Dasatinib for the treatment of chronic phase chronic myeloid leukemia

Victoria Campbell¹ & Mhairi Copland*¹

Practice Points

- Chronic myeloid leukemia is a clonal myeloproliferative disorder that arises from the presence of the oncogenic tyrosine kinase BCR-ABL.
- Dasatinib is a multitargeted tyrosine kinase inhibitor that inhibits BCR-ABL.
- Dasatinib has increased potency compared to imatinib and is effective against the majority of imatinib-resistant BCR-ABL kinase domain mutations (excluding V299L, T315I and F317L).
- The recommended dose of dasatinib is 100 mg once daily for chronic phase chronic myeloid leukemia.
- Important dasatinib-related side effects include cytopenias, pleural effusion and pulmonary arterial hypertension.

SUMMARY  Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder driven by the oncogenic tyrosine kinase BCR-ABL. The discovery of the tyrosine kinase inhibitor imatinib revolutionized the management of patients with CML. However, imatinib can have significant side effects, and is not effective in all patients. The development of second-generation (dasatinib and nilotinib) and third-generation (ponatinib) tyrosine kinase inhibitors sought to address the issue of imatinib-resistance and -intolerance and furthermore, to determine if these agents are superior to imatinib. Dasatinib, a multitargeted inhibitor, is effective against most BCR-ABL kinase domain mutations resistant to imatinib and capable of inducing faster and deeper molecular responses. This article describes the development of dasatinib and documents its current clinical use in chronic phase CML.

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Chronic myeloid leukemia

Chronic myeloid leukemia (CML) accounts for 15–20% of all adult leukemia in the western world; the annual incidence is approximately 1–2 per 100,000 [1]. It can affect all ages, with a median age at diagnosis of 60–65 years [1] and a slightly higher incidence in men than women. CML is a clonal myeloproliferative disorder driven by the Philadelphia (Ph) chromosome. The Ph chromosome arises from a reciprocal translocation between the long arms of chromosomes 9 and 22, resulting in the apposition of the BCR gene at band 22q11 and the ABL gene at band 9q34, leading to the production of the constitutively active BCR-ABL tyrosine kinase. For CML to develop, this mutation of the constitutively active BCR-ABL tyrosine kinase at band 9q34, leading to the production of additional chromosomal abnormalities and increased numbers of more primitive leukemia cells in the bone marrow and peripheral blood. If untreated after a further 12–18 months, then lymphoid or myeloid CML-BP develops. This behaves as an aggressive acute leukemia and is poorly responsive to therapy, often developing resistance to both conventional and targeted therapies [4].

Tyrosine kinase inhibitor therapy

Tyrosine kinase inhibitors (TKIs) are small molecules that selectively inhibit tyrosine kinases; enzymes that, through phosphorylation, activate downstream cell signaling pathways in both normal and malignant cells [5]. TKIs act via competitive inhibition of ATP. As a class of drug, TKIs have shown efficacy in the targeted treatment of various hematological and nonhematological malignancies such as breast and prostate cancer [5–8]. Although TKIs share the same mechanism of action, the spectrum of targeted kinases, pharmacokinetics, pharmacodynamics and adverse effects differ between compounds. However, compared with conventional chemotherapy, TKIs are generally well tolerated.

The first kinase inhibitor, developed for clinical use in the early 1990s, was imatinib mesylate (formerly STI571; Novartis) and is marketed as Gleevec® in the USA and Glivec® in Europe [9,10]. Imatinib, designed as a selective inhibitor of BCR-ABL, has revolutionized the outlook for CML patients [11]. Imatinib induces hematological and cytogenetic responses in the majority of patients with CML-CP [12]. However, imatinib-resistance and -intolerance are well described, particularly in CML-AP and CML-BP. Extensive experience with imatinib in CML-CP has enabled the European LeukemiaNet to develop guidelines (updated in 2009) for identifying patients with treatment failure or a suboptimal response to imatinib [13]. Importantly, despite impressive rates of response, imatinib does not cure CML in the vast majority of patients [14] and therefore, BCR-ABL remains an important target for the development of selective TKIs. A number of second- and third-generation compounds, including dasatinib, are in clinical use or development.

