# Systematic Literature Review of Treatment Options and Clinical Outcomes for Patients With Higher-Risk Myelodysplastic Syndromes and Chronic Myelomonocytic Leukemia

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## Abstract

High-dose chemotherapy with allogeneic hematopoietic stem cell transplantation (allo-HSCT) can produce long-term remission in patients with higher-risk myelodysplastic syndromes (HR-MDS) and chronic myelomonocytic leukemia (CMML). However, this treatment regimen is not appropriate for elderly and/or comorbid patients; in these cases, azacitidine is a standard treatment. This systematic review was conducted to evaluate real-world evidence of treatment options for patients with HR-MDS/CMML. Medline and Embase (January 2006 to May 2016) were searched, in addition to conference proceedings and treatment guideline reviews. Studies on clinical effectiveness/efficacy outcomes with a sample size ≥50 patients were included. From 1061 unique citations identified, 87 full-text articles were reviewed, of which 24 articles reported at least 1 outcome of interest. Studies showed that HR-MDS/CMML patients treated with a conventional chemotherapy regimen (CCR) have poorer overall survival (OS). Key findings from individual HR-MDS studies showed improved survival with azacitidine over CCRs and higher overall response rates with clofarabine relative to low-dose cytosine arabinoside (but no significant difference in 2-year OS favoring clofarabine). OS was highest for patients treated with allo-HSCT. Findings indicate limited real-world data on treatment strategies available for HR-MDS/CMML patients. Most studies address the effect of chemotherapy or allo-HSCT on clinical outcomes, so are not applicable to elderly/comorbid patients who are too frail for those treatments. In particular, our analysis revealed limited evidence on viable options after failure of treatment with azacitidine, identifying a significant unmet need in this patient population.

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## Introduction

Myelodysplastic syndromes (MDS) are a group of hematological malignancies with an estimated incidence rate of 5.3 to 13.1 cases per 100,000 persons in the United States[1] and a median age of diagnosis of 71 to 76 years.[2] Transformation to acute myeloid leukemia (AML) occurs in approximately 10% and 70% of lower- and higher-risk (HR) patients, respectively.[3] MDS is categorized pathologically on the basis of morphology, cytochemistry,[4] immunophenotype, genetics, and clinical features. Patients with HR disease have a poor prognosis and might not be candidates for some treatments because of advanced age and/or comorbidities.[5]

Chronic myelomonocytic leukemia (CMML) is a rare, heterogeneous hematologic neoplasm, characterized by persistent peripheral blood monocytosis and by increased risk to AML transformation,[6] which occurs in 20% to 30% of patients.[7] Median age at diagnosis is approximately 70 years,[8] and the incidence of CMML is estimated to be 0.4 per 100,000.[6] CMML shares clinical

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and biological features with MDS, including cytopenia and bone marrow failure, risk of progression to AML, and overlapping, recurring, cytogenetic abnormalities. Indeed, epidemiological studies estimate that approximately 10% of diagnosed MDS cases should have been diagnosed as CMML.[9] As with MDS, HR CMML patients have a poorer prognosis compared with patients with lower-risk disease.[10]

Diagnostic criteria for pathological categorization have been developed for MDS as well as CMML. However, those categorizations do not increase predictability in patient clinical outcomes; a high degree of variability is still observed in both conditions. In an effort to better predict an individual's risk for transformation to AML and to inform treatment goals and regimens, risk-based stratification systems have been developed.[11] The International Prognostic Scoring System (IPSS), revised to the IPSS-R in 2012, is used to assign individuals to different risk stratification categories on the basis of the percentages of bone marrow myeloblasts, cytogenetics, and significant cytopenias.[11] The IPSS-R defines 5 risk groups: HR disease is defined as IPSS-R scores of intermediate, high, or very high, which are predictive of lower survival outcomes and higher likelihood of transformation to AML.[11] Treatment goals and regimens are on the basis of whether an individual is considered to be lower-risk or HR.[11]

The National Comprehensive Cancer Network (NCCN) guidelines have outlined treatment strategies for MDS. CMML treatment recommendations generally follow those set for MDS or AML patients,[11] depending on the CMML classification. Current treatment options for patients with HR MDS (HR-MDS) and CMML include conventional chemotherapy regimens (CCRs), chemotherapy with hypomethylating agents (HMAs), and allogeneic (allo) hematopoietic stem cell transplantation (HSCT).[11] It is recommended that patients with HR-MDS and CMML who can tolerate a high-intensity therapy be treated with intensive induction chemotherapy and/or allo-HSCT.[11] Allo-HSCT is the only potentially curative treatment, but eligibility is limited by older age and comorbidities.

