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Dasatinib: a potent SRC inhibitor in clinical development for the treatment of solid tumors

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Abstract

SRC is a tyrosine kinase that plays a role in oncogenic, invasive and bone-metastatic processes. It has therefore been prioritized as a candidate therapeutic target in patients with solid tumors. Several SRC inhibitors are now in development, of which dasatinib has been most explored. Preclinical studies in a wide variety of solid tumor cell lines, including prostate, breast and glioma, have shown that dasatinib acts as a cytostatic agent, inhibiting the processes of cell proliferation, invasion and metastasis. Dasatinib also inhibits the activity of osteoclasts, which have a major role in the development of metastatic bone lesions. Dasatinib has additive or synergistic activity in combination with a number of other agents, including cytotoxic agents and targeted therapies, providing a rationale for combination treatment in a clinical setting. Emerging clinical data with dasatinib support experimental observations, with preliminary phase 1 and 2 data demonstrating activity, both as a single agent and as combination therapy, in a range of solid tumors. Future clinical trials will further assess the clinical value of SRC inhibition with dasatinib.

Keywords

Dasatinib; SRC kinase; Solid tumors; Bone metastases; Preclinical; Phase 1 clinical trials; Phase 2 clinical trials

Introduction

Tyrosine kinases regulate cell proliferation, growth, migration, differentiation and death, and have therefore emerged as a promising target for cancer therapy. The development of imatinib (Gleevec[®], Novartis), a selective inhibitor of the BCR-ABL tyrosine kinase, revolutionized the treatment of chronic myeloid leukemia (CML).¹ Because constitutively activated BCR-ABL was found to be the cause of more than 90% of CML cases, imatinib became one of the first examples of how understanding the molecular pathogenesis of a disease could guide development of a targeted therapy and produce significant clinical benefits.

Approximately 90 tyrosine kinase genes have been identified. Receptor tyrosine kinases (RTKs) include the epidermal growth factor receptor (EGFR) family, platelet-derived

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growth factor receptor (PDGFR) family, stem cell factor receptor c-KIT, vascular endothelial growth factor receptor family (VEGFR), the ephrin (EPH) receptor family and the fibroblast growth factor receptor (FGFR) family. Nonreceptor tyrosine kinases are cytoplasmic and include SRC and SRC-family kinases (SFKs), C-terminal SRC kinase (CSK), focal adhesion kinase (FAK), the ABL family and the AXL family.² Because a significant number of tyrosine kinases are associated with cancer, many tyrosine kinase inhibitors (TKIs) are currently registered or in an advanced stage of development for the treatment of a wide variety of hematologic malignancies or solid tumors (Table 1). In addition to inhibiting BCR-ABL, imatinib is also active against c-KIT and PDGFR, and is approved for use in patients with gastrointestinal stromal tumors (GIST).³ Because overexpression of the EGFR family, including HER2, is associated with several human malignancies,⁴ TKIs of the EGFR family have been developed, including erlotinib (Tarceva[®], Genentech), gefitinib (Iressa[®], AstraZeneca) and lapatinib (Tykerb[®], GlaxoSmithKline), which are approved treatments for nonsmall cell lung cancer (NSCLC) (erlotinib/gefitinib)⁵ and breast cancer (lapatinib),⁶ and are currently being investigated for other solid tumor indications. Similarly, the VEGF pathway, which plays an important role in tumor angiogenesis, is targeted by sorafenib (Nexavar[®], Bayer) and sunitinib (Sutent[®], Pfizer), both of which are approved for the treatment of renal cell carcinoma.^{7,8} Sorafenib is also approved for the treatment of hepatocellular carcinoma and sunitinib for the treatment of GIST. Other indications currently under investigation include brain and central nervous system tumors, mesotheliomas and neuroendocrine tumors. Multiple clinical trials are in progress for novel agents and alternative indications, further illustrating the broad clinical potential of TKIs.

