ACTA ONCOLOGICA
2023, VOL. 62, NO. 12, 1767–1774
https://doi.org/10.1080/0284186X.2023.2263152

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Comparison of cutaneous adverse events between second-generation tyrosine kinase inhibitors and imatinib for chronic myeloid leukemia: a systematic review and meta-analysis

Seung-Hyeon Cha[a], Kyungim Kim[b] and Yun-Kyoung Song[a]

[a]College of Pharmacy, Daegu Catholic University, Gyeongbuk, Republic of Korea; [b]College of Pharmacy, Korea University, Sejong, Republic of Korea

ABSTRACT

Background: Patients with chronic myeloid leukemia (CML) treated with tyrosine kinase inhibitors (TKIs) often experience cutaneous adverse events, such as rashes and pruritus. In this study, we aimed to compare the risks of cutaneous adverse events between imatinib- and second-generation TKI-treated patients with CML.

Material and Methods: Paired reviewers independently obtained studies from PubMed, Embase, and Cochrane Library published until 15 March 2022. The following terms were searched: (Leukemia, Myelogenous, Chronic and BCR-ABL Positive), chronic myeloid leukemia, tyrosine kinase inhibitor, TKI, imatinib, dasatinib, nilotinib, bosutinib, and radotinib. Two independent reviewers screened the results and selected articles on cutaneous adverse events. RevMan 5.4 and the Cochrane Collaboration tool were used to perform the meta-analysis and risk of bias assessment.

Results and Conclusion: Eleven trials involving 4502 patients were analyzed in this study. Patients treated with second-generation TKIs were significantly more likely to experience cutaneous adverse events than those treated with imatinib with a relative risk (RR) of 1.62 (95% confidence interval [CI], [1.25–2.09]). Except dasatinib (RR [95% CI], 1.39 [0.75–2.56]), the risk of adverse events was more with second-generation TKIs than with imatinib as follows: nilotinib (2.11 [1.53–2.90]), bosutinib (1.41 [1.07–1.86]), and radotinib (1.87 [1.33–2.63]). Rash was the most common cutaneous adverse event that was observed in 21.6% of cases across all grades, followed by pruritus (5.7%) and alopecia (4.3%). In conclusion, our findings suggest that cutaneous adverse events occur more frequently with second-generation TKIs than with imatinib. Therefore, effective management of the cutaneous outcome is necessary to achieve high patient adherence to medication and successful treatment with TKIs.

ARTICLE HISTORY
Received 16 June 2023
Accepted 20 September 2023

KEYWORDS
chronic myeloid leukemia; tyrosine kinase inhibitors; cutaneous; adverse events; meta-analysis

Background

Chronic myeloid leukemia (CML) is a hematological disease characterized by the uncontrolled proliferation of hematopoietic stem cells due to a genetic anomaly that causes the fusion of Abelson tyrosine-protein kinase 1 (ABL1) and breakpoint cluster region protein (BCR), a protein with increased tyrosine kinase activity [1]. Tyrosine kinase inhibitors (TKIs) specifically targeting this protein are the frontline treatment options for patients with chronic-phase CML that have drastically changed the prognosis from a largely lethal to a chronic disease with a 10-year survival rate >90% [2, 3]. After the emergence of resistance and intolerance to the first available TKI, imatinib, second-generation TKIs (2G-TKIs) were subsequently developed to inhibit ABL1 and/or SRC and have gained approval for clinical use in various regions worldwide: dasatinib, nilotinib, bosutinib, and radotinib and used as first-line agents in patients with newly diagnosed with CML [1–4].

Although most patients are recommended to take the drug for several years or over a lifetime owing to the risk of recurrence after TKI cessation, most studies have raised concerns regarding TKI-related adverse events (AEs) in patients [4–6]. Cutaneous AEs that may be mild-to-moderate, such as rash, psoriasis, alopecia, and xeroderma, or cause life-threatening conditions, such as the Stevens–Johnson syndrome (<1%), are the most common non-hematologic AEs reported with TKIs [7, 8]. Particularly, 7–89% of patients taking imatinib, 35% of patients taking dasatinib, and 10–28% of patients taking nilotinib were reported to experience cutaneous AEs in previous studies [9, 10]. Although these AEs are manageable and reversible after drug discontinuation, they can negatively affect the patient's quality of life (QoL) and medication adherence, potentially leading to disease relapse or drug resistance [11, 12]. Although the exact mechanisms of TKI-induced cutaneous AEs remain unclear, various TKIs may exert different effects on the skin due to differences in their molecular targets [9, 13]. Cutaneous AEs with 2 G-TKIs are

CONTACT Yun-Kyoung Song yksong@cu.ac.kr College of Pharmacy, Daegu Catholic University, 13-13 Hayang-ro, Hayang-eup, Gyeongsan-si, Gyeongbuk 38430, Republic of Korea

Supplemental data for this article can be accessed online at https://doi.org/10.1080/0284186X.2023.2263152.

more common than imatinib-induced reactions but tend to be less severe [13].

To the best of our knowledge, only a few studies have specifically focused on the incidence and relative risk (RR) of cutaneous AEs associated with different BCR::ABL1 TKIs to improve the patient safety and QoL *via* the rapid identification of AEs and discontinuation of the causative drug. Recent large-scale cohort studies analyzed the AEs of TKIs used by CP-CML patients, but cutaneous AEs were not included in the analysis [14]. Therefore, in this systematic review and meta-analysis, we aimed to compare the risks of cutaneous AEs between 2 G-TKIs and imatinib in patients with CML.

Material and methods

Search strategy and study selection

We searched the PubMed, Embase, and Cochrane Library databases for clinical studies on patients with chronic phase (CP)-CML treated with TKIs that were published until 15 March 2022. In our search, we obtained studies that compared imatinib with dasatinib, nilotinib, bosutinib, and radotinib, based on terms related to leukemia, such as leukemia, myelogenous, chronic, and BCR::ABL1-positive, chronic myeloid leukemia, tyrosine kinase inhibitors, and TKIs. Studies were included if they met the following criteria: (1) randomized controlled trials (RCTs) or cohort studies evaluating TKIs *via* one-on-one comparisons of 2 G-TKIs, such as dasatinib, nilotinib, bosutinib, and radotinib with imatinib, (2) articles focused exclusively on patients with CP-CML, excluding those in accelerated phase (AP) or blast phase (BP), (3) articles specifically describing cutaneous AEs of TKIs monotherapy, (4) studies used TKIs as first-line therapy, and (5) articles written in English. If there were multiple publications on the same trial, the most recent and informative publication was selected. Review papers, case reports, and conference papers were excluded. This study was conducted in accordance with the preferred reporting items for systematic reviews and meta-analyses guidelines [15].

