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Cardiovascular and pulmonary adverse events in patients treated with *BCR-ABL* inhibitors: Data from the FDA Adverse Event Reporting System

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Abstract

Rare but serious cardiovascular and pulmonary adverse events (**AEs**) have been reported in patients with chronic myeloid leukemia treated with *BCR-ABL* inhibitors. Clinical trial data may not reflect the full AE profile of *BCR-ABL* inhibitors because of stringent study entry criteria, relatively small sample size, and limited duration of follow-up. To determine the utility of the FDA AE Reporting System (FAERS) surveillance database for identifying AEs possibly associated with the *BCR-ABL* inhibitors imatinib, dasatinib, and nilotinib in the postmarketing patient population, we conducted Multi-Item Gamma Poisson Shrinker disproportionality analyses of FAERS reports on AEs in relevant system organ classes. Signals consistent with the known safety profiles of these agents as well as signals for less well-described AEs were detected. Bone marrow necrosis, conjunctival hemorrhage, and peritoneal fluid retention events were uniquely associated with imatinib. AEs that most commonly reached the threshold for dasatinib consisted of terms relating to hemorrhage and fluid retention, including pleural effusion and pericardial effusion. Most terms that reached the threshold solely with nilotinib were related to peripheral and cardiac vascular events. Although this type of analysis cannot determine AE incidence or establish causality, these findings elucidate the AEs reported in patients treated with *BCR-ABL* inhibitors across multiple clinical trials and in the community setting for all approved and nonapproved indications, suggesting drug-AE associations warrant further investigation. These findings emphasize the need to consider patient comorbidities when selecting amongst *BCR-ABL* inhibitors.

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Additional Supporting Information may be found in the online version of this article.

Introduction

Chronic myeloid leukemia (CML) has become a manageable chronic disease for most patients treated with imatinib, dasatinib, and nilotinib, the *BCR-ABL* inhibitors currently approved for first- and second-line treatment [1–3], and bosutinib and ponatinib, approved in 2012 for second-line or subsequent treatment [4,5]. Because imatinib, dasatinib, and nilotinib were first approved in 2001, 2006, and 2007, respectively, and are widely used, a significant amount of postmarketing data are available, potentially allowing for identification of rare or late-onset adverse events (AEs).

The safety profiles for imatinib, dasatinib, and nilotinib all include hematologic, fluid retention-related, gastrointestinal, cardiovascular, and musculoskeletal AEs, among others [1–3], but differ in the type, incidence, severity, and reversibility of specific AEs. Since these *BCR-ABL* inhibitors are often used sequentially, strict association of specific AEs with a specific inhibitor may be limited by the consideration of prior exposure. Clinical trial data, particularly safety data, are limited by the study sample size, entry criteria, and treatment or follow-up duration specified in the protocols. Many clinical trials evaluating *BCR-ABL* inhibitors have now reported long-term (4- to 5-year) follow-up periods, which include rigorous monitoring of toxicity, causality assessments by treating physicians, and analysis of incidence per patient-years of exposure. Even so, it is not unusual for rare or late-onset AEs to become more apparent after approval, when the drug is prescribed to a broader population (including those who may not have met study entry criteria). Examples include pulmonary arterial hypertension (PAH) reported for dasatinib [6–14] and peripheral arterial occlusive disease (PAOD) reported for nilotinib [15–22].

Data-mining techniques, such as signal detection algorithms, are increasingly being used to explore medical databases and analyze large volumes of accumulated data to identify potential associations between drugs and AEs that may have escaped detection in clinical trials [23]. The US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) is one of the largest databases of AEs designed to support the FDA postmarketing safety surveillance program for approved drugs and biologics [24]. All AEs reported to pharmaceutical manufacturers are submitted and included as specified by US regulations. The database includes AEs defined by the FDA as serious if they: (1) resulted in death, hospitalization, disability, or permanent damage; (2) were potentially life-threatening; (3) may have caused a congenital anomaly or birth defect; (4) required medical or surgical intervention to prevent permanent damage; or (5) were considered important medical events that could have jeopardized the patient and/or required medical or surgical intervention to prevent one of the above mentioned outcomes [25]. In addition, voluntary reports from patients and health care professionals directly to the FDA may be included [24]. Data from FAERS are publically available and routinely used by the FDA, health systems, clinical scientists, and pharmaceutical manufacturers to identify potential safety signals.

We conducted an analysis of the FAERS database up to and including September 30, 2012, including patients treated outside of clinical trials, to gather additional information about the cardiac, vascular, and pulmonary/mediastinal/thoracic safety profiles of imatinib, dasatinib, and nilotinib across all uses, which may encompass a variety of diagnoses and stages, as

well as both approved and non-approved indications. These areas were of interest as they are the target organ systems of the late-onset and emerging toxicities noted with kinase inhibitor therapy for CML. Although the FAERS database includes AEs and diagnoses, we were limited in our analysis by how both were reported to the FAERS database, as well as by the details provided regarding particular events. Of note, bosutinib and ponatinib were not included; FAERS data on these agents were insufficient for meaningful analysis, as they were approved in September 2012 and December 2012, respectively.

