Brano Heart Failure Forum 2023 Conference Proceedings Paper

Late Cardiotoxicity from the Tyrosine Kinase Inhibitor, Dasatinib: Pleural Effusions, Pulmonary Arterial Hypertension, and Right Heart Failure

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Abstract

Despite the remarkable progress made over the past few decades in the management of patients with both solid and hematologic malignancies, radiation- and chemotherapy-related cardiotoxicity remains an ongoing problem. This is true even for newer highly targeted therapies, including tyrosine kinase inhibitors (TKIs). This report presents a case of late/severe right heart dysfunction secondary to pulmonary hypertension, developed after ten years of therapy with dasatinib. We also review the history of this known, but often unrecognized, and potentially reversible complication, and we suggest treatment options. Additionally, this case highlights the remarkable effectiveness of TKIs in patients with chronic myelogenous leukemia while also emphasizing the ever-present concern that even in the absence of clinical or laboratory evidence of residual leukemic disease, discontinuing chemotherapeutic agents may result in prompt recrudescence and death.

Introduction

Among the many fears and anxieties afflicting the human species, cancer may top the list. Fortunately, over the past few decades, early detection, thanks to standardized screening protocols, complemented by better therapeutic options, has resulted in a marked improvement in survival rates. Even so, most oncologists are still reluctant to characterize an inability to identify disease as 'cured.' They refer to patients as cancer 'survivors' instead of being in remission. Regardless of whether one characterizes the cancer patients as 'cured' or 'in remission,' the number of survivors continues to increase. In 1971, 1.5% of all Americans were living with cancer in one form or another. By 2001, that figure had increased to 3.5%, and in 2023 measures nearly 5%.[1]

Of the many new therapeutic options available for treating cancer, including the biologicals, chimeric antigen receptor (CAR)-T cell therapy, and immunotherapy, the one class of medication that has most altered the landscape over the past decade is the tyrosine kinase inhibitor (TKI). Initially introduced in 1996 as a selective inhibitor of the Abelson (Abl) tyrosine kinase to halt the replication of breakpoint cluster region-Abelson (BCR-ABL) positive chronic myelogenous leukemia cells, the role of these agents has rapidly expanded and now encompasses virtually all types of cancer. As of 2023, the United States Food and Drug Administration has approved approximately 100 TKIs, and the pipeline is burgeoning, with dozens of other new agents presently under investigation.[2]

As life expectancy after a cancer diagnosis increases, adverse short- and long-term cardiovascular effects of cancer treatments are becoming an increasingly encountered problem, and effective strategies to prevent and manage these adverse effects are needed.[3] Although most physicians are familiar with the risk of cardiac dysfunction due to anthracycline derivatives and trastuzumab, the cardiovascular and pulmonary toxicities of TKIs are less well recognized but nonetheless ever present.[4, 5]

Case Report

An 87-year-old woman with no significant medical history, except for experiencing palpitations since her late teens and a long history of tobacco abuse, remained in her usual state of health until age 61 (1996) when she was diagnosed with chronic myelogenous leukemia (CML). She received standard therapy until 2001, when imatinib was initiated.

In 2002, the patient developed left-sided breast cancer and underwent treatment with lumpectomy followed by radiation therapy, but chemotherapy was not administered. Five years later, she developed a large pericardial effusion requiring a pericardial window procedure.

In 2007, imatinib was discontinued due to her persistent lower extremity edema. In 2013, dasatinib was initiated, although the reasons for this change in treatment are not entirely clear.

Despite the CML and a history of breast cancer, the patient did well until 2018, when she was found to have severe mitral regurgitation requiring mitral valve repair with an annuloplasty ring. Three years later, a transthoracic echocardiogram demonstrated left atrial enlargement with normal left ventricular (LV) function. Moreover, severe right atrial (RA) enlargement, mild right ventricular (RV) enlargement, moderate tricuspid regurgitation, and severe pulmonary hypertension were noted. However, no intervention was undertaken, nor was it apparently advised at that time.

Four years later (2022), a transesophageal echocardiogram was performed. This study demonstrated normal LV function but revealed compression of the LV due to translocation of the septum resulting from the enlargement of the RV. The RV was visually estimated to be 4-5 times the size of the LV. Right atrial enlargement was again noted, and no patent foramen ovale or atrial septal defects were identified. The mitral ring was intact, but there was wide-open tricuspid regurgitation with a vena contracta measuring greater than 1 cm. No comment was made with respect to the pulmonary pressure.

