Case Report

Dasatinib-induced pleural effusions, pericardial effusion and pulmonary arterial hypertension: a case report

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Background: Pleural effusion, pericardial effusion, and pulmonary arterial hypertension have been shown to have potential associations with the use of dasatinib in adults. However, due to the limited data regarding the efficacy and safety of tyrosine kinase inhibitors (TKIs) in pediatric patients necessities reliance on clinical experience gained from treating adults.

Case Description: We present a case of a 12-year-old female patient with chronic myelogenous leukemia (CML) who developed significant right-sided pleural effusion, moderate pericardial effusion, and pulmonary arterial hypertension during dasatinib therapy. Dasatinib was promptly discontinued upon identification of these adverse events. This was followed by the use of bosentan for pulmonary hypertension, furosemide and spironolactone diuretics, prednisone anti-inflammatory, and especially a bold attempt to improve pulmonary endothelial permeability with acetyl cysteine aerosolization. At the same time, according to the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) data reported by the patient and combined with the actual situation, the appropriate TKI was selected for the patient to continue the CML treatment.

Conclusions: FAERS data gathered on OpenVigil indicates that the signal associated with pericardial effusion is stronger among individuals under the age of 18 when imatinib is used instead of dasatinib (exactly the reverse of the results in the adult group). However, this does not imply that dasatinib is safer for the smaller group. In our situation, dasatinib-induced adverse effects include pericardial effusion. As a result, while administering TKIs to pediatric patients, we still need to increase monitoring—particularly for pulmonary and cardiovascular toxicity—and take swift action in the event that a major adverse reaction occurs. In addition, it is important to report these adverse effects as much as possible in order to give pediatric patients utilizing TKIs more helpful information.

Keywords: Dasatinib; pulmonary and cardiovascular toxicity; acetyl cysteine; children; case report

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Introduction

Pediatric chronic myelogenous leukemia (CML) is a rare disease with a global annual incidence of (0.6 to 1.2)/1,000,000, and the incidence increases with age. In children under 15 years old, CML accounts for 2% to 3% of leukemias, while in adolescents aged 15 to 19 years, CML makes up 9% of leukemias (1). The same treatment objectives apply to both adults and children with CML:

illness remission, lowered risk of progression, and survival. However, the additional challenge of attaining these aims while reducing toxicity for many decades must be taken into consideration while treating CML in youngsters (1). Dasatinib, a second-generation tyrosine kinase inhibitor (TKI), is used to treat CML [chronic phase (CP), accelerated phase, and blast phase] and Philadelphia chromosome-positive (*Ph+*) acute lymphoblastic leukemia (ALL) in both adult and pediatric patients (2). Dasatinib was approved by the US Food and Drug Administration (FDA) and the European Medicines Agency in 2006 (in some European countries) for the treatment of newly diagnosed CML adult patients. On November 9, 2017, the US FDA approved dasatinib for the treatment of CML in pediatric patients.

Dasatinib acts by inhibiting several tyrosine kinases, including *BCR-ABL1*, *c-KIT*, *EPHA2*, platelet-derived growth factor receptor (*PDGFR*)-*β*, and the SRC kinase family (such as *SRC*, *LCK*, *YES*, *FYN*), at nanomolar concentrations (3). Unlike imatinib, dasatinib is capable of binding to the functionally relevant catalytic conformations of the *BCR-ABL* kinase, resulting in 325-fold greater potency in inhibiting wild-type *BCR-ABL in vitro* (4). Dasatinib has demonstrated superior clinical response compared to imatinib and is recommended as a first-line treatment for newly diagnosed CML patients, as well as a second-line treatment for patients who are resistant or intolerant to imatinib. However, dasatinib can cause adverse reactions including myelosuppression, pleural effusion, pericardial effusion, and pulmonary arterial hypertension. Most of these adverse reactions are mild and self-limiting. The potential pulmonary toxicity associated with dasatinib, such as pulmonary hypertension and pleural effusion, may limit its clinical use (5).

This article reports a case of a CML pediatric patient developing pleural effusion, pericardial effusion, and pulmonary hypertension after taking dasatinib (Bristol-Myers Squibb, 8012989) and discussed in the literature. This study aims to summarize the experience of diagnosis and treatment of severe adverse drug reactions of dasatinib, in order to improve medical staff's understanding of adverse drug reactions, especially the different characteristics of adverse drug reactions in children and adults. We present this article in accordance with the CARE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-23-517/rc).