Among tyrosine kinases, SRC has arguably had the longest association with cancer. In the early 1970s, a virus-encoded form of *SRC* was the first oncogene to be identified. Since then, a multitude of experimental studies have shown that SRC is involved in oncogenic and invasive processes, and that SRC partly mediates signaling from multiple potentially oncogenic receptors, including EGFR, HER2, PDGFR, FGFR and VEGFR.⁹⁻¹² SRC signaling is also involved in normal bone remodeling and in the formation of bone metastases.¹³⁻¹⁷ On the basis of this evidence, SRC has been prioritized as a candidate therapeutic target in solid tumors, and several SRC inhibitors are now in clinical development, including dasatinib (SPRYCEL[®], Bristol-Myers Squibb), bosutinib (formerly SKI-606, Wyeth) and saracatinib (formerly AZD0530, AstraZeneca).

Dasatinib is the most clinically studied SRC inhibitor. In addition to potently inhibiting SRC and SFKs, dasatinib also inhibits other TKIs including c-KIT, PDGFR, c-FMS and EPHA2 receptor.¹⁸⁻²⁰ Like imatinib, dasatinib is a potent inhibitor of BCR-ABL, and dasatinib is also approved for the treatment of CML and Philadelphia chromosome-positive acute lymphoblastic leukemia following resistance or intolerance to imatinib therapy.²¹ Because of this, the safety and tolerability of dasatinib treatment has already been extensively tested in patients with hematologic malignancies. The aim of this review is to summarize experimental data with dasatinib in solid tumors and to discuss the rationale for using dasatinib in combination with other agents. Emerging clinical data supporting experimental observations are also discussed.

Preclinical activity of dasatinib

The activity of dasatinib has been studied in cell lines derived from various solid tumors, including prostate, breast, glioblastoma and others.

Prostate cancer

SFKs, including SRC and FYN, are highly expressed in prostate cancer cell lines in a stage-dependent manner, and are associated with the progression of prostate cancer from an androgen-dependent to androgen-independent state.²²⁻²⁴ Prostate cancer cell lines exhibiting low androgen receptor (AR) activity by transcriptional profiling exhibit high SRC activity,²⁵ and a correlation between increased SRC activity and both a short duration of response to androgen-ablation therapy and shorter overall survival has recently been reported.²⁶ These findings provide a clear rationale for investigating the potential of dasatinib-mediated SRC inhibition in prostate cancer.

In preclinical studies in prostate cancer, dasatinib rapidly inhibited SFK activity in all cell lines and selectively inhibited downstream FAK signaling, resulting in the inhibition of cell adhesion, migration and invasion.^{27,28} Specific inhibition of SRC in cultured prostate tumor cells indicated that SRC activation is predominantly required for cellular properties associated with metastasis rather than proliferation.²⁸ In an orthotopic nude mouse model of prostate cancer, tumors from dasatinib-treated mice were of significantly lower weight than tumors from control mice, and dasatinib administration significantly reduced the incidence of lymph node metastases.²⁸ This was an important finding, because lymph node metastases in patients with prostate cancer are associated with a poor prognosis, increased risk of recurrence and reduced disease-free survival. The prognosis for patients with prostate cancer that progresses despite castrate levels of androgens, ie, castration-resistant prostate cancer (CRPC), is also poor. Tatarov et al. investigated the effects of dasatinib in LNCaP-SDM cells, which were derived from the hormone-responsive LNCaP cell line by selection in an androgen-depleted environment and were therefore considered to reflect the castration-resistant state. Importantly, LNCaP-SDM cells express the AR, which is also found in the majority of prostate tissue specimens taken from patients with CRPC. In vitro, dasatinib inhibited the proliferation and migration of LNCaP-SDM cells, whereas only migration was suppressed in the parental LNCaP cell line. These findings suggest that dasatinib might have additional activity in patients with CRPC compared with hormone-sensitive prostate cancer.²⁶

Breast cancer

The increased expression and activity of SFKs in human breast cancer tissue compared with matched nontumor tissue suggests an important role for SFKs in breast cancer biology.²⁹ The effects of dasatinib were investigated using a panel of 39 human breast cancer cell lines that were categorized into luminal or basal breast cancer subtypes based on their gene expression profile. Sensitivity to dasatinib was determined according to the ability of dasatinib to inhibit cell growth in a proliferation assay. A strong correlation was observed between in vitro sensitivity to dasatinib and the basal subtype of human breast cancer (triple negative, ie, estrogen receptor [ER] negative, progesterone receptor [PgR] negative and HER2 negative). Response to dasatinib was sensitively and specifically predicted by increased expression of moesin, caveolin-1 and YAP-1, suggesting that these genes could have clinical utility as predictive markers.³⁰ Similarly, when profiling 23 breast cancer cell lines, Huang et al. identified a baseline gene expression signature that correlated with in vitro sensitivity to dasatinib and interestingly, was expressed by patients with triple-negative breast cancer.³¹ Some investigators partly attributed growth inhibition by dasatinib in triple-negative breast cancer cell lines to c-KIT inhibition.³²