Data extraction

Two investigators (S.H.C. and K.K.) independently extracted data from the published studies and supplements, and any differences were resolved *via* discussion with a third reviewer (Y.K.S.). The following data were extracted from the selected articles: (1) study information (first authors' names, study design, year of publication, study type, and population), (2) patient characteristics (number of enrolled participants, median age, and sex), (3) type of intervention (drugs used in the test and control arms, dosage, and treatment duration), and (4) data on cutaneous AEs (AEs and incidence of all grades or grade $\geq$3). Only terms listed as skin and subcutaneous tissue disorders in the common terminology criteria for adverse events (CTCAE) were considered cutaneous AEs. Severe AEs (SAEs) were defined as grade $\geq$3 AEs according to the CTCAE guidelines [16].

Risk of bias assessment

The Cochrane Collaboration tool was used to assess the risk of bias, encompassing the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of the reported result, by two independent investigators (S.H.C. and K.K.). The quality of RCTs was evaluated using the Risk of Bias 2 tool (RoB 2) [17]. For non-RCTs, methodological quality and risk of bias were evaluated using the risk of bias in non-randomized studies of interventions (ROBINS-I) assessment tool [18]. Each assessed domain was classified as low, high, or unclear depending on the level of bias. If a study had a low risk in all domains, it was classified as low risk. However, if the study had a high risk in at least one domain or had concerns in multiple domains, it was classified as high risk. Studies with concerns in at least one domain but without high risk in any domain were classified as having some concerns [17]. Bias analysis results were visualized using the risk-of-bias visualization (Robvis) tool [19]. Any conflicts or disagreements between the researchers were resolved *via* discussion and consensus with a third reviewer (Y.K.S.). Moreover, the publication bias of the included studies was assessed using funnel plots.

Statistical analyses

All statistical analyses were performed using the Review Manager 5.4 statistical software. I^2 statistic was used to assess the heterogeneity of the study. The pooled estimate was calculated based on the random-effects model when substantial heterogeneity was observed ($I^2 > 50\%$); otherwise, the fixed-effects model was applied. RR and 95% confidence interval (CI) were calculated using the Mantel–Haenszel method. Post hoc meta-analysis was also conducted for studies in which standard dosage of TKIs was used in patients with CML as first-line agents (i.e., imatinib at 400 mg/day, dasatinib at 100 mg/day, nilotinib at 600 mg/day, bosutinib at 400 mg/day, and radotinib at 600 mg/day) [2]. Statistical significance was set at $p < 0.05$, and all tests were two-sided.

Results

Study characteristics and quality assessment

As shown in Figure 1, 19,963 articles were identified during the preliminary analysis. After subsequent screening of titles and abstracts, 15,801 studies were excluded, and 308 articles were assessed for further eligibility. Eight studies were excluded from the analysis due to their lack of reporting on cutaneous AEs (Supplementary Table S1). Finally, 11 studies with 4502 patients were included in the statistical analysis.

This study included seven RCTs and four non-RCTs published between 2012 and 2021 (Table 1). All the included trials were performed in a population of patients with CML who reported new-onset skin-related AEs following TKI treatment. All studies were head-to-head in comparison with imatinib and included dasatinib ($n = 5$), nilotinib ($n = 6$), bosutinib ($n = 2$), and radotinib ($n = 1$). The eligible patients'

