A systematic review and meta-analysis of the efficacy and adverse events of azacitidine-plus-lenalidomide treatment for patients with acute myeloid leukemia, myelodysplastic syndromes and chronic myelomonocytic leukemia

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ABSTRACT

Objectives: The addition of lenalidomide (LEN) to azacitidine (AZA) may further improve the outcomes of acute myeloid leukemia (AML) patients as well as patients with high-risk myelodysplastic syndrome (MDS) and chronic myelomonocytic leukemia (CMML) patients although the evidence for this combination treatment is still relatively limited. This meta-analysis aimed to evaluate efficacy and adverse effects of AZA plus LEN for the treatment of patients with high-risk MDS, AML or CMML.

Methods: The current study systematically identified all cohort studies of patients with AML and/or MDS and/or CMML who received AZA in combination with LEN that reported the overall complete remission (CR) rate and/or overall response rate (ORR). A DerSimonian–d random–effects model with double arc sine transformation was used for the pooled rates and 95% confidence interval (CI) of the all outcomes.

Results: A total of 10 studies with 406 patients were identified and included into the meta-analysis. The pooled CR rate after the treatment with AZA-plus-LEN regimen was 33.0% (95% CI, 27.7%–38.7%, I² = 18%) while the pooled ORR was 49.9% (95% CI, 38.4%–61.5%, I² = 72%). Nonetheless, adverse events including grade 3–4 neutrophil toxicity events, platelet toxicity events and febrile neutropenia were common with AZA-plus-LEN regimen.

Conclusions: The current study may serve as a preliminary data to suggest that the addition of LEN may offer incremental benefit to patients with high-risk MDS, AML and CMML. However, randomized-controlled studies that directly compare the efficacy and adverse events of AZA-plus-LEN regimen versus AZA monotherapy are still needed.

Introduction

Acute myeloid leukemia (AML) is a common subtype of leukemia with the median age of onset of approximately 70 years [1]. Prognosis of AML is relatively unfavorable with the reported median overall survival (OS) time of only 9.2 months and 5-year overall survival rate of only 13.5% [2]. Poor prognostic factors for survival include age of over 75 years, poor performance status, high-risk cytogenetics, previous hematologic diseases and treatment with less intensive therapy [3,4]. The National Comprehensive Cancer Network (NCCN) recommends hypomethylating agents (HMAs), such as decitabine and azacitidine (AZA), as the preferred treatment options for elderly AML patients who have unfavorable cytogenetics, poor molecular markers, a history of antecedent hematologic disorder, therapy-related AML or unfit performance status [5]. These medications are also recommended for a patient with high-risk myelodysplastic syndrome (MDS) and chronic myelomonocytic leukemia (CMML) [6]. The recommendations are based on studies that showed a better OS associated with treatment with HMAs compared with other treatment options for elderly patients with AML, including low/dose cytosine arabinoside and intensive chemotherapy [7]. A study on AZA for treatment of high-risk MDS and CMML also found a fairly favorable median OS time of 21.5 months [8].

Lenalidomide (LEN) is an immunomodulatory drug that has been approved for the treatment of a specific subtype of MDS (patients with deletion (del) (5q) cytogenetic abnormalities) [9]. The addition of LEN to AZA may help improving the outcomes of patients with AML, MDS and CMML. However, the evidence for the efficacy of this combination treatment is still relatively limited as the available published studies are generally small in size, yielding considerably varied results [10–19]. This systematic review and meta-analysis was conducted with the aims to identify all studies that used the combination therapy of AZA and LEN for the treatment of patients with high-risk MDS, AML or CMML and summarize their results together in order
to comprehensively evaluate its efficacy and adverse effects.

**Methods**

**Data sources and searches**

Three investigators (C.K., P.T. and W.O.) independently searched for studies published before September 2018 in MEDLINE and EMBASE database. The search strategy consisted of search terms for acute myeloid leukemia, myelodysplastic syndrome, chronic myelomonocytic leukemia, azacitidine and lenalidomide (Supplementary Data 1). The references of the eligible articles were also reviewed to identify additional studies. The guideline for processing this systematic review and meta-analysis (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) is available as Supplementary Data 2 [20].

