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A Benefit-Risk Assessment of Imatinib in Chronic Myeloid Leukaemia and Gastrointestinal Stromal Tumours

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Abstract

Targeting constitutively activated tyrosine kinases, such as BCR-ABL, in chronic myeloid leukaemia (CML) and c-KIT in gastrointestinal stromal tumours (GIST) has substantially changed the clinical management of both diseases. The introduction of imatinib, a tyrosine kinase inhibitor mainly targeting BCR-ABL, c-KIT and PDGFR, has profoundly improved the

prognosis of both entities, while being surprisingly well tolerated. This article summarizes recent data on clinical efficacy as well as safety aspects of imatinib for treatment of CML and GIST, including a final benefit-risk assessment. Imatinib induces high rates of cytogenetic and molecular responses in all phases of CML and also has substantial activity in GIST patients. In both diseases, only a few adverse effects, such as musculoskeletal and joint pain, muscle cramps, oedema and gastrointestinal symptoms, occur. Most of these are grade I or II toxicities and generally occur during the early phase of treatment (i.e. within the first 2 years). Thus, in view of the low rates of severe toxicities and the extraordinary efficacy of the drug in both diseases, imatinib represents an oral drug with a high benefit-risk ratio for the treatment of CML and GIST.

1. Targeting BCR-ABL by Imatinib as a Therapeutic Principle

Reversible tyrosine phosphorylation, which is governed by the balanced action of protein tyrosine kinases (PTK) and protein tyrosine phosphatases, regulates important signalling pathways involved in the control of cell proliferation, adhesion and migration. Perturbation of PTK activity due to mutations or over expression can induce malignant transformation,[1] and PTK inhibitors are now established anticancer drugs.[2] Imatinib, also named STI571 or Glivec® (Novartis, Basel, Switzerland) has been approved for the treatment of chronic myeloid leukaemia (CML) and represents the most prominent member of the tyrosine kinase inhibitor (TKI) family. Imatinib also has excellent clinical efficacy in gastrointestinal stromal tumours (GIST), systemic mastocytosis and hypereosinophilic syndromes, for which it is also approved. Imatinib reversibly binds to several target kinases, among which c-KIT (the concentration that produces 50% inhibition [IC_{50}] = 0.41 μmol/L), c-ABL (IC_{50} = 0.2 μmol/L), BCR-ABL (IC_{50} = 0.025 μmol/L), platelet-derived growth factor receptor (PDGFR)-α (IC_{50} = 0.38 μmol/L) and PDGFR-β (IC_{50} = 0.3 μmol/L) are most sensitive to drug-induced kinase inhibition.[3] The constitutive activation of these kinases is known to be causally involved in the pathogenesis of the above-mentioned diseases.

2. Imatinib in Chronic Myeloid Leukaemia (CML)

Since its introduction in 1996 and following rapid approval in 2002, imatinib has revolutionized the treatment of patients with CML. Its clinical efficacy is outstanding and far superior to the recent standard for non-transplantable patients, i.e. interferon (IFN)-α in combination with cytarabine.[4] Moreover, imatinib has potent antileukaemic activities in patients with advanced-phase CML, and is often a valuable tool for bridging to transplantation or other alternative treatment modalities.[5-7]

2.1 Clinical Efficacy of Imatinib in Chronic-Phase CML

The standard of care for newly diagnosed CML in chronic phase is imatinib at a dose of 400 mg once daily. This is based on a randomized, phase III study that compared imatinib 400 mg once daily to IFNα in combination with cytarabine in newly diagnosed chronic-phase CML patients. The 5-year follow-up data revealed high cumulative best response rates of complete haematological response (98%), major cytogenetic response (92%) and complete cytogenetic response (87%) [see table I]. In addition, fewer patients treated with imatinib had discontinuation of the assigned therapy due to intolerance (3% vs 31%), and fewer had progression to accelerated phase or blast crisis. The major molecular response

Table I. Efficacy of imatinib in chronic myeloid leukaemia (percentage of patients responding)

Response	Phase of the disease		
	chronic phase[a]	accelerated phase[b]	blast crisis[c]
Any HR		83	52
CHR	98	53	15
McyR	92	24	16
CcyR	87	17	7
PcyR		7	9
Minor CyR		17	13
No CyR		45	66
Return to chronic phase		19	28

a First-line treatment.

b Second-line treatment.

c Both untreated and previously treated patients were included.

CCyR = complete cytogenetic response; **CHR** = complete haematological response; **CyR** = cytogenetic response; **HR** = haematological response; **MCyR** = major cytogenetic response; **PCyR** = partial cytogenetic response.

(MMR) rate at 12 months (defined as at least a 3 log reduction from a fixed standardized baseline) was 39% for imatinib and 2% for IFNα together with cytarabine.[4] With prolonged therapy, Branford and co-workers[5] described in a subgroup of patients from the IRIS (International Randomized Study of IFN versus STI571) cohort that BCR-ABL levels continued to decline and that (using strict criteria of polymerase chain reaction [PCR] negativity) undetectable levels are not infrequent (the probability of undetectable BCR-ABL levels are 7% at 36 months, rising to 52% at 81 months). PCR negativity was associated with a lower risk of MMR-loss compared with patients remaining PCR positive. Moreover, the annual event rate peaks 2 years after initiation of therapy and declines with increasing duration of imatinib therapy, reaching 0% (progression to accelerated phase or blast crisis) and 0.4% (all events) in the sixth year.[6] Landmark analyses of the imatinib data demonstrated that patients achieving a complete cytogenetic response after 12 months of imatinib therapy show only minimal progression rates (3%) to accelerated phase or blast crisis within 5 years.[4] In contrast, the percentage of patients not achieving a major cytogenetic response at 12 months and subsequently progressing to accelerated phase or blast crisis was 19% within the observed time-span. This landmark analysis helped to establish the recommendations of the European Leukemia Net, which defines treatment-related response parameters, enabling the assignment of the individual patient to one of the following response groups: (i) optimal responder; (ii) warnings; (iii) suboptimal responder; and (iv) failing patients.[7] Obviously, compliance and pharmacodynamic as well as pharmacokinetic reasons might at least in part explain different response types.[8-10]

