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Comparison between Decitabine and Azacitidine for the Treatment of Myelodysplastic Syndrome: A Meta-analysis with 1,392 Subjects

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A meta-analysis for hypomethylating agents

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Conflict of interest

All authors have no conflicts of interest.
Abstract
The hypomethylating agents, decitabine and azacitidine, have been shown to improve the outcome of patients with myelodysplastic syndrome; however, the clinical choice between them is controversial. Therefore we performed a meta-analysis to compare the efficacy, toxicity and survival advantage of decitabine and azacitidine in patients with MDS. Eleven trials with a total of 1,392 MDS patients (decitabine n=768, azacitidine n=624) were included for analysis. The pooled estimates of partial response (PR), hematological improvement (HI) and overall response (OR) rates for azacitidine were significantly higher than for decitabine. There were no differences between these two drugs regarding complete response (CR), RBC transfusion-independent rates and grade 3/4 hematological toxicity. When compared to best supportive care, azacitidine significantly improved overall survival (hazard ratio [HR], 0.69; 95% confidence interval [CI], 0.54-0.87) and time to acute myeloid leukemia (AML) transformation (HR, 0.51, 95%CI, 0.35-0.74). But these benefits were not shown for decitabine. Among patients with higher risk (IPSS-3) or over 75 years of age, treatment with azacitidine was a favorable factor while decitabine showed no advantage. Therefore, with higher OR rates and better survival benefits, azacitidine is recommended as the first-line hypomethylating agents for MDS, especially in elderly or high risk patients.

Keywords: myelodysplastic syndrome, hypomethylating agents, decitabine, azacitidine, meta-analysis
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 epidemiological statistics show the increasing incidence of MDS [1-2]. In the United States, the average annual incidence of MDS in 2001-2003 was about 3.4/100,000. In 2004 the incidence increased to 3.8/100,000, close to the incidence of AML, thus making MDS a common malignant blood tumor [1-2].

Hypomethylating agents are nucleoside analogs inhibiting the DNA methyltransferases to activate expression of some tumor suppressor genes. These agents, including decitabine and azacitidine, are currently approved for the treatment of MDS by the US Food and Drug Administration. 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 two drugs play a role in different specific mechanisms: azacitidine is incorporated into both RNA and DNA, while 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 additional, 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 comparing decitabine or azacitidine with conventional care regimens including best supportive care (BSC) and conclude that the two drugs are effective and show a significant overall survival (OS) benefit in patients with MDS [8-10].

However, which of decitabine and azacitidine, has better efficacy is not clear. In 2013, two retrospective studies comparing decitabine with azacitidine demonstrated that there were no significant differences in overall response (OR) rates and survival advantage between these two 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 two hypomethylating agents in clinical practice, we identified 1,392 patients from 11 phase II or III trials for meta-analysis comparing efficacy, toxicity and survival advantage between the two 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 MDS patients 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 our inclusion criteria. In the event of disagreement between the two reviewers, we obtained and independently inspected the full text article. 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 (FAB) criteria: <30% marrow blasts); (3) treatment with hypomethylating agents (decitabine or azacitidine), without chemotherapy, immunotherapy, hematopoietic stem cell transplantation 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; overall response (OR)
rate or at least one 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; (4) the outcome measures (CR rate, PR rate, HI rate, OR rate, RBC or platelet transfusion-independent rates, drug-related adverse events rate, OS and time to AML transformation).

When extracting time-to-event data, we attempted to use the measure reported within the text of the report. When a study did not report this information in the text, we used a digitizing software, Engauge Digitizer (version 2; available at http://digitizer.sourceforge.net), 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. We conducted the overall pooled effects using a fixed-effects model. In case of significant heterogeneity, we used a random-effects model. We assessed heterogeneity in the results of the trials using the $\chi^2$-squared test of heterogeneity and the $I^2$ measure of inconsistency. We considered that heterogeneity was present when the $P$ value of the Cochran $Q$ test was $<0.05$ 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, STATA Corp LP, College Station, TX, USA.]

