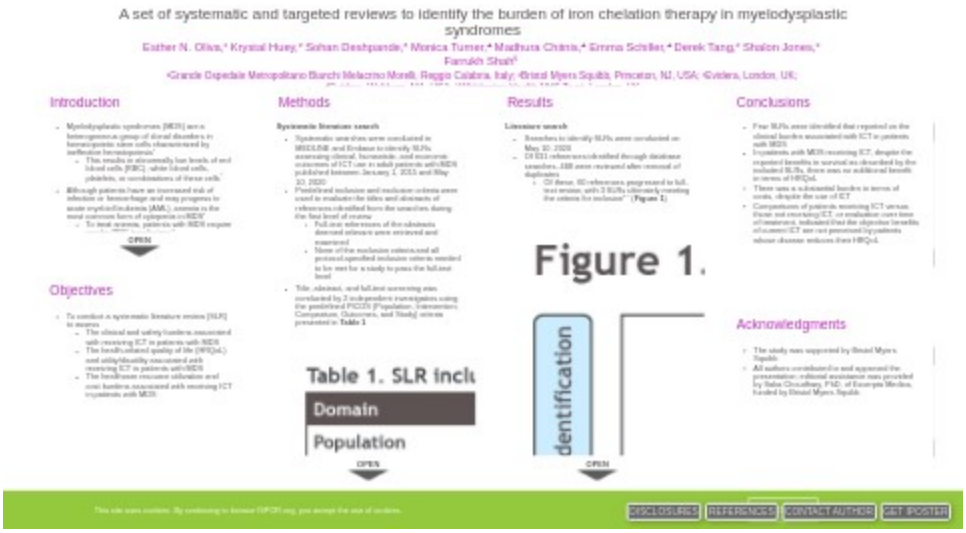
A set of systematic and targeted reviews to identify the burden of iron chelation therapy in myelodysplastic syndromes



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INTRODUCTION

- Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal disorders in hematopoietic stem cells characterized by ineffective hematopoiesis[1]
  - This results in abnormally low levels of red blood cells (RBC), white blood cells, platelets, or combinations of these cells[1]
- Although patients have an increased risk of infection or hemorrhage and may progress to acute myeloid leukemia (AML), anemia is the most common form of cytopenia in MDS[2]
  - To treat anemia, patients with MDS require regular RBC transfusions[3]
- RBC transfusions can ultimately result in iron overload with harmful consequences such as organ damage and increased mortality[4]
- Iron chelation therapy (ICT) can limit overload by binding with excess iron, allowing it to be excreted[4]
  - However, ICT carries the risk of adverse events such as reduction in renal function and gastrointestinal side effects[4]
  - With treatment typically being lifelong, ICT can be physically, emotionally, and financially demanding[4]

OBJECTIVES

- To conduct a systematic literature review (SLR) to assess
  - The clinical and safety burdens associated with receiving ICT in patients with MDS
  - The health-related quality of life (HRQoL) and utility/disutility associated with receiving ICT in patients with MDS
  - The healthcare resource utilization and cost burdens associated with receiving ICT in patients with MDS

METHODS

Systematic literature search

- Systematic searches were conducted in MEDLINE and Embase to identify SLRs assessing clinical, humanistic, and economic outcomes of ICT use in adult patients with MDS published between January 1, 2015 and May 10, 2020
- Predefined inclusion and exclusion criteria were used to evaluate the titles and abstracts of references identified from the searches during the first level of review
  - Full-text references of the abstracts deemed relevant were retrieved and examined
  - None of the exclusion criteria and all protocol-specified inclusion criteria needed to be met for a study to pass the full-text level
- Title, abstract, and full-text screening was conducted by 2 independent investigators using the predefined PICOS (Population, Intervention, Comparison, Outcomes, and Study) criteria presented in **Table 1**

Table 1. SLR inclusion criteria

Domain	Inclusion criteria
Population	Adult (≥18 years) patients with MDS
Intervention/comparators	Patients must have received ICT
Outcomes	Clinical outcomes: • Number of RBC transfusions (units and/or visits) • PFS and EFS • OS and mortality • Time to development of high-risk disease, transfusion-dependent MDS or AML • Adherence and discontinuation • Total number of patients experiencing SAEs • Grade 3 or 4 AEs, all-grade AEs, treatment-related AEs, and treatment-related SAEs • Incidence of complications related to iron overload, including cardiac failure, hypogonadism, hypothyroidism, carcinoma, diabetes, liver failure • Number of patients with treatment discontinuations: - Total - Due to safety tolerability - Due to lack of efficacy - Lost to follow-up Humanistic outcomes: • Utility studies • HRQoL (e.g. EQ-5D, SF-36, and EORTC QLQ-C30) Economic outcomes: Healthcare resource utilization • Specialist visits • Unscheduled physician visits • Emergency room visits • Transfusion clinic visits • Hospitalization Costs • Direct costs • Total treatment costs • Costs of healthcare and social care • Indirect costs • Productivity • Absenteeism and presenteeism
Study designs	SLRs, NMAs, MAs
Duplicate	If duplicates are identified, the copy of the record with the lower refID number will be included
Study limits	Only English-language articles/conference abstracts will be included • Studies published from January 1, 2015 to May 10, 2020
Geography	None

