Insights into dasatinib use and outcomes in real-world patients with chronic myeloid leukemia

Patients with chronic myeloid leukemia (CML) in routine clinical practice likely differ substantially from clinical trial populations, which can have implications for the extrapolation of trial outcomes to the general population. In the DASISION trial, mean patient age was 46 years and the study excluded patients with Eastern Cooperative Oncology Group (ECOG) performance status ≥3, uncontrolled or serious medical disorders (including cardiovascular disease) or active infections, hepatic or kidney dysfunction, and previous or concurrent cancer.[1] Over 30% of patients failed to achieve deep molecular response (DMR) and 20% experienced adverse drug reactions (ADR) necessitating treatment discontinuation within 5 years.[1] The now well-recognised cardiovascular and pulmonary toxicities associated with dasatinib were reported in subsequent studies.[2] The aim of this study was to investigate prescribing patterns, tolerability, and effectiveness of dasatinib in patients with CML in real-world clinical practice, with a focus on patients considered ineligible for a pivotal CML clinical trial.

In this retrospective observational study, patients with CML who had at least 3 months of dasatinib treatment (2006-2018) were identified through hematology registries at two University hospitals in Sydney, Australia. Demographics, CML disease characteristics, and dasatinib prescribing patterns were collected and described according to indication (treatment-naïve *vs*. second-line or later). Concomitant medicines, including complementary and alternative medicines, were documented. Molecular response endpoints were defined using quantitative *BCR-ABL1* transcript levels according to the international scale.[3] All documented ADR during dasatinib treatment were defined using the Common Terminology Criteria for Adverse Events version 5.0,[4] and were evaluated for causality to dasatinib using the Naranjo algorithm.[5] Time to first dasatinib dose modification, time to treatment discontinuation, overall survival (OS) and progression-free survival (PFS) were evaluated using the Kaplan-Meier method, with a log-rank test comparing between-group differences. The cumulative incidences of major molecular response (MMR), deep molecular response (DMR) and dasatinib-related ADR were modeled using the cumulative incidence competing risk method with Gray's weighted log-rank test comparing between-group differences. Fine-Gray subdistribution hazard model was used to assess the independent factors associated with achievement of DMR and grade ≥3 ADR occurrence, with the subdistribution hazard ratios (SHR) reported. The Fine-Gray subdistribution hazard model, compared with traditional Cox models, considers competing risks that may hinder the observation of the event of interest such as treatment discontinuation or death prior to DMR or observation of the ADR. The hazard of recurrent ADR was modeled using the Prentice, Williams and Peterson Total Time model, and reported as hazard ratios (HR). Subgroup analyses were performed based on whether patients did or did not meet the original eligibility criteria for the DASISION[1] trial. The study was conducted in accordance with ethical requirements of local institutions. The research included in this study was approved by the Sydney Local Health District Human Research Ethics Committee (reference number: LNR/17/CRGH/248) on October 13, 2017. Site specific approval was also obtained for Concord Repatriation General Hospital (reference number: LNRSSA/17/CRGH/249) and Royal North Shore Hospital (reference number: RESP/18/146). A waiver of consent according to the National Statement on Ethical Conduct in Human Research was granted by the Human Research Ethics Committee. The statistical analyses were performed using R (version 3.3.3).[6] A detailed description of the study design and statistical methods are described in Adattini *et al.*[7]

Fifty-two patients who started dasatinib from 2006 to 2018 met eligibility criteria and were included in the analysis, with data collected on a total of 54 dasatinib treatment courses (22 treatment-naïve, 32 second-line or later). Most treatments (n=48) were initiated at the standard dasatinib dose of 100 mg/day (Table 1). Applying the eligibility criteria from DASISION, 30 (56%) patients would likely have been excluded due to serious or poorly controlled medical conditions (n=26, 50% of patients), hepatic or kidney dysfunction (n=4, 8%), concurrent cancer (n=3, 6%), or Eastern Cooperative Oncology Group ≥3 (n=1, 3%). This group also had a higher Charlson Comorbidity Index (CCI) compared with patients meeting eligibility criteria (median CCI score 5 vs. 2, $P<0.001$), and were significantly older at treatment initiation (median age 67 vs. 41 years, $P<0.001$; Table 1). A larger proportion of patients in the ineligible group were receiving one or more potentially interacting medicines during dasatinib treatment (87% *vs*. 41% if eligible, $P<0.001$; Table 1).