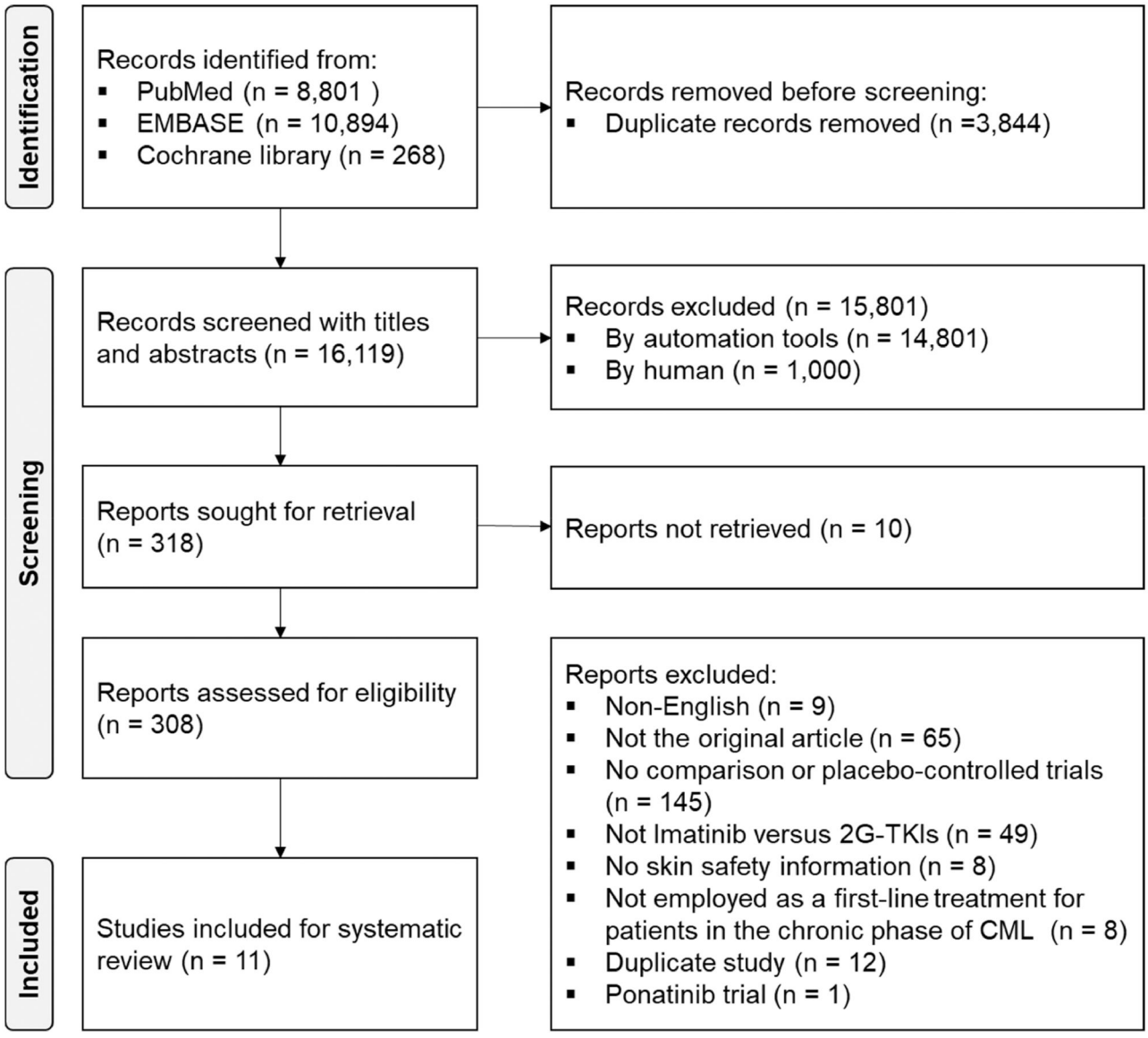


Figure 1. Flow diagram of the study selection process for systematic reviews according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.

ages ranged from 2 to 93 years and their treatment durations ranged up to 199 months. Ten trials reported cutaneous AEs, such as rash, pruritus, or alopecia, associated with TKIs, and eight studies reported severe cutaneous AEs. A quality assessment of the trials included in this systematic review is presented in Supplementary Figure S1. The quality of the included studies was considered high and acceptable.

Incidence of cutaneous AEs with TKIs in patients with CML

Table 2 shows aggregated data on the incidence of cutaneous AEs caused by all TKIs for CML. All grades of cutaneous AEs occurred in 27.7% (1248/4502) of patients treated with TKIs, but only 1.0% (47/4502) experienced severe cutaneous AEs. Among all grades of AEs, the rash was the most common (21.6%, 875/4052), followed by pruritus (5.7%, 232/4052), and alopecia (4.3%, 176/4052). Cutaneous AEs of all grades occurred most frequently in patients taking radotinib (60.0%, 96/160), whereas only 17.2% (372/2157) of the patients administered imatinib experienced these AEs. The incidence of each major cutaneous AE was relatively high with nilotinib and radotinib (rash, 35.9 and 26.3%; pruritus, 13.6 and 22.5%; and alopecia, 11.8 and 11.3%, respectively). Severe cutaneous AEs were mainly presented as a rash, with the highest incidence observed in radotinib (1.9%, 3/160), followed by nilotinib (1.4%, 13/920), and imatinib (0.9%, 18/1,902). Among the 11 studies included in this systematic review, there was a patient who discontinued TKI treatment permanently due to a rash caused by bosutinib (Supplementary Table S2).

Comparison of the RRs of cutaneous AEs between 2 G-TKIs and imatinib

As shown in Figure 2(A), all grades of cutaneous AEs occurred in 37.7% (884/2345) of patients treated with 2G-TKIs and 19.3% (416/2157) of patients treated with imatinib.

Table 1. Characteristics of studies included in the systematic review.

Study	Trial design	Drug	Daily dose, mg	No. of patients	Median age (range), years	Median treatment duration (range), months	No. of patients with cutaneous AEs, all grade (grade ≥3)			
							Total	Rash	Pruritus	Alopecia
Radich et al. [41]	RCT	Dasatinib	100	122	47 (18–90)	NR	41 (0)	41 (0)	NR	NR
		Imatinib	400	123	50 (19–89)		35 (2)	35 (2)		
Nakamae et al. [42]	RCT	Dasatinib	100	258	NR	60 (0–73)	30 (0)	30 (0)	NR	NR
		Imatinib	400	258	NR	60 (0–75)	37 (3)	37 (3)		
Ota et al. [38]	Cohort	Dasatinib	NR	95	59 (19–88)	32.2 (11.2–38.5)	1	NR	NR	NR
		Nilotinib		100	63 (15–92)	34.8 (14.8–85.5)	2			
		Imatinib		255	59 (2–93)	82.8 (13.5–143.9)	14			
Kizaki et al. [43]	Cohort	Dasatinib	100	144	56 (18–91)	60.8 (0–82.7)	24 (2)	24 (2)	NR	NR
		Nilotinib	600	169	54 (18–88)	65.3 (2.0–89.2)	27 (1)	27 (1)		
		Imatinib	400	139	58 (19–92)	77.9 (1.7–97.8)	2 (0)	2 (0)		
Bostan et al. [44]	Cross-sectional	Dasatinib	NR	30	51 (28–82)	39 (3–72)	23	12	NR	11
		Nilotinib		30	48 (28–84)	29 (6–116)	22	13		9
		Imatinib		61	57.3 (29–90)	51 (3–154)	25	10		15
Wang et al. [45]	RCT	Nilotinib	600	133	41 (18–76)	NR	47 (2)	47 (2)	NR	NR
		Imatinib	400	132	39 (19–74)		17 (1)	17 (1)		
Kantarjian et al. [46]	RCT	Nilotinib	600	279	47 (18–85)	82.8	213 (5)	110 (3)	61 (2)	42 (0)
		Nilotinib	800	277	47 (18–81)	87.5	239 (8)	125 (7)	56 (1)	58 (0)
		Imatinib	400	280	46 (18–80)	64.0	99 (5)	58 (5)	20 (0)	21 (0)
Chen et al. [39]	Cohort	Nilotinib	800	32	34 (20–61)	30 (6–62)	16	8	8	NR
		Imatinib	400	312	40 (2–79)	64 (6–199)	88	44	44	
Cortes et al. [47]	RCT	Bosutinib	500	248	48 (19–91)	13.8	50 (3)	50 (3)	NR	NR
		Imatinib	400	251	47 (18–89)		38 (2)	38 (2)		
Cortes et al. [48]	RCT	Bosutinib	400	268	53 (18–84)	14.1	53 (1)	53 (1)	NR	NR
		Imatinib	400	265		13.8	35 (3)	35 (3)		
Kwak et al. [49]	RCT	Radotinib	600	79	45 (20–75)	NR	50 (2)	28 (1)	13 (1)	9 (0)
		Radotinib	800	81	43 (18–84)		46 (5)	14 (2)	23 (3)	9 (0)
		Imatinib	400	81	45 (18–83)		26 (2)	17 (2)	7 (0)	2 (0)

NR: not reported; AEs: adverse events.
[a]Interquartile range.