However, in most cases, inherent leukaemia cell-intrinsic mechanisms determining sensitivity to imatinib are largely unknown, especially when mutations cannot be detected in patients with insufficient response (i.e. suboptimal response or treatment failure). In the case of the appearance of mutations, inherent genetic instability of CML stem cells is causally involved in the development of resistant disease.[11] However, the fraction of leukaemic stem cells is small and changes are difficult to detect prospectively, meaning that prognostication, in terms of which patient will develop mutations (and subsequent resistant disease) and which patient will not, is difficult. Thus, apart from the phase of the disease, treatment-related response parameters are currently most important for prediction of long-term outcome. It is a major goal to establish biomarkers that can be determined prior to imatinib therapy, which may prospectively predict an optimal response. This would also help to identify patients with primary resistance to imatinib prior to initiation of TKI therapy, who might be valuable candidates for alternative experimental therapies within clinical trials or for allogeneic stem cell transplantation.

Concerning the initial starting dose, Cortes and colleagues[12] presented preliminary evidence that high-dose imatinib (i.e. 800 mg once daily) may be more efficacious compared with the standard dose of 400 mg once daily used in the IRIS trial. Despite the fact that data from randomized studies comparing both dosing schedules are still not available, high-dose imatinib seems to be superior with respect to quality of responses. Data from a phase II study[12] conducted at the MD Anderson Cancer Center

demonstrate that high-dose imatinib induces a complete cytogenetic response in 85% of patients after 12 months of high-dose imatinib, including 44% of patients achieving an MMR (≥3 log reduction of BCR-ABL transcripts) and 35% achieving a ≥4.5 log reduction. Dose intensity at 12 months was 98%, already depicting good adherence to high-dose imatinib therapy due to an acceptable toxicity profile.[12,13] Recently, data (also non-randomized) from the Australian trial of imatinib with dose escalation in CML (TIDEL) showed that starting with 600 mg once daily and subsequent dose escalation to 800 mg once daily in case of suboptimal response in the first-line setting leads to cumulative complete cytogenetic response rate of 90% at 24 months and a 73% MMR rate. The authors describe that patients not able to tolerate 600 mg once daily do have an inferior response rate, suggesting that early dose intensity might be critical for response optimization in early, chronic-phase CML.[14] In summary, data from randomized studies will help to define the role of high-dose imatinib, which currently cannot be regarded as standard care for first-line treatment.

Importantly, data from Rousselot et al.[15] highlight the need for continuous TKI application. The authors demonstrated that most patients with long-lasting complete molecular response (CMR) under imatinib therapy develop rapid relapse of the disease upon treatment discontinuation. This is most likely due to the fact that imatinib is not able to eradicate leukaemic stem cells, giving rise to rapid recurrence of the disease. However, Carella and Lerma[16] suggested that patients in CMR might benefit from low-dose imatinib maintenance therapy with 200 mg/day dosages.

2.2 Clinical Efficacy of Imatinib in Advanced-Phase CML

Advanced-phase CML usually requires intensive therapy, including chemotherapy and, if a suitable donor is available, allogeneic stem cell transplantation. However, imatinib has proven very useful as bridging medication for the reintroduction of a secondary chronic phase (return to chronic phase) in advanced-phase CML patients. In general, due to the high genetic instability with the rapid occurrence of imatinib-resistant clones, responses in patients with either accelerated-phase CML or blast crisis are relatively short-lived. Notably, a higher dosage of imatinib (i.e. 600 mg/day) has proven to be more effective in accelerated phase and blast crisis, and therefore represents the standard dose for this patient group. In accelerated phase, 12-month progression-free survival (PFS) is 59% (600 mg: 67% vs 400 mg: 44%) and overall survival 74% (78% vs 65%). Eighty-three percent of patients exhibited a haematological response (HR), including 53% complete, 10% marrow responses and 19% with a return to chronic phase of the disease. Fourteen percent did not show any HR. Response was more pronounced in patients receiving imatinib 600 mg (i.e. CHR 37% in the 600 mg group vs 27% in the 400 mg group). The rate of major cytogenetic response was 24%, including 17% complete cytogenetic response and 7% partial response. Seventeen percent of the patients had a minor cytogenetic response and 45% of patients did not show any cytogenetic response (table I).[17] A recent report from the MD Anderson Cancer Center supports the value of imatinib, as the authors demonstrate that imatinib therapy is an independent favourable prognostic factor for overall survival compared with historic treatment modalities in accelerated-phase patients.[18]

