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RESEARCH ARTICLE

Real-world study of the use of azacitidine in myelodysplasia in Australia

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Abstract

Hypomethylating agents are the most widely used upfront therapy for patients with myelodysplastic syndrome (MDS) who are not suitable for hematopoietic stem cell transplantation. In Australia, azacitidine was, until recently, the only approved and subsidized treatment for patients with intermediate-2 and high-risk MDS, chronic myelomonocytic leukemia, and low blast acute myeloid leukemia. We analyzed prescription data to evaluate the real-world persistence and overall survival (OS) of patients prescribed azacitidine for the first time in Australia. A retrospective cohort analysis of patients who had been prescribed Pharmaceutical Benefits Scheme (PBS)-listed azacitidine for the first time, between January 2016 and April 2021, was conducted using the PBS 10% dataset. Treatment persistence and OS were estimated using Kaplan–Meier methods. The impact of the number of treatment cycles and treatment adherence on OS was also estimated. There were 351 patients in the PBS 10% dataset who initiated treatment with azacitidine. The average age (standard deviation [SD]) at azacitidine initiation was 71.9 (11.1) years and the average number (SD) of azacitidine prescriptions was 5.6 (0.2). The median persistence on azacitidine was 15.6 months, and the OS was 13.4 months. The median OS for patients who had six or more cycles of azacitidine treatment was greater compared to patients who had five or less cycles of treatment. The data from this real-world study illustrate the unmet medical needs of patients with MDS treated with azacitidine in Australia. The majority of patients are not treated with the optimal number of cycles of azacitidine, which is negatively correlated with patient outcomes.

KEYWORDS
azacitidine, hypomethylating agents, myelodysplastic syndromes, real-world, survival

1 | INTRODUCTION

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal hematopoietic stem cell disorders. MDS is characterized by cytopenias, ineffective hematopoiesis, and a risk of progression to an acute myeloid leukemia (AML) [1].

The prognosis of patients with MDS varies significantly, and as a result, patients with MDS are categorized using risk stratification tools such as the International Prognostic Scoring System (IPSS) and the revised version, IPSS-R [2, 3]. According to IPSS-R, patients are classified from very low to very high risk based on their cytogenetic features, bone marrow blast percentage, and the extent of peripheral blood cytopenias.

Hematopoietic stem cell transplantation (HSCT) is the only potentially curative option for MDS, with high-risk patients obtaining the biggest benefit [4]. However, only younger patients, who are also fit, are eligible for HSCT, given the higher mortality associated with this procedure in older patients and patients with comorbidities [4, 5]. For patients who are not suitable for HSCT, hypomethylating agents (HMAs), azacitidine and decitabine, are the most appropriate therapy [1]. Azacitidine and decitabine are both approved by the United States Food and Drug Administration for the treatment of MDS and the agents are considered to be comparable by most clinicians [1].

In Australia, azacitidine has been the only approved and subsidized treatment for patients with intermediate-2 and high-risk MDS (HR-MDS) (according to the IPSS), chronic myelomonocytic leukemia (CMML), and low blast (LB)-AML and multi-lineage dysplasia (according to the World Health Organization classification) since 2011 until November 2022. It should be noted that approval for azacitidine use is based on categorization of patients using IPPS clinical criteria (the IPPS categorization was used in the AZA-001 study). However, IPSS-R is a better risk stratification tool, particularly in terms of decisions regarding HSCT, and is more widely used by clinicians in practice in Australia. Clinically, there is discordance between the two risk stratification tools, and some patients, whose disease is classified as higher risk using IPSS-R, may not be able to access subsidized azacitidine in Australia. More recently, although the use of myeloid molecular markers has improved the risk categories for MDS, this has not changed the criteria for accessing HMAs in Australia [6].

Clinical trial data from the AZA-001 study have demonstrated a median overall survival (OS) of 24.5 months for patients with intermediate-2/HR-MDS treated with azacitidine compared to 15 months for patients treated with conventional care regimens [7]. More recently, the PANTHER randomized phase 3 trial investigated pevonedistat plus azacitidine compared to azacitidine monotherapy in patients with HR-MDS (n = 324); a median OS of 17.5 months was observed for the azacitidine monotherapy group [8]. Real-world data on the use of azacitidine for intermediate-2/HR-MDS have indicated more modest benefits compared to clinical trial data [9–12]. These differences may be due to lack of adherence to dosing schedules, treatment duration, and less rigorous patient selection.