**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 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 1,392 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 four evaluated azacitidine [9,10,19-20]. A total of 768 patients for decitabine and 624 patients for azacitidine were accrued in 11 studies. Hypomethylating agents were compared to 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 subjects, 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 one trial [13] were considered to have low risk MDS, while in another seven trials, more than 50% 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 15–20 mg/m$^2$ for decitabine and 75 mg/m$^2$ for azacitidine. For response data, five 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 IWG 2000 [9,17]. For adverse events data, nine trials applied Common Toxicity Criteria for Adverse Events, one trial applied World Health Organization grade criteria [17] and one other trial applied standard CALGB criteria.
Resulting Bias

No evidence of publication bias was detected for the OR rates of this study by either the Begg or Egger test. (Begg test p=0.624; Egger test p=0.811 for decitabine; Begg test p=0.602; Egger test p=0.743 for azacitidine)

Results of Meta-analysis

Efficacy of Decitabine vs Azacitidine

The efficacy end points were CR, PR, HI and OR rates and RBC or platelet transfusion-independent rates. For the sake of uniform criteria, we converted marrow complete response (mCR) rates as found in the IWG 2006 criteria into HI rates to allow pooling with estimates based on IWG 2000 criteria. Because of the high proportion of low risk patients in 1 trial [13], to guarantee the study homogeneity we included the other 10 trials for pooled estimates. The pooled estimates of response outcomes are listed in Table 3. The heterogeneity test of CR event rates from 10 trials revealed the Cochran Q test P value of 0.111 and I² of 38.6%, indicating low heterogeneity. Therefore, the CR event rates were calculated using a fixed-effects model. There was no significant difference in CR rates between the decitabine and azacitidine groups (P=0.835). As for the PR, HI and OR rates with high heterogeneity, we used a random-effects model. There were seven trials available for a pooled estimate of PR event rates. The proportion of patients with PR was significantly higher for azacitidine (12%; 95% CI, 7%-17%) than for decitabine (5%; 95% CI, 1%-9%) (P < 0.001). In 8 trials with 645 MDS patients, the HI rates in the azacitidine group (48%; 95% CI, 40%-56%) were significantly higher than in the decitabine group (21%; 95% CI, 12%-31%) (P < 0.001). But when we included three trials for hematological improvement of erythroid, platelet or neutrophil lineages, there were no significant differences between the two drugs (Table 3). In analysis of OR rates (Figure 2), azacitidine (73%; 95% CI, 61%-85%)
was superior to decitabine (42%; 95% CI, 32%-52%) (P < 0.001). There were four trials providing data on RBC transfusion-independent rates. The advantage of azacitidine (48%, 95% CI, 38%–58%) over decitabine (33%, 95% CI, 22%–44%) was not statistically significant (P = 0.065). For platelet transfusion-independent rates, we lacked sufficient data for analysis.

**Drug-Related Adverse Events for Decitabine vs. Azacitidine**

A large number of studies have shown that treatment with hypomethylating agents are associated with a higher rate of grade 3/4 adverse events, most of which are hematologic effects. There were nine trials applying Common Toxicity Criteria for Adverse Events [8, 10, 13-16, 18-20], and these were included for pooled estimates. The pooled estimates of grade 3/4 drug-related adverse events are listed in Table 4. Because of the high heterogeneity, the grade 3/4 adverse events rates were calculated using a random-effects model. There were no significant differences in grade 3/4 neutropenia, thrombocytopenia, anemia and febrile neutropenia rates between the two drugs. In most patients hematological toxicity was transient, and patients usually recovered in time for the next treatment cycle. Non-hematological toxicity such as nausea, vomiting, fatigue, and diarrhoea was mild and reversible.

**Survival Advantage of Decitabine or Azacitidine Compared to Conventional Care**

There were 952 patients from four randomized controlled trials available for the analysis of OS and time to AML transformation. Compared with BSC, treatment with azacitidine significantly prolonged OS (HR 0.69; 95% CI, 0.54-0.87; 2 trials [9-10]; fixed model) (Figure 3). But this survival benefit was not shown for the decitabine groups (HR 0.83; 95% CI, 0.65-1.05; 2 trials [8,18]; fixed model). In the subgroup analysis of patients over 75 years old, compared with conventional care, treatment with azacitidine favorably influenced OS (HR 0.48; 95% CI, 0.31-0.76; 2 trials [10,20]; random model), whereas decitabine showed no advantage (HR 1.29; 95% CI, 0.64-2.59; 1 trails[18]). Among patients with high risk (IPSS-3), the result was similar (azacitidine: HR 0.50; 95% CI, 0.35-0.70, 1 trails [10];
decitabine: HR 1.06; 95% CI, 0.61-1.86, 1 trial [18]). Similarly, regarding time to AML transformation, there was an advantage for the azacitidine groups (HR 0.51; 95% CI, 0.35-0.74, 2 trials [9-10]; random model) but not for the decitabine groups (HR 0.84; 95% CI, 0.66-1.07, 2 trials [8,18]; random model) (Figure 4).

