Int J Clin Oncol (2014) 19:10–15
DOI 10.1007/s10147-013-0651-5

REVIEW ARTICLE

Novel therapeutic strategies using hypomethylating agents in the treatment of myelodysplastic syndrome

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Received: 28 November 2013 / Published online: 20 December 2013

Abstract Myelodysplastic syndrome (MDS) is a clonal hematopoietic neoplasm with high rates of leukemic transformation. MDS had been an intractable disease for which the mainstream of therapeutic approach was best supportive care. Recently, however, treatment of hematological malignancies has benefited from advances in molecular targeted drug discovery such as the revolutionary drug imatinib for chronic myeloid leukemia, and from the reappraisal of forgotten drugs such as thalidomide for multiple myeloma. Two azanucleotide drugs, azacitidine (AZA) and decitabine, were created as anti-neoplastic drugs in the 1960s with little success. In the 1980s, they were reassessed as hypomethylating agents (HMAs), and the introduction of low-dose schedules of them has shown dramatic effects in the delay of leukemic evolution for high-risk MDS. AZA was approved in Japan in March 2011 and has become a standard drug of choice in the treatment of high-risk MDS. Its position as a treatment for low-risk MDS remains to be established. Only half of patients with high-risk MDS can gain benefit from AZA. For example, those with complex karyotypes experience only a limited extension in survival. In addition, AZA resistance develops sooner or later. To achieve a more sustained disease control of high-risk MDS, the combined use of HMAs with other therapeutic approaches will be inevitable. Clinical trials of histone deacetylase inhibitors, lenalidomide, thrombopoietin agonists, or anticancer drugs in combination with HMAs are ongoing. In addition, HMAs are being used as a bridging therapy prior to allogeneic stem cell transplantation (AHSCT) and the salvage therapy of relapsed disease after AHSCT. Thus, HMAs will continue to be key drugs for the management of MDS.

Keywords Azacitidine · Decitabine · Hypomethylating agents · Myelodysplastic syndrome

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Introduction

Myelodysplastic syndromes (MDS) comprise a group of biologically and clinically heterogeneous clonal hematopoietic neoplasms characterized by morphologically dysplastic changes, ineffective hematopoiesis that results in peripheral cytopenia, and high rates of leukemic transformation [1]. The incidence of MDS increases with age, with a median age at diagnosis of 71–76 years. In general, MDS is subdivided into low- and high-risk diseases according to their likelihood of leukemic evolution. The life expectancy of patients diagnosed with low-risk MDS exceeds 5 years [2]. However, the refractory cytopenia suffered by these patients requires management with blood transfusions and carries the increased risk of developing an overwhelming infection. By contrast, high-risk MDS patients face a considerable risk of leukemic transformation. Many attempts had been made to prevent or delay transformation without success. While allogeneic hematopoietic stem cell transplantation (AHSCT) has the potential to save lives [3], most high-risk MDS patients are not suitable candidates because of their advanced age, lack of a suitable donor, or presence of co-morbidities.

The demonstration by Fenaux and colleagues in 2009 that azacitidine (AZA) delays the onset of leukemia and prolongs the survival of high-risk MDS patients had great impact on clinical practice.

Development and reappraisal of azanucleosides

In the 1960s, two azanucleosides, AZA and decitabine (DAC), were developed as anticancer agents [4]. Both are ring analogues of cytidine, and DAC is a 2′-deoxy derivative of AZA. DAC is exclusively incorporated into DNA. AZA, on the other hand, is mainly incorporated into RNA; , and a proportion, which is deoxylated in the course of intracellular metabolism, is also incorporated into DNA. Unlike cytarabine, uptake of azanucleotides does not terminate DNA replication; their cytotoxicity results from incorporation, which renders the DNA unstable.

