Deferasirox therapy is associated with reduced mortality risk in a medicare population with myelodysplastic syndromes

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Aims: Iron overload adversely affects patients with myelodysplastic syndromes (MDS), but benefits of iron chelation therapy have not been clearly demonstrated. We examined the association between deferasirox (DFX) therapy and mortality in transfusion-receiving Medicare patients. **Patients & methods:** MDS patients from 2005 to 2008 were identified using ICD-9 codes from 100% Medicare claims. Patients receiving ≥ 20 blood units were observed until death or end of study. Marginal structural models were used for estimation. **Results:** 3926 patients (10.1% used DFX) were observed for a mean of 48.8 weeks. Each incremental week of DFX was associated with a significant reduction in mortality risk (hazard ratio [HR]: 0.989; 95% CI: 0.983–0.996; $p = 0.001$). **Conclusion:** DFX therapy is associated with a reduced mortality risk among older MDS patients who received a minimum transfusion threshold.

Keywords: deferasirox • iron chelation therapy • iron overload • mortality • myelodysplastic syndromes

Background

Up to 90% of patients with myelodysplastic syndromes (MDS) develop anemia [1,2], most will require red blood cell (RBC) transfusions during the course of the disease, and as many as 40% will become RBC transfusion-dependent (TD) [3]. Chronic RBC transfusion therapy places patients at significant risk of developing iron overload (IO) and its associated complications [1–3]. TD anemia leading to secondary IO has been associated with adverse clinical outcomes and adverse effects on survival in patients with MDS [3–6]. Although no randomized prospective data examining the impact of ICT on survival in MDS have been reported to date, iron chelation therapy (ICT) is commonly prescribed to MDS patients with TD anemia, especially patients with lower-risk (LR) MDS [7,8]. We have recently shown that ICT use in MDS has increased since the US FDA approval of the first oral chelator deferasirox (DFX) in 2005 [9].

The majority of current evidence supporting the beneficial effects of ICT on survival and hard clinical outcomes in patients with

MDS comes from observational studies. Analysis of observational data is subject to multiple biases that affect the association between treatment and outcomes. In addition, when treatment and clinical status change over time, there may be problems with time-varying confounding, in which therapy administered in one time period may affect the values of covariates in subsequent time periods, as well as have an independent effect on the outcomes of interest (Figure 1). Marginal structural outcome models (MSM) represent a strategy for addressing this problem.

MSM are estimated with time-varying exposures and covariates. In a traditional propensity score (PS) analysis, a multivariable model treatment model is estimated, and the results are used to predict a treatment probability. This PS can be used to match, stratify or weight-treated and -untreated observations, with the objective of addressing confounding based on observed characteristics. The observations in MSM are weighted by the inverse treatment propensity, but unlike the traditional PS approaches, the treatment

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Figure 1. Time-varying effects of health status, clinical parameters on iron chelation therapy use and outcomes in heavily transfused myelodysplastic syndromes patients. Illustrates how treatment in period 1 is determined by the constellation of general life expectancy, MDS progression, ferritin levels and anticipated need for additional transfusions. Treatment in period 2 is based on updated information, including parameters that may be influenced by treatment in period 1.
AML: Acute myeloid leukemia; CHF: Congestive heart failure; ICT: Iron chelation therapy; MDS: Myelodysplastic syndrome; RBC: Red blood cell.

propensities in a MSM are calculated for each time period based on time-varying characteristics. MSM can, therefore, examine the effects of therapy with variable duration, and where there is the potential for time-varying confounding [10–12]. We used MSM to study the association between ICT using DFX with important clinical outcomes and survival in a large USA Medicare-based patient cohort with MDS.

Patients & methods

Materials & study population

We developed a large database of patients with MDS using Medicare enrollment information linked to claims data, generated from the 100% Medicare files from 2004 through 2008 (Figure 2) [13,14]. Medicare is the US federally administered insurance program for adults aged 65 years and older, or younger disabled adults. The enrollment files included monthly

indicators of participation in Medicare Parts A (covering inpatient, skilled nursing and hospice services), B (covering health professional and laboratory services), C (enrollment in alternative delivery systems such as health maintenance organizations) and D (prescription drug coverage), as well as selected demographic characteristics. Claims for Medicare Parts A, B and D included detailed information on dates, diagnoses and services provided based on International Classification of Diseases 9-Clinical Modification (ICD-9-CM) procedure codes, Healthcare Common Procedure Diagnosis Coding System (HCPCS) codes and/or National Drug Codes (NDC). Inclusion required one inpatient claim with an MDS diagnosis (238.7 prior to October 2006, 238.72–5 beginning October 2006), or two outpatient claims ≥30 days apart but within 12 months. MDS index date was set at 1 January 2005 for those who met the criteria for MDS in 2004, and

otherwise at the date of the first claim with a diagnosis that qualified them for the MDS cohort. Beneficiaries had to be enrolled in Medicare Parts A and B but not enrolled in a Medicare Advantage plan for the entire observation.