Highlight box

Key findings

- The data collected from the OpenVigil website on cardiovascular adverse reactions in pediatric chronic myelogenous leukemia (CML) patients undergoing TKI therapy revealed discrepancies between the population under 18 years old and the overall population in Food and Drug Administration Adverse Event Reporting System (FAERS) results.

What is known and what is new?

- The impact of TKI therapy on pediatric CML patients, particularly in terms of adverse reactions, may persist for several years or even more than a decade.
- Literature reports suggest that N-acetylcysteine exerts a protective effect on pulmonary endothelium and can improve pleural effusion caused by TKIs. This provides a novel insight for the treatment of such patients in the future.

What is the implication, and what should change now?

- When pediatric CML patients experience severe cardiovascular adverse reactions due to the use of a particular TKI, the subsequent treatment plan should consider the different characteristics of various TKIs. Additionally, it is essential to conduct routine pulmonary and cardiovascular examinations. The decision of whether to continue TKI therapy or change the treatment regimen should be made based on these considerations.

Case presentation

A patient, female, 12 years old, was admitted to the hospital on May 11, 2023 with a 10-day cough and found to have pulmonary hypertension for 6 days. Upon admission, the patient's axillary temperature was 36.5 ℃, pulse rate was 100 bpm, respiration rate was 28 bpm, and blood pressure was measured at 116/68 mmHg. The patient was clear-minded with normal mental reactions and development. The complexion was normal, and the skin had good elasticity. The extremities were warm, and there were no signs of pallor, yellow staining, bluish purple discoloration, bleeding, obvious rash, or neck stiffness. No jugular vein distention was observed. No prominence was noticed in the precordial region, but there was asymmetry on both sides of the chest and dullness on the right side. The blood oxygen saturation was measured at 92%. No murmurs were detected in all valvular areas of the heart. The patient experienced slight shortness of breath, no inspiratory triple depression sign, asymmetrical respiratory sounds in both lungs, absence of expiratory sounds in the right lower lungs, and no dry or wet rales. The liver was palpable 4–5 cm below the right subcostal margin, and a 2-cm hard-edged subxiphoid mass was felt. The spleen was palpable 1 cm

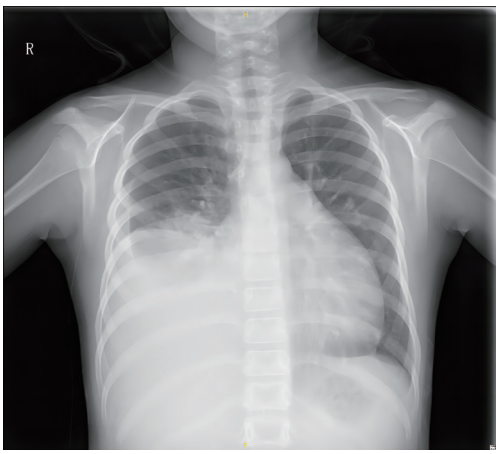

Figure 1 Significant pleural effusion prior to treatment.

Figure 2 The patient undergoes closed thoracic drainage to perform thoracic drainage.

below the left subcostal margin. The frontal chest X-ray (2023-5-11) revealed patchy dense shadows in the right chest cavity, right pleural effusion, and right lower lung atelectasis (*Figure 1*). The ultrasonic cardiography (UCG) (2023-5-11) showed widening and <50% collapse of the inferior vena cava, enlargement of the right atrium and right ventricle, slight enlargement of the left atrium, and normal left ventricular contractile activity. The pulmonary artery exhibited enlargement, with a total trunk diameter of 2.94 cm, right pulmonary artery diameter of 1.90 cm, and left pulmonary artery diameter of 1.84 cm. The tricuspid valve displayed mild to moderate regurgitation with a regurgitant velocity of 4.56 m/s and a pressure gradient of 83 mmHg. Massive pleural effusion and medium pericardial effusion were observed on the right side. The right ventricular systolic and diastolic function were weakened, while the left ventricular systolic function was normal. The initial diagnosis was pulmonary hypertension, pericardial effusion (moderate), pleural effusion (massive), and cardiac insufficiency (New York Heart Association class II). Considering the seriousness of the patient's condition, closed chest drainage was performed on the same day of admission, and 1,410 mL of fluid was drained on May 11th (*Figure 2*). Routine examination of pleural fluid (2023-05-11) showed: appearance (jaundice), color (yellow), transparency (muddy), no coagulation, nucleated cell count of $4,454.0\times10^6$/L, with 5% multi-nuclear cells and 95% mononuclear cells. The Rivalta test was positive (+). Complete blood count (2023-05-11): lymphocyte count 5.37×10^9/L (↑); lymphocyte percentage 64.4% (↑); the rest are normal. C-reactive protein was 2.4 mg/L (normal). Blood ammonia and lactate levels were both normal. Urinalysis was normal. Liver and kidney functions, as well as electrolyte levels, were within normal ranges.