AE, adverse event; AML, acute myeloid leukemia; EFS, event-free survival; EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D, EuroQol Questionnaire, 5 dimensions; HRQoL, health-related quality of life; ICT, iron chelation therapy; MA, meta-analysis; MDS, myelodysplastic syndromes; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; RBC, red blood cell; SAE, serious adverse event; SF-36, 36-item Short Form Health Survey; SLR, systematic literature review.

Targeted literature search

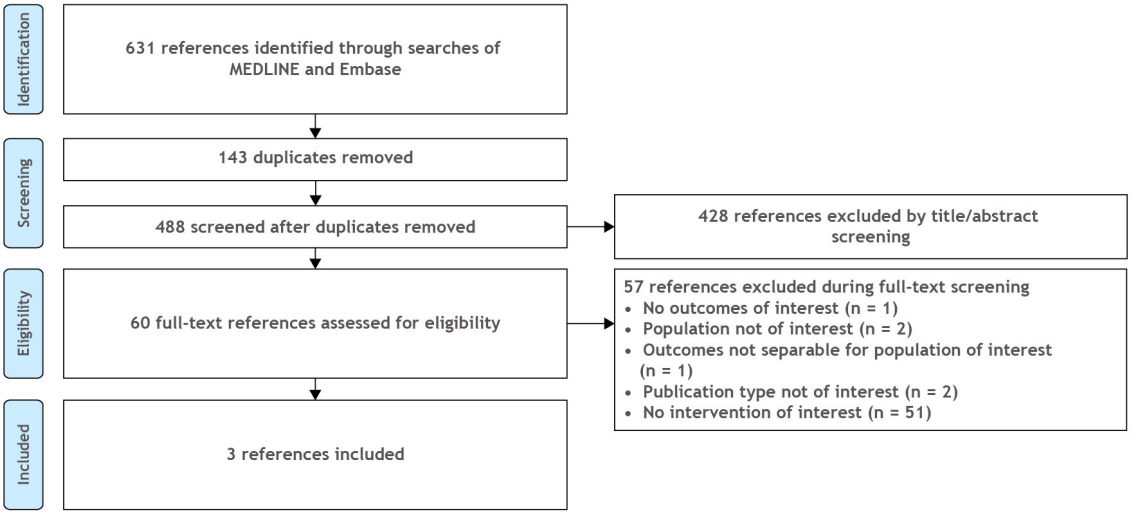
- To fill remaining gaps in data, a subsequent targeted search was conducted in Embase to identify references from 2009 to 2020
- Selection criteria mirrored those used to identify SLRs, but focused on primary studies

RESULTS

Literature search

- Searches to identify SLRs were conducted on May 10, 2020
- Of 631 references identified through database searches, 488 were reviewed after removal of duplicates
  - Of these, 60 references progressed to full-text review, with 3 SLRs ultimately meeting the criteria for inclusion[5–7] (**Figure 1**)

Figure 1. PRISMA diagram of study attrition



PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

- Given the small amount of data identified from the included SLRs, additional targeted searches were conducted to fill the data gaps
  - Despite the targeted searches, few studies were identified exploring the burden that remains for patients treated with ICT

Overview of included SLRs

- 3 SLRs were identified that reported on the burden of ICT in adult patients with MDS[5–7]
  - The SLRs and their objectives are shown in **Table 2**
  - The studies focused primarily on the benefits experienced by patients who received ICT, particularly compared with patients who did not receive ICT

Table 2. Summary of included SLRs

Author, year	Stated objective of SLR	Studies included in SLR
Yang et al, 2019[5]	To better elucidate the association between elevated serum ferritin and OS of MDS and AML patients, as well as investigate the impact of ICT on OS of patients with MDS and the progression of MDS to AML	20 observational studies were included in the review. Of those, 7 studies reviewed the impact of ICT on patients with MDS, and 7 studies reported on the impact of ICT in the progression of MDS to AML; as data were reported separately for these studies, those data points were included in the review
Zeidan et al, 2019[6]	To explore the relationship between ICT and clinical outcomes in patients with MDS by performing a systematic review and meta-analysis	9 observational studies
Zhang et al, 2019[7]	To systematically evaluate the efficacy and safety of iron chelators for transfusion-dependent patients with MDS	13 observational studies

AML, acute myeloid leukemia; ICT, iron chelation therapy; MDS, myelodysplastic syndromes; OS, overall survival; SLR, systematic literature review.