The outcomes of patients with MDS treated with azacitidine in the real-world in Australia are unknown. The Pharmaceutical Benefits Scheme (PBS) subsidizes the costs of prescription drugs in Australia and their sample data contain a record of medicines dispensed to individuals through the scheme [13]. We analyzed a 10% longitudinal sample of PBS data from January 2016 to April 2021 to evaluate the treatment persistence and OS of patients with intermediate-2/HR-MDS, LB-AML, and CMML, who were prescribed azacitidine for the first time, in Australia.

2 | METHODS

This retrospective cohort analysis was conducted using the Services Australia PBS. The PBS 10% dataset is a fully longitudinal 10% sample of community-based dispensing of prescription medicines subsidized by the Australian Government and is considered to be representative of the Australian population [14]. Longitudinal data were extracted for patients who received a PBS-listed azacitidine prescription between January 2016 and April 2021 for the treatment of intermediate-2/HR-MDS, LB-AML, or CMML. Azacitidine became available on the PBS in June 2011. However, only patients who initiated treatment with azacitidine in January 2016 were analyzed in this study, since prior to this date, the data were not stratified for the different approved indications for azacitidine. This study and publication of subsequent results were approved by Services Australia (EREC approval number RMS1333).

The PBS 10% dataset used in this analysis was analyzed by Prospection, a company who are approved PBS data custodians [15]. The data included patient-level de-identified prescription claims data that were updated every quarter [13]. Extracted data from the PBS 10% dataset included year of birth, sex, PBS item code (Table 1), drug dispensing date, and year of death. From these data, variables used for analysis included age at initiation (dispensing year minus year of birth), indication (inferred from the PBS item code and its corresponding authority information), and line of therapy (calculated based on order of therapy). Azacitidine has a listed Authority Required restriction on the PBS for each indication, which has an associated PBS authority code. The PBS 10% dataset contains the drug to authority code mapping and so data for each indication could be extracted.

2.1 | Treatment

Azacitidine is administered at a dose of 75 mg/m^2 given subcutaneously or by intravenous infusion daily for 7 days, followed by a rest period of 21 days (28-day cycle). The 7-day continuous administration schedule of azacitidine can be difficult due to the logistical challenges of delivering an intravenous or subcutaneous therapy over a weekend. As such azacitidine is usually given for 5 days, followed by 2 days without treatment, and then azacitidine for an additional 2 days (5-0-2). There is real-world evidence indicating that there is no difference in outcomes based on administration schedule for intermediate-2/HR-MDS and LB-AML population [11]. It is recommended that azacitidine is given for a minimum of six cycles [16], although treatment may be continued as long as the patient continues to benefit or until dis-

TABLE 1 Pharmaceutical Benefits Scheme (PBS) item codes and indication restrictions for azacytidine.

PBS code	Authority ID	Authority description
6100C	6177	Myelodysplastic syndrome. The condition must be classified as intermediate-2 or high risk according to the IPPS.
	6132	Chronic myelomonocytic leukemia. The condition must have 10%–29% marrow blasts without myeloproliferative disorder.
	6143	Acute myeloid leukemia. The condition must have 20%–30% marrow blasts and multi-lineage dysplasia according to WHO classification.
6138C	6199	Myelodysplastic syndrome. The condition must be classified as intermediate-2 or high risk according to the IPPS.
	6144	Chronic myelomonocytic leukemia. The condition must have 10%–29% marrow blasts without myeloproliferative disorder.
	6186	Acute myeloid leukemia. The condition must have 20%–30% marrow blasts and multi-lineage dysplasia according to WHO classification.
9597D	6177	Myelodysplastic syndrome. The condition must be classified as intermediate-2 or high risk according to the IPPS.
	6132	Chronic myelomonocytic leukemia. The condition must have 10%–29% marrow blasts without myeloproliferative disorder.
	6143	Acute myeloid leukemia. The condition must have 20%–30% marrow blasts and multi-lineage dysplasia according to WHO classification.
9598E	6199	Myelodysplastic syndrome. The condition must be classified as intermediate-2 or high risk according to the IPPS.
	6144	Chronic myelomonocytic leukemia. The condition must have 10%–29% marrow blasts without myeloproliferative disorder.
	6186	Acute myeloid leukemia. The condition must have 20%–30% marrow blasts and multi-lineage dysplasia according to WHO classification.