Azacitidine and decitabine are the only 2 HMAs approved for treating patients with HR-MDS.[11] Azacitidine, initially approved by the Food and Drug Administration in 2004 for treatment of MDS, was given expanded approval in 2009 to reflect new overall survival (OS) data from the AZA-001 study in patients with HR-MDS.[12] In that study, azacitidine showed significant and clinically meaningful prolongation of OS in HR-MDS patients, with a median OS of 24.5 months compared with 15.0 months with conventional care (best supportive care [BSC], low-dose cytarabine, or intensive chemotherapy). Although azacitidine and decitabine are considered to be similar on the basis of their mechanism of action, no head-to-head trials have compared their effectiveness.[11] Azacitidine remains the preferred treatment because of the improved survival of HR-MDS patients observed in AZA-001.[11]

Overall, there is a lack of clinical evidence regarding effective treatments for HR-MDS/CMML patients, and current guideline therapies in real world practice settings have not confirmed the survival benefits identified in pivotal trials. Furthermore, there is limited knowledge regarding health care resource utilization and economic burden for these patient populations. As a result, this review was designed to systematically collect and review real-world evidence for treatment patterns and outcomes associated with therapies used to treat patients with HR-MDS or CMML.

## Materials and Methods

Conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, the goal of our systematic literature review (SLR) was primarily to identify real-world evidence of effectiveness among heterogeneous sets of patients in real life practice settings; because search algorithm structures did not target HR-MDS/CMML randomized controlled trials (RCTs), only a few were located. The MEDLINE and Embase electronic databases were searched using a prospective protocol to identify studies published between January 1, 2006 and May 11, 2016 that reported HR-MDS/CMML treatment outcomes. The term "higher-risk" was author-defined, and consequentially, the specific cutoffs as well as risk scores used to define the HR-MDS subset of patients varied from study to study.

In addition to the 2 databases, we reviewed conference abstracts for the 2 most recent meetings of the American Society of Clinical Oncology, European Society for Medical Oncology, American Society of Hematology, European Hematology Association, International Symposium on Myelodysplastic Syndromes, and International Society for Pharmacoeconomics and Outcomes Research (international as well as European annual meetings).

We also reviewed the National Guidelines Clearinghouse and NCCN guidelines to identify the most recent, relevant clinical practice guidelines.

Appendix A shows the search algorithm implemented for the search in Embase. Analogous search terms, algorithms, and limits were used to conduct the searches in MEDLINE (via PubMed).

The screening process began with an investigator screening all titles and abstracts against the study inclusion/exclusion criteria, using the Participants, Interventions, Comparisons, Outcomes, Study Design, and Time Period elements (Table 1). A second

**Table 1 Study Selection Criteria (PICOS-T)**

| Criteria | Inclusion Criteria |
|---|---|
| Population(s) | Adult patients (18 years or older) with high-risk MDS or CMML |
| Interventions | Chemotherapeutic/immunotherapy agents for these conditions, where applicable |
| Comparisons | NA |
| Outcomes[a] | Effectiveness: treatment response rates (cytogenetic and hematologic responses), duration of response, progression-free survival, overall survival |
| Time | Indexed database: January 1, 2006 to May 11, 2016<br>Gray literature: 2 most recent meetings |
| Study Design | Observational (prospective/retrospective)<br>RCT |
| Other | English language only; geographic emphasis on the US and on Europe (including United Kingdom, Germany, France, Spain, and Italy), and Japan |

Abbreviations: CMML = chronic myelomonocytic leukemia; MDS = myelodysplastic syndromes; PICOS-T = Participants, Interventions, Comparisons, Outcomes, Study Design, and Time Period; RCT = randomized controlled trial; US = United States.
[a]Outcomes listed in the data collection section.

investigator double-checked 10% of the rejected abstracts to confirm accuracy. The full-text articles still of interest were retrieved and screened. All excluded studies were confirmed; any discrepancies were resolved by an independent investigator.

To be included, all accepted articles had to meet the inclusion criteria: articles in English focused on adult patients with HR-MDS or CMML in an RCT or observational study (prospective or retrospective) that reported outcomes of clinical effectiveness/efficacy (OS, treatment response rate, or duration of response).

Full data extraction was performed on all articles included.

## Results

Figure 1 shows the PRISMA diagram of study attrition. After applying all criteria to the 1061 unique citations identified, 24 articles,[3,13-35] reporting on 22 studies, examined efficacy and/or effectiveness of therapy in patients with HR-MDS or CMML. Because the search criteria were tailored to identify real-world evidence, 18 of the studies (82%) used observational study designs, whereas 4 (18%) were RCTs. One study took place in Japan; the remainder were in the United States and/or Europe.

### *Higher-Risk MDS*

As noted previously, a high degree of variability across study populations and specific subgroups, including age, number of previous therapy lines received, and distribution across IPSS risk categories, made comparisons across studies difficult. Data on the 18 HR-MDS trials are shown in Table 2.[3,13-16,18-23,26-30,32-34]