EGFR overexpression is associated with breast cancer disease progression and is implicated in the development of drug resistance.^{33,34} Studies in breast cancer cells have highlighted interactions between SRC and EGFR, with SRC overexpression observed in tumors that overexpress EGFR.³⁵ In vitro, dasatinib inhibited the growth of human breast cancer cell

lines representing both basal and luminal breast cancer subtypes, including cells with high-level EGFR expression. The range of dasatinib-mediated effects has been illustrated using the MDA-MB-468 breast cancer cell line, which expresses high constitutive levels of EGFR. In MDA-MB-468 cells, dasatinib inhibited G1/G0 to S-phase cell cycle progression and stimulated apoptosis through the activation of caspases-8 and -9. At a cellular level, dasatinib inhibited the metastatic processes of colony formation, migration and invasion.¹² These data suggest that SRC inhibition could have the potential to decrease oncogenic effects of EGFR and augment responses to EGFR-targeted agents.

Glioma

Transgenic mice spontaneously expressing v-SRC develop glioblastoma tumors with a molecular biology closely matching that of the human form, suggesting a role for SRC in glioma development and progression.³⁶ Indeed, dysregulated signaling by SRC kinases is involved in glioma-related proliferation, angiogenesis, migration and survival.³⁷ Using a bead-based method to profile tyrosine kinase phosphorylation, Du et al. showed that SRC was activated in glioblastoma cell lines and primary patient samples.³⁸ In a panel of 71 cell lines, dasatinib inhibited proliferation and cell migration, in addition to inducing apoptosis. Notably, dasatinib consistently inhibited glioblastoma cell migration even in cells where no growth inhibition was observed, supporting studies from other tumor types suggesting that SRC has a particularly important role in metastasis. In an orthotopic mouse model of glioblastoma described in the same report, dasatinib treatment significantly attenuated tumor growth. When kinase targets of dasatinib other than SRC were engineered to be dasatinib resistant and introduced into glioblastoma cells, mutant kinases failed to rescue cells from the inhibitory effects of dasatinib, confirming that SRC was the relevant target in this setting.³⁸

Other solid tumors

Because there is evidence to suggest a role for SRC in other tumor types, including NSCLC,^{39,40} colorectal cancer,⁴¹ pancreatic cancer,⁴² head and neck squamous cell carcinoma (HNSCC),⁴³ and melanoma,⁴⁴ the effects of dasatinib have also been investigated in cell lines derived from these solid tumors.^{19,45-52} Across different studies, dasatinib had variable effects on cell proliferation. For example, although dasatinib inhibited the proliferation of NSCLC and pancreatic cell lines, it had limited effects on the proliferation of cell lines derived from human melanomas. Interestingly, differential effects on proliferation extended to cell lines derived from the same tumor type. In epithelial colon tumor lines, dasatinib treatment at SRC-inhibitory concentrations inhibited proliferation in only two of the 12 cell lines studied.

In vitro apoptotic effects of dasatinib have been minimal; however, dasatinib has consistently inhibited cell migration and invasion, supporting the antimetastatic effects previously observed in animal models of prostate cancer.²⁸ In addition, in an orthotopic nude mouse model, the incidence of pancreatic tumor metastasis was significantly reduced with dasatinib treatment, with only 14% of treated mice developing metastases compared with 60% of control mice.⁴⁸

Predicting clinical effects of dasatinib using preclinical data

Overall, preclinical studies demonstrate that dasatinib has variable effects on cell proliferation and infrequently induces apoptosis, but consistently inhibits cell adhesion, migration and invasion. As such, the effects of dasatinib could be described as cytostatic rather than cytotoxic. Because cytostatic agents are likely to inhibit tumor growth but are unlikely to induce tumor shrinkage, this information is important for the clinical setting and trial endpoints should be selected accordingly. However, additional effects of dasatinib

could also result in clinical benefits, particularly the prevention of metastases. With regard to the effects of SRC inhibitors on osteoclasts (summarized below), this may be of particular relevance in patients with tumors that commonly metastasize to bone.

