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ORIGINAL ARTICLE

Cardiac failure in patients treated with azacitidine, a pyrimidine analogue: Case reports and disproportionality analyses in Vigibase

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Aims: Azacitidine (AZA), a pyrimidine analogue, is validated for high-risk myelodysplastic syndrome or low-blast acute myeloid leukaemia in unfit patients for more intensive treatment. This study assessed the putative link between cardiac failure (CF) and AZA exposure.

Methods: Cases of CF in patients treated with AZA were retrospectively collected and described from several centres of the *Groupe Francophone des Myélodysplasies*. A description analysis and a disproportionality analysis using Vigibase, the WHO Global Individual Case Safety Reports (ICSRs) database, were conducted on ICSRs by the Standardized MedDRA Queries (SMQ broad) *cardiac failure* and by preferred terms *cardiac failure* and *cardiac failure acute*. The reported odds ratio (ROR) and its 95% 2-sided confidence interval was computed by comparing the proportion of CF reports with the suspected drug (AZA) and the proportion of reports of the same adverse drug reaction with all other suspected drugs in the database during the same period.

Results: In the 4 case reports, all patients presented a cardiovascular history. In 1 patient, CF recurred after AZA re-challenge. The pharmacovigilance analysis in Vigibase retrieved 307 ICSRs of CF (SMQ) with AZA. Significant disproportionality signals associated with AZA were identified by using the SMQ *cardiac failure* (ROR 1.3) and the preferred terms *cardiac failure* (ROR 5.1) and *cardiac failure acute* (ROR 23.2).

Conclusion: This study points to the potential role of AZA in the occurrence of CF. Cardiac evaluation before AZA initiation and regular monitoring of cardiac function during AZA treatment should be performed in patients with a history of cardiovascular disease.

KEYWORDS

anticancer drugs, drug safety, heart failure

1 | INTRODUCTION

Azacitidine (AZA), a pyrimidine analogue, is a hypomethylating agent approved by the European Medicines Agency in December 2008 for the treatment of high-risk myelodysplastic syndrome (MDS) in patients unfit for more intensive treatment such as allogeneic hematopoietic stem cell transplantation. It is also indicated for chronic myelomonocytic leukaemia with bone marrow blast levels of 10–19% without myeloproliferative syndrome, and for low-blast acute myeloid leukaemia (AML; < 30% bone marrow blasts).[1-6]

The main serious adverse drug reaction (ADR) reported to date is myelosuppression. Several clinical trials have reported adverse cardiac events with AZA, but in most cases, it was not suspected in the occurrence of cardiac failure (CF).[7,8] A recent prospective phase II study reported sudden death attributed to CF in a patient treated with AZA, but no other details were given.[9]

In the European product information,[10] pericardial effusion and pericarditis are the only cardiac ADRs mentioned for AZA and are thought to occur in fewer than 10% of patients. The European Summary of Product Characteristics[10] also mentions data from a clinical trial where newly diagnosed AML patients with a known history of cardiovascular or pulmonary disease presented a significant increase in the incidence of cardiac events when treated with AZA, but again no other details were provided. More recently, the updated version of the European Summary of Product Characteristics (May 2019) recommended cardiopulmonary assessment before and during treatment in the *Warnings and Precautions for Use* section but did not mention CF as a possible adverse effect. Moreover, the British National Formulary from the National Institute of Health and Care Excellency cautions the use of AZA in patients with severe congestive CF.[11]

We became particularly interested in cardiac events after AZA exposure after the recent observation of several cases of CF possibly associated with AZA in several centres of the *Groupe Francophone des Myelodysplasies* (GFM). We decided to describe some of these cases, to investigate this potential adverse cardiac reaction, which is probably underestimated for this drug, and to provide more precise statistical analyses on safety by analysing pharmacovigilance data in Vigibase.

We hypothesized a link between CF and AZA exposure requiring an update of the safety profile of this drug.

What is already known about this subject

- Cardiac toxicity such as atrial fibrillation or pleuropericardial effusion has been reported in the literature in patients treated with azacitidine (AZA).
- To date, no case of cardiac failure in patients treated with AZA has been reported in the literature.

What this study adds

- This study highlights the possible role of AZA in the occurrence of cardiac failure.
- A strong signal emerging from disproportionality analysis in Vigibase was found, especially for acute cardiac failure.
- Patients treated with AZA should have a cardiac evaluation before and during AZA administration so that their cardiac treatment can be adjusted and their patient optimized.