The specific study cohort consisted of MDS patients who met a minimum transfusion threshold of either 10 total weeks with transfusions (two units each) or 20 RBC units after their index MDS date (Figure 2). Observation began the week immediately after the patient met the minimum transfusion threshold and ended at the incident diagnosis of a condition of interest, death or end of study. Patients were excluded if they received ICT prior to the start of the observation period, received parenteral ICT during observation or progressed to acute myeloid leukemia (AML) before the beginning of study. To ensure that all relevant prescription drug transactions would be captured, the cohort was limited to patients continuously enrolled in Medicare Part D beginning the later of 1 January 2006 or cohort entry, and continued enrollment throughout the observation. All risk groups were eligible.

Measurement of key variables

Mortality

All-cause mortality was captured from indicators in the Medicare enrollment files, and summarized using a monthly indicator.

Other clinical outcomes & covariates

Clinical outcomes were derived from the medical care claims using algorithms that included a combination of diagnoses, place of service (e.g., inpatient hospitalization) and/or prescription drug claims. Similar to identifying onset of MDS, diagnosis of a new condition required that it be coded in an inpatient hospital or two outpatient claims at least 29 days apart, but within 12 months. Baseline (prevalent) conditions were based on the presence of clinical indicators present at the time of MDS diagnosis or in the 12 preceding months. For those without a baseline history of a condition, we created a weekly indicator for new condition onset after cohort entry. Conditions included: first, acute events, including acute myocardial infarction and stroke and, second, chronic conditions, including congestive heart failure (CHF), cardiac conduction disorder, chronic organ failure (liver, renal), diabetes, thyroid dysfunction, severe mental illness and dementia, and we also observed for progression to AML. Although mental illness and dementia are not associated with IO, they may affect treatment and outcomes. We recorded weekly hospitalizations for sepsis and diagnoses of infections based on inpatient or outpatient visits.

Patient characteristics

Age at MDS diagnosis, race and sex were determined from Medicare enrollment files. MDS risk group was

Figure 2. Derivation of the study cohort.

AML: Acute myeloid leukemia; CHF: Congestive heart failure; DM: Diabetes; ICT: Iron chelation therapy; MDS: Myelodysplastic syndrome; PRBC: Packed red blood cell unit; w/o: Without.

measured based on ICD-9 diagnostic codes on claims that qualified the patient for the study. For data spanning from 2005 to September 2006, MDS patients were identified using 238.7 ICD-9 codes. Beginning in October 2006, the ICD-9 classification included a 5th digit permitting additional classification by MDS risk. The ICD-9 codes 238.72 identified LR-MDS patients, 238.74 identified del(5q) MDS patients, 238.73 identified high-risk MDS patients and 238.75 MDS patients not-otherwise-specified (NOS). Predicted poor disability status (DS), a claims-based measure that uses regression weights to generate an indicator for patients with a high probability of poor DS [15,16], was assessed based on claims during the 12 months prior to MDS diagnosis.

Medications and other therapies used in management of MDS were captured based on specific HCPCS, NDC or revenue codes on claims. We captured exposure to ICT, RBC transfusions, erythropoiesis-stimulating agents (ESAs), hypomethylating agents (HMAs), lenalidomide, granulocyte colony-stimulating factor (G-CSF) and platelet transfusions. We created discrete indicators that flagged exposure during the 12 months prior to cohort entry.