In blast crisis, 260 patients were included into the phase II trial,[19] which also included approximately 60% of *de novo* patients. Overall HR rate was 52%, including 15% CHR, 9% marrow responses, 28% return to chronic phase and 47% without any HR. A major cytogenetic response rate was detected in 16%, with 7% complete cytogenetic response, 9% partial cytogenetic response, 2% minor cytogenetic response, 13% minimal cytogenetic response and 66% of patients not showing any reduction of Philadelphia chromosome positive (Ph^+) metaphases in bone marrow (BM) [table I]. Overall survival at 12 months was 32%. A trend towards higher response rates in previously untreated patients was observed.[19,20] However, since more potent second-generation TKIs (e.g. dasatinib) have been introduced into the clinical management of

CML, especially in blast crisis, dasatinib appears to be more effective and therefore currently represents the treatment of choice for this patient group, especially because most patients develop advanced-phase disease under first-line imatinib treatment.[21]

2.3 Clinical Efficacy of Imatinib in CML after Interferon-α Pre-Treatment

The recent 6-year follow-up from 532 patients enrolled into the phase II study in patients receiving imatinib in late chronic phase post-IFNα treatment (median time to diagnosis was 34 months) revealed high cumulative best response rates under second-line imatinib treatment, including 67% major cytogenetic response and 57% complete cytogenetic response.[22] At 5 years after initiation of imatinib treatment, 41% were in complete cytogenetic response. At >6 years, 44% of the patients were still on imatinib therapy. A CHR was detectable in 96% of the patients at any timepoint during imatinib therapy. Despite the observation that late responses occur under imatinib therapy (as is also observed in newly diagnosed patients), most responses are observed during the first 12 months post-imatinib initiation. Median time to major cytogenetic response and complete cytogenetic response was 3.4 and 8.3 months, respectively. The PFS rate after 6 years was 61%, with the lowest rates observed after haematological resistance or relapse to prior IFNα therapy. Achievement of a complete cytogenetic response correlated with superior PFS (88% PFS in complete cytogenetic response vs 76% PFS in partial cytogenetic response). The estimated 6-year overall survival rate is 76%, again with patients achieving a better cytogenetic response (i.e. major cytogenetic response vs non-major cytogenetic response) doing much better (91% PFS in major cytogenetic response vs 63% PFS in non-major cytogenetic response). These data demonstrate that imatinib is also of high clinical benefit for patients after non-TKI based first-line therapies. This finding is of particular importance from the global perspective as, in many countries, CML patients are still treated with substances from the pre-imatinib era (e.g. IFN, busulfan, hydroxycarbamide) and those will obviously gain substantial long-term benefit upon switching to imatinib in the case of an approval of imatinib in the respective countries.

2.4 Clinical Efficacy of Imatinib in Childhood CML

Stem cell transplantation still represents the only proven curative approach for childhood Ph^+ CML. Overall survival is 70–80% if a matched related donor is available and 40–60% in cases in which the donor is matched but unrelated. However, as initial therapy, or in cases of relapse after stem cell transplantation, imatinib represents a valuable therapeutic option for paediatric Ph^+ CML patients. In December 2006, the US FDA approved imatinib as first-line treatment for paediatric patients with Ph^+ CML. The recommended dose is 360 mg/m^2 for newly diagnosed patients. There is no experience in patients under the age of 2 years. The recommended dose for children with Ph^+ chronic-phase CML recurrent after stem cell transplantation or who are resistant to IFNα, is 240 mg/m^2. The approval is based on the recent report from a multicentre trial involving 51 newly diagnosed children with Ph^+ CML receiving 340 mg/m^2/day (study no. 2108 for the Children's Oncology Group [Clinical Trials.gov identifier: NCT00030394]). CHR was observed in 78% of paediatric patients 8 weeks after the start of imatinib therapy. Sixty-five percent achieved a complete cytogenetic response and 16% a partial cytogenetic response. The majority of children achieving a complete cytogenetic response achieved their response within 3–10 months (median time to complete cytogenetic response 6.7 months). The estimated survival rate after 12 months of imatinib therapy was 98%, and 84% after 24 months. Moreover, data from the phase I study[23] performed in 14 patients after IFNα failure or relapse after stem cell transplantation, which were treated in different dose cohorts of imatinib (260, 340, 440 and 570 mg/m^2), revealed a major cytogenetic response in 11 of 13 evaluable patients (7 complete cytogenetic responses and 4 partial cytogenetic responses), further demonstrating the high anti-leukaemic activity of imatinib in childhood Ph^+ CML.[23] However, despite the high response rates of childhood Ph^+ CML to

imatinib, all children should proceed to stem cell transplantation when a suitable donor is available, thus providing the only proven curative treatment option for this patient group.

3. Imatinib in Gastrointestinal Stromal Tumour (GIST)

GIST represents the most common form of a rare family of sarcomas, which comprises more than 70 different categories. Historically, GIST has been considered a rare tumour, whereas recent studies have led to a revised estimated incidence of 10–20 cases per million persons, with an age maximum of between 50 and 65 years.[24-26]

GIST can occur in every region of the gastrointestinal tract. However, it is most often detected in the stomach (60%), followed by the small intestine (25%) and the rectum (5%). The most aggressive biology, however, is seen in GIST of the colon and the oesophagus, whereas 75% of gastric GIST is characterized by a benign clinical course. Malignant GIST predominantly spreads intraabdominally throughout the peritoneal cavity and to the liver. Comparable with other smooth muscle tumours, lymph node metastases are rarely seen.