Many clinical studies involving AZA and DAC were carried out in the late 1960s and 1970s. Clinical results in solid tumors are not encouraging, and although AZA and DAC showed consistent antitumor activity in patients with acute myeloid leukemia (AML), overall response rate did not exceed that of cytarabine; hence these agents were forgotten [5]. Around 1980, preclinical studies demonstrated that AZA and DAC trigger gene expression in several murine and human systems by interfering with DNA methylation [6, 7]. Incorporation of azanucleotide into the DNA replication process results in loss of methylated cytidine in the daughter strand, which causes a reversal of the repression of various tumor suppression-inducing, apoptotsis-inducing, and differentiation-inducing genes (Fig. 1). In vitro studies confirmed that low concentrations of azanucleosides in a primary culture of AML cells induces terminal differentiation of leukemic blasts without affecting cell viability [8]. Encouraged by these preclinical data that indicated AZA and DAC are hypomethylating agents (HMAs), clinical trials using low doses were re-started. In 1993, Silvermann et al. and Zagonell et al. [9, 10] independently reported promising results using low-dose AZA and DAC for the treatment of high-risk MDS.

Clinical trials using a single agent

Azacitidine

The first study on the use of AZA for high-risk MDS was conducted by the Cancer and Leukemia Group B (CALGB) research cooperative in the USA [9]. In this Phase II study, a daily dose of 75 mg/m^2 of AZA was administered as a continuous intravenous infusion for 7 days every 28 days for 4 months. Responses were seen in 21 (49 %) of 43 evaluable patients; five achieved complete remission (CR), 11 partial remission (PR), and five improved. 'Improved' was defined as a ≥50 % restoration in the deficit from normal of one or more peripheral blood cell lineages and/or a ≥50 % decrease in transfusion requirements. The median survival for all patients was 13.3 months, and the median duration of remission for those in CR and PR was 14.7 months. Of note, the frequency of severe adverse events was low. Mild to moderate nausea and/or vomiting was the most common adverse event. CALGB then assessed administering AZA treatment on an ambulatory basis. A second Phase II study, this time of 67 patients with high-risk MDS, showed that AZA given as a subcutaneous daily bolus injection at the same dose and schedule described above produced comparable results in response rate, response duration, and survival [11]. These two Phase

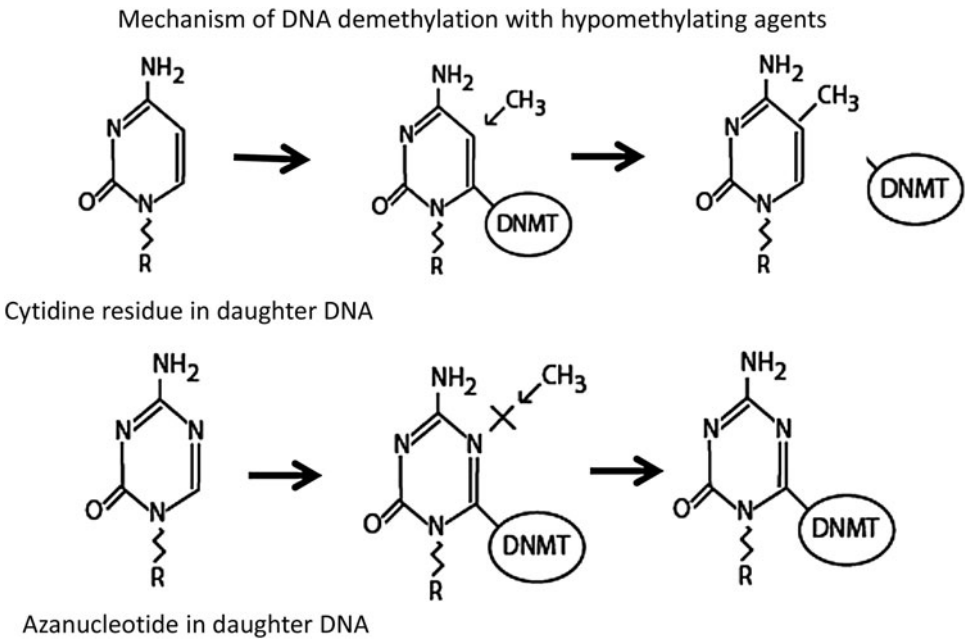

Fig. 1 Upon DNA duplication, DNA methyltransferase (DNMT) covalently binds cytosine residue of daughter strand. After successful methylation, DNMT is released and binds the next cytidine. When azanucleotide is incorporated instead of cytidine, bound DNMT can not only add a methyl group to azanucleotide, but also be released. Trapped DNMT is eventually degraded