Statistical considerations

The analytic file was structured with monthly patient observations. Beginning with cohort entry, each monthly record included a cumulative count of weeks with receipt of DFX, RBC units and cumulative indicators for prior or current month receipt of ESAs, lenalidomide, HMA, platelets and indicators for new diagnoses of chronic conditions and acute outcome events, progression to AML, death or censoring. Cumulative DFX exposure was captured in both a continuous and categorical measure. Each person-month record included a counter of weeks since cohort entry. We also linked time-invariant measures to each observation. The analyses included univariate and bivariate descriptions of the characteristics of patients in the cohort, exposures to therapies and outcomes of interest. MSM were used to examine the contributions of DFX use to the morbidity outcomes of incident AML, CHF, diabetes, hypothyroidism, renal disease and mortality [11,17–18]. Cases with prior experience of the outcome of interest were excluded from the analysis of that outcome, but not from the mortality analysis. Outcome models were estimated using repeated logistic regression, a technique commonly used to analyze survival data with time-varying covariates. The dependent variable was an indicator for whether the outcome of interest occurred in the month, as a function of the time-varying exposures to DFX, other MDS therapies, RBC, covariates and with controls for time since cohort entry. Because each indi-

vidual contributed multiple monthly observations, the analysis corrected the standard errors using a clustering adjustment. All analyses used Stata 12 (StataCorp, TX, USA). Details of the MSM analysis and the propensity models are provided in the [Supplementary Material](#) (see online at www.futuremedicine.com/doi/full/10.2217/CER.15.20). The study was approved by the University of Maryland Institutional Review Board.

Results

Demographic & baseline characteristics

The characteristics of 3926 patients who met eligibility criteria, overall and stratified by DFX use, are shown in [Table 1](#). The mean age of the group was 77.8 years (standard deviation [SD]: 8.6 years), 54.5% were female and 90.3% were white. The majority of MDS patients (78.8%) were coded as MDS NOS. The remaining patients were coded as follows: 13.6% as low-risk, 2.1% MDS associated with del(5q) and 5.5% high-risk MDS. Prevalent baseline co-morbidities included CHF (47.1%), history of arrhythmias or cardiac conduction abnormalities (42.2%), history of a solid tumor (25.4%), renal disease (29.7%), thyroid disease (28.0%), diabetes mellitus (36.6%) and hepatitis/liver failure (10.6%). Approximately, 84% of patients received ESAs, 18.3% HMAs and 7% lenalidomide prior to start of study. A total of 15.6% had poor predicted DS. DFX users had fewer baseline co-morbidities and better DS compared with nonusers ([Table 1](#)).

DFX, MDS therapies, new medical diagnoses & blood transfusion utilization

Patients were observed for a mean of 48.8 weeks (median: 34 weeks; range: 1–207 weeks). DFX was used by 398 patients (10.1%) during the observation period, with a mean duration of use of 29.5 weeks (SD: 27.6 weeks; median: 21.5 weeks). Duration of DFX therapy varied from ≤13 (35.9%), 14–26 (20.9%), 27–52 (27.6%) to ≥53 weeks (15.6%). Approximately, 84.9, 25.1, 28.5 and 13.0% of patients had received ESAs, HMAs, G-CSF or lenalidomide, respectively, by the end of the observation period. The follow-up period was significantly longer for DFX users compared with nonusers (73 vs 31 weeks; $p < 0.001$). [Table 2](#) shows the frequency of new medical diagnoses during the observation period. During the observation period, 85.6% of patients received additional RBC transfusions above the minimum eligibility threshold, with a mean of 19.4 units (SD: 25.8 units) and a median of 10 units.

DFX use & mortality

By the end of the follow-up period, 2331 patients (59.4%) had died (43.0% of DFX users vs 61.2% of DFX non-users; $p < 0.001$). [Figure 3](#) shows the Kaplan–Meier

