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Using Clinical Data Standards to Facilitate Comparisons of Acute Myeloid Leukemia Treatment Patterns and Outcomes in Real-World Clinical Care and Pooled Clinical Trial Populations

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Background

- Randomized controlled trials (RCT) are the gold standard for demonstrating clinical efficacy of therapies.
- However, there is a need to develop cohorts that contain both the real-world and clinical trial data to better understand patient characteristics, monitor safety events, improve trial design, and inform regulatory submission.
- Some initiatives have tried to address this challenge by generating real-world data (RWD) in the early stages of drug development or exploring the replicability of RCT findings in RWD sources.[1,2]
- Regulatory-grade analyses utilizing both types of data may be strengthened by using common data models and vocabularies that allow for consistent deployment of analytics, whether it be in cohort definition, variable creation, or outcome characterization.
  - When analyzing disparate datasets, differences due to variations in the analytic approach can be minimized by using the same code.
- In this study, we compare Acute Myeloid Leukemia (AML) in a pooled synthetic cohort of clinical trial subjects to real-world clinical practice.
  - Comparison is achieved through the use of two common data standards: Clinical Data Interchange Standards Consortium Study Data Tabulation Model (CDISC SDTM) for clinical trial data and the Observational Medical Outcomes Partnership Common Data Model (OMOP CDM) for RWD.

Objectives

- To understand the impact of inclusion and exclusion criteria on patient attrition in RCT
- Compare patient demographics, treatment patterns, and outcomes in RCT versus real-world populations

Methods

Data Source

- The clinical trial data cohort was derived from a pooled dataset of 7 clinical trials (n=719) for relapsed/refractory AML, conducted from March 2008 - Nov 2017, from the Medidata archive of > 3,000 trials.[3]
  - Pooling was accomplished through harmonization to Clinical Data Interchange Standards.
  - CDISC SDTM version 1.4.[4]
- The real-world data was derived from Electronic Medical Record (EMR) and health plan claims data sources.
  - De-identified Oncology EMR data was sourced from the Guardian Research Network™ (GRN) of integrated delivery systems from Jan 1990 – July 2018.
    - GRN is a nationwide consortium that aggregates hundreds of thousands of cancer patients' electronic medical records from multiple integrated community health systems into a single searchable database.[5]
  - Health plan claims were obtained from the HealthVerity™ Marketplace platform of data suppliers from Feb 2014 – Dec 2018.
    - HealthVerity™ has the most complete coverage of United States healthcare, consumer and purchase data, with access to over 330 million patients and 30 billion transactions.[6]

Data Transformation and Analysis

- All data were converted to the OMOP CDM, version 5.[7]
- Analyses were conducted in SHYFT Quantum version 6.7.0.

Inclusion/Exclusion Criteria

- Study window was set to be between March 2008 – Nov 2017
- Inclusion criteria were applied to the EMR and claims data sources to match the pooled clinical trial data cohort
- Patients with ≥1 AML diagnosis (International Classification of Diseases [ICD]-10: C92.0, C92.4, C92.5, C92.6, C92.A, or ICD-9: 250.0) with evidence of any oncologic treatment claims reimbursed (i.e., injectable, infusible)
- Index date: First diagnosis claim code within observation period
- Age ≥18 at index
- ≥12-month pre-index continuous enrollment
- Exclusion criteria: No evidence of other malignancy (including acute promyelocytic leukemia and myelodysplastic syndrome)
- Inclusion/exclusion criteria were kept inclusive to maximize available population for comparison

Study Measures & Outcomes

- Cohort Attrition: Patient exclusion rates with application of inclusion/exclusion criteria were recorded to compare representativeness of the RCT population.
- Baseline descriptive statistics of demographic and clinical characteristics were assessed.
- Patient treatment patterns by line of therapy: New line of therapy was defined as a gap > 60 days between treatment administrations.
- Utilization rates were estimated for cytotoxic therapy, demethylation agents, anthracyclines, and tyrosine kinase inhibitors.
- Patient treatment response was assessed using Time-to-Treatment Discontinuation, Time-to-Next Treatment, and Mortality (EMR and RCT data only).
- Rates of transfusion dependence (≥ 2 transfusions between 4-60 days apart after Index Date) were evaluated.[8]