Discussion

DNA methylation, catalyzed by DNA methyltransferase (DNMT), is one of the most important epigenetic modifications. DNA methylation, along with the performance of hypermethylation of particular genes, is usually considered to be an early feature of malignant transformation of cells. [21]. The molecular mechanism of the exact gene targets for hypomethylating agents has not been identified yet. In the last decade some studies have found hypermethylation of tumor suppressor genes in MDS patients, namely, the p21, p18, p15INK4B, fragile histidine triad (FHIT), calcitonin and DAP kinase genes [22-23]. Moreover, in a study published by Zhao et al, decitabine restores the p53 family p73 gene expression in cells and enhances the effects of apoptosis induced by cytarabine [23]. Azacitidine and decitabine have been approved by the FDA for the treatment of MDS, and several other hypomethylating agents are currently in development, including zebularine, SGI-110, and RG108 [24].

Our systematic review aimed to compare the efficacy of decitabine and azacitidine, and to suggest the optimization of treatment for patients with MDS. Our meta-analysis demonstrates that, there were no significant differences in CR rates, RBC transfusion-independence rates and grade 3/4 drug-related hematological toxicity between the two drugs. Treatment with azacitidine was associated with higher PR, and OR rates, which showed that azacitidine have better overall efficacy in MDS. Although azacitidine had an advantage over decitabine in overall HI rates, there were no differences between them when controlling for erythroid, platelet or neutrophil lineages. This difference may be due to the limited number of trials for each lineage. When compared with BSC,
especially in patients over 75 years of age or with high risk according to IPSS score, survival was significantly better in the azacitidine groups. Two retrospective studies published in 2013 directly compared the efficacy of decitabine and azacitidine; a greater effect on survival was shown for azacitidine compared with decitabine in patients who were elderly (≥ 65 years) or who had poor performance status or MDS duration exceeding 1 year [11-12]. These results suggest the advantage of azacitidine over decitabine in the elderly population and are consistent with our findings. However, our results demonstrated that azacitidine was superior to decitabine regarding OR rates, which was contrary to the results of the two studies that there were no differences between two drugs. As for the drug-related hematological toxicity, our meta-analysis showed that there were no differences between decitabine and azacitidine, while the two studies considered decitabine to be associated with more frequent episodes of neutropenia and infections. Compared with the retrospective studies [11-12], we included more information on phase II or III trials to enlarge the sample size to ensure the reliability of the conclusion, although we lacked the raw data for propensity-score matching analysis, which was used in the studies above.

In order to ensure the homogeneity and comparability of our analysis, we excluded one trial with a high proportion of low risk patients [13] and included the rest of 10 trials for treatment response analysis. In the included trials, the age of patients was between 65 and 72 years, and the performance status scores were from 0 to 2. The trials differed in the distribution of risk groups according to IPSS, while most patients had intermediate-2 or high risk. The clinical heterogeneity between the trials might account for the statistical heterogeneity in some of the analyses. Except for the high dose of decitabine in one study by Wijermans et al [17], the included studies used 15–20 mg/m\(^2\) decitabine and 75 mg/m\(^2\) azacitidine. For the duration of treatment each study varied widely, with the median number of courses ranging from 3 to 7 for decitabine and from 4.5 to
9 for azacitidine. This is probably one of the reasons leading to the high heterogeneity of the response rates results. Because of subsequent changes in the IWG criteria (5 trials for IWG 2000 criteria, 4 trials for IWG 2006 criteria), we converted mCR rates of IWG 2006 into HI rates to achieve the same response criteria as in the IWG 2000 criteria. This may, however, lead to inaccuracy in the overall HI rates. For the analysis of grade 3/4 adverse events, to ensure homogeneity we included the seven trials using the Common Toxicity Criteria. Our analysis demonstrated a significantly prolonged OS or time to AML transformation in the azacitidine group, especially among patients over 75 years old or with IPSS-3. This finding was shown only in four randomized controlled trials, and the small number of trials might influence the reliability of results.

