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Clinical efficacy and safety of flumatinib in newly diagnosed chronic myelogenous leukemia

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The present study aimed to investigate the efficacy and safety of flumatinib in patients newly diagnosed with chronic myeloid leukemia in the chronic phase (CML-CP). A retrospective study was conducted using five patients newly diagnosed with CML-CP who received flumatinib (600 mg/day). Results of the present study demonstrated that all five patients with CML-CP that were treated with flumatinib achieved the optimal molecular response within three months. In addition, two patients experienced major molecular response (MMR), and one patient acquired undetectable molecular residual disease, which was maintained for more than one year. Moreover, one patient exhibited grade 3 hematological toxicity, two patients exhibited transient diarrhea, one patient exhibited vomiting and one patient exhibited a rash with pruritus. No second-generation tyrosine kinase inhibitor-specific adverse cardiovascular events occurred in any patients. In conclusion, flumatinib exhibits high efficacy and high early molecular response rate in patients newly diagnosed with CML-CP. The majority of patients obtained MMR within three months, and the adverse reactions experienced were mild and tolerable.

1. Introduction

Chronic myeloid leukemia (CML) is a myeloid malignancy formed by the clonal proliferation of bone marrow hematopoietic stem cells, accounting for ~15% of leukemia cases in adults (Siegel et al. 2021). The use of breakpoint cluster region (BCR)-ABL1 tyrosine kinase inhibitor (TKI) has greatly improved the prognosis of patients with CML, and has become the first-line treatment strategy for patients newly diagnosed with chronic phase CML (CML-CP) (Cortes et al. 2021). Notably, the use of TKIs has also improved disease outcomes, aiding the formation of a manageable and potentially curable disease (Cortes et al. 2021). Flumatinib is a second-generation TKI (2G-TKI) developed in China. In a multi-center, randomized, open phase III clinical trial using imatinib as a positive control, flumatinib was used to treat patients newly diagnosed with CML-CP. Notably, results using flumatinib demonstrated higher rates of cytogenetic and molecular responses than when using imatinib. Furthermore, patients treated with flumatinib exhibited a lower incidence of adverse events (AEs) (Zhang et al. 2021). Therefore, China Food and Drug Administration approved flumatinib as the first-line treatment in patients newly diagnosed with CML-CP. At present, there are no real-world reports on patients with CML-CP using flumatinib. The present study aimed to investigate the efficacy and safety of flumatinib in five patients newly diagnosed with CML-CP in our department.

2. Investigations and results

2.1. Patient characteristics

As shown in Table 1, five patients newly diagnosed with CML-CP that were either BCR-ABL1 positive or displayed a Philadelphia (Ph) chromosome were enrolled in the present study. Three and two patients were male and female, respectively, with a median age of 55 years (range, 43-72 years) and a median body weight of 59.4 kg (range, 48-73 kg). Prior to TKI treatment, four patients exhibited a peripheral white blood cell (WBC) count >50×10^9/l, whereas three patients exhibited anemia and two patients exhibited a platelet count >450×10^9/l. All five patients displayed increased proportions of basophils. The spleens were enlarged in four out of five patients, whereas the remaining patient exhibited a healthy spleen. The stratification results according to the Sokal index were as follows: One case at low risk, two cases at medium risk, and two cases at high risk. The chromosome karyotype of four patients was as follows: t(9;22)(q34;q11.2). One patient exhibited a poor cell culture with no mitotic phase. The BCR-ABL1 fusion gene type results were as follows: A total of four patients were positive for P210 expression, and one patient was positive for both P210 and P190 expression. Hydroxyurea was administered to reduce the number of leukocytes in four patients. It was also administered in the remaining patient and was accompanied with cell isolation and collection therapy.