One month later, the patient developed worsening abdominal bloating and ascites, leading to referrals for repeated paracenteses, during which approximately 6 liters of fluid were removed on most occasions. At that point, she was referred for further evaluation at the regional advanced heart failure center.

During the initial evaluation at the heart failure center, she denied chest pain, orthopnea, paroxysmal nocturnal dyspnea (PND), dizziness, lightheadedness, palpitations, and syncope. However, she reported marked lower extremity edema, recurrent abdominal bloating, anorexia, and an inability to walk more than 50 feet. An electrocardiogram demonstrated atrial fibrillation with right ventricular abnormalities (Figure 1), and a chest x-ray demonstrated pleural effusions (Figure 2).

Figure 1. *Electrocardiogram*

Figure 2. *Chest X-ray*

The patient was admitted three months later. During the hospitalization, a right heart catheterization was performed, showing the following results: mean RA pressure of 20 mm Hg, pulmonary artery (PA) pressure of 89/45 (61) mm Hg, and pulmonary capillary wedge (PCW) pressure of 22 mm Hg at end-expiration (Figure 3). The patient's mixed venous saturation was 54.9%, with an estimated Fick cardiac index of 1.8 L/min/m^2.
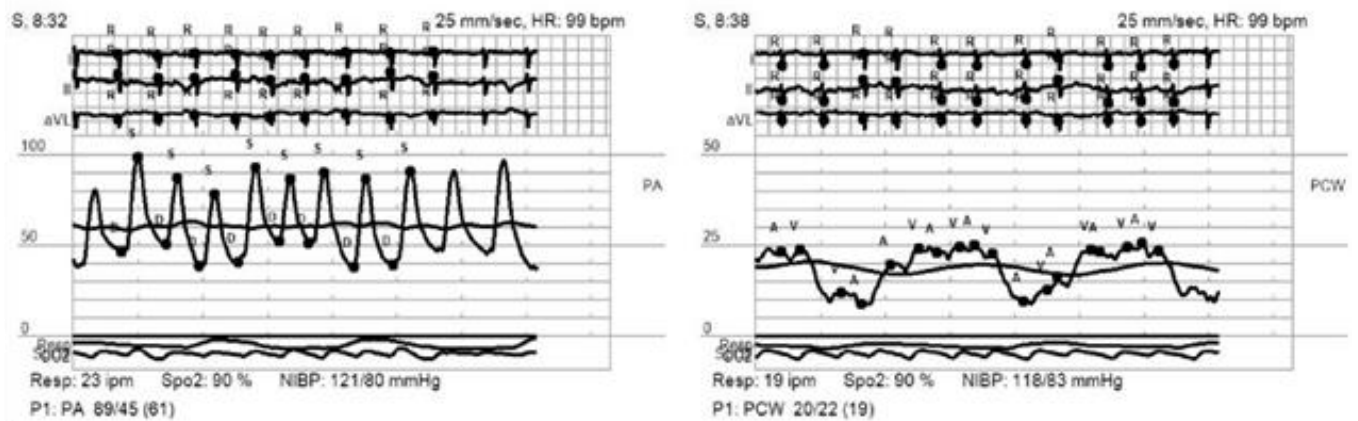

Figure 3. Results of right heart catheterization

The patient was diuresed with over 30 liters of intravenous torsemide. Sildenafil (60 mg) was administered three times a day. The right heart catheterization was repeated after the initiation of the therapy, revealing a mild improvement in the PA pressure to 70/21 mm Hg and a more significant decrease in the PCW pressure, with an end-expiratory value of 13 mm Hg (Figure 4).
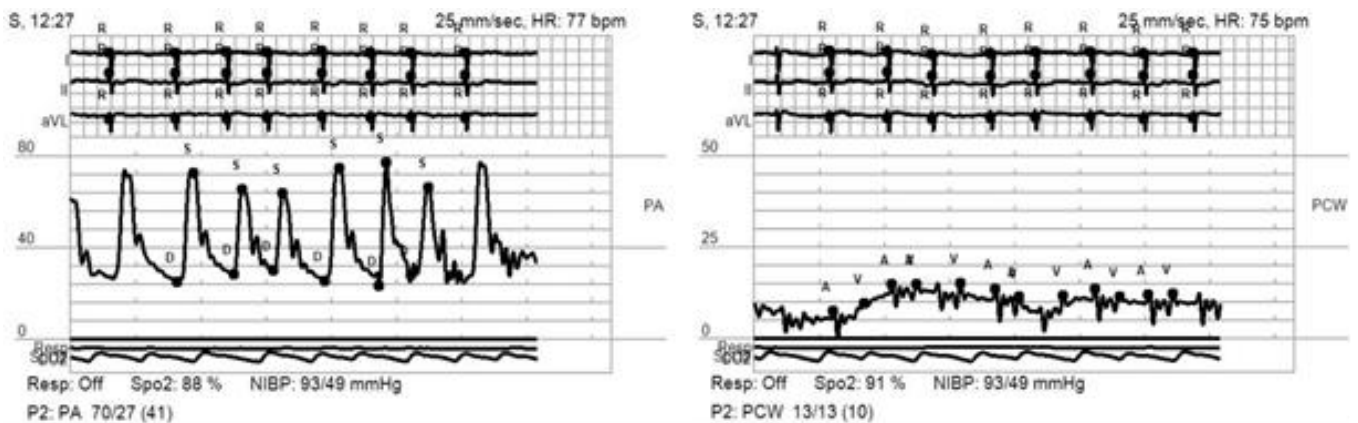