Osteoclast activity

Bone metastases frequently occur in patients with advanced solid tumors and are an important cause of morbidity and mortality. In most cases, the resulting bone lesions have a predominantly osteolytic phenotype; however, in prostate cancer, bone lesions tend to be predominantly osteoblastic.⁵³ Regardless of overall phenotype, excessive osteoclast activity is detectable in bone metastases and is a key cause of pathology.¹³ Because SRC signaling has a central role in osteoclast proliferation and function, the ability of dasatinib to inhibit osteoclast activity is an important area of research (Fig. 1).⁵⁴

In a study by Luo et al., dasatinib potently inhibited osteoclast proliferation in bone marrow cell culture and rapidly suppressed serum calcium levels in a dose-dependent manner in a rat model of bone resorption.⁵⁵ Vandyke et al. examined the effects of dasatinib on human and murine osteoclast formation and activity in vitro.⁵⁶ Peripheral blood mononuclear cells from healthy volunteers were cultured to induce osteoclastogenesis and treated with either dasatinib 20 nM or control. After 14 days, dasatinib treatment resulted in a significantly lower number of osteoclasts than in the control culture. In a murine osteoclastogenesis assay, calcium resorption was significantly inhibited, indicating that dasatinib significantly reduced osteoclast activity. The authors suggested dasatinib inhibition of FMS, a tyrosine kinase receptor for macrophage colony-stimulating factor (M-CSF), could be responsible for antiosteoclast effects of dasatinib and in a separate study by Brownlow et al., dasatinib inhibition of FMS activity and osteoclast production were confirmed.¹⁸ In a recent study involving mice inoculated with bone metastatic cells derived from a triple-negative breast cancer cell line, dasatinib treatment significantly prevented the formation of osteolytic metastases.¹⁷ Similarly, when prostate cancer cells were injected into tibiae of mice, dasatinib treatment decreased tumor growth in the bone environment and increased the bone mineral density of both normal bone and bone harboring osteolytic lesions.⁵⁷ Overall, these studies have demonstrated antiosteoclast activity with dasatinib across a variety of models, which could potentially increase the range of effects of dasatinib in tumors that commonly metastasize to bone.

Rationale for combination treatment with dasatinib

In many patients with solid tumors, it is unlikely that a single tyrosine kinase abnormality is the sole pathologic cause of malignancy, and as individual tumors progress, they develop multiple genetic abnormalities within the same cell or among different cellular clones. In addition, although excessive expression of SRC or other SFKs can be oncogenic, cell signaling is complex and compensatory prosurvival pathways might be activated following SRC inhibitor treatment through feedback mechanisms. Interestingly, increased SRC activation has been shown to contribute to chemoresistance, which can be counteracted in vitro using SRC inhibitors.⁵⁸ Taken together, these facts strongly suggest that using dasatinib or other SRC inhibitors in combination with other therapeutic agents is a rational strategy. This could involve combining these potentially cytostatic therapies with another targeted therapy or with nonspecific cytotoxic agents that can induce tumor shrinkage.

Cetuximab is a monoclonal antibody inhibitor of EGFR. In NSCLC cell lines with acquired resistance to cetuximab, SFK activation was increased relative to the parental line. When cetuximab-resistant cells were treated with the EGFR inhibitors (erlotinib or gefitinib) or siRNA directed against EGFR, SFK activity was downregulated. Following dasatinib treatment, cetuximab-resistant cells exhibited a decrease in total EGFR phosphorylation and

SFK activity, resulting in inhibition of cell proliferation. To examine whether dasatinib could resensitize cetuximab-resistant cells to cetuximab therapy, cells were treated concurrently with both drugs. Combination treatment augmented growth inhibition, indicating that dual targeting of EGFR and SFKs might have a greater clinical impact than either agent alone.⁵⁹

When the effects of dasatinib in combination with doxorubicin, an anthracycline, were evaluated in a variety of breast cancer cell lines with differing sensitivities to dasatinib, combination treatment synergistically decreased cell metabolism, proliferation and viability in a dasatinib-insensitive cell line and increased the inhibition of migration and invasion of dasatinib-sensitive cells compared with either drug alone.⁶⁰