**Selection criteria and data extraction**

Studies were considered eligible for inclusion into this meta-analysis if they were (1) cohort studies (either prospective or retrospective) of patients with AML and/or MDS and/or CMML who received AZA in combination with LEN that (2) reported the primary outcomes of interest (overall complete remission [CR] rate and/or overall response rate [ORR]). The secondary outcomes of interest were complete cytogenetic response rate, disease progression rate, grade 3–4 neutrophil toxicity rate, grade 3–4 platelet toxicity rate, febrile neutropenia rate, thrombotic events rate, acute renal failure rate and treatment/related mortality (TRM) rate. Secondary outcomes were extracted from each study and combined together when available but they were not part of the inclusion criteria. Evaluation of eligibility was independently performed by the three investigators. If different assessments were made regarding the eligibility of the study, the study in question was jointly reviewed by the three investigators and the final determination was reached by consensus.

**Definition of treatment response and outcomes**

A CR was defined as the presence of all of the following: a bone marrow blast count of < 5%; the absence of circulating blasts and blasts with Auer rods; the absence of an extramedullary disease; a hemoglobin level of ≥11 g/dL; an absolute neutrophil count of ≥1.0 x 10⁹/L; and a platelet count of ≥100 x 10⁹/L. A CR with incomplete recovery of peripheral blood counts (CRi) was defined as meeting the CR criteria except that the peripheral blood counts were not fully restored. A partial remission was defined as a bone marrow blast count which declined by at least 50% relative to the pretherapy level but still remained above 5% [21]. The overall CR rate was the proportion of patients who achieved CR or CRi after therapy; similarly, the ORR was defined as the proportion of patients who achieved CR, CRi or partial remission after therapy. A complete cytogenetic response was defined as disappearance of cytogenetic abnormality [21]. A progressive disease was defined as an increase in percent of blast comparing to the prior treatment level [21]. TRM was defined as death during treatment. Grade 3–4 neutrophil toxicity, grade 3–4 platelet toxicity, febrile neutropenia, thrombosis and acute renal failure were defined according to common terminology criteria for adverse events [22].
| References   | Sex (M/F) | Median age (years, range) | Diseases                                           | Cytogenetics                        | Period of study              | Median follow up (months, range) | Median cycles (cycles, range) | Study design           |
|--------------|-----------|---------------------------|----------------------------------------------------|-------------------------------------|-----------------------------|---------------------------------|-----------------------------|------------------------|
| Scherman 2012 [10] | 8/5/3     | 66.5 (23–76)              | 4 MDS, RAEB-2                                      | Sq del complex: 4                  | August 2008–March 2010       | 15 (0–18)                       | 4.5 (1–13)                  | Retrospective cohort   |
|              |           |                           | 4 secondary AML                                    | Non-Sq: 4                          |                             |                                 |                             |                        |
| Sekeres 2012 [11] | 36/23/13  | 68 (47–68)                | RA: 2                                              | Data available 19 patients          | May 2005–April 2011          | 11.5 (3–55)                     | 5 (1–7)                    | Retrospective-prospective cohort |
|              |           |                           | CMMoL: 2, RAEB-1                                  | and 1 patient NG                    |                             |                                 |                             |                        |
|              |           |                           | MDS, RAEB-2: 9                                    | Normal: 8                          |                             |                                 |                             |                        |
|              |           |                           | MDS, RAEB-1: 3                                    | Sq del complex: 3                   |                             |                                 |                             |                        |
|              |           |                           | MDS, RAEB-2: 1                                    | Non-Sq: 7                          |                             |                                 |                             |                        |
| Plabecker 2013 [12] | 20/11/9   | 69 (45–78)                | AML: 5                                            | Sq del alone: 3                    | No data                     | 15.3 (0.4–33.7)                 | 2 (1–6)                    | Prospective cohort     |
|              |           |                           | Secondary AML: 1                                   | Sq del complex: 16                  |                             |                                 |                             |                        |
|              |           |                           | MDS, RAEB-2: 9                                    |                                      |                             |                                 |                             |                        |
|              |           |                           | MDS, RAEB-1: 3                                    |                                      |                             |                                 |                             |                        |