Abbreviations: IPPS, International Prognostic Scoring System; WHO, World Health Organization.

ease progression. If hematological toxicity, as defined by a decrease in platelets or absolute neutrophil count (ANC), is observed following azacitidine treatment, then it is recommended that the next cycle of azacitidine therapy should be delayed until platelet levels and ANC levels have recovered. If recovery has not occurred within 14 days, then a dose reduction is recommended [16].

2.2 | Sequencing of therapy

The overall patient journey allows a visualization of the treatment sequence for patients who have been prescribed azacitidine at least once during their treatment. The journey shows the hierarchical relationship between each drug and the most prescribed drugs for patients initiating treatment, as well as the subsequent lines of treatment. The treatment sequence was obtained for patients who had initiated treatment between January 2016 and April 2021 on the PBS, and who had been prescribed azacitidine at least once during their treatment. Both drop-off and death were computed as described below for persistence and OS, with the drop-off computed with a 3-month gap from the last prescription, and death computed based on the year of death and the last prescription in the database.

The list of PBS item codes used to define the treatment groups in the treatment sequence is shown in Table S1.

2.3 | Statistical analysis

2.3.1 | Persistence and overall survival

Treatment persistence was defined as the time from the date of first azacitidine prescription until the date of last prescription of azacitidine and excluded those with a gap of 3 months. OS was defined from the date of first azacitidine prescription to date of death. Treatment persistence and OS were estimated using Kaplan–Meier methods, stratified by the indication. A 3-month gap was chosen for treatment persistence estimations as this was considered a reasonable time period that indicated that the patient had discontinued treatment. The year of death is recorded in the PBS 10% dataset and the date of death is attributed to the date of the patient's last claim for any medication (both hematology-related and non-hematology-related medicines).

2.3.2 | Definition of adherent or sub-adherent for overall survival analyses

As per the guidelines for azacitidine treatment, the expected time between two azacitidine prescriptions is 28 days [16]. A patient was defined as adherent if they took 32 days or less to obtain the azacitidine prescription; otherwise, they were regarded as sub-adherent. The rationale for defining adherent as 32 days or less (rather than 28 days) was based on enabling the patient some flexibility in starting the next cycle to fit in with hospital schedules and bookings. The medication possession ratio (MPR) was calculated for every month of treatment as the expected time between two scripts divided by the actual time taken to refill the prescriptions. MPR is calculated using a monthly rolling window sized at 2 months. The algorithm skips the MPR calculation if the script is missing in the MPR window. For each patient, an MPR value was calculated for each month and the average of the MPRs was the final MPR value. The average MPR values, calculated over the entire treatment period with azacitidine, were used to classify patients into either adherent or sub-adherent categories.

Patients with less than six treatment cycles were not included in the adherence analysis as they were considered to have insuffi-

