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ORIGINAL RESEARCH

Real-World Treatment Patterns, Clinical Outcomes, and Costs in Patients with Higher-Risk Myelodysplastic Syndromes Across France, Germany, and the United Kingdom

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Background: Higher-risk myelodysplastic syndromes (HR-MDS) are associated with increased progression to acute myeloid leukemia (AML) and poor prognosis.

Patients and Methods: This chart review characterizes real-world treatment patterns, outcomes, and costs of HR-MDS in France, Germany, and the United Kingdom (UK). Treating oncologists collected data (01 January 2014–31 December 2016) for adult patients with HR-MDS (revised International Prognostic Scoring System [IPSS-R] score >3), who received first-line treatment (1LOT) and had ≥1 year follow-up post diagnosis or until death. Demographics, clinical characteristics, treatment patterns, outcomes, and healthcare resource use were collected during 1LOT. Kaplan-Meier methods were used for time-to-event outcomes. Costs, applied to resource use, were calculated through 1LOT.

Results: Forty-one physicians provided data for 95 patients (France, n=31; Germany, n=29; UK, n=35). At HR-MDS diagnosis, median patient age was 75 years, 62.1% were men, and 60.0% had very high-risk disease per the IPSS-R. Median follow-up was 34.5 months. In 1LOT, 89.5% of patients received azacitidine (median, 12.0 cycles). At the end of 1LOT, 24.2% of patients had a complete and 30.5% a partial remission. From start of 1LOT, median progression-free survival was 24.3 months. Overall survival (unadjusted) was 32.9 months in all patients and shorter in the 33.7% of patients with versus without AML transformation (17.0 vs 52.9 months). Costs for 1LOT were driven by adjunctive therapy and were higher for patients who were transfusion-dependent versus -independent at the start of therapy and who did versus did not have transformation to AML.

Conclusion: These results provide real-world data from France, Germany, and the UK on HR-MDS treatment patterns, clinical outcomes, and costs.

Keywords: real-world evidence, HR-MDS, IPSS-R, AML

Introduction

Myelodysplastic syndromes (MDS) are bone marrow neoplasms characterized by ineffective hematopoiesis and resulting cytopenia(s).[1] Morbidity and mortality in patients with MDS are largely due to complications of cytopenias and transformation to acute myeloid leukemia (AML).[2] MDS is a heterogeneous disease, and thus prognostication is important for treatment selection and disease management.[3] Risks of AML transformation and survival are impacted by cytogenetics, bone marrow blast percentage, hemoglobin, platelets, and absolute neutrophil count, as described by the revised International Prognostic Scoring System (IPSS-R). Patients with MDS having an IPSS-R score of >3.5 (collectively, "higher-risk") have a poor prognosis.[3,4]

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The treatment landscape for higher-risk MDS (HR-MDS) has changed little in the last 2 decades.[5] Patients with HR-MDS are recommended to undergo allogeneic stem cell transplantation with curative intent, while older patients and/or those with significant comorbidities or without a suitable stem cell donor can be treated with chemotherapy or hypomethylating agents (HMA).[6] Of the available HMA, azacitidine is recommended over decitabine due to a demonstrated survival benefit compared to conventional therapy consisting of low-dose cytarabine, intensive chemotherapy, and/or best supportive care.[6,7] However, many patients fail to achieve a durable response with HMA therapy for a variety of reasons, including challenges with persistence or treatment burden.[8,9] Limited treatment options are available for patients who fail to respond to HMA therapy or stop responding to HMA therapy.

Real-world evidence on the burden of HR-MDS in Europe is limited, and results from a systematic literature review from 2022 highlight differences in outcomes across clinical and observational studies enrolling patients with HR-MDS.[10] Previous studies in the United States have found high costs associated with HR-MDS, particularly among patients with AML transformation,[11,12] but there is limited evidence on the real-world costs of HR-MDS management in Europe. The objective of this study was therefore to provide a historical perspective on real-world treatment patterns, clinical outcomes, and costs in patients with HR-MDS, per the IPSS-R, in France, Germany, and the United Kingdom (UK).

Materials and Methods

Study Design

This retrospective, multicenter study used patient chart data collected by MDS-treating physicians recruited from national databases in France, Germany, and the UK. Data were collected from the time of HR-MDS diagnosis to most recent patient visit or death. The study was conducted in accordance with the Declaration of Helsinki and ethics waiver and/or approval was secured according to requirements in each country. Additional details are provided in the Supplementary Appendix.

Patients

The study included adult patients (≥18 years) who were diagnosed with HR-MDS (IPSS-R score >3; prognostic IPSS-R risk categories of intermediate, high, or very high) between January 1, 2014, and December 31, 2016. Patients were required to have at least 12 months of follow-up after diagnosis, unless they died during that period, and to have received at least first-line treatment (1LOT) for HR-MDS (eg, HMA or intensive chemotherapy with or without allogeneic stem cell transplant). Patients enrolled in a clinical trial for 1LOT or who received only first-line supportive care (eg, chelating agents, transfusions, platelet, or hematopoietic cytokine support) were excluded. Adjunctive therapy (ie, deferoxamine, deferasirox, deferiprone, darbepoetin, epoetin, granulocyte colony-stimulating factor [G-CSF]) was allowed.