Methods

Signal detection.

In FAERS, each report includes treatment indications, limited demographic information, and 1 or more AEs (occurring in a single patient) that may be associated with administration of 1 or more drugs. Methodologies for detecting safety signals in databases of spontaneous and clinician-reported AEs, such as FAERS, assess the potential association of AEs with a specific therapy by evaluating the frequency of reports in which a specific drug-event combination co-occurs. Multi-Item Gamma Poisson Shrinker (MGPS) [23,26] is one of the most established and commonly-used methods for identifying drug-event associations using large AE databases. As described in the Supplemental Materials and Methods, MGPS analysis is a validated Bayesian method that provides a robust estimate of disproportionality (the degree to which the reporting frequency of a drug-event pair is disproportionally higher than would be expected in cases with no drug-event association) called the Empirical Bayesian Geometric Mean (EBGM). The EBGM is calculated by adjusting the observed frequency of the drug-event pair using *b*, the frequency of reports of the event of interest with all other drugs, and *c*, the frequency of all other events reported for the drug of interest. The EBGM 90% confidence interval (CI) is defined by EB05 and EB95. Although disproportionality analyses do not measure AE incidence or establish that a drug is causative, higher EBGM or EB05 values indicate higher probability of association, warranting further evaluation. Although EB05 ≥2 is commonly used for identifying drug-event associations warranting further investigation, EB05 ≥4 was chosen for this report to identify events more likely to be clinically relevant and potentially attributable to drug therapy.

Medical Dictionary for Regulatory Activities terminology (MedDRA®R 15.0) preferred term analysis.

FAERS adheres to international safety reporting guidance from the International Conference on Harmonisation, and AEs are coded using preferred MedDRA terms [27]. MGPS disproportionality analysis [23,26] was used to assess the reporting frequency of all preferred terms in three MedDRA system organ classes with known *BCR-ABL* inhibitor safety signals [(1). cardiac; (2). respiratory, thoracic and mediastinal; and (3). Vascular] for imatinib, dasatinib, and nilotinib in the FAERS database through September 30, 2012 [24]. Our data analysis included as “drug-event pairs” all cases in which a drug and event co-occurred in the same report and the drug was assessed as either suspect in or concomitant with the event.

A second analysis focused on year-by-year analyses of MedDRA preferred terms in the three selected system organ classes to assess the trajectory of disproportionality in drug-event pairs over time for pairs with EB05 ≥4. To evaluate the AE profile in different age groups, MGPS analysis for all preferred terms in the system organ classes of interest was run separately for three cohorts of patients based on age cutoffs typically used in regulatory reporting: 18 to 45, 46 to 64, and ≥65 years.

Standardized MedDRA query analysis.

To identify drug-event pairs that did not reach the signal threshold with single-term analysis, and to correct for underestimation of drug-event pair significance due to variability in the terms chosen to describe essentially the same AE, MGPS disproportionality analysis was performed using select narrow standardized MedDRA queries (SMQs), which combine similar clinically relevant preferred terms [28,29]. SMQs were selected broadly for potentially relevant cardiovascular and pulmonary AEs: (1) cardiac arrhythmias; (2) cardiac failure; (3) hemodynamic edema, effusions, and fluid overload; (4) interstitial lung disease; (5) ischemic heart disease; (6) myocardial infarction; (7) pulmonary hypertension; and (8) torsades de pointes/QT prolongation.

Results

MGPS analysis of MedDRA preferred terms

The MGPS disproportionality analysis of preferred terms in the FAERS database (including patients treated for any indication) identified 956 unique preferred terms in the three system organ classes included in this analysis, recorded as a drug-event pair for one or more of the following *BCR-ABL* inhibitors: imatinib, dasatinib, and nilotinib. Twenty-three of 956 terms reached EB05 ≥4, with most reaching the threshold for only one of the three *BCR–ABL* inhibitors evaluated (seven for imatinib, five for dasatinib, and nine for nilotinib; Table I, Supporting Information Table I). Pleural effusion reached the threshold for all three agents albeit with a much higher EB05 with dasatinib (30.77 for dasatinib, 5.59 for imatinib, and 5.65 for nilotinib). Pericardial effusion also had a higher EB05 with dasatinib (11.75) compared with imatinib (4.57) or nilotinib (3.86).

Preferred terms reaching the threshold uniquely with imatinib included: the vascular preferred terms gastric antral vascular ectasia and bone marrow necrosis (EB05 ≥25); tumor necrosis, tumor hemorrhage, and conjunctival hemorrhage (EB05 ≥8); and ascites and hemorrhagic ascites (EB05 ≥4–<8; Table I). Terms reaching the threshold only with dasatinib included several related to fluid retention: chylothorax and malignant pleural effusion (EB05 >15), and pleural hemorrhage, pulmonary edema, and PAH (EB05 ≥4–<8; Table I). Terms reaching the threshold only with nilotinib included femoral arterial stenosis (EB05 >50); intermittent claudication, PAOD, and coronary artery stenosis (EB05 >15); and angina pectoris, acute myocardial infarction, femoral artery occlusion, acute coronary syndrome, and peripheral ischemia (EB05 ≥4–<8; Table I).