**Conclusion**

Azacitidine tends to be superior to decitabine in treatment responses. There are no significant differences between azacitidine and decitabine in CR rates, RBC transfusion-independent rates and grade 3/4 hematological toxicity. In pairwise comparisons with BSC, azacitidine showed a greater advantage over decitabine in term of OS and time to AML transformation, especially for elderly (>75 years) or high risk patients. Because of the limited number of randomized controlled trials in our review, future studies are needed to confirm the results of comparisons between decitabine and azacitidine. Future trials should also focus on further issues including the role of hypomethylating agents compared to intensive chemotherapy or bone marrow transplant; optimal treatment regimens such as dose, the number of cycles with the higher efficacy and lower incidence of adverse events.
Authorship

Mixue Xie and Qi Jiang: conception and design of the study, protocol development, searching for trials, acquisition, analysis and interpretation of data, drafting the article;

Yanhui Xie: conception and design of the study, protocol development, revision of the article. All authors approved the final version of the article to be published.
References:


Comparison of 7-day azacitidine and 5-day decitabine for treating myelodysplastic syndrome. *Ann Hematol* 2013;92:889-97.


Table 1 Characteristics of Each Study

<table>
<thead>
<tr>
<th>Author</th>
<th>Research Time</th>
<th>Study Type</th>
<th>Drug</th>
<th>Usage and Dosage (Median cycles)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guillermo</td>
<td>2008-2009</td>
<td>II</td>
<td>Decitabine</td>
<td>20mg/m²/d,sc,day1-3, q4w(7)</td>
</tr>
<tr>
<td>Oki</td>
<td>NR</td>
<td>II</td>
<td>Decitabine</td>
<td>20mg/m²/d,iv, &gt;1h, day1-5, q4w(5.5)</td>
</tr>
<tr>
<td>Lee</td>
<td>2008-2009</td>
<td>II</td>
<td>Decitabine</td>
<td>20mg/m²/d,iv, &gt;1h, day1-5, q4w(5)</td>
</tr>
<tr>
<td>Steensma</td>
<td>NR</td>
<td>II</td>
<td>Decitabine</td>
<td>20mg/m²/d,iv, &gt;1h, day1-5, q4w(5)</td>
</tr>
<tr>
<td>Wijermans</td>
<td>1996-1997</td>
<td>II</td>
<td>Decitabine</td>
<td>45mg/m²/d, iv, &gt;1h, day1-3, q6w</td>
</tr>
<tr>
<td>Martin</td>
<td>NR</td>
<td>II</td>
<td>Azacitidine</td>
<td>75mg/m²/d, iv, 20min, day1-5, q4w(4.5)</td>
</tr>
<tr>
<td>Uchida</td>
<td>NR</td>
<td>II</td>
<td>Azacitidine</td>
<td>75mg/m²/d, sc or iv, d1-7, q4w(7)</td>
</tr>
<tr>
<td>Lubbert</td>
<td>2002-2007</td>
<td>III</td>
<td>Decitabine</td>
<td>15mg/m²/d, iv, &gt;4h, tid, day1-3, q6w(4)</td>
</tr>
<tr>
<td>Kantarjian</td>
<td>2001-2004</td>
<td>III</td>
<td>Decitabine</td>
<td>15mg/m²/d, iv, &gt;3h, q8h, day1-3, q6w(3)</td>
</tr>
<tr>
<td>Silverman</td>
<td>1994-1996</td>
<td>III</td>
<td>Azacitidine</td>
<td>75 mg/m²/d, sc, day1-7, q4w</td>
</tr>
<tr>
<td>Fenaux</td>
<td>2004-2006</td>
<td>III</td>
<td>Azacitidine</td>
<td>75 mg/m²/d, sc, day1-7, q4w(9)</td>
</tr>
</tbody>
</table>

Abbreviations: BSC = best supportive care; CCR = conventional care regimens; NR = Not Reported; sc = subcutaneously; iv = intravenous.
## Table 2: Participant Characteristics of Included Trials