Dasatinib

Preclinical development

Dasatinib (formerly BMS-354825), manufactured by Bristol-Myers Squibb and marketed as Sprycel®, is a second-generation, oral, small molecule multitargeted inhibitor (chemical information shown in Box 1; pharmacokinetic data shown in Box 2; chemical structure shown in Figure 1) [15]. Dasatinib targets BCR-ABL, SRC, c-KIT, PDGFR and ephrin A receptor kinases, with an IC_{50} of 3, 0.55, 13, 28 and 17 nM, respectively [16]. Dasatinib has increased potency relative to imatinib (~325-fold in vitro), binding...
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both the active and inactive conformations of the ABL kinase domain [17].

Dasatinib has enhanced efficacy compared with imatinib, mediated through BCR-ABL dependent and independent mechanisms. Dasatinib effectively targets the majority of BCR-ABL kinase domain mutations (although exceptions include V299L, T315I and F317L) responsible for imatinib resistance in a proportion of CML patients [17–19]. In addition, overexpression of SRC kinases, which are targeted by dasatinib but not imatinib or nilotinib, has been implicated in CML progression and imatinib resistance [20,21]. However, further in vitro studies indicate that while dasatinib targets a more primitive progenitor cell population than imatinib, it fails to eliminate the quiescent CML stem cell compartment [22], postulated to be responsible for persistent minimal residual disease and, ultimately, disease relapse or progression.

Phase I clinical trials: safety & tolerability

A Phase I, open-label, dose-escalation study, trialed dasatinib at doses ranging from 15 to 240 mg once or twice daily in patients with all phases of imatinib-resistant or -intolerant CML or Ph-positive acute lymphoblastic leukemia (Ph+ ALL). Dasatinib induced major cytogenetic responses (Table 1 shows definitions of treatment response) in all CML patients, irrespective of previous disease status (45% in CML-AP, 25% in CML-BP) or imatinib status, and in Ph+ ALL. Responses were maintained in 95% of patients with CML-CP at 12 months [23]. Grade 3–4 myelosuppression necessitating treatment interruption was recorded in 60% of patients; 25% of patients required a reduction in the dose of dasatinib and 18% had treatment-related pleural effusions. Additional adverse effects are documented in Table 2. No patient withdrew from the study due to toxicity; a maximum tolerated dose was not determined.

Phase II clinical trials: clinical efficacy

The START trials were a collection of international Phase II studies designed to establish the tolerability and efficacy of dasatinib in patients with all phases of imatinib-resistant or -intolerant CML and Ph+ ALL. The START-C trial included patients with CML-CP and imatinib-resistance or -intolerance. At 24 months, progression-free survival (PFS) was 80% (initial dose of dasatinib 70 mg twice daily, with dose adjustment according to response/toxicity); major molecular response (MMR) rate was 47% [24]. This trial confirmed in vitro data with responses across all mutations except T315I. The START-R trial compared dasatinib (70 mg twice daily) to high-dose imatinib (400 mg twice daily) in patients with CML-CP resistant to standard dose imatinib (400–600 mg daily). At 24 months, PFS was 86% for dasatinib and 65% for high-dose imatinib (p = 0.012) and MMR was 29 and 12%, respectively (p = 0.028), demonstrating the superiority of dasatinib [25].
Initially, supported by Phase I and II trial data, dasatinib was recommended at a dose of 70 mg twice-daily for patients with all phases of imatinib-resistant or -intolerant CML or Ph+ ALL. However, considering the reported adverse events of dasatinib at 70 mg twice daily, CA180–034, a randomized, prospective, open-label Phase III trial, sought to determine the safety and efficacy of different dosing schedules. Patients with imatinib-resistant or -intolerant CML-CP were randomized to one of four treatment arms: 100 mg once daily, 50 mg twice daily, 140 mg once daily, or 70 mg twice daily. 100 mg once daily demonstrated equivalent efficacy to 70 mg twice daily in CML-CP, with a more favorable side-effect profile. At 6 year follow-up, PFS was 49%, overall survival 71% and risk of progression to CML-AP/BP was 6% in patients randomized to receive 100 mg once-daily. This trial concluded that dasatinib 100 mg once-daily offered the most favorable risk–benefit ratio in CML-CP. This dose is currently considered the optimal dose in patients with imatinib-resistant or -intolerant CML-CP.

