REVIEW

Clinical efficacy and safety of imatinib in the management of Ph+ chronic myeloid or acute lymphoblastic leukemia in Chinese patients

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Abstract: Imatinib mesylate is considered the standard first-line systemic treatment for patients with chronic myeloid leukemia (CML) and functions by targeting BCR-ABL tyrosine kinases. Imatinib has substantially changed the clinical management and improved the prognosis of CML and Philadelphia chromosome-positive acute lymphocytic leukemia (Ph+ ALL). Here, we review the pharmacology, mode of action, and pharmacokinetics of imatinib; Chinese efficacy studies in CML and Ph+ ALL; safety and tolerability; patient-focused perspectives, such as quality of life, patient satisfaction, acceptability, and adherence; and uptake of imatinib.

Keywords: imatinib, Philadelphia chromosome-positive acute lymphocytic leukemia, chronic myeloid leukemia, safety, clinical efficacy

Introduction

The development of imatinib represents one of the most important milestones in the history of medicine. In the 1990s, allogeneic stem cell transplantation (allo-SCT) was the frontline therapy in eligible patients with chronic myeloid leukemia (CML); however, this therapy was accompanied by high mortality, even when using human leukocyte antigen (HLA)-matched donors. Imatinib mesylate, a BCR-ABL tyrosine kinase activity inhibitor (TKI), was the first targeted therapy available for patients with CML, providing major clinical advantages and better quality of life outcomes compared with previous interferon (IFN)-based treatments.[1,2] Today, the majority of CML patients can expect to have a generally normal quality of life and much better survival/prognosis, even with the possibility of discontinuing long-term therapy safely.

Imatinib is a selective inhibitor of the BCR-ABL tyrosine kinase and is generally well tolerated by the majority of patients. Other tyrosine kinases inhibited by imatinib include c-KIT and platelet-derived growth factor receptors (PDGFRs).[3] The well-known International Randomised Study (IRIS) of Interferon versus Imatinib, which randomly assigned 1,106 patients with newly diagnosed CML to receive 400 mg/day of imatinib or IFN (5,000,000 U/m²/day) plus 10-day cycles of cytarabine (20 mg/m²/day) every month, resulted in a 69% 12-month complete cytogenetic response (CCyR) rate and a 76.2% 18-month CCyR rate for imatinib, versus 14.5% for IFN plus cytarabine ($P<0.001$)[4] in 2003. In 2006,[5] after a median follow-up of 60 months in IRIS, the cumulative CCyR rose to 87%. Hochhaus et al[6] published 6-year follow-up data and reported no further cases of disease progression. Cumulative CCyR rates were 82%, and 57% of the patients who achieved CCyR remained adherent to imatinib therapy after randomization to the imatinib therapy group, and these numbers were stable at the 7-year follow-up.[7] At the

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8-year follow-up,[8] 55% of patients initially randomized to the imatinib were still on study treatment, and an estimated overall survival (OS) rate of 85% was reported.

Apart from CML, imatinib is also a powerful agent for the treatment of Philadelphia chromosome-positive acute lymphocytic leukemia (Ph+ ALL). Single-agent imatinib therapy for relapsed or refractory Ph+ ALL and lymphoid CML cells in Blast Crisis (CML-BC) was associated with response rates of 40%–50%; complete response (CR) rates were 5%–7%, with a median survival of 2–5 months.[9–11] These data led to a number of studies of imatinib as a first-line treatment in elderly patients, especially patients who could not tolerate allogeneic stem cell transplantation (allo-SCT). The current consensus is that imatinib, administered along with chemotherapy, improves outcomes compared with chemotherapy alone.[12–16] The number of patients who are able to receive allo-SCT, and the outcomes of allo-SCT, have improved as well.[13,14,17,18] When imatinib was combined during induction, consolidation, and maintenance phases of therapy, 96% of patients with Ph+ ALL achieved CR. A complete molecular response (CMR) was achieved in 60% of patients. Half of the patients were able to proceed with allo-SCT. Compared with previous chemotherapy regimens without imatinib, the combination did not result in unexpected toxicities, and published follow-up studies reported a 2-year disease-free survival (DFS) of 87% with hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD) and imatinib, far superior to historical outcomes with hyper-CVAD alone, with 2-year DFS rates of 28% ($P<0.001$).[19]