Table 1: Clinical characteristics of the examined patients

Case	Sex	Age, years	Body weight, kg	WBC, 10^9/l	Hb, g/l	Plt, 10^9/l	Basophils, %	Spleen size, cm x cm	Sokal score	Karyotype	BCR-ABL type	ABL mutation	Hydroxyurea treatment
1	F	46	48	25.58	123	343	6.3	128x29	Low	46,XX,t(9;22)(q34;q11.2)[10]	p210, p190	NA	No
2	M	43	73	525.01	60	392	3.9	207x86	High	46,XY,t(9;22)(q34;q11.2)[3]/46,XY[2]	p210	No	Yes + cell isolation
3	F	60	59.4	133.30	98	305	1.3	185x59	Medium	NA	p210	NA	Yes
4	M	55	61	88.00	99	453	1.7	192x82	High	46,XY,t(9;22)(q34;q11.2)[20]	p210	NA	Yes
5	M	72	51.5	62.26	122	492	8.6	145x49	Medium	46,XY,t(9;22)(q34;q11.2)[20]	p210	No	Yes

F, female; M, male; WBC, white blood cell; Hb, hemoglobin; Plt, platelet; NA, not available.

Table 2: Changes in the levels of WBC, Plt, and in the proportion of basophils at diagnosis and at 3 months

Case	WBC, 10^9/l		Plt, 10^9/l		Basophils, %	
	At diagnosis	3 months	At diagnosis	3 months	At diagnosis	3 months
1	25.58	5.65	343	171	6.3	0.8
2	525.01	8.23	392	134	3.9	0.3
3	133.30	6.1	305	288	1.3	0.4
4	88.00	4.36	453	80	1.7	0.1
5	62.26	3.68	492	78	8.6	0.7

WBC, white blood cell; Plt, platelet.

Table 3: Changes in P210 levels

Case	P210 at diagnosis, IS	P210, 3 months	P210, 6 months	P210, 12 months	P210, 18 months	P210, 24 months
1	83.8380%	0	0.0080%	0	0	0
2	65.1724%	0.0431%	0.0133%	0.0073%	NA	NA
3	111.4815%	0.3541%	0.1194%	NA	NA	NA
4	239.4483%	0.7269%	0.1560%	NA	NA	NA
5	40.9684%	0.9733%	0.5700%	NA	NA	NA

IS, international scale; NA, not available.

2.2. Hematological response evaluation

Routine blood tests, peripheral blood smears, and physical examinations were performed three months following flumatinib treatment to assess hematological responses. As shown in Table 2, all five patients demonstrated a WBC count $<10\times10^9$/l; their platelet count was $<450\times10^9$/l, and the proportion of basophils was <1% following three months of evaluation. All patients displayed absence of myeloid immature cells in the peripheral blood and exhibited no palpable splenomegaly. All five patients achieved complete hematological response [CHR (Wang et al. 2020)] at the 3-month period.

2.3. Molecular response evaluation

The results of the present study demonstrated that flumatinib treatment lasted for more than three months in all five patients (Table 3). The fusion gene test was performed in the third month of treatment. All patients achieved optimal response (BCR-ABL^{IS}<1% in all five patients. IS, international scale), and two patients attained the major molecular response (MMR, BCR-ABL^{IS}≤0.1%). Case 1 attained an undetectable molecular residual disease (UMRD) at 12 months and retained the therapeutic benefit of TKI for >1 year. Case 2 attained an MR4.0 (defined as BCR-ABL^{IS}≤0.01%) at 12 months. In addition, case 1 was positive for P190 expression at initial diagnosis; this expression pattern was maintained after turning negative at 3 months.

2.4. Cytogenetic response evaluation

Chromosome karyotype assessment was performed every three months in all five patients. As shown in Table 4, both cases 1 and 2 achieved complete cytogenetic responses (CCyR, defined as 0% Ph+ metaphase cells) at three months and maintained the optimal efficacy. Case 4 attained partial cytogenetic response (defined as 1-35% Ph+ metaphase cells) at three months and achieved CCyR at six months. Case 5 exhibited 20 Ph+ metaphase cells at initial diagnosis; these cells had turned negative by six months.