II studies revealed unique characteristics of AZA treatment. AZA undoubtedly improved cytopenia and decreased transfusion needs without obtaining CR or PR. Indeed, the frequency of patients who achieved CR was low; most responses were judged as PR or improved. These findings contrasted with past experience of improved survival being strongly associated with obtaining CR in AML as well as in high-risk MDS. Hence, the Phase III studies to ascertain the survival benefits of AZA that followed attracted attention. A randomized controlled trial was undertaken in 191 patients with MDS to compare AZA with supportive care. AZA treatment resulted in significantly higher response rates, improved quality of life, and reduced risk of leukemic transformation. However, intention-to-treat analysis did not conclusively manifest a survival advantage of AZA treatment over best supportive care [11]. Several problems in the study protocol of this Phase III trial were identified. First, patients who were assigned to supportive care and whose disease was worsening were permitted to cross over to the AZA treatment arm after a minimum interval of 4 months. In fact, 49 out of 92 patients assigned to supportive care crossed over, and 23 of them responded. The high crossover rate and high response rate in the crossover group obscured the beneficial effects of AZA on survival. Second, the protocol stated that patients who achieved CR would terminate AZA treatment after three further cycles. Many patients who entered in CR and stopped AZA relapsed early, which also obscured the beneficial effects of AZA.

With the aim of revealing the benefits of AZA for the treatment of high-risk MDS, a subsequent randomized Phase III study was conducted. In this study, investigators determined which of the three conventional care treatments (best supportive care, low-dose cytarabine, or intensive chemotherapy) was most appropriate for each patient before randomization. Among 358 patients enrolled, best supportive care was selected for 222, low-dose cytarabine for 94, and intensive chemotherapy for 42 patients. Patients were then randomly assigned to receive AZA (179 patients) or conventional care regimens (105 on best supportive care, 49 on low-dose cytarabine, and 25 on intensive chemotherapy), and crossover was not permitted. AZA was given subcutaneously for at least six cycles and continued until relapse, disease progression, or unacceptable toxicity occurred. At 2 years, on the basis of Kaplan–Meier estimates, 50.8 % of patients in the AZA group were alive compared with 26.2 % in the conventional care group ($p < 0.0001$) [12]. Subgroup analysis confirmed that AZA prolonged survival in patients preselected to receive best supportive care and low-dose cytarabine [13, 14]. As a result of this study, best supportive care and low-dose cytarabine as the first-choice therapeutic options for the elderly or unfit with high-risk MDS were relegated, and hence for nearly all high-risk MDS patients, AZA become the drug of choice.

Decitabine

In 1993, an Italian group reported the promising effects of DAC on advanced MDS patients [10]. Ten patients, including two with refractory anemia with excess blasts (RAEB) and eight with RAEB in transformation, were treated with DAC at a daily dose of 45 mg/m^2 divided into three 4-h infusions for 3 days or as a continuous infusion of 50 mg/m^2 over 3 days. Treatment with DAC resulted in a significant increase in circulating neutrophils, platelets, and hemoglobin with respect to pretreatment values in over 50 % of patients. A German group conducted Phase I/II and Phase II studies on 124 patients with low- and high-risk MDS, and DAC treatment resulted in a 31 % major cytogenetic response rate, including 10 out of 26 in the International Prognostic Scoring System (IPSS) defined high-risk cytogenetic category [15]. The prognosis of patients with a major cytogenetic response was significantly better than for those in whom the cytogenetically abnormal clone persisted. Randomized Phase III studies comparing DAC with best supportive care conducted in the USA and Europe followed. In the study from the USA, a total of 170 patients classified as IPSS intermediate-/high-risk were randomized to receive either 15 mg/m^2 DAC intravenously every 8 h for 3 days and repeated every 6 weeks, or best supportive care [16]. Of the patients treated with DAC, 9 % achieved CR and 8 % PR; an additional 12 patients (13 %) achieved hematologic improvement. Patients treated with DAC had a trend toward a longer median time to AML progression or death compared with patients who received supportive care alone. A significant survival advantage of DAC over best supportive care was not observed in this study, although median time to AML progression or death was significantly longer in the DAC group in patients with IPSS intermediate-2/high-risk disease. The European study, into which 233 MDS patients were enrolled, used the same DAC treatment schedule as the USA study [17]. In the DAC arm, 13 % of patients achieved CR; 6 % achieved PR, and 15 % had hematologic improvement. The median number of DAC courses administered was four, approximating 6 months of treatment. Although the incidence of AML transformation was significantly reduced at 1 year in the DAC arm, the difference in overall survival duration with DAC *versus* best supportive care was not statistically significant. A trial conducted by the M. D. Anderson Cancer Center used a different DAC schedule: 20 mg/m^2 per day as a 1-h intravenous infusion for 5 consecutive days every 4 weeks. They consider the 3-day DAC schedule to be so myelosuppressive that most