Pharmacokinetics of imatinib

Studies have evaluated the absolute bioavailability of a single oral dose of imatinib mesylate (Glivec®; Novartis, Basel, Switzerland) 400 mg (capsules versus [vs] oral solution), compared with imatinib 100 mg (intravenous [iv] infusion) in 12 healthy subjects. Both the rate and extent of imatinib absorption, as measured by maximum concentration (C_{max}), partial area under the curve (AUC), and total AUC, were similar for the oral solution and the imatinib capsule intended for the market. Absolute bioavailability values for the imatinib capsule and oral solution were 98.3% and 97.2%, respectively;[20] this outcome showed that the 400 mg oral dose of imatinib, as a capsule or a solution, was completely absorbed and was almost completely bioavailable (>97%).[20] Peak plasma concentrations (C_{max}) of imatinib were detected after a mean time of 3.84 and 4.07 hours following oral intake of 400 or 600 mg imatinib, respectively.[21]

The main elimination pathway is via the biliary–fecal route.[22,23] Potential inactivation of imatinib through excessive binding to the plasma protein α1-acid glycoprotein may result in decreased levels of active drug, which consequently may result in the induction of resistance.[22]

The main circulating metabolite of imatinib after it is metabolized by cytochrome P450 (CYP) 3A4 is N-desmethyl-imatinib (CGP74588), which has in vitro activity similar to that of imatinib, and the systemic exposure represents approximately 10%–15% of that for imatinib.[21–23] Imatinib is absorbed and interacts slightly with P-glycoprotein (P-gp) or adenosine triphosphate (ATP)-binding cassette (ABC) transporters at the membranes of intestinal epithelial cells and is then transported to the intestinal lumen.[20,21,24] In the liver, imatinib is transported into hepatocytes by organic cation transporter 1 (OCT1), where it may undergo metabolism to CGP74588 by hepatic CYP3A4 and a number of other enzymes, such as CYP1A2, CYP2D6, CYP2C9, and CYP2C19 (Figure 1).[25–27] Imatinib is known to be a
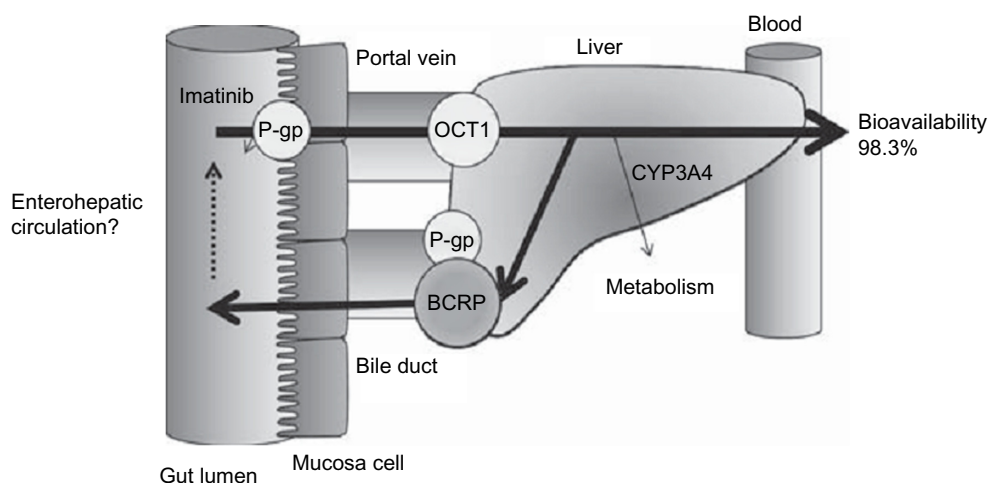
Figure 1 Schematic diagram of the transport and metabolism of imatinib.
Abbreviations: P-gp, P-glycoprotein; OCT1, organic cation transporter 1; CYP, cytochrome P450; BCRP, breast cancer resistance protein.