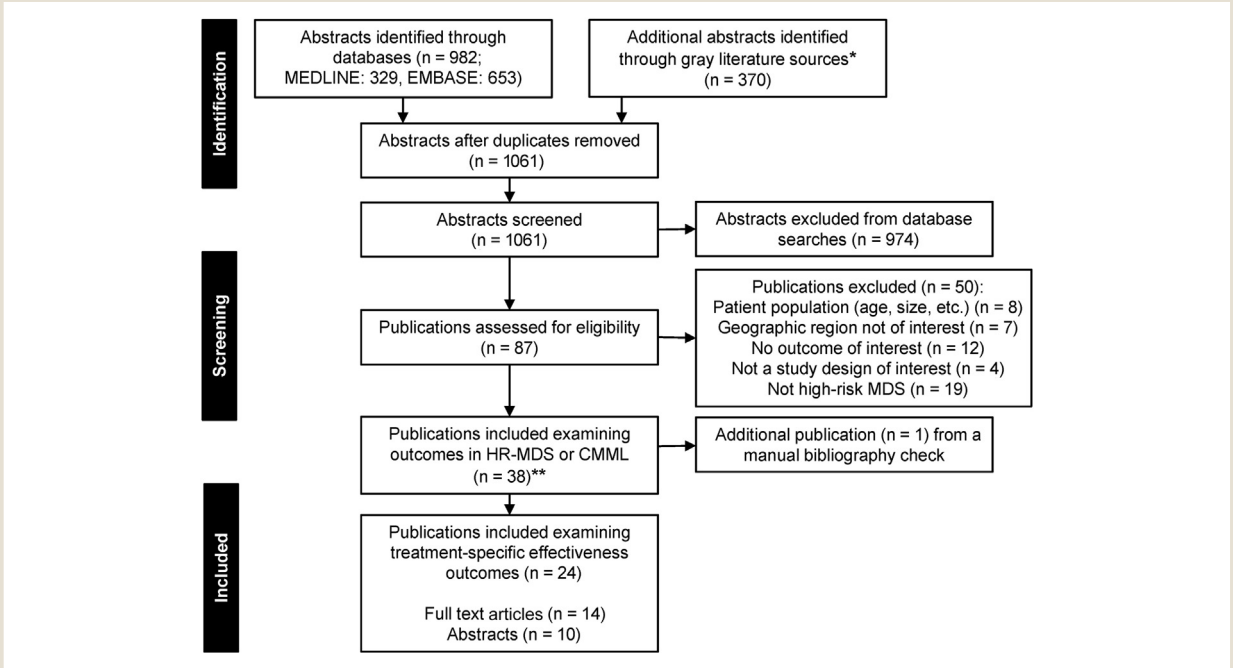
### *Chemotherapy: Conventional Chemotherapy Regimens*

Overall, the prognosis of patients treated with CCRs in real-world settings was poor, particularly with respect to longer-term OS. Among patients receiving CCRs, 2 studies, Bernal et al[13] and Kantarjian et al[23] reported median OS of 12.2 and 34 weeks (3 and 8.5 months), respectively. Longer-term survival among patients receiving CCRs was low, with 3- and 5-year OS rates of only 19%[30] and 8%,[22] respectively.

In 1 RCT, 2-year OS rates were similar among patients receiving low-dose cytosine arabinoside (LD-AraC; 12%) versus clofarabine (13%).[14] In the subset of patients achieving complete response (CR), OS was higher with 2-year rates from CR at 44% for LD-AraC and 26% for clofarabine ($P = .5$).

The study reported by Musto et al[29] enrolled patients with HR-MDS with a median age of 67 years and median red cell transfusions of 24.5 for treatment with the iron-chelating drug deferasirox; 70% had received previous therapy with azacitidine and/or recombinant erythropoietin. Median OS was reported as 38 months after diagnosis and 24.1 months after start of iron chelator therapy. Evidence of a durable CR was observed in 1 patient who had not received any active treatment other than deferasirox when hematological improvement occurred.[29]

**Figure 1** PRISMA Diagram of Study Attrition. *Includes Publications From National Guidelines Clearinghouse and National Comprehensive Cancer Network, and Proceedings From the Past 2 Meetings of the American Society of Clinical Oncology; American Society of Hematology; European Hematology Association; European Society for Medical Oncology; International Society for Pharmacoeconomics and Outcomes Research; and the International Symposium on Myelodysplastic Syndromes. **Among the 38 Publications Included, 21 Were Full-Text Articles and 17 Were Abstracts




Abbreviations: CMML = chronic myelomonocytic leukemia; HR-MDS = higher-risk myelodysplastic syndrome; MDS = myelodysplastic syndrome; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