Study Variables and Outcomes

Data collected from patient charts included patient demographics and clinical characteristics (eg, MDS subtype, Eastern Cooperative Oncology Group performance status [ECOG PS], transplant eligibility, cytogenetic/molecular genetic testing). IPSS-R scores were calculated and categorized as intermediate (>3 to 4.5), high (>4.5 to 6) or very high (>6).[4] For each line of therapy, information was collected on medications administered, therapy duration, and number of cycles administered. Transfusion dependence was defined as needing at least 1 red blood cell transfusion every 8 weeks over 4 months. Clinical outcomes included response to each line of therapy, assessed using International Working Group response criteria,[13] and included complete remission and partial remission. Progression-free survival (PFS), overall survival (OS), and AML transformation were also evaluated. Lastly, costs from the government payor perspective were determined. Costs sourced from governmental databases, public information, and published literature[14–42] were applied to the healthcare resource use collected in the chart review to estimate total costs through 1LOT. If the number of treatment cycles was missing, the cost for one cycle was assigned; no other imputations were made. Costs were inflation-adjusted to 2024 Euros.

Additional details on the study design and variables and outcomes are provided in the Supplementary Appendix.

Statistical Analysis

Analyses of patient demographics, clinical characteristics, treatment patterns, clinical outcomes, and healthcare resource use were descriptive in nature and conducted in the overall population and by country. Categorical outcomes were summarized using counts and percentages; continuous endpoints were summarized using mean, standard deviation, median, range, and interquartile range (IQR). Time to best response, duration of response, PFS, OS, and time to AML transformation were analyzed using Kaplan–Meier methods. For time to response, patients were censored at the documentation of any other response, start of next line of therapy, death, or loss to follow up (whichever occurred first). For PFS, patients were censored at end of follow-up or initiation of a subsequent line without documented progression (whichever occurred first). For AML transformation, patients were censored if they experienced progression, death, or AML transformation (whichever occurred first).

Patients across the 3 countries were matched using the covariate balancing propensity score (CBPS) method to address the measurable differences at baseline.[43] The CBPS method enables efficient parametric estimation of the propensity score thus maximizing the covariate balance compared to conventional propensity score matching methods. The baseline covariates selected for the model were ECOG PS, IPSS-R, Charlson comorbidity index, and HR-MDS subtype based on initial descriptive analysis and clinical input. Based on clinical input, Germany was used as the reference group and weighted as 1 since the results for German patients were closest to expected outcomes in real-world setting. Balances in variables before and after weighting were compared and were considered well-balanced if standardized mean differences were less than 0.1.[43] The propensity score weights were then used to obtain an adjusted/weighted OS.

All analyses were conducted using SAS® software, version 9.4.

Results

Forty-one physician investigators (France, n=13; Germany, n=14; UK, n=14) provided data for the study. Physicians had a median (IQR) of 18 (15 to 21) years of practice experience and treated a median of 23 (13 to 35) patients with HR-MDS in the year prior to study participation. All participating physicians in France and most (85.7%) physicians in the UK practiced in hospital settings, whereas physicians in Germany were divided between office-based (28.6%), hospital-based (28.6%), and mixed settings (office- and hospital-based; 42.9%). Additional physician characteristics are provided in Supplementary Table 1.

A total of 95 patients with HR-MDS (France, n=31; Germany, n=29; UK, n=35) were included in the study. Overall, patients were predominantly men (62.1%) with a median age at HR-MDS diagnosis of 75 years (Table 1). At HR-MDS diagnosis, 61.1%

Table 1 Patient Demographics and Clinical Characteristics at Diagnosis of HR-MDS

	All N = 95	France n = 31	Germany n=29	United Kingdom n = 35
Male, n (%)	59 (62.1)	18 (58.1)	20 (69.0)	21 (60.0)
Age, median (range), years	75.0 (22.0–92.0)	76.0 (22.0–92.0)	77.0 (55.0–84.0)	74.0 (42.0–83.0)
MDS subtype, n (%)[a]				
MDS-EB-2	58 (61.1)	20 (64.5)	20 (69.0)	18 (51.4)
MDS-EB-1	22 (23.2)	6 (19.4)	8 (27.6)	8 (22.9)
MDS-RS-MLD	11 (11.6)	3 (9.7)	1 (3.4)	7 (20.0)
MDS with isolated del(5q)	2 (2.1)	2 (6.5)	0 (0.0)	0 (0.0)
MDS-RS-SLD	1 (1.1)	0 (0.0)	0 (0.0)	1 (2.9)
MDS, unclassifiable	1 (1.1)	0 (0.0)	0 (0.0)	1 (2.9)
Transfusion-dependent MDS	53 (55.8)	18 (58.1)	19 (65.5)	16 (45.7)

(*Continued*)

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Table 1 (Continued).

	All N = 95	France n = 31	Germany n=29	United Kingdom n = 35
ECOG performance status, n (%)				
0	11 (11.6)	1 (3.2)	1 (3.4)	9 (25.7)
1	53 (55.8)	20 (64.5)	16 (55.2)	17 (48.6)
2	30 (31.6)	10 (32.3)	11 (37.9)	9 (25.7)
3	1 (1.1)	0 (0.0)	1 (3.4)	0 (0.0)
IPSS-R, n (%)				
Intermediate (>3-4.5)	20 (21.1)	4 (12.9)	4 (13.8)	12 (34.3)
High (>4.5–6)	18 (18.9)	8 (25.8)	5 (17.2)	5 (14.3)
Very high (>6)	57 (60.0)	19 (61.3)	20 (69.0)	18 (51.4)
Transplant eligibility, n (%)[b]				
Yes	19 (20.0)	4 (12.9)	4 (13.8)	11 (31.4)
No	76 (80.0)	27 (87.1)	25 (86.2)	24 (68.6)
Reasons for transplant ineligibility[c]				
Advanced age	63 (82.9)	22 (81.5)	20 (80.0)	21 (87.5)
Frailty	32 (42.1)	11 (40.7)	13 (52.0)	8 (33.3)
ECOG performance status	31 (40.8)	7 (25.9)	15 (60.0)	9 (37.5)
Other relevant comorbid condition(s)	25 (32.9)	5 (18.5)	7 (28.0)	13 (54.2)
IPSS/IPSS-R Score	4 (5.3)	3 (11.1)	0 (0.0)	1 (4.2)
Charlson Comorbidity Index, n (%)				
0	45 (47.4)	13 (41.9)	13 (44.8)	19 (54.3)
1	21 (22.1)	12 (38.7)	6 (20.7)	3 (8.6)
2	10 (10.5)	1 (3.2)	3 (10.3)	6 (17.1)
≥3	19 (20.0)	5 (16.1)	7 (24.1)	7 (20.0)