2.5. Adverse reactions

In the present study, certain hematological adverse reactions occurred, including Common Terminology Criteria for Adverse Events (CTCAE) grade 3 thrombocytopenia in case 4 (at 1 month) and grade 1 thrombocytopenia in case 5. Biochemical abnormalities including alanine aminotransferase elevation (grade 1) and aspartate transaminase elevation (grade 1) were noted in case 5. No other biochemical abnormalities were observed in other patients. Adverse reactions associated with quality-of-life included transient diarrhea, which occurred in two patients, vomiting, which occurred in one patient, and rash with pruritus, which occurred in one patient. Notably, no adverse reactions, such as edema and muscle/joint pain were observed. TKI-specific cardiovascular AEs included QT interval prolongation, pulmonary hypertension, and pleural effusion. None of the five patients presented with these AEs. The AEs were effectively controlled following symptomatic treatment and no patient received reduced dosage or discontinued the treatment due to AEs.

2.6. Follow-up

The median follow-up time of flumatinib treatment was twelve months in the group comprising five patients newly diagnosed with CML-CP (range, 6-24 months). Moreover, the median progression-free survival (PFS) and overall survival (OS) time periods were not reached; no mortalities or loss of follow-up were noted.

3. Discussion

At present, TKIs are the primary choice for the treatment of CML-CP. The first-line TKIs include imatinib (first-generation TKI), nilotinib, dasatinib, and bosutinib [second generation (2G)-TKI] (Hochhaus et al. 2020; Jabbour et al. 2020). The 2G-TKIs used as a first-line treatment exhibit higher rates of response and faster and deeper responses compared with those of imatinib, which may reduce disease progression and significantly improve

Table 4: Changes in karyotype features

Case	Karyotype, at diagnosis	Karyotype, 3 months	Karyotype, 6 months	Karyotype, 12 months	Karyotype, 18 months	Karyotype, 24 months
1	46,XX,t(9;22)(q34;q11.2)[10]	46,XX[20]	46,XX[20]	46,XX[20]	46,XX[20]	46,XX[20]
2	46,XY,t(9;22)(q34;q11.2)[3]/46,XY[2]	46,XY[20]	46,XY[20]	46,XY[20]	NA	NA
3	NA	NA	NA	NA	NA	NA
4	46,XY,t(9;22)(q34;q11.2)[20]	46,XY,t(9;22)(q34;q11.2)[1]/46,XY[19]	46,XY[20]	NA	NA	NA
5	46,XY,t(9;22)(q34;q11.2)[20]	45,X,-Y[4]/46,XY[16]	46,XY[13]	NA	NA	NA

NA, not available.

PFS in patients with moderate- and high-risk CML-CP (Cortes et al. 2016, 2018; Hochhaus et al. 2016).

Flumatinib mesylate is a novel orally available small-molecule TKI, which has demonstrated a stronger inhibitory potency for the activity of BCR-ABL1 kinase, and a lower inhibitory potency for the activity of platelet derived growth factor receptor β and c-KIT kinase compared with those of imatinib. Moreover, treatment with flumatinib exerted no effect on the phosphorylation of EGFR, VEGFR, c-Src, or the HER2 kinase (Luo et al. 2010). The results of a previous study demonstrated that flumatinib exerted significant inhibitory effects on CML cell lines expressing the wild-type BCR-ABL1 kinase and numerous mutant BCR-ABL1 kinases, which were resistant to imatinib, with the exception of those with the T315I mutation (Luo et al. 2010; Qiu et al. 2008; Yang et al. 2019). In patients with Ph+ acute lymphoblastic leukemia (Ph+ ALL), flumatinib combined with multidrug chemotherapy demonstrated clinical efficacy and was well tolerated, highlighting its potential use as an alternative TKI for patients with Ph+ ALL (Mi et al. 2021). Moreover, flumatinib treatment significantly reduced the expression levels of C-Myc, hypoxia inducible factor-1α, and vascular endothelial growth factor in the multiple myeloma (MM) cell line U266 (Chang et al. 2013). In addition, using activating loop mutations in gastrointestinal stromal tumors (GISTs), flumatinib effectively bypassed the drug resistance of certain KIT mutants (Zhao et al. 2014). These findings suggested that flumatinib may act as a promising therapeutic agent in the treatment of MM and GISTs.