Although a more stringent reporting threshold of EB05 ≥4 was selected for this analysis, a threshold of EB05 ≥2 is commonly considered meaningful when identifying safety signals

for further evaluation [30,31]. To investigate the potential for a class effect to be masked by the higher threshold selected, we checked results for preferred terms reaching EB05 ≥4 with at least one drug of interest to determine whether EB05 was ≥2 with the other *BCR-ABL* inhibitors (Table I, footnotes f and g). EB05 values ≥2 to <4 were observed for ascites with dasatinib and nilotinib (EB05 ≥4 for imatinib), and for pericardial effusion with nilotinib (EB05 ≥4 for dasatinib and imatinib; Supporting Information Table I).

MGPS analysis of SMQs

Analysis of cardiovascular and pulmonary SMQs [28] (Supporting Information Table II) showed that signals reaching the threshold with nilotinib were torsades de pointes/QT prolongation (EB05 = 15.29) and cardiac arrhythmias (4.08), and with dasatinib were pulmonary hypertension (4.17), and hemodynamic edema, effusions, and fluid overload (4.79). There were no SMQs with EB05 ≥4 for imatinib.

By-year MGPS analysis of MedDRA preferred terms

Analysis of drug-event associations by year of observation showed different time to threshold and final EB05 levels across events. Signals that arose quickly and reached the threshold of EB05 ≥4 within 1 to 2 years of approval (Table II) included pleural effusion, pericardial effusion, and malignant pleural effusion for dasatinib and coronary artery stenosis and angina pectoris for nilotinib. Drug-event associations that reached EB05 ≥4 within 3 to 5 years included tumor hemorrhage, gastric antral vascular ectasia, and pleural effusion with imatinib; chylothorax with dasatinib; and pleural effusion and cardiovascular events with nilotinib (Table II). Some of these AEs were included in the prescribing information Warnings and Precautions at the time of approval or in subsequent label updates. Signals reaching the threshold generally stayed above the threshold in subsequent years (Supporting Information Figure 1).

Age cohort MGPS analysis of MedDRA preferred terms

The analysis of AEs by age cohort (Tables I and III) demonstrated that in the youngest patients (those aged 18–45 years), the only term with EB05 ≥8 was pleural effusion with dasatinib; terms with EB05 ≥4–8 were pericardial effusion with dasatinib, pleural effusion and ascites with imatinib, and coronary artery stenosis with nilotinib. In the cohort of patients aged 46 to 64 years, terms reaching EB05 ≥8 were pleural effusion and PAH with dasatinib; gastric antral vascular ectasia, tumor hemorrhage, tumor necrosis, and conjunctival hemorrhage with imatinib; and femoral artery stenosis, coronary artery stenosis, PAOD, and angina pectoris with nilotinib. Terms with EB05 ≥4 to 8 in patients aged 46 to 64 years were ascites, pleural effusion, and subdural hematoma with imatinib and acute coronary syndrome with nilotinib. In the oldest patient cohort (≥65 years), terms with EB05 ≥8 were pleural effusion and pericardial effusion with dasatinib; tumor necrosis, gastric antral vascular ectasia, and tumor hemorrhage with imatinib; and femoral arterial stenosis, PAOD, intermittent claudication, coronary artery stenosis, and peripheral ischemia with nilotinib. AEs with EB05 ≥4 to 8 in the oldest patient cohort were pulmonary edema with dasatinib; pleural effusion, ascites, and pericardial effusion with imatinib; and pleural effusion with nilotinib.

As in the analysis for all patients, the potential for a class effect to be masked by selecting the higher EB05 ≥4 threshold was investigated by checking, in each age cohort, whether EB05 was ≥2 for any other *BCR-ABL* inhibitors. Drug-event pairs with EB05 ≥2 to 4 included pericardial effusion with imatinib and pleural effusion with nilotinib for patients aged 18 to 45 years, and pericardial effusion with all agents and pleural effusion with nilotinib for patients aged 46 to 64 years. In the age cohort analysis, neither imatinib nor dasatinib had any terms relating to peripheral or coronary arteriopathy reach EB05 ≥2.