Monitoring response to therapy
There is no consensus for monitoring second-line TKIs at present. However, draft guidelines have been published by the European LeukemiaNet [13].

Phase III clinical trials: clinical efficacy in newly diagnosed CML-CP
Three Phase II/III trials have studied dasatinib use in newly diagnosed CML-CP: the Phase III DASISION trial (CA180-056 [101]), a Phase II study at the MD Anderson Cancer Center (MDACC [102]) and a study performed by the four North American co-operative groups [28–30,103]. The MDACC study randomized 50 patients between dasatinib 100 mg once daily and dasatinib 50 mg twice daily. Early data, with a minimum of 3 months follow-up, showed that dasatinib rapidly induced high rates of complete cytogenetic response (CCyR; 98%) and MMR (82%) with 94% of patients achieving a CCyR by 6 months [28]. Hematological toxicity, defined as grade 3–4 neutropenia or thrombocytopenia occurred in 21 and 10% of patients, respectively. Nonhematological toxicities were mainly grade 1–2.

The co-operative group study randomized 246 patients between dasatinib 100 mg once daily and imatinib 400 mg once daily [30]. At 12 months, dasatinib achieved a greater CCyR rate (84 vs 69% in the imatinib arm; p = 0.04)

Table 1. Definitions of treatment response.

<table>
<thead>
<tr>
<th>Response</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHR</td>
<td>Platelets &lt;450 × 10^9/l</td>
</tr>
<tr>
<td></td>
<td>White cell count &lt;10 × 10^9/l</td>
</tr>
<tr>
<td></td>
<td>Basophils &lt;5%</td>
</tr>
<tr>
<td></td>
<td>Differential: no myelocytes, promyelocytes, myeloblasts present</td>
</tr>
<tr>
<td></td>
<td>Spleen not palpable</td>
</tr>
<tr>
<td>CCyR</td>
<td>0% Ph+ metaphases; minimum of 20 cells analyzed</td>
</tr>
<tr>
<td>PCyR</td>
<td>1–35% Ph+ metaphases detectable</td>
</tr>
<tr>
<td>MCyR (CCyR and PCyR combined)</td>
<td>0–35% Ph+ metaphases detectable</td>
</tr>
<tr>
<td>Minor cytogenetic response</td>
<td>36–65% Ph+ metaphases detectable</td>
</tr>
<tr>
<td>Minimal cytogenetic response</td>
<td>66–95% Ph+ metaphases detectable</td>
</tr>
<tr>
<td>CMR</td>
<td>No transcripts detectable by real-time quantitative and/or nested PCR in two consecutive blood samples of adequate quality (sensitivity &gt;10^4)</td>
</tr>
<tr>
<td>MMR</td>
<td>Ratio of BCR-ABL to control gene ≤0.1% on the international scale</td>
</tr>
</tbody>
</table>

CCyR: Complete cytogenetic response; CHR: Complete hematological response; CMR: Complete molecular response; MCyR: Major cytogenetic response; MMR: Major molecular response; PCyR: Partial cytogenetic response.
Dasatinib was associated with increased hematological toxicity (grade 3/4 thrombocytopenia 18 vs 8%), and at a median follow-up of 3 years, the improved early cytogenetic and molecular responses had not translated into a survival advantage.