Table 2. Incidence of cutaneous AEs for TKIs in patients with CML, number of AEs/total patients (%) in 11 published studies.

Grade	First-generation TKIs	Second-generation TKIs				
	Imatinib	Dasatinib	Nilotinib	Bosutinib	Radotinib	Total
All grades						
Total	372/2157 (17.2)	119/649 (18.3)	558/1020 (54.7)	103/516 (20.0)	96/160 (60.0)	1248/4502 (27.7)
Rash	293/1902 (15.4)	107/554 (19.3)	330/920 (35.9)	103/516 (20.0)	42/160 (26.3)	875/4052 (21.6)
Pruritus	71/1902 (3.7)	NR	125/920 (13.6)	NR	36/160 (22.5)	232/4052 (5.7)
Alopecia	38/1902 (2.0)	11/554 (2.0)	109/920 (11.8)	NR	18/160 (11.3)	176/4052 (4.3)
Grade ≥3						
Total	18/2157 (0.8)	2/649 (0.3)	16/1020 (1.6)	4/516 (0.8)	7/160 (4.4)	47/4502 (1.0)
Rash	18/1902 (0.9)	2/554 (0.4)	13/920 (1.4)	4/516 (0.8)	3/160 (1.9)	40/4052 (1.0)
Pruritus	0/1902 (0)	NR	3/920 (0.3)	NR	4/160 (2.5)	7/4052 (0.2)
Alopecia	0/1902 (0)	NR	0/920 (0)	NR	0/160 (0)	0/4052 (0)

AEs: adverse events; NR: not reported; TKIs: tyrosine kinase inhibitors; CML: chronic myeloid leukemia.

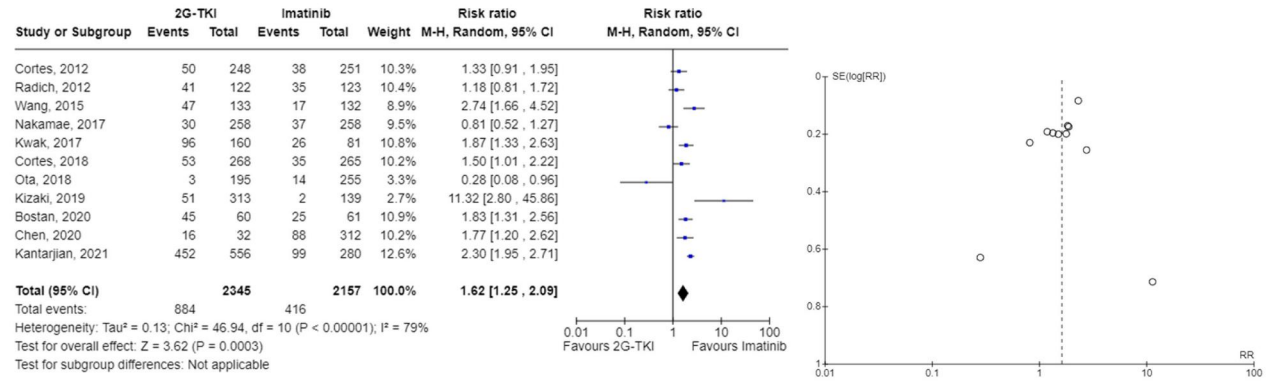
The pooled analysis of 11 studies demonstrated that 2G-TKIs caused a statistically significant increase in the risk of cutaneous AEs, with an RR (95% CI) of 1.62 (1.25–2.09). Sub-analysis of 7 RCTs also showed increased risks with 2G-TKIs compared to imatinib, with an RR (95% CI) of 1.58 (1.17–2.12). However, an insignificant difference was observed in the analysis of only four non-RCTs (Figure 3). Subgroup analysis for each 2G-TKI showed that the risk increased with nilotinib, bosutinib, and radotinib, with RR (95% CI) of 2.11 (1.53–2.90), 1.41 (1.07–1.86), and 1.87 (1.33–2.63), respectively. However, the difference was not statistically significant for dasatinib (1.39 [0.75–2.56]; Table 3 and Supplementary Figure S2).

Figure 2(B) showed that the number of patients who experienced grade ≥3 cutaneous AEs with 2G-TKIs and imatinib was 29 in 2058 patients (1.4%) and 18 in 1529 patients (1.2%), respectively. 2G-TKIs were not associated with an increased risk of severe cutaneous AEs compared with imatinib (RR [95% CI], 1.03 [0.57–1.86]). Subgroup analysis revealed that each of the 2G-TKIs did not significantly increase the risk of severe cutaneous AEs compared to imatinib (Table 3 and Supplementary Figure S3). When we conducted post hoc analysis involving the studies that used standard dosage of TKIs for these patients, the risk for all-grade AEs was increased significantly with the RR (95% CI) of 1.63 (1.20–2.22), while no difference was found for the severe AEs (0.75 [0.36–1.53); Figure S4)

Discussion

This systematic review and meta-analysis compared the severe and mild cutaneous AEs between 2G-TKIs and imatinib for the optimal treatment of patients with CML. We could vindicate that the treatment with 2G-TKIs led to a higher risk of cutaneous AEs across all grades compared to imatinib, whereas no significant increased risks were found for grade ≥3 AEs. To the best of our knowledge, this is the

(A)



(B)