2 | METHODS

2.1 | Clinical data collection

Several cases of CF in patients treated with AZA were retrospectively collected from centres in the GFM. Patient data (age, sex and medical history), treatment (dose and cycle of AZA treatment, associated treatments) and occurrence of CF (clinical and echocardiographic data) were reported and analysed. Other causes of CF (anaemic, ischaemic, infectious, arrhythmic, metabolic etc.) were systematically ruled out. For patient data used in the case report section, we obtained the written informed consent from patients or their families.

2.2 | Pharmacovigilance data from Vigibase

Vigibase is the World Health Organization (WHO) global individual case safety report (ICSR) database. It includes reports of suspected ADRs from health professionals, patients and pharmaceutical companies gathered during the post-marketing phase of a drug.[12] Currently, it includes more than 19 million reports of ICSRs sent to the WHO Uppsala Monitoring Centre by the national pharmacovigilance systems of over 130 countries worldwide since 1967.

All CF cases after AZA administration recorded in Vigibase up to 29 October 2018 were identified using the Vigibase browser Vigilyse and the standardized MedDRA Query (SMQ) *cardiac failure (broad)*. SMQs include pre-defined combinations of preferred terms (PTs) that typically correspond to commonly encountered drug safety concerns. SMQs can be defined in several different ways. In the present work, we chose the so-called *broad* scope definitions (see supplementary material for the list of PTs included in the broad SMQ *cardiac failure*). Characteristics of patients (age, sex) and of reports (geographical region, year of ADR occurrence, type of ADR, seriousness and clinical outcome, suspected/interacting drugs, concomitant drugs and their therapeutic indications, route of administration, type of reporter) were collected and analysed.

The strength of association between CF and the suspected drug (AZA) was assessed by a disproportionality analysis by calculating a reported odds ratio (ROR) and its 2-sided 95% confidence interval (CI).[13] The ROR was computed by comparing the proportion of CF reports (SMQ broad) associated with the suspected drug (AZA) and

the proportion of the reports of the same ADR for all other drugs in the database during the same period.

One may conclude in disproportionality, and consequently in an association between AZA and the occurrence of CF, if the odds of exposure to AZA, compared to other drugs, is significantly higher in CF cases than for other types of events recorded in the database. To assess the robustness of the results, sensitivity analyses were performed by changing the outcome definition in the MedDRA classification by using the PTs *cardiac failure* and *cardiac failure acute*.

2.3 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY.

3 | RESULTS

3.1 | Case reports (Table 1)

3.1.1 | First case

Presentation

A 67-year-old man with acute myocardial infarction in 2005 treated with angioplasty and a coronary stent had low-risk MDS since 2011, which progressed to AML in 2013. Given his cardiac history, standard induction chemotherapy was contraindicated. In June 2013, subcutaneous AZA was started at the dose of 75 mg/m^2, 7 days every 28 days. Just before AZA administration, left ventricular ejection fraction (LVEF) was 50% with normal filling pressures and antero-apical akinesia. The patient was receiving angiotensin-converting-enzyme (ACE) inhibitor, β-blocker and 2 antiplatelet drugs.

TABLE 1 Four case reports

	Case 1	Case 2	Case 3	Case 4
Main patient characteristics				
Age	67	79	60	63
Sex	M	F	M	M
Cardiac history	CAD	No	CAD	Diastolic dysfunction with preserved ejection
Cardiovascular risk factor	Hypertension, age	Hypertension, age	Hypertension, age, Dyslipidaemia	Smoking, SAS, COPD, age
Medication				
Chemotherapy history	No	No	No	VTD, ASCT Melphalan, LD
Concomitant cardiac medication	AP, BB, ACEi	Diuretic, BB, ACEi, CCB	AP, BB, ARB	Diuretic
First complication				
Nature	Cardiac failure	APE	APE	APE
Cure (C) and day (D) of AZA	C9D1	C6D8	C1D7	C2D1
Total received dose of AZA (g)	9.07	5.52	0.980	1.2
Clinical and biological parameters at time of first complication				
eGFR (mL/min/1.73 m^2) (MDRD)	78	36	Dialysed	71
SBP/DBP (mmHg)	120/65	160/80	190/90	120/70
NT-pro BNP (pg/mL)	3420	299	2170	420
NYHA stage	II	III	IV	IV
Pedal oedema	No	Yes	Yes	Yes
Echocardiographic parameters				
LVEF (%)	27	55	57	55