|              |           |                           | MDS, RCMD: 1                                      |                                      |                             |                                 |                             |                        |
| Pollyea 2013 [13] | 42/27/15  | 74 (62–86)                | *Available data 19                                | Normal: 18                         | April 2009–June 2011         | 22 (0.25–30)                    | Mean 4.7 cycles          | Prospective cohort     |
|              |           |                           | AML: 2                                            | Intermediate: 28                    |                             |                                 |                             |                        |
|              |           |                           | Secondary AML (7 MDS turn; 9 t-AML): 16            | Unfavorable: 8                      |                             |                                 |                             |                        |
|              |           |                           |                                                    | Monosomial karyotype: 5             |                             |                                 |                             |                        |
| Ramsingh 2013 [14] | 5/3/2     | 75 (65–81)                | AML: 4                                            | No data                            | No data                     | 2 (1–4)                        |                           | Prospective cohort     |
|              |           |                           | Secondary AML: 1                                   | Non Del 5: 4                        |                             |                                 |                             |                        |
| Dinardo 2015 [15] | 88/No data | 67 (32–88)                | MDS/CMMIL 45                                      | Normal–Y: 24                       | Dec 30, 2009–June 17, 2013  | 14.25 (2.5–43)                  | Overall: 3 (1–1.16)      | Prospective cohort     |
|              |           |                           | AML/RAEB-T 43                                     | Del 5 alone: 2                      |                             |                                 | Phase 2a: 2 (1–12) |                        |
|              |           |                           |                                                    | Del 5 complex: 24                   |                             |                                 | Phase 2b: 5 (1–16) |                        |
|              |           |                           |                                                    | Non Del 5: 33                       |                             |                                 |                             |                        |
|              |           |                           |                                                    | No metaphase: 5                     |                             |                                 |                             |                        |
| Narayan 2015 [17] | 32/18/14  | 73.5 (61–86)              | Previously treated AML and MDS                    | No data                            | August 2011–February 2013   | NR                             | 2 (1–11)                   | Prospective cohort     |
|              |           |                           | De novo AML 3                                      |                                      |                             |                                 |                             |                        |
|              |           |                           | Secondary AML 13                                   |                                      |                             |                                 |                             |                        |
|              |           |                           | T-AML 5                                            |                                      |                             |                                 |                             |                        |
|              |           |                           | MDS, RAEB-2: 6                                    |                                      |                             |                                 |                             |                        |
| Mittelman 2015 [16] | 25/17/8   | 76.3 (60–87)              | MDS, RCMD: 3                                      | Normal–Y: 10                       | NR                          | 6.3 (0.1–29.4)                  | No data                    | Prospective cohort     |
|              |           |                           | MDS, RCMD-RS: 1 MDS, Sq: 1 MDS, RAEB 1: 3 MDS,    | Del 5 alone: 3                      |                             |                                 |                             |                        |
|              |           |                           | RAEB 2: 15 CMMIL: 2                               | Del 5 complex: 4                    |                             |                                 |                             |                        |
|              |           |                           |                                                    | Non Del 5: 6                        |                             |                                 |                             |                        |
|              |           |                           |                                                    | no metaphase: 2                     |                             |                                 |                             |                        |
|               |           |                           | Azacitidine + lenalidomide                         | Normal: 27                          | June 2012–June 2014         | 23 (1–43)                      | 23 weeks                    | Prospective cohort     |
Statistical analysis

