Adv Ther (2011) 28(Suppl.3):1-9.
DOI 10.1007/s12325-011-0002-8

REVIEW

Azacitidine for the Treatment of Patients with Acute Myeloid Leukemia with 20%-30% Blasts and Multilineage Dysplasia

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Received: September 13, 2010 / Published online: March 9, 2011

ABSTRACT

Azacitidine is approved in the EU for the treatment of adult patients who are not candidates for allogeneic stem cell transplantation, and who have intermediate-2 risk or high-risk myelodysplastic syndromes, according to the International Prognostic Scoring System. The approval includes the treatment of patients with acute myeloid leukemia (AML) with 20%-30% blasts and multilineage dysplasia, according to the World Health Organization (WHO) classification. This review focuses on the outcomes with azacitidine in this latter group of patients, previously classified as refractory anemia with excess of blasts in transformation, as defined by the French-American-British classification criteria. The main clinical evidence is based on the results of two large phase III clinical trials (Cancer and Leukemia Group B 9221, and AZA-001). The AZA-001 trial shows azacitidine significantly prolongs median overall survival in older patients with low marrow blasts (20%-30%) according to WHO-defined AML, and significantly improved several patient morbidity measures, compared with conventional care regimens. In addition, the review examines the results of azacitidine in combination with other treatments currently used in AML.

Keywords: azacitidine; acute myeloid leukemia; myelodysplastic syndromes

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INTRODUCTION

Azacitidine is a pyrimidine nucleoside analog of cytidine, with antineoplastic activity, attributed to different mechanisms. The drug inhibits DNA methyltransferase, resulting in hypomethylation and transcription of quiescent genes, and shows a cytotoxic effect on abnormal hematopoietic cells in the bone marrow.[1,2] It was approved by the US Food and Drug Administration (FDA) in May 2004 for the treatment of myelodysplastic syndromes (MDS). In March 2009, azacitidine was also approved by the European Medicines Agency (EMA) for patients who are not eligible for an allogeneic hematopoietic stem cell transplantation (SCT) with the following diagnoses: intermediate-2 or high-risk MDS according to the International Prognostic Scoring System (IPSS),[3] or chronic

myelomonocytic leukemia with 10%-29% blasts without myeloproliferative disorder, or patients with acute myeloid leukemia (AML) with 20%-30% blasts and multilineage dysplasia according to the World Health Organization (WHO) classification.[4]

The recommended dose of azacitidine is 75 mg/m^2/day subcutaneously for 7 days, every 28 days, for at least six cycles.[5] Treatment should be continued as long as it benefits the patient, until disease progression or the development of unacceptable toxicity. The most common grade 3 or 4 adverse events (AEs) in patients receiving azacitidine are peripheral cytopenias. Injection-site reactions and gastrointestinal side effects are frequent nonhematological AEs.[6]

This is a review of the clinical evidence of treatment with azacitidine in patients with AML and multilineage dysplasia with blasts between 20% and 30%. These patients have a particularly poor prognosis, and conventional treatments such as chemotherapy yield disappointing outcomes.[7] In addition, they are usually older and have comorbidities, which are associated with high mortality from intensive chemotherapy.[7-9] Moreover, the responses of patients eligible for intensive chemotherapy are of short duration, with median survivals of 5 to 13 months.[9-11]

The most reliable evidence for treatment with azacitidine is obtained from phase III studies. Additionally, we examine the outcomes of compassionate use programs and of trials combining other treatments.

PHASE III CLINCAL TRIALS WITH AZACITIDINE

The results of two large phase III clinical trials, Cancer and Leukemia Group B (CALGB) 9221[12] and AZA-001,[6] were deciding factors for the approval of azacitidine by the FDA and EMA, respectively.