In human small cell lung cancer (SCLC), activated AKT is associated with resistance to the chemotherapy drug amrubicin, and combination treatment of SCLC cells with amrubicin and AKT-suppressing agents resulted in synergistic growth inhibition. Because a link between SRC signaling and AKT has been proposed, Ueda et al. investigated the effects of dasatinib alone and in combination with amrubicin in a SCLC cell line.⁶¹ Dasatinib inhibited SRC and AKT phosphorylation in parallel, and demonstrated synergistic inhibition of cell growth in combination with amrubicin.⁶¹

The combination of dasatinib with chemotherapeutic agents has also been investigated in cell lines from various other tumors. In melanoma cell lines, dasatinib enhanced antiproliferative effects of cisplatin, epirubicin and docetaxel, but not paclitaxel, and contrasting effects were reported with temozolomide in different cell lines.^{50,62} In colorectal cancer models, a combination of oxaliplatin, which has been shown to activate SRC, and dasatinib also resulted in higher levels of tumor growth inhibition. This finding was substantiated in a mouse model in which dasatinib or oxaliplatin alone resulted in no statistically significant reductions in tumor volume, whereas combination therapy resulted in a 92% reduction relative to untreated controls.⁶³ Dasatinib has also shown synergistic inhibition of proliferation, and increased apoptosis of HNSCC, NSCLC and keratinocyte cell lines in combination with an experimental inhibitor of Janus-activated kinase.⁶⁴ Additionally, combination treatment of glioma cells with dasatinib and temozolomide resulted in a significant increase in autophagic cell death compared to either agent alone, and the combination was more effective than dasatinib plus carboplatin or irinotecan.⁶⁵

In addition to synergistic antitumor effects, combination therapy could also result in increased antiosteoclast effects. Inhibitors of heat shock protein (HSP) 90, such as 17-AAG, have shown promising antitumor activity in vivo and are currently being tested in clinical trials. HSP90 inhibition promotes osteoclast maturation by prolonging M-CSF-induced SRC activation and potentiating the association of SRC with FMS. In a xenograft mouse model of prostate cancer, 17-AAG significantly increased tumor growth in bone compared with vehicle-treated controls. When administered in combination with 17-AAG, dasatinib abrogated the in vivo tumor-stimulatory effect in bone, suggesting that in clinical situations, dasatinib coadministration has the potential to counter the osteoclastogenic activity of HSP90 inhibitors.⁶⁶

Clinical experience to-date with dasatinib in solid tumors

The promising preclinical activity of dasatinib, both as a single-agent and in combination, has provided the basis for investigating dasatinib as a targeted agent in the clinic. Patients with a variety of solid tumors have been treated with dasatinib in a series of phase 1 and 2 trials (Tables 2 and 3),^{54,67-84} and for patients with CRPC, clinical development is now in phase 3. Results from these clinical trials are summarized below.

Phase 1

The safety, tolerability and pharmacokinetics of dasatinib monotherapy were assessed in two phase 1 dose-escalation studies (CA180-021 and CA180-003). In CA180-021, the maximum tolerated dose (MTD) was determined as 180 mg QD continuous dosing.⁶⁷ In CA180-003, in which 67 patients received dasatinib 35–160 mg BID in 28-day cycles either for five consecutive days followed by two non-treatment days (5D2) or as continuous BID dosing, MTDs were 120 mg BID (5D2) and 70 mg BID (continuous schedule). Pharmacokinetic data indicated rapid absorption, dose proportionality and a lack of drug accumulation.⁶⁸

Several phase 1 studies have been initiated to assess dasatinib-based combination therapy in patients with solid tumors refractory to standard therapy. Because increased SRC phosphorylation has been associated with gemcitabine resistance in pancreatic cell lines,⁸⁵ combining dasatinib with gemcitabine may be one approach for overcoming clinical resistance. To investigate this, a phase 1 study was conducted in which 12 patients received both dasatinib and gemcitabine. Three patients had SD for 4 months or longer and one patient with inflammatory breast cancer had a confirmed PR.⁶⁹ This was investigated further in a study of patients treated with either dasatinib plus gemcitabine or dasatinib plus gemcitabine and cetuximab. In this study, eight patients had SD as their best response, which was maintained for a median of 5 months.⁷⁰ When dasatinib was investigated in combination with cetuximab alone, early onset, self-limited headache was the predominant toxicity, and dasatinib 150 mg QD administered 3 days after a loading dose of cetuximab was recommended for further study. The pharmacokinetic parameters of dasatinib administered alone or in combination with cetuximab were comparable and of 17 patients, nine had SD as best response.⁷¹