substrate for CYP3A4, and there is great potential for drug interactions with coadministered drugs, food, and nutritional supplements, potentially leading to subtherapeutic exposure or concentrations associated with greater-than-acceptable toxicity for imatinib.[25]

The data from Phase I and pharmacokinetic studies[28] demonstrate that urinary excretion of imatinib and CGP74588 accounts for less than 10% of the imatinib dose and is not significantly different among the various groups, indicating that imatinib pharmacokinetics will not be significantly affected in patients with compensated renal failure.[22]

Degradation of imatinib predominantly occurs in a CYP3A4-dependent manner, leading to the formation of CGP74588.[25] Both imatinib and CGP74588 are mainly glucuronidated to inactive O- and N-glucuronides[23] by UDP-glucuronosyltransferases. These glucuronides are excreted into the bile, where they may be converted back to the parent drug and CGP74588 by bacterial glucuronidases in the gut lumen and reabsorbed through the process of enterohepatic recirculation, which is evidenced by a secondary plasma peak in the concentration–time profile of imatinib. However, the extent of biliary excretion of imatinib glucuronic acid conjugates, which are present in the plasma and urine, but are not detected in the feces, as well as their metabolites, has not yet been reported.[23]

Nevertheless, imatinib has a restricted ability to penetrate the blood–brain barrier.[18,22,29–31] le Coutre et al[22] detected imatinib and CGP74588 levels in cerebrospinal fluid (CSF) probes from 17 patients treated with 400 or 600 mg per day imatinib. The mean imatinib concentration in the CSF was 38 ng/mL (39 and 34 ng/mL in the CSF from patients without and with meningeosis, respectively), indicating that only a small fraction of plasmatic imatinib crosses the blood–brain barrier, regardless of the presence of meningeosis leukemia. Moreover, peak levels of CGP74588 were below 10 ng/mL. Imatinib is therefore ineffective at preventing or treating central nervous system leukemia.

Mode of action of imatinib

The BCR-ABL tyrosine kinase is a constitutively active kinase that functions by binding to ATP and transferring a phosphate group from ATP to tyrosine residues on various substrates. This activity causes the excess proliferation of myeloid cells that is characteristic of CML. Imatinib functions by blocking the binding of ATP to the BCR-ABL tyrosine kinase, thus inhibiting the activity of the kinase. In the absence of tyrosine kinase activity, substrates required for BCR-ABL function cannot be phosphorylated.[32]

Pharmacology of imatinib

Significant correlations between imatinib trough plasma levels (C_{min}) and cytogenetic and molecular responses of Caucasian patients with CML have been found.[32–34] In a pharmacokinetics/pharmacodynamics (PK/PD) analysis from the IRIS study, imatinib plasma C_{min} levels higher than 1,000 ng/mL correlated significantly with improved cytogenetic and molecular response rates.[33] In the Tyrosine Kinase Dose Optimization Study (TOPS), evaluation of the effects of imatinib 400 mg twice daily compared with imatinib 400 mg daily in previously untreated patients with newly diagnosed CML cells in Chronic Phase (CML-CP) showed that imatinib trough plasma levels were proportional to dose and stable over time.[35] Patients with imatinib C_{min} in the lowest quartile showed a lower major molecular response (MMR) at 12 months, whereas patients in the highest C_{min} quartile showed a higher frequency of all grades of some adverse events.[35]