**Table 2** Higher-Risk MDS Studies, Observational and RCT

| Reference | Source | Country/Region | Sample Size | Design | Therapy | Survival/Disease Progression | Response |
|---|---|---|---|---|---|---|---|
| Kantarjian et al[22] | Full text | US | 510 | Observational study, single center (MD Anderson Cancer Center) 1991 to 2004 | Cytarabine with: Topotecan Topotecan and cyclophosphamide Anthracyclines with or without fludarabine Fludarabine | 5-Year survival: 8% (overall), 36% (allo-HSCT if first CR), 9% (allo-HSCT after first CR) | CR (after induction): 55% (52%-56% depending upon regimen) |
| Kantarjian et al[23] | Full text | US | 998 | Observational study, single center (MD Anderson Cancer Center) since 1980 | Intensive induction chemotherapy regimens | Median OS: 8.5 months OS rate at 1 year: 36% | NR |
| Bernal et al[13] | Full text | EU | 821 | Retrospective study, multicenter (Registry Spanish Cooperative Group on Myelodysplastic Syndromes), patient accrual years 2000 to 2013 | Azacitidine versus CCR | Median OS: 13.4 months, azacitidine ($P = .41$) versus 12.2 months, CCR AML progression: 26% azacitidine ($P = .42$) versus 23% CCR | NR |
| Prébet et al[33] | Full text | EU/US | 435 | Retrospective study, multicenter, patient accrual years from 2000 to 2009 | Treatment failure after azacitidine therapy | Median OS: 5.6 months (overall), 19 months (allo-HSCT); 2-year survival rate: 15% | NR |
| Cabrero et al[15] | Abstract | US | 216 | Retrospective study, single center (MD Anderson Cancer Center), patient accrual years from 2004 to 2012 | HMAs with or without allo-HSCT | Median OS, all patients: 14 months HMA alone: 14 months, HMA with allo-HSCT as consolidation: 16 months ($P = .498$) | ORR: 43% (HMA) versus 45% (HMA with allo-HSCT; $P = .03$) CR: 37% (HMA) versus 38% (HMA with allo-HSCT) |
| Fujimaki et al[18] | Abstract | Japan | 50 | Retrospective study, single center (Fujisawa City Hospital), patient accrual years from 2011 to 2013 | Azacitidine | Median OS: 12 months | NR |
| Molteni et al[26] and Molteni et al[27] | Full text/abstract | EU | 197 | Retrospective study, multicenter (10 in Lombardia Italy), patient accrual years March 2007 to February 2014 | Azacitidine | Median OS: WPPS risk score (n = 102) 13.8 Months ("very high") and 23.2 months ("high risk") Median OS: IPSS-R risk score (n = 99) 13.8 Months ("very high") and 33.8 months ("high risk") Median PFS: 31.5 months | Overall response: 79.1% (of 134 patients evaluable) |
| Dièz Campello et al[16] | Abstract | EU | 235 | Retrospective study, multicenter (French and Spanish MDS registries), patient accrual years NR | Azacitidine in patients with abnormality chromosome 7 | OS: 16% at 2 years At 2 years, AML-free survival: 31% | CR: 16.4% |
| Mutetwa et al[30] | Full text | US | 214 | Observational, multicenter, 2004 to 2007 | Unselected MDS cohort receiving chemotherapy | 36-Month OS Overall: 19.0% (95% CI, 14.0%-24.5%) HR-MDS: 5.0% (95% CI, 0.1%-14.8%); AML evolution Yes: 32.9% No: 64.8% Unknown: 2.3% | NR |

**Table 2 Continued**

| Reference | Source | Country/Region | Sample Size | Design | Therapy | Survival/Disease Progression | Response |
|---|---|---|---|---|---|---|---|
| Montoro et al[28] | Abstract | EU | 254 | Observational, multicenter, 2013 to 2014 | Azacitidine with or without chemotherapy/HSCT/BSC | Median OS<br>Azacitidine/azacitidine with chemotherapy: NR (95% CI, 9.86-NR)<br>HSCT: 11.6 (95% CI, 5.59-NR)<br>BSC: 7.89 (95% CI, 2.17-NR) | NR |
| Gerds et al[20] | Abstract | EU/US | Overall: 1766<br>High/very high risk: 56 | Retrospective, multicenter, 2004 to 2013 | Umbilical cord blood transplantation | High/very high risk versus very low/low risk:<br>OS<br>RR: 1.55 (95% CI, 1.12-2.14), $P = .01$<br>Disease-free survival<br>RR: 1.39 (95% CI, 1.02-1.91), $P = .04$ | NR |
| Grabska et al[21] | Abstract | US | Overall: 1948<br>Higher risk: 609 | Retrospective, single center | Transplant | Median OS in higher-risk IPSS group:<br>Young adult: 82 months<br>Older/higher risk group: 17 months ($P = .001$)<br>Median OS for patients who received transplantation:<br>Young adult: 55 months<br>Older group: 46 months ($P = .4$) | NR |
| Musto et al[29] | Abstract | EU | 58 | Retrospective, multicenter | Deferasirox | Median OS: 38 months (after diagnosis) and 24.1 months (after start of iron chelator therapy); Evidence of 1 patient with a durable CR | NR |
| Pavesi et al[32] | Abstract | EU | 124 | Retrospective, single center 2003 to 2014 | Allo-HSCT | Median OS from allo-HSCT was 1149 days (38.3 months) for HR-MDS patients | 108 of 110 had CR (98%) at day 28; 61 of 73 transplantation patients with active disease achieved CR (84%)<br>54 Patients alive in CR at end of follow-up (median: 1230 days) |
| Seymour et al[34] | Full text | EU | 229 | RCT, multicenter | Azacitidine versus CCR | Hypocellular<br>Azacitidine median OS not reached by 33 months versus CCR, median: 16.9 months (95% CI:, 11.1-19.3) ($P = .001$);<br>No azacitidine patients achieved CR or PR (0%);1 patient receiving CCR had CR or PR (6%)<br>Nonhypocellular<br>azacitidine median OS 21.1 months (95% CI, 16.2-34.7) versus CCR median 15.3 months (95% CI, 9.3-17.6; $P = .012$) | Ten azacitidine patients with CR or PR (8%); 1 CCR patient with CR or PR (1%) |
| Burnett et al[14] | Full text | EU | 406 | RCT, multicenter (2006-2011) | LD-AraC versus clofarabine (first-line) | Two-year OS<br>LD-AraC 12% versus clofarabine: 13%; HR, 0.96 (95% CI, 0.78-1.19), $P = .7$<br>Two-year OS from CR<br>LD-AraC: 44%<br>Clofarabine: 26% | ORR<br>clofarabine: 38%<br>LD-AraC: 19% ($P < .0001$) |