Combination therapy has also been investigated in a number of specific indications, including dasatinib plus capecitabine in women with advanced breast cancer, dasatinib plus erlotinib in patients with recurrent NSCLC or glioma, and dasatinib with 5-fluorouracil, leucovorin, oxaliplatin (FOLFOX) and cetuximab in patients with treatment-refractory colorectal cancer. In each case, combination therapy was well-tolerated with preliminary evidence of antitumor activity reported (Table 2).^{75,78,80,82}

Phase 2

In patients with CRPC, dasatinib has been examined both as monotherapy (CA180-085) and in combination with docetaxel, the current standard of care for patients with metastatic CRPC (CA180-086). In different enrollment periods of study CA180-085, patients received dasatinib as either 100 mg BID (n=25), 70 mg BID (n=22), or 100 mg QD (n=48). Of 95 treated patients, two had a confirmed PSA response, one had a PR and 22 (23%) had RECIST-criteria SD. In patients who had bone marker assessments at baseline and on study, 57/82 (70%) experienced a 35% decrease in urinary N-telopeptide (UNTx), a marker of osteoclastic bone resorption, and 54/88 (61%) experienced a decrease in bone-specific alkaline phosphatase (BAP), a marker of osteoblast differentiation and activity that is also elevated in patients with metastatic bone disease.^{54,72,86} Efficacy was similar in different dasatinib dosing groups. However, in addition to fewer dose interruptions, fewer treatment-related AEs were reported with dasatinib 100 mg QD than with BID dosing (any AE: 90% vs 100%, $P=0.06$; grade 3/4 AEs: 13% vs 32%, $P=0.03$; pleural effusion: 19% vs 51%, $P=0.001$).^{54,72} Indeed, in several phase 2 studies of dasatinib in solid tumors that have been performed or are underway, treatment was initiated at 100 mg BID but was subsequently amended to 70 mg BID or 100 mg QD to improve tolerability.

CA180-086 was a phase 1/2 study in 46 patients with CRPC designed to assess combination treatment with dasatinib and docetaxel. In the phase 1 portion, combination treatment was

well tolerated, with no dose limiting toxicities observed and the MTD not reached. In addition, PK parameters of dasatinib and docetaxel alone or in combination were similar, indicating no drug–drug interactions. Dasatinib 100 mg QD and docetaxel 75 mg/m² Q21D doses were selected for the phase 2 portion of the study.⁷³ Among 46 treated patients from phase 1 and 2, 13 patients (28%) achieved a confirmed PR and eight additional patients achieved an unconfirmed PR or SD lasting at least 18 weeks. A PSA response was observed in 21/43 patients (49%), 17/34 (50%) patients experienced a 35% decrease in uNTX and 24/32 (75%) experienced a decrease in BAP. Bone scans showed a reduction in the size and number of lesions in 11/39 (28%) patients after at least 6 weeks of treatment and 11 patients experienced a grade 3 AE.⁷⁴ Additional endpoints, including overall survival, time to skeletal-related events and pain, will be evaluated at later time points.

These two studies in patients with CRPC demonstrate that dasatinib favorably modulates bone turnover, both as a single agent and in combination with docetaxel, supporting the notion of dual antitumor and antiosteoclast targeting. Bone-targeting activity was also observed in a subset of patients enrolled in a phase 2 trial of dasatinib in relapsed multiple myeloma. In this study, markers of bone metabolism, including serum NTX, osteocalcin and BAP were measured at baseline and after each 28-day treatment cycle. Dasatinib therapy was associated with decreased osteoclast function, with a lack of paraprotein responses suggesting that the effect was due to osteoclast inhibition.⁸⁷

Three further phase 2 studies of dasatinib are ongoing in prostate cancer. CA180-097 is investigating dasatinib as a single agent in patients with CRPC who have previously been treated with chemotherapy (NCT00570700). A second trial is investigating dasatinib in combination with leuprolide acetate, a luteinizing hormone-releasing hormone analog, in patients with high-risk localized prostate cancer (NCT00860158) and in the third study, dasatinib is being investigated in patients with CRPC and low level AR activity, selected according to patient-specific genomic expression signatures of AR activity in tissue harvested from metastatic lesions (NCT00918385).