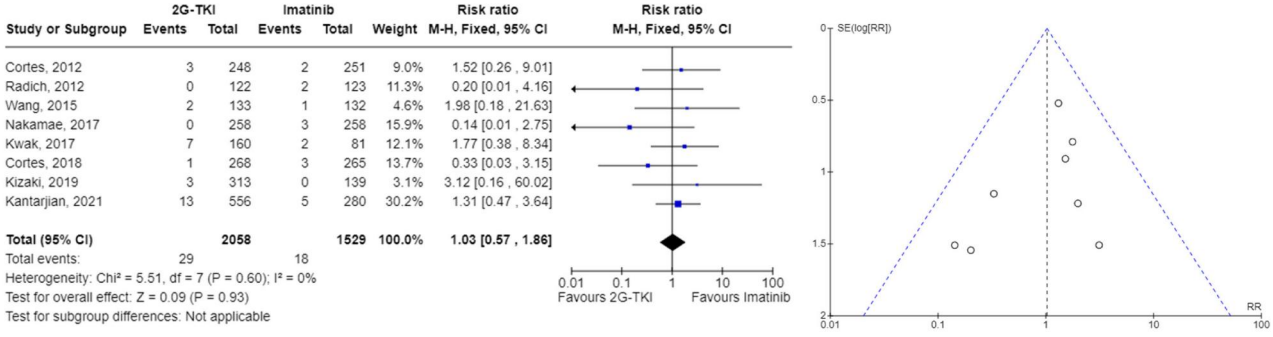
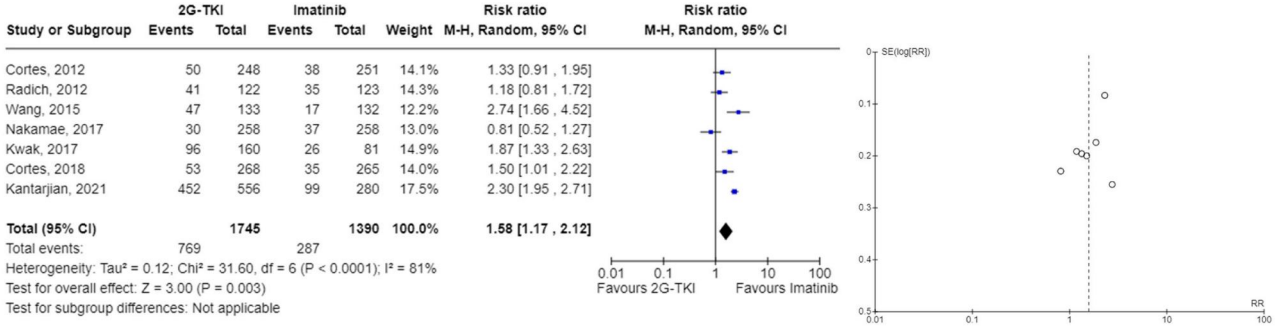


Figure 2. Forest plots of the meta-analysis for the relative risks of (A) all grades and (B) grade ≥3 cutaneous adverse events between second-generation tyrosine kinase inhibitors (2 G-TKIs) and imatinib in patients with chronic myeloid leukemia.

(A)



(B)

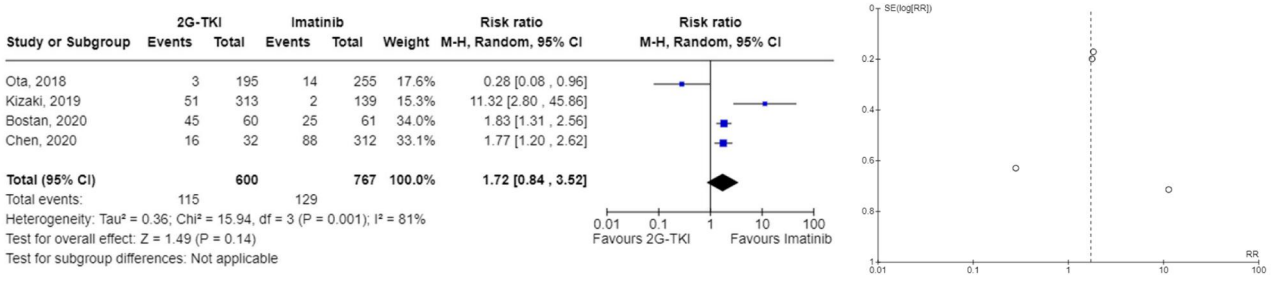


Figure 3. Forest plots of the meta-analysis for the relative risks of all-grade cutaneous adverse events between second-generation tyrosine kinase inhibitors and imatinib in (A) randomized controlled trials (RCTs) and (B) non-RCTs for patients with chronic myeloid leukemia.

first study to focus on cutaneous AEs associated with 2 G-TKIs compared to the first-generation TKI, imatinib, in patients with CML.

Cutaneous AEs with 2G-TKIs frequently contrast imatinib-induced reactions [13]. The pathophysiology of TKI-induced cutaneous AEs is not completely understood. However, it is

Table 3. Relative risks of cutaneous AEs associated with each 2G-TKI compared to imatinib in patients with CML.

2G-TKIs	RR (95% confidence interval)	I^2 statistic, %	*p*-value
All grades			
Dasatinib	1.39 (0.75–2.56)	81	0.29
Nilotinib	2.11 (1.53–2.90)	66	<0.001
Bosutinib	1.41 (1.07–1.86)	0	0.01
Radotinib	1.87 (1.33–2.63)	NA	<0.001
Grade ≥3			
Dasatinib	0.53 (0.14–1.96)	37	0.34
Nilotinib	1.46 (0.59–3.60)	0	0.41
Bosutinib	0.80 (0.22–2.96)	8	0.74
Radotinib	1.77 (0.38–8.34)	NA	0.47

AEs: adverse events; NA: not applicable; 2G-TKIs: second-generation tyrosine kinase inhibitors; CML: chronic myeloid leukemia; RR: relative risk.

reasonable to assume that these AEs are mediated by tyrosine kinase signaling rather than by immunological or allergic mechanisms [20]. The higher risk of cutaneous AEs with 2 G-TKIs than with imatinib may be due to differences in their mechanisms of action. TKIs used for the treatment of CML primarily target BCR::ABL1; however, their inhibitory potency and range of action on other kinases, including the platelet-derived growth factor receptor (PDGFR) and stem cell factor receptor (c-Kit), vary. These properties result in some AEs that are common to all TKIs and others that are specific to each molecule [21, 22]. 2G-TKIs, such as nilotinib and dasatinib, block collagen synthesis and the formation of dermal matrix by inhibiting the tyrosine kinase activities of BCR::ABL1, PDGFR, and transforming growth factor-beta [23–25]. As most of these kinases are active in the skin, skin vessels with loosened connective tissue may be recruited by inflammatory mediators and metabolites, leading to cutaneous AEs, such as rashes [24].