Upon inquiring with the relatives of the pediatric patient, it was learned that the patient was diagnosed with CML in 2017 at Sichuan Provincial People's Hospital in Sichuan and has been receiving treatment locally. Recently, the patient has been taking dasatinib (Sprycel) (Lot number: 8012989) 100 mg once daily. On May 5, 2023, during a routine follow-up examination in Sichuan, pulmonary hypertension was detected, prompting the discontinuation of the previous medication and a switch to imatinib 300 mg once daily. At that time, the patient's blood count (2023-5-2): lymphocyte count 6.235×10^9/L (↑); lymphocyte percentage 69.2% (↑). Quantitative assay of the internal reference gene *ABL* expression (2023-5-2): *BCR-ABL 210/ABL* 0.051%; International Scale (IS) 0.048%. The patient herself has no history of heart disease or family history of it, no known drug allergies, and has never experienced similar issues before. Our doctors, taking into consideration the patient's medical history, medication history, laboratory test results, and imaging findings, believe that the cause of the pediatric patient's pulmonary hypertension may be related to the chemotherapy drugs used for the leukemia treatment. Bosentan was administered to alleviate pulmonary hypertension, furosemide and spironolactone for diuresis, acetylcysteine nebulization to improve pulmonary endothelial permeability, and prednisone for

Table 1 Medication for children in hospital

Drugs admission day	Date	Medication				
		Reduce pulmonary hypertension	Diuresis		Improve pulmonary endothelial permeability	Anti-inflammatory
		Bosentan	Furosemide	Spironolactone	Nebulized acetylcysteine	Prednisone
1	May 11th	64 mg po q12h	20 mg po bid	20 mg po bid	–	–
2	May 12th	32 mg po q12h			–	–
3	May 13th				–	–
4	May 14th				–	–
5	May 15th				–	–
6	May 16th				–	–
7	May 17th				0.3 g inh bid	–
8	May 18th					–
9	May 19th					–
10	May 20th					–
11	May 21st					–
12	May 22nd					–
13	May 23rd					–
14	May 24th					–
15	May 25th					–
16	May 26th					–
17	May 27th					–
18	May 28th					–
19	May 29th					15 mg po bid
20	May 30th					

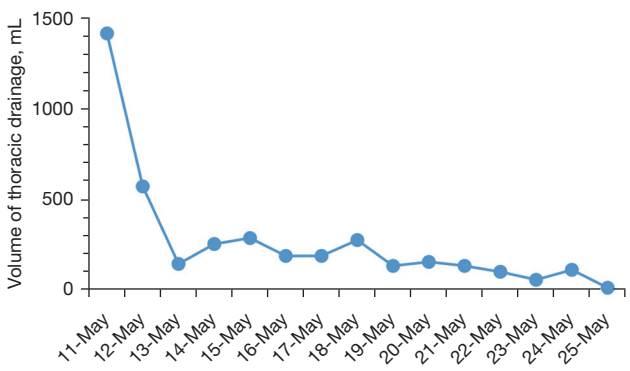

Figure 3 The volume of thoracic drainage fluid.

anti-inflammatory treatment. The timing and dosage of these medications are shown in *Table 1*, and the volume of thoracic puncture drainage is illustrated in *Figure 3*.

