

Impact of transformation to acute myeloid leukemia on overall survival among patients with higher-risk myelodysplastic syndromes in the USA

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Background

- Myelodysplastic syndromes (MDS) are characterized by cytopenia and progressive bone-marrow deterioration.¹
- Over 40% of patients with MDS are classified as higher-risk, defined as having intermediate-, high- or very high-risk disease according to the Revised International Prognostic Scoring System (IPSS-R).²
- Hypomethylating agents (HMAs) are the standard of care for higher-risk MDS.³
 - Approximately 50% of patients with higher-risk MDS respond to treatment with HMAs.⁴
 - For patients with higher-risk MDS, the risk of their disease transforming to acute myeloid leukemia (AML) is 40%.³ After disease transformation from higher-risk MDS to secondary AML, life expectancies of patients are limited to weeks or months.⁵
 - Treatment response rates and outcomes are very poor in patients with secondary AML.^{4–8} In a retrospective study of treatment outcomes in patients with secondary AML (with or without a low platelet count), the complete response rate was as low as 23%.⁶
 - In the same study, median overall survival (OS) was 4.76 months in patients ≥ 60 years of age, with secondary AML and a history of MDS.⁶
- Prospectively, transformation to AML was associated with poor survival outcomes in a randomized, global, proof-of-concept, phase 2 study (P-2001; NCT02610777) that compared pevonedistat + azacitidine (AZA) with AZA alone in patients with higher-risk MDS.⁷
 - Median OS was shorter (13.6 months) in 14 patients who experienced transformation to AML compared with 53 patients who did not experience transformation to AML (27.7 months; hazard ratio, 0.289; $p = 0.0002$).⁷
 - Median OS was 2.6 months (95% confidence interval [CI]: 0.01–10.78) from the time of transformation to AML.⁷
 - Exploratory analyses of data from this study demonstrated that transformation to AML was also associated with trends in the deterioration of quality of life, physical functioning and worsening of fatigue in the small number of patients who had experienced this transformation (n = 12) compared with those who had not (n = 51).⁸

Objective

- This retrospective study assessed the impact of transformation to AML on survival outcomes in patients with higher-risk MDS receiving any first-line therapy and in those receiving AZA and decitabine (DEC) as first-line therapy.

Methods

Study population

- Patients with higher-risk MDS aged ≥ 18 who initiated first-line therapy between January 1, 2008, and June 30, 2019, were identified from a large US electronic medical record (EMR) database.
 - Owing to a lack of complete cytogenetics in the EMR, higher-risk MDS were defined based on International Classification of Diseases (ICD) coding for higher-risk MDS (≥ 1 ICD-9/10 codes: 238.73, D46.2 [0–2]) or using an adapted higher-risk MDS algorithm based on IPSS-R (intermediate- or higher-risk).⁹
- Patients were followed from the start of first-line therapy for higher-risk MDS until death, loss to follow-up or study end (September 30, 2019).
- In addition to the overall study population, a subgroup of patients who received AZA and DEC as first-line therapy were analyzed.

Outcomes and analyses

- Rate of transformation to AML following initiation of first-line therapy for higher-risk MDS was assessed using a Kaplan–Meier (KM) analysis.
- Two approaches were used for comparing OS between patients who experienced transformation to AML and those who did not, to control for bias due to differential follow-up time between groups: 1) the main landmark analysis; and 2) the sensitivity analysis using the time-varying Cox proportional-hazards regression.
 - The landmark time of 6 months after initiation of first-line therapy was chosen based on the guideline-recommended minimum duration of MDS treatment of six cycles and the median time to transformation of 5.9 months among patients treated with AZA in the phase 2 study.⁷
 - AML status (transformation to AML or not) was defined at the landmark time of 6 months after initiation of first-line therapy in patients with ≥ 6 months of follow-up.
 - The Cox proportional-hazards model was used to assess the impact of transformation from higher-risk MDS to AML on OS after the 6-month landmark.
 - The model was adjusted for differences in baseline characteristics, including age, sex, race, ethnicity, region, payer type, index year, Charlson Comorbidity Index score, transfusion status and supportive care, between patients with higher-risk MDS who had experienced transformation to AML and those who had not.
 - To validate the association between transformation to AML and OS further, a time-varying Cox proportional-hazards model with AML transformation status as the time-varying variable was performed; the model was also adjusted for the baseline characteristics.
- A subgroup analysis for those treated with first-line AZA and DEC therapy was also conducted.