ACEi: angiotensin converting enzyme inhibitor; AP: anti-platelet drug; APE: acute pulmonary oedema; ARB: angiotensin receptor blocker; ASCT: autologous stem cell transplantation; BB: β-blocker; CAD: coronary arterial disease; CCB: calcium channel blocker; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; LD: lenalidomide–dexamethasone; LVEF: left ventricular ejection fraction; MDRD: modification of diet in renal disease (equation); NYHA: New York Heart Association Functional Classification; SAS: sleep apnoea syndrome; SBP/DBP: systolic blood pressure/diastolic blood pressure; VTD, bortezomib–thalidomide–dexamethasone

Investigations

His cardiac function gradually decreased after each AZA cycle, with LVEF at 43% in December 2013, 38% in January 2014, and 27% in February 2014 with, at that time, significant CF (increased N-terminal pro-brain natriuretic peptide [NT-proBNP], left ventricular dilatation and increased left filling pressures).

Differential diagnosis

No trigger (ischaemia, systemic hypertension, other medications, anaemia, valvulopathy etc.) was identified and renal function and liver parameters remained unchanged.

Treatment and evolution

He continued the same cardiac treatment with ACE inhibitor dose adjustment. AZA was suspected to be the cause of the worsening cardiac function, but as no better therapeutic option was available, it was maintained until October 2014 thanks to optimization of his cardiac medication. After 17 cycles of AZA, treatment was no longer efficient and best supportive care was initiated. The patient died in April 2015 from AML.

3.1.2 | Second case

Presentation

A 79-year-old woman with hypertension treated with 4 antihypertensive drugs (calcium channel blocker, β-blocker, ACE inhibitor and thiazide diuretic) was diagnosed with chronic myelomonocytic leukaemia in 2015, with marrow blasts >10%. She started treatment with AZA 75 mg/m^2/day, 7 days a month in January 2016. She achieved complete haematological remission and continued AZA. After 6 AZA cycles, in August 2016, she presented grade III dyspnoea, which progressively increased despite the introduction of furosemide.

Investigations

Arterial pressure was around 160/80 mmHg and was associated with bilateral leg oedema and pleural effusion. The echocardiogram was normal with an LVEF of 67%. Except for systemic hypertension, no cardiac or pulmonary cause was found to explain the dyspnoea, and furosemide doses were increased. Control echocardiography 1 month later showed a decreased LVEF at 55%. During the following months, 2 acute hypertensive episodes occurred. As dyspnoea progressively worsened, the patient was hospitalized in January 2017 in the wake of a new episode of acute hypertension complicated by acute pulmonary oedema (APE). Systolic arterial pressure was 200 mmHg, despite good compliance with treatment. The echocardiogram showed stable LVEF at 60% but grade I diastolic dysfunction appeared with left atrial dilatation. Renal artery Doppler was normal, and no reason was found to explain the hypertensive APE.

Differential diagnosis

No infectious event, dysrhythmia or anaemia was observed when these cardiac events appeared. AZA was highly suspected to be the cause of these hypertensive episodes and CF, based on the chronology of the events in relation to the drugs administered.

Treatment and evolution

Antihypertensive treatment was increased. A similar episode occurred in June 2017 in the week following AZA injections, with systemic hypertension at 180/100 mmHg, cardiogenic APE and diastolic dysfunction on the echocardiography. Nevertheless, in the absence of a therapeutic alternative and considering its efficacy on the haematological disease, AZA was continued with optimization of cardiac therapy. The patient died from pneumonia after 9 AZA cycles.

3.1.3 | Third case

Presentation

A 60-year-old man was diagnosed in 2017 with MDS with 16% marrow blasts. He had chronic renal failure on a unique kidney dialysed since 2007, systemic arterial hypertension, monotruncular ischaemic cardiomyopathy with passive stenting in 2009, hypogastric artery aneurysm and prostate adenocarcinoma treated with total prostatectomy followed by radiotherapy. He was receiving a β-blocker, a preventive antiplatelet drug and statin. Allogeneic stem cell transplantation was contraindicated, and AZA was started at 75 mg/m^2/day dose, 7 days a month. During the first week of the first cycle, he experienced sudden constrictive chest pain and dyspnoea.