All data analyses were performed using the Comprehensive Meta/Analysis program, version 2.2 (Biostat, Englewood, NJ, United States) and Review Manager 5.3 software from the Cochrane Collaboration (London, United Kingdom). Three authors (C.K., P.T. and W.O.) extracted the data from each study by using a pre/defined data extraction form. A DerSimonian–Laird random/effects model with double arcsine transformation was used for the pooled rates and 95% confidence interval of the overall CR rate, ORR, complete cytogenetic response rate, disease progression rate, rate of grade 3–4 neutrophil toxicity, rate of grade 3–4 platelet toxicity, febrile neutropenia rate, thrombotic events rate, acute renal failure rate and TRM rate [23]. We used the random/effect model, rather than the fixed/effect model, because the included studies were not conducted under the exactly same condition, which would invalidate the assumption of the fixed/effect model. The between/study heterogeneity was assessed using Cochran’s Q test and the I² statistic. The I² values were classified as follows: 0–25% indicated insignificant heterogeneity; 26–50%, low heterogeneity; 51–75%, moderate heterogeneity; and > 75%, high heterogeneity [24].

Results

The search strategy yielded 1222 relevant articles (155 from MEDLINE and 1067 from EMBASE). After the exclusion of 142 duplicated articles using EndNote X8 software, 1080 underwent a title and abstract review. A total of 1063 articles were excluded at this stage because they did not meet the inclusion criteria based on the type of article, study design, subjects and/or interventions. Seventeen articles were full/text reviewed and seven of them were excluded on the basis that they did not report the primary outcomes of interest. The 10 remaining studies (eight prospective cohort studies, one retro/prospective cohort study and one retrospective study) fulfilled the eligibility criteria and were included in the meta/analysis [10–19]. Figure 1 demonstrates the literature review and identification process.