Another data analysis from patients with newly diagnosed untreated CML-CP from both the IRIS and TOPS trials confirmed that the higher steady-state imatinib levels correlated with better complete CCyR and MMR, but also resulted in more grade 3 and 4 treatment-related toxicities.[36] In a study by Singh et al, mean plasma levels in nonresponders were shown to be significantly lower than those in responders (413 vs 1,380 ng/mL; P=0.002) in 40 patients with CML (20 responders and 20 nonresponders to imatinib).[34]

However, the imatinib trough level in Chinese patients has a higher imatinib C_{min} than that of Caucasian patients; Li et al[37] reported that the C_{min} values for imatinib 400 mg and 600 mg daily were 1,325.61 and 1,550.90 ng/mL, respectively, in 46 CML patients. Zhong et al[38] confirmed that the plasma imatinib trough concentration in 59 CML patients treated with a dose of 400 mg/day was 1,252 ng/mL. Different from the results above and some other studies,[39] molecular responses were not correlated with imatinib C_{min} values in the study by Li et al.[37] This outcome was consistent with research by Zhou et al,[40] who found that the median imatinib C_{min} was 1,271 ng/mL in 416 Chinese CML patients, and that no significant difference was observed in terms of imatinib C_{min} in patients reaching CCyR. However, Chen et al[41] found that the mean C_{min} of imatinib was significantly higher in the CCyR group (1,472 ng/mL) than in the non-CCyR group (1,067 ng/mL) after the administration of imatinib for 1 year. These inconsistent results did not confirm the imatinib concentration–response relationship in Chinese patients and demonstrated a major metabolic distinction between Chinese and Caucasian individuals.

For the 400 and 600 mg/day dose regimens, the reported C_{min} values were 1,058 and 1,444 ng/mL, respectively, in a study conducted in France.[39] In Canada, these same values were 1,065 and 999 ng/mL, respectively.[42] These values are clearly lower than the C_{min} values achieved in Chinese patients. However, similar to the Chinese patients, Korean patients exhibited a C_{min} value of 1,378 ng/mL in the group treated with 400 mg/day imatinib. Based on these results, we speculate that the different imatinib trough plasma levels from Chinese and Caucasian patients could be attributed to body weight. The relatively high C_{min} may account for the fact that some Chinese studies have failed to find a correlation between the C_{min} and CCyR or MMR, if only because the majority of the population reached the effective imatinib concentration.

Chinese efficacy studies and comparative studies of imatinib

Imatinib (Glivec®) launched in mainland China in 2001, and a large number of CML and Ph+ ALL patients achieved good efficacy with imatinib treatment. The Glivec International Patient Assistance Program (GIPAP) made it possible for thousands of Chinese patients to receive imatinib in this developing country. Hence, we will summarize the relatively large amount of clinical research in imatinib in the past decade in the People's Republic of China (Table 1 and Table 2).

In a retrospective study from GIPAP in Ruijin Hospital in Shanghai,[43] the relative efficacy and toxicity of imatinib therapy in 151 CML patients were described. In CML-CP, with a median follow-up duration of 21.5 months, complete hematological remission (CHR), major cytogenetic remission (MCyR), CCyR, and CMR were 96.9%, 82.6%, 76.1%, and

29.4%, respectively. According to the Sokal scoring system, the rates of MCyR and CCyR in low-risk patients were significantly higher than those in intermediate-risk and high-risk patients (P=0.0013 and P=0.0024, respectively). The adverse events experienced after imatinib treatment were acceptable. A univariate analysis from 241 CML patients[44] suggested that factors such as the course of disease before treatment, hemoglobin count, white blood cell count, CCyR achievement, and MMR achievement influenced imatinib resistance.