Investigations

Oxygen saturation was 60% and cardiogenic APE was confirmed by chest radiography and increased BNP. The echocardiogram showed normal LVEF, no right-cavity dysfunction but left-cavity dilatation, which was absent on previous echocardiograms.

Differential diagnosis

No classical causes of CF such as anaemia, ischaemia, infection, arrhythmia or metabolic anomaly were observed.

Treatment and evolution

The treatment consisted in intravenous isosorbide dinitrate, nonnvasive ventilation and extra-renal dialysis. The symptoms resolved within 24 hours, allowing oxygen weaning. The patient was discharged with the addition of an ACE inhibitor to his cardiac medications. Under optimized cardiac treatment, he received 6 cycles of AZA at 75 mg/m^2/day dose, 7/28 days without recurrence of any cardiac event. However, despite an initial response after 4 cycles, he relapsed after 6 cycles and died from an infectious disease.

3.1.4 | Fourth case

Presentation

A 63-year-old man with a history of morbid obesity, sleep apnoea syndrome, non-weaned smoking with chronic obstructive pulmonary

disease and diastolic dysfunction with preserved ejection fraction (treated with furosemide) was diagnosed with multiple myeloma in 2014 and treated with bortezomib–thalidomide–dexamethasone, followed by autologous stem cell transplantation after melphalan 200 mg/m^2 conditioning, then bortezomib–thalidomide–dexamethasone consolidation. He relapsed with a vertebral fracture and lenalidomide–dexamethasone was started, leading to complete remission. During lenalidomide–dexamethasone treatment, he was diagnosed with MDS, 10% marrow blasts and normal karyotype. He started treatment with subcutaneous AZA 75 mg/m^2 7 days/month. After the first day of cycle 2, he was admitted for dyspnoea with oxygen saturation <90 %. Physical examination revealed global cardiac insufficiency with diffuse pulmonary crackles and bilateral leg oedema.

Investigations and differential diagnosis

Cardiogenic APE was confirmed by chest radiography and increased NT-proBNP. No classical causes of CF such as anaemia, ischaemia, infection, arrhythmia or metabolic disorder were observed. The echocardiogram performed 24 hours after admission revealed a normal systolic function (LVEF 55%), without anomaly.

Treatment and evolution

Treatment consisted of intravenous furosemide with oxygen therapy and temporary discontinuation of the second cycle of AZA. On the second day of the third cycle, the patient experienced the same respiratory symptoms with good response to furosemide, and no specific trigger was identified. A fourth cycle with a lower dose of AZA (50 mg/m^2/day) was administered. However, on the second day, the patient was readmitted with similar signs of acute respiratory distress and signs of global CF. This episode resolved with oxygen therapy, inhaled bronchodilators, broad-spectrum antibiotics and intravenous furosemide. Of note, no steroids were given during the AZA administration. Given these repeated cardio-respiratory events and without any identified causative factor or specific trigger, AZA was highly suspected as being responsible. AZA treatment could not be maintained because no efficient cardiac medication adjustment compatible with AZA administration was found. Palliative therapy was then proposed, and the patient died 3 months later due to myeloma and MDS progression.

3.2 | Analysis of Vigibase data

Among the 9141 ADRs recorded in Vigibase involving AZA therapy, 307 were identified as *cardiac failure* (SMQ broad; Appendix 1), 268 of them (87.3%) being reported by health professionals. Reports originated from all continents, especially the USA (112 ICSRs), Japan (69 ICSRs) and Germany (30 ICSRs), while 11 ICSRs came from France. Reporting started in 2005 and remained stable with 24–43 ICSRs per year from 2010 to 2018.

For the 213 ICSRs of CF for which the patient's age was available, 64.6% were older than 65 years and 52.9% of patients were males. Among the 307 ICSRs, 281 were considered serious; 96 (34.2%) led to death and 20 to a life-threatening condition. When documented, the AZA administration route was mostly subcutaneous (57.9%) and intravenous (38.2%). Medicinal products more frequently co-reported were furosemide (21.5%), levofloxacin (13.4%), whereas the most frequently coded drugs in the database as *suspect* or *interacting* with AZA in the occurrence of CF were lenalidomide (7.2%), and gemtuzumab ozogamicin (3.3%). Among the drug classes, β-blockers were present in 45 cases (14.6%) ICSRs, ACE inhibitors in 30 (9.8%) and anthracyclines in 12 (3.9%).