**Table 2 Continued**

| Reference | Source | Country/Region | Sample Size | Design | Therapy | Survival/Disease Progression | Response |
|---|---|---|---|---|---|---|---|
| Faderl et al[3] | Full text | US | 59 | RCT, single center | I.V. clofarabine 15 mg/m$^2$ versus 30 mg/m$^2$ doses | Median OS: 7.4 months (overall) with no significant differences reported between dose groups | ORR: 36% (overall)<br>CR: 26% (overall) |
| Garcia-Manero et al[19] | Abstract | EU/US | 299 | RCT, multicenter (2010-2013) | Rigosertib or BSC (after failure with previous HMA) | Median OS: rigosertib 8.2 months versus 5.9 months BSC ($P$ = .33). HR, 0.87; 95% CI, 0.67-1.14<br>Subset with primary HMA failure, OS rigosertib 8.6 months versus 5.3 months BSC ($P$ = .04) | NR |

Abbreviations: allo-HSCT = allogeneic hematopoietic stem cell transplantation; AML = acute myeloid leukemia; BSC = best supportive care; CCR = conventional care regimen; EU = France, Germany, Italy, Spain, United Kingdom; HMA = hypomethylating agent; HR = hazard ratio; HR-MDS = higher-risk myelodysplastic syndrome; HSCT = hematopoietic stem cell transplantation; IPSS = International Prognostic Scoring System; IPSS-R = International Prognostic Scoring System-Revised; LD-AraC = low-dose cytosine arabinoside; MDS = myelodysplastic syndrome; OS = overall survival; PFS = progression-free survival; RCT = randomized controlled trial; RR = relative risk; US = United States; WPPS = WHO classification-based prognostic scoring system.

One study (Kantarjian et al[22]) reported survival for patients who underwent allo-HSCT after chemotherapy (cytarabine with or without topotecan with or without cyclophosphamides, or fludarabine with or without anthracyclines); those who had the procedure while experiencing a first CR had a higher estimated 5-year survival rate (36%) than those who underwent the procedure after a first CR failed (9%).

The CCR was the treatment in the only 2 studies that reported rates of progression to AML; Bernal et al[13] reported rates of 26% over a 9-month median follow-up, whereas Mutetwa et al[30] reported 33% over a 22-month median follow-up.

Finally, in a phase III RCT of rigosertib versus BSC,[19] although the primary OS end point did not reach statistical significance, in a subset of patients with primary HMA treatment failure, those treated with rigosertib had a median OS that was 3.3 months longer compared with BSC (median OS 8.6 vs. 5.3 months; $P$ = .04).

### *Chemotherapy with HMAs*

Ten observational studies (11 articles) reported patient survival rates (Table 2)[13,15,16,18,22,23,26-28,30,33] and most of those (n = 7 of 10) investigated the efficacy of azacitidine. Reported median OS ranged from 10.9 to 34 months.

Seymour et al[34] reported significantly improved OS with azacitidine compared with CCRs in patients with hypocellular and nonhypocellular bone marrow. In nonhypocellular patients, the median OS was 21.1 months with azacitidine versus 15.3 months in patients who received CCRs ($P$ = .012), whereas among hypocellular patients, median OS had not been reached at 33 months with azacitidine versus 16.9 months for those who received CCRs ($P$ = .001).

There were limited data on progression-free survival (PFS), with some partial evidence suggesting treatment with HMAs might delay disease progression. One study reported a median PFS of 31.5 months in patients treated with azacitidine.[26]

Overall response (OR) and, in particular, CR, are important end points in blood cancers, because they are associated with fewer infections, and less bleeding or need for supportive care.[36] Response rates were reported in 5 studies. The CR rates ranged from 37% (Kantarjian et al[22]) to 55% (Cabrero et al[15]) for therapy with HMA and allo-HSCT after induction. In HR-MDS with chromosome 7 abnormality, the CR rate was only 16.4% in patients treated with azacitidine with an OR rate (ORR) of 42.8%.[16] ORR was similar among patients treated with HMAs alone (43%) compared with patients treated with allo-HSCT after HMA (45%).[15] Durable CR, often considered an established end point of clinical benefit in leukemia, was reported in only 1 observational study, with 16% experiencing CR for at least 5 years.