The DASISION trial recruited a significantly larger patient cohort of 519 patients with previously untreated CML-CP, comparing dasatinib 100 mg once daily with imatinib 400 mg once daily [29]. Dasatinib induced faster and deeper responses, with confirmed CCyR and MMR by 12 months of 77 and 46%, respectively, for dasatinib and 66 and 28%, respectively, for imatinib (p = 0.007 and p = 0.0001, respectively). This was associated with lower progression rates and higher overall survival. Importantly, 2 year follow-up data have shown this superior response to be sustained [31]. Safety analyses found that fluid retention, edema, vomiting, myalgia and rash occurred at a reduced rate with dasatinib compared with imatinib. However, pleural effusions and grade 3–4 thrombocytopenia were more frequent with dasatinib. These trials support a dose of 100 mg once daily for those with newly diagnosed CML-CP. The recommended starting dose in CML-AP, CML-BP and Ph+ ALL is 140 mg once daily [104].

Table 2. Adverse events recorded in a first- and second-line study.

<table>
<thead>
<tr>
<th>Side effect</th>
<th>CA180-034 (second line; Phase II)†</th>
<th>DASISION (first line; Phase III)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100 mg once daily</td>
<td>70 mg twice daily</td>
</tr>
<tr>
<td>Hematological</td>
<td>All grades (%)</td>
<td>Grade 3/4 (%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>89</td>
<td>10</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>63</td>
<td>33</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>60</td>
<td>22</td>
</tr>
<tr>
<td>Nonhematological</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superficial edema</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>23</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Nausea</td>
<td>15</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Myalgia</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Headache</td>
<td>30</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>20</td>
<td>1</td>
</tr>
</tbody>
</table>

†Data taken from [26]. ‡Data taken from [31]. Data taken from [26,29,31].

and MMR rate (59 vs 44% in the imatinib arm). However, dasatinib was associated with increased hematological toxicity (grade 3/4 thrombocytopenia 18 vs 8%), and at a median follow-up of 3 years, the improved early cytogenetic and molecular responses had not translated into a survival advantage.

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The starting dose of 100 mg once daily has since been questioned by the OPTIM trial, a prospective, randomized Phase II optimization study based on the monitoring of drug plasma levels in patients with newly diagnosed CML-CP who received dasatinib as first-line therapy [32]. Preliminary results showed the pharmacokinetic parameters of dasatinib differed in older patients (defined as those >47 years). Additionally, the Cmax (peak dasatinib concentration) correlated with response time, and the Cmin (residual dasatinib concentration) with adverse effects, in particular fluid retention and pleural effusion. This trial raises the question of whether a 100 mg once-daily regime is appropriate for all patients.

**Dasatinib in clinical practice**

In the UK, under NICE guidance, dasatinib is currently licensed but not recommended for the treatment of CML-CP, as either first- or second-line treatment. Dasatinib can therefore only be accessed through the Cancer Drugs Fund or privately. In other EU countries, dasatinib is approved for the treatment of adults with CML or Ph+ ALL with imatinib-resistance or -intolerance and, in some countries, is also approved for first-line use. In the USA, under guidance from the US FDA, dasatinib is licensed for both first- and second-line use.

**Safety & tolerability**

Tyrosine kinase inhibitors cause both hematological and nonhematological side effects. The
hematological side effects (anemia, thrombocytopenia and neutropenia) range from mild to severe; in some instances necessitating drug interruption, dose reduction and occasionally drug discontinuation. Erythropoietin and G-CSF have been shown to be effective in patients with TKI-induced anemia and neutropenia, respectively [33]. The most common nonhematological adverse effects include rash, edema (including plural effusions and ascites), nausea, endocrine dysfunction (specifically thyroid abnormalities), vomiting and diarrhea (Table 2) [24–26,28,29,31].

**Dasatinib-specific side effects**

A number of studies have shown impaired platelet aggregation and activation irrespective of platelet count, in vitro and in vivo, resulting in impaired thrombus formation and prolonged bleeding following dasatinib use [34,35]. These effects are rapidly reversible after interruption of the treatment. Additionally, dasatinib may cause thrombocytopenia, thought to arise due to impaired megakaryocytopoiesis and ineffective thrombopoiesis [36].