Notes: [a] MDS subtypes per World Health Organization 2016 criteria. [b] Identified by investigator on case report form with the response: "Significant comorbid condition(s) that are, in the opinion of the investigator, likely to have a negative impact on tolerability of HDT-SCT." [c] More than one reason could be reported as a reason for transplant ineligibility.

Abbreviations: EB, excess blasts; ECOG, Eastern Cooperative Oncology Group; IPSS-R, Revised International Prognostic Risk Grouping System for Myelodysplastic Syndromes; MDS, myelodysplastic syndrome; MLD, multi-lineage dysplasia; RS, ring sideroblasts; SLD, single lineage dysplasia.

of patients were diagnosed with MDS with excess blasts-2, and 55.8% were transfusion-dependent. Eighty percent of patients were transplant-ineligible at diagnosis; the most common reason for transplant ineligibility was advanced age (82.9%). Cytogenetic test results were available for 86.3% of patients and molecular genetic test results for 32.6% of patients.

Patients in the UK compared with those from France and Germany generally had a more favorable clinical profile at HR-MDS diagnosis with fewer patients from the UK at diagnosis having very high IPSS-R scores or being transplant ineligible, and more patients having MDS multi-lineage dysplasia with ring sideroblasts (MDS-RS-MLD), an ECOG PS of 0, or intermediate IPSS-R scores (Table 1). Across the 3 countries, median (IQR) duration of follow-up was 34.5 (13.8 to 50.9) months, ranging from 15.1 (10.0 to 46.9) months in Germany to 33.9 (14.6 to 54.7) months in France and 44.9 (17.3 to 50.7) months in the UK.

In the 1LOT setting, 89.5% of patients received azacitidine (France, 90.3%; Germany, 100%; UK, 80.0%) with the remaining patients receiving combinations including cytarabine, daunorubicin, idarubicin, and/or fludarabine (7.4%) or single agent lenalidomide (3.2%). Patients treated with azacitidine received a median (IQR) of 12 (7 to 18) cycles of therapy (France, 14.5 [7 to 28]; Germany, 9 [6 to 12]; UK, 13.5 [9 to 17]; Supplementary Table 1). Nine patients (9.5%) received an allogeneic stem cell transplant during 1LOT. In total, 84 patients (88.4%) discontinued therapy during the follow-up period, the most common reason was disease progression (overall, 32.1%; France, 48.0%; Germany, 33.3%; UK, 18.8%).

Across all patients, the mean (SD) number of red blood cell transfusions per patient during 1LOT was 14.1 (11.3), ranging from 11.3 (6.9) transfusions in France to 14.8 (13.5) transfusions in the UK and 15.8 (12.0) transfusions in Germany. Among the 43 patients who were transfusion-dependent at the start of 1LOT, 23 (53.5%) achieved transfusion independence (France, n/N=6/13; Germany, 8/18; UK, 9/12).

Across all countries, 24.2% of patients achieved a complete remission and 30.5% achieved a partial remission during 1LOT with lower remission rates generally seen in patients with higher-risk disease by IPSS-R and with MDS with excess blasts compared with MDS-RS-MLD (Figure 1; Supplementary Tables 2–3). A complete remission was achieved by 16.1% of patients in France, 13.8% of patients in Germany, and 40.0% of patients in the UK. The median (IQR) time from start of 1LOT to complete or partial remission was 10.6 (7.8 to 16.6) months (France, 11.8 [7.8 to 78.7] months; Germany, 7.4 [6.1 to not evaluable] months; and 13.5 [9.5 to 22.3] months in the UK). Median (IQR) duration of response was 28.8 (10.5 to 39.5) months overall, 23.2 (13.3 to 39.5) months in France, 11.4 (5.3 to 37.5) months in Germany, and 33.9 (13.8 to 41.5) months in the UK.