Within the first 12 months of treatment, 45% of patients (95% confidence interval [CI]: 29–57) required a dasatinib dose modification (any type), 41% (95% CI: 25–54) a dose reduction or temporary treatment interruption, and 15% (95% CI: 4–25) a dose escalation. Occurrence of an ADR was the stated reason for 90% of dose reductions/inter-

ruptions, whilst dose escalation was due to poor clinical response in 73%. After a median follow-up of 26 months (interquartile range [IQR]: 7–48 months), 59% of patients were still receiving dasatinib. Estimated rates of dasatinib discontinuation were 32% (95% CI: 17–44) at 2 years and 47% (95% CI: 28–60) at 5 years. Reasons for dasatinib discontinuation were occurrence of ADR (64% of discontinuations), poor clinical response (23%), relapse or disease progression (14%), achievement of sustained DMR for ≥2 years (9%), and death (9%). There were no significant differences in the risk of dasatinib dose modifications or discontinuation between patients receiving dasatinib first-line compared to second-line or later.

After 2 years of dasatinib treatment, 71% (95% CI: 56–82) of patients had experienced at least one dasatinib-related ADR requiring modification of existing long-term medicines or commencement of new medicines, 51% (95% CI: 32–59) a grade ≥3 ADR, and 38% (95% CI: 24–52) an ADR

Table 1. Baseline demographic and chronic myeloid leukemia disease characteristics, including comparison by likely eligibility for the DASISION trial.

Characteristics[†]	All dasatinib-treated patients (N=52)	Eligibility for DASISION		
		Eligible (N=22)	Ineligible (N=30)	*P* value
Age at diagnosis in years, median (range; IQR)	52 (23-89; 36-67)	39 (23-66; 32-49)	62 (32-89; 51-76)	<0.001
CCI score, median (range; IQR)	3 (2-10; 2-5)	2 (2-4; 2-3)	5 (2-10; 4-6)	<0.001
Male, N (%)	31 (60)	13 (60)	18 (60)	0.95
Geographic ancestry, N (%)				
European	35 (67)	13 (59)	22 (73)	
East Asian	9 (17)	5 (23)	4 (13)	0.40
South Asian	4 (8)	3 (14)	1 (3)	
Other	4 (8)	1 (5)	3 (10)	
Hepatic dysfunction at diagnosis, N (%)	3 (6)	0	3 (11)	0.25
Comorbidities at diagnosis, N (%)				
Cardiovascular disease	12 (23)	0	12 (40)	<0.001
Chronic pulmonary disease	11 (21)	0	11 (37)	<0.001
Poorly controlled hypertension	5 (7)	0	5 (17)	0.07
Poorly controlled diabetes	3 (6)	0	3 (10)	0.25
Peripheral vascular disease	3 (6)	0	3 (10)	0.25
Hypothyroidism post thyroidectomy	2 (4)	0	2 (7)	0.50
Congenital long QTc syndrome	1 (2)	0	1 (3)	1
Cerebrovascular disease	1 (2)	0	1 (3)	1
None of the above	26 (50)	22 (100)	4 (13)	<0.001
Concomitant medicines, N (%)				
CYP3A4 substrate	27 (52)	6 (27)	21 (70)	<0.001
Antiplatelet	23 (44)	3 (14)	20 (67)	<0.001
H2 antagonist, PPI or antacids	18 (35)	2 (9)	16 (53)	<0.001
QTc prolonging drug	8 (15)	0	8 (27)	<0.05
Paracetamol	6 (12)	2 (9)	4 (13)	1
Antineoplastic	6 (12)	0	6 (20)	<0.05
Digoxin	3 (6)	0	3 (10)	0.25
CYP3A4 inhibitor	1 (2)	0	1 (3)	0.25
CYP3A4 inhibitor, CAM	2 (4)	0	2 (7)	
CYP3A4 inducer	1 (2)	0	1(3)	1
None of the above	17 (33)	13 (59)	4 (13)	<0.001
Disease phase, N (%)				
Chronic	49 (94)	19 (87)	30 (100)	0.07
Accelerated	3 (6)	3 (14)	0	
ECOG PS, N (%)				
ECOG PS 0	35 (69)	17 (81)	18 (60)	
ECOG PS 1	15 (29)	4 (19)	11 (37)	0.11[§]
ECOG PS 2	0	0	0	
ECOG PS 3-4	1 (2)	0	1 (3)	
Additional BM karyotype abnormalities, N (%)	7 (17)	6 (33)	1 (4)	<0.05