Rates of CR varied widely from 0%[34] to 26%[3] for patients with hypocellular bone marrow treated with azacitidine and all patients treated with intravenous clofarabine, respectively. In Burnett et al,[14] OR for clofarabine (38%) was nearly double that of LD-AraC (19%; $P$ < .001), although clofarabine did not improve OS.

## Allogeneic HSCT

Provision of allo-HSCT is very expensive for health care systems because it is a highly specialized and labor-intensive procedure that requires prolonged isolation of the patient within specialized

hospital facilities, with a high requirement for blood products and expensive medications.[37]

We examined rates of allo-HSCT after treatment with previous therapy in the studies included in this review. Four studies in HR-MDS reported rates of allo-HSCT ranging from 6% to 14%.[18,22,29,33] Despite the fact that populations and previous treatments received were variable across studies, rates of allo-HSCT after therapy were fairly consistent. The study reporting the lowest rate examined patients treated with azacitidine who underwent allo-HSCT before their third treatment cycle[18]; additionally, only 22% of patients in this study were classified as high-risk according to IPSS.

Prébet et al[33] in 2011 examined rates of allo-HSCT after failure with azacitidine therapy, and reported that these cases had the highest rate of allo-HSCT (37 patients [14%]). Of the patients enrolled in this study, 106 [40%] were classified as having a high IPSS risk score. Median OS among patients who received allo-HSCT after azacitidine failure was 19 months.

Pavesi et al reported that 98% of patients treated with allo-HSCT had experienced CR at day 28.[32] This study population had a median age of 60 years; approximately 40% were already in CR at the time of allo-HSCT.[32]

In another study, OS in adults ages 18 to 39 years was compared with OS in patients older than 39 years.[21] Median OS was 82 months in the younger group compared with 17 months in the older group ($P = .001$). This study reported the highest median OS estimate of all the studies included in this review. Interestingly, no statistically significant difference was observed for the subset of patients who underwent transplantation; the median OS was 55 months in adults and adolescents, and 46 months in older patients ($P = .4$).

Gerds et al 2015[20] reported that high-/very high-risk patients who received umbilical cord blood transplantation were more likely to die from any cause (relative risk [RR], 1.55; $P = .01$) and also more likely to experience relapse (RR, 1.39; $P = .04$) compared with those classified as having very low-/low-risk disease.

### *Chronic Myelomonocytic Leukemia*

Of 24 articles in this review, only 5 reported results for CMML (Table 3)[17,24,25,31,35]; those represented 4 observational studies, only 1 of which had more than 85 patients (n = 513; Symeonidis et al[35]).

One study (reported in Kongtim et al[24] and Kongtim et al[25]) reported survival rates for CMML patients who received chemotherapeutic agents before allo-HSCT—3-year OS rates of 45% versus 39% ($P = .22$, not significant), and 3-year PFS rates of 43.2% versus 27.4% ($P = .04$), for HMAs versus CCRs, respectively.[24,25]

Three studies[17,31,35] evaluated allo-HSCT in CMML patients. Consistent results were reported across the studies; OS at 3 and 4 years was 32%[31] and 33%,[35] respectively. Eissa et al reported a median OS of 5.2 years (range, 0.5-19.1 years).[17]

Symeonidis et al[35] reported no significant differences in relapse-free survival or OS at 4 years on the basis of World Health Organization 2000 or 2008 classifications of CMML-1 and CMML-2. Cumulative incidence of relapse at 4 years was lower for patients with a normal karyotype compared with those with an abnormal one (35% vs. 49%; $P = .07$). However, 4-year

**Table 3 CMML Studies**

| Reference | Source | Country/Region | Sample Size | Design | Therapy | Survival/Disease Progression | Response |
|---|---|---|---|---|---|---|---|
| Kongtim, 2016 et al[24] and Kongtim et al[25] | Full text | US | 83 | Retrospective study, single center (MD Anderson Cancer Center) patient accrual years from 1991 to 2013 | Induction with HMA (either 5-azacitidine or decitabine) versus cytotoxic chemotherapy (idarubicin with cytarabine, or idarubicin with cytarabine and clofarabine) before allo-HSCT | At 3 years, OS: HMA 45% versus cytotoxic chemotherapy 39% ($P = .22$)<br>3-Year PFS: HMA 43.2% versus cytotoxic chemotherapy 27.4% ($P = .04$) | NR |
| Park et al[31] | Full text | France | 73 | Retrospective study, multicenter, 1992 to 2009 | Allo-HSCT | 2-Year OS: 42%<br>3-Year OS: 32% | NR |
| Symeonidis et al[35] | Full text | EU | 513 | Retrospective study, multicenter, patients received transplantation before 2009 | Allo-HSCT | 4-Year OS: 33% | CR at transplant: 26.2% |
| Eissa et al[17] | Full text | US | 85 | Prospective study, single center (Fred Hutchinson Cancer Center) 1986 to 2008 | Allo-HSCT | Median (range) OS: 5.2 (0.5-19.1) years<br>10-Year PFS: 38% | NR |

Abbreviations: allo-HSCT = allogeneic hematopoietic stem cell transplantation; CMML = chronic myelomonocytic leukemia; EU = France, Germany, Italy, Spain, United Kingdom; HMA = hypomethylating agent; OS = overall survival; PFS = progression-free survival; US = United States.