The most common reasons for the development of a GIST are mutations of the *KIT* gene. In more than 80–85% of GIST cases, the *KIT* gene is affected by mutations of exon 9, exon 11, exon 13 or exon 17 (most of the mutations are detected in exon 11),[27] whereas mutations affecting exons 12 and 18 of the *PDGFR*-α gene are present in 5–7% of cases.[28] In 12% of GIST cases none of these mutations can be detected. The described mutations are all gain-of-function mutations, thereby resulting in abnormal, constitutively activated receptor tyrosine kinase activity. This leads to an unlimited stimulation of downstream signalling pathways, including ligand-independent mitogenic activity.

The knowledge that both KIT and PDGFR-α are constitutively activated in GIST and that these tyrosine kinases are targets of imatinib in therapeutic doses achieved in patients (the IC_{50} of imatinib is much lower for KIT [120 nmol/L] and PDGFR [39 nmol/L] as compared with BCR-ABL [649 nmol/L]),[29] has led to the idea of testing imatinib for the treatment of GIST.

3.1 Clinical Efficacy of Imatinib in Metastatic GIST

Imatinib was initially tested in patients with advanced stage GIST. The clinical efficacy was documented in a large, randomized, non-blinded, multicentre study.[30] Imatinib 400 mg once daily (n = 73) or 600 mg once daily (n = 74) was administered to GIST patients until disease progressed or limiting toxicity occurred. In the case of disease progression at 400 mg, the dose was escalated to 600 mg. More than 80% of the patients benefited in terms of partial response (PR) or disease stabilization. There was no statistically significant difference between the 400 mg and the 600 mg group. In the 64-month follow-up of this study, complete remission was achieved in 2.7% of patients. Progressive disease occurred in 13.6% of the patients. Patients harbouring *KIT* exon 9 mutations showed a slightly better response to imatinib 600 mg; however, because of the low number of patients, this difference did not reach statistical significance (table II).

Two consecutive phase III studies tried to clarify if dose escalation to 800 mg is more sufficient than the standard 400 mg regimen. A meta-analysis of these two studies (European Organisation for Research and Treatment of Cancer [EORTC] 6200 [ClinicalTrials.gov identifier: NCT00685828] and the North American S0033 study,[32] comparing imatinib 400 vs 800 mg in metastatic or unresectable KIT-positive GIST) showed that the 800 mg dose did

Table II. Clinical efficacy of imatinib in metastatic gastrointestinal stromal tumours (B2222-study)[31]

Response/ mutational status	400 mg group (n = 73) [%]	600 mg group (n = 74) [%]	All patients (n = 147) [%]
Complete remission	0	2.7	1.4
Partial response	68.5	64.9	66.7
Stable disease	13.7	17.6	15.6
Median TTP (mo)	20	26	24
Complete remission/partial response according to patient mutational status			
KIT exon 9 mutation	17	59	48
KIT exon 11 mutation	85	86	86

TTP = time to progression.

not have a significant advantage in terms of overall survival.[33] However, patients having exon 9 mutations of *KIT* had slightly better PFS when treated with 800 mg once daily. Although these data were not confirmed in the North American study S0033, they remained significant in the pooled dataset.[34,35] A significant effect of high-dose imatinib was also not shown in the B2222-study[31] and the same results were obtained from the recently updated data of the North American S0033 study.[32] Because of these data, imatinib at 400 mg/day has been approved as first-line treatment of advanced GIST that cannot be cured by surgery.

3.2 Clinical Efficacy of Adjuvant Imatinib in Surgically Resected GIST

Clinical trials have been initiated to investigate the use of imatinib in the adjuvant setting. This is reasonable because recurrence of the disease after surgical resection (the treatment of choice in localized disease) is frequently observed, especially in patients with high-risk GIST. The 5-year survival after removal of primary localized GIST is only about 50%. Four studies designed to evaluate the effect of adjuvant imatinib in patients who have undergone R0 resection are currently being conducted and differ in their inclusion criteria, especially in terms of malignant potential according to the consensus grading system of Fletcher.[24] Two of these trials have been initiated by the American College of Surgeons Oncology Group (ACOSOG). Z9000 is a phase II study that includes patients with high-risk primary GIST who receive adjuvant imatinib therapy (400 mg once daily) for 1 year without a control arm, and Z9001 is a phase III study that is placebo-controlled and tested in patients with resected primary GIST ≥3 cm who receive adjuvant imatinib therapy (400 mg once daily) for 2 years (low-, intermediate- and high-risk tumours). Furthermore, the EORTC 62024 is a placebo-controlled study that includes patients with intermediate- and high-risk GIST who are treated with imatinib 400 mg once daily for 2 years. Lastly, the Scandinavian Study Group (SSG) trial XVIII includes patients with high-risk GIST who are treated with imatinib 400 mg on a once-daily basis for either 1 or 3 years.