BM: bone marrow; CAM: complementary or alternative medicine; CCI: Charlson Comorbidity Index; CYP: cytochrome P450; ECOG PS: Eastern Cooperative Oncology Group Performance Status; IQR: interquartile range; PPI: proton pump inhibitor. [†]Hepatic function missing 4 observations (2 eligible, 2 ineligible), ECOG PS missing 1 observation (eligible), additional BM karyotype abnormalities missing 11 observations (4 eligible, 7 ineligible). [§]Comparison is between ECOG PS of 0 *vs*. 1 or more.

resulting in hospitalisation (Figure 1; Table 2). The most frequent dasatinib-related grade ≥3 ADR at 24 months included cardiovascular disorders, neutropenia, pleural effusion or pulmonary edema, and infection (*Online Supplementary Table S1*).

Independent risk factors for a grade ≥3 ADR on dasatinib included poorly controlled hypertension ($SHR_{adjusted}$: 6.24; 95% CI: 2.70–14.20), higher ECOG ($SHR_{adjusted}$: 1.65; 95% CI: 1.16–2.36), and higher dasatinib starting dose of 70 mg twice daily compared with 50 mg/day and 100 mg/day ($SHR_{adjusted}$: 9.09; 95% CI: 2.63–25.00 and 7.69; 95% CI: 3.13–20.00), respectively). Independent risk factors for recurrent grade ≥3 ADR included age >60 years ($HR_{adjusted}$: 4.28; 95% CI: 1.73–10.57), higher ECOG ($HR_{adjusted}$: 2.15; 95% CI: 1.37–3.37), higher dasatinib starting dose of 70 mg twice daily ($HR_{adjusted}$, 3.45; 95% CI: 1.16–10.00 *vs.* 100 mg/day) and geographic ancestry ($HR_{adjusted}$: 2.73; 95% CI: 1.06–7.02 for East Asian compared with European ancestry).

The 2-year cumulative incidences of MMR and DMR were 81% (95% CI: 61–92) and 73% (95% CI: 55–85), respectively (*Online Supplementary Figure S1*). Poorer ECOG was the only independent predictor of inferior DMR rates with dasatinib ($SHR_{adjusted}$: 0.34; 95% CI: 0.12–0.96). Estimated 3-year OS and PFS rates of dasatinib-treated patients were