In 1984, the CALGB began a series of clinical trials with azacitidine. The first phase II study, CALGB 8421,[13] included 48 patients with refractory anemia with excess blasts (RAEB), or RAEB in transformation (RAEB-T) according to the French-American-British (FAB) classification criteria.[14] Azacitidine 75 mg/m^2/day was administered by intravenous infusion for 7 consecutive days in a 28 day cycle. The next study was CALGB 8921, including 70 patients with MDS,[15] where the drug was administered by subcutaneous injection. Finally, the CALGB 9221, a phase III randomized clinical trial comparing azacitidine and supportive care for patients with MDS. A total of 191 patients with a median age of 68 years were randomized to receive azacitidine 75 mg/m^2/day subcutaneously for 7 days every 28 days, or supportive care. Most of the patients had RAEB or RAEB-T. Responses were observed in 60% of patients in the azacitidine arm: 7% complete response (CR), 16% partial response (PR), and 37% hematologic improvement. Median time-to-progression to AML or death was 21 months for azacitidine, compared with 12 months for supportive care (P=0.007). Patients in the supportive care arm whose disease worsened after 4 months were permitted to cross over to azacitidine, and responses were observed in 47% of these patients. Additionally, patients treated with azacitidine experienced significant improvement in quality of life, in specific aspects such as physical functioning, fatigue, and dyspnea.[16]

These three trials conducted by the CALGB were designed following the FAB criteria, and included a large number of patients with RAEB-T. According to WHO criteria, RAEB-T is reclassified as AML with multilineage dysplasia, and with blasts between 20% and 30%.

In 2006, CALGB reanalyzed the results of protocols CALGB 8421, 8921, and 9221 by applying the WHO classification and the

International Working Group (IWG) criteria for response.[15] The three studies encompassed 309 patients, of whom 268 were treated with azacitidine, and 41 were offered the best supportive care in the observation arm of protocol CALGB 9221.

Using WHO criteria, 103 patients were reclassified as AML, 90 of whom received azacitidine. Overall, 33 patients with AML according to WHO criteria achieved some degree of response.

Protocol CALGB 9221 included 27 patients with AML (per WHO criteria) in the azacitidine treatment arm, and 25 in the supportive care arm (13 of whom were treated with azacitidine after the observation phase). The median survival of patients in the azacitidine arm was 19.3 months, compared with the 12.9 months in the supportive care arm. The rate of CR was 7%, and the overall rate of response, including CR, PR, and hematologic improvement, was 36% for these patients with AML. Although the number of patients who achieved complete remission was lower than expected for AML patients on chemotherapy, survival was prolonged to 19.3 months. These results led the authors to suggest that azacitidine can affect the natural history of the disease independently from complete remission. Additionally, there was no increase of infection or hemorrhage in the azacitidine group beyond what is expected for AML patients.

AZA-001 was a phase III, international, randomized study with 358 patients with high-risk MDS; 113 (about one-third of the study cases) had AML with trilineage dysplasia.[6] Treatment with azacitidine at a dose of 75 mg/m^2/day for 7 days every 28 days was compared with conventional treatment with three standard therapeutic options: supportive care, low-dose cytarabine, or intensive chemotherapy combining cytarabine and one anthracycline. The conventional treatment was selected by the researcher before randomization according to the patient's age, performance status, comorbidities, and preferences. A total of 179 patients were assigned to the azacitidine group, and 179 were assigned to the conventional treatment group. Analysis of results used the intent-to-treat population. Patients received a median of nine cycles. Treatment was discontinued in case of relapse, disease progression, or toxicity; 86% of patients remained on the planned dose. In responders, a median of 14 cycles were administered. After a follow-up of 21 months, the median survival in the azacitidine arm was 24.5 months, versus 15 months in the conventional treatment arm (P=0.0001). At 2 years, overall survival was 50.8% in the azacitidine arm, versus 26.2% in the conventional treatment arm (P<0.0001).

In the analysis by treatment subgroups, the survival of those treated with azacitidine was significantly longer than that of patients on low-dose cytarabine and those on supportive care. In contrast, no significant differences were found between the survival of patients on azacitidine and those receiving chemotherapy. However, this group had a small number of patients: 17 in the azacitidine arm, and 25 in the chemotherapy arm.

