Review

Comparison Between Decitabine and Azacitidine for the Treatment of Myelodysplastic Syndrome: A Meta-Analysis With 1392 Participants

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Abstract

The hypomethylating agents decitabine and azacitidine have been found to improve the outcome of patients with myelodysplastic syndrome (MDS); however, the clinical choice between them is controversial. Therefore, this meta-analysis was performed to compare the efficacy, toxicity, and survival advantage of decitabine and azacitidine in patients with MDS. Eleven trials with a total of 1392 patients with MDS (decitabine, n = 768; azacitidine, n = 624) were included for analysis. The pooled estimates of partial response, hematologic improvement, and overall response rates for azacitidine were significantly higher than for decitabine. There were no differences between these 2 drugs regarding complete response, red blood cell transfusion-independent rates, and grade 3 or 4 hematologic toxicity. When compared with best supportive care, azacitidine significantly improved overall survival (hazard ratio [HR], 0.69; 95% CI, 0.54-0.87) and time to acute myeloid leukemia transformation (HR, 0.51; 95% CI, 0.35-0.74). But these benefits were not found with decitabine. Among patients with higher risk (International Prognostic Scoring System value of 3) or older than 75 years, treatment with azacitidine was a favorable factor, whereas decitabine showed no advantage. Therefore, with higher overall response rates and better survival benefits, azacitidine is recommended as the first-line hypomethylating agent for MDS, especially in elderly patients or those with high risk.

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Introduction

Myelodysplastic syndrome (MDS) is characterized by myeloid cell differentiation dysplasia, ineffective hematopoiesis, refractory cytopenia, hematopoietic function failure, and high risk of progression to acute myeloid leukemia (AML). A large number of epidemiologic statistics indicate the increasing incidence of MDS.[1-2] In the United States, the average annual incidence of MDS in 2001-2003 was about 3.4 per 100,000. In 2004 the incidence increased to 3.8 per 100,000, close to the incidence of AML, thus making MDS a common malignant blood tumor.[1-2]

Hypomethylating agents are nucleoside analogues inhibiting the DNA methyltransferases to activate expression of some tumor suppressor genes. These agents, including decitabine and azacitidine, are approved for the treatment of MDS by the US Food and Drug Administration (FDA). Azacitidine and decitabine, as common hypomethylating agents, are slightly different in structure: azacitidine is a ribonucleoside, and decitabine is a deoxyribonucleoside.[3] Although both azacitidine and decitabine act by depletion of DNA methyltransferases, these 2 drugs play a role in different specific mechanisms: azacitidine is incorporated into both RNA and DNA, whereas decitabine is phosphorylated by different kinases and is incorporated only into DNA.[4] Because of incorporation into RNA, azacitidine inhibits protein synthesis as an additional function.[5] In addition, several comparative studies found that azacitidine and decitabine have different effects on the gene expression profiles of various cancer cell lines, and this may cause them to have different clinical activities.[6-7] Several multicenter phase III clinical studies have compared decitabine or azacitidine with conventional care regimens including best supportive care (BSC) and conclude that the 2 drugs are effective and show a significant overall survival (OS) benefit in patients with MDS.[8-10] However, which of the 2 drugs has better efficacy is not clear. In 2013,

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2 retrospective studies comparing decitabine with azacitidine found that there were no significant differences in overall response (OR) rates and survival advantage between these 2 drugs. However, in patients who were elderly (≥ 65 years) or who had poor performance status or MDS duration exceeding 1 year, azacitidine showed greater survival benefit.[11-12] To guide the choice between the 2 hypomethylating agents in clinical practice, the present authors identified 1392 patients from 11 phase II or III trials for meta-analysis comparing efficacy, toxicity, and survival advantage between the 2 drugs.

Design and Methods

Data Sources

The databases of PubMed, Wanfang Data, and the American Society of Hematology were searched for articles published in English or Chinese between January 2000 and December 2013. Eligible studies were relevant clinical trials on patients with MDS treated with hypomethylating agents. Key words used were "decitabine", "5-aza-2′-deoxycytidine", "azacitidine", "5-azacitidine", "myelodysplastic syndrome" and "MDS".

Study Selection, Meta-Analysis Inclusion Criteria, and Data Extraction

The publications identified were carefully screened. Only the latest updated reports were included for meta-analysis. Preclinical studies, case reports, and reviews were excluded. Two reviewers (Mixue Xie, Qi Jiang) screened all references identified through the inclusion criteria. In the event of disagreement between the 2 reviewers, the full text of the article was obtained and independently inspected. In total, 11 studies were chosen for the final analysis.