Demographics and baseline characteristics	Overall		By DFX use				p-value [†]
			No		Yes		
	n = 3926		n = 3528		n = 398		
	Frequency	%	Frequency	%	Frequency	%	
Demographic variables							
Sex:							
– Male	1785	45.47	1582	44.84	203	51.01	0.019
– Female	2141	54.53	1946	55.16	195	48.99	
Race:							
– Nonminority (white)	3546	90.32	3194	90.53	352	88.44	0.181
– Minority (non-white)	380	9.68	334	9.47	46	11.56	
Age at diagnosis (mean, standard deviation)	(77.76, 8.57)		(78.06, 8.52)		(75.16, 8.53)		<0.001
Cohort entry year:							
– 2005	547	13.93	469	13.29	78	19.60	<0.001
– 2006	1043	26.57	929	26.33	114	28.64	
– 2007	1140	29.04	1008	28.57	132	33.17	
– 2008	1196	30.46	1122	31.80	74	18.59	
MDS disease characteristics							
MDS dx subtype:							
– Lower grade (ICD-9 238.72)	535	13.63	480	13.61	55	13.82	0.010
– Higher grade (ICD-9 238.73)	215	5.48	192	5.44	23	5.78	
– With 5q deletion (ICD-9 238.74)	84	2.14	*				
– Not otherwise specified (ICD-9 238.7 or 238.75)	3092	78.76	2779	78.77	313	78.64	
Treatments prior to cohort entry:							
– Erythropoiesis-stimulating agents	3296	83.95	2948	83.56	348	87.44	0.046
– Hypomethylating agents	720	18.34	614	17.40	106	26.63	<0.001
– Granulocyte-colony stimulating factor	969	24.68	850	24.09	119	29.90	0.011
– Lenalidomide	276	7.03	241	6.83	35	8.79	0.146
Health status prior to MDS diagnosis							
Predicted disability status:							
– Good	3315	84.44	2946	83.50	369	92.71	<0.001
– Poor	611	15.56	582	16.50	29	7.29	
Specific disease conditions prior to cohort entry:							
– Solid cancer	997	25.39	917	25.99	80	20.10	0.010
– Acute myocardial infarction	265	6.75	249	7.06	16	4.02	0.022
– Arrhythmia, cardiac conduction disorder	1655	42.15	1536	43.54	119	29.90	<0.001
[†] Comparison of deferasirox users to nonusers, using either a Chi-squared or <i>t</i> -test.							
[‡] Estimate suppressed due to small cell size.							
[§] Included major depression, bipolar disorder, and schizophrenia.							
del (5q): Chromosome 5q deletion; DFX: Deferasirox; MDS: Myelodysplastic syndrome.							

Table 1. Demographics and baseline characteristics of the study cohort (overall and as stratified by deferasirox use) (cont.).

Demographics and baseline characteristics	Overall		By DFX use				p-value [†]
			No		Yes		
	n = 3926		n = 3528		n = 398		
	Frequency	%	Frequency	%	Frequency	%	
– Congestive heart failure	1848	47.07	1724	48.87	124	31.16	<0.001
– Hepatitis/liver failure	417	10.62	388	11.00	29	7.29	0.023
– Renal disease	1167	29.72	1104	31.29	63	15.83	<0.001
– Diabetes	1438	36.63	1323	37.50	115	28.89	0.001
– Thyroid	1099	27.99	1013	28.71	86	21.61	0.003
– Mental illness [§]	828	21.09	760	21.54	68	17.09	0.039
– Alzheimer’s disease	619	15.77	597	16.92	22	5.53	<0.001
– Venous thromboembolism	374	9.53	347	9.84	27	6.78	0.049
– CNS bleeding	94	2.39	*				0.597
– Gastrointestinal bleeding	1307	33.29	1238	35.09	69	17.34	<0.001
– Neutropenia	1092	27.81	985	27.92	107	26.88	0.662
– Pancytopenia	672	17.12	633	17.94	39	9.80	<0.001
– Thrombocytopenia	1169	29.78	1070	30.33	99	24.87	0.024
– Hospitalization for sepsis	301	7.67	278	7.88	23	5.78	0.135

[†]Comparison of deferasirox users to nonusers, using either a Chi-squared or t-test.

*Estimate suppressed due to small cell size.

[§]Included major depression, bipolar disorder, and schizophrenia.

del (5q): Chromosome 5q deletion; DFX: Deferasirox; MDS: Myelodysplastic syndrome.

survival estimates for the study cohort stratified by any DFX use during the observation period. The median time to death was 54 weeks (116 weeks for DFX users vs 47 weeks for DFX nonusers; $p < 0.001$) (Figure 3).

Factors associated with mortality

After adjustment for the observed time-varying confounders, estimates from MSM indicate that each incremental week of DFX was associated with a statistically significant reduction in the risk of death (hazard ratio [HR]: 0.989; 95% CI: 0.983–0.996; $p = 0.001$) (Table 3). While there was no evident change in risk of death for patients who received ≤ 13 weeks of DFX (HR: 1.03; 95% CI: 0.813–1.297; $p = 0.8270$), the magnitude of risk reduction was significant for patients receiving 14–26 weeks of DFX (HR: 0.590; 95% CI: 0.386–0.902; $p = 0.0150$) and the risk decreased further for patients who received ≥ 53 weeks of DFX therapy (HR: 0.395; 95% CI: 0.197–0.792; $p = 0.009$).