On May 25, the thoracic drainage tube was removed. After approximately 2 weeks of thoracic drainage and 3 weeks of drug treatment, the echocardiography conducted on May 29 revealed no significant enlargement of atrioventricular chambers or the pulmonary artery. Mild tricuspid regurgitation was present with a regurgitation velocity of 2.53 m/s and a pressure difference of 25 mmHg. A small amount of pericardial effusion measuring 0.61 cm

in the right posterior atrioventricular groove and 0.51 cm near the apex of the diaphragm was detected. The chest X-ray taken on May 28 demonstrated a notable decrease in pleural effusion on the right side (*Figure 4*). Blood count (2023-05-20): lymphocyte count 2.1×10^9/L; lymphocyte percentage 25.8%; indicators were normal. Due to the mother's refusal, cardiac catheterization was not performed, and all the calculations regarding pulmonary artery pressure difference were derived from echocardiography results. On May 30, the patient was in good condition, and the family requested discharge from the hospital for outpatient follow-up. The patient was discharged with a prescription of oral prednisone tablets, to be taken continuously for 7 days. At the same time, follow-up treatment of CML was considered, relevant FDA Adverse Event Reporting System (FAERS) data of TKIs were collected from the OpenVigil website (see *Table 2*), and ultimately imatinib 300 mg QD was chosen for oral treatment with the guidance of relevant hematological oncology specialists.

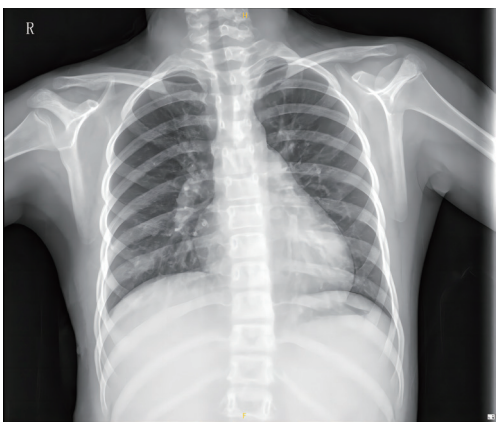

Figure 4 Significant reduction in pleural effusion after treatment.

In recent follow-up, the UCG (2023-07-27) of the patient showed a slightly enlarged right ventricle, trace tricuspid regurgitation during systole, and trace pericardial effusion. Additionally, after discharge, due to recurrent pulmonary arterial hypertension, the patient has been continuing with the use of bosentan (31.25 mg Q12h PO) till date. On September 17, 2023, the patient had a follow-up UCG in Sichuan, where the pulmonary hypertension had resolved, and at the same time, bosentan was discontinued. Quantitative assay of the internal reference gene *ABL* expression (2024-1-9): *BCR-ABL 210/ABL* 0.071%; IS 0.067%. Blood count (2024-01-8): lymphocyte count 3.29×10^9/L, lymphocyte percentage 49.5%, normal.

Table 2 The associations of pericardial effusion, pleural effusion and pulmonary arterial hypertension with different TKIs*

Adverse event	Drugs	<18 years						All ages					
		Number of occurrences	Rate (%)	χ^2	RRR	PRR	ROR	Number of occurrences	Rate (%)	χ^2	RRR	PRR	ROR
Pericardial effusion	Imatinib	9	1.302	44.207	7.453	7.556	7.642	201	0.49	337.135	3.385	3.415	3.427
	Nilotinib	0	0.0	0.972	0.0	0.0	0.0	133	0.738	435.229	5.097	5.131	5.162
	Dasatinib	1	0.348	0.0	1.994	1.995	1.999	279	1.351	2,075.2	9.336	9.483	9.599
	Bosutinib	0	0.0	22.893	0.0	0.0	0.0	45	1.042	234.486	7.199	7.217	7.282
Pleural effusion	Imatinib	9	1.302	24.159	4.883	4.924	4.975	606	1.477	2,604.462	6.117	6.234	6.313
	Nilotinib	0	0.0	0.411	0.0	0.0	0.0	343	1.903	2,061.063	7.878	7.967	8.102
	Dasatinib	8	2.787	59.457	10.451	10.538	10.811	1,654	8.012	51,794.59	33.171	35.275	38.26
	Bosutinib	0	0.0	14.677	0.0	0.0	0.0	123	2.849	1,207.615	11.793	11.843	12.161
Pulmonary arterial hypertension	Imatinib	2	0.289	0.586	0.496	0.496	0.494	255	0.622	72.995	1.698	1.702	1.707
	Nilotinib	0	0.0	0.004	0.0	0.0	0.0	145	0.804	93.863	2.197	2.201	2.211
	Dasatinib	1	0.348	0.018	0.597	0.597	0.596	777	3.764	6,536.668	10.28	10.46	10.83
	Bosutinib	0	0.0	6.215	0.0	0.0	0.0	68	1.575	169.688	4.301	4.307	4.36