Data from the ASCOG Z9001 trial have been published recently. Patients in this study had tumours of at least 3 cm diameter and were gross resected after starting imatinib at a dose of 400 mg/day (n=359) or placebo (n=354). This resulted in a significant recurrence-free survival after 1 year in the imatinib arm (98% vs 83%; HR 0.35).[36]

Furthermore, a prospective, open-label, multicentre trial was conducted in 16 hospitals in China and was presented at the ASCO meeting in 2007. The authors included 57 patients with high-risk GIST and treated with adjuvant imatinib (400 mg once daily) for 1 year. In their interim analysis (including 51 patients, 43 of whom had finished the 1-year treatment schedule), 3.9% had recurrent disease.[37]

Corroborating data have been demonstrated by a small study comparing 23 patients with high-risk GIST with 48 patients from a historical control population. Both were treated with radical (R0) surgery. The historical control group (mean follow up 40 months) did not receive any further treatment, while the test group (mean follow up 36 months) was administered imatinib 400 mg once daily for 1 year after surgery. In this study, imatinib also proved effective in terms of survival free of recurrence: only 1 of 23 patients (4%) had a relapse in the imatinib arm, whereas 32 of 48 (67%) had recurrent disease in the control group.[38] All of these studies stopped imatinib treatment 12 months after radical resection. In the case of CML, it has become evident that the interruption of imatinib causes a relapse of the disease, which fortunately is sensitive to imatinib again. In a prospective, randomized, multicentre phase III study, the French sarcoma group addressed this particular question if interruption of imatinib after 1 year of treatment in high-risk patients can be recommended. They stopped imatinib treatment in 58 patients, who were either responding or stable under adjuvant imatinib treatment. Subsequently, patients were randomized to either watch and wait or to a further course of imatinib 400 mg once daily. In the watch-and-wait group, 81% experienced recurrent

disease (mean PFS 18 months) compared with 31% in the imatinib group (mean PFS 18 months). Subsequently, imatinib was restarted immediately in the watch-and-wait group, which resulted in a tumour control (i.e. partial remission or stable disease) in 92% of these patients. The authors conclude that the interruption of imatinib 1 year after surgery cannot be recommended safely in routine practice unless the patient experiences limiting drug toxicity.[39] The Scandinavian trial (SSGXVIII) investigating the same issue (1 vs 3 years of imatinib after surgery) is still ongoing and the results can be expected with interest.

Promising early results for imatinib in combined neoadjuvant and adjuvant use have been published recently.[40] In this prospective study of the Radiation Therapy Oncology Group (RTOG 0132/ACRIN 6665), patients with locally advanced or recurrent/metastatic GIST have been included. If surgery was possible (stable disease or partial remission after imatinib), patients received imatinib 600 mg prior to resection (stopped 48 hours before surgery) and was continued thereafter for 2 years. The 2-year estimated PFS was 82.7% for the primary GIST group and 77.3% for the recurrent/metastatic GIST group and further data on overall survival are expected.

3.3 *c-KIT*/*PDGFR* Mutational Status and Imatinib Sensitivity

The first reports on mutations in the *KIT* and *PDGFR* genes are from patients recruited in the B2222[31] phase II trial. As mentioned in section 3, mutations in exon 11 were the most frequently found alterations (approximately 66%), followed by mutations in exon 9 (18%). Others such as *KIT* exon 13 and 17 and *PDGFR*-α exon 12 and 18 mutations are rare events that can be observed in 1.6%, 1.6%, 0.8% and 3.6% of patients, respectively. Exon 11 mutations showed the highest response to imatinib (84%), whereas *KIT* exon 9 mutations showed a response rate of 48%. This was reflected in the higher progression-free and overall survival for patients harbouring *KIT* exon 11 mutations compared with exon 9 mutations and non-mutated (so called wild type) GIST and *PDGFR*-α mutations.[28] These data were corroborated by the North American phase III study group SWOG (Southwest Oncology Group) and S0033/CALGB (Cancer and Leukemia Group B) 150105, which demonstrated a 2-fold decrease in response to imatinib in patients with *KIT* exon 9 mutations.[41] This again corresponded to a shorter progression-free survival. These patients benefited from higher doses of imatinib (800 mg/day) with a median progression-free survival of up to 18 months compared with 6 months in the standard-dose group (400 mg/day). This observation was confirmed by Debiec-Rychter et al.[42] In a subgroup analysis of the metaGIST analysis,[33] the authors demonstrated a benefit from imatinib 800 mg/day compared with 400 mg/day for patients harbouring a *KIT* exon 9 mutation. However, in both studies, these results did not translate into a prolonged overall survival of the high-dose group. Nonetheless, the National Comprehensive Cancer Network[43] and the European Society for Medical Oncology[44] recommended imatinib 800 mg/day for patients with *KIT* exon 9 mutations.

Apart from different responses to imatinib, the mutational status is also significantly related to progression. Early progression is more associated with *KIT* exon 9 mutations as well as wild-type *KIT* and *PDGFR*-α than with *KIT* exon 11 mutations. Late progression in most cases seems to be associated with secondary mutations in either the KIT or *PDGFR*-α gene.

4. Adverse Effects of Imatinib in CML

4.1 Haematological Toxicity

Imatinib has been established as novel standard first-line therapy in the randomized IRIS trial, which tested the efficacy and safety of imatinib against the, at the time, actual standard combination therapy of cytarabine together with IFNα. In this study, grade 3 or 4 haematological toxicity was relatively frequent. This apparently does not reflect direct toxic effects on haematopoiesis, but rather mirrors the efficient elimination of the BCR-ABL-positive leukaemia and the delayed restoration of normal haematopoiesis. Neutropenia occurred in 14.3%, anaemia in 3.1%

Table III. Haematological grade 3 or 4 toxicity of first-line imatinib in chronic myeloid leukaemia (percentage of patients)

Toxicity	Phase of the disease		
	chronic phase	accelerated phase	blast crisis
Neutropenia	14	60	50
Anaemia	3	47	
Thrombocytopenia	8	43	59

and thrombocytopenia in 7.8% of the patients (table III).[45] However, despite high rates of neutropenia and thrombocytopenia, relevant infectious and bleeding complications remained rare.