Figure 4 represents a forest plot of the association of other factors with risk of mortality. High-risk MDS diagnosis, cumulative RBC transfusions and increasing age during the observation period were all associated with excessive mortality. In addition, the following baseline ICD-9 codes were associated with increased mortality: solid tumor diagnosis, CHF, renal disease, Alzheimer's

disease, neutropenia, thrombocytopenia, pancytopenia and sepsis. Poor DS at baseline was also associated with increased mortality risk, while female gender was associated with reduced mortality. Receipt of HMAs and lenalidomide were associated with increased risk of mortality. Sensitivity analyses using unweighted repeated logistic regression and Cox proportional hazard models with time-varying covariates showed qualitatively similar results (Supplementary Material).

Factors associated with leukemic progression

In total, 361 patients (9.2%) were diagnosed with AML during the observation period. Adjusted analysis using MSM estimates showed a statistically insignificant trend for reduction in risk of AML progression in association with cumulative exposure to DFX (HR: 0.983; 95% CI: 0.966–1.002; $p = 0.053$). Factors associated with increased risk of progression to AML included high-risk MDS ICD-9 code, cumulative RBC transfusions and receipt of HMAs or lenalidomide during the observation period (Supplementary Material).

DFX use & development of end-organ damage

Estimates using MSM did not find an effect of DFX on the occurrence of incident CHF, diabetes, thyroid disease or renal disease with DFX use (data not shown).

There were not enough events to allow meaningful comparisons of the rates of infections or incident liver disease between the two groups.

Discussion

In this large population-based Medicare study, we evaluated the association between DFX use and morbidities associated with IO and mortality in Medicare-enrolled TD-MDS patients who met a minimum transfusion threshold. By using repeated observation for each individual over time, with controls for time since cohort entry, we were able to assess the relationship between duration of therapy and time to the outcomes of interest. Using MSM techniques allowed addressing potential time-varying confounding between DFX therapy and outcomes. We found a significantly decreased risk of death that was proportional to the duration of DFX therapy. Interestingly, we did not find any significant association between IO-related morbidities and DFX therapy although there was a trend of reduction in leukemic progression.

Evidence from registry studies and other observational sources suggests that patients with MDS

and IO have worse survival and outcomes even after adjusting for transfusion burden [3–5], with increased rates of diabetes and glucose intolerance [4,19]. Most nonleukemic deaths were from cardiac and hepatic events as well as infections [3–5]. Increased leukemic progression in transfused versus nontransfused MDS patients was also observed retrospectively, though it is not clear whether this results from a worse underlying disease biology or reflects iron-mediated damage due to IO [19,20].

Despite the well-documented association of IO with outcomes and survival in MDS, demonstrating beneficial effects of ICT in MDS has been challenging. Early results from prospective studies of DFX in LR-MDS patients with IO demonstrated significant reductions in serum ferritin, liver iron concentration and hepatic transaminases within 3–6 months, but these studies had limited follow-up and did not report on survival or organ damage outcomes [21–24]. ICT has been associated in observational studies with improved survival in MDS patients with IO [5–6,25–30]. Retrospective data regarding effects of ICT on end-organ damage in MDS patients with IO are incon-

Table 2. The frequency of new medical diagnoses during the observation period.

Diseases or conditions	Number of subjects free of condition at start of observation (frequency)	New diagnoses	
		Frequency	%
Death	3926	2331	59.4
Solid cancer	2929	179	6.1
Acute myocardial infarction	3661	159	4.3
Acute myeloid leukemia	3926	361	9.2
Arrhythmia, cardiac conduction disorder	2271	367	16.2
Congestive heart failure	2078	380	18.3
Hepatitis/liver failure	3509	127	3.6
Renal disease	2759	365	13.2
Diabetes	2488	283	11.4
Thyroid	2827	312	11.0
Mental illness [†]	3098	255	8.2
Alzheimer's disease	3307	264	8
Venous thromboembolism	3552	152	4.3
CNS bleeding	3832	104	2.7
Gastrointestinal bleeding	2619	287	11
Neutropenia	2834	250	8.8
Pancytopenia	3254	374	11.5
Thrombocytopenia	2757	480	17.4
Hospitalization for sepsis	3625	143	3.9

[†]Included major depression, bipolar disorder and schizophrenia.

Figure 3. Kaplan–Meier overall survival estimates for patients with myelodysplastic syndromes who received deferasirox therapy and those who did not.

DFX: Deferasirox; OS: Overall survival.

sistent and subject to significant selection and other forms of bias [4–6,30–32].