*, using the FDA Adverse Event Reporting System (FAERS) data from 2004Q1 to 2023Q1. TKIs, tyrosine kinase inhibitors; RRR, relative reporting ratio; PRR, proportional reporting ratio; ROR, reporting odds ratio; FDA, Food and Drug Administration; Q1, first quarter.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's guardian for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

CML is a type of myeloproliferative neoplasm characterized by the fusion of two genes, *BCR* and *ABL1*, leading to the formation of a unique *BCR::ABL1* fusion protein, which contains an enzymatic domain derived from normal ABL1 and possesses tyrosine kinase catalytic activity. Compared to normal *ABL1*, the *BCR::ABL1* fusion protein exhibits heightened kinase activity and is expressed continuously. This aberrant tyrosine kinase activity plays a key role in the development of CML (6).

TKIs are a class of medications used to treat various forms of cancer, particularly certain leukemias and malignant tumors. They function by inhibiting the activity of specific tyrosine kinase enzymes. Imatinib was the first TKI to be approved and was initially prescribed for patients who did not respond to interferon treatment (7). It can be seen that our patient was diagnosed with CML in February 2017 and the initial treatment chosen was imatinib, which was continued for 2 years. At that time, imatinib was the first TKI approved for use in children. It wasn't until November 2017 that the U.S. FDA approved dasatinib for the treatment of CML in children. In China, as of the time of the case report writing, the use of dasatinib in pediatric CML patients had not yet received official approval from the China Food and Drug Administration (CFDA). However, during the following 2 years, her CML treatment never achieved an optimal state. In August 2021, the patient started using dasatinib and gradually increased the dose to 100 mg once daily. On February 13, 2023, a follow-up check of the *BCR::ABL* gene expression revealed a quantitative result: *BCR-ABL 210/ABL* at 0.027%, with the IS value being 0.026%. The dasatinib treatment has achieved satisfactory results. Dasatinib, as a second-generation TKI, can inhibit *BCR-ABL*, *KIT*, and *PDGFR*, as well as other signaling pathways including Src kinases. It is often used in patients who develop resistance or intolerance to imatinib.

Fluid retention and pericardial effusion are the most common cardiovascular side effects of TKIs. Less common are cardiac dysfunctions, including cardiomegaly, angina, congestive heart failure, and cardiac arrhythmias. However, the mechanisms of toxicity are not yet clear, and there are several prevailing hypotheses at present: (I) dasatinib inhibits *PDGFRβ*; (II) increased pleural and/or pulmonary vascular permeability due to inhibition of Src family kinases; and (III) allergic or immune-mediated reaction rather than liquid reaction (8-10). These TKIs exhibit different levels of kinase inhibition and have varying off-target effects, which leads to different characteristics of drug-generated toxicity. For example, pleural effusion is commonly associated with dasatinib and bosutinib. The DASISION trial, a phase III study, revealed a higher incidence of pulmonary embolism (PE) with dasatinib (28%) compared to imatinib (0.8%) when TKIs were used (11). The risk factors for pleural effusion caused by dasatinib include high drug frequency, large initial dose, pre-existing lung diseases, patient age, as well as the presence of hypertension and heart disease (8). In addition to this it was found that the pleural effusion caused by TKIs is an exudate composed mainly of lymphocytes (5), which is consistent with the results of the routine pleural fluid examination of the patient in our case report.

The potential link between dasatinib and pulmonary arterial hypertension (PAH) was initially noted in the 2015 European Society of Cardiology guidelines (12). Subsequently, the correlation between dasatinib and PAH was confirmed at the 6th World Symposium on Pulmonary Hypertension in 2018 (9). However, the diagnosis requires the exclusion of other etiologies of pulmonary hypertension, such as congenital heart disease, chronic PE, and left heart failure, before attributing the condition to the use of dasatinib. While PAH may not completely resolve after discontinuing dasatinib, if any improvement is seen following cessation of the medication, it is reasonable to diagnose dasatinib-induced PAH. Currently, no risk factors or predictive factors have been identified for dasatinib-related PAH (10). This was also noted in a retrospective study by Kubota *et al.* (13), where clinical data from 128 patients with CML (94 cases) and *Ph*+ ALL (34 cases) were analyzed, showing no time or dose dependency for dasatinib-induced PAH. Most cases of dasatinib-induced PAH are reversible upon discontinuation of the medication. However, a study by Weatherald *et al.* (14) reported 21 cases of dasatinib-induced PAH diagnosed through right heart catheterization in France. They found that this type of PAH, although improved after discontinuing dasatinib, persisted in over one-third of the patients.