In chronic-phase CML patients pre-treated with IFNα, grade 3 or 4 neutropenia occurred in 36%, thrombocytopenia in 22% and anaemia in 8% of imatinib-exposed patients.[22] This higher rate of toxicity most likely reflects the more advanced disease stage in these patients (i.e. late chronic phase).

In CML accelerated-phase, haematological toxicity was substantially more frequent compared with CML chronic phase due to the more advanced phase of the disease, including a more intense bone marrow (BM) involvement and expansion of blasts within the BM compartment. Grade 3 or 4 leukopenia was observed in 38% of patients receiving 600 mg once daily. Severe neutropenia was detectable in 60%, anaemia in 47% and thrombocytopenia in 43% of patients (table III). Notably, as already described for chronic-phase CML, severe life-threatening infectious complications were again not detected in accelerated-phase CML or blast crisis. In contrast, most likely due to thrombocytopenia, 2% of the patients developed grade 3 or 4 haemorrhage (see section 4.2).[17]

The clinical trials testing imatinib in CML blast crisis revealed that, in line with the findings from accelerated-phase CML patients, haematological grade 3 and 4 toxicities were frequently observed due to the progressive disease. However, in blast crisis patients, haematological adverse effects are sometimes difficult to separate from the initial grade of myelosuppression due to the underlying leukaemia. Among patients with pre-treatment granulocyte counts exceeding 1×10^9/L and platelet counts exceeding 100×10^9/L, grade 4 neutropenia was noted in 50% of patients, and thrombocyte counts $<50 \times 10^9$/L were observed in 59% (table III). Febrile episodes were substantially more frequent compared with the less advanced phases of the disease, with 17% of febrile episodes of any grade. Again, it appears to be difficult to dissect the causality of these episodes (drug- vs disease-related).[20,19]

4.2 Non-Haematological Toxicity

In the study of O'Brien et al.,[45] the most frequent non-haematological toxicities (occurring in >1% of patients) [table IV] were musculoskeletal pain (2.7%), joint (2.4%) and abdominal pain (2.4%), rash (2.0%), diarrhoea (1.8%), vomiting (1.5%), myalgia (1.5%), dyspnoea (1.5%), muscle cramps (1.3%) and fatigue (1.1%). Typical toxicities such as superficial oedema were frequent (55.5%), but generally mild to moderate (only 0.9% grade 3 or 4). Other important mild (i.e. grade 1 or 2) non-haematological toxicities included nausea (43.7%), muscle cramps (38.3%), musculoskeletal pain (36.5%), rash (33.9%), fatigue (34.5%), diarrhoea (32.8), headache (31.2%), joint pain (28.3%), abdominal pain (27%), myalgia (21.4%) and haemorrhage (20.9%).[45]

Table IV. Non-haematological grade 3 or 4 toxicity (>1% of all cases) of first-line imatinib in chronic myeloid leukaemia (percentage of patients)

Toxicity	Phase of the disease		
	chronic phase	accelerated phase	blast crisis
Musculoskeletal pain	2.7	NR	NR
Joint pain	2.4	3	NR
Rash	2	NR	NR
Diarrhoea	1.8	NR	NR
Vomiting	1.5	1	1
Myalgia	1.5	NR	NR
Dyspnoea	1.5	NR	NR
Muscle cramps	1.3	NR	1
Nausea	1.1	3	1
Hepatic toxicity	NR	NR	8
Haemorrhage	NR	2	NR
Fluid retention/ weight gain	NR	1	7
Oedema	NR	3	NR

NR = Not reported.

In chronic-phase CML patients pre-treated with IFNα, grade 3 or 4 hepatic toxicity (demonstrated by AST or ALT increase) was detected in 3% of the patients. Three percent of the patients had severe (grade 3 or 4) fluid retention; other adverse effects were nausea (3%), diarrhoea (3%), headache (3%), haemorrhage (5%) and abdominal pain (2%).[22]

Non-haematological grade 3 or 4 toxicities in accelerated-phase CML (table IV) were generally rarely observed. Most frequently, nausea (3%), oedema (3%), arthralgia (3%), haemorrhage (2%), fluid retention/weight increase (1%) and vomiting (1%) were documented.[17]

As already described for CML in chronic or accelerated phase, grade 3 or 4 non-haematological toxicities were rare in CML blast crisis patients. However, it is noteworthy that liver dysfunction was substantially more frequently observed compared with the less advanced phases of the disease. Grade 3 or 4 elevation of liver enzymes was observed in 8% of CML blast crisis patients; in almost half of the patients (47%) the elevation was mild to moderate. Grade 3 or 4 fluid retention was observed in 7% of the patients (grade 1 and 2 in 36%). Severe muscle cramps (1%), and nausea and vomiting (1%) were observed in comparable frequencies compared with the other phases of the disease (table IV).[20,19]

In general, grade 3 or 4 toxicities occurred during the first 12 months of imatinib treatment irrespective of the phase of the disease and recently presented follow-up data from the IRIS trial[6] did not reveal any novel safety concerns under long-term imatinib administration.

