it an attractive choice for patients as well as physicians. In this review we summarize the published literature about the use of azacitidine in myeloid neoplasms, and shed the light on some ongoing trials.

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Introduction

Azacitidine is a nucleoside analogue that was manufactured in the 1960s. The original Investigational New Drug application for azacitidine was submitted by the National Cancer Institute in 1971 to the US Food and Drug Administration (FDA) for various antineoplastic indications.[1] Epigenetics is the change in gene expression without DNA sequence alteration.[2] DNA methylation and histone modifications are the primary, potentially reversible, epigenetic modifications. DNA methyltransferases (DNMT) mediate methylation by incorporating a methyl group into position 5 of the cytosine ring resulting in 5-methyl cytosine. This modification occurs most frequently in cytosines that precede guanosine in the DNA sequence called cytosine phosphodiester guanine dinucleotides that occur in asymmetric clusters called cytosine phosphodiester guanine islands.[3,4] These islands are often associated with the promoter regions of genes[5] and are usually unmethylated irrespective of whether the gene is being transcribed.[6] Aberrant methylation of such promoter regions can occur in disease, particularly cancers and correlates with gene silencing.[7] Azacitidine inhibits DNMT causing demethylation.[8] It is incorporated into DNA as well as RNA. In DNA it irreversibly binds DNMT, leading to loss of its activity,[9] which results in almost complete demethylation of genomic DNA.[10] The DNMT and azacitidine adducts are also toxic and mutagenic.[11] In vitro azacitidine leads to chromosomal instability, decondensation of chromatin, and extends the replication time of normally late replicating heterochromatin.[12] At high doses azacitidine is cytotoxic whereas at lower doses it induces differentiation and demethylation.[9] The discovery of hypermethylation of the *p15(INK4B)* gene in myelodysplastic syndrome (MDS)[13,14] suggested that azacitidine might be effective in the treatment of MDS. Several other hypermethylated genes have been implicated in the pathogenesis of MDS, including *p15(INK4B)* gene, which is involved in cell cycle regulation,[15] dedicator of cytokinesis 4, a GTPase regulator,[16] and *GATA* binding protein 2, a transcription factor involved in erythropoiesis.[17] Additionally a number of genes that regulate DNA methylation and histone function are mutated in patients with MDS (*tet methylcytosine dioxygenase 2*, *isocitrate dehydrogenase*, *enhancer of zeste homolog 2*, *additional sex combs like 1*, *DNMT3a*).[18-22] Although hypomethylating agents (HMAs) seem like a promising treatment in MDS, resistance frequently occurs leading to short responses. The in vitro resistance results from failure to incorporate azacitidine into the DNA,[23] whereas in vivo resistance is multifactorial and mainly due to preexisting genetic instability or the emergence of resistant clones after therapy.[24]

Azacitidine and MDS

Myelodysplastic syndromes are neoplastic stem cell disorders characterized by clinical bone marrow failure, cytopenias, morphologic dysplasia, and tendency to progress to acute myeloid leukemia (AML). MDS are categorized and classified morphologically by the French-American-British (FAB) and World Health Organization[25,26] classifications. Prognosis is determined by using the International Prognostic Scoring System (IPSS).[27] Patients with

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MDS who have intermediate-2 or high-risk scores on the IPSS (known as higher-risk MDS) have a median survival of 1.2 years and 0.4 years, respectively,[27] and a high risk for progression to AML.[27] Although increasing survival and suppression of leukemic transformation are the primary goals of treatment,[28] no treatment strategies other than allogeneic hematopoietic cell transplantation (allo-HCT) offers cure. Because of disease heterogeneity, establishing standard response criteria was difficult. Old trials used different response criteria, and interpreting results was difficult. Currently responses are categorized on the basis of the International Working Group standardized response criteria first published in 2000 and modified in 2006.[29,30] In clinical practice hematological improvement is the goal when treating lower-risk MDS with HMAs and therapy is usually discontinued after 4 to 6 cycles if no response is seen.[31] For higher-risk MDS, response is assessed after 4 cycles of HMAs and patients with stable disease or better response continue therapy.[31,32]

In 2004 the FDA approved injectable azacitidine for treatment of patients with the following MDS subtypes: refractory anemia or refractory anemia with ringed sideroblasts (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia.[1] Azacitidine was the first agent approved for treatment of MDS. Before azacitidine, the mainstay of therapy was supportive care (except in patients eligible for allo-HCT); therapy with high-dose cytotoxic agents yielded disappointing results. Three multicenter Cancer and Leukemia Group B (CALGB) trials[33-35] and multiple single-center trials[36-38] showed azacitidine activity in MDS.