Although dasatinib are robust multitargeted inhibitor, boasting a wider spectrum of targets compared to imatinib or nilotinib, the risk of cutaneous AEs for dasatinib was not significantly different from that of imatinib [26]. Dasatinib particularly excels as a small-molecule inhibitor, effectively targeting various tyrosine kinases, including those within the Src-family kinase (SFK), Btk, and Syk [27]. There has been a long-standing interest in the correlation between SFK and skin reactions. Cutaneous inflammation, presenting various inflammatory symptoms on the skin's surface, might involve these SRC kinases, playing a central role in signaling pathways associated with inflammatory cells [27]. In a murine model, the local application of dasatinib demonstrated efficacy for allergic contact dermatitis [28]. Hence, it is conceivable that dasatinib, through its inhibition of SFK, may have manifested different proclivities compared to the other 2G-TKIs such as nilotinib and radotinib.

Although 2G-TKIs have been shown to have better molecular responses than imatinib overall, a greater burden of common AEs, such as skin changes, itching, and nausea, can impair the patient's QoL, resulting in dose reduction or even discontinuation, which may negatively affect treatment outcomes [29]. The relationship between multitargeted kinase inhibitors and cutaneous AEs is complex and may involve multiple mechanisms, thus further research is needed to fully understand this relationship [20].

Hair loss was a representative cutaneous AE observed in this study. The association between 2 G-TKIs and alopecia may be explained by the role of PDGFR in hair follicles. The anti-PDGF antibody induces the transition from hair growth to catagen; therefore, the inhibition of PDGFR may cause hair loss [30]. In this study, no hair loss was observed after bosutinib treatment. On the approved labels of TKIs, there were no reports of bosunitib-related alopecia, whereas for other TKIs, approximately 6–15% of the patients reported hair loss as a drug side effect [7]. Bosutinib does not inhibit PDGFR alpha and beta, which are inhibited by imatinib, dasatinib, and nilotinib [1] Further research is needed to determine why hair loss is only observed with imatinib, dasatinib, and nilotinib, but not with bosutinib.

This study showed that 2 G-TKIs were not associated with an increased risk of severe AEs compared with imatinib. A previous study also reported that cutaneous AEs caused by 2G-TKIs tend to be less severe [13]. So far, the most severe cutaneous adverse reactions (SCARs), such as the Steven–Johnson syndrome, toxic epidermal necrolysis, and drug reaction with eosinophilia, and systemic symptoms have been reported for imatinib [1, 31–33]. However, only a few studies reporting any cases of SCARs were included here because we only selected studies that directly compared the safety of imatinib and 2 G-TKIs. Although most cutaneous AEs associated with TKIs are not life-threatening, SCARs can occur with TKIs because of their high morbidity and mortality [34]. Therefore, the mechanism by which BCR::ABL1 TKIs are associated with cutaneous AEs, including severe scars, and the manner in which these AEs affect treatment outcomes need to be investigated *via* a large-scale retrospective study in the future.

The rapid-onset AEs including hepatotoxicity and gastrointestinal toxicity might lead to dose adjustments or even discontinuation of the medication, which in turn would mask the occurrence of cutaneous AEs [2]. Nevertheless, it is evident from our analysis of the 11 studies that skin toxicity remains a prevalent and noteworthy AE especially associated with 2G-TKIs. Consequently, the evaluation of skin adverse reactions holds paramount clinical significance.

In addition to BCR::ABL1 TKIs, a variety of TKIs have been utilized for the treatment of different types of cancer, including a number of cutaneous AEs. A meta-analysis reported a significant increase in the risk of rash, dry skin, and pruritus for the epidermal growth factor receptor TKIs (i.e., erlotinib, gefitinib, dacomitinib, afatinib, and osimertinib) used in patients with non-small cell lung cancer [35]. Vascular endothelial growth factor receptor (VEGFR) TKIs such as cabozantinib, pazopanib, sorafenib, sunitinib, and tivozanib have been employed in the treatment of metastatic renal cell carcinoma (mRCC) [36]. An analysis of the spontaneous AE reports showed that cutaneous AEs ranked as the second most commonly reported AEs in patients receiving VEGFR TKIs [37]. The occurrence of cutaneous toxicity across TKIs is a shared manifestation frequently observed as a notable AE. To further enhance the understanding of TKI-induced cutaneous toxicity and its associated risk factors, additional research is warranted.

Our study has some limitations. In the case of radotinib, only one study met the inclusion criteria, and information on AEs of grade ≥3 was lacking in the subgroup analysis. Due to specific research objectives, only clinical studies directly comparing imatinib and 2 G-TKIs were included, leading to the omission of some studies on TKI-related cutaneous AEs. There was also a lack of reports on cutaneous AEs in many studies, which may have introduced bias into the analysis as a result of their exclusion. Moreover, only English-language studies were analyzed, which may not represent all the evidence on AEs in the literature. In two trials included in this study, some of the patients administered imatinib were under 20 [38, 39]. It was reported that the incidence rate and clinical manifestation of cutaneous AEs associated with targeted anticancer agents in children were similar to those in adults [40]. Therefore, the inclusion of pediatric patients might have a minimal impact on the overall study results.

Conclusion

This systematic review and meta-analysis compared the risk of skin-related AEs between 2 G-TKIs and imatinib in patients with CML. For all grades of AEs, 2G-TKIs exhibited a higher risk of skin-related AEs than imatinib. However, no significant differences were observed between grades 3 and 4 skin-related AEs. Therefore, effective management of cutaneous AEs is necessary to achieve high patient adherence to medication and successful treatment with TKIs.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (NRF-2022R1C1C1011730).

Data availability statement

The data that support the findings of this study are available from the corresponding author, Y.K.S., upon reasonable request.