Baseline patient characteristics

The meta/analysis evaluated the efficacy and toxicity of the AZA/plus/LEN regimen for a total of 406 patients with AML, MDS and CMML across 10 cohort studies [10–19]. The age of the patients ranged from 23 to 88 years, with a male predominance (59.3%) [10–19]. MDS was the most common diagnosis (55.3%), followed by AML (37.5%) and CMML (7.2%). Approximately one/third (35.5%) of patients had 5q deletion, while 35.1% and 29.4% had non/5q deletion and normal karyotype, respectively. Baseline clinical characteristics of these...
| References                  | Regimen                                                                 |
|-----------------------------|--------------------------------------------------------------------------|
| Scherman 2012 [11]          | 28-day cycle 3 patients                                                  |
|                             | – Azacitidine 75 mg/m² i.v. or s.c. × 7 days                             |
|                             | – Lenalidomide 10 mg orally × 21 days                                    |
|                             | 5 patients                                                               |
|                             | – Azacitidine 75 mg/m² i.v. or s.c. × 5 days                             |
|                             | – Lenalidomide 10 mg orally × 9 days (1); × 15 days (2); × 21 days (2)  |
| Sekeres 2012 [11]           | Phase 1: 28-day cycle                                                    |
|                             | – Azacitidine 75 mg/m² i.v. or s.c. × 5 days or 10 days                 |
|                             | – Lenalidomide orally                                                    |
|                             | • 5 or 10 mg × 14 days or                                                 |
|                             | • 10 mg × 21 days                                                        |
|                             | Phase 2: 28-day cycle                                                    |
|                             | – Azacitidine 75 mg/m² i.v. or s.c. × 5 days                             |
|                             | – Lenalidomide 10 mg orally × 21 days                                    |
| Plabecker 2013 [12]         | 28-day cycle                                                             |
|                             | – Azacitidine 75 mg/m²/day s.c. × 5 days                                 |
|                             | – Lenalidomide orally                                                    |
|                             | 42-day cycle                                                             |
|                             | – Azacitidine 75 mg/m²/day i.v. or s.c. × 7 days                         |
|                             | – Lenalidomide orally                                                    |
|                             | 42-day cycle                                                             |
|                             | – Azacitidine 25 (cohort 1), 50 (cohort 2), 75 (cohort 3) mg/m²/day i.v. × 5 days |
|                             | – Lenalidomide orally 50 mg orally × 21 days D1–21                      |
|                             | Maintenance until 12 cycles 28-day cycle                                 |
|                             | – Azacitidine 75 mg/m²/day i.v. × 5 days                                 |
|                             | – Lenalidomide orally 10 mg orally × 21 days D1–21                      |
| Dinardo 2015 [15]           | 28-day cycle                                                             |
|                             | – Azacitidine 75 mg/m² i.v. × 5 days in all phases                       |
|                             | – Lenalidomide oral for 5 or 10 days, starting on day 6, dosing as below  |
|                             | Phase 1: 3 + 3 dose escalation design                                     |
|                             | – Lenalidomide 7 dose levels oral: 10, 15, 20, 25, 50, and 75 mg once a day × 5 days, and 75 mg × 10 days |
|                             | Phase 2:                                                                 |
|                             | – Lenalidomide 50 mg orally for 10 days, starting on day 6                |
|                             | Phase 2b: because of adverse events                                      |
|                             | – Lenalidomide 25 mg orally for 5 days, starting on day 6 of each cycle   |
| Narayan 2015 [17]           | 42-day cycle                                                             |
|                             | – Azacitidine 75 mg/m²/day i.v. or s.c. × 7 days                         |
|                             | – Lenalidomide oral 30 mg orally × 21 days starting on day 8             |
|                             | If response after 6th cycle, would continue until PD                     |
| Mittleman 2016 [16]         | Induction 6 cycles 28-day cycle                                          |
|                             | – Azacitidine 75 mg/m²/day s.c. × 5 days                                 |
|                             | – Lenalidomide orally 10 mg orally × 14 days D6–21                      |
|                             | Consolidation 6 cycles 28-day cycle                                      |
|                             | – Azacitidine 75 mg/m²/day s.c. × 5 days                                 |
|                             | Maintenance until 12 cycles 28-day cycle                                 |
|                             | – Lenalidomide orally 10 mg orally × 21 days D1–21                      |
| Sekeres 2017 [18]           | Azacitidine plus lenalidomide: 28-day cycle                             |
|                             | – Azacitidine 75 mg/m² i.v. or s.c. × 7 days (7–0–0 or 5–2–2)            |
|                             | – Lenalidomide 10 mg oral × 21 days                                      |
| Medeiros 2018 [19]          | Azacitidine plus lenalidomide: 42-day cycle                             |
|                             | – Azacitidine 75 mg/m²/day i.v. or s.c. × 7 days                         |
|                             | – Lenalidomide orally 50 mg orally × 21 days, starting on day 8          |
patients are summarized in Table 1. There were a variety of AZA/plus/LEN regimens with almost all of the included studies used AZA at the dose of 75 mg/m²/day for 5–7 days[10–19] but the dose of LEN varied from 5 to 50 mg per day, as detailed in Table 2.

**Efficacy of AZA plus LEN**

The pooled CR rate after treatment with AZA/plus/LEN regimen was 33.0% (95% CI, 27.7–38.7%, $I^2 = 18%$; Figure 2(A)) [10–19], while the pooled ORR was 49.9% (95% CI, 38.4–61.5%, $I^2 = 72%$; Figure 2(B)) [10–18].

The pooled analysis revealed that approximately one quarter (24.6%) of the patients achieved a complete cytogenetic response (95% CI, 49.0–67.5%, $I^2 = 71%$; Figure 2(C)) [10,12,16]. The pooled proportion of patients showing disease progression after their treatment was 18.8% (95% CI, 8.8–36.0%, $I^2 = 54%$; Figure 2(D)) [12–14,19].