From start of 1LOT, median (95% CI) PFS for all patients was 24.3 (18.7 to 42.1) months, ranging from 4.7 (9.0 to 32.0) months in Germany, to 24.7 (16.1 to 58.2) months in France and 51.4 (24.3 to not estimable) months in the UK. Across all patients, PFS was generally shorter and the probability of surviving without an event for up to 60 months lower in patients with higher-risk disease by IPSS-R criteria and also by MDS subtype (excess blasts compared with ring sideroblasts multi-lineage dysplasia) (Supplementary Table 3). Median (95% CI) unadjusted OS from start of 1LOT was 32.9 months overall (France, 32.9 [20.6 to not estimable]; Germany, 14.7 [10.0 to 50.0]; and UK, 52.9 [37.5 to not

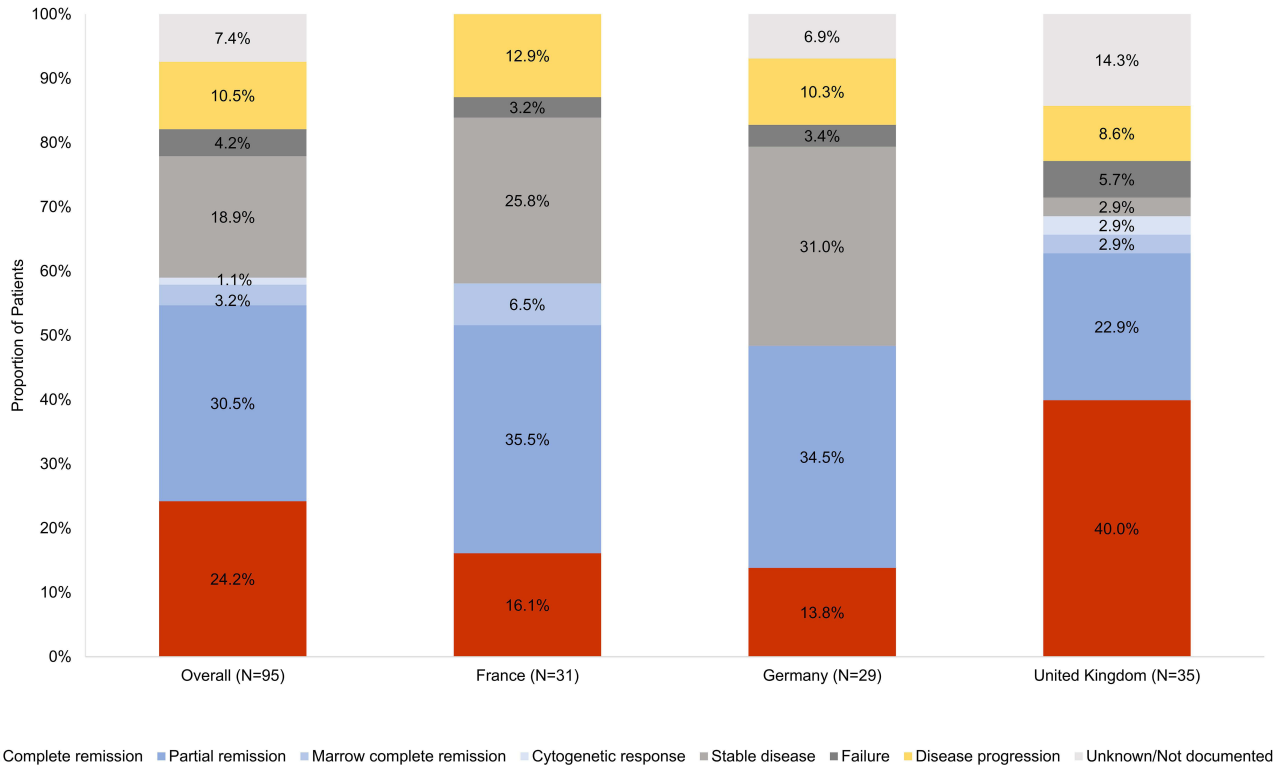

Figure 1 Response at end of first-line therapy overall and by country.

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estimable]). Following adjustment using propensity scores to balance differences in patient clinical characteristics at diagnosis across the 3 countries, median (95% CI) adjusted OS was 23.4 (14.7 to 37.2) months overall, ranging from 14.7 months in Germany, to 25.5 months in France and 37.2 months in the UK (Figure 2).

Costs per patient for 1LOT were €122,621 overall ranging from €76,576 in the UK to €171,233 in Germany (Figure 3). Overall, the cost of adjunctive therapy (eg, granulocyte colony-stimulating factor, erythropoiesis-stimulating agents, transfusions, iron chelators, thrombopoietin antagonists) constituted 69% of the total treatment costs, while the first-line drug costs were the second highest contributor to the total cost (13% of total costs). Total costs were 19% higher among patients who were transfusion-dependent at the start of treatment (€130,731 vs €109,430; Figure 4). This difference was almost completely attributable to the difference in adjunctive therapy costs, which were approximately €24,000 higher among transfusion-dependent patients.

Subgroup Analysis: AML Transformation

Thirty-two patients (33.7%) experienced AML transformation during the follow-up period, at a median (IQR) of 12.4 (8.6–23.9) months after initiation of 1LOT (France, 14 patients [45.2%]; Germany, 10 patients [34.5%]; UK, 8 patients [22.9%]). Demographic and clinical characteristics were similar between patients who transformed to AML and those without transformation, with the exception of ECOG performance status at diagnosis and IPSS-R score (Supplementary Table 4). The median (IQR) duration of follow up for those with and without AML transformation was 17.5 (10.0 to 36.4) and 46.7 (14.9 to 52.9) months with 84.4% and 47.6% of patients dying during the study period. The median (IQR) duration of follow up from diagnosis and from start of 1LOT in patients with AML transformation was 13.5 (9.0 to 26.0) and 12.0 (8.0 to 23.5) months and for those without transformation was 46.0 (15.0 to 53.0) and 43.0 (15.0 to 49.0) months. In the 1LOT setting, 93.8% of patients with AML transformation and 87.3% of patients without transformation were treated with azacitidine. Patients with AML transformation treated with azacitidine received a median (IQR) of 10.5 (7.0 to 16.0) cycles of therapy and those without AML transformation received a median of 13.0 (7.0 to 23.0) cycles of therapy. All patients with AML transformation versus. 82.5% of patients without transformation discontinued therapy