Flumatinib was successfully used in the first-line treatment of patients newly diagnosed with CML-CP in clinical trials, which resulted to its recommendation by the Chinese guidelines as the first-line treatment for patients with CML-CP (Wang et al. 2020). To date, the use of flumatinib in patients with CML-CP has not been reported. The present study investigated five patients newly diagnosed with CML-CP, who were treated with flumatinib as a first-line therapy. The molecular response was assessed at baseline and every three months following treatment, via the detection of the BCR-ABL1 mRNA expression levels. All five patients achieved optimal response at three months of treatment and two patients attained an MMR. Only one patient attained an MR4.0 at twelve months, and one patient retained UMRD for more than one year. With the significant extension of patient survival, an increasing number of studies have focused on the impact of adverse reactions following long-term TKI treatment, including quality-of-life adverse reactions and treatment-free remission (TFR), which has become the long-term goal of CML treatment. According to drug withdrawal experiments reported recently, obtaining a molecular reaction that lasts >MR4.0/MR4.5 and >2 years is the prerequisite for drug withdrawal tests (Wang et al. 2020). In the present study, case 1 retained UMRD for more than one year, and was expected to initiate drug withdrawal early in order to reach TFR.

The cytogenetic efficacy was also evaluated in the present study. Case 3 was not evaluated for lack of metaphases at initial diagnosis, which was mainly due to inadequate bone marrow samples and poor cytogenetic culture. The loss of chromosome Y in the bone marrow cells is frequently noted in healthy elderly individuals, which could be detected in both normal and malignant cells of patients with CML (Kirk et al. 1994). Loss of the Y chromosome in Ph+ cells predicts a poor response to imatinib therapy (Lippert et al. 2010). In the present study, case 5 obtained the Y chromosome at three months and turned negative at six months by karyotype examination. This probably was related to the administration of the 2G-TKI flumatinib. In the present study, all five patients achieved the best response within three months, and the effective rate was higher than that noted in the clinical trials (Zhang et al. 2021). This may be associated with the small number of patients enrolled and the statistical deviation. Therefore, further verification is required by the use of a larger sample size.

The AEs of TKI therapy include hematological toxicity, quality-of-life-associated AEs, and TKI-specific cardiovascular adverse reactions. The comparisons between non-head-to-head studies demonstrated that treatment with flumatinib was safer than the existing 2G-TKIs and the incidence of hematological toxicity was similar to that of imatinib and nilotinib, but significantly lower than that of dasatinib. Flumatinib was associated with a lower incidence of quality-of-life adverse reactions, notably digestive tract adverse reactions and rashes. Flumatinib treatment did not lead to cardiovascular events specific to 2G-TKIs (Hochhaus et al. 2016; Nakamae et al. 2017; Patel et al. 2017). In the present study, the incidence of grade 3 or higher hematological toxicity and quality-of-life-associated adverse reactions was consistent with that reported by previous studies (Zhang et al. 2021). The lower incidence of grade 1 or 2 hematological abnormality and biochemical abnormality were recorded mainly due to the fact that patients who received flumatinib at home did not monitor their blood biomarker and biochemical indicator levels weekly. By contrast, they were only tested every three months during their visit to the hospital for efficacy evaluation. No 2G-TKI-specific adverse cardiovascular events were noted and no notable intolerance to treatment was present in any of the patients examined. A previous study demonstrated that cytochrome P450 (CYP) 3A4 inhibitors could increase the plasma concentration of flumatinib, which indicated that lower doses of flumatinib should be considered (Chen et al. 2020). In the present study, the patients examined did not have their dosage reduced or their treatment discontinued due to AEs or co-administration with CYP3A4 inhibitors. These results indicated that flumatinib used as the first-line treatment strategy for patients with CML-CP resulted in mild and controllable adverse reactions.

In conclusion, the present study indicated that flumatinib used as a first-line therapeutic option exhibited notable efficacy with high rates of responses. These responses were faster and deeper in patients newly diagnosed with CML-CP. In addition, patients treated with flumatinib exhibited reduced rates of AEs that were well tolerated; therefore, flumatinib may be used as a primary choice of first-line 2G-TKI in patients newly diagnosed with CML-CP.

