PATTERNS OF CARE IN PATIENTS WITH MYELODYSPLASTIC SYNDROMES TREATED WITH HYPOMETHYLATING AGENTS

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Introduction

Myelodysplastic Syndrome (MDS) is a heterogeneous group of disorders characterized by impaired bone marrow production (cytopenias). Signs and symptoms of anemia, bleeding, and/or infections predominate and features of autoimmunity are present.[1]

MDS has an incidence of about 5/100,000 people in the general population, while incidence in people age >70 years ranges from 20-40/100,000.[2] Median survival for de novo MDS ranges from 5 months to 6 years depending on the risk category.[3]

After diagnosis, some patients receive supportive care only and others are treated with chemotherapy, such as hypomethylating agents (HMAs).

Two HMAs, decitabine (DEC) and azacitidine (AZA), are U.S. Food and Drug Administration (FDA) approved for use in the treatment of MDS.[4-6] Two common FDA-approved regimens of these HMAs include:

- 20 mg/m^2 of DEC by continuous 1 hour intravenous infusion daily for 5 days, repeated every 4 weeks.
- Subcutaneous injection or intravenous infusion of 75 mg/m^2 of AZA daily for 7 days, repeated every 4 weeks.

Clinicians may also commonly use other approaches to treatment, including shorter duration of treatment, such as 5 days[7] instead of 7 days for AZA.

Objective

Our objective was to examine patterns of treatment associated with FDA-approved 5-day decitabine (DEC-5), 7-day azacitidine (AZA-7), and off-label 5-day azacitidine (AZA-5) in MDS patients.

Methods

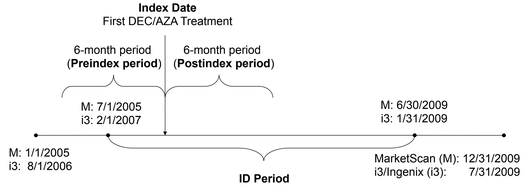
Study Design and Data Sources

- Retrospective cohort study.
- Two Health Insurance Portability and Accountability Act–compliant administrative claims databases: Thomson Reuters MarketScan and i3/Ingenix LabRx.

Study Population and Study Timeframe

- Study included patients diagnosed with MDS and newly-treated with DEC or AZA in 7/1/2005-6/30/2009 for MarketScan and in 2/1/2007-1/31/2009 for i3/Ingenix (identification [ID] period).
- The date of the first active treatment in the ID period was defined as the index date, and patients were followed for 6 months after the index date (postindex period).

MDS Patients Newly Treated with DEC/AZA in the ID period



Inclusion criteria: Patients were included if they:

- Had a medical claim in the ID period with a diagnosis of MDS (ICD-9-CM codes 238.72-238.75) in any diagnosis field, *and*
- Had a claim of either DEC or AZA during the ID period.

Exclusion criteria: Patients were excluded if they:

- Had a claim of DEC or AZA during the preindex period, *or*
- Had a first treatment regimen that was not DEC-5, AZA-7, or AZA-5, *or*
- Had a diagnosis of acute myeloid leukemia in the preindex period, *or*
- Were not continuously enrolled in the preindex and postindex periods.

Exclusion of duplicate patients: Patients found in both databases who had the same age, gender, region, study regimen, and date of first study treatment were considered duplicates.

Measures

Baseline measures:

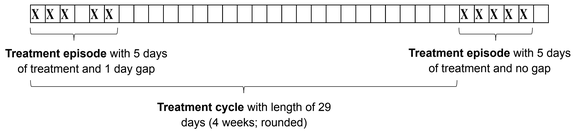
All outpatient pharmacy and medical claims in the 6-month preindex period were reviewed to derive the baseline measures, including:

- Demographics: age, gender, and region.
- Bone marrow biopsy.
- Comorbidities: Charlson Comorbidity Index[8] and solid organ malignancy.
- Cytopenias: anemia (includes erythropoietin and iron chelation), transfusions, neutropenia, potential complication of neutropenia, thromobocytopenia, pancytopenia.