**Toxicity of AZA plus LEN**

The pooled rate of grade 3–4 neutrophil toxicity and platelet toxicity were 48.8% (95% CI, 27.6–63.4%, $I^2 = 79%$; Figure 3(A)) [10,12,13,16,17,19] and 54.7% (95% CI, 34.1–73.9%, $I^2 = 76%$; Figure 3(B)) [10,12,16,17,19], respectively. The pooled rate of febrile neutropenia was 36.7% (95% CI, 25.8–49.1%, $I^2 = 70%$; Figure 4(A)) [10–17,19]. The pooled rate of thrombotic events after the treatment was 5.3% (95% CI, 2.2–12.3%, $I^2 = 0%$; Figure 4(B)) [10–13], while 9.2% of the patients suffered from acute renal failure (95% CI, 3.5–22.2%, $I^2 = 0%$; Figure 4(C)) [10,11,14]. The pooled TRM rate was 18.8% (95% CI, 8.8–35.7%, $I^2 = 60%$; Figure 4(D)) [10–12,14,17,19].

**Subgroup analysis**

Given that approximately one/third of the patients in this study had 5q deletion and another one/third had normal karyotype, we therefore categorized the patients into two subgroups based on these cytogenetic findings and analyzed the primary outcomes, which are displayed in Supplementary Data 3. As for the patients with 5q deletion, the pooled CR rate was 43.8% (95% CI, 11.9–81.8%, $I^2 = 12%$) [10,16], and the
pooled ORR was 64.5% (95% CI, 46.8–79.0%, \( I^2 = 0\)) [10,16,18]. The patients with normal karyotype had the pooled CR rate of 29.2% (95% CI, 7.4–68.1%, \( I^2 = 46\%\)) [14,16] while the pooled ORR yielded 54.7% (95% CI, 39.8–68.7%, \( I^2 = 0\%\)) [14,16,18].

**Discussion**

This is the first systematic review and meta-analysis that comprehensively evaluated the efficacy and toxicity of the AZA/plus/LEN regimen for the treatment of AML, MDS and CMML. The pooled results across 10 studies with 406 patients found that about half of patients achieved at least partial remission and about one/third achieved CR. This observation may suggest an incremental benefit of adding LEN into AZA regimen as a recent systematic review found the ORRs of AZA monotherapy for AML, MDS and CMML in the range of low 40% [25]. In addition, 25% of the included patients in the present study had a complete cytogenetic response after the treatment with AZA/plus/LEN regimen which is higher than the results of a previous study of AZA monotherapy in patients with AML and MDS patients that found the complete cytogenetic response rate in the range of 2–10% [26].

Different actions of the two medications covering different stages of AML, MDS and CMML could be the foundation of the additional benefit of the combination therapy [13].

On the other hand, the addition of LEN appears to increase the rate of adverse events, particularly high/grade platelet toxicity and febrile neutropenia that was seen in over half and one/third of patients, respectively. This appears to be higher than the results from a recent systematic review and meta-analysis of HMAs monotherapy the found the rate of high/grade platelet toxicity of 38% and the rate of febrile neutropenia of 25% [27].

Nonetheless, comparisons of efficacy and adverse effects of the two treatment regimens from different studies are of limited validity as patients were not randomized to receive one of the treatment options. Therefore, baseline characteristics of patients between the groups were likely to be different and any observed difference in outcome/adverse effect could simply be a result of the difference in patient’s characteristics, not a consequence of the therapy. Therefore, randomized, head-to-head studies to compare the efficacy of these two regimens are still needed before any definite conclusions can be drawn. In addition, the subgroup analysis in the 5q deletion group demonstrated a high CR rate and ORR. Although, the extracted number of patients was low as several included studies do not demonstrate patient’s outcome separately by cytogenetic abnormalities, this promising response is of interest for further study in this group of patients to clarify the efficacy of this combination.

**Conclusion**

The current study may serve as preliminary data to suggest that the addition of LEN may offer incremental benefit to patients with high/risk MDS, AML and CMML. However, randomized/controlled studies that directly compare the efficacy and adverse events of AZA/
plus/LEN regimen versus AZA monotherapy are still needed before any recommendations can be made.

**Disclosure statement**

No potential conflict of interest was reported by the authors.

**Ethics approval and consent to participate**

The need for ethics approval by an institutional board review was waived as this study does not directly involve human subjects.

**Availability of data and material**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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