patients would be unable to continue for more than four cycles, and that the schedule's 6-week interval is long enough for tumor regrowth to occur. They report that in advanced MDS patients receiving a median of nine courses of DAC treatment, 34 % achieved CR and 73 % had hematologic improvement [18]. Unfortunately, this excellent outcome has not yet been verified in randomized trials.

Current status of hypomethylating agents in Japan

A Phase I/II study of AZA in Japanese patients with all risk group of MDS has been conducted, and the outcomes were similar to those of previous international studies [19]. In March 2011, AZA was approved in Japan for the treatment of low- and high-risk MDS defined according to the FAB classification. Clinical trials of DAC have also been conducted for low- and high-risk MDS with a 5-day schedule; however, as of November 2013, DAC has not been approved as a treatment for MDS in Japan.

Eleven of the 19 patients with low-risk MDS, namely refractory anemia (RA) and RA with ringed sideroblasts (RARS) by FAB classification, enrolled in the Japanese Phase I/II AZA trial mentioned above showed hematologic improvements. The frequencies of erythroid, platelet, and neutrophil responses were almost equivalent, although the number of patients with neutropenia was low. Several clinical trials aimed at restoring bone marrow function in low-risk MDS patients have been reported from outside Japan [20–22]. The schedule of AZA administration varied between these trials; for example, two used a daily dose of 50 mg/m^2 and one used a 5-day, instead of the standard 7-day, regimen. Overall response rates were around 50 %; however, in most cases the hematologic response was lost after AZA therapy was terminated. Low-risk MDS encompasses heterogeneous diseases with variable prognoses and, therefore, whether to treat with AZA or not is a difficult clinical decision. The presence of symptomatic thrombocytopenia and/or neutropenia and a gradual increase in bone marrow blasts would encourage the use of AZA. However, we should bear in mind that it has not been confirmed that AZA treatment improves survival in low-risk MDS.

Although the beneficial effects of AZA for high-risk MDS have been demonstrated, the best time to commence AZA therapy has not been fully established, especially for patients with untreated stable disease. In addition, AZA treatment of patients with hypoplastic MDS with increased bone marrow blasts can sometimes result in prolonged neutropenia. In spite of this, AZA has become a drug of choice in the management of high-risk MDS. A retrospective analysis has shown that since the approval of AZA, the survival of high-risk MDS patients referred to our hospital has improved (unpublished observation).

Combined use of HMA with other therapeutic approaches

Although the introduction of HMAs has changed the principles of MDS treatment, the air of excitement that immediately followed AZA approval has gradually waned. There are several problems associated with HMA therapy to overcome. First, only half of MDS patients can gain benefit from HMAs. Patients with a complex karyotype, for example, experience only a limited survival extension [23]. Second, patients who achieve a response to HMAs develop HMA resistance sooner or later, and the prognosis of patients with HMA treatment failure is dismal [24]. Now that we are aware of the limitations of HMA monotherapy, the combined use of HMA with other therapeutic approaches will be essential to improve the prognosis of MDS further.