Logistic regression analysis of MedDRA preferred terms

Logistic regression analysis of the FAERS database was used to provide independent assessment of the likelihood of drug-event associations, adjusting for known covariates that could potentially influence the frequency of drug-event pairs: sex, age group, and year the event was reported (Supplemental Materials and Methods). For all drug-event pairs with EB05 ≥4 in the MGPS disproportionality analysis, the logistic regression analysis indicated a likely association (LR05 ≥2; Table I, footnotes d and e) when analyzed using all three covariates (n = 17 drug-event pairs) or only sex and age group (n = 6 drug-event pairs: gastric antral vascular ectasia, bone marrow necrosis, and hemorrhagic ascites with imatinib; chylothorax and pleural hemorrhage with dasatinib; and femoral arterial stenosis with nilotinib). Some drug-event pairs reached LR05 ≥2 in the logistic regression analysis (using three covariates) but not EB05 ≥4 in the MGPS disproportionality analysis (Table I, footnotes d and e; Supporting Information Table III). Because adjustment for covariates should improve the detection of true associations, these safety signals warrant further investigation: fluid retention events for all three *BCR-ABL* inhibitors (ascites with dasatinib and nilotinib, pulmonary edema and malignant pleural effusion with imatinib, and pericardial effusion with nilotinib), PAH with imatinib, and tumor hemorrhage and tumor necrosis with nilotinib.

Discussion

The FAERS database was selected for this analysis as it is a reputable, publicly accessible database with consistent and reproducible data reported over a broad time frame from a heterogeneous patient population, including patients typically excluded from clinical trials because of comorbidities or other factors. However, there are recognized limitations to and possible sources of bias in these data [32–37]: (1) The database primarily includes spontaneous (voluntary) serious AE reports, with varying level of detail and quality of clinical content, as well as entries from clinical trials. AE reports from either source may include incorrect AE coding or classification [32] or not meet the FDA criteria for classification as serious AEs, and have limited information regarding the nature and severity of the events and details that would aid in assessment of causality, such as drug dose, timing and duration of exposure relative to the event, and prior treatment history. (2) Reporting rate and classification of AEs may change over time because of changes in terminology or outside influences, such as academic publications, reports in the press, marketing, or publicity. Typically, AE reports for a drug increase during the first 2 years after approval before decreasing (the Weber effect) [33,38], and increase after release of drug safety alerts or publications (notoriety bias) [34,39–41]. (3) The number of patients receiving a marketed

drug is not known, and AE rates cannot be calculated in the absence of this denominator. EB05 values are based on reporting frequency for the drug-event pair of interest and are adjusted based on rates reported for other drugs and rates of all other AEs reported for the drug of interest. Although higher EB05 values represent greater confidence that an AE and drug are associated, EB05 values do not represent AE incidence. EB05 values reaching the threshold for imatinib, dasatinib, and nilotinib suggest the AE of interest is likely associated with all 3, but it does not indicate the relative frequency of that AE between drugs. (4) The database may include multiple reports of the same event, although resulting bias is minimized through implementing an algorithm to flag and exclude duplicate reports. (5) Since reports are not prospective, required, or monitored, the level of reporting may be influenced by the type of AE. AEs that are easy to detect and diagnose (e.g. pleural effusion) may be more likely to be reported than AEs that are more challenging to diagnose accurately (e.g. PAH). AEs that could be drug-related but also associated with relatively common comorbidities may be less likely to be reported as drug-related because of the prevalence of the underlying condition. Unusual AEs with a few possible causalities (e.g. pleural effusion) or AEs occurring in otherwise healthy patients are more likely to be reported as drug-related. (6) Selection of only 3 system organ classes provided relevant data but prevented identification of other safety signals of interest. In addition, some of the preferred terms included in the system organ classes of interest may not be considered by all clinicians to be cardiovascular or pulmonary (e.g. bone marrow necrosis in the vascular category). (7) This analysis did not adjust for differences in treatment indication across AE reports for the agents analyzed.

Despite these caveats, the MGPS methodology is a well-established tool for identifying drug-event pairs reported more frequently than anticipated, as it is likely that many of the limitations mentioned are equalized across different drugs and over time. In this analysis, the following steps were taken to control for the limitations of MGPS analysis of FAERS data: (1) selection of EB05 ≥4 threshold to increase the certainty of identifying relevant signals; (2) logistic regression to exclude false signals and confounding medications; (3) correlation of MGPS results, where possible, with data from published peer-reviewed reports; (4) SMQ analysis to correct for underestimation of drug-event pair significance due to variability in the terms chosen to describe the same AE; and (5) a “by year of observation” temporal analysis to identify when signals arose related to time from drug approval or publications increasing awareness of certain drugassociated AEs. Logistic regression analysis supported the results of the MGPS analysis, suggested additional possible drug-event pair associations, and uniformly suggested that AEs previously thought to be associated uniquely with one *BCR-ABL* inhibitor may be associated with multiple *BCR–ABL* inhibitors. These findings underscore the importance of treating physicians remaining alert to all potential AEs, not only those typically considered to be associated with a specific *BCR-ABL* inhibitor based on clinical trial reports.