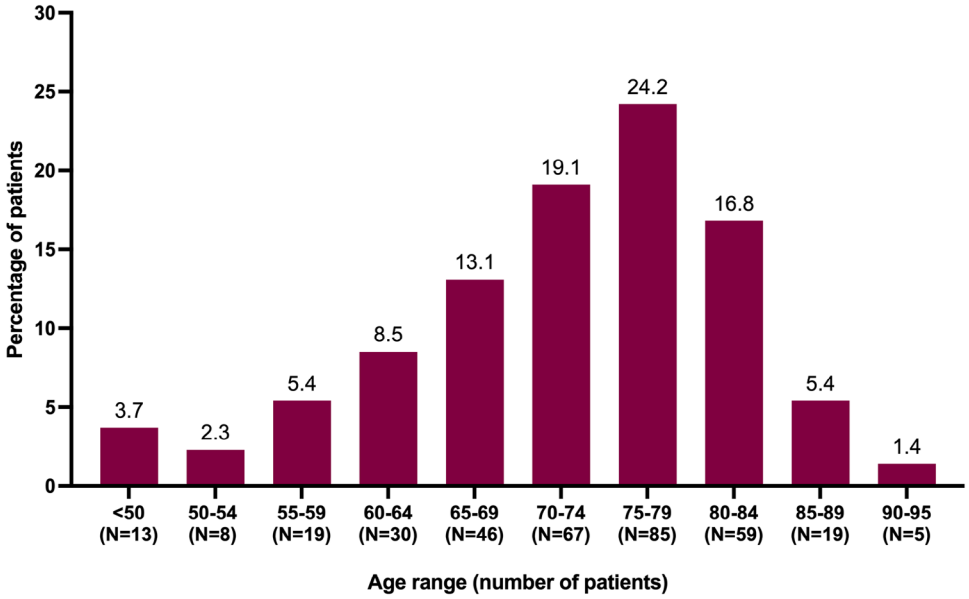


FIGURE 1 Age distribution of patients at initiation of azacitidine (Pharmaceutical Benefits Scheme 10% dataset).

cient data for the calculation. Patients with less than six treatment cycles were categorized into two separate groups for the OS analyses: less than four treatment cycles and four to five treatment cycles.

3 | RESULTS

3.1 | Baseline characteristics

Between January 2016 and April 2021, there were 351 patients in the PBS 10% dataset who initiated treatment with azacitidine. There were 196 patients with intermediate-2/HR-MDS, 55 patients with CMML, and 135 patients with LB-AML. Patients may have been prescribed azacitidine for more than one indication; hence, the total number of patients from each indication was greater than the total number of patients who received azacitidine. Two-thirds of the patients were male (n = 232, 66%) and the average age at azacitidine initiation was 71.9 (±11.1) years (Figure 1). Between January 2016 and December 2020, the total average number of azacitidine prescriptions per patient was 5.6 (±0.2) prescriptions. The median follow-up for all patients between January 2016 and April 2021 was 8.8 months.

3.2 | Treatment persistence

The overall median persistence on azacitidine for patients with intermediate-2/HR-MDS, LB-AML, or CMML was 15.6 months, and the median persistence for patients with intermediate-2/HR-MDS, LB-AML, and CMML were 13.9, 12.5, and 45.3 months, respectively (Figure 2). The persistence needs to be interpreted with caution, especially as the patient numbers become significantly low in some months.

3.3 | Overall survival

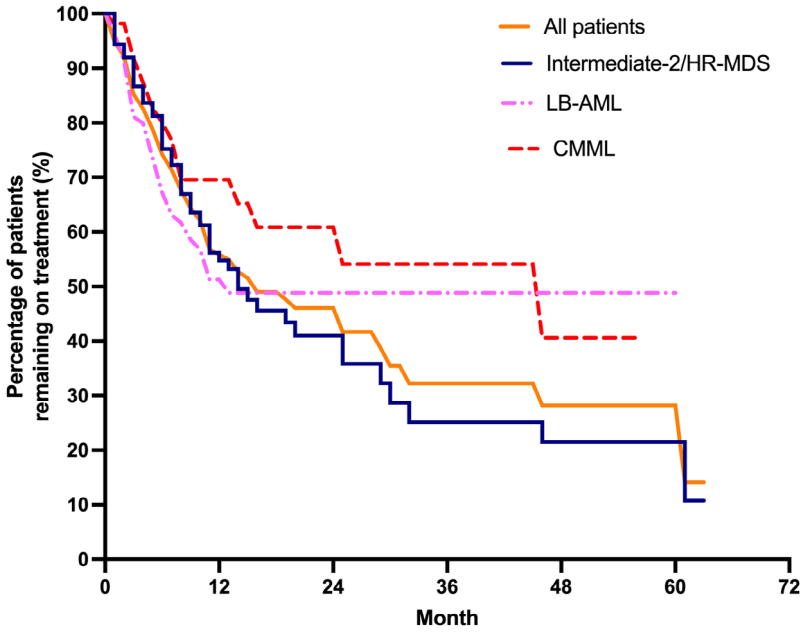
The median OS for all patients on azacitidine for intermediate-2/HR-MDS, LB-AML, or CMML was 13.4 months (PBS 10% dataset). Patients with intermediate-2/HR-MDS, LB-AML, and CMML had median OS of 15.6, 13.4, and 16.0 months, respectively (Figure 3).