OS and relapse-free survival were not significantly different between patient subgroups.[35] Finally, Eissa et al[17] showed that relapse correlated with poor cytogenetics and with risk determined according to the MD Anderson Prognostic score. In addition, the authors also reported statistically significant associations between poor cytogenetics and nonrelapse mortality (hazard ratio, 3.09; $P = .02$) and overall mortality (hazard ratio, 2.73; $P = .004$).

## Discussion

This first SLR to explore real-world effectiveness of treatment regimens specifically for patients with HR-MDS or CMML began with >1000 unique citations that were reduced to only 24 articles (representing 22 studies). Because the review goal was real-world information, the data included in this analysis came from 18 observational studies; 4 RCTs were also included.

Survival outcomes were reported across all modes of treatment; patients who received chemotherapy alone had much shorter OS than did those who received allo-HSCT. Among studies that examined chemotherapy, the highest median OS reported was 34 months, in a study of azacitidine.[26,27] In the allo-HSCT setting, Grabska et al[21] reported 46-month median OS for older patients, significantly lower than younger patients' 55-month median. For CMML patients, median OS was 62 months.[17,21] The best chance for achieving long-term remission for HR-MDS/CMML patients is currently offered by allo-HSCT. However, the procedure is performed in only a fraction of potential patients—the median age range was 52 to 60 years for patients enrolled in studies of allo-HSCT, substantially lower than the 68- to 74-year median age range reported for the patients in studies of HMA/azacitidine.

There was some comparative evidence from 1 RCT suggesting better survival with azacitidine compared with a CCR.[34] Another RCT reported improved survival with rigosertib over BSC in the second-line setting after failure with primary HMAs.[19] Although rigosertib improved survival by only a few months, the result is encouraging, because dismal outcomes often follow failure of azacitidine treatment, and only approximately one-half of patients achieve objective response.[38]

Data on outcomes related to PFS or AML progression were much more limited, and were reported in only a quarter of the studies included in this review. One observational study that compared azacitidine with CCR observed no difference in the rate of AML progression.[13]

Overall response and CR outcomes were reported in one-half of the studies. Only 1 HR-MDS study of allo-HSCT reported CR rates; these ranged from 84% to 98%.[32] Studies that evaluated HMA therapy reported much lower CRs of 37% to 55%.[15]

By design, all studies in this review included a sample size of at least 50 patients. However, 60% of studies enrolled 200 or more patients. An adequate sample size is important; many of the studies with 100 or fewer patients were single-arm studies in which the purpose was to establish a response as proof of concept for a therapy under investigation. Several of the observational studies included in this review compared effectiveness across 2 or more treatment regimens.[13,15,24,28] Although observational studies by design cannot completely eliminate selection bias, and are hence considered inferior to RCTs, most did use multivariate methods in an effort to reduce these sources of bias. In addition, observational studies not only can offer important insights into the use and effectiveness of therapies in real-world settings, but also can often be complementary to RCTs.

In this SLR we sought to identify studies of patients with HR-MDS or CMML; however, much of the published literature included mixed populations of HR-MDS patients within a broader, lower-risk MDS population, or CMML patients among a broader AML population, with no discernible reporting of outcomes according to disease identity or severity. When subgroup results were presented for a population of interest, often the patient numbers were too low to show a data trend. This was further compounded by the variation in classification systems used to define "high risk" patients; these have evolved over time to incorporate not just clinical features but also transfusion requirements and prognostic factors.

## Conclusion

Overall, these results indicate there are limited real-world data regarding approved treatment strategies and associated clinical outcomes in patients with HR-MDS or CMML. The reviewed studies focused on patient outcomes associated with chemotherapy and/or stem cell transplantation. Patients ineligible for these treatments because of age or comorbidities, and related poor response, are not represented in these studies, which might limit broader application of the findings. The variability observed in study design, patient characteristics, risk-based disease scoring/classification, and numbers of previous therapeutic regimens complicates interpretation of the relative merit of therapeutic regimens. Although prognosis varied among studies, it was generally poor, and the data related to survival and response outcomes were insufficient to identify an optimal therapeutic approach, aside from allo-HSCT.

There is a general lack of data suitable to inform health care decisions and practices regarding patient care. In particular, the appropriateness of allo-HSCT as a treatment for older adults and the role of lower-intensity therapies such as azacitidine or decitabine as alternative options are still unclear. Our analysis shows the paucity of viable treatment options for older patients. This represents a critical, unmet medical need, especially because these conditions are most commonly diagnosed in elderly patients. Additional studies on the use of allo-HSCT in older adults along with a delineation of exclusionary factors are necessary to fill this knowledge gap.