Many of the drug-event associations identified in this analysis are supported by the literature, whereas others are emerging signals. As expected from previous reports and as described in the product label, pleural effusion and pericardial effusion demonstrated the strongest signal with dasatinib [1,42,43], but EB05 was also ≥4 for both terms with imatinib and for pleural effusion with nilotinib, suggesting a possible association not apparent in

previously-published data [2,3,19]. The clinical scenarios in which these events occur (e.g. sequential drug exposure) cannot be defined by the methodology used in this report.

Bone marrow necrosis was uniquely associated with imatinib and has been previously reported in patients treated for either leukemia or solid tumor indications [44–48]. Prior reports suggest this may be due to massive necrosis of tumor cells leading to cytokine release and destruction of marrow elements or to potential perturbations of cell egress from the bone marrow [44–49]. Other terms reaching the threshold only with imatinib were conjunctival hemorrhage, peritoneal fluid retention events, and AEs possibly related to solid tumor indications (tumor necrosis, gastric antral vascular ectasia, and tumor hemorrhage). Tumor necrosis and hemorrhage reached the threshold in the older two cohorts (46–64 and ≥65 years), likely because of the incidence of solid tumors increasing with age. Results of the logistic regression analysis also suggest an association of tumor hemorrhage and tumor necrosis with nilotinib (LR05 ≥2), likely due to clinical trials testing nilotinib for solid tumors.

Similar to the results with imatinib, MGPS analysis showed that for dasatinib most of the terms reaching the threshold involved either fluid retention (pleural effusion, malignant pleural effusion, chylothorax, pulmonary edema, or pericardial effusion) or hemorrhage (pleural hemorrhage). Malignant pleural effusions and chylothorax are clinically associated with the recognized AE of pleural effusion and are commonly diagnosed when thoracentesis is performed for treatment or diagnosis of pleural effusion. The MGPS analysis suggested PAH was also uniquely associated with dasatinib, reaching the threshold in the cohort of patients aged 46 to 64 years. EB05 for PAH and dasatinib did not reach the threshold until 2012, 6 years after approval. It is unclear whether the late appearance of this signal reflects delayed onset of PAH or increased reporting following changes to the dasatinib product labeling (October 2011 [50]) and publication of case reports suggesting that PAH be considered in cases of unexplained dyspnea (2 in 2009 [6,7], 3 in 2011 [8–10], 11 in 2012 [11–13]). Most published cases of PAH associated with dasatinib had late onset (>2 years for 15/18 cases) and were atypical in being at least partly reversible on dasatinib discontinuation [6–14,51]. Although PAH with imatinib did not reach the threshold in the MGPS analysis (EB05 <2), PAH with imatinib has been reported in the FAERS database, and logistic regression analysis showed LR05 >2. Although this might suggest an association, studies of imatinib as a treatment for PAH [52,53] could account for the reported cases.

Most terms reaching the threshold uniquely with nilotinib were related to peripheral and cardiac vascular events or the symptoms or consequences thereof. Coronary artery stenosis (EB05 ≥8) and angina pectoris (EB05 ≥4) were observed in the first year after approval; PAOD (EB05 ≥8) and myocardial infarction (EB05 ≥4) reached the threshold in year 3. The remaining unique terms for nilotinib (reaching the threshold after year 3) include both cardiac (acute coronary syndrome) and peripheral arterial events (femoral artery stenosis, intermittent claudication, peripheral ischemia, and femoral artery occlusion), further supporting a potential association between nilotinib and vascular disease. These results suggest an association between cardiovascular AEs and nilotinib, consistent with published literature describing cardiovascular AEs detected during extended follow-up of the

ENESTnd trial and other studies [3,15–22,54,55]. In these reports, serious patient morbidity has been described, including amputation resulting from de novo PAOD [54].

The MGPS age cohort analysis suggests that coronary artery stenosis was associated with nilotinib in all three age groups, including the youngest patients anticipated to be at lowest risk. Additional terms reached the threshold with nilotinib in the older patient groups: femoral arterial stenosis and PAOD in the two older cohorts; angina pectoris and acute coronary syndrome in patients aged 46 to 64 years; and intermittent claudication and peripheral ischemia in patients aged ≥65 years. The MGPS analysis indicates that the likelihood of association between nilotinib and femoral arterial and coronary artery stenosis may be slightly reduced in the oldest cohort compared with those aged 46 to 64 years, perhaps because vascular disease is common in older patients and therefore less likely to be reported as a drug effect. Under-reporting of these events for dasatinib and/or imatinib cannot be excluded, since they may be considered not drug-related in patients with other cardiovascular risk factors.

In this FAERS database analysis, the late appearance of PAH signal with dasatinib (EB05 reached the threshold in 2012, 6 years after approval) is likely due to public reports at the time and resulting notoriety bias [34,39–41], as PAH is difficult to diagnose and thus unlikely to be reported before product warnings and publications raising awareness [1,6–14,51]. In contrast, signals for AEs related to vascular disease beginning early after nilotinib authorization are unlikely due to notoriety bias because literature raising awareness of the risk of these AEs with nilotinib did not begin to accumulate until 2011 to 2012 [3,15–22,54,55]. However, the nilotinib prescribing information has included a warning that nilotinib prolongs the QT interval, which should be monitored by echocardiograms, since approval in 2007 [56]. This, in addition to a report of imatinib cardiovascular toxicity in 2006 [57], may have led to an early bias to identify and report more cardiovascular AEs.