Results

Study population

- In total, 874 patients with higher-risk MDS who received first-line therapy were identified.
- At baseline, the median age was 73.0 years, and 43.0% of patients had a Charlson Comorbidity Index score of 2 or higher (**Table 1**).

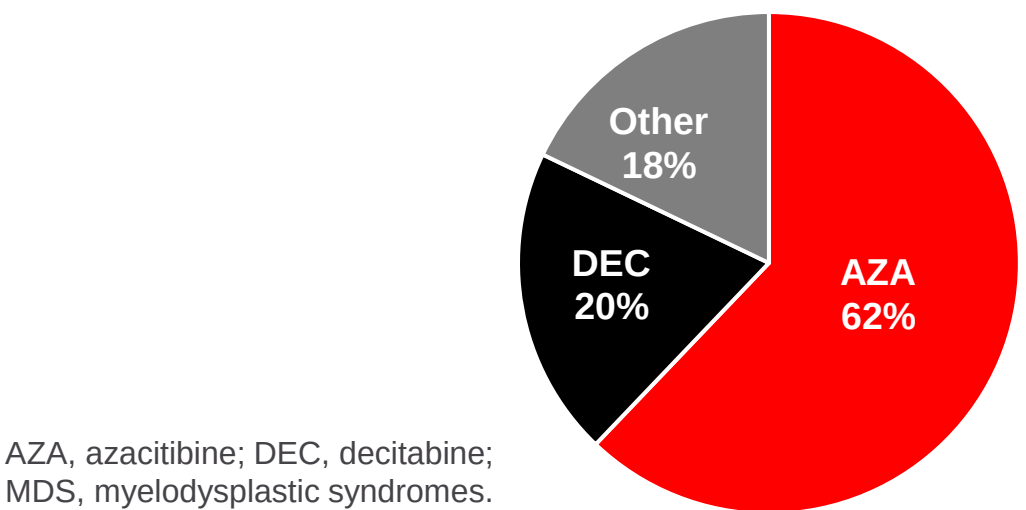
Table 1. Baseline demographic and clinical characteristics of patients with higher-risk MDS prior to first-line therapy initiation.

Demographic characteristics at start date of first-line therapy for higher-risk MDS	
	Overall population (N = 874)
Age	
Median, years	73.0
≥ 75 years, n (%)	402 (46.0)
Race	
Caucasian, n (%)	791 (90.5)
Geographic region	
USA (Midwest), n (%)	518 (59.3)
Clinical characteristics in the 12 months before the start date of first-line therapy for higher-risk MDS	
	Overall population (N = 874)
Charlson Comorbidity Index score, n (%)	
0	333 (38.1)
1	165 (18.9)
2+	376 (43.0)
Supportive care	
Any, n (%)	519 (59.4)
Transfusion, n (%)	455 (52.1)

MDS, myelodysplastic syndromes.

- Of the 861 patients with chemotherapy-based first-line therapy, HMAs were the most common first-line therapy used: 62.1% of patients (n = 535) received AZA and 20.0% (n = 172) received DEC (**Figure 1**).
 - In the overall higher-risk MDS population (N = 874), 13 patients had evidence of treatment with only stem-cell transplantation.

Figure 1. First-line therapies used by the overall population with higher-risk MDS, excluding patients who underwent stem-cell transplantation (n = 861).