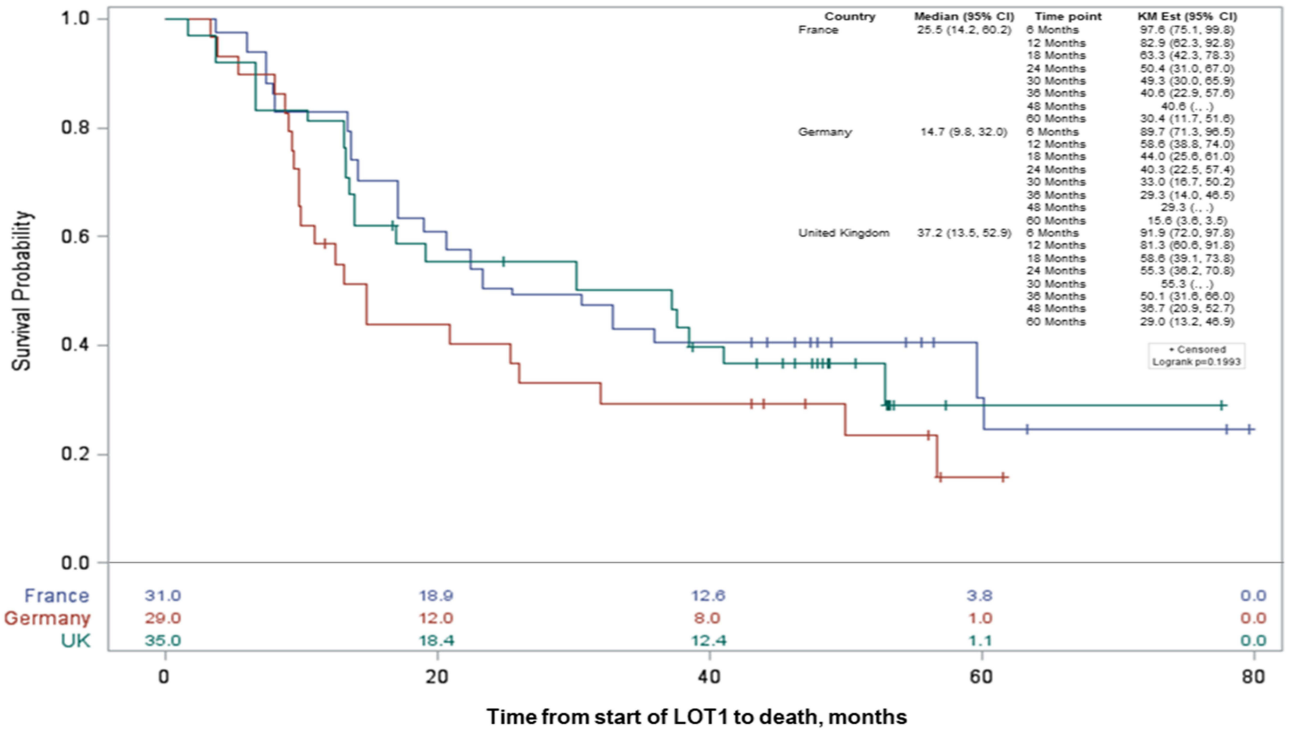
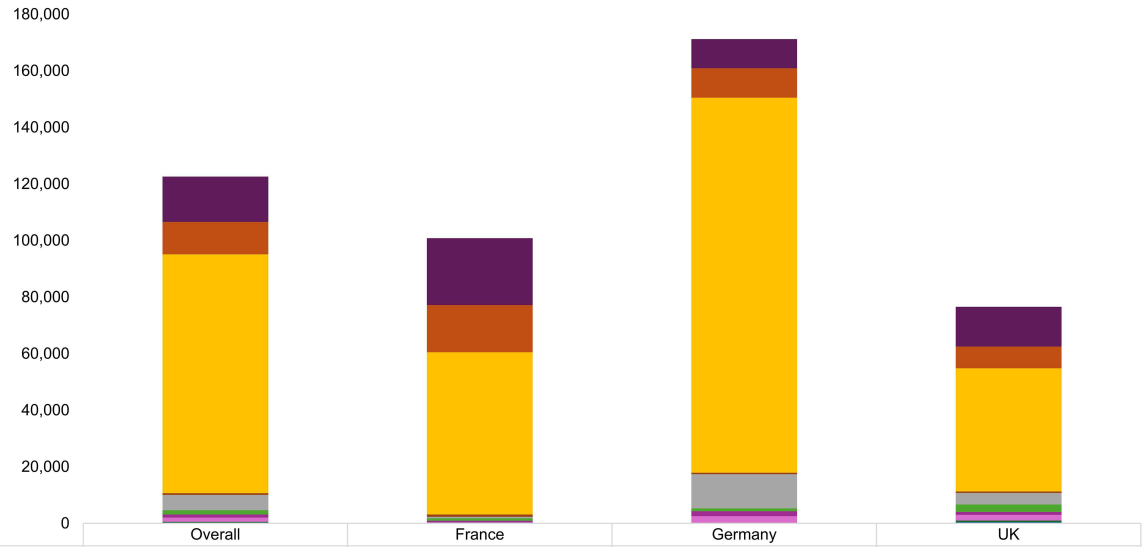
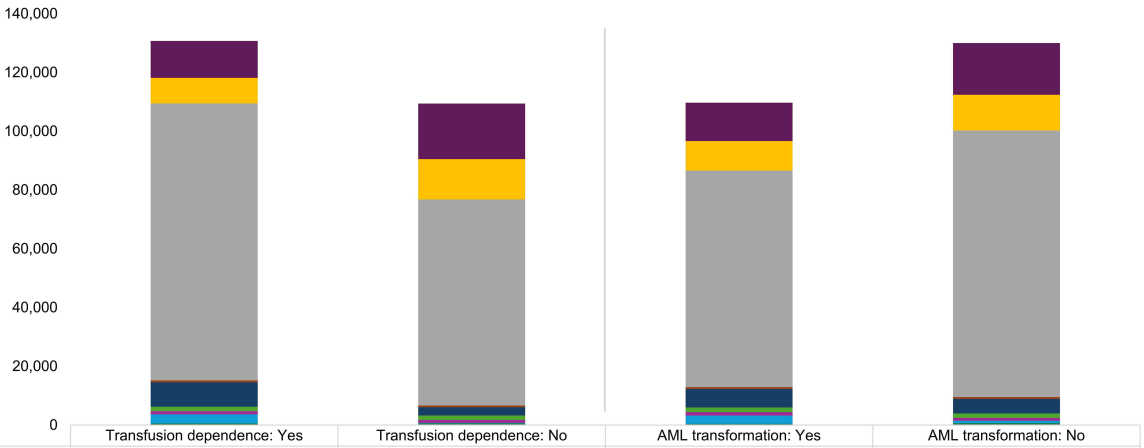