Therapeutic decisions that affect patient outcome are not static and occur on an ongoing basis during the disease course in response to changes in the patient's condition, which may also influence survival. For example, continuing receipt of RBC transfusions may positively influence physicians' decisions to prescribe ICT, but simultaneously may negatively influence patient survival. Previous retrospective studies of ICT relied on case–control designs to minimize selection bias; however, case–control matching occurred only at baseline, and could not account for changes in therapies and patient condition between initiation of ICT and study end points. By contrast, MSM can control for dynamic therapy and health status changes over the observation period [10–12]. Several studies have used MSM to estimate the effectiveness of therapies in various clinical settings [10,12,17–18,33–36]. Observation of a survival benefit to ICT in a transfusion-requiring MDS cohort in this MSM analysis adds confidence to the conclusion from previous case–control literature that the observed impact of ICT is unlikely to be

attributable solely to selection of healthier patients and persistence in treatment.

It may seem problematic to estimate the effects of variable duration of therapy, as individuals need to live at least as long as the number of weeks they are observed receiving treatment. However, individual observation time may be substantially longer than the treatment period. Including the control for observation time addresses this problem. By including this control, MSM accounts for difference in the length of follow-up time between the two groups, therefore controlling for the potential confounding effect of longer survival of DFX users being associated with longer DFX use.

The association of improved survival with relatively brief exposure to ICT found in the current study is biologically plausible. In addition to direct iron accumulation, labile plasma iron (LPI), non-transferrin-bound iron (NTBI) and reactive oxygen species (ROS) appear to play an important role in the pathogenesis of iron-related organ damage in patients with IO [22,32,37–42]. DFX therapy leads to sustained and rapid reductions in levels of LPI, NTBI and ROS within 3 months of initiation of DFX therapy [21–24,43], consistent with

Table 3. Adjusted estimates of the odds ratios of death of various variables as derived from the marginal structural models (n = 3926).[†]

Treatment variables	Model for cumulative DFX use			Model for categorical DFX use		
	Odds ratio	95% CI		Odds ratio	95% CI	
Cumulative DFX up to current month	0.9892	0.9829	0.9955	–	–	–
Cum DFX, categorical (ref = no DFX):						
– ≤13 weeks	–	–	–	1.0264	0.8126	1.2965
– 14–26 weeks	–	–	–	0.5895	0.3855	0.9016
– 27–52 weeks	–	–	–	0.7956	0.5677	1.1151
– 53+ weeks	–	–	–	0.3953	0.1973	0.7922
Cumulative RBC transfusion units up to current month	1.0105	1.0077	1.0133	1.0105	1.0077	1.0132
Had ESAs at least once prior to and including current month (ref = no)	0.9417	0.8354	1.0617	0.9401	0.8340	1.0597
Had HMA at least once prior to and including current month (ref = no)	1.1993	1.0716	1.3422	1.2001	1.0727	1.3426
Had lenalidomide at least once prior to and including current month (ref = no)	1.1909	1.0379	1.3665	1.1923	1.0392	1.3679
Demographic variables						
Sex:						
– Male (ref)	–	–	–	–	–	–
– Female	0.8230	0.7513	0.9015	0.8213	0.7499	0.8995
Race:						
– Nonminority (white) (ref)	–	–	–	–	–	–
– Minority (non-white)	0.9108	0.7887	1.0518	0.9073	0.7857	1.0477
Baseline age	1.0206	1.0149	1.0264	1.0207	1.0149	1.0265
MDS disease characteristics						
Risk group at diagnosis:						
– Lower grade (ICD-9 238.72) (ref)	–	–	–	–	–	–
– Higher grade (ICD-9 238.73)	1.4551	1.1563	1.8312	1.4444	1.1494	1.8151
– With 5q deletion (ICD-9 238.74)	1.2868	0.9063	1.8269	1.2952	0.9152	1.8329
– Not otherwise specified, (ICD-9 238.7 or 238.75)	1.0079	0.8727	1.1641	1.0029	0.8701	1.1560
Co-morbid diseases/treatments						
Baseline predicted disability status:						
– Good (ref)	–	–	–	–	–	–
– Poor	1.2460	1.1049	1.4051	1.2476	1.1066	1.4066
Baseline specific disease conditions prior to cohort entry (ref = no):						
– Solid cancer	1.2101	1.0976	1.3340	1.2080	1.0960	1.3316
– Acute myocardial infarction	1.0417	0.8743	1.2413	1.0397	0.8725	1.2389
– Arrhythmia, cardiac conduction disorder	1.0841	0.9886	1.1888	1.0846	0.9894	1.1889

[†]The first column represents the model for cumulative deferiasirox use, while the second column reports the estimated odds ratios from the model for categorical deferiasirox use.

[‡]Included major depression, bipolar disorder and schizophrenia.