4.3 Adverse Effects of Imatinib in Childhood CML

Imatinib was generally well tolerated in children with CML. Grade 3 or 4 toxicities were primarily haematological. Non-haematological toxicities included allergic reactions/hypersensitivity, avascular osteonecrosis and desquamating rash. The incidence of weight gain (all grades 14%) remained low. Grade 3 or 4 myelosuppression was comparable with adult patients receiving imatinib in chronic-phase CML. In one patient, grade 3 or 4 elevation of liver enzymes was reported and they were diagnosed with autoimmune hepatitis. No other unusual laboratory abnormalities were observed in this patient group. The data from the phase II study (2108; ClinicalTrials.gov identifier: NCT00030394) are in line with the previously reported adverse effects from the phase I study.[23]

4.4 Special Safety Considerations

4.4.1 Cardiac Safety

A preclinical study suggested that imatinib may exert cardiac toxicity in some patients.[46] However, a recent retrospective review of all reported serious adverse events in 1276 patients on clinical trials involving imatinib demonstrated only in a minority of patients (1.7%) symptoms that could be attributed to systolic heart failure.[47] The median age of these patients was 70 years, the median time to onset of cardiac symptoms was 162 days and only 0.5% of these events were considered possibly or probably related to imatinib therapy. Eighteen patients of 22 had previous medical problems predisposing to heart problems, i.e. congestive heart failure (6 patients), diabetes mellitus (6), hypertension (10), coronary heart disease (8), arrhythmia (3) and cardiomyopathy (1). Fifty percent of the 22 patients continued imatinib therapy with dose adjustment and optimized management of heart failure without any further complications. Thus, imatinib is an uncommon reason for heart failure. If heart failure occurs, predisposing factors such as age and pre-existing cardiac conditions are likely to contribute to the development of clinical symptoms. Thus, especially in this patient population, cardiac history should be monitored intensively and treated aggressively with standard medication (e.g. diuretics) to avoid the need for dose reduction of imatinib.[47]

4.4.2 Imatinib and Bone Metabolism

As imatinib targets c-Fms and PDGFR, which are both involved in osteoclast and osteoblast activity, it has already been suggested that it modulates bone homeostasis. The observation that imatinib induces hypophosphataemia in CML and GIST patients supports this hypothesis.

Fitter and co-workers[48] have recently delineated the bone-promoting activity of imatinib. Of 17 patients, eight developed a substantial increase of total bone mass as shown by biopsy. Imatinib-exposed patients exhibited elevated serum calcium and decreased phosphate levels (nine patients). Accordingly, imatinib suppressed osteoblast proliferation and stimulated osteogenic gene expression as well as the production of mineralized matrix via inhibition of PDGFR function *in vitro*.

4.4.3 Imatinib-Induced Mutagenesis

Recent reports demonstrated the appearance of cytogenetic abnormalities in Philadelphia chromosome negative (Ph^-) haematopoietic cells in patients receiving imatinib.[49] There are only sporadic data reporting the development of secondary malignancies carrying novel cytogenetic abnormalities appearing under imatinib therapy for CML. Finally, it remains elusive so far, whether the appearance of cytogenetic aberrations in Ph^- cells is due to direct mutagenesis, induction of the TKI or whether it rather reflects an inherent genetic instability in patients developing CML.

5. Adverse Effects of Imatinib in GIST

The toxicity profile of imatinib in the treatment of GIST was evaluated in the EORTC–ISG (Italian Sarcoma Group)–AGITG (Australasian Gastrointestinal Trials Group) phase III trial. 946 patients were assigned to a standard dose (400 mg once daily) and a high dose (400 mg twice daily) arm; in instances of progressive disease in the low-dose arm, a crossover to the high-dose arm was scheduled.[30] According to the Common Toxicity Criteria, the most striking haematological toxicities observed were anaemia (94% all grades; 13% grade 3 or 4) and neutropenia (42% all grades/7% grade 3 or 4). The most prominent non-haematological toxicity was oedema (80% all grades/35% grade >1), skin rash (37% all grades/15% grade >1), fatigue (75% all grades/36% grade >1) and gastrointestinal toxicity, i.e. nausea (56%/20%) and diarrhoea (54%/18%). For a detailed view see table V. A low haemoglobin level at initiation of therapy and high-dose imatinib therapy were predictive for the development of anaemia. In addition, development of neutropenia was also dependent on a low haemoglobin start level, but was dose-independent. The most common non-haematological adverse effect was rash (60%). Rash predominantly occurred in advanced-aged patients with small size lesions receiving high-dose imatinib.

Table V. Distribution of common adverse effects in imatinib-treated patients with gastrointestinal stromal tumours

Toxicity	Grade 3 (%)	Grade 4 (%)
Neutropenia	4	3
Anaemia	10	4
Oedema	6	0.3
Fatigue	9	0.2
Diarrhoea	4	0.1
Nausea	3	
Rash	4	0.1

In general, treatment of GIST with imatinib is well tolerated as most adverse effects are mild to moderate (grade 1–2).[30,50]

6. Drug Interactions of Imatinib

A rifampicin (rifampin)-imatinib drug-drug interaction study was performed in 14 healthy volunteers, with the final aim to determine the effect of a potent cytochrome P450 (CYP) 3A4 induction on the pharmacokinetics of imatinib, which is metabolized primarily by this enzyme system. Rifampicin increased the apparent oral clearance of imatinib 3.8-fold and reduced area under the plasma concentration-time curve by 70%.[51] This interaction may produce subtherapeutic imatinib concentrations. It is therefore suggested that patients receiving co-treatment with a potent inducer of the CYP3A4 system, e.g. phenytoin, phenobarbital (phenobarbitone) or carbamazepine, initiate treatment with an imatinib dose 50% higher than the usual recommended dose in association with close clinical monitoring.