Analyses

- Population heterogeneity was assessed between the RCT and EMR populations by comparing the extreme quartile risk ratio (EQRR, ratio of outcomes rates in lowest quartile to the highest) and median-to-mean risk ratio (MMRR, ratio of median outcome to mean outcome) for mortality[9] (Table 2).
- Time-to-event comparisons were conducted for mortality using Kaplan-Meier analysis across the RCT and the RWD (EMR and claims) data sources.
  - Kaplan-Meier analyses were conducted on overall populations and factored for age (< 65 or ≥ 65), transfusion dependence, fms-like tyrosine kinase 3 status, and presence of bone marrow-derived stem cell (BMSC) transplant.

Table 1: Patient Attrition

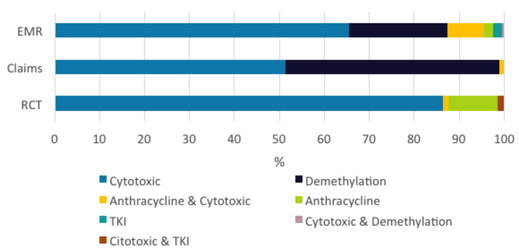
		RCT/SCD (MEDS)				RWD							
		EMR (GRN)						Claims (HealthVerity™)					
	Patients	Remaining		Excluded		Remaining		Excluded		Remaining		Excluded	
		N	%	N	%	N	%	N	%	N	%	N	%
Inclusion	Total Patients	719	100	–	–	1,400	100	–	–	1,602	100	–	–
	Gender	719	100	0	0.0	1,400	100	0	0.0	1,568	97.9	34	2.1*
	Age ≥18 years	662	92.1	57	7.9	1,360	97.1	40	2.9	1,566	99.9	2	0.1
Exclusion	Acute Promyelocytic Leukemia	662	100	0	0.0	1,260	92.7	100	7.3	1,512	96.5	54	3.5
	Myelodysplastic Syndrome	662	100	0	0.0	1,048	83.2	212	16.8	1,015	67.1	497	32.9
	Secondary Cancer	662	100	0	0.0	1,015	96.9	33	3.1	981	96.7	34	3.3

*unknown

MEDS, Medidata Enterprise Data Store; SCD, Synthetic Control Database™

Results

Figure 1: First-Line Treatment Patterns in Real-World Clinical Practice and RCT



TKI, tyrosine kinase inhibitor

Results

Table 2: Patient Demographics

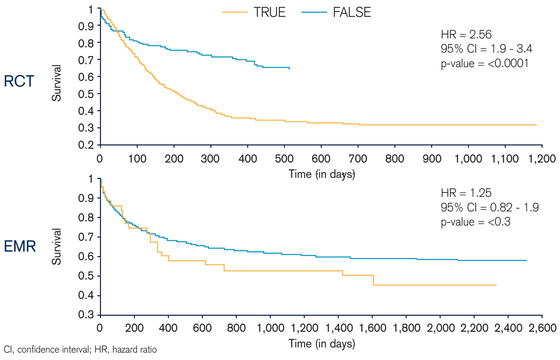
	RCT/SCD (MEDS)	EMR (GRN)	Claims (HealthVerity™)
Age at Index			
Mean (SD)	61.6 (15.8)	63.3 (16.6)	69.0 (10.2)
Median	65	66	70
Ethnicity			
Hispanic or Latino	27 (4.1)	153 (10.7)	–
Not Hispanic or Latino	430 (65.0)	1,240 (86.8)	–
Missing/Other	205 (31.0)	35 (2.5)	981 (100)
Race			
Asian	61 (9.2)	15 (1.1)	–
Black or African American	33 (5.0)	70 (4.9)	–
White	536 (81.0)	1,278 (89.5)	–
Missing/Other	32 (4.8)	65 (4.6)	981 (100)
Gender			
Female	289 (43.7)	716 (50.1)	450 (45.9)
Male	373 (56.3)	712 (50.0)	531 (54.1)