In addition to utilizing diuretics to reduce fluid retention, administering bosentan for the treatment of pulmonary arterial hypertension, and performing surgical pleural drainage, nebulized N-acetylcysteine (NAC) was also employed to enhance pulmonary endothelial permeability in this patient. This approach was based on the research findings of Phan *et al.* (15), who established the first animal model of dasatinib-induced pleural effusion. Their study demonstrated that dasatinib alters pulmonary endothelial permeability *in vitro* and *in vivo* through a reactive oxygen species (ROS)-dependent mechanism, resulting in pleural effusion. They also found that NAC reduces dasatinib-induced ROS production, thereby preventing the increase in pulmonary endothelial permeability *in vitro* and the occurrence of pleural effusion in rats. We initiated the use of NAC on the 7th day of treatment, and the chest tube was subsequently removed on the 15th day. Since there was no control group for comparison, the exact efficacy of NAC cannot be determined. However, the patient did not experience any discomfort and showed positive progress throughout the medication period. This was an exploratory attempt that may serve as a therapeutic reference for similar patients in the future.

Regarding the development of dasatinib-induced pleural effusion, pericardial effusion, and PAH, it is necessary to discuss the next steps in the treatment of CML for this patient. Dasatinib-induced pulmonary hypertension may need to be treated with pulmonary vasodilators, but there have been numerous reports of improvement when dasatinib is stopped on its own (16,17). However, when selecting alternative TKIs, what factors should be taken into consideration? In a study using the FAERS, Cirmi *et al.* (18) found that nilotinib accounted for more than half of the reported cases of TKI-related cardiovascular adverse events. Nilotinib showed the highest Signal of Disproportionate Reporting (SDR) in association with ischemic heart disease, torsades de pointes/QT interval (the QT interval is a parameter in an electrocardiogram that measures the electrical activity of the heart) prolongation, and arrhythmias. Dasatinib and bosutinib were most closely associated with heart failure, while dasatinib and imatinib were associated with pulmonary arterial hypertension. However, the data obtained from the OpenVigil website for the population under 18 years old provided different results compared to the overall population data. Please refer to *Table 1* for specific data. Based on the data obtained, imatinib exhibited a stronger signal in association with pericardial effusion in the population under 18 years old. This may be attributed to the fact that imatinib was the earliest TKI approved (in 2003) for the treatment of pediatric and adolescent CML, while second-generation TKIs, such as dasatinib, were approved after 2017. Therefore, imatinib currently has more reported data in the pediatric and adolescent group. However, there is no clear correlation between TKIs and the development of pediatric pulmonary arterial hypertension. A phase II clinical trial focusing on pediatric patients with CML-CP reported a safety profile of dasatinib consistent with adult findings, with no cases of pleural effusion, pericardial effusion, or pulmonary arterial hypertension observed in pediatric patients (19). However, longer-term monitoring and observation are still required to establish the true situation. Ultimately, based on the advice of hematologists, we have temporarily chosen imatinib as the treatment for this pediatric patient with CML. This decision was primarily based on the consideration that while imatinib may not be as effective as dasatinib for this particular patient, no significant adverse events were observed during the initial 2 years of treatment.

There are still some limitations in our study. First of all, there are few reported data of adverse events in children with TKIs, especially the reference data obtained by the second generation TKIs; are basically not reported in China; finally, the use of acetylcysteine cannot be completely affirmed because there is no control group.

Conclusions

While the reported rate of cardiovascular adverse events in children and adolescents receiving TKI therapy remains low, these effects may manifest after several decades of exposure. Long-term TKIs treatment also significantly affects the quality of life of young patients (20). Therefore, it is crucial to regularly monitor TKIs medications and conduct routine pulmonary and cardiovascular examinations. When selecting a second-generation TKI, it would be beneficial to consider factors such as the dosing regimen, feasibility, underlying medical conditions, potential impact on known adverse events, and other relevant considerations. Besides, obtaining a deep and sustained molecular response with the aim of discontinuing therapy is also one of our criteria for selecting a TKI.

In this case, the patient eventually stopped using dasatinib and returned to imatinib, mainly based on the

consideration that imatinib may not be as effective for this patient as dasatinib. However, no major adverse events were observed during the initial 2 years of treatment.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-23-517/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-23-517/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's guardian for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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