- The 3 SLRs included several observational studies[5-7]

- 1 SLR reported on a broader population including patients with AML; results were presented separately for studies including patients with MDS[5]

Survival and disease progression

- Across the 3 SLRs, receiving ICT had a protective effect on survival when compared with patients who did not receive ICT (**Table 3**)

Table 3. OS and mortality outcomes reported in included SLRs

Author, year	Population	Outcome evaluated	Effect size
Zeidan et al, 2019[6]	Patients with Low- to Intermediate-risk MDS	Pooled estimate of the ratio median OS, unadjusted data for ICT vs no ICT (6 studies)	HR 2.10 (95% CI 1.77-2.56)
		Random-effects model of OS in patients who received adequate ICT (2 studies)	HR 0.26 (95% CI 0.16-0.40); $P < 0.01$
		Random-effects model of OS in patients who received any ICT (5 studies)	HR 0.55 (95% CI 0.40-0.7); $P < 0.01$
		Risk of mortality, ICT vs no ICT (7 studies)	HR 0.42 (95% CI 0.28-0.62); $P < 0.01$
		Change in risk of death associated with ICT vs no ICT	HR 0.42 (95% CI 0.28-0.62)
		Survival in patients who received the higher adequate dose of ICT	HR 0.26 (95% CI 0.16-0.40); $P < 0.01$
Yang et al, 2019[5]	Patients with Low- to Intermediate-risk MDS	Pooled estimate of the median OS, ICT vs no ICT (7 studies)	HR 0.30 (95% CI 0.23-0.40)
	Patients with lower-risk MDS	Pooled estimate of the median OS, ICT vs no ICT, (3 studies)	HR 0.35 (95% CI 0.21-0.59)
	Patients with Low- to Intermediate-risk MDS (does not include studies with lower IPSS risk patients only or unspecified risk level MDS patients)	Pooled estimate of the median OS, ICT vs no ICT (3 studies)	HR 0.32 (95% CI 0.20-0.51)
	Patients with MDS (IPSS risk not specified)	Pooled estimate of the median OS, ICT vs no ICT (1 study)	HR 0.22 (95% CI 0.12-0.41)
Zhang et al, 2019[7]	Patients with transfusion-dependent MDS	Pooled estimate of the median OS, ICT vs no ICT (13 studies)	HR 0.52 (95% CI 0.43-0.62); $P < 0.001$
	Patients with lower-risk MDS	Pooled estimate of the median OS, ICT vs no ICT (8 studies)	HR 0.50 (95% CI 0.43-0.59); $P < 0.001$
	Patients with MDS treated with DFX monotherapy	Pooled estimate of OS in MDS patients receiving DFX monotherapy vs those not receiving iron chelators (3 studies)	HR 0.43 (95% CI 0.27-0.69); $P < 0.001$

CI, confidence interval; DFX, deferasirox; HR, hazard ratio; ICT, iron chelation therapy; IPSS, International Prognostic Scoring System; MDS, myelodysplastic syndromes; OS, overall survival; SLR, systematic literature review.

- Disease progression was also reported as leukemia-free survival (**Table 4**) and as progression to AML (**Table 5**)
  - 1 SLR showed a small improvement in leukemia-free survival for patients receiving ICT compared with those not receiving ICT[7]
  - 2 SLRs evaluated progression to AML and found no significant association between receiving ICT and either the rate of progression to AML or the occurrence of progressing to AML[5,6]

Table 4. Leukemia-free survival outcomes reported in included SLRs

Author, year	Population in SLR	Outcome evaluated	Effect size
Zhang et al, 2019[7]	Patients with MDS (risk not specified)	Pooled estimate of leukemia-free survival in patients with ICT vs without ICT	HR 0.84 (95% CI 0.76-0.93); $P = 0.001$

CI, confidence interval; HR, hazard ratio; ICT, iron chelation therapy; MDS, myelodysplastic syndromes; SLR, systematic literature review.

Table 5. Disease progression to AML reported in included SLRs

Author, year	Population in SLR	Outcome evaluated	Effect size
Yang et al, 2019[5]	Patients with Low- to Intermediate-risk MDS	Pooled estimate for progression to AML (7 studies)	RR 0.84 (95% CI 0.61-1.16)
Zeidan et al, 2019[6]	Patients with Low- to Intermediate-risk MDS	Rate of transformation to AML, ICT vs no ICT (7 studies)	OR 0.68 (95% CI 0.31-1.43); $P = 0.30$

AML, acute myeloid leukemia; CI, confidence interval; ICT, iron chelation therapy; MDS, myelodysplastic syndromes; OR, odds ratio; RR, relative risk; SLR, systematic literature review.