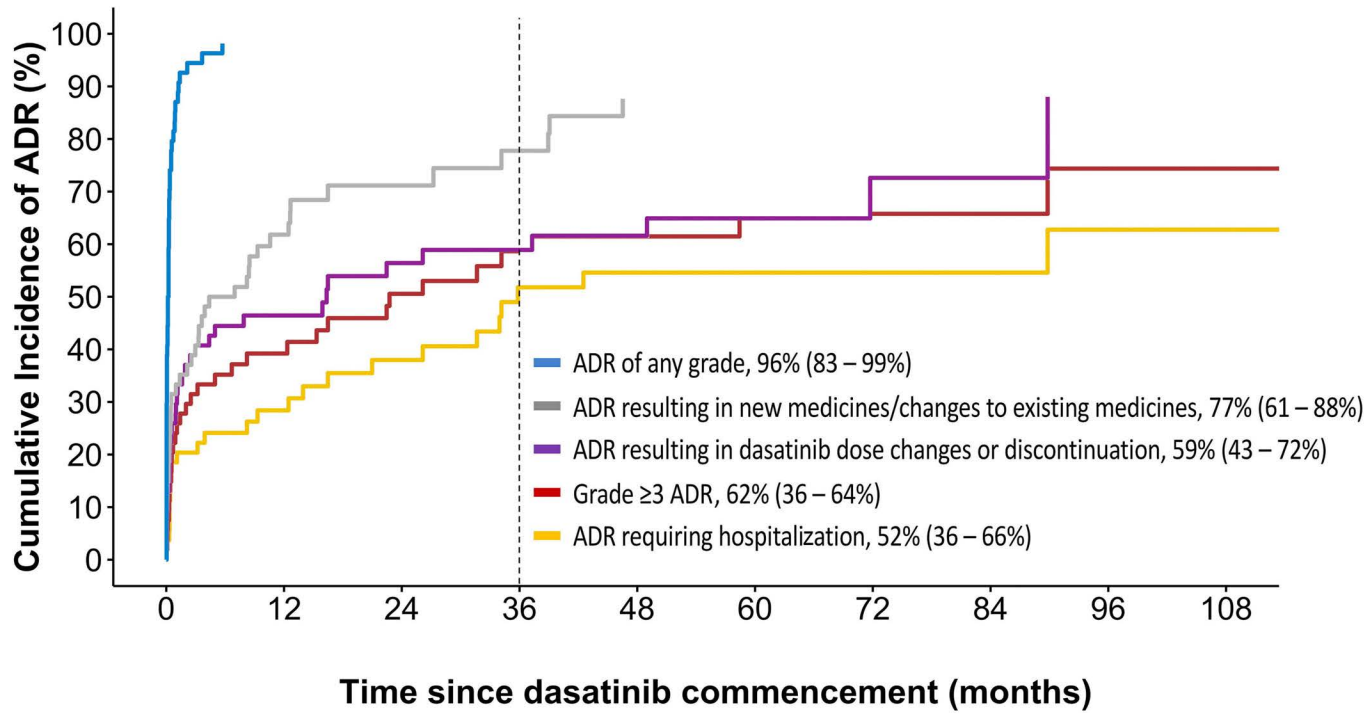

Figure 1. Cumulative incidence of dasatinib-related adverse drug reactions. Cumulative incidence of dasatinib-related adverse drug reactions (ADR) by 3 years (95% confidence intervals) calculated using the cumulative incidence competing risk method.

Table 2. Cumulative incidence of dasatinib-related adverse drug reactions, including comparison by likely eligibility for the DASISION trial.

Event	All dasatinib treatments (N=54)	Eligibility for DASISION Ineligible (N=31) *vs.* eligible (N=23)			
	Cumulative incidence at 24 months, % (95% CI)	SHR (95% CI) of an event	*P* Value	HR (95% CI) of event recurrence	*P* Value
Any ADR	96 (83-99)	1.23 (0.72-2.11)	0.45	1.12 (0.98-1.28)	0.11
Hematological or biochemical ADR	94 (82-98)	1.12 (0.64-1.94)	0.70	1.03 (0.84-1.27)	0.76
Non-hematological ADR	95 (79-99)	1.66 (0.96-2.86)	0.07	1.24 (1.04-1.50)	<0.05
Any ADR, grade ≥ 3	51 (32-59)	1.51 (0.75-3.04)	0.25	1.23 (0.68-2.21)	0.50
Hematological or biochemical ADR, grade ≥ 3	27 (15-29)	2.16 (0.69-6.74)	0.19	1.30 (0.55-3.08)	0.55
Non-hematological ADR, grade ≥ 3	40 (26-53)	1.70 (0.79-3.67)	0.18	1.49 (0.71-3.09)	0.29
ADR resulting in dasatinib dose modification or discontinuation	56 (41-69)	3.02 (1.44-6.33)	<0.05	2.06 (1.10-3.88)	<0.05
ADR resulting in commencement of medicines or changes to existing medicines	71 (56-82)	1.27 (0.71-2.30)	0.42	1.02 (0.70-1.49)	0.92
ADR resulting in hospitalisation	38 (24-52)	2.65 (1.11-6.33)	<0.05	2.12 (0.97-4.60)	0.06

ADR: adverse drug reactions; CI: confidence interval; HR: hazard ratio; SHR: subdistribution hazard ratio.

94% (95% CI: 87–100) and 94% (95% CI:87-100), respectively (*Online Supplementary Figure S2*).