With a 6-year follow-up of molecular responses in late CML-CP patients after CCyR with imatinib, Qin et al[45] also found that imatinib could induce most late CML-CP patients to achieve long-term durable responses after achieving CCyR. Both the time when CCyR was first achieved and the depth of BCR-ABL reduction after CCyR are relevant to long-term event-free survival (EFS). A recent analysis of 171 patients with CML-CP who received imatinib monotherapy at the People's Hospital of Peking University in Beijing compared the 7-year response to imatinib monotherapy as initial treatment (n=73) and retreatment (n=98).[46] Similar to the results of the IRIS study,[47] the expected 7-year progression-free survival (PFS) in patients with CCyR plus MMR in both groups was 100% at 12 months. There was a significant benefit to the use of imatinib as an initial treatment, compared with its use as a second-line retreatment. The 7-year EFS was significantly higher in the initial treatment group than in the retreatment group (92% vs 70%, respectively; P=0.049).

Two studies evaluated the efficacy and safety of imatinib in the treatment of adult patients with CML cells in Accelerated Phase (CML-AP) and CML-BC.[48,49] Both studies also showed high hematological response (HR: 93.3%) and CHR (46.7%–85.3%). The estimated 4-year PFS and OS rates were 48.2% and 52.2%, respectively, in patients with HR.[49]

Table 1 The clinical efficacy of imatinib in Chinese CML patients

Reference number	Author	Publication year	Patients enrolled	Number	Cumulative CCyR	Cumulative MMR	Cumulative CMR
43	Zhou L	2008	CML	151	76.1%		29.4%
73	Wang GR	2008	CML	95			39.4%
74	Zou WY	2008	CML	85	92.9%		26.3%
75	Zhao Y	2009	CML	116	69.6%		54.9%
45	Qin Y	2009	CML-CP	56		73.9%	
76	Zhou KS	2010	CML-CP	85	67.1%		36.4%
50	Jiang Q	2011	CML-AP	132	47.1%	34.5%	
46	Jiang H	2011	CML-CP	171	84.0%	37.0%	
77	Wu SH	2012	CML	155		52.8%	
78	Haiyan He	2012	CML	275	61.9%		
44	Zhou M	2013	CML	214	69.2%	31.3%	
51	Zhou L	2013	CML-CP	37		68.0%	

Abbreviations: AP, accelerated phase; CCyR, complete cytogenetic response; CML, chronic myeloid leukemia; CMR, complete molecular response; CP, chronic phase; MMR, major molecular response.

Table 2 The clinical efficacy of imatinib in Chinese Ph+ ALL patients

Reference number	Author	Publication year	Patients enrolled	Number	OS
79	Li Y	2009	Ph+ ALL (with additional chromosomal abnormalities)	110	1-year (69.5%)
52	Li CX	2010	Ph+ ALL	30	3-year (12.4%)
53	Huang J	2011	Ph+ ALL	16	3-year (9.3%)
80	Guo Z	2011	Ph+ ALL	36	3-year (66.7%)
55	Chen J	2013	Ph+ ALL	35	5-year (62.6%)
54	Zhang FH	2013	Ph+ ALL	69	3-year (11.4%)

Abbreviations: OS, overall survival; Ph+ ALL, Philadelphia chromosome-positive acute lymphocytic leukemia.

Imatinib can rescue patients with CML-AP, but almost half of these patients relapse within 4–5 years. In order to clarify the role of allo-hematopoietic (H)SCT in the treatment of CML-AP, a recent study[50] was designed to compare the outcomes of imatinib (n=87) versus allo-HSCT treatment (n=45) in CML-AP patients. Both treatments resulted in similar survival rates in low-risk (no factor) patients, with 6-year EFS, OS, and PFS rates of more than 80.0% each. In intermediate-risk patients, EFS and OS did not differ in terms of therapy, with 6-year EFS and OS rates for imatinib (n=43) and allo-HSCT (n=16) of 47.1% versus 61.9% (P=0.788) and 61.3% versus 81.3% (P=0.773), respectively. However, in high-risk patients, imatinib was by far inferior to allo-HSCT, with 5-year EFS, OS, and PFS rates for imatinib (n=27) and allo-HSCT (n=6) of 9.3% versus 66.7% (P=0.030), 17.7% versus 100% (P=0.008), and 18.8% versus 100% (P=0.006), respectively. Therefore, allo-HSCT is a viable option for all patients with CML-AP; it is superior to imatinib, conferring significant survival advantages to high- and intermediate-risk patients.