DFX: Deferiasirox; ESA: Erythropoiesis-stimulating agent; HMA: Hypomethylating agent; MDS: Myelodysplastic syndrome; RBC: Red blood cell.

Table 3. Adjusted estimates of the odds ratios of death of various variables as derived from the marginal structural models (cont).[†]

Treatment variables	Model for cumulative DFX use			Model for categorical DFX use		
	Odds ratio	95% CI		Odds ratio	95% CI	
Baseline specific disease conditions prior to cohort entry (ref = no) (cont.):						
– Congestive heart failure	1.1961	1.0848	1.3188	1.1957	1.0849	1.3178
– Hepatitis/liver failure	0.9823	0.8462	1.1403	0.9833	0.8470	1.1415
– Renal disease	1.3020	1.1771	1.4400	1.3034	1.1787	1.4413
– Diabetes	1.0958	0.9718	1.2356	0.9173	0.8354	1.0072
– Thyroid	0.9329	0.8269	1.0526	1.0255	0.9291	1.1318
– Mental illness [†]	1.0809	0.9691	1.2056	1.0802	0.9685	1.2048
– Alzheimer’s disease	1.4418	1.2780	1.6267	1.4407	1.2769	1.6255
– Venous thromboembolism	1.1328	0.9738	1.3177	1.1298	0.9712	1.3143
– CNS bleeding	1.2098	0.9315	1.5711	1.2137	0.9339	1.5773
– Gastrointestinal bleeding	0.9070	0.8222	1.0005	0.9070	0.8222	1.0005
– Neutropenia	1.1877	1.0712	1.3168	1.1889	1.0726	1.3179
– Pancytopenia	1.2697	1.1049	1.4590	1.2652	1.1014	1.4533
– Thrombocytopenia	1.7684	1.5970	1.9583	1.7744	1.6031	1.9640
– Hospitalization for sepsis	1.2294	1.0470	1.4435	1.2368	1.0563	1.4481
Time progression variables						
Current week from cohort entry	0.9341	0.9058	0.9634	0.9337	0.9054	0.9630

[†]The first column represents the model for cumulative deferasirox use, while the second column reports the estimated odds ratios from the model for categorical deferasirox use.

[†]Included major depression, bipolar disorder and schizophrenia.

DFX: Deferasirox; ESA: Erythropoiesis-stimulating agent; HMA: Hypomethylating agent; MDS: Myelodysplastic syndrome; RBC: Red blood cell.

the exposure associated with improved survival in the present study.

Despite the survival advantage we observed, we could not find significant associations between DFX use and new diagnoses of CHF, diabetes or thyroid disease. In the only other retrospective study of clinical outcomes and survival in relation to adequacy of ICT (based on dose/duration) in MDS patients, the authors similarly did not observe significant differences in cardiac, hepatic, infectious or leukemic causes of death between the chelated and nonchelated patients despite the documented survival advantage [5]. Although treatment with HMAs or lenalidomide was associated with excess mortality risk in our analysis, it should be noted that the MSM adjusts for time-varying confounding in terms of receipt of DFX, but does not address this potential confounder for the other drugs. Therefore, prior receipt of those agents should be viewed as an indication of disease severity and progression over time, and not as representing a causal relationship.

Limitations to our study include its retrospective nature, the dependence on accuracy of claims data

to capture clinical conditions, drug prescription and PRBC administration. Our ability to identify outcomes other than mortality relied on the presence of diagnostic codes on claims and intensity of monitoring for outcomes. Since we tracked oral drug use by claims and codes, we could not ascertain whether DFX was actually taken by patients, and the degree of adherence to the prescribed regimen. While DFX has been associated with hematologic improvement [21–22,44], our study did not address this question. Our study did not assess the rates and causes of discontinuation of the drug. The small proportion of patients diagnosed in 2004 or before were assigned an MDS index date of 1 January 2005 by study design and therefore have an actual longer duration of disease than estimated which might influence the estimates of chelation effects on outcomes. Finally, the use of MSM allows for estimation, from observational data, of the causal effects of a time-dependent exposure (such as DFX use) in the presence of time-dependent covariates (such as RBC transfusions) that may be both confounders and intermediate variables [11]. Nonetheless, the MSM cannot address

Figure 4. A forest plot representing the adjusted estimates of odds ratios for death as derived from the marginal structural models. Note that the repeated logistic regression analysis produces odds ratios, but they are equivalent to a hazard ratio from a survival model.