3.4 | Overall survival for patients who were adherent and sub-adherent to treatment

Patients who received at least six cycles of azacitidine and were adherent to azacitidine treatment (106/351, 30.2%) had a median OS of 22.9 months, whereas patients who were sub-adherent (54/351, 15.4%) had a median OS of 16.7 months. The reasons for sub-adherence to treatment were not recorded in the PBS 10% dataset. Patients who received between four and five cycles of azacitidine (51/351, 14.5%) had a median OS of 8.8 months and those who received less than four cycles (140/351, 39.9%) had a median OS of 3.4 months (Figure 4).

3.5 | Sequencing of therapy

The majority of patients with intermediate-2/HR-MDS, LB-AML, or CMML received azacitidine as a first-line treatment (93.8%). The majority of patients who received azacitidine in the first line (89.4%) did not transition to another agent. Figure S1 shows the sequencing of treatment for patients who had been prescribed azacitidine at



Risk Table	0	12	24	36	48
All patients	351	59	21	10	7
Intermediate-2/HR-MDS	196	35	16	7	6
LB-AML	135	21	4	3	2
CMML	55	16	9	6	3

FIGURE 2 Kaplan–Meier estimate of persistence for patients with intermediate-2/high-risk myelodysplastic syndrome (HR-MDS), low blast acute myeloid leukemia (LB-AML), or chronic myelomonocytic leukemia (CMML) (Pharmaceutical Benefits Scheme 10% dataset). Patients may have been prescribed azacitidine for more than one indication; hence, the total number of patients with each indication was greater than the total number of patients who received azacitidine.

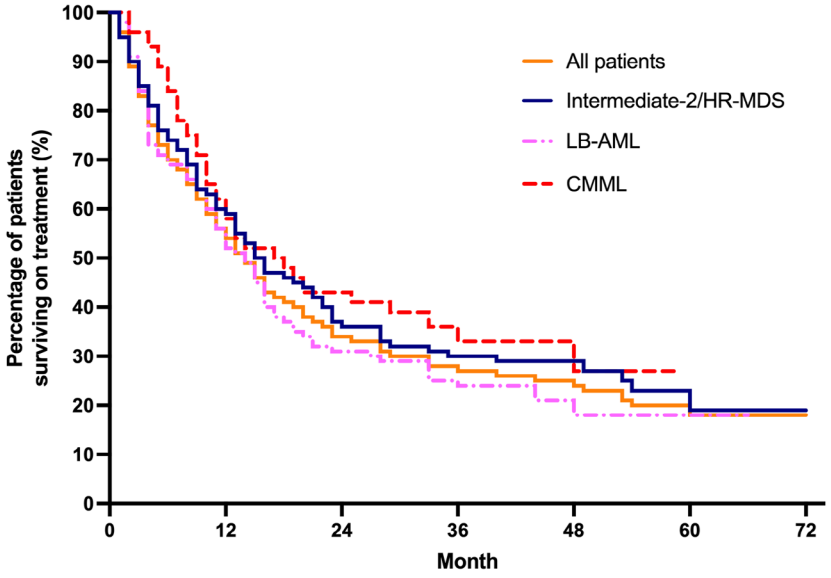
least once. A small proportion of patients received cytarabine (3.2%) or ruxolitinib (Jakavi) (1.80%) as the first treatment.

4 | DISCUSSION

This study identified patients with intermediate-2/HR-MDS, LB-AML, or CMML who were prescribed azacitidine through the PBS and highlighted important real-world findings related to persistence and OS of patients prescribed azacitidine.