More recently, a randomized study was conducted to compare dasatinib (100 mg/day) with imatinib (400 mg/day) in 37 CML-CP patients.[51] The cumulative CCyR and MMR at 36 months were higher in the dasatinib group than in the imatinib group; however, no significant differences were observed.

Imatinib in combination with chemotherapy can significantly improve the CR rate, molecular CR rate, and CR duration for Ph+ ALL patients.[52,53] Therefore, application of imatinib pretransplant might have benefits for patients with Ph+ ALL.[54] In a retrospective analysis of 69 patients with Ph+ ALL,[54] 44 patients received imatinib therapy, including 24 pretransplant, 9 post-transplant, and 11 both pre- and post-transplant. The 3-year estimated OS and DFS were 62.3% and 53.6%, respectively, in patients who received imatinib therapy pretransplant, and 25.9% and 23.6%, respectively, in patients who did not receive imatinib therapy pretransplant. Moreover, additional chromosome

abnormalities and blasts with myeloid lineage conferred a survival disadvantage in terms of OS and DFS. Huang et al[53] reported that patients who received imatinib combined with intensive chemotherapy pretransplant significantly increased the CR rate and improved OS. The estimated OS and DFS at 3 years were 85.9% and 83.9%, respectively, and the cumulative relapse incidences at 3 years were 16.1% and 14.1%, respectively.[53] Chen et al[55] retrospectively compared the outcomes of allo-HSCT with and without imatinib in 35 patients. The data showed that the first complete remission (CR1) in the imatinib group was higher than that in the control group (20/23 vs 6/12, P=0.038). The estimated 5-year OS was significantly better with allo-HSCT plus imatinib than for allo-HSCT without imatinib. Importantly, there is no evidence that imatinib has an adverse effect on transplant-related morbidity or mortality.

Safety and tolerability of imatinib

Generally, imatinib is well tolerated overall, though mild-to-moderate toxicities are common in both CML and Ph+ ALL patients, with almost all patients experiencing at least one mild or moderate treatment-related adverse event (grade 1–2).[2,8] The toxicity of imatinib is closely associated with the disease phase and drug dose. Obviously, patients with advanced-phase disease,[56,57] receiving higher doses,[58,59] suffered from more frequent and severe toxicities. Patients with advanced disease had more usual dose interruptions and reductions because of the higher dose of imatinib administration.[58,59] Successful treatment in these patients relies on prompt and effective management of adverse events.

In the IRIS trial, a large percentage of CML-CP patients experienced grade 3 or 4 hematological toxicity from the administration of imatinib 400 mg.[2] Despite high rates of neutropenia (14.3%) and thrombocytopenia (7.8%), grade 3–4 anemia was observed in only 3% of patients.[2] Respective infectious and bleeding complications remained rare. Zhou et al[43] reported that grade 3–4 neutropenia, anemia, and thrombocytopenia occurred in 17.8%, 5.9%, and 21.8%

of Chinese patients with CML-CP, respectively. Grade 3–4 hematological toxicity presented in 40%–60% of patients with advanced disease.