Vice versa, CYP3A4 inhibitors such as ritonavir (protease inhibitor), macrolide antibacterials (erythromycin, telithromycin, clarithromycin), azole antifungals (ketoconazole, itraconazole),

nefazodone (serotonin-2 receptor antagonist), bergamottin (constituent of grapefruit juice) or quercetin may increase imatinib plasma levels, finally leading to unexpected toxicities. If unexpected toxicities occur and interacting comedication is applied, plasma level monitoring might help to fine-tune the required dosing schedule in the individual patient. It is known that plasma levels <1000 ng/mL are associated with an inferior response and outcome,[11] whereas very high levels of imatinib (>2500 ng/mL) might explain unexpected toxic adverse effects.

7. Imatinib and Pregnancy and Breastfeeding

Imatinib is characterized by potential teratogenicity in animals.[51] A recent report presented by Ault and co-workers[52] reported on 19 (10 female and 9 male) patients who were exposed to imatinib during conception. Three pregnancies (two female and one male) ended in spontaneous abortion, and one patient had an elective abortion. All other reported pregnancies were uneventful. Two of 16 babies had minor abnormalities at or shortly after birth, including hypospadias in one baby and rotation of the small intestine, which was surgically repaired. All babies continued with normal growth and development. All female patients interrupted therapy after receiving information on pregnancy. Five of nine patients in complete haematological response lost their complete haematological response during discontinuation of imatinib therapy, including six patients showing an increase of Ph^+ metaphases in conventional cytogenetics. At a median of 18 months after resuming imatinib therapy, eight patients had a cytogenetic response (three complete cytogenetic responses). Other reports also demonstrated uneventful pregnancies after being on imatinib during conception.[53] Choudhary et al.[54] recently reported on a case of meningocele with fatal outcome while being on imatinib alone during the first 1.5 months of pregnancy. In the case of uncontrolled leukocytosis with leukostasis, one can consider leukapharesis[55] or IFNα[56] therapy. However, it is still a matter of debate when it is the optimal timepoint for initiation of therapy during pregnancy. In summary, taking into consideration the risk for the fetus and the mother, and in the lack of sufficient information, it is currently recommended that a safe contraception method should be applied during intake of imatinib. In the case of pregnancy, imatinib should be immediately discontinued. If pregnancy is continued, the effect of imatinib exposure at the time of conception and during pregnancy on the development of the fetus still remains elusive so far.

It is known from animal experiments that imatinib and its metabolites are extensively excreted into the milk.[57] A recent report demonstrated also that in humans imatinib and its metabolite CGP74588 are detectable in active concentrations in maternal blood (imatinib: 886 ng/mL; CGP74588: 338 ng/mL), placenta (imatinib: 157 ng/mL; CGP74588: 1462 ng/mL) and breast milk (imatinib: 596 ng/mL; CGP74588: 1513 ng/mL).[57] It is therefore suggested that women taking imatinib should not breastfeed.

8. Summary

8.1 Benefit-Risk Assessment of Imatinib in CML

Considering the very low rates of severe nonhaematological adverse effects, as well as the acceptable haematological toxicity (which is due to the rapid removal of CML cells from the BM and delayed recovery of normal Ph^- haematopoiesis) and the extraordinary efficacy of the drug in all phases of the disease, imatinib represents an oral drug with a high benefit-risk ratio for treatment of CML. However, physicians taking care of patients treated with imatinib should be aware of the potential adverse effects as well as the possibility that severe toxicities might be due to modified pharmacokinetics, which might be induced by concomitant medications altering imatinib metabolism (i.e. inhibitors of the imatinib-metabolizing enzyme CYP3A4, such as ketoconazole, itraconazole, clarithromycin or erythromycin). The recently published European Leukemia Net recommendations help to guide physicians through the increasingly complex management of CML patients and should help with decision

making, especially in the case of insufficient therapeutic response or toxicity.[7] Finally, it has to be noted that in advanced-phase disease, the novel second-generation compounds nilotinib and dasatinib are superior, and should be preferred even in the first-line setting in this patient group.

8.2 Benefit-Risk Assessment of Imatinib in GIST

Before imatinib was available for the treatment of GIST, the overall chance of patients surviving 5 years was <50%, with a median survival of 19 months.[58] For patients who had a single primary tumour that was completely surgically removed, the 5-year survival was 50–65% and the median survival was 66 months. The situation in metastatic or recurrent diseases was even worse, with a median survival of 9–12 months.[59,60] With the introduction of imatinib, this situation has changed in favour of the patients' survival, in particular reducing the occurrence of recurrent disease. This is paralleled by a very favourable risk profile of the drug, which supports its application for the treatment of GIST.

9. Conclusion

In summary, imatinib has a good safety profile and is very effective in the treatment of CML and GIST, even when applied as durable long-term therapy. It is currently the only approved first-line TKI for first-line treatment of CML in chronic phase. In unresectable, metastatic or surgically incomplete resected GIST, imatinib is also the first-line treatment of choice. Second-generation TKIs are approved for the treatment of GIST when imatinib fails or is not tolerated. If severe adverse events occur, plasma level monitoring as well as accurate survey of concomitant medication can help to address this issue. In more advanced stage CML (i.e. accelerated or blastic phase), more potent novel second-generation compounds (i.e. nilotinib and dasatinib) are the therapy of choice, but have, however, a more unfavourable adverse event profile.

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