The recommended course of therapy of azacitidine is at least six cycles and complete or partial response may, in some patients, require more than six treatment cycles [16]. However, some patients discontinue HMA therapy before completing the recommended course [17–19]. In this study, patients received an average of 5.6 prescriptions (or equivalent cycles) through the PBS 10% dataset [16]. A similar number of average cycles of treatment have been reported in other real-world studies [9, 17]. In one real-world study, only 30% of patients with MDS reached six cycles of HMA treatment (either azacitidine or decitabine) [18] and in another study, 47.1% of patients discontinued azacitidine early, with five or less cycles of treatment [17].

Treatment interruption is not recommended for patients with a hematological response, as evidence indicates that patients who discontinue therapy quickly experience relapse and subsequently have a poor prognosis and outcome [19–21]. The treatment discontinuation may be for a number of reasons including hematological toxicity, disease complications or progression, patients bridging to HSCT or patient withdrawal or death. In this study, the median OS for patients who had more than six cycles of treatment was greater compared to patients who had less than five cycles of treatment. A decreased OS with lower treatment cycles has also been observed in other studies. A Canadian study from the Ontario Cancer Registry of 1101 patients with intermediate-2/HR-MDS and LB-AML observed a significant improvement in OS for those who received four or more cycles of azacitidine versus those who received three or fewer cycles [11]. Another real-world study of patients with MDS using the United States Surveillance, Epidemiology, and END results (SEER)-Medicare linked database found that the median OS was significantly longer for patients who received six or more cycles of HMA (azacitidine or



Risk Table	0	12	24	36	48
All patients	351	178	80	39	20
Intermediate-2/HR-MDS	196	109	50	28	16
LB-AML	135	67	27	14	6
CMML	55	30	19	8	5

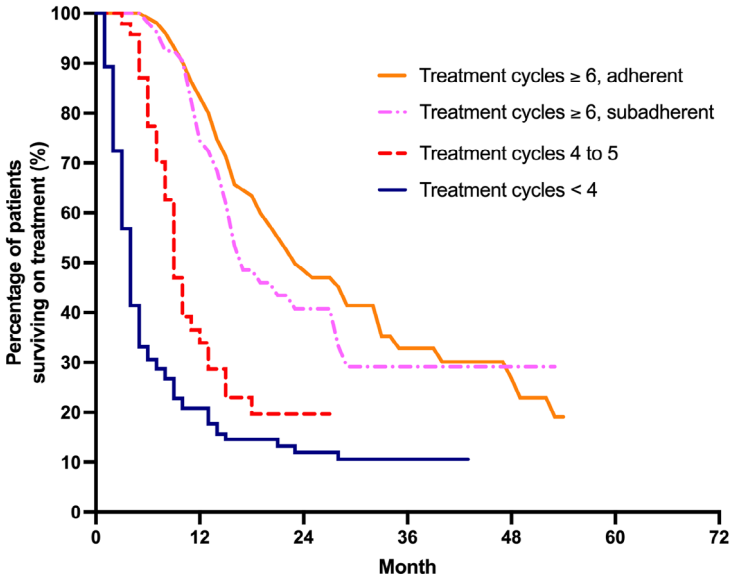
FIGURE 3 Kaplan–Meier estimate of overall survival for patients with intermediate-2/high-risk myelodysplastic syndrome (HR-MDS), low blast acute myeloid leukemia (LB-AML), or chronic myelomonocytic leukemia (CMML) (Pharmaceutical Benefits Scheme 10% dataset). Patients may have been prescribed azacitidine for more than one indication; hence, the total number of patients with each indication was greater than the total number of patients who received azacitidine.

decitabine) than those who received less than six cycles (21 months vs. 8 months) [12].

Overall, patients on azacitidine from the PBS 10% dataset had an OS of 13.4 months and there was not a significant difference in OS between intermediate-2/HR-MDS, LB-AML, or CMML. This estimate of OS is similar to that observed in other real-world studies, where median OS has been reported to be between 11 and 16 months [9–12]. The value of OS reported in real-world studies is significantly less than that reported in the pivotal azacitidine clinical trial, which reported a median OS of 24.5 months for patients with intermediate-2/HR-MDS [7]. An OS of 17.5 months was observed in the azacitidine monotherapy arm of the PANTHER phase 3 randomized study for patients with HR-MDS [8], perhaps indicating that the OS in the pivotal AZA-001 may have been uncharacteristically high. Differences in OS between real-world studies and randomized clinical trials could be partly due to the unselected nature of patients in real-world analyses [22]. Other potential factors for the difference in OS could be a higher incidence of patients with higher risk features and/or a lower number of cycles of treatment in the real-world studies; participants received a median of nine cycles of treatment in the pivotal AZA-001 clinical trial [10].