Figure 4. *Results of repeated right heart catheterization*

The echocardiogram was likewise repeated and again confirmed the presence of severe RV dilation and severe tricuspid regurgitation (Figures 5 and 6).
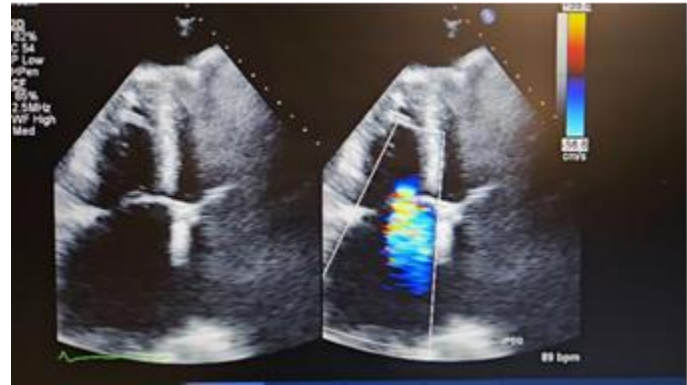

Figure 5. *Severe right ventricular dilation*

Figure 6. *Severe tricuspid regurgitation*

The patient was discharged home on torsemide, without edema, and with plans to initiate macetentan as an outpatient. Dasatinib was discontinued based on the absence of any markers of active CML.

After discharge, she did reasonably well from the cardiac point of view. Although she did report the reappearance of mild lower extremity edema, no repeated paracenteses were required, and her exercise tolerance (on 2 L nasal cannula oxygen) was approximately 150 feet. A CT-scan demonstrated bilateral pleural effusions (left greater than right) with moderately severe interstitial lung disease, pulmonary venous congestion, and chronic obstructive pulmonary disease (COPD). Macetentan was never started due to persistent volume overload.

In 2023, her white blood cell count rose to 45,000. BCR-ABL p210 studies were re-ordered and returned positive (13.8%). Active CML was diagnosed 27 years after the initial diagnosis and less than 6 weeks after discontinuing her TKI. Given the situation, she was treated with third-line therapy for CML using asciminib, which did result in a clinical response, although her creatinine levels rose. The plan was to repeat the echocardiogram to assess the pulmonary pressure and decide on inhaled, subcutaneous, or intravenous therapy for pulmonary hypertension. However, shortly after that visit, she fell, was readmitted at her local hospital, and sadly succumbed to her injuries.

Discussion

There are over 90 known tyrosine kinases at work in the human body, and not surprisingly, TKIs are highly effective in cancer regimens. They are commonly used in combination or alone in the treatment of a variety of cancers, including CML, chronic lymphocytic leukemia,

myeloproliferative neoplasms, lung cancer (particularly non-small cell lung cancer), hepatocellular carcinoma, colon cancer, sarcoma, thyroid cancer, gynecologic malignancies, and renal cell carcinoma. Unfortunately, despite their efficacy, they are known to be associated with serious adverse events. In some cases, the adverse events present early, while in other situations, they appear after many years of treatment.

As of August 2023, the FDA has approved approximately 100 different TKIs for use. First-generation (imatinib), second-generation agents (nilotinib, sunitinib, dasatinib, and bosutinib), and third-generation agents (ponatinib and asciminib) have all been shown to be remarkably effective in treating CML. In fact, life expectancy with CML is nearly the same as it is for an age-matched control.[6] Although each of these agents warrants independent discussion, for the purpose of this case report, we shall limit that discussion to a brief overview of only imatinib, nilotinib, ponatinib, and sunitinib prior to focusing on dasatinib, the offending agent in the case at hand.