SD, standard deviation

Table 3: Heterogeneity between RCT and RWD EMR Populations

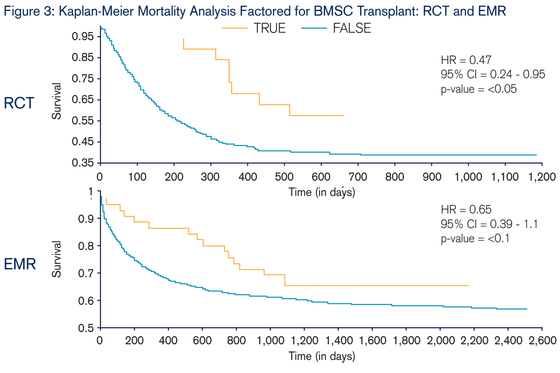
	RCT/SCD (MEDS)	EMR (GRN)	Mean	Median
EQRR	4.1	4.3	159.1	118.0
MMRR	1.4	1.5	482.4	331.5

Figure 2: Kaplan-Meier Mortality Analysis Factored by Transfusion Dependence: RCT and EMR



CI, confidence interval; HR, hazard ratio

Figure 3: Kaplan-Meier Mortality Analysis Factored for BMSC Transplant: RCT and EMR



Summary

- Real-world patient attrition due to age was < 3%, while secondary malignancy accounted for 27% and 40% of patient exclusions in the EMR and claims datasets, respectively (Table 1).
- Real-world populations showed similar age and gender distributions to clinical trial populations (Table 2).
- Heterogeneity of mortality was remarkably consistent between RWD EMR and RCT populations, with EQRR of 4.3 vs. 4.1 and MMRR of 1.5 vs. 1.4, respectively (Table 3).
- With respect to treatment patterns, lower rates of cytotoxic agents and higher rates of demethylation therapy were seen in first-line therapy in real-world clinical practice than in RCT populations (Figure 1).
- Comparisons of RWD vs. RCT populations when examining the impact of transfusion dependence show shorter time-to-death in the RCT population, but comparable magnitudes of relative benefit for transfusion-independent patients (Figure 2).
- RCT populations have similarly shorter time-to-death when examining the impact of BMSC transplant but clear benefits for patients receiving BMSC transplants. RWD populations, by contrast, do not reach median time-to-death, and the benefit of BMSC transplant is not readily apparent. Divergences indicate further opportunities to understand differences in patients receiving transplant between the RWD and RCT setting, as well as potential stratification by allogeneic vs. autologous transplant recipient (Figure 3).
- Overall time-to-death comparisons indicate potentially different severity levels between RCT and RWD populations. While this study kept inclusion/exclusion criteria relatively unrestrictive, there is further opportunity to enhance comparative assessments through the closer matching of inclusion/exclusion criteria, incorporation of available performance status data, use of formal propensity matching, or weighting approaches.

Limitations

- This is a side-by-side comparison of real-world and RCT data, and not a linked real-world and clinical dataset.
- The endpoints and covariates traditional to drug development in specific indications are present in the RCT dataset in the way they are usually measured. This contrasts with real-world cohorts where data capture is subject to missingness, inconsistency of collection time intervals, and possible misclassification.

Conclusions

- Use of common data standards can enable systematic and consistent comparisons and drive potential applications ranging from in silico modeling and synthetic control arm creation to extrapolation of clinical trial findings to real-world practice.

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Disclosures

- JR, AG, ER, CM, AS, and BL are employees of Medidata Solutions. MB provided consultancy to Medidata Solutions.

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