In conclusion, analysis of AEs reported in the postmarketing setting supports the association between pleural effusion and pericardial effusion with dasatinib [1,42,43] and suggests that pleural effusion with imatinib or nilotinib may be seen in clinical practice. Similarly, these findings support the association between dasatinib and PAH [1,6–14,51]. This analysis supports an association between nilotinib and certain cardiovascular AEs [3,15–22,54,55], and suggests this association is likely even in the youngest age cohort analyzed. These results underscore the value of continued reporting of AEs to regulatory authorities to improve accuracy and understanding of the patterns of events occurring in daily clinical practice. This information is helpful for prescribing the most appropriate *BCR-ABL* inhibitor dependent on the individual patient's risks and for increasing awareness in the medical community of the AEs to be expected, including those not clearly evident from clinical trial reports.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict of interest:

J.C. has received research funding from Ariad, BMS, Novartis, Pfizer, and Teva and has acted as a consultant for and received honoraria from Ariad, BMS, Novartis, Pfizer, and Teva. M.M. has received research funding from Ariad, BMS, and Novartis and has acted as a consultant or speaker for and received honoraria from Ariad, BMS, Novartis, and Pfizer. J.L.S. has acted as a consultant for and received honoraria from Ariad, BMS, Novartis, and Pfizer. G.S. has acted as a consultant for and received honoraria from Ariad, BMS, Celgene, Novartis, and Pfizer. R.M. and N.T.W. are employees of BMS. R.M. owns stock in BMS. J.A.U. was an employee of BMS at the time of analysis.

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TABLE I.

Drug-Event Pairs with EB05 ≥2 Based on the MGPS Analysis of the FAERS Database

Imatinib					Dasatinib					Nilotinib				
Preferred term	**EBGM**	**EB05**	**EB95**	***N***	**Preferred term**	**EBGM**	**EB05**	**EB95**	***N***	**Preferred term**	**EBGM**	**EB05**	**EB95**	***N***
Gastric antral vascular ectasia[b–d]	44.415	30.771	62.46	22	Chylothorax[d]	92.302	58.861	139.279	15	Femoral arterial stenosis[b,d]	78.281	50.688	116.616	16
Bone marrow necrosis[d]	41.142	26.64	61.291	16	Pleural effusion[a–c,e]	33.084	30.771	35.532	523	Intermittent claudication[c,e]	32.196	23.157	43.825	27
Tumor necrosis[b,c,e]	21.425	15.502	29.009	28	Malignant pleural effusion[e]	25.417	15.529	39.69	13	PAOD[b,c,e]	27.318	21.28	34.637	46
Tumor hemorrhage[b,c,e]	18.559	14.233	23.861	41	Pericardial effusion[a,c,e,f]	14.348	11.745	17.37	72	Coronary artery stenosis[a–c,e]	21.573	16.707	27.496	44
Conjunctival hemorrhage[b,e]	11.447	8.783	14.408	57	PAH[b,e]	7.944	4.892	13.532	22	Angina pectoris[b,e]	8.432	6.796	10.461	80
Pleural effusion[a–c,e]	6.03	5.59	6.497	478	Pulmonary edema[c,e]	5.45	4.424	6.664	64	Femoral artery occlusion[e]	20.698	6.157	38.852	9
Ascites[a–c,e,g]	6.132	5.488	6.836	225	Pleural hemorrhage[d]	24.764	4.024	59.419	6	Pleural effusion[c,e]	6.574	5.654	7.62	125
Pericardial effusion[c,e,f]	5.277	4.566	6.073	132						Peripheral ischemia[c,e]	10.273	5.117	18.2	17
Hemorrhagic ascites[d]	13.852	4.087	30.915	9						Acute myocardial infarction[e]	6.235	5.07	7.633	67
										Acute coronary syndrome[b,e]	6.989	4.929	10.396	30
Subdural hematoma	4.338	3.562	5.242	71	Pleurisy	5.994	3.819	10.411	17	Pericardial effusion[e,f]	5.139	3.86	6.752	34
Lung infiltration	3.845	3.234	4.544	92	Gastrointestinal hemorrhage	4.353	3.602	5.222	77	Myocardial ischemia	4.985	3.747	6.54	34
Lung adenocarcinoma	4.518	3.093	6.447	19	Lung infiltration	4.922	3.505	6.796	24	Arteriosclerosis	5.059	3.712	6.793	29
Bronchopulmonary aspergillosis	3.974	2.98	5.216	33	Pulmonary hypertension	4.705	3.476	6.267	30	Arterial disorder	8.124	3.645	19.708	11
Intra-abdominal hemorrhage	4.326	2.934	6.214	18	Subdural hematoma	4.978	3.458	7.047	21	Arterial stenosis	10.16	3.248	28.798	8
Eye hemorrhage	3.498	2.814	4.309	58	Atelectasis	4.307	3.005	6.03	21	Dyspnea exertional	4.173	3.1	5.523	31
Papilledema	3.879	2.789	5.284	25	Hypoxia	3.735	2.776	4.94	31	Arteritis	13.313	2.861	43.639	6
Alveolitis allergic	4.206	2.754	6.233	15	Pneumonitis	3.993	2.739	5.67	19	Lung infiltration	4.048	2.802	5.703	20
Alveolar proteinosis	7.556	2.697	26.94	7	Respiratory failure	3.055	2.474	3.737	62	Pericarditis	4.054	2.578	6.159	13
Disseminated intravascular coagulation	3.13	2.625	3.709	89	Lower gastrointestinal hemorrhage	4.045	2.35	6.71	9	Left ventricular hypertrophy	3.92	2.571	5.79	15