Cardiac events

- 2 SLRs reported on reduction in cardiac events in patients with MDS who received ICT[6,7] (**Table 6**)

Table 6. Cardiac events reported in included SLRs

Author, year	Population in SLR	Outcome evaluated	Effect size
Zeidan et al, 2019[6]	Patients with Low- to Intermediate-risk MDS	Median cardiac event-free survival in chelated patients compared with nonchelated patients (1 study)	137 vs 96 months; $P = 0.017$
Zhang et al, 2019[7]	Patients with MDS (risk not specified)	Cardiac adverse events in patients who received ICT vs those who did not receive ICT	RR 64% (95% CI 57-71); $P < 0.001$

CI, confidence interval; ICT, iron chelation therapy; MDS, myelodysplastic syndromes; RR, relative risk; SLR, systematic literature review.

Overview of targeted search

- The targeted search identified studies that reported on humanistic or economic outcomes
  - 3 studies provided data on HRQoL[8,9,12]
    - 36-item Short Form Health Survey (SF-36)[8]
    - EuroQol Questionnaire, 5 Dimensions (EQ-5D)[9]
    - European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)[12]
  - 2 studies provided cost data associated with ICT[13,14]

SF-36

- A cohort of 24 French patients with MDS treated with deferoxamine (for an unspecified amount of time) was compared with the general French population[8]
  - In all SF-36 domains, the average HRQoL for patients with MDS was worse than that of the general population, with differences ranging from 1.9 to 51.9 points
    - The domains where the patients with MDS scored > 5-point difference (a clinically meaningful worsening in HRQoL) compared with the general population were physical functioning (32.4-point difference), physical role (51.9-point difference), emotional role (38.2-point difference), vitality (17.5-point difference), social functioning (14.9-point difference), general health (30.1-point difference), and both the composite scores for physical (18-point difference) and psychological (6.4-point difference)
  - Patients with MDS receiving treatment with deferoxamine reported a clinically meaningful worse HRQoL compared with the general population, despite their treatment with ICT

EQ-5D

- In a cohort of European patients with MDS, the mean (SD) index score for non-chelated patients (n = 591) and chelated patients (n = 197) was 0.7 (0.2) for both groups (P = 0.186), indicating there were no differences in HRQoL between non-chelated and chelated patients[9]
  - This suggests that ICT did not provide an added benefit nor a negative impact on HRQoL over non-chelated patients as measured by the EQ-5D
- General population norms reported by the EuroQoL Group for interpreting the EQ-5D in 12 European countries ranged from 0.82 to 0.91[10]
  - Based on the minimal clinically important difference for the EQ-5D being 0.061 in Spain and 0.063 in England,[11] these findings indicate that patients with MDS experienced a discernibly worse HRQoL than the general population despite treatment with ICT

EORTC QLQ-C30

- A cohort of Italian patients with MDS (n = 146) receiving oral deferasirox over the course of 12 months reported no significant change from baseline in HRQoL over time with treatment[12]
  - Assessments were at baseline, 3, 6, 9, and 12 months; global health status (P = 0.56), physical functioning (P = 0.41), diarrhea (P = 0.81), fatigue (P = 0.47), constipation (P = 0.29), or nausea/vomiting (P = 0.64)
  - Patients remained stable approximately 10 points below the normal global health status score for the Italian population, indicating reduced HRQoL

Economic burden

- In 2 studies, ICT generated a substantial cost burden among patients with MDS[13,14]

- 1 study of 35 patients in the United Kingdom (UK) reported the expected 10-year costs (in United States dollars [USD] from 2000 to 2010) of deferasirox, desferrioxamine, and deferiprone; projected costs were USD 2,064,800, USD 526,880, and USD 561,056, respectively, across all patients[13]
- A UK-based cost-effectiveness analysis compared costs (in 2018 British pounds [GBP]) associated with deferasirox to those associated with desferrioxamine[14]
  - Per-patient lifetime costs including drug acquisition, administration, and monitoring for patients treated with deferasirox were reported as GBP 98,700, compared with GBP 77,201 for desferrioxamine
    - These costs were in addition to a lifetime cost of GBP 66,951 for blood transfusions

CONCLUSIONS

- Few SLRs were identified that reported on the clinical burden associated with ICT in patients with MDS
- In patients with MDS receiving ICT, despite the reported benefits in survival as described by the included SLRs, there was no additional benefit in terms of HRQoL
- There was a substantial burden in terms of costs, despite the use of ICT
- Comparisons of patients receiving ICT versus those not receiving ICT, or evaluation over time of treatment, indicated that the objective benefits of current ICT are not perceived by patients whose disease reduces their HRQoL

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DISCLOSURES

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