4. Experimental

4.1. Patients

A total of five patients newly diagnosed with CML-CP, who were recruited between April 1st 2020 and December 31st 2021 in The First Affiliated Hospital of Anhui Medical University (North District), were retrospectively analyzed. The inclusion criteria for the patients were as follows: Age 18-80 years, being newly diagnosed with CML-CP, and previous administration of flumatinib as a first-line therapy. The exclusion criteria for the patients were as follows: Administration of interferon-α, other chemotherapeutic agents, or any other TKIs for the treatment of CML. However, the administration of hydroxyurea prior to flumatinib to reduce the number of leukocytes was accepted for inclusion in the present study. The diagnosis was based on the Chinese Guidelines for Diagnosis and Treatment of Chronic Myeloid Leukemia (Wang et al. 2016). The patients with typical clinical manifestations combined with the presence of Ph+ metaphase cells (detected by conventional cytogenetic assessment) and/or the presence of P210 BCR-ABL transcripts (detected by molecular assessment) were diagnosed as CML. CML-CP was defined according to the Chinese guidelines (Wang et al. 2016). The Sokal risk scoring system was used to divide the enrolled patients into different groups as previously described (Sokal et al. 1984). All enrolled patients provided written informed consent for participation in the present study, which was approved by the Ethics Committee of The First Affiliated Hospital of Anhui Medical University North District (Hefei, China).

4.2. Detection of fusion genes

Reverse transcription-PCR was performed for the detection of the BCR-ABL fusion gene. If the BCR-ABL fusion gene was positive, its copy number was further determined using quantitative (q) PCR; the mutations in the ABL kinase region were detected using first-generation sequencing.

4.3. Cytogenetic studies

Bone marrow samples were obtained at the time of CML diagnosis and 20 metaphase cells were counted and analyzed in each patient according to the International System for Human Cytogenomic Nomenclature (ISCN2016) recommendations.

4.4. Treatment

For patients newly diagnosed with CML-CP, flumatinib (600 mg/day) was administered orally under fasted conditions (no food or drink 2 h prior to and 1 h following TKI treatment). This was used as an initial therapy in case WBC counts were <50×10g/l. Hydroxyurea (30-50 mg/kg/day) was administered to reduce the number of leukocytes when the peripheral WBC counts were >50×10^9/l prior to TKI

treatment. Hydroxyurea combined with blood cell isolation and collection therapy were administered to reduce leukocytes in case the peripheral WBC counts were $>200\times10^9$/l. Flumatinib treatment was subsequently initiated when the WBC counts decreased to a point below 50×10^9/l. Hydration, alkalinization, and uric acid reduction were administered to prevent tumor lysis syndrome.

4.5. Assessment of the treatment response and follow-up

The molecular responses were evaluated using quantification of BCR-ABL1 mRNA expression via qPCR. MMR was defined as BCR-ABL1 transcript levels ≤0.1% (ABL transcript >10,000) according to the International Scale, and UMRD was defined as undetectable BCR-ABL1 transcripts at the level of amplifiable ABL transcripts, as previously described in the Chinese guidelines (Wang et al. 2020). The PFS time was defined as the time from the beginning of flumatinib treatment to the therapeutic failure for any reason, including increased BCR-ABL1 transcript levels, progression of disease, recurrence, or death. The OS time was defined as the time between flumatinib initiation and the end of the follow-up period. Follow-up was carried out via telephone, outpatient follow-up, and the hospital case registration system. The follow-up period ended on June 30th 2022.

4.6. Assessment of safety

AEs were divided between grades 1-5 according to the National Cancer Institute CTCAE (version 5.0). The major AEs of flumatinib treatment, including hematological adverse reactions, non-hematological adverse reactions, quality-of-life associated adverse reactions, and TKI-specific cardiovascular adverse reactions, were observed and recorded.

Conflicts of interest: The authors declare no conflicts of interest.