Imatinib					Dasatinib					Nilotinib				
Preferred term	**EBGM**	**EB05**	**EB95**	***N***	**Preferred term**	**EBGM**	**EB05**	**EB95**	***N***	**Preferred term**	**EBGM**	**EB05**	**EB95**	***N***
Peritoneal hemorrhage	4.059	2.623	6.08	14	Pulmonary hemorrhage	3.576	2.24	5.485	12	Supraventricular extrasystoles	4.202	2.565	6.656	11
Metastases to lung	3.449	2.608	4.492	35	Ascites[e,g]	2.939	2.101	4.024	24	Angina unstable	3.893	2.553	5.749	15
Dyspnea exertional	3.047	2.548	3.621	86	Acute pulmonary edema	3.483	2.095	5.53	10	Chest pain	2.89	2.529	3.289	155
Edema peripheral	2.498	2.332	2.672	582						Coronary artery disease	2.855	2.268	3.555	52
Vitreous hemorrhage	3.413	2.269	4.974	16						Cardiac tamponade	3.85	2.248	6.309	9
Rales	3.055	2.26	4.057	30						Ascites[e,g]	3.023	2.201	4.072	27
Interstitial lung disease	2.552	2.21	2.934	133						Atrial fibrillation	2.643	2.188	3.171	77
Pulmonary mass	3.248	2.159	4.733	16						Cardiomegaly	3.07	2.127	4.317	20
Lung consolidation	3.203	2.155	4.622	17						Carotid arteriosclerosis	3.53	2.123	5.607	10
Pleural fibrosis	3.363	2.108	5.152	12						Carotid arterial stenosis	4.288	2.066	13.329	6
Cerebral hemorrhage	2.486	2.095	2.932	94						Cardiac failure	2.552	2.045	3.154	56
Pleuritic pain	3.064	2.083	4.38	18						Arteriosclerosis coronary artery	3.187	2.032	4.811	13
Hypoxia	2.45	2.074	2.878	99						Sinus tachycardia	3.083	2.024	4.54	15
Pneumonitis	2.559	2.05	3.162	56						Rales	3.334	2.006	5.287	10
Lung disorder	2.381	2.025	2.785	105										
EB05:	≥2–<4	≥4–<8	≥8–∞											

EB05 and EB95, lower and upper limits of EBGM 90% CI; *N*, number of events in the FAERS database.

[a-c]EB05 ≥4 for cohorts of patients aged 18 to 45 (a), 46 to 64 (b), and ≥65 years (c); in the cohort of patients aged 46 to 64 years, subdural hematoma with imatinib also had EB05 ≥4 (Table III).

[d,e]Logistic regression analysis supports significant association (LB05 ≥2) when analyzed with two covariates (sex and age; d) or three covariates (sex, age, and year event was observed; e). LB05 was ≥2 for the following drug-event pairs with EB05 <4: pulmonary edema, malignant pleural effusion, and PAH with imatinib; ascites, gastric antral vascular ectasia, and bone marrow necrosis with dasatinib; and tumor hemorrhage, tumor necrosis, pericardial effusion, chylothorax, and ascites with nilotinib (Supporting Information Table III).

[f]For pericardial effusion, EB05 ≥4 with imatinib or dasatinib, EB05 ≥2 to <4 with nilotinib, and LR05 ≥2 for all three drugs.

[g]For ascites, EB05 ≥4 with imatinib, EB05 ≥2 to <4 with dasatinib or nilotinib, and LR05 ≥2 for all three drugs.

TABLE II.