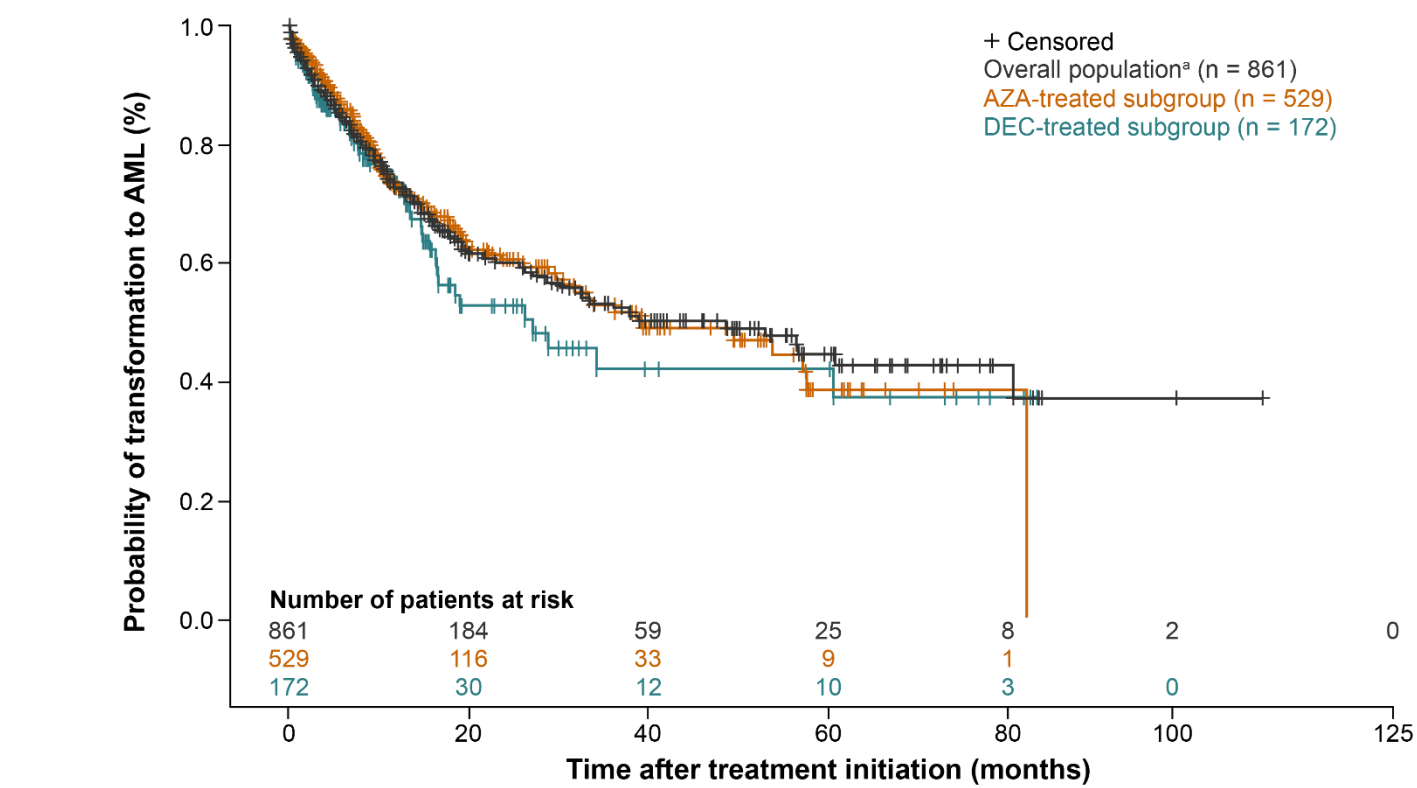
AZA, azacitidine; DEC, decitabine; MDS, myelodysplastic syndromes.

- The median (mean [standard deviation]) follow-up time from first-line therapy initiation was:
 - 11.2 (17.1 [18.1]) months for the overall population, excluding patients who underwent stem-cell transplantation (n = 861)
 - 11.4 (16.5 [15.9]) months for the AZA subgroup (n = 529)
 - 11.3 (18.4 [21.0]) months for the DEC subgroup (n = 172).
- The median (95% CI) OS from first-line therapy in patients with higher-risk MDS was:
 - 14.9 (13.5–16.3) months for the overall population, excluding patients who underwent stem-cell transplantation (n = 861)
 - 15.2 (13.5–17.4) months for the AZA subgroup (n = 529)
 - 14.8 (11.8–17.5) months for the DEC subgroup (n = 172).

Transformation to AML

- In total, 247 patients with higher-risk MDS experienced transformation to AML. In these patients, the median time between initiation of first-line therapy and transformation to AML was 7.0 months, and median OS from time of transformation to AML was 5.0 months..
- The probability of transformation from higher-risk MDS to AML after initiation of first-line therapy was similar in the overall population (rate of transformation, 27% at 12 months and 39% at 24 months), the AZA subgroup (rate of transformation, 28% at 12 months and 40% at 24 months) and the DEC subgroup (rate of transformation, 26% at 12 months and 48% at 24 months) (**Figure 2**).

Figure 2. Probability of transformation from higher-risk MDS to AML after initiation of first-line therapy in the overall population and AZA subgroup (KM analysis).



*Excluding the 13 patients who underwent stem-cell transplantation.
AML, acute myeloid leukemia; AZA, azacitidine; DEC, decitabine; KM, Kaplan–Meier; MDS, myelodysplastic syndromes.