References

[1] Cortes J, Pavlovsky C, Saußele S. Chronic myeloid leukaemia. Lancet. 2021;398(10314):1914–1926. doi:10.1016/S0140-6736(21)01204-6.

[2] Radich JP, Deininger M, Abboud CN, et al. Chronic myeloid leukemia, version 1.2019, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2018;16(9):1108–1135. doi:10.6004/jnccn.2018.0071.

[3] Osman AEG, Deininger MW. Chronic myeloid leukemia: modern therapies, current challenges and future directions. Blood Rev. 2021;49:100825. doi:10.1016/j.blre.2021.100825.

[4] Hochhaus A, Baccarani M, Silver RT, et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. Leukemia. 2020;34(4):966–984. doi:10.1038/s41375-020-0776-2.

[5] Lipton JH, Brümmendorf TH, Gambacorti-Passerini C, et al. Long-term safety review of tyrosine kinase inhibitors in chronic myeloid leukemia—What to look for when treatment-free remission is not an option. Blood Rev. 2022;56:100968. doi:10.1016/j.blre.2022.100968.

[6] Pinilla-Ibarz J, Sweet K, Emole J, et al. Long-term BCR-ABL1 tyrosine kinase inhibitor therapy in chronic myeloid leukemia. Anticancer Res. 2015;35(12):6355–6364.

[7] Lexi-Drugs Online [Internet]. Hudson (OH): Lexicomp, Inc.; [cited 2022 Sep 23]. Available from: http://online.lexi.com.

[8] Marzano AV, Borghi A, Cugno M. Adverse drug reactions and organ damage: the skin. Eur J Intern Med. 2016;28:17–24. doi:10.1016/j.ejim.2015.11.017.

[9] Amitay-Laish I, Stemmer SM, Lacouture ME. Adverse cutaneous reactions secondary to tyrosine kinase inhibitors including imatinib mesylate, nilotinib, and dasatinib. Dermatol Ther. 2011;24(4):386–395. doi:10.1111/j.1529-8019.2011.01431.x.

[10] Lupu I, Voiculescu N, Bacalbasa N, et al. Cutaneous complications of molecular targeted therapy used in oncology. J Med Life. 2016;9(1):19–25.

[11] Dreno B, Amici JM, Demessant-Flavigny AL, et al. The impact of acne, atopic dermatitis, skin toxicities and scars on quality of life and the importance of a holistic treatment approach. Clin Cosmet Investig Dermatol. 2021;14:623–632. doi:10.2147/CCID.S315846.

[12] Radich JP. Treatment milestones in chronic myelogenous leukemia: stay the course or change therapy? J Natl Compr Canc Netw. 2015;13(5 Suppl):697–699. doi:10.6004/jnccn.2015.0207.

[13] Delgado L, Giraudier S, Ortonne N, et al. Adverse cutaneous reactions to the new second-generation tyrosine kinase inhibitors (dasatinib, nilotinib) in chronic myeloid leukemia. J Am Acad Dermatol. 2013;69(5):839–840. doi:10.1016/j.jaad.2013.07.025.

[14] Dahlén T, Edgren G, Ljungman P, et al. Adverse outcomes in chronic myeloid leukemia patients treated with tyrosine kinase inhibitors: follow-up of patients diagnosed 2002-2017 in a complete coverage and nationwide agnostic register study. Am J Hematol. 2022;97(4):421–430. doi:10.1002/ajh.26463.

[15] Page MJ, Moher D, Bossuyt PM, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ. 2021;372:n160. doi:10.1136/bmj.n160.

[16] U.S. Department of Health and Human Services [INTERNET]. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.; [cited 2022 Mar 21]. Available from: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_60.

[17] Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898. doi:10.1136/bmj.l4898.

[18] Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919. doi:10.1136/bmj.i4919.

[19] McGuinness LA, Higgins JPT. Risk-of-bias visualization (robvis): an R package and shiny web app for visualizing risk-of-bias assessments. Res Synth Methods. 2021;12(1):55–61. doi:10.1002/jrsm.1411.

[20] Del Pozzo-Magana BR, Liy-Wong C. Drugs and the skin: a concise review of cutaneous adverse drug reactions. Br J Clin Pharmacol. 2022. doi:10.1111/bcp.15490.

[21] Coleman EL, Olamiju B, Leventhal JS. Potentially lifethreatening severe cutaneous adverse reactions associated with tyrosine kinase inhibitors (review). Oncol Rep. 2021;45(3):891–898. doi:10.3892/or.2020.7911.

[22] Salih J, Hilpert J, Placke T, et al. The BCR/ABL-inhibitors imatinib, nilotinib and dasatinib differentially affect NK cell reactivity. Int J Cancer. 2010;127(9):2119–2128. doi:10.1002/ijc.25233.

[23] Akhmetshina A, Dees C, Pileckyte M, et al. Dual inhibition of c-abl and PDGF receptor signaling by dasatinib and nilotinib for the treatment of dermal fibrosis. FASEB J. 2008;22(7):2214–2222. doi:10.1096/fj.07-105627.

[24] Jung YS, Kim M, Lee JH, et al. Acneiform eruptions caused by various second-generation tyrosine kinase inhibitors in patients