Criteria for including studies in the meta-analysis were (1) phase II-III clinical trials; (2) at least 20 patients with MDS (French-American-British criteria: < 30% marrow blasts); (3) treatment with hypomethylating agents (decitabine or azacitidine), without chemotherapy, immunotherapy, hematopoietic stem cell transplant, or other epigenetic therapy in treatment groups; (4) reporting in English or Chinese; (5) reporting of complete response (CR) rate, partial response (PR) rate, hematologic improvement (HI) rate, OR rate, or at least 1 form of survival data. Extracted data included the following: (1) study characteristics (author, publication time, research time, study type); (2) patient characteristics (age, gender, disease stage using International Prognostic Scoring System [IPSS] criteria); (3) the hypomethylating treatment regimen; and (4) the outcome measures (CR rate, PR rate, HI rate, OR rate, red blood cell [RBC] count, or platelet transfusion−independent rates, drug-related adverse events rate, OS, and time to AML transformation).

When extracting time-to-event data, the authors attempted to use the measure reported within the text of the report. When a study did not report this information in the text, digitizing software (Engauge Digitizer, version 2; http://digitizer.sourceforge.net) was used to extract the data directly from the Kaplan-Meier survival curve reported in the article.

Statistical Analysis

Pooled estimates of treatment response and adverse events were computed when there was sufficient reporting of these measures. The overall pooled effects assessment was conducted using a fixed-effects model. In case of significant heterogeneity, a random-effects model was used. Heterogeneity in the results of the trials was assessed using the χ^2 test of heterogeneity and the I^2 measure of inconsistency. Heterogeneity was considered present when the P value of the Cochran Q test was $< .05$ and the I^2 statistic was $> 50\%$.

All statistical analyses were performed using the Meta-Analysis program of Stata software (version 12.0 for Windows; StataCorp LP, College Station, TX).

Results

Study Selection

The search strategy identified 137 records that were screened for inclusion. Based on title and abstract review, 84 studies were irrelevant to hypomethylating agents and were excluded. Another 42 studies were eliminated on the grounds of inadequate information, duplicated or overlapping reporting, retrospective studies, or inclusion of leukemia (> 30% marrow blasts). Thus, 11 trials performed between the years 1994 and 2010, which included 1392 patients, fulfilled the inclusion criteria (Figure 1).

Study Characteristics

Characteristics of the 11 trials are listed in Tables 1 and 2. Of the 11 publications for the meta-analysis, 7 trials examined the effect of decitabine[8,13-18] and 4 evaluated azacitidine.[9,10,19,20] A total of 768 patients for decitabine and 624 patients for azacitidine were accrued in the 11 studies. Hypomethylating agents were compared with conventional care regimens in 4 randomized controlled trials with 952 patients. The research period, study type, author, drug regimen, dosing, and median number of cycles for each of these studies are listed in Table 1. As shown in Table 2, the median age ranged from 65 to 72 years, with 58% to 91% male participants, among those studies that reported gender. The Eastern Cooperative Oncology Group (ECOG) performance status scores of all patients from 11 trials are between 0 and 2. According to IPSS scores, most patients in 1 trial[13] were considered to have low-risk MDS, whereas in another 7 trials, more than 50% of patients had intermediate-2 or high-risk MDS.[8,10,14,17-20] With the exception of the study by Wijermans et al,[17] in which a high dose of decitabine (45 mg/m^2) was used, all other included studies were conducted using 15 to 20 mg/m^2 for decitabine and 75 mg/m^2 for azacitidine. For response data, 5 trials[8,10,14,18,19] applied International Working Group (IWG) 2000 response criteria,[25] 4 trials[13,15,16,20] applied IWG 2006 response criteria,[26] and 2 trials applied custom criteria that are similar to those of IWG 2000.[9,17] For adverse events data, 9 trials applied CTCAE (Common Terminology Criteria for Adverse Events), 1 trial applied World Health Organization grade criteria,[17] and 1 other trial applied standard CALGB (Cancer and Leukemia Group B) criteria.[9]

Publication Bias

No evidence of publication bias was detected for the OR rates of this study by either the Begg or Egger test (for decitabine: Begg test, $P = .624$; Egger test, $P = .811$; for azacitidine: Begg test, $P = .602$; Egger test, $P = .743$).