The improvement in survival with azacitidine was observed in all IPSS cytogenetic groups. Specifically, patients with a -7/7q- abnormality who were treated with azacitidine achieved a median survival of 13.1 months, compared with 4.6 months in the conventional treatment arm.

The results of study AZA-001 also suggested that prolonged survival is not a result of CR, and that the rate of response increases with the number of cycles administered, with 90% of responses happening after nine treatment cycles.

A subanalysis of the AZA-001 study, regarding elderly patients with AML and 20%-30% bone marrow blasts, was recently published.[17] One

hundred and six cases were assessed, of which 53 received a median of eight cycles of azacitidine, and 53 received conventional treatment (25 patients treated with best supportive care, 18 patients treated with low-dose cytarabine, and 10 patients treated with intensive chemotherapy). The median age was 70 years. The median survival of patients treated with azacitidine was 24.5 months, versus 16 months for the conventional treatment group (*P*=0.004). The overall 2-year survival rate was 50% in the azacitidine group and 16% in the conventional treatment group. No significant difference was observed for azacitidine versus low-dose cytarabine, with median overall survival of 24.5 versus 17.0 months. Median overall survival was not reached for azacitidine (*n*=5), compared with 14.2 months for intensive chemotherapy. The group of intensive chemotherapy was the smallest, because most of patients (86%) were considered unfit for intensive chemotherapy. Regarding data previously published, the 2-year overall survival rate (50%) observed with azacitidine in this trial is higher than that reported in elderly patients with AML, irrespective of treatment. Indeed, considering the experience with patients treated with intensive chemotherapy, despite reported CR rates up to 60%, median overall survival (OS) ranged from 7 to 12 months, with 2-year OS rates of 10%-27%.[9,11,18] Again, the CR rate obtained with azacitidine was low in this population (18%), suggesting that the survival benefit is not associated with the achievement of CR. In addition, azacitidine significantly reduced the number of days in hospital, compared with conventional care, even when patients treated with intensive chemotherapy were excluded. [17]

Tolerability and AEs in AZA-001

In the AZA-001 trial, the most common grade 3 or 4 AEs were neutropenia, thrombocytopenia, and anemia, either in the group of patients treated with azacitidine or conventional care.[6,19] Neutropenia was observed in 91% of patients who received azacitidine, and in 76% of patients treated with conventional care regimens. Thrombocytopenia occurred in 85% of patients treated with azacitidine, versus 80% in the group with conventional care. Cytopenias were frequent during the first two cycles of azacitidine, and decreased when patients showed hematological improvement. Early discontinuation because of cytopenias was required in less than 5% of patients treated with azacitidine, and in 2% of patients in conventional care.[6] The rate of infections requiring intravenous antimicrobials was lower in patients treated with azacitidine than in patients with conventional care (0.60 vs. 0.92 per patient-year, relative risk [RR]: 0.66, 95% confidence intervals [CI]: 0.49, 0.87; *P*=0.0032). Hospitalization rate was also significantly less frequent (*P*<0.0001) in patients receiving azacitidine than in the group of conventional care regimens (29% vs. 38.8% per patient-year).[19]

The most common nonhematological AEs in the group of patients receiving azacitidine included injection site reactions, nausea, vomiting, fatigue, and diarrhea. Usually these were transient effects, and resolved during the study.[6,19]

During the AZA-001 trial, deaths occurred in 46% of patients treated with azacitidine, and in 63% of patients in the conventional care group. During the first 3 months of treatment, deaths occurred in 11% of patients in the group of azacitidine, and 9% in the conventional care group.[6]

Some strategies are recommended for managing AEs, including monitoring blood cell counts, and administering transfusions and antibiotics to those patients treated with intensive chemotherapy. According to expert opinion, dose modifications are not recommended during the first three cycles, except in the presence of

life-threatening complications, such as sepsis.[20] Antiemetics are recommended before each dose of azacitidine.