Transformation to AML and survival

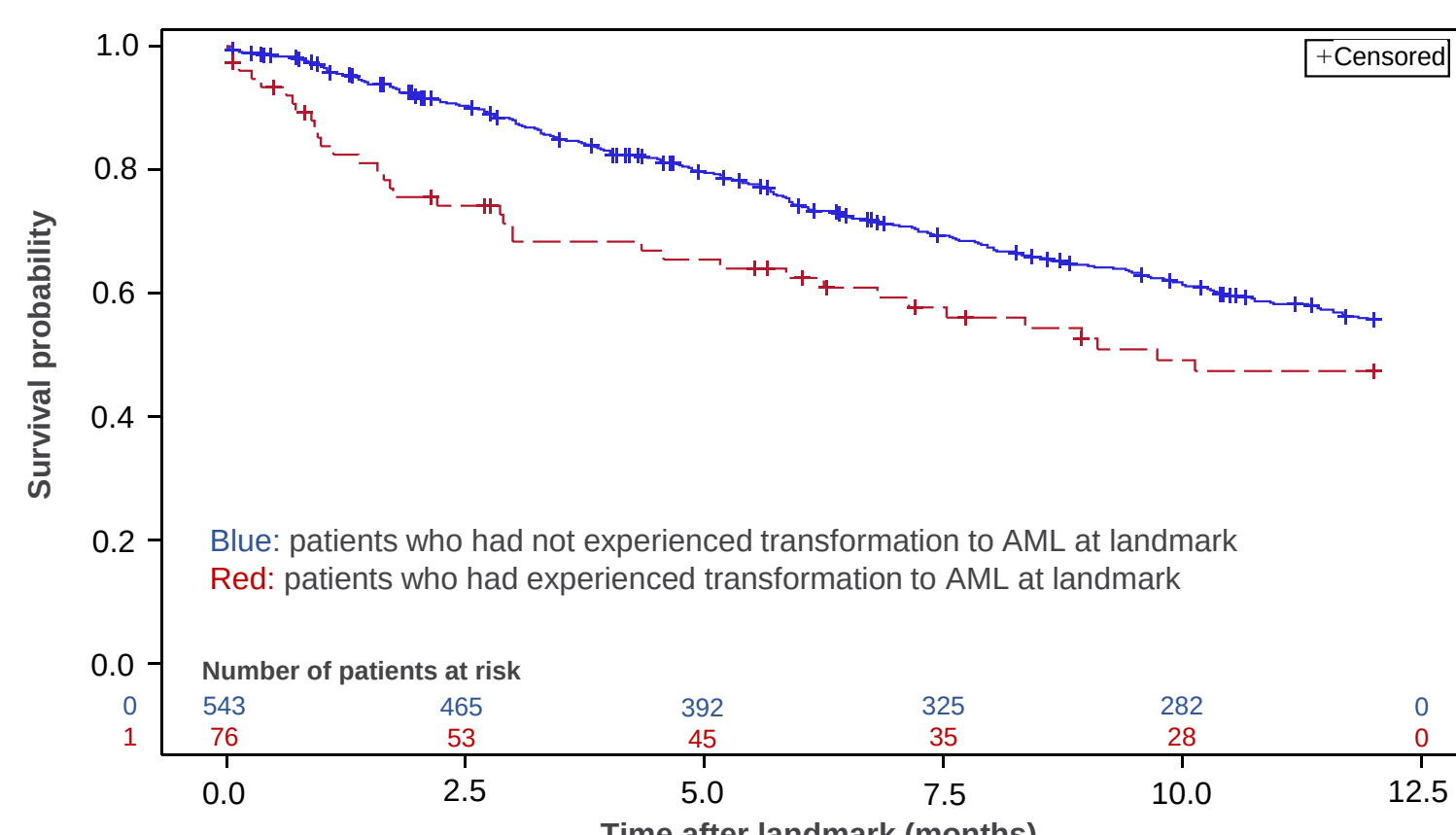
- The landmark analysis included 619 patients with higher-risk MDS who had at least 6 months of follow-up after initiating first-line therapy. Of these, 76 (12.3%) had experienced transformation to AML by the 6-month landmark and formed the cohort who transformed to AML (**Figure 3**).
- In the unadjusted landmark analysis, the KM survival rate 6 months after the landmark was significantly lower in patients who had experienced transformation to AML than in those who had not in the overall population (62.5% vs 74.2%, $p = 0.0006$) and the AZA subgroup (63.9% vs 74.6%, $p = 0.029$; **Table 2** and **Figure 3**). The DEC subgroup 6-month landmark analysis was not feasible owing to the small sample size (patients who had experienced transformation to AML at 6 months, n = 18; patients who had not, n = 105).