5q-: Chromosome 5q deletion; AMI: Acute myocardial infarction; CHF: Congestive heart failure; cum: Cumulative; DFX: Deferasirox; DS: Disability status (a code-derived indicator of performance status); ESA: Erythropoiesis-stimulating agent; GI: Gastrointestinal; HMA: Hypomethylating agent; Len: Lenalidomide; NOS: Non-otherwise specified; OR: Odds ratio; RBC: Red blood cell; ref: Reference; Rx: Prescription; Tx: Treatment; VTE: Venous thromboembolism.

potential confounding associated with unobserved factors that may influence physician selection of patients for ICT and may independently affect the outcomes of therapy.

Conclusion

Our study is the first large database study to evaluate the use of DFX in a Medicare-based cohort of TD 'ICT-eligible' MDS patients. After adjustment for time-varying-known confounders using MSM, we found a statistically significant survival benefit associated with DFX use in this patient population. The decrease in risk of death was proportional to the duration of DFX therapy but we could not detect significant differences in IO-related morbidities. The survival advantage noted with DFX in this study, and with ICT in several other retrospective studies, along with other possible beneficial clinical effects of ICT in MDS, should ideally be confirmed in randomized trials.

Future perspective

The association between transfusional IO and adverse patient outcomes in patients with MDS is becoming more evident especially for patients with LR-MDS with longer life expectancy. Nonetheless, most of the available data are retrospective or pertain to surrogate end points rather than prospective evidence and clinical hard end points. Additionally, while there is a potential relationship between IO and inferior outcomes for

patients with high-risk MDS, especially in the peri-transplantation setting, the evidence in this setting is weaker and the association is more controversial. Therefore, most of the current clinical recommendations for ICT use in MDS pertain to LR-MDS.

Over the next 5–10 years, we expect more data supporting the causal association between IO and end-organ damage in patients with MDS. In addition, the ongoing Phase III international large MDS event-free survival with ICT study (TELESTO [45]) in which patients with LR-MDS and transfusional IO are randomized to DFX or placebo is expected to be completed by the end of 2017. It is hoped that they study can provide more conclusive answers regarding the clinical benefits with ICT in patients with MDS. This study will not address the question of benefit with ICT in patients with high-risk MDS and IO and therefore more research will still be needed in this area.

As more oral iron chelators (e.g., deferiprone [FER-RIPROX®], ApoPharma Inc. [Ontario, Canada]) and newer more patient-friendly formulations of DFX (e.g., Jadenu®, Novartis Inc. [NY, USA], a newly approved oral once-daily pill that can be ingested with or without food compared with Exjade® which is a dispersible tablet that needs to be mixed with water or juice and taken on an empty stomach) are becoming available, the use of ICT in patients with MDS and IO will likely increase, especially if stronger evidence for beneficial

Executive summary

Background

- Iron overload adversely affects patients with myelodysplastic syndromes (MDS), but benefits of iron chelation therapy have not been clearly demonstrated.

Aims

- In this large population study, we examined the association between deferasirox (DFX) therapy and mortality in transfusion-receiving Medicare patients with MDS.

Methods

- MDS patients from 2005 to 2008 were identified using ICD-9 codes from 100% Medicare claims.
- Patients who received ≥ 20 blood units were observed until death or end of study.
- Marginal structural models estimated the effects of cumulative DFX, controlling for time-dependent effects of transfusions, MDS therapies and patient characteristics in a dynamic fashion throughout the observation period.

Results

- 3926 patients (10.1% used DFX) were observed for a mean of 48.8 weeks, and 59.4% died.
- In the adjusted model, each incremental week of DFX was associated with a significant reduction in mortality risk (hazard ratio: 0.989; 95% CI: 0.983–0.996; $p = 0.001$).
- There was a trend for reduction in risk of progression to acute myeloid leukemia in association with cumulative DFX exposure (hazard ratio/week: 0.983; 95% CI: 0.966–1.002; $p = 0.053$).
- DFX use was not significantly associated with altered risk of development of congestive heart failure, diabetes or thyroid disease.

Conclusion

- This first large population-based Medicare study demonstrated a reduced risk of death and of progression to acute myeloid leukemia associated with DFX use for MDS patients who received a minimum threshold of red blood cell transfusions.

clinical effects emerges. Nonetheless, the controversy regarding the optimal ways of using ICT in patients with MDS and IO, especially those with high-risk disease is likely to continue over the next few coming years.

Disclaimer

This research was initiated while AJ Davidoff was employed by the University of Maryland School of Pharmacy.

Financial & competing interests disclosure

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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