MGPS By-Year Analysis Results: First Year Drug-Event Signal Reached EB05 ≥4

	Years						
Imatinib (Initial US Approval in 2001[a])							
	1[a]	2	3	4	5	6	7–10
Necrosis						Bone marrow necrosis Tumor necrosis	
Hemorrhage[b]			Tumor hemorrhage[b]	Gastric antral vascular ectasia		Hemorrhagic ascites[c]	Conjunctival hemorrhage
Fluid-related				Pleural effusion[c]		Ascites[c]	Pericardial effusion[c]
Dasatinib (Initial US Approval in 2006[d])							
	<1[d]	1	2	3	4	5	6
Fluid-related	Pleuraleffusion[e]		Malignant pleural effusion Pericardial effusion[e]	Chylothorax			Pulmonaryedema[e]
Hemorrhage[f]							Pleural hemorrhage
Pulmonaryhypertension							PAH[g]
Nilotinib (Initial US Approval in 2007[h])							
	1[h]	2	3	4	5		
Vascular stenosis[i]	Coronary artery stenosis Angina pectoris		PAOD Acute myocardial infarction	Femoral arterial stenosis Intermittent claudication	Acute coronary syndrome Peripheral ischemia Femoral artery occlusion		
Fluid-related			Pleural effusion				

[a] First approval for CML in 2001, for gastrointestinal stromal tumors in 2002; year 1 is 2002; other FDA-approved indications (all in 2006): Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph1 ALL), myelodysplastic/myeloproliferative diseases, aggressive systemic mastocytosis, hypereosinophilic syndrome, and/or chronic eosinophilic leukemia, and dermatofibrosarcoma protuberans.

[b] Tumor hemorrhage included in prescribing information hemorrhage Warnings and Precautions as of 2002.

[c] Pleural effusion, ascites, and pericardial effusion included in prescribing information fluid retention Warnings and Precautions as of initial approval in 2001.

[d] First approval for CML and Ph1 ALL in 2006; year 1 is 2006.

[e] Pleural effusion, pericardial effusion, and pulmonary edema included in prescribing information fluid retention Warnings and Precautions as of initial approval in 2006.

[f] Bleeding-related events included in prescribing information Warnings and Precautions as of initial approval in 2006, although pleural hemorrhage is not specifically mentioned.

[g] PAH included in prescribing information Warnings and Precautions as of 2011.

[h] First approval for CML in 2007; year 1 is 2008.

[i] Cardiac and vascular events, including ischemic heart disease, arterial vascular occlusive events, PAOD, and ischemic cerebrovascular events, included in prescribing information Warnings and Precautions as of January 2014.

TABLE III.

Drug-Event Associations with EB05 ≥4 Based on the MGPS Analysis of Cohorts of Patients Aged 18–45, 46–64, and ≥65 Years

	EBGM	EB05	EB95	*N*
Imatinib				
18–45 yr				
Pleural effusion	5.774	4.564	7.247	51
Ascites	5.701	4.266	7.548	34
46–64 yr				
Gastric antral vascular ectasia	34.088	14.199	68.889	6
Tumor hemorrhage	18.614	11.735	28.257	15
Tumor necrosis	19.785	10.999	32.705	11
Conjunctival hemorrhage	15.363	10.266	22.113	20
Ascites	5.085	4.163	6.175	70
Pleural effusion	4.832	4.149	5.603	119
Subdural hematoma	6.187	4.131	9.935	25
≥65 yr				
Tumor necrosis	28.518	18.187	43.029	15
Gastric antral vascular ectasia	25.443	13.232	45.179	8
Tumor hemorrhage	17.385	11.05	26.288	15
Pleural effusion	5.996	5.304	6.769	209
Ascites	6.361	5.08	7.904	79
Pericardial effusion	6.773	5.015	8.89	53
Dasatinib				
18–45 yr				
Pleural effusion	27.843	21.43	35.688	42
Pericardial effusion	11.98	4.485	24.875	11
46–64 yr				
Pleural effusion	29.118	25.257	33.431	138
Pulmonary arterial hypertension	23.839	13.319	39.895	10
≥65 yr				
Pleural effusion	26.294	23.284	29.603	188
Pericardial effusion	17.915	13.115	24.01	30
Pulmonary edema	6.116	4.108	9.131	32
Nilotinib				
18–45 yr				
Coronary artery stenosis	32.652	6.641	69.714	6
46–64 yr				
Femoral arterial stenosis	60.8	30.698	110.721	7
Coronary artery stenosis	26.428	18.465	36.892	23
Peripheral arterial occlusive disease	19.292	10.566	32.015	11
Angina pectoris	12.872	9.6	16.883	36

	EBGM	EB05	EB95	*N*
Acute coronary syndrome	9.71	4.408	17.451	15
≥65 yr				
Femoral arterial stenosis	52.247	27.724	91.509	8
Peripheral arterial occlusive disease	31.001	22.696	41.547	30
Intermittent claudication	29.153	18.279	44.616	14
Coronary artery stenosis	15.25	9.355	23.586	14
Peripheral ischemia	15.454	8.172	25.828	11
Pleural effusion	7.267	5.633	9.092	67
EB05:	≥4–<8	≥8–∞		

EB05 and EB95, lower and upper limits of EBGM 90% CI; N, number of events in the FAERS database.