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References

Chang MX, Ma YP (2013) [Effect of flumatinib mesylate on C-MYC, HIF-1alpha and VEGF in U226 line]. Zhongguo Shi Yan Xue Ye Xue Za Zhi 21: 1496–1500.

Chen J, Guo S, Yu X, Lei J, Xu T, Zhu S, Chen L, Xu P, Zhou X, Yu L (2020) Metabolic interactions between flumatinib and the CYP3A4 inhibitors erythromycin, cyclosporine, and voriconazole. Pharmazie 75: 424–429.

Cortes J, Pavlovsky C, Saussele S (2021) Chronic myeloid leukaemia. Lancet 398: 1914–1926

Cortes JE, Gambacorti-Passerini C, Deininger MW, Mauro MJ, Chuah C, Kim DW, Dyagil I, Glushko N, Milojkovic D, le Coutre P, Garcia-Gutierrez V, Reilly L, Jeynes-Ellis A, Leip E, Bardy-Bouxin N, Hochhaus A, Brummendorf TH (2018) Bosutinib versus imatinib for newly diagnosed chronic myeloid leukemia: results from the randomized BFORE Trial. J Clin Oncol 36: 231–237.

Cortes JE, Saglio G, Kantarjian HM, Baccarani M, Mayer J, Boque C, Shah NP, Chuah C, Casanova L, Bradley-Garelik B, Manos G, Hochhaus A (2016) Final 5-year study results of DASISION: The dasatinib versus imatinib study in treatment-naive chronic myeloid leukemia patients Trial. J Clin Oncol 34: 2333–2340.

Hochhaus A, Baccarani M, Silver RT, Schiffer C, Apperley JF, Cervantes F, Clark RE, Cortes JE, Deininger MW, Guilhot F, Hjorth-Hansen H, Hughes TP, Janssen J, Kantarjian HM, Kim DW, Larson RA, Lipton JH, Mahon FX, Mayer J, Nicolini F, Niederwieser D, Pane F, Radich JP, Rea D, Richter J, Rosti G, Rousselot P, Saglio G, Saussele S, Soverini S, Steegmann JL, Turkina A, Zaritskey A, Hehlmann R (2020) European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. Leukemia 34: 966–984.

Hochhaus A, Saglio G, Hughes TP, Larson RA, Kim DW, Issaragrisil S, le Coutre PD, Etienne G, Dorlhiac-Llacer PE, Clark RE, Flinn IW, Nakamae H, Donohue B, Deng W, Dalal D, Menssen HD, Kantarjian HM (2016) Long-term benefits and risks of frontline nilotinib vs imatinib for chronic myeloid leukemia in chronic phase: 5-year update of the randomized ENESTnd trial. Leukemia 30: 1044–1054.

Jabbour E, Kantarjian H (2020) Chronic myeloid leukemia: 2020 update on diagnosis, therapy and monitoring. Am J Hematol 95: 691–709.

Kirk JA, VanDevanter DR, Biberman J, Bryant EM (1994) Y chromosome loss in chronic myeloid leukemia detected in both normal and malignant cells by interphase fluorescence in situ hybridization. Genes Chromosomes Cancer 11: 141–145.

Lippert E, Etienne G, Mozziconacci MJ, Laibe S, Gervais C, Girault S, Gachard N, Tigaud I, Dastugue N, Huguet F, Fort MP, Legros L, Eclache V, Mahon FX (2010) Loss of the Y chromosome in Philadelphia-positive cells predicts a poor response of chronic myeloid leukemia patients to imatinib mesylate therapy. Haematologica 95: 1604–1607.

Luo H, Quan H, Xie C, Xu Y, Fu L, Lou L (2010) HH-GV-678, a novel selective inhibitor of Bcr-Abl, outperforms imatinib and effectively overrides imatinib resistance. Leukemia 24: 1807–1809.

Mi RH, Chen L, Yang HP, Wei XL, Liu J, Yin QS, Zhang LN, Wei XD (2021) [Clinical efficacy and safety of flumatinib combined with multidrug chemotherapy in the treatment of 12 cases with Ph(+) acute lymphoblastic leukemia]. Zhonghua Xue Ye Xue Za Zhi 42: 858–861.