Patients likely ineligible for the DASISION trial had a significantly higher risk of requiring a dasatinib dose reduction or interruption compared with the likely eligible patients (HR: 2.27; 95% CI: 1.00–5.24; *P*<0.05). Furthermore, the likely ineligible cohort had a higher risk of ADR resulting in dasatinib dose changes or treatment discontinuation (SHR: 3.02; 95% CI: 1.44–6.33) and ADR resulting in hospitalization (SHR: 2.65; 95% CI: 1.11–6.33; Table 2). Recurrent grade ≥3 infection was more likely to occur in patients considered ineligible for DASISION compared to those considered eligible (HR: 4.09; 95% CI: 1.00–17.03; *P*<0.05). There were no significant differences in molecular response rates or survival in the likely ineligible *versus* eligible groups.

Reassuringly, rates of MMR and DMR with dasatinib treatment in this real-world study were at least comparable to, if not higher than previously reported in controlled clinical trials.[1,8,9] We observed a higher incidence of many non-hematologic ADR than is reported in clinical trials. In a 3-year follow-up of the DASISION trial,[10] grade ≥3 fluid retention (pleural effusion and superficial edema) was reported in only 3% (*vs*. a 3-year cumulative incidence of 13% in this study; *Online Supplementary Table S1*), with all other non-hematological grade ≥3 ADR occurring in 3% or less of patients. Additionally, we observed a 3-year cumulative incidence of 14% for grade ≥3 cardiovascular events compared with less than 5% in published studies.[9-11]

The higher rates of observed ADR in this study compared with controlled clinical trials may be explained by the differences in patient characteristics in this real-world population who were of older age, with poorer performance status, more likely to have poorly controlled hypertension and other concomitant medical conditions and more likely to be co-prescribed medications with potential interactions. Our population also included some patients of East Asian ancestry, a population known to be more susceptible to dasatinib-related ADR likely due to increased drug exposure.[12]

An important insight was the significant healthcare resources utilized for the management of dasatinib-related ADR, including a substantial proportion requiring hospitalization. The incidence of ADR-related short-term therapeutic interventions observed in this study (e.g., glucocorticosteroids, diuretics, antimicrobials and thoracocentesis) is higher than those reported by Fox *et al.*,[13] whereby 21% of patients treated in routine clinical practice experienced dasatinib-related pleural effusion requiring therapeutic intervention. Most patients in our study experienced a dasatinib-related ADR requiring commencement of (or changes to) long-term medications; a clinically important implication of ADR which has not been highlighted in previous studies. Increased medication burden has the potential to increase adverse events, increase medical costs, reduce medication adherence, and negatively affect health outcomes such as frailty and mortality.[14]

The sample size of this study was limited by the number of patients diagnosed and treated with dasatinib at the two clinical centers over the period of data collection. As such, certain baseline predictor variables could not be evaluated in multivariable regression. Furthermore, as anticipated in a CML study, there were a small number of events such as death, disease progression, CML transformation or relapse on dasatinib treatment. Larger patient samples and longer observation times would be ideal in a future study to identify predictors of survival. Despite the small sample size of this study, it is notable that statistically significant findings were made, however caution should be applied in the interpretation. Importantly, the patients in our study were representative of patients receiving dasatinib treatment for CML in Australia with respect to age and sex distribution.[15] This real-world data on 54 dasatinib treatments represents a total of 154 patient years of experience with dasatinib treatment in CML. The detail and depth of collection of comorbidity data, patient outcomes and disposition, are some of the novel contributions of our study. Here, we present new insights on the relationship between patient and disease characteristics and real-world dasatinib treatment outcomes. We also identify the impact of clinical trial eligibility criteria on obtaining a patient sample representative of the real-world clinical population and on real-world treatment outcomes. These results can be used to inform the joint clinical decision-making process by patient and doctor as to the individualized benefits and risks of dasatinib. Biological and clinical factors should be considered prior to tyrosine kinase inhibitor selection to aid in dose and drug selection, and to identify those who require careful monitoring or intervention to optimize risk factors for the development of ADR.

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Disclosures

No conflicts of interest to disclose.

Contributions

All authors conceived the study. JA collected, analyzed and interpreted the data, and wrote the manuscript. ASG, AJM and NWD also contributed to the interpretation of the data and revised the manuscript. All authors approved the final manuscript.

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Data-sharing statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available because of privacy or ethical restrictions.

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