Figure 2 Adjusted overall survival from start of first-line treatment by country.
Abbreviation: 1LOT, first-line treatment.



	Overall	France	Germany	UK
1L Drug cost	16,046	23,600	10,338	14,084
1L Drug admin cost	11,457	16,712	10,393	7,685
Adjunctive therapy	84,431	57,403	132,578	43,522
Bone marrow biopsy	623	779	527	548
Transfusions	5,439	550	12,125	4,034
Office visit	1,517	862	976	2,706
Hospitalization	1,074	547	1,722	1,004
Emergency department	1,492	111	2,369	1,989
Outpatient visit	290	237	197	447
Ancillary service	0	0	0	0
Palliative care outpatient visit	252	21	7	558

Figure 3 Average cost per capita by country (in Euro).
Abbreviation: UK, United Kingdom.



	Transfusion dependence: Yes	Transfusion dependence: No	AML transformation: Yes	AML transformation: No
1L Drug cost	12,561	18,927	13,015	17,585
1L Drug admin cost	8,703	13,734	10,069	12,162
Adjunctive therapy	94,272	70,117	73,703	90,741
Bone marrow biopsy	643	605	629	619
Transfusions	8,306	2,787	6,311	4,941
Office visit	1,514	1,520	1,565	1,491
Hospitalization	1,143	1,016	1,211	1,004
Emergency department	3,074	185	2,742	858
Outpatient visit	329	253	139	371
Ancillary service	0	0	0	0
Palliative care outpatient visit	186	285	307	223

Figure 4 Average cost per capita by transfusion dependence at start of treatment and by AML transformation (in Euro).
Abbreviation: AML, acute myeloid leukemia.

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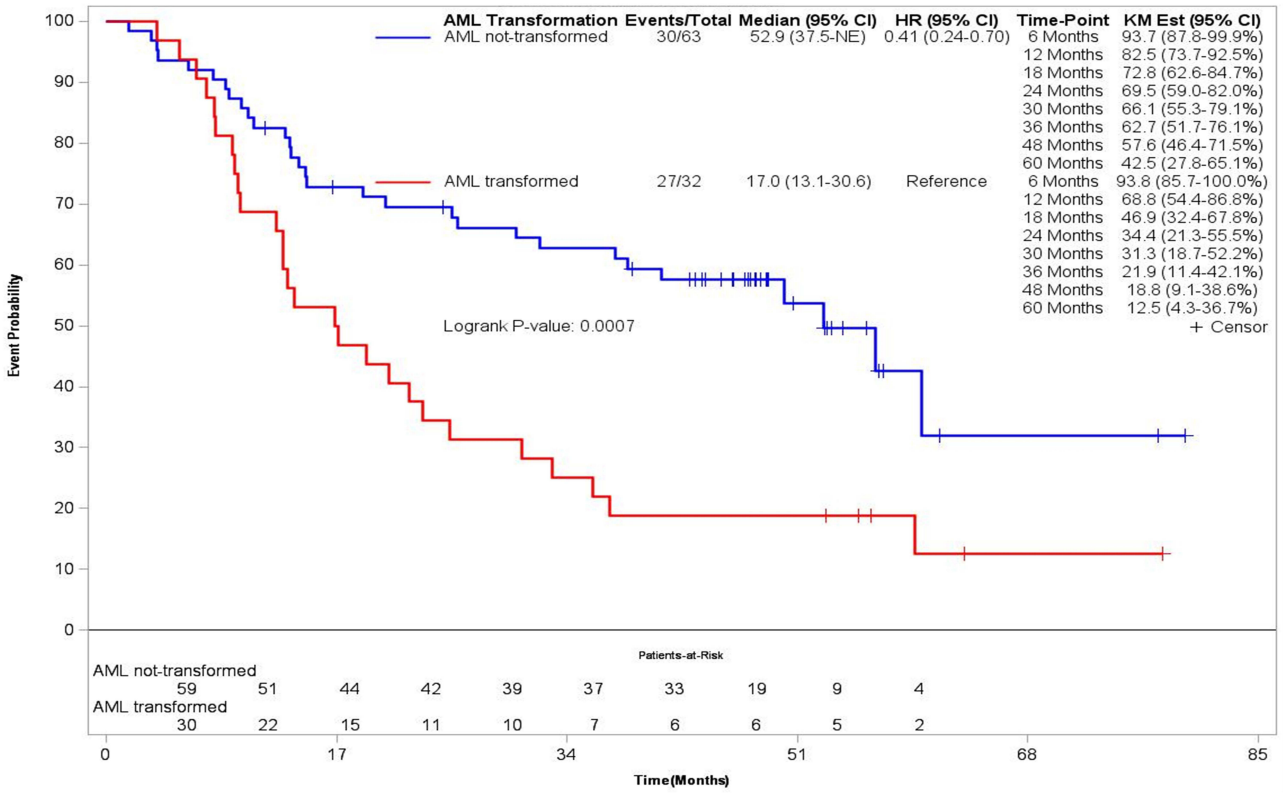