Imatinib

The first tyrosine kinase inhibitor shown to be clinically beneficial was imatinib. The medication, which was used as a treatment for Philadelphia chromosome-positive leukemia (CML), revolutionized the treatment of what had previously been an often-fatal illness, despite interferon and cytarabine, converting it into a chronic lifelong medical problem.[7, 8]

In 2006, the medication, which was already known to cause fluid retention, was also shown to be associated with the development of congestive heart failure (CHF).[9] Many authorities, understanding that using all medications involves a risk-benefit analysis, still consider the long-term safety of the medication excellent, and the concern about clinical CHF is overstated.[10] In fact, despite the concerns about heart failure and volume overload, the medication has been investigated as a possible treatment for pulmonary hypertension.[11, 12]

Nilotinib and Ponatinib

Second-generation nilotonib (and bosutinib) and third-generation ponatinib represent alternative treatments for CML. Depending upon risk scores, they may be used as front-line therapy. Both nilotinib and ponatinib can lead to very rapid progression of coronary artery disease, even in young individuals with no prior evidence of disease. The use of nilotinib is also associated with cardiac conduction disturbances, ST-T–wave changes, and an incidence of heart rate-corrected QT interval (QTc) prolongation greater than 30 ms.[13] Cardiovascular events have been reported in up to 40% of patients receiving ponatinib within two years. [14-17]

Intravascular ultrasound imaging is particularly impressive, and the risk of atherosclerosis progression persists, even after stopping the medication. When using these medications, one must remain vigilant for thrombotic events, vasospasms, myocardial infarctions, and

stroke.[18,19] Some experts have proposed that all patients treated with either of these medications be placed on aspirin and undergo routine ankle-brachial index screening, irrespective of patient age, at baseline and 3-6 months intervals. However, it is not clear how long this screening should be continued.[20]

Sunitinib

Although not normally used for CML, sunitinib does have significant cardiac toxicity and warrants a few comments for the sake of completeness. The drug has been shown to strip pericytes off capillaries, increase the risk of thrombosis, and impair coronary flow reserve. It does this by uncoupling the pericyte's vascular endothelial growth factor (VEGF) and platelet-derived growth factor receptor-beta (PDGFR-β) from the endothelial cell's VEGF receptor (VEGFR) and platelet-derived growth factor-beta (PDGFβ).[21] As a result, nitric oxide production is decreased, and the incidence of hypertension is markedly increased.

Sunitinib is also associated with the development of dose-dependent QTc prolongation, with <0.1% incidence of torsades de pointes.[22-24] Its effect on global cardiac function is less clear. In a study involving five centers and 90 patients, about 10% developed LV dysfunction, defined as an absolute LVEF decline by ≥ 10% to an absolute LVEF value of < 50%. The finding became evident in 8 out of 9 patients within 5 weeks. However, virtually all patients improved regardless of whether the sunitinib was continued or discontinued.

Dasatinib

Dasatinib, the presumptive offending agent in this case, is a second-generation TKI. It is known to be associated with pleural effusions in 28% to 59% of patients within 5 years (as compared to 1% in patients on imatinib); to a lesser degree, dasatinib is associated with pulmonary arterial hypertension (PAH).[25-27] Discontinuing dasatinib does not invariably result in restoration of normal PA pressures. In an analysis of the French Pulmonary Hypertension Registry, dasatinib-induced PAH persisted in over one-third of the patients, even with PAH-specific therapy.[28,29]

How and/or why dasatinib induces PAH is not well understood. It is known that dasatinib has a broader range of action than other TKIs. Beyond inhibiting BCR-ABL receptor kinases, it also obstructs steroid receptor coactivator (SRC) family kinases and Tec family kinases.[30,31] This may be an explanation for dasanitib's negative effects, but it requires further investigation to establish it. Other researchers have demonstrated that in animal models, dasatinib can cause pulmonary endothelial damage and negatively affect hypoxic pulmonary vasoconstriction. Interestingly, as noted above, the effects can be attenuated by imatinib, reminding us that not all medications in the same class are the same.[32] Last, dasatinib was associated with increased reactive oxygen species, regardless of their effect on SRC kinases.