with chronic myeloid leukaemia. Br J Dermatol. 2016;174(2):456–458. doi:10.1111/bjd.14185.
[25] Hsiao LT, Chung HM, Lin JT, et al. Stevens-Johnson syndrome after treatment with STI571: a case report. Br J Haematol. 2002;117(3):620–622. doi:10.1046/j.1365-2141.2002.03499.x.
[26] Lee H, Basso IN, Kim DDH. Target spectrum of the BCR-ABL tyrosine kinase inhibitors in chronic myeloid leukemia. Int J Hematol. 2021;113(5):632–641. doi:10.1007/s12185-021-03126-6.
[27] Szilveszter KP, Németh T, Mócsai A. Tyrosine kinases in autoimmune and inflammatory skin diseases. Front Immunol. 2019;10:1862. doi:10.3389/fimmu.2019.01862.
[28] Jung SH, Sun X, Ryu WS, et al. Topical administration of the pan-src kinase inhibitors, dasatinib and LCB 03-0110, prevents allergic contact dermatitis in mice. Br J Dermatol. 2013;168(1):112–119. doi:10.1111/bjd.12069.
[29] Mahapatra M, Mishra P, Kumar R. Imatinib-induced Stevens-Johnson syndrome: recurrence after re-challenge with a lower dose. Ann Hematol. 2007;86(7):537–538. doi:10.1007/s00277-007-0265-y.
[30] Hansen T, Little AJ, Miller JJ, et al. A case of inflammatory non-scarring alopecia associated with the tyrosine kinase inhibitor nilotinib. JAMA Dermatol. 2013;149(3):330–332. doi:10.1001/jamadermatol.2013.1375.
[31] Douxfils J, Haguet H, Mullier F, et al. Association between BCR-ABL tyrosine kinase inhibitors for chronic myeloid leukemia and cardiovascular events, major molecular response, and overall survival: a systematic review and meta-analysis. JAMA Oncol. 2016;2(5):625–632. doi:10.1001/jamaoncol.2015.5932.
[32] Pan P, Wang L, Wang Y, et al. Systematic review and Meta-Analysis of -New-Generation tyrosine kinase inhibitors versus imatinib for newly diagnosed chronic myeloid leukemia. Acta Haematol. 2020;143(3):204–216. doi:10.1159/000501537.
[33] Bauer S, Buchanan S, Ryan I. Tyrosine kinase inhibitors for the treatment of Chronic-Phase chronic myeloid leukemia: long-Term patient care and management. J Adv Pract Oncol. 2016;7(1):42–54.
[34] Drucker AM, Wu S, Busam KJ, et al. Rash with the multitargeted kinase inhibitors nilotinib and dasatinib: meta-analysis and clinical characterization. Eur J Haematol. 2013;90(2):142–150. doi:10.1111/ejh.12052.
[35] Sun W, Li J. Skin toxicities with epidermal growth factor receptor tyrosine kinase inhibitors in cancer patients: a meta-analysis of randomized controlled trials. Cancer Invest. 2019;37(6):253–264. doi:10.1080/07357907.2019.1634089.
[36] Manz KM, Fenchel K, Eilers A, et al. Efficacy and safety of approved first-line tyrosine kinase inhibitor treatments in metastatic renal cell carcinoma: a network meta-analysis. Adv Ther. 2020;37(2):730–744. doi:10.1007/s12325-019-01167-2.
[37] Xue Y, Feng S, Li G, et al. Safety profile of vascular endothelial growth factor receptor tyrosine-kinase inhibitors in pediatrics: a pharmacovigilance disproportionality analysis. Front Pharmacol. 2023;14:1160117. doi:10.3389/fphar.2023.1160117.
[38] Ota S, Matsukawa T, Yamamoto S, et al. Severe adverse events by tyrosine kinase inhibitors decrease survival rates in patients with newly diagnosed chronic-phase chronic myeloid leukemia. Eur J Haematol. 2018;101(1):95–105. doi:10.1111/ejh.13081.
[39] Chen Y, Yin H, Chen L, et al. Feasibility study of switching to nilotinib after first-line imatinib in the chronic phase of chronic myeloid leukemia. Clin Lymphoma Myeloma Leuk. 2020;20(2):e43–e49. doi:10.1016/j.clml.2019.12.001.
[40] Belum VR, Washington C, Pratilas CA, et al. Dermatologic adverse events in pediatric patients receiving targeted anticancer therapies: a pooled analysis. Pediatr Blood Cancer. 2015;62(5):798–806. doi:10.1002/pbc.25429.
[41] Radich JP, Kopecky KJ, Appelbaum FR, et al. A randomized trial of dasatinib 100 mg versus imatinib 400 mg in newly diagnosed chronic-phase chronic myeloid leukemia. Blood. 2012;120(19):3898–3905. doi:10.1182/blood-2012-02-410688.
[42] Nakamae H, Fujisawa S, Ogura M, et al. Dasatinib versus imatinib in japanese patients with newly diagnosed chronic phase chronic myeloid leukemia: a subanalysis of the DASISION 5-year final report. Int J Hematol. 2017;105(6):792–804. doi:10.1007/s12185-017-2208-2.
[43] Kizaki M, Takahashi N, Iriyama N, et al. Efficacy and safety of tyrosine kinase inhibitors for newly diagnosed chronic-phase chronic myeloid leukemia over a 5-year period: results from the Japanese registry obtained by the new TARGET system. Int J Hematol. 2019;109(4):426–439. doi:10.1007/s12185-019-02613-1.
[44] Bostan H, Toptas T, Tanrikulu FP, et al. Quality of life and symptom burden with first- and second-generation tyrosine kinase inhibitors in patients with chronic-phase chronic myeloid leukemia. Clin Lymphoma Myeloma Leuk. 2020;20(12):836–842. doi:10.1016/j.clml.2020.08.009.
[45] Wang J, Shen ZX, Saglio G, et al. Phase 3 study of nilotinib vs imatinib in chinese patients with newly diagnosed chronic myeloid leukemia in chronic phase: ENESTchina. Blood. 2015;125(18):2771–2778. doi:10.1182/blood-2014-09-601674.
[46] Kantarjian HM, Hughes TP, Larson RA, et al. Long-term outcomes with frontline nilotinib versus imatinib in newly diagnosed chronic myeloid leukemia in chronic phase: ENESTnd 10-year analysis. Leukemia. 2021;35(2):440–453. doi:10.1038/s41375-020-01111-2.
[47] Cortes JE, Kim DW, Kantarjian HM, et al. Bosutinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: results from the BELA trial. J Clin Oncol. 2012;30(28):3486–3492. doi:10.1200/JCO.2011.38.7522.
[48] Cortes JE, Gambacorti-Passerini C, Deininger MW, et al. Bosutinib versus imatinib for newly diagnosed chronic myeloid leukemia: results from the randomized BFORE trial. J Clin Oncol. 2018;36(3):231–237. doi:10.1200/JCO.2017.74.7162.
[49] Kwak JY, Kim SH, Oh SJ, et al. Phase III clinical trial (RERISE study) results of efficacy and safety of radotinib compared with imatinib in newly diagnosed chronic phase chronic myeloid leukemia. Clin Cancer Res. 2017;23(23):7180–7188. doi:10.1158/1078-0432.CCR-17-0957.