Table 2. Unadjusted 6-month landmark analysis of survival by AML transformation status.^a

Parameter	Patients who had experienced transformation to AML at 6-month landmark	Patients who had not experienced transformation to AML at 6-month landmark
Overall population, n	76	543
OS after landmark, median (95% CI), months	9.7 (6.3–18.8)	15.4 (12.3–18.0)
KM survival rate 6 months after the landmark, %	62.5	74.2
	p = 0.006	
AZA subgroup, n	42	343
OS after landmark, median (95% CI), months	9.1 (2.9–14.8)	15.4 (12.6–18.2)
KM survival rate 6 months after the landmark, %	63.9	74.6
	p = 0.029	

AML, acute myeloid leukemia; AZA, azacitidine; CI, confidence interval; KM, Kaplan–Meier; OS, overall survival.

Figure 3. Association between transformation to AML at the 6-month landmark and subsequent OS rates.



OS was the time from the 6-month landmark to death for patients who died; patients who did not die were censored at the end of follow-up.
AML, acute myeloid leukemia; OS, overall survival.

- Similar results were obtained from the multivariable Cox proportional-hazards analyses, which were adjusted for differences in baseline patient characteristics between patients who had experienced transformation to AML and those who had not (**Table 3**).

Table 3. Multivariable Cox proportional-hazards analyses of OS in patients who experienced transformation to AML compared with those who did not.

		Patients who experienced transformation to AML vs those who did not		
Analysis		Hazard ratio	95% CI	p value
OS at 6 months after landmark, adjusted for baseline characteristics ^a	Overall population (n = 619)	1.82	1.18–2.81	0.0072
	AZA subgroup (n = 385)	1.72	0.93–3.15	0.0824
OS at 1 year after initiation of first-line therapy, adjusted for baseline characteristics, ^a with AML status as a time-varying variable	Overall population (n = 861)	2.85	2.19–3.72	< 0.0001
	AZA subgroup (n = 529)	2.79	1.98–3.94	< 0.0001
	DEC subgroup (n = 172)	6.35	3.37–11.98	< 0.0001

^aBaseline characteristics included age, sex, race, ethnicity, region, payer type, index year, Charlson Comorbidity Index score, transfusion status and supportive care.
AML, acute myeloid leukemia; AZA, azacitidine; CI, confidence interval; DEC, decitabine; OS, overall survival.

Limitations

- The two approaches used for comparing OS between patients who experienced transformation to AML and those who did not, to control for bias, have benefits and drawbacks as follows:
 - For the landmark analysis:
 - pros include that it eliminates survival time bias present in patients who experienced transformation to AML, given that they cannot experience the outcome of interest (i.e. death) between the first-line therapy initiation date and the date of AML transformation
 - cons include choosing the landmark time, because an earlier landmark omits AML transformation events, and a later landmark (longer follow-up) allows for more deaths to occur before AML transformation events.
 - For the sensitivity analysis, using the time-varying Cox proportional-hazards regression:
 - pros include that it does not exclude patients and that there is no misclassification
 - cons include that results are difficult to interpret.

Conclusions

- Among patients with higher-risk MDS who received first-line therapy, which predominantly included AZA or DEC, transformation to AML was associated with poor survival outcomes.
- Our findings were consistent with those from P-2001 (NCT02610777), in which median OS was shorter in patients who experienced transformation to AML than in those who did not.
- These results highlight the importance of delaying transformation from higher-risk MDS to AML as a treatment goal and the need to develop treatments that are of benefit to this patient population.

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Funding statement

This study was supported by Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.

Disclosures

VK: honorarium from Novartis, Pfizer and Takeda; research funding from Incyte.
AO, EF, BKS and AR: employees of Xcenda, which has received research funding from Millennium Pharmaceuticals, Inc., for the conduct of this study. FK: employee of Takeda. MD: employee and stockholder of Takeda.

Acknowledgements

We thank all of the patients and their families, and the investigators and staff at all clinical sites, for their participation in the study.
Editorial assistance was provided by Jacquelyn Williams of Oxford PharmaGenesis, Newtown, PA, funded by Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.

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