Although generally reported to be well-tolerated, pleural or pericardial effusions are not infrequent complications reported with dasatinib use [37]. These effusions are exudative in nature. The median age of patients developing an effusion is 63 years [38]. In first-line therapy, the plural effusion rate was 14% (all grades) in the DASISION trial with 1% grade 3/4 effusions [23,26]. In patients receiving dasatinib as second-line treatment, effusion rates have varied between 7 and 18% [23,26]. The plural effusion rate was significantly correlated with dose in the second-line CA180-034 trial, with 7% of patients receiving 100 mg once daily and 16% of patients receiving 70 mg twice daily developing an effusion (p = 0.024) [26]. Dose reduction or drug discontinuation may be required and dasatinib interruption is the first management step. Pre-existing comorbidity and risk factors should therefore be screened for prior to commencing dasatinib and imaging considered either routinely or determined by symptoms [39,40]. Effusions can generally be effectively managed with diuretics, short courses of steroids and, very occasionally, therapeutic pleural tap.

Postlicensing data have found that dasatinib may induce pulmonary arterial hypertension, suggesting a direct and specific effect of dasatinib on pulmonary vessels. Improvement is usually observed after withdrawal of dasatinib [41].

Occasionally an acute and often marked lymphocytosis may be identified in patients [42]. Morphologically these lymphocytes resemble large granular cells. This develops after a median of 3 months, persisting while dasatinib is continued. These cells are sometimes clonal, displaying either a cytotoxic T-cell or NK-cell phenotype. Patients with lymphocytosis have been shown to have a favorable clinical response and distinct adverse-effect profile in a number of small studies [42,43].

**Drug interactions**

Dasatinib is metabolized by the CYP3A4 isoenzyme, and has inhibitory activity against CYP2C8 and CYP3A4 [44]. A comprehensive list of drug–drug interactions can be found in the dasatinib summary of product characteristics [104]. Interactions are expected between dasatinib and CYP3A4 inhibitors, such as ketoconazole, voriconazole and levothoroxine, leading to a potentially marked increase in plasma drug concentrations of dasatinib; or CYP3A4 inducers such as rifampicin, resulting in reduced plasma drug concentrations. Drugs that inhibit both BCRP (ABCG2) and CYP3A4, such as verapamil, may result in even higher plasma drug concentrations while inhibitors of both CYP3A4 and P-glycoprotein, such as clarithromycin and ciclosporin, increase not only plasma but also intracellular concentrations of dasatinib.

The solubility of dasatinib appears to be pH-dependent. The concomitant use of agents causing gastric acid suppression, such as H2-antagonists and proton pump inhibitors, is therefore not recommended as plasma drug concentrations are likely to be reduced [45]. While the coadministration of antacids also results in reduced plasma drug concentrations, drug levels are unchanged when antacids are administered at least 2 h before or after dasatinib. This is therefore the recommended practice if this class of drug is necessary.

Prolongation of the QTc interval on ECG and, very occasionally, sudden cardiac death have been associated with dasatinib treatment. While not frequent, physicians are advised to take care when co-administrating QT-prolonging drugs such as digoxin, quinolones and selective serotonin-reuptake inhibitors, which may increase the risk by an additive effect. If
unavoidable, regular ECGs are strongly recommended [46]. Dasatinib may also inhibit other drug transporters and enzymes leading to changes in the exposure of co-administered drugs. Presently there is no data on interactions involving protein binding [47].

Specific patient groups

Pediatric practice

A number of studies have evaluated dasatinib in the pediatric population. The CA180-018 trial was a Phase I study designed to establish a Phase II dose of dasatinib in pediatric patients with refractory solid tumours or imatinib-refractory Ph+ leukemia [48,49]. This concluded that overall pharmacokinetics and pharmacodynamics were similar to those observed in the adult population. As a result, the recommended Phase II dose of dasatinib in pediatric patients with CML-CP is 60 mg/m² once daily. However, the safety and efficacy of dasatinib in children and adolescents below 18 years of age have not yet been established. Dasatinib treatment in this age group is not licensed and is not recommended by Bristol-Myers Squibb.