Outcome measures:

- Outcome measures were treatment cycles and duration of treatment gaps within cycles.
- We used the following definitions (see diagram below):
  - *Treatment episode*: the period from first to the last day within days of treatment.
  - *Treatment cycle*: the period from the first day of a treatment episode to the day before the next episode of the same drug.
  - *Treatment gap*: missed days of treatment within an episode in a cycle.

Example of Treatment Episode and Cycle

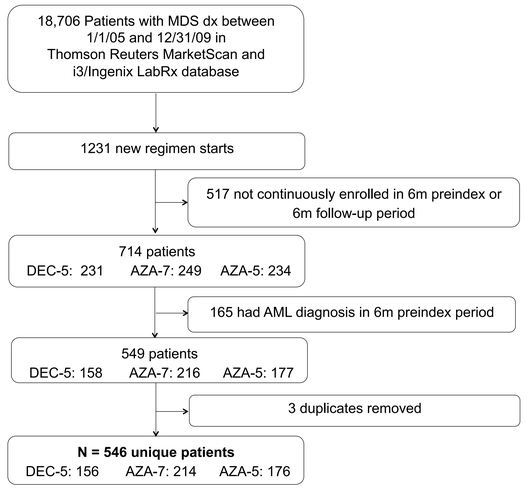


Statistical Analysis

- Descriptive statistics for all measures were stratified by the 3 treatment cohorts with patients classified based on their first cycle of treatment:
  - DEC-5: Patient received 5 days of DEC without a gap ≥7 days.
  - AZA-7: Patient received 7 days of AZA without a gap ≥7 days.
  - AZA-5: Patient received 5 days of AZA without a gap ≥7 days.
- All categorical variables were compared using the X^2 test. Mean number of treatment cycles where compared using the F-test.
- All data transformations and statistical analyses were conducted using SAS® version 9.2 (SAS Institute, Cary, NC)

Results

MDS Patients Newly Treated with DEC-5, AZA-7, or (Off-Label) AZA-5



- Of 18,706 patients with MDS, 546 unique, continuously-enrolled, and newly treated with HMAs were included in the study.
- There were no statistically significant differences by treatment regimen for baseline demographics, Charlson comorbidity index, and occurrence of malignancy, so overall estimates among 546 patients include:
  - Mean age was 70.2 (standard deviation [SD]: 11.1) years,
  - 35.9% were female,
  - 42.7% were from the South, 32.4% from North Central, 14.5% from West, and 10.4% from Northeast,
  - Mean Charlson comorbidity index was 2.1 (SD: 2.1), and
  - 21.1% had solid organ malignancy.

Baseline Cytopenias by Treatment Group

		DEC-5 N = 156; 28.6%	AZA-7 N = 214; 39.2%	AZA-5 N = 176; 32.2%	All Regimens N = 546	*P* Value [a]
Anemia	no. (%)	137 (87.8)	187 (87.4)	145 (82.4)	469 (85.9)	0.265
Anemia diagnosis	no. (%)	130 (83.3)	176 (82.2)	134 (76.1)	440 (80.6)	0.187
Erythropoietin use	no. (%)	83 (53.2)	122 (57.0)	87 (49.4)	292 (53.5)	0.327
Iron chelation therapy	no. (%)	7 (4.5)	5 (2.3)	10 (5.7)	22 (4.0)	0.233
Transfusions	no. (%)	43 (27.6)	49 (22.9)	55 (31.3)	147 (26.9)	0.176
Neutropenia	no. (%)	54 (34.6)	57 (26.6)	40 (22.7)	151 (27.7)	0.049
Neutropenia diagnosis [b]	no. (%)	34 (21.8)	37 (17.3)	27 (15.3)	98 (17.9)	0.295
G-CSF use	no. (%)	32 (20.5)	30 (14.0)	24 (13.6)	86 (15.8)	0.154
Potential complication of neutropenia	no. (%)	18 (11.5)	26 (12.1)	21 (11.9)	65 (11.9)	0.984
Pneumonia	no. (%)	15 (9.6)	22 (10.3)	19 (10.8)	56 (10.3)	0.939
Unspecified fever	no. (%)	4 (2.6)	5 (2.3)	3 (1.7)	12 (2.2)	0.854
Outpatient Rx IV ATB use	no. (%)	0 (0.0)	0 (0.0)	2 (1.1)	2 (0.4)	0.121
Thrombocytopenia	no. (%)	51 (32.7)	48 (22.4)	45 (25.6)	144 (26.4)	0.083
Pancytopenia	no. (%)	49 (31.4)	57 (26.6)	45 (25.6)	151 (27.7)	0.451