Figure 5 Unadjusted overall survival from start of LOT1 by AML transformation.
Abbreviations: 1LOT, first-line treatment; AML, acute myeloid leukemia.

during the study period. The primary reasons cited for 1LOT discontinuation were disease progression (43.8%) and AML transformation (37.5%) for patients with AML transformation and disease progression (25.0%) and in remission/maximum clinical benefit achieved (25.0%) for patients without transformation.

Among patients with and without AML transformation, 37.5% and 63.5% of patients achieved a complete or partial remission during 1LOT. Median (IQR) duration of response was 13.5 (5.4 to 17.5) months in patients with AML transformation and 35.2 (13.0 to 42.3) months in patients without transformation. Median (IQR) unadjusted PFS and OS were shorter in patients with AML transformation (13.4 [11.1 to 21.9] and 17.0 [13.1 to 30.6] months) than those without transformation (51.4 [30.8 to not evaluable] and 52.9 [37.5 to not evaluable] months; Figure 5). First-line treatment costs were €109,690 for patients with AML transformation and €129,996 for patients without transformation (Figure 4).

Additional details on AML transformation by country (Supplementary Table 5), IPSS-R category (Supplementary Table 6), and MDS subtype (Supplementary Table 7) are provided in the Supplementary Appendix.

Discussion

The results of our analysis of patients diagnosed between January 2014 and December 2016 suggest that little has changed in the treatment of HR-MDS since the approval of HMA therapies. The goal of treatment for patients with HR-MDS is to modify the disease course[6] as survival following AML transformation is poor, with an increased risk of death at 6 months (hazard ratio: 1.8) and 1 year (hazard ratio: 2.9) reported for patients who transform to AML versus those with no transformation.[44] For patients with HR-MDS able to undergo transplantation with curative intent, allogeneic stem cell transplantation is recommended;[45] for patients who are older or have significant comorbidities and, therefore not candidates for transplantation, chemotherapy or HMA therapy with azacitidine or decitabine may be an option. Recently, combination therapy with venetoclax is also considered especially for patients with a loss of response to azacitidine or decitabine.[46] However, the risk of death at 6-months (hazard ratio, azacitidine: 1.7) and 1-year (hazard ratio, azacitidine/decitabine: 2.8/6.4) remains increased in patients treated with HMA therapy who transform to AML compared with those without transformation.[44]

Results from this observational study from France, Germany, and the UK, provide a unique perspective on the unmet needs of patients in these countries with HR-MDS during the study period (2014 to 2016), particularly for patients deemed transplant ineligible. Most patients included in this study were transplant ineligible due to advanced age and consequently were treated with azacitidine for a median of 12 cycles. These treatment patterns are consistent with the 2014 ESMO guidelines available during the study period.[47] Although approximately 50% of patients achieved a complete or partial remission after 1LOT with a median duration of response of about 29 months, most patients discontinued therapy due to disease progression. Among patients who were transfusion dependent at the start of 1LOT, close to 50% of patients continued to require transfusions during 1LOT. Transfusion dependence has been found to be associated with decreased OS in patients with HR-MDS, and as was also seen in this study, higher costs.[48] In our study, total costs were 19% higher among patients who were transfusion-dependent at the start of treatment, which was mostly attributable to higher adjunctive therapy costs among transfusion-dependent patients.

Across the 3 countries included in the analysis, differences in median unadjusted OS were found in patients from Germany (14.7 months) having the shortest survival and those from the UK (52.9 months) having the longest survival. However, patient baseline characteristics differed across the countries with patients from the UK generally having a more favourable profile than those from France and Germany at diagnosis. Specifically, fewer patients from the UK than France and Germany were transplant ineligible or were classified as very high risk per the IPSS-R at diagnosis. Additionally, at diagnosis, more patients from the UK than France and Germany had MDS-RS-MLD or an ECOG PS of 0 or were classified as intermediate risk per the IPSS-R. Results for all patients generally showed lower response rates and poor survival outcome for patients classified as high or very high risk per the IPSS-R and for patients with MDS with excess blasts compared with MDS-RS-MLD. After adjustment for differences in baseline characteristics, patients from Germany continued to have the shortest OS and those from the UK the longest OS.