Pregnancy & lactation

There are no controlled studies of dasatinib use in pregnant women. Preclinical data using rats and rabbits, however, observed embryo–fetal toxicity including skeletal malformation at concentrations below the therapeutic dose. A category D warning therefore accompanies dasatinib, with the manufacturer advising that it may cause harm when administered to pregnant women and to avoid becoming pregnant while receiving dasatinib. There are however, case reports of successful pregnancy outcomes in patients treated with dasatinib [50]. There is no data regarding the effects of dasatinib on male fertility and caution is advised.

Elderly

Age as a poor prognostic factor in CML is well documented. Before the advent of TKIs elderly patients had shorter survival compared with younger patients. There is data, however, to show the use of imatinib in older patients’ results in similar rates of cytogenetic and molecular response compared with younger patients but with overall more frequent toxicity, probably due to the presence of concomitant comorbidities [51]. However, there is limited data available for dasatinib. A subanalysis of the DASISION trial showed CCyR rates in those treated with dasatinib of 88% for patients aged <46 years, 78% for those aged 46–65 years and 85% for those aged ≥65 years, with corresponding MMR rates of 45, 47 and 50%, respectively. While safety profiles were similar across age groups in both treatment arms, the incidence of dose or drug suspension and, in particular, the incidence of pleural effusions in elderly patients appears to be associated with the presence of comorbidities. In conclusion, although the data are limited, studies indicate that response is not affected by age, although adverse effects may be increased [52].

Quality of life

Most studies evaluating quality of life (QOL) among patients with CML have focused on imatinib. These studies indicate that TKIs have less unwanted effects than previous forms of treatment and can result in improvements in QOL over pretreatment baselines. However, TKIs are not without side effects, with intolerance being a significant issue for some patients. Phillips et al. studied QOL in CML patients on TKIs (imatinib, dasatinib or nilotinib) [53]. Patients reported a worse physical QOL, although no difference in mental QOL or sleep quality. Specifically, compared with the control group, CML patients on a TKI reported higher levels of fatigue and depression, in addition to symptom burden (skin changes, nausea, diarrhoea, edema, itching, dizziness and changes in appearance); all symptoms were reported as potential adverse events.

Economic evaluations

Within the UK, NICE has issued guidance on the use of second-generation TKIs in both newly diagnosed CML-CP and in those with imatinib-resistance or -intolerance, determined by clinical effectiveness and cost [105]. In the context of first-line treatment, while there is evidence to support an advantage for dasatinib compared with imatinib, as measured by MMR or CCyR, dasatinib was not deemed cost effective if a decision threshold of UK£20,000–30,000 per quality adjusted life year was used [106]. It is important however, to be aware that these decisions are made with relatively immature data that required survival/treatment duration assumptions [54]. Furthermore, a review of high-dose imatinib, dasatinib and nilotinib found data to support beneficial effects for all three agents. However,
the cost was determined to be too high for all agents when referencing a quality adjusted life year of UK£30,000 [59]. This decision differs from other members of the EU; for example, in Sweden, dasatinib is deemed cost effective in those with imatinib-resistance [56].

- Stopping dasatinib

The issue of drug discontinuation is an area of intense interest in the field of CML. While there is an active, prospective study investigating the impact of discontinuing imatinib in patients with CML who have maintained complete molecular response for at least 2 years [44], there is presently no data on the optimal duration of dasatinib therapy in patients obtaining a complete molecular response. Consequently, discontinuation of dasatinib is not recommended outside of clinical trials, although there are isolated case reports of sustained response after stopping dasatinib [57, 58]. Early results have been presented of the STOP 2G-TKI study, which aimed to establish if second-generation TKIs (dasatinib or nilotinib), with their increased molecular response rates, offer a better opportunity for therapy discontinuation [59]. A total of 33 who were PCR-negative for at least 24 months were recruited. The end point of the study was maintenance of MMR. Of the patients 27% lost MMR within 6 months, with relapse occurring rapidly, a median 2 months after drug cessation; 73% remained off any therapy after a median follow-up of 11 months. No predictive factor for identifying patients suitable for treatment discontinuation could be identified.