[a] Comparisons across 3 treatment groups using the X^2 test.
[b] Diagnosis of neutropenia, febrile neutropenia, or decreased white blood cell count.

- Neutropenia was significantly more common before treatment initiation in the DEC-5 group than in AZA-5 and AZA-7 groups (P<0.05).

Postindex Treatment Cycles and Treatment Gaps

		DEC-5 N = 156; 28.6%	AZA-7 N = 214; 39.2%	AZA-5 N = 176; 32.2%	All Regimens N = 546	*P* Value
Treatment cycles						
Mean (SD) per patient		2.8 (2.0)	3.2 (2.1)	3.3 (2.1)	3.1 (2.1)	0.034[a]
Median per patient		2	3	3	3	
Number of unique treatment cycles		431	684	586	1,701	
Duration of treatment gaps within unique treatment cycles						<0.001[b]
0 days	no. (%)	409 (94.9)	160 (23.4)	522 (89.1)	1,091 (64.1)	
1 day	no. (%)	3 (0.7)	11 (1.6)	4 (0.7)	18 (1.1)	
2 days	no. (%)	14 (3.2)	455 (66.5)	42 (7.2)	511 (30.0)	
3+ days	no. (%)	5 (1.2)	58 (8.5)	18 (3.1)	81 (4.8)	

[a] Comparison of mean number of treatment cycles across 3 treatment groups was done using the *F*-test.
[b] Comparison across 3 treatment groups was done using the X^2 test.

- There were 1,701 treatment cycles: 431 in the DEC-5 group (per patient mean: 2.8; median: 2), 684 in AZA-7 (mean: 3.2; median: 3), and 586 in AZA-5 (mean: 3.3; median: 3) (P<0.05 for means).
- DEC-5 cycles had the fewest gaps: 94.9% had no treatment gaps, compared to 23.4% for AZA-7 and 89.1% for AZA-5 (P<0.001).
- Among DEC-5 cycles, 3.2% had a 2 day gap, compared to 66.5% for AZA-7 and 7.2% for AZA-5 (P<0.001).

Conclusions

Conclusions

- In this retrospective analysis, few patients with MDS were treated with HMAs.
- Among those who received HMAs, decitabine patients were more likely to have prior neutropenia.
- Between the two FDA-approved regimens, DEC-5 and AZA-7, there were significantly fewer treatment gaps with decitabine treatment.
- More treatment gaps were observed with use of the longer AZA regimen.

Limitations

- This was a retrospective study using health care claims. Claims are collected and processed for payment rather than research purposes and, as a result, may be subject to undercoding or miscoding. Additionally, claims lack data on clinical factors, such as disease severity.
- Our study included patients with commercial insurance, so Medicare patients were underrepresented. Hence, our results may not be representative of the general MDS population, and different populations may have different outcomes.
- Small sample size may have limited us in detecting significant differences.

References

1. De Roos, *Am J Hematol* 2010; 2. Germing, *Haematologica* 2004; 3. NCCN Guidelines, 2011; 4. Atallah, *Cancer Invest* 2008; 5. DACOGEN (decitabine) [package insert]. Woodcliff Lake, NJ: Eisai Inc.; 2006.; 6. VIDAZA (azacitidine) [package insert]. Summit, NJ: Celgene Corporation; 2004.; 7. Martin, *Am J Hematol* 2009; 8. Deyo, *J Clin Epidemiol* 1992.

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