Results from the adjusted OS analysis for all patients treated with at least 1LOT in this study (23.4 months) are comparable to the 24.5-month median OS reported for azacitidine-treated patients with HR-MDS enrolled in the pivotal Phase III azacitidine trial.[49] In contrast, shorter OS in azacitidine-treated patients with HR-MDS, ranging from 11.0 to 17.6 months, was reported in a meta-analysis of 5 retrospective studies from the United States, the Netherlands, and Greece.[10] In additional real-world analyses of azacitidine- or HMA-treated patients from Canada and the United States, median OS ranged from 11.6 months to 14.9 months.[44,50–52] Differences in baseline characteristics between study samples and in healthcare systems between countries may explain some of the differences observed. Differences in azacitidine treatment duration may also explain some of these differences as treatment duration varied not only among the countries included in this chart review but also when comparing results from our study, the pivotal phase III azacitidine study, and other real-world and clinical studies.[10,44,49–52] In a review of studies that evaluated HMA persistence, increased persistence was found to increase 1-year PFS, OS, time to AML transformation, and lower incidence of AML.[8] In this chart review, patients from Germany received both the fewest treatment cycles and had the shortest OS after adjusting for differences in baseline characteristics. When assessing the OS in aggregate for the 3 countries in this chart review, the overall median duration of frontline azacitidine therapy was 12 months which is longer than the 4 to 9 months reported in other real-world studies,[10,44,50–52] potentially supporting a benefit of treatment persistence on OS.

Patients included in this chart review were of similar age (median, 75 years) as previously published analyses (range: 68 to 77 years).[10,44,50–52] However, patients included in this analysis appeared to have fewer comorbidities than patients included in some previously reported studies. In the study by Egloff et al that described treatment, resource utilization, and clinical outcomes in patients with HR-MDS treated in community practices in the United States, patients had a high comorbidity burden with 44% of patients having at least 3 comorbidities included in the NCI Comorbidity Index with the most common (>20% of patients) being chronic pulmonary disease (40%), diabetes without chronic complications (33%), renal disease (31%), peripheral vascular disease (28%), and congestive heart failure (27%).[51] In contrast, in this analysis the incidence of any of the comorbidities in the NCI Comorbidity Index was less than 20% with the most common being diabetes without chronic complications (18.9%), chronic pulmonary disease (12.6%), and congestive heart failure (11.6%); 9.5% of patients had peripheral vascular disease and 7.4% of patients had renal disease.

Other factors that could explain some of the differences between our results and those from other real-world studies include differences in provider and other patient characteristics, the time-horizon of the studies, treatment regimens administered, and geographical differences in treatment and evaluation of disease progression in patients with HR-MDS.

A goal of treatment in MDS is to delay transformation to AML, as the treatment of patients with MDS who transform to AML is more difficult than the treatment of patients with de novo AML.[44] In this real-world analysis, 33% of patients who received 1LOT transformed to AML at a median of 12 months post treatment initiation which is similar to the 29% of patients who transformed in a real-world analysis from the United States where patients also received at least 1 LOT.[44] In this analysis, unadjusted OS was shorter for patients with AML transformation compared with patients who did not transform (9.7 vs 15.4 months). No difference in unadjusted OS was seen for patients with versus without AML transformation in the US study.[44] However, contrast in study design may account for the observed difference in outcome.

We did find that costs during 1LOT were lower for patients with AML transformation compared with patients who did not transform. However, the cost analyses reflected all costs accrued during 1LOT, regardless of treatment duration, as there was insufficient information on dates to adjust or to estimate a cost per unit of time during 1LOT. The higher costs reported for patients who did not transform compared with patients with AML transformation potentially reflect the increased number of treatment cycles received by patients without transformation and the approximately 3.5-times longer duration of follow-up for these patients.

Other comparisons of costs by patient characteristics were somewhat limited, as some cost categories had very few observations contributing to them, therefore these data may not be generalizable to a broader population. However, the relative proportion of total costs associated with adjunctive therapy provides useful insight on how important supportive therapy costs are for HR-MDS patients. While we report overall adjunctive therapy costs, future studies could explore the costs specifically for supportive care drug use within 1LOT. Though there are only a few published studies on the cost of MDS that looked at transfusion burden, our results corroborate other findings that patients with MDS and a high transfusion burden have higher medical resource utilization than patients without a high transfusion burden.[48]

This study has several strengths. The chart review design allowed for the collection of detailed clinical data such as treatment response and PFS that are difficult to assess using secondary data. This study's sample size is similar to other chart review studies among individuals with MDS.[53,54] The design also reduces recall error associated with patient-reported survey studies and benefits from physician confirmation of the clinical data, in contrast to analysis of administrative claims data, which requires researchers to make a number of assumptions about the accuracy and completeness of data that may not be fit for purpose.

In addition to its strengths, this study has some limitations. Patient populations were not balanced across countries, which may have resulted from an unidentified selection bias. Cytogenetic testing was not available for 14% of patients, which resulted in the impossibility of precisely defining the IPSS-R risk in this fraction of patients. The clinical practice of physicians who agreed to participate in the study could differ from those of physicians who were not approached or declined to participate, limiting the generalizability of the results. Assessment of treatment response and disease progression may be different in the routine clinical setting as compared with clinical trials. It is also possible that not all relevant clinical details are recorded in patient records, particularly if patients seek care at other facilities. Unmeasured confounding could also impact the results. Finally, country-specific analyses and subgroup analyses must be interpreted with caution, as some comparisons included data from few patients.

Conclusion

Results from this chart review from France, Germany, and the UK conducted from 2014 to 2016 shed light on treatment patterns, clinical outcomes, and costs of treatment for HR-MDS in these countries during this time. The results provide a valuable clinical and economic perspective to compare with more extensive, modern-day studies on this topic, including future studies on newer MDS treatments (eg, venetoclax + azacitidine).

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