Combined use of HMAs with various agents

Several agents have been tried as partners for HMAs. Histone deacetylase inhibitors (HDACIs) inhibit a group of enzymes called histone deacetylases that are important in post-translational histone modification and exert epigenetic control over gene expression. The combination of HMA and HDACI shows synergistic antileukemic activity in vitro [25]. Several clinical studies using this combination have been performed; however, limited success has been observed so far [26, 27]. It is well known that lenalidomide has remarkable clinical activity against the subtype of low-risk MDS bearing del(5q). Lenalidomide also improves cytopenia in patients with non-del(5q) low-risk MDS through its effects on the bone marrow microenvironment. As Phase I studies of the combined use of HMA and lenalidomide were encouraging [28, 29], larger studies of simultaneous or sequential use of both drugs have been undertaken [30]. A randomized trial comparing two combination regimens (AZA + lenalidomide and AZA + vorinostat) with AZA monotherapy is ongoing [31]. Other AZA-based combinations have been evaluated in high-risk MDS such as AZA + cytarabine [32] and AZA + anti-CD33- gemtuzumab ozogamicin [33]. As patients with low-risk MDS receiving HMAs commonly develop thrombocytopenia, the efficacy of romiplostim, a thrombopoietin mimetic, to prevent the occurrence of severe thrombocytopenia has been evaluated [34, 35]. Romiplostim successfully raised platelet counts and decreased platelet transfusion needs.

Combined use of HMAs with AHSCT

AHSCT is the only therapeutic approach with known curative potential for patients with MDS. Although the recent introduction of reduced-intensity conditioning (RIC) regimens have considerably broadened the age range of AHSCT recipients, the high risk of transplant-related mortality and disease relapse after AHSCT prevents the use of AHSCT as routine practice. The outcomes of AHSCT for MDS are largely dependent on disease- and patient-related factors, such as cytogenetic status, bone marrow blast percentage, age, performance status, and co-morbidities. Among them, pre-AHSCT tumor burden is one of the most important determinants of AHSCT success. Several retrospective studies have explored the efficacy of intensive induction chemotherapy before AHSCT, and found that it may reduce the incidence of relapse but is associated with a considerable increase in transplant-related morbidity and mortality [36, 37]. As administration of HMAs can delay MDS progression to AML with only mild toxicity, they could represent an attractive alternative for pre-AHSCT cytoreductive therapy. Two retrospective analyses of patients with high-risk MDS who received chemotherapy (AZA or intensive chemotherapy) and AHSCT have been reported [38, 39]. No statistical differences were found between the AZA and the intensive chemotherapy groups in terms of overall survival, relapse, and non-relapse mortality in either of the analyses. However, it is possible that AZA given before AHSCT could reduce tumor burden without impacting physical condition and, therefore, as an alternative to pre-transplant intensive chemotherapy, give more patients the opportunity to receive AHSCT. Another application of AZA to increase the success of AHSCT is as salvage therapy after AHSCT relapse. Preliminary studies using AZA alone or in combination with donor lymphocyte infusion have yielded promising results [40, 41].

Conclusion

Until recently, MDS was a disease with limited therapeutic options. Indeed, best supportive care was the mainstream therapy for elderly patients. The introduction of two HMAs, AZA and DAC, dramatically changed clinical practice for the management of MDS. AZA has undoubtedly prolonged the survival of high-risk MDS patients in clinical trials as well as in the real world setting. In recent years, considerable progress has been made in elucidating genetic abnormalities in MDS, and a substantial proportion of the genetic alterations seen in MDS are now known to be associated with epigenetic pathways [42, 43]; the precise mechanism by which HMAs delay leukemic transformation, however, is as yet unknown. Judging from the rapid progress in genomic investigation of MDS, it is plausible that in the near future MDS patients will be offered a prescription of HMA or HMA combined with other agents that is tailored to their genetic background.

Conflict of interest The author declares that he has no conflict of interest.

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