In the SMQ *cardiac failure*, PTs mostly reported were *cardiac failure* in 100 ICSRs (32.6%) followed by *peripheral oedema* in 64 ICSRs (20.9%), *congestive heart failure* in 31 ICSRs (10.1%) and *cardiac failure acute* in 21 ICSRs (6.8%). Among the other PTs co-reported with the SMQ *cardiac failure*, pneumonia was present in 17% of ICSRs, followed by pyrexia (15.2%) and dyspnoea (12.7%). AZA was the only suspected drug in 81 of the 100 *cardiac failure* (PT term) ICSRs and in 18 of the 21 *cardiac failure acute* (PT term) ICSRs, respectively.

For the SMQ *cardiac failure*, the disproportionality associated with AZA was statistically significant with an ROR of 1.3 (95% CI 1.2–1.5). For PT terms, ROR values for AZA were estimated at 5.1 (95% CI 4.2–6.2) for *cardiac failure* and at 23.2 (95% CI 15.1–35.7) for *cardiac failure acute* (Table 2).

4 | DISCUSSION

The present findings, which are based both on individual case reports and disproportionality analyses in Vigibase, trigger a safety signal concerning a possible relationship between AZA treatment and the occurrence of CF, especially in patients presenting a cardiac history and other serious comorbidities.

TABLE 2 ROR for risk of cardiac failure (SMQ broad), cardiac failure acute (PT) and cardiac failure (PT) with azacitidine (as *suspected drug*), alone and in combination, in the World Health Organization pharmacovigilance database Vigibase

Reaction	Azacitidine	Any other drug	ROR	95% CI
Cardiac failure (SMQ)	307	470802	1.31	1.17–1.47
Any other ADR	8834	17725151	Ref	
Cardiac failure (PT)	100	39414	5.09	4.18–6.21
Any other ADR	9041	18156539	Ref	
Cardiac failure acute (PT)	21	1805	23.21	15.08–35.70
Any other ADR	9120	18194148	Ref	

ADR: adverse drug reaction; PT: preferred term (MedDRA); ROR: reporting odds ratio; SMQ: standardised MedDRA queries

In the 4 clinical cases of major worsening of cardiac function, the responsibility of AZA was strongly suspected. All 4 patients had cardiovascular risk factors and 3 of them had a past medical cardiovascular history. No obvious alternative aetiological cause was identified for any of these cardiac events assigned to AZA. Furthermore, the time to onset of the cardiac event after the introduction of AZA in cases 3 and 4, and the recurrence of the event after AZA rechallenge for case 4, are highly suggestive of the responsibility of AZA. The cardiovascular history of patients and the eventual existence of other serious comorbidities seem to play a major role in the intensity of CF. Patients 3 and 4 had a serious cardiac history and other significant comorbidities, and were those who presented with the most sudden cardiac events. In cases 1 and 2, the CF occurred more insidiously. Interestingly, in 3 patients, AZA treatment could be maintained with adjustment of cardiac medication.

The strong signal ensuing from disproportionality analyses in Vigibase for acute CF is consistent with the present case series characterized by APE or rapid deterioration of cardiac function.

In the literature, some data on cardiac disorders associated with AZA such as atrial fibrillation and pleuro-pericardial effusion were retrieved (see Table 3),[7-11,14-26] but with a frequency below 5%. Furthermore, data about the occurrence of CF in patients treated with AZA[7-9] are scarce. Interestingly, in a pilot phase II study, the combination of AZA 75 mg/m^2 with standard induction chemotherapy showed an increased cardiac toxicity compared to induction chemotherapy and led to interruption of the trial.[18] The pathophysiological mechanisms for the occurrence of CF in patients treated with AZA remain elusive. Some authors suggested that this toxicity could be a class effect of hypomethylating agents.[19-21] Recently, Ambesh *et al.* reported a case of rapid heart failure in a patient treated with capecitabine, a pyrimidine analogue of AZA.[22] Cardiac toxicity was also observed in patients treated with decitabine, another hypomethylating agent.[23,24] An immune reaction[24,25] or dose-dependent toxicity[26] have also been suggested as a possible mechanism. Even though *in vitro* studies cannot be extrapolated to exposure in humans, a potential effect of AZA on human cardiac cells cannot be excluded. *In vitro* assays showed that AZA promotes cardiomyogenic differentiation of mesenchymal stem cells[27,28] and promotes the transdifferentiation of cardiac cells to skeletal myocytes on cultures of adult mouse atrial tissue.[29]