Results from two phase 2 studies of dasatinib in breast cancer have been reported. CA180-059 was a study of dasatinib 100 or 70 mg BID monotherapy in 44 patients with advanced triple-negative breast cancer. One patient discontinued because of unrelated AEs. Of the 43 remaining patients, two achieved confirmed PR, 11 achieved SD (two for >16 weeks) and four additional patients achieved transient clinical benefit documented as anecdotal decrease in bone pain or short-term tumor shrinkage (11–29%).⁷⁶ CA180-088 evaluated dasatinib 100 mg BID (initially) or 70 mg BID in 70 patients with advanced breast cancer and progressive measurable disease. Patients with HER2-amplified tumors (n=24) or estrogen receptor (ER) and/or PgR-positive tumors (n=46) were recruited. Three patients had a confirmed PR and six had SD lasting at least 16 weeks; all nine had had ER+ and/or PgR+ tumors. The most frequent AEs of any grade were fatigue (or asthenia), gastrointestinal symptoms, headache, pleural effusion and rash.⁷⁷ Ongoing phase 2 studies are assessing dasatinib in women with treatment-naïve, locally advanced, triple-negative breast cancer (NCT00817531), and dasatinib in combination with hormonal therapies, including fulvestrant (CA180-158; NCT00754325), exemestane (CA180-261; NCT00767520) and letrozole (CA180-185; NCT00696072). In addition, a phase 2 study is underway to determine if patient selection, based on the molecular features of their breast cancer can increase clinical responses to dasatinib (2007-0574; NCT00780676).

Separate phase 2 studies are also ongoing in NSCLC, HNSCC, glioblastoma and melanoma and preliminary data have been reported. In 16 patients with metastatic NSCLC treated with dasatinib 100 mg BID as front-line therapy, one had a PR with no evidence of recurrence for at least 18 months, six had SD (including three lasting 4, 6 and 18 months), and nine had

progressive disease.⁷⁹ Fifteen patients with recurrent or metastatic HNSCC were treated with dasatinib 100 mg BID for 28-day cycles. In this study, no grade 3/4 hematologic toxicities were noted, and grade 2–4 nonhematologic toxicities included pleural effusion, nausea/vomiting, dehydration, diarrhea and dyspnea. One patient had SD at 12 weeks but discontinued treatment at 15 weeks because of toxicity, leading to disease progression.⁸³ Of 26 patients treated with dasatinib 100 mg BID for glioblastoma multiforme, evidence of activity was observed in three patients; including one patient with a PR who remained free of PD after 9 months, and two patients with SD remaining free of PD after 13 and 7 months.⁸¹ Lastly, Of 25 evaluable patients with melanoma, three had a confirmed PR lasting 16, 6 and 5 months, one had an unconfirmed PR, which progressed after four 4-week cycles, and one patient had a minor response and remained on study after 24 cycles. In this study, the most frequent toxicities were fatigue, dyspnea and pleural effusion (Table 3).⁸⁴ Point mutations in the *KIT* gene have recently been identified in patients with mucosal, acral lentiginous or chronically sun-damaged melanoma. Interestingly, the most common mutation, L576P, is sensitive to dasatinib but not imatinib. When two patients with L576P-mutated metastatic melanoma were treated with dasatinib, there was a marked reduction in tumor metabolic activity, suggesting dasatinib may have selective activity in a subset of melanoma patients. However, because both patients had tumor regrowth after 4 months of treatment, combinatorial approaches may be required.⁸⁸

Phase 3

Based on encouraging results from the CA180-086 study in CRPC, a randomized phase 3 trial comparing dasatinib plus docetaxel with docetaxel plus placebo is ongoing (NCT00744497). The primary endpoint is overall survival, and secondary evaluations include bone markers, skeletal-related events, pain, time to PSA progression, bone scans, tumor response and safety.