- Dasatinib use in other malignancies

Dasatinib use is not limited to CML and Ph+ ALL. Early preclinical work in solid tumor cell lines has shown that dasatinib inhibits cell proliferation at clinically achievable IC<sub>50</sub>s. It is therefore being investigated as a single agent and in combination with cytotoxic chemotherapy in Phase I and II clinical trials in a variety of metastatic solid tumours, including renal, ovarian, prostate, lung, pancreas, gastrointestinal stromal cell, breast, melanoma and head and neck malignancies [60,61]. Early results show dasatinib alone, and in combination, to be relatively well tolerated with predictable side effects, including anemia, neutropenia, thrombocytopenia and fluid retention, including pleural effusions. Further results are awaited to determine the role of dasatinib in the wider oncology market.

Conclusion & future perspective

The outlook for patients with CML-CP has changed dramatically since the development of imatinib. Dasatinib has increased potency compared with imatinib and is effective against the majority of imatinib-resistant BCR-ABL mutations. Phase I–III studies have demonstrated the efficacy of dasatinib in patients with imatinib-resistance or -intolerance, and also its superiority to high-dose imatinib in patients resistant to standard-dose imatinib. Phase III studies have also demonstrated the superiority of dasatinib to imatinib in newly diagnosed CML-CP. The current recommended dose is 100 mg once daily for those with CML-CP, both in treatment naive patients and those with imatinib-resistant or -intolerant disease, and the side-effect profile is manageable in the great majority of patients at this dose. What is currently lacking is a head-to-head trial of second-generation TKIs. Dasatinib use remains controversial in some countries, however, with licensing laws differing between the USA, Europe and the UK. It is clear that longer follow-up will be required for dasatinib to further define its superiority over imatinib and further assess its side-effect profile. Dasatinib is likely to remain an important drug in the management of CML in the future.

Disclosure

Bristol-Myers Squibb have reviewed this article for factual accuracy of dasatinib.

Financial & competing interests disclosure

M Copland has received research funding from Bristol-Myers Squibb and Novartis, honoraria from Bristol-Myers Squibb and Novartis, attended Advisory Boards for Bristol-Myers Squibb and Pfizer and travel funding from Bristol-Myers Squibb. V Campbell is funded by the Wellcome Trust via the STMTI programme. M Copland is funded by the Scottish Funding Council (SCD/04) and Leukaemia and Lymphoma Research (Grant No.: 11017). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in this manuscript apart from those discussed.

No writing assistance was utilized in the production of this manuscript.
Identification of dasatinib as a compound of considerable interest

Papers of special note have been highlighted as:

- References


14. Guidelines to identify patients who have a suboptimal response or are failing tyrosine kinase inhibitor (TKI) therapy.


16. Identification of dasatinib as a compound with anti-tumor activity.


21. Describes the ability of dasatinib to overcome imatinib-resistant BCR-ABL kinase domain mutation in vitro.


26. Phase I clinical trial of dasatinib in imatinib-resistant chronic myeloid leukemia (CML) and Ph+ acute lymphoblastic leukemia.


28. Phase II study demonstrating efficacy of dasatinib in imatinib-resistant and -intolerant chronic phase CML (CML-CP).


30. Phase II study demonstrating the superiority of dasatinib to high-dose imatinib in patients with CML-CP resistant to standard-dose imatinib.


32. Phase III clinical trial identifying dasatinib 100 mg once daily as the recommended treatment schedule in patients with CML-CP.


35. First clinical trial of dasatinib in newly diagnosed CML-CP.


- Large randomized Phase III trial demonstrating the superiority of dasatinib to imatinib in newly diagnosed CML-CP.


- Follow-up paper, confirming that dasatinib maintains superiority over imatinib after 2 years follow-up.


- Discusses management of pleural effusion.


- Identifies pulmonary arterial hypertension as a possible side effect of dasatinib.


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