Mortality data from the Australian Institute of Health and Welfare (AIHW) indicate that the mortality rate for patients with MDS has not changed dramatically from 1998 to 2020. From 2013 to 2017, on average 37.1% (95% confidence interval 35.8–38.5) of people diagnosed with MDS survived 5 years after diagnosis [23]. The AIHW mortality data also include patients with low- and intermediate-risk MDS (according to IPSS) who have higher OS rates, which may explain the higher survival rate for the AIHW data compared to that obtained in this study.

This study has several limitations. The PBS 10% dataset does not distinguish patients who may be receiving additional therapy funded by the hospital or by an individual patient, or those patients who received additional therapy through a clinical trial. It is also difficult to understand if a bias toward a better-than-expected persistence and mortality curve is illustrated in the absence of being able to define the number of patients exposed to combination treatment or at what time point combination therapy may have been initiated. Furthermore, it is not known if patients who received less than six cycles of azacitidine progressed or had other complications, such as severe infective complications, which may have precluded further therapy. Other limitations related to the use of the PBS 10% dataset include the fact that patients could not be



Risk Table	0	12	24	36	48
Adherent	106	79	34	13	7
Sub adherent	54	37	14	6	5
Treatment cycles 4 to 5	51	13	5		
Treatment cycles < 4	140	20	9	5	

FIGURE 4 Kaplan–Meier estimate of overall survival for all patients with intermediate-2/high-risk myelodysplastic syndrome (HR-MDS), low blast acute myeloid leukemia (LB-AML), or chronic myelomonocytic leukemia (CMML) who received six cycles or more of treatment and who were adherent and sub-adherent to azacitidine (Pharmaceutical Benefits Scheme 10% dataset). Overall survival data are also shown for patients who received treatment for either four to five cycles or less than four cycles.

matched to the stem cell transplant patient population, patients could not be grouped based on genetic mutations, patients who were not treated could not be identified, and the time from diagnosis to initiation of treatment could not be extracted.

5 | CONCLUSIONS

The Australian PBS 10% dataset confirms real-world observations specifically in a cohort that was treated as per the AZA-001 indications but in a contemporary era. The majority of patients received less than the recommended number of cycles of azacitidine, which was negatively correlated with patient outcomes. The data from this real-world study indicate that continued efforts are required to optimize care and that additional agents are needed beyond those currently available for MDS patients.

AUTHOR CONTRIBUTIONS

The project was conceived by Taleisha Paine and Anoop Enjeti. The data analysis was carried out by Vincent Caillet, Arif Alam, Taleisha Paine, and Anoop Enjeti. Anoop Enjeti, Asma Ashraf, Jonathan Silar, and Harold Keer reviewed the analysis and its clinical relevance. All authors wrote and reviewed the manuscript.

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CONFLICT OF INTEREST STATEMENT

Anoop Enjeti has acted as an advisor and received honoraria on speaker panel for ASTEX/OTSUKA. The authors declare no conflicts of interest specifically related to this retrospective review. Francesco Castaldi and Taleisha Paine are employees of ASTEX/OTSUKA but are not the commercial manufacturers of any of the drugs analyzed in this PBS dataset analysis. Harold Keer was employed by ASTEX Pharmaceuticals, Inc. (USA) during manuscript development. Harold Keer is currently employed by Taiho Oncology, Inc. (USA). Asma Ashraf, Jonathan Silar, Vincent Caillet, and Arif Alam declare they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from Services Australia for approved research purposes. Restrictions apply to

the availability of these data, which were used under licence for this study.

ETHICS STATEMENT

This study and publication of subsequent results were approved by Services Australia (EREC approval number RMS1333).

PATIENT CONSENT STATEMENT

The authors have confirmed patient consent statement is not needed for this submission.

CLINICAL TRIAL REGISTRATION

The authors have confirmed clinical trial registration is not needed for this submission.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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