In the CALGB 8421 trial (phase I), the overall response rate (ORR) to intravenous azacitidine was 49%, similarly in the phase II trial (CALGB 8921) the ORR with subcutaneous azacitidine was 53%. The CALGB 9221, a randomized, multicenter, open-label trial compared the safety and efficacy of subcutaneous azacitidine with supportive care in patients with any of the 5 MDS subtypes.[33] The ORR for subjects randomized to azacitidine was 60% compared with 5% among subjects randomized to supportive care ($P < .0001$). The ORR in subjects who crossed over to azacitidine treatment was 47% compared with 5% in patients who remained in the observation arm. The clinical benefit of response to azacitidine treatment was shown in long-lasting increases in blood counts, which made transfusions unnecessary; decreased bone marrow blast percentages were similarly long-lasting. No overall survival (OS) benefit or delay in progression to AML was noted in this trial because of the crossover design.

The AZA-001 (phase III randomized trial) established the use of azacitidine as standard of care for higher-risk MDS patients. This study randomized 358 higher-risk MDS patients to receive azacitidine (n = 179) or conventional care (n = 179).[39] The control arm included the 3 most commonly used treatments in high-risk MDS (supportive care, low-dose cytarabine, or intensive chemotherapy). The median OS was 24.5 months for the azacitidine group versus 15 months for the conventional care group ($P = .0001$). At 2 years, on the basis of Kaplan–Meier estimates,91 patients (50.8%) in the azacitidine group were alive compared with 47 patients (26.2%) in the conventional care group ($P < .0001$).[39] This large, prospective, randomized, phase III trial confirmed the OS benefit with azacitidine. The OS benefit with azacitidine was seen across all prognostic subgroups, including patients with poor, intermediate, and good cytogenetics according to the IPSS. The survival advantage in the azacitidine group was observed early in the treatment course compared with conventional care, with separation of the Kaplan–Meier survival curves occurring after 3 months of treatment, corresponding to completion of 3 cycles of azacitidine. The difference in median OS between the azacitidine and intensive chemotherapy groups was not statistically significant, possibly because of the small number of patients in this analysis (n = 25 patients who had intensive chemotherapy). The proportion of patients with complete remission with intensive chemotherapy (40%) was in the range of published reports of MDS[40-44] and higher than that observed with azacitidine in the CALGB studies.[33] Use of azacitidine in lower-risk MDS had been mainly limited to the United States, where original approval by the FDA on the basis of CALGB studies included all FAB subtypes. In the lower-risk population, with refractory anemia relapsing after or resistant to erythropoietic stimulating agents, azacitidine alone showed superiority over azacitidine with epoetin-β in an intention to treat randomized phase II trial with an ORR of 34.7% versus 24.5%, after 6 cycles of azacitidine. Patients with mutated splicing factor 3b subunit 1 showed a significant erythroid response.[45] Azacitidine (75 $mg/m^2/d$) for 7 days every 4 weeks is the approved dosing schedule. For lower-risk MDS the 5-day azacitidine schedule was as efficacious and less toxic than the 7- or 10-day schedule.[46] The MDS clinical consortium is currently examining 3 days azacitidine, 3 days decitabine versus 5 days azacitidine in lower-risk MDS.

CC-486, the oral formulation of azacitidine, is in clinical development. A phase I/II clinical trial tested the safety and efficacy of oral azacitidine (300 mg daily on different schedules) in patients with lower-risk MDS. Twenty-eight patients received the 14-day dosing schedule, whereas 27 patients were given the 21-day dosing schedule. The study reported good tolerability and better long-term effectiveness of the extended dosing schedule.[47]

The QUAZAR (Efficacy of Oral Azacitidine Plus Best Supportive Care as Maintenance Therapy in Subjects With Acute Myeloid Leukemia in Complete Remission) trial, a phase III randomized clinical trial, is currently evaluating the extended-dose schedule of oral azacitidine versus placebo in lower-risk MDS patients.[48] Phase I trials have already shown the clinical and biological activity of CC-486 in this subgroup of patients.[49,50] The combination of azacitidine with lenalidomide or with vorinostat versus azacitidine monotherapy in higher-risk MDS patients did not show any difference in ORR or OS between the groups in a phase II randomized trial (subgroup analysis showed potential survival benefit for the combination arms in patients with normal cytogenetics or chromosome 5 abnormalities).[51] The prognosis of MDS patients after HMA failure is dismal, and a limited number of these patients ultimately receive subsequent lines of therapy. Different groups have published retrospective reviews addressing the outcomes of patients in whom HMAs fail. Regardless of the risk category (low or high), the survival is very limited after failure (approximately 17 months for low-risk, approximately 5 months for high-risk).[52-56] Currently there is no standard salvage therapy after HMA treatment failure; the best outcomes are achieved by enrolling patients in clinical trials or by allo-HCT if feasible.