As expected, higher doses of imatinib (600–800 mg/day) in CML-CP patients resulted in higher rates of grades 3–4 hematologic adverse events in several single-armed studies[60] and in the Phase III study (TOPS) that compared imatinib 400 mg versus 800 mg in untreated CML-CP.[59] Moreover, myelotoxicity is generally an early event, more commonly observed during the first 12 months of treatment with imatinib.[61] In a Phase II single-arm trial of imatinib in CML-CP after failure of IFN after 12 months of treatment, neutropenia decreased from 33% to 13%, thrombocytopenia decreased from 18% to 1.9%, and anemia decreased from 6% to 1.4%.[61] More frequent grade 3–4 hematological toxicity has also been observed in CML-AP patients compared with CML-CP patients; grade 3–4 neutropenia was observed in 60% of CML-CP patients receiving 600 mg once daily, while severe anemia was observed in 47% and thrombocytopenia in 43% of CML-AP patients.[57] Similarly, in CML-BC, grade 3–4 neutropenia, thrombocytopenia, and anemia were observed in 64%, 62%, and 52% of patients, respectively. CML-BC patients undergoing imatinib treatment experienced more frequent fever than CML-CP and CML-AP patients.[56] However, it is suggested not to withdraw treatment or reduce the dose of imatinib, and continuation of imatinib despite myelotoxicity may be appropriate in some patients.[62] No hematological toxicity has been reported in Chinese patients receiving higher doses of imatinib.

Gastrointestinal toxicity (GI), presenting either as nausea and vomiting or diarrhea, is among the most common side effects of imatinib in CML patients. In CML, nausea is the most common adverse event, occurring in 43%–65% of patients taking 400–600 mg/day imatinib.[63] However, grade 3–4 nausea occurs in less than 1% of patients.[2,59] Diarrhea is also common, occurring in 45% of imatinib-treated patients, while severe diarrhea occurs in between 1.8% and 2.5% of patients.[63] Fluid retention is the most typical nonhematological adverse reaction to imatinib in patients with CML and is the main reason for dose reductions in patients taking high-dose imatinib.[64] The majority of patients have nonspecific edema,[5,65] which is usually grade 1–2, dose dependent, and present in the periorbital regions and ankles. The imatinib-induced fluid retention syndrome is a characteristic side effect. Skin toxicity, mostly as a rash or dermatitis, is frequently reported[32] and typically mild to moderate, usually being observed shortly after beginning treatment with imatinib. All grades of rash have been reported; with an incidence of 40% in CML patients.[2,59] High-grade

reactions are rare, with an incidence of 2%–3% with 400 mg imatinib and 5%–7% with 800 mg imatinib.[2,59,66] Severe dermatologic reactions, including erythema multiform and Stevens–Johnson syndrome, have been reported in both diseases in individual case studies.[67] Other commonly observed nonhematologic toxicities in CML patients treated with imatinib include fatigue, musculoskeletal toxicity cramps, myalgias and arthralgias, headache, dizziness, cough, and anorexia. Severe toxicity (grade 3–4) has been observed more frequently in patients receiving imatinib 800 mg/day.[59] Non-hematological side effects have not been carefully researched in Chinese patients; however, because Chinese patients have higher plasma concentrations of imatinib, nonhematological toxicities will be more frequent.

Patient-focused perspectives

In the targeted therapy (TT) era, dramatic increases in clinical response rates and expected survival durations have rarely been shown in solid tumors. However, patients who are treated with TKIs need to continue treatment on a daily basis and for their entire life to control the disease. The long-term effects of such treatments on patients' health-related quality of life (HRQOL) have been studied.[68]

In an IRIS study,[1] HRQOL was evaluated in 1,049 CML-CP patients. Patients receiving IFN plus low-dose cytarabine experienced a large decline in the trial outcome index (TOI), whereas those receiving imatinib maintained their baseline level. Treatment differences at each visit were significant ($P<0.001$) and clinically relevant in favor of imatinib. Mean social and family well-being (SFWB), emotional well-being (EWB), and utility scores were also significantly better for patients taking imatinib. Patients who crossed over to imatinib experienced a large increase in TOI; significant differences ($P<0.001$) were observed between patients who did and did not cross over in favor of imatinib; this was noted to be one of the largest changes ever seen in HRQOL trial-based reports.