Nakamae H, Fujisawa S, Ogura M, Uchida T, Onishi Y, Taniwaki M, Utsunomiya A, Matsue K, Takamatsu Y, Usuki K, Tanimoto M, Ishida Y, Ohashi K, Li L, Miyoshi M (2017) 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 105: 792–804.

Patel AB, Wilds BW, Deininger MW (2017) Treating the chronic-phase chronic myeloid leukemia patient: which TKI, when to switch and when to stop? Expert Rev Hematol 10: 659–674.

Qiu L, Wang XD, Yu BH, Lu RZ, Ge F, Wang XL, Chen LJ, Han BH, Zhan ZM, Zhang BL, Ma J (2008) [Effect of a novel tyrosine kinase inhibitor HHGV678 on growth inhibition of Bcr-Abl wild type and IM-resistant cell lines in vitro]. Zhongguo Shi Yan Xue Ye Xue Za Zhi 16: 1039–1043. Clin

Siegel RL, Miller KD, Fuchs HE, Jemal A (2021) Cancer Statistics, 2021. CA: A Cancer J Clin 71: 7–33.

Sokal JE, Cox EB, Baccarani M, Tura S, Gomez GA, Robertson JE, Tso CY, Braun TJ, Clarkson BD, Cervantes F, Et A (1984) Prognostic discrimination in "good-risk" chronic granulocytic leukemia. Blood 63: 789–799.

Wang J, Han M, Liu B, Shen Z, Li J, Huang X, Jiang Q, Liu T, Wang J, Hu J, Zhao Y, Ma J, Wang J, Wang X, Wang C, Sun Z, Li J, Li J, Liu Q, Song Y, Chen X, Du X, Chen G, Zhang X, Yang L, Zou P, Hu Y, Wu D, Jing J, Huang H, Hou M, Liang Y, Lai Y, Zhang G, Luo J, Li Y, Liu Z, Zhou J, Yu L, Du X (2016) [The guidelines for diagnosis and treatment of chronic myelogenous leukemia in China (2016 edition)]. Zhonghua Xue Ye Xue Za Zhi 37: 633–639.

Wang J, Han M, Liu B, Shen Z, Li J, Huang X, Jiang Q, Liu T, Wang J, Hu J, Zhou D, Ma J, Wang J, Wang X, Song X, Sun Z, Li J, Li J, Liu Q, Song Y, Zhang Y, Chen X, Du X, Chen G, Zhang X, Yang L, Hu Y, You Y, Wu D, Chen S, Jing J, Huang H, Hou M, Liu L, Lai Y, Zhang G, Li Y, Liu Z, Zhou J, Liu D, Luo J (2020) [The guidelines for diagnosis and treatment of chronic myelogenous leukemia in China (2020 edition)]. Zhonghua Xue Ye Xue Za Zhi 41: 353–364.

Yang M, Xi Q, Jia W, Wang X (2019) Structure-based analysis and biological characterization of imatinib derivatives reveal insights towards the inhibition of wild-type BCR-ABL and its mutants. Bioorg Med Chem Lett 29: 126758

Zhang L, Meng L, Liu B, Zhang Y, Zhu H, Cui J, Sun A, Hu Y, Jin J, Jiang H, Zhang X, Li Y, Liu L, Zhang W, Liu X, Gu J, Qiao J, Ouyang G, Liu X, Luo J, Jiang M, Xie X, Li J, Zhao C, Zhang M, Yang T, Wang J (2021) Flumatinib versus imatinib for newly diagnosed chronic phase chronic myeloid leukemia: a phase III, randomized, open-label, multi-center FESTnd study. Clin Cancer Res 27: 70–77.

Zhao J, Quan H, Xu Y, Kong X, Jin L, Lou L (2014) Flumatinib, a selective inhibitor of BCR-ABL/PDGFR/KIT, effectively overcomes drug resistance of certain KIT mutants. Cancer Sci 105: 117–125.