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**Appendix A** Embase Search Algorithm

| Search Number | Search Terms | Yield |
|---|---|---|
| #1 | 'acute myeloblastic leukemia'/exp/mj OR 'acute myeloblastic leukemia' OR 'acute granulocytic leukemia'/exp/mj OR 'acute granulocytic leukemia' OR 'acute myeloid leukemia':ab,ti OR 'acute myelocytic leukemia':ab,ti OR 'acute granulocytic leukemia':ab,ti OR 'acute nonlymphocytic leukemia':ab,ti OR 'acute myeloblastic leukemia':ab,ti OR 'acute myelogenous leukemia':ab,ti OR aml:ab,ti OR 'anll':ab,ti OR (acute:ab,ti AND (myelogenous:ab,ti OR myeloid:ab,ti OR myeloblastic:ab,ti OR granulocytic:ab,ti OR nonlymphocytic:ab,ti) AND leukemia:ab,ti) | 90,471 |
| #2 | 'low-blast':ab,ti OR 'low blast':ab,ti OR oligoblast*:ab,ti | 205 |
| #3 | #1 AND #2 | 141 |
| #4 | 'myelodysplastic syndrome'/exp OR 'myelodysplastic syndrome' OR 'myelodysplastic myeloproliferative disease' OR 'myelodysplastic myeloproliferative disorder' OR 'myeloproliferative disease' AND ('high risk':ab,ti OR 'high-risk':ab,ti) | 3498 |
| #5 | 'chronic myelomonocytic leukemia'/exp OR 'chronic myelomonocytic leukemia':ab,ti OR 'chronic myelomonocytic leukaemia':ab,ti OR 'oligoblastic leukaemia':ab,ti OR 'oligoblastic leukemia':ab,ti | 4018 |
| #6 | #3 OR #4 OR #5 AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND [humans]/lim AND [english]/lim AND [abstracts]/lim AND [2006-2016]/py | 1680 |
| #7 | 'Case Reports'/exp OR 'letter'/exp OR 'editorial'/exp | 1,508,230 |
| #8 | 'review'/exp NOT (systematic OR (meta AND (analys* or analyz*)) OR (indirect OR mixed AND 'treatment comparison')) | 1,986,918 |
| #9 | #6 NOT (#7 OR #8) | 1306 |
| #10 | 'effectiveness:ab,ti OR safety:ab,ti OR 'adverse event':ab,ti OR 'unmet need':ab,ti OR mortality:ab,ti | 1,564,299 |
| #11 | ((epidemiol*:ab,ti OR incidence:ab,ti OR prevalence:ab,ti OR (('risk factor':ab,ti OR 'risk factors':ab,ti) AND (incidence:ab,ti OR prevalence:ab,ti)) NOT (randomi*:ab,ti OR control*:ab,ti OR phase:ab,ti))) | 1,190,304 |
| #12 | (((treatment*:ab,ti OR therap*:ab,ti) AND (manage*:ab,ti OR pattern*:ab,ti OR 'use':ab,ti OR prescrib*:ab,ti OR trend*:ab,ti OR 'survey':ab,ti)) NOT (randomi*:ab,ti OR control*:ab,ti)) | 1,248,859 |
| #13 | (cost:ab,ti OR costs:ab,ti OR fee:ab,ti OR fees:ab,ti OR budget*:ab,ti OR expenditure*:ab,ti OR 'resource utilization':ab,ti OR 'resource utilisation':ab,ti OR 'resource use':ab,ti OR economic*:ab,ti OR pharmacoeconomic*:ab,ti OR productivity:ab,ti OR 'work loss':ab,ti OR employment:ab,ti OR retirement:ab,ti OR absenteeism:ab,ti OR presenteeism:ab,ti OR 'sick leave':ab,ti OR 'sick day':ab,ti OR 'caregiver burden':ab,ti) | 827,924 |
| #14 | ('quality of life':ab,ti OR 'quality-of-life':ab,ti OR satisfaction:ab,ti OR utilities:ab,ti OR disability:ab,ti OR 'health status':ab,ti OR 'health utility':ab,ti OR 'health utilities':ab,ti OR 'health state utility':ab,ti OR 'health state utilities':ab,ti OR 'utility score':ab,ti OR 'utility value':ab,ti OR 'standard gamble':ab,ti OR 'time trade-off':ab,ti OR 'time tradeoff':ab,ti OR 'time trade off':ab,ti OR preference*:ab,ti OR eq-5d:ab,ti OR EQ5D:ab,ti OR 'utility assessment':ab,ti OR hui:ab,ti OR 'short form 6d':ab,ti OR 'short-form 6d':ab,ti OR sf6d:ab,ti OR sf-6d:ab,ti OR 'sf 6d':ab,ti) | 654,901 |
| #15 | (#9 AND #10) | 287 |
| #16 | (#9 AND #11) | 169 |
| #17 | (#9 AND #12) | 145 |
| #18 | (#9 AND #13) | 21 |
| #19 | (#9 AND #14) | 33 |
| #20 | (#15 OR #16 OR #17 OR #18 OR #19) | 500 |