Similarly, the explanation for the development of lymphocyte-rich exudative pleural effusions in patients on dasatinib, as seen in our patient, remains unknown. Although an immune-mediated process (possibly attributable to the expansion of large granular lymphocyte clones including cytotoxic T and NK-cells) has been suggested, the role of corticosteroids is unestablished.[33-35] Other investigators have attributed the effusions to inhibition of the PDGFR-β, which is known to play a role in the regulation of angiogenesis. It has been shown that decreasing the dose from 100 mg daily to 70 mg daily, or even 40 mg daily, may decrease the rate of recurrence.[36,37] It is not known whether the effusions in this patient were transudative or exudative, as no thoracenteses were performed.

Pericardial effusions, although observed, are less common, occurring with pleural effusion in about 25-30% of the cases.[38,39] In rare instances, dasatinib has been associated with pericardial tamponade.[40]

The development of both bilateral pleural effusions and severe pulmonary hypertension in our patient is consistent with the known literature and most likely attributable to dasatinib. Typically, the process is insidious, developing slowly over the years, and not dose-dependent.[41] Indeed, this was true with our patient. The echocardiograms demonstrated RA and RV abnormalities at least two years prior to the presentation. Arguably, the RA and RV dysfunction could have been due to severe longstanding tricuspid regurgitation, but in this case, the presence of severe pulmonary hypertension suggests that it is a secondary phenomenon rather than a primary phenomenon. Severe pulmonary hypertension could have been due to longstanding severe mitral regurgitation, but in such cases, one would expect an elevated pulmonary wedge pressure,[42] which was not found in this scenario.

It is difficult to definitely state whether earlier recognition of the etiology followed by earlier intervention would have altered the outcome, as there are no established risk factors to predict an individual's response to discontinuation of dasatinib. Nonetheless, the standard of care in cases like this remains of medication discontinuation property and the introduction of pulmonary vasodilator therapy. Whether this approach would have been effective in our patient is unknown, as she unfortunately passed away after an unexpected mechanical fall.

CML

Despite the efficacy of TKIs in treating CML, treatment-free remission is relatively rare. Nonetheless, some patients with deep molecular responses (DMR) show no clinical or molecular evidence of recurrent CML. For them, discontinuing TKI therapy may be considered appropriate based on the belief that once the majority of CML cells have been eliminated below a certain threshold, the patient's immune system can control the growth of residual leukemic (stem) cells.[43-46]

Particularly interesting in this case is the duration of treatment with TKIs. In total, this individual was on a TKI for more than 16 years. By all measures (to our knowledge based on the

available information), she either had a DMR or an MMR (major molecular response). Yet, within six weeks of discontinuing the TKI, the disease returned. This highlights oncologists' concern alluded to earlier and serves as a warning that the inability to identify residual leukemic disease does not mean that there is no residual disease, irrespective of the BCR-ABL transcript level.

Fortunately, she did respond to third-line therapy with a prompt normalization of her white blood cell count. What would have happened over the long term remains unknown.

Conclusion

In summary, we report the late development (>10 years) of severe pulmonary hypertension, pleural effusions, and right heart failure (with secondary tricuspid regurgitation) after the initiation of dasatinib-based CML therapy.

This case emphasizes two things. First, and most obvious from the oncologic point of view, is the fact that achieving an MMR or DMR does not necessarily mean that the malignancy has been cured. Second, from the cardiac point of view, there is the need to ensure that all clinicians are aware of TKI-associated pulmonary hypertension, pleural effusions, and vasculopathy and recognize the indications for serial imaging.

A discussion regarding the frequency and modality of choice, whether echocardiography (with and without global strain) or cardiac magnetic resonance imaging, is beyond the scope of this case report. Nonetheless, one thing is certain: early recognition of subtle changes in cardiac function offers the best opportunity to arrest or reverse the developing vasculopathy or myopathy. Therefore, at least in certain patients, routine cardiovascular monitoring is indicated, which should be determined based on the known adverse event profile of the specific agent. Hence, it underscores the importance of early referral to cardio-oncology specialists for patients on chemotherapeutic medications.

Limitations

Despite the well-established association between TKIs and pulmonary hypertension, pulmonary vasculopathy, and pleural and pericardial effusions, diagnosing these conditions remains a matter of clinical suspicion, as they cannot be ascertained through laboratory testing or histology. Furthermore, since our patient died before the targeted therapy for pulmonary hypertension was initiated, we cannot state whether the process might have reversed, as it sometimes does. Finally, we cannot access the full details of her hematologic history. Therefore, while we assume that she had either an MMR or DMR, we cannot confirm this with absolute certainty.

Acknowledgements and Funding

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