CLINICAL EVIDENCE WITH AZACITIDINE IN COMPASSIONATE SETTINGS

In addition to evidence from clinical trials, there are data about the use of azacitidine for AML in compassionate use settings. As preliminary evidence, the Francophone Myelodysplasia Group reported their experience with a compassionate use program developed between 2004 and 2008.[21,22] Two groups of patients were analyzed retrospectively: patients not eligible for intensive chemotherapy who received azacitidine as first-line treatment, and refractory or relapsed AML patients receiving azacitidine as rescue treatment.

The first group consisted of 138 patients, of whom 67 had an unfavorable karyotype; the median age was 73 years. They received a median 4.5 cycles. A response was observed in 21% of patients (n=29), with CR in 14%. One-year OS was 40%, and the 2-year survival was 18%. Median survival was 10.2 months. The unfavorable karyotype and the presence of more than 10×10^9 leukocytes/L had a negative impact on survival, while the percentage of marrow blasts was not associated with a poor prognosis.

The second group consisted of 184 patients with relapsed or refractory AML.[22] The retrospective analysis of these very-poor-prognosis patients showed 11% responses and 7% CR. Patients with a normal karyotype had a slightly better overall response rate: 18% versus 7% in patients who did not have normal karyotype (P=0.04).

Very recently, Itzykson et al., on behalf of the Francophone Myelodysplasia Group, published the outcomes of 282 patients treated with azacitidine, with high or intermediate-2 risk MDS, in a compassionate program.[23] Diagnosis was AML with 21%-30% marrow blasts in 22% of patients. The authors identified some factors independently associated with lower response rates: previous low-dose cytosine arabinoside treatment, bone marrow blasts >15%, and abnormal karyotype. Complex karyotype predicted significantly shorter responses. Performance status >2, intermediate- and poor-risk cytogenetics, presence of circulating blasts, and red blood cell transfusion-dependency >4 units/8 weeks independently predicted poorer OS.[23]

COMBINATION OF AZACITIDINE AND OTHER TREATMENTS

Azacitidine can also be combined with other treatments. Several teams have studied the role of azacitidine in patients with AML who have achieved CR with chemotherapy with the intention of preventing leukemia relapse. This is an interesting option, as the low toxicity profile of azacitidine permits an ambulatory treatment regimen.

The Nordic MDS Group have recently published the results of a phase II study, in which azacitidine was the maintenance treatment in AML and high-risk MDS patients who had achieved complete remission with chemotherapy.[24] The study included 60 patients who were not eligible for allogeneic transplantation (37 AML patients with prior MDS, and 23 patients with high-risk MDS). Azacitidine was given to 23 patients who achieved CR after one cycle of daunorubicin and cytarabine. The median age was 68 years. The dose was 60 mg/m^2 for 5 days every 28 days, until relapse or unacceptable toxicity. The median duration of response was 13.5 months (2-49+ months). Thirty percent of patients maintained complete remission for >20 months.

The Francophone Myelodysplasia Group also conducted a phase II clinical trial with azacitidine in postremission patients after conventional chemotherapy.[25] It included 46 patients (33 with AML and 13 with high-risk MDS). Thirty-three patients had achieved complete remission, 11 had complete remission with incomplete cytopenia recovery, and two had PR. The mean age was 66 years and the median number of cycles administered was 5.5, with doses between 60 and 75 mg/m^2 for 5 days every 28 days. Treatment was well tolerated, and there was minimal hematologic toxicity. The disease-free 18-month survival rate among patients receiving azacitidine in complete remission was 30%, and the overall 18-month survival rate was 56%. Median survival was 24 months. The outcomes of patients with AML in complete remission were compared with those published by the same French team, with a very similar cohort treated with a second consolidation cycle of anthracyclines and cytarabine. Overall and disease-free survival for patients in complete remission were practically identical in the two groups.[11]

Several authors have studied combinations of azacitidine simultaneously with other agents, with the purpose of achieving synergy and improving the outcomes reported with azacitidine. However, to date no randomized trial has compared the efficacy of azacitidine in combination versus azacitidine alone. The outcomes of treatment with azacitidine, valproic acid and ATRA,[26] azacitidine and gemtuzumab ozogamicin,[27] and azacitidine and thalidomide[28] have been published, and new combinations with drugs such as vorinostat have been developed.[29] The preliminary results reported with this drug are particularly promising; in a phase I trial with 28 patients with AML and MDS, Silverman et al. found a 53% CR. Surprisingly, 10 of the 12 patients with AML/high-risk MDS (83%) reached CR.[29]