Recent data from the ADAGIO (Adherence Assessment with Glivec: Indicators and Outcomes) study,[69] which recruited a total of 202 patients suggested that nonadherence is associated with poorer response to imatinib. One-third of all patients were considered to be nonadherent, and only 14.2% of patients were perfectly adherent, with 100% of prescribed imatinib taken. Patients with suboptimal responses had significantly higher mean percentages of nonadherence to imatinib treatment (23.2%) than did those with optimal responses (7.3%, $P=0.005$).

A study by Hirji et al[69] aimed to assess the impact of patient-reported treatment restrictions and negative

medication experiences (NMEs) on satisfaction among patients with CML treated with oral TKIs. Among 303 patients with CML, approximately 30% of patients reported treatment difficulties; treatment difficulties were higher among patients taking nilotinib (63.3%) than among those taking dasatinib (2.6%) or imatinib (19.2%; $P<0.0001$). Nonadherence was generally low; however, patients on nilotinib versus imatinib reported missing doses more often ($P<0.05$). Treatment satisfaction was associated with significantly increased HRQOL ($P<0.05$) and lower activity impairment ($P<0.01$). NMEs were associated with decreased treatment satisfaction ($P<0.01$) and HRQOL ($P<0.05$) and greater activity impairment ($P<0.01$). Higher overall treatment restrictions were associated with greater treatment difficulty ($P<0.001$), which correlated with nonadherence ($P<0.01$).

To investigate patient-reported personal factors associated with adherence behavior, Efficace et al[70] analyzed adherence behavior in 413 CML patients receiving long-term therapy with imatinib by the Morisky Medication Adherence Scale and investigated the following personal factors: quality of life, perceived social support, fatigue, symptom burden, psychological well-being, desire for additional information, key sociodemographic factors, and treatment-related factors. Univariate and multivariate logistic regression analyses showed that 53% of patients present optimal adherence behaviors. The final multivariate model retained the following variables as independent predictors of optimal adherence to therapy: desire for more information (odds ratio [OR]: 0.43; $P<0.001$); social support (higher score representing greater support; OR: 1.29; $P<0.001$); and concomitant drug burden (OR: 1.82; $P<0.006$), which suggests that a higher level of social support, satisfaction with information received, and concomitant drug burden are the main factors associated with greater adherence to long-term imatinib therapy.

Place in therapy

The introduction of TKIs has changed the landscape of therapy for CML. Imatinib, as the first TKI for BCR-ABL-positive disease, has greatly changed the treatment and management of CML and Ph+ ALL. Second-generation TKIs, such as nilotinib and dasatinib, have now been developed, and this has sparked heated discussions as to whether these therapies could take the place of imatinib as the first-line therapy for untreated CML patients or act as more appropriate combination therapies in Ph+ ALL patients.

Second-generation TKIs show slight, but significant, increases in the proportion of patients achieving early CCyR

on nilotinib (Evaluating Nilotinib Efficacy and Safety in clinical Trials-newly diagnosed patients [ENESTnd])[71] and dasatinib (DASatinib versus Imatinib Study In treatment-Naive CML patients [DASISION])[72] compared with patients receiving imatinib. Furthermore, both studies showed that nilotinib and dasatinib induced deep MMR, such as MMR3 and MMR4, in a larger proportion of patients than did imatinib. However, the most appropriate treatment choice is not only the most efficacious, and it is also important to consider other factors, such as side effects and pharmacoeconomic characteristics. Notably, the proportion of patients who are still taking the study drug allocated at randomization 2 years prior is practically identical to the proportion still taking imatinib in both the DASISION and the ENESTnd trials, indicating that the superior efficacies of nilotinib and dasatinib are offset by other factors, most likely the drugs' side effects. Therefore, with a longer duration of follow-up, the place of imatinib for CML and Ph+ ALL treatment will be more accurately assessed.

Disclosure

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