TABLE 3 Literature data on azacitidine (AZA) involvement in cardiac events

Clinical trial	AZA protocol	Event	Frequency (n)
AZA in combination with thalidomide in MDS[17]	75 mg/m^2 for 5 days every 28 days	Pericarditis atrial fibrillation	2% (1) 5% (2)
Phase II, 3 alternative dosing schedules of AZA in MDS[8]	75 or 50 mg/m^2 with various time intervals	Congestive heart failure	3% (5)
Phase II, addition of AZA to standard chemotherapy in older patients with AML[14]	75 mg/m^2 for 5 days every 28 days	Recruitment halted due to increased rate of cardiac toxicity in the experimental arm	No details
Phase I, lenalidomide and AZA in high-risk MDS[18]	75 or 50 mg/m^2 with various time intervals	Atrial fibrillation grade 3 or 4	3% (1)
Phase II, AZA and lenalidomide in with higher-risk MDS[7]	75 mg/m^2 for 5 days every 28 days	Congestive heart failure, arrhythmia, vasovagal episode	11% (4)
Phase II, prophylactic AZA and donor lymphocyte infusion following allogenic hematopoietic stem cell transplantation for high-risk AML and MDS[9]	32 mg/m^2 for 5 days every 28 days	Sudden death due to heart failure	3% (1)

MDS, myelodysplastic syndrome; AML, acute myeloid leukaemia

4.1 | Strengths and limitations

This study has several strengths. This is the first study to evaluate the hypothesis of an increased risk of CF in patients treated with AZA. Several hypotheses can explain the delay in suspecting this adverse reaction. First, AZA is now more extensively used than during the years following its launch in 2008. Second, the population treated is nowadays older and presents more comorbidities. It is thus possible that CF occurs more frequently and with a more acute presentation. Third, our main analysis was performed in Vigibase, which is the largest pharmacovigilance database worldwide and contains both a large and representative study sample. Fourth, the disproportionality signal emerged from Vigibase in the absence of any previous publication on CF, making a notoriety bias unlikely. Fifth, a de-duplicated dataset was used to minimize information bias in Vigibase. Finally, most ICSRs ensued from physicians and can therefore be considered as relevant and medically consistent.

By contrast, any analysis in Vigibase may suffer some limitations such as the lack of detailed information for appropriate control for potential confounders. Another issue is the selective reporting and the heterogeneity of the data in Vigibase, which originate from a variety of sources including different countries and different types of

reporters. However, even if case reports cannot be interpreted in terms of frequency, these clinical data are congruent with the analyses performed in Vigibase.

Finally, all case reports were reported in patients with a known underlying cardiovascular disease (two patients with coronary artery disease, 1 with hypertension and 1 with diastolic heart failure). Furthermore, no specific triggers (including anaemia, arrhythmia, infection, ischaemia, iatrogenic or compliance for specific cardiac treatment) for CF were found. In addition, the time between the introduction of AZA and the occurrence of cardiac events is suggestive of the involvement of AZA. The intensity and time to onset of CF, which can be influenced by the presence of other serious comorbidities, does not rule out its involvement.

Even if disproportionality analyses, such as this performed in Vigibase, are a valuable tool to generate drug safety signals, they suffer too many limitations to confirm or rule out a causal association. Given both the seriousness of this ADR and the few data available about it, it is crucial that further studies investigate the likelihood of a causal link, e.g. by means of a prospective observational design.

5 | CONCLUSION

The present findings highlight an important concern about the cardiac safety of AZA, which is frequently used in elderly patients who may have underlying cardiovascular disease and other risk factors. For such patients, cardiac monitoring focused on signs of CF should be performed before and during AZA administration so as to adjust the cardiac treatment for optimal patient safety.

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CONTRIBUTORS

Justine Perino, Nathan Mottal, Hélène Théophile and Sophie Dimicoli-Salazar wrote the manuscript and participated in the final proofreading.

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COMPETING INTERESTS

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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SUPPORTING INFORMATION

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

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