Azacitidine has begun to be used as posttransplant treatment. The MD Anderson team used low-dose azacitidine to treat nine AML patients in relapse after allogeneic transplantation, and as maintenance treatment for eight patients in remission. Of the nine relapsed patients, five responded and presented no relevant toxicity.[30]

Finally, with regards to a specific subgroup of AML, erythroleukemia, interesting results with hypomethylating agents have recently been reported in abstract form. Researchers from the MD Anderson and the Lee Moffit Cancer Center observed CR in 10 of 17 patients treated with azacitidine and decitabine. Despite the small number of patients, these results could be interpreted as a special sensitivity of erythroleukemia to these drugs.[31]

CURRENT RECOMMENDATIONS WITH AZACITIDINE AND AML WITH 20%-30% BLASTS IN ELDERLY PATIENTS

Azacitidine and decitabine are pyrimidine-analog approved in the US for the treatment of MDS, but decitabine is not currently approved in the EU. Both drugs inhibit DNA methyltransferase, but show different patterns of gene induction and repression, and in vitro did not show cross resistance. In phase III trials, decitabine is associated with higher response rates with MDS patients, and improved progression-free survival versus best supportive care, but the drug did not significantly prolong OS.[32]

The recent treatment guidelines from the US National Comprehensive Cancer Network (NCCN) for MDS recommend azacitidine, preferred over decitabine, for patients with higher-risk MDS, including RAEB-T, who are not candidates for allogeneic hematopoietic SCT.[33]

Azacitidine is preferred, given the survival benefit shown in the AZA-001 trial (category 1). Intensive chemotherapy is another option considered in NCCN guidelines, or participation in clinical trials. Before selecting a treatment, some factors such as age or performance status should be considered, as these will affect the ability of the patient to tolerate the high intensive chemotherapy.[33]

Although response rate and durability is lower than for standard AML, high intensive chemotherapy could be beneficial in some patients, especially in those with a potential stem-cell donor, and who require a decrease in blast count; achievement of at least partial remission may be adequate to permit the SCT.[33]

The NCCN guidelines for the treatment of AML noted that in patients with AML evolving from MDS the disease may progress slowly, and may behave more like MDS than overt AML.[7] The authors suggest that patients aged >60 years with AML, with prior MDS, unfavorable cytogenetics, or therapy-related MDS/AML, may be managed by clinical trials, azacitidine or decitabine, or standard intensive chemotherapy. For patients >60 years with good functional status and good risk cytogenetics or molecular mutations, standard chemotherapy is preferred.[7]

Recently, recommendations from an expert panel have been published. The authors recommended that azacitidine should be considered as the first-line treatment, instead of low-dose cytarabine, or best supportive care, for the majority of intermediate-2 and high-risk patients ineligible for SCT. However, there is not yet sufficient evidence to choose between azacitidine and intensive chemotherapy for patients ineligible for SCT, but potential candidates for aggressive chemotherapy.[20]

CONCLUSION

In conclusion, the experience with azacitidine in patients with AML with 20%-30% blasts and multilineage dysplasia obtained with phase III randomized studies shows benefits in terms of survival despite a low rate of complete remission. The low incidence of complications and the ambulatory administration renders treatment with azacitidine especially appealing for older patients, for whom chemotherapy is usually not indicated. There is not yet enough evidence to recommend azacitidine versus intensive chemotherapy for patients with good functional status—potential candidates for aggressive chemotherapy. The efficacy of azacitidine in patients with >30% blasts is currently being researched; combinations with various drugs or nonfirst-line situations are promising, but more studies are necessary to demonstrate its activity.

ACKNOWLEDGMENTS

The author has no conflict of interest or financial relationships to declare. This supplement was supported by Celgene.

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