<table>
<thead>
<tr>
<th>Author</th>
<th>Drug</th>
<th>No. Patients</th>
<th>Median Age (Range)</th>
<th>NO.Male (%)</th>
<th>low risk</th>
<th>IPSS-1 (%)</th>
<th>IPSS-2 (%)</th>
<th>IPSS-3 or high (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guillermo(2013)[13]</td>
<td>Decitabine</td>
<td>43</td>
<td>67(53-81)</td>
<td>25(58%)</td>
<td>NR</td>
<td>31(72%)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>22</td>
<td>71(61-81)</td>
<td>20(91%)</td>
<td>NR</td>
<td>15(68%)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Oki(2012)[14]</td>
<td>Decitabine</td>
<td>34</td>
<td>69(52-81)</td>
<td>26(76%)</td>
<td>1(3%)</td>
<td>9(27%)</td>
<td>7(21%)</td>
<td>11(32%)</td>
</tr>
<tr>
<td>Lee(2011)[15]</td>
<td>Decitabine</td>
<td>101</td>
<td>65(23-80)</td>
<td>68(67%)</td>
<td>NR</td>
<td>52(52%)</td>
<td>34(34%)</td>
<td>12(12%)</td>
</tr>
<tr>
<td>Steensma(2009)[16]</td>
<td>Decitabine</td>
<td>99</td>
<td>72(34-87)</td>
<td>71(72%)</td>
<td>1(1%)</td>
<td>52(53%)</td>
<td>23(23%)</td>
<td>23(23%)</td>
</tr>
<tr>
<td>Wijermans(2000)[17]</td>
<td>Decitabine</td>
<td>66</td>
<td>68(38-84)</td>
<td>46(70%)</td>
<td>0</td>
<td>16(24%)</td>
<td>25(38%)</td>
<td>25(38%)</td>
</tr>
<tr>
<td>Martin(2009)[18]</td>
<td>Azacitidine</td>
<td>22</td>
<td>69.5(17-79)</td>
<td>13(59%)</td>
<td>1(5%)</td>
<td>8(36%)</td>
<td>7(32%)</td>
<td>6(27%)</td>
</tr>
<tr>
<td>Uchida(2011)[19]</td>
<td>Azacitidine</td>
<td>53</td>
<td>65(35-77)</td>
<td>36(68%)</td>
<td>0</td>
<td>23(43%)</td>
<td>15(28%)</td>
<td>15(28%)</td>
</tr>
<tr>
<td>Lubbert(2011)[20]</td>
<td>Decitabine</td>
<td>119</td>
<td>69(60-90)</td>
<td>76(64%)</td>
<td>NR</td>
<td>8(7%)</td>
<td>64(53%)</td>
<td>46(39%)</td>
</tr>
<tr>
<td></td>
<td>BSC</td>
<td>114</td>
<td>70(60-86)</td>
<td>73(64%)</td>
<td>NR</td>
<td>8(7%)</td>
<td>63(55%)</td>
<td>42(37%)</td>
</tr>
<tr>
<td>Kantarjian(2006)[8]</td>
<td>Decitabine</td>
<td>89</td>
<td>70(65-76)</td>
<td>59(66%)</td>
<td>0</td>
<td>28(31%)</td>
<td>38(43%)</td>
<td>23(26%)</td>
</tr>
<tr>
<td></td>
<td>BSC</td>
<td>81</td>
<td>70(62-74)</td>
<td>57(70%)</td>
<td>0</td>
<td>24(30%)</td>
<td>36(44%)</td>
<td>21(26%)</td>
</tr>
<tr>
<td>Silverman(2002)[9]</td>
<td>Azacitidine</td>
<td>99</td>
<td>69(31-92)</td>
<td>72(73%)</td>
<td>2(5%)</td>
<td>21(54%)</td>
<td>9(23%)</td>
<td>7(18%)</td>
</tr>
<tr>
<td></td>
<td>BSC</td>
<td>92</td>
<td>67(35-88)</td>
<td>60(65%)</td>
<td>5(12%)</td>
<td>16(38%)</td>
<td>13(31%)</td>
<td>8(19%)</td>
</tr>
<tr>
<td>Fenaux(2009)[10]</td>
<td>Azacitidine</td>
<td>179</td>
<td>69(42-83)</td>
<td>132(74%)</td>
<td>NR</td>
<td>5(3%)</td>
<td>76(43%)</td>
<td>82(46%)</td>
</tr>
<tr>
<td></td>
<td>CCR</td>
<td>179</td>
<td>70(38-88)</td>
<td>119(67%)</td>
<td>NR</td>
<td>13(7%)</td>
<td>70(39%)</td>
<td>85(48%)</td>
</tr>
</tbody>
</table>

**Abbreviations:** NR = not reported; BSC = best supportive care; CCR = conventional care regimens; IPSS = International Prognostic Scoring System.
Table 3  Pooled Estimates of Response Rates for Decitabine and Azacitidine

<table>
<thead>
<tr>
<th>Outcome (pooled estimates)</th>
<th>Pooling Model</th>
<th>No. Studies Including (Decitabine/Azacitidine)</th>
<th>Decitabine</th>
<th>Azacitidine</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR rates(95%CI)</td>
<td>Fixed</td>
<td>4(^\text{[8,14,16,18]})/4(^\text{[9,10,19,20]})</td>
<td>13% (10%-16%)</td>
<td>12% (9%-16%)</td>
<td>0.835</td>
</tr>
<tr>
<td>PR rates(95%CI)</td>
<td>Random</td>
<td>4(^\text{[8,14-15,18]})/3(^\text{[9,10,19]})</td>
<td>5% (1%-9%)</td>
<td>12% (7%-17%)</td>
<td>0.000</td>
</tr>
<tr>
<td>HI rates(95%CI)</td>
<td>Random</td>
<td>5(^\text{[8,14-16,18]})/3(^\text{[9,10,20]})</td>
<td>23% (12%-35%)</td>
<td>46% (37%-55%)</td>
<td>0.000</td>
</tr>
<tr>
<td>HI-E rates(95%CI)</td>
<td>Fixed</td>
<td>1(^\text{[15]})/2(^\text{[10,20]})</td>
<td>36% (26%-46%)</td>
<td>41% (35%-48%)</td>
<td>0.426</td>
</tr>
<tr>
<td>HI-P rates(95%CI)</td>
<td>Random</td>
<td>1(^\text{[15]})/2(^\text{[10,20]})</td>
<td>46% (34%-58%)</td>
<td>49% (16%-83%)</td>
<td>0.728</td>
</tr>
<tr>
<td>HI-N rates(95%CI)</td>
<td>Random</td>
<td>1(^\text{[15]})/2(^\text{[10,20]})</td>
<td>37% (24%-52%)</td>
<td>32% (4-61%)</td>
<td>0.433</td>
</tr>
<tr>
<td>OR rates(95%CI)</td>
<td>Random</td>
<td>5(^\text{[8,14-16,18]})/3(^\text{[9,10,20]})</td>
<td>42% (32%-52%)</td>
<td>73% (61%-85%)</td>
<td>0.000</td>
</tr>
<tr>
<td>Transfusion independent rates for RBC (95%CI)</td>
<td>Fixed</td>
<td>1(^\text{[16]})/4(^\text{[9,19,20]})</td>
<td>33% (22%-44%)</td>
<td>48% (38%-58%)</td>
<td>0.065</td>
</tr>
</tbody>
</table>

International Working Group 2000 response criteria define the cases subject to evaluation of hematologic improvement (HI) as follows: baseline hemoglobin <11 g/dL for erythroid improvement (HI-E), baseline platelet count <10 \(^*10^4\)/mm3 for platelet improvement (HI-P), and baseline absolute neutrophil count <1000 /mm3 for neutrophil improvement (HI-N).
Table 4  Pooled Estimates of Drug-Related Adverse Events for Decitabine and Azacitidine

<table>
<thead>
<tr>
<th>Outcome (pooled estimates)</th>
<th>Pooling Model</th>
<th>No. Studies Including (Decitabine/Azacitidine)</th>
<th>Dectabine (95%CI)</th>
<th>Azacitidine (95%CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3/4 neutropenia rates (95%CI)</td>
<td>Random</td>
<td>4[8,14-16] / 3[10,19-20]</td>
<td>69% (44%-94%)</td>
<td>76% (58%-94%)</td>
<td>0.065</td>
</tr>
<tr>
<td>Grade 3/4 Anemia rates (95%CI)</td>
<td>Random</td>
<td>4[8,14-16] / 2[19-20]</td>
<td>53% (25%-68%)</td>
<td>66% (50%-82%)</td>
<td>0.067</td>
</tr>
<tr>
<td>Grade 3/4 thrombocytopenia rates (95%CI)</td>
<td>Random</td>
<td>4[8,14-16] / 3[10,19-20]</td>
<td>59% (25%-92%)</td>
<td>56% (19%-94%)</td>
<td>0.468</td>
</tr>
<tr>
<td>Grade 3/4 febrile neutropenia rates (95%CI)</td>
<td>Random</td>
<td>3[14,16,18] / 2[19-20]</td>
<td>21% (12%-31%)</td>
<td>29% (19%-39%)</td>
<td>0.133</td>
</tr>
</tbody>
</table>

Note: Adverse events are defined according to Common Toxicity Criteria for Adverse Events criteria.
Figure 1: Overview Flow Chart of Study Inclusion. Details of the number of articles identified at each step and reasons for exclusion.
Figure 2: Meta-Analysis and Forest Plot of Overall Response Rates
Figure 3: Overall survival (OS) in patients and associations as compared to their supportive care.
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