Conclusions

SRC signaling is involved in various oncogenic cellular activities, including growth, invasion and metastasis. Furthermore, SRC regulates osteoclast activity in bone metastases. Together, these facts illustrate that SRC is an attractive therapeutic target for anticancer development. Dasatinib is the most clinically studied SRC inhibitor, and available data provide the first opportunity to evaluate whether targeting SRC represents a viable therapeutic strategy. Preclinical studies in a wide variety of solid tumor cell lines have shown that dasatinib consistently inhibits cell proliferation by inducing cell cycle arrest, ie, cytostatic activity, although dasatinib has been shown to induce apoptosis in some tumor cell lines. Importantly, dasatinib also inhibits cellular activities required for metastasis and osteoclast activity, which may be of particular relevance in preventing tumor progression and blocking metastatic bone activity. In addition, dasatinib has shown additive or synergistic activity in combination with several chemotherapeutics or biologics in vitro, such as those targeting the EGFR receptor, thereby providing a rationale for investigating combination treatment in the clinical setting. Preclinical data with other SRC inhibitors are less extensive, but have shown a similar range of effects as those observed with dasatinib, further supporting SRC inhibition as a therapeutic strategy.

Emerging trial data have demonstrated clinical activity and safety of dasatinib during treatment of patients with solid tumors. At present, studies are most advanced in prostate cancer, although several other tumor types remain under examination. Combination treatment with dasatinib and several other agents has been well tolerated with no unexpected toxicities. Ongoing clinical trials include a phase 3 trial in CRPC in combination with docetaxel, and phase 2 trials in breast cancer in combination with hormonal therapies.

Overall, available clinical data support preclinical studies demonstrating the antitumor, antimetastatic and antiosteoclast activity of dasatinib, both as a single agent and in combination therapy. These pioneering studies with dasatinib demonstrate that SRC inhibition is a strategy worthy of further exploration for the treatment of solid tumors.

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Figure 1.

During bone metastasis, systemic factors within the bone environment and bone-derived growth factors activate the release of factors from metastatic tumor cells that stimulate osteoclast activity. Because SRC signaling has a central role in tumor cell and osteoclast function, the ability of dasatinib to inhibit SRC activity has a potential role in the prevention of osteolytic metastases [adapted from ⁵⁴].

Table 1

Tyrosine kinase inhibitors in clinical practice

Tyrosine kinase inhibitor	Kinase target(s)	FDA-approved indications
Dasatinib (Sprycel)	SRC, SFKs, BCR-ABL, c-KIT, PDGFR, c-FMS, EPHA2	CML (2nd-line), Ph+ ALL
Erlotinib (Tarceva)	EGFR	NSCLC
Gefitinib (Iressa)	EGFR	NSCLC
Imatinib (Gleevec/Glivec)	BCR-ABL, c-KIT, PDGFR	CML, Ph+ ALL, GIST
Lapatinib (Tykerb)	EGFR, HER2/neu	Advanced breast cancer
Nilotinib (Tasigna)	BCR-ABL, c-KIT, PDGFR	CML (2nd-line)
Sorafenib (Nexavar)	VEGFR, PDGFR	renal cell carcinoma, hepatocellular carcinoma
Sunitinib (Sutent)	VEGFR2, PDGFR, c-KIT, FLT3	GIST, renal cell carcinoma

Abbreviations: CML, chronic myeloid leukemia; EGFR, epidermal growth factor receptor; EPHA, ephrin A; FLT3, FMS-like tyrosine kinase 3; GIST, Gastrointestinal stromal tumors; NSCLC, nonsmall cell lung carcinoma; PDGFR, platelet-derived growth factor receptor; Ph+ALL, Philadelphia chromosome-positive acute lymphoblastic leukemia; VEGFR2, vascular endothelial growth factor receptor-2.

Table 2

Results from phase 1 clinical trials of dasatinib in patients with solid tumors

Treatment and study population	Treated patients, n	Tumor response (RECIST) n/n (%)	Most frequent drug-related adverse events	Dose-limiting toxicities
Dasatinib in patients with advanced solid tumors (CA180-021) ⁶⁷	28	1/28 (4) PR	Vomiting, pleural effusion, fatigue	8 reported (not specified)
Dose-escalation study in patients with refractory solid tumors (CA180-003) ⁶⁸	67	11/67 (16) SD	Nausea, fatigue, diarrhea, vomiting, anorexia	17 reported (not specified)
Gemcitabine and dasatinib in advanced solid tumors (2006-0574) ⁶⁹	12	1/5 (20) PR 3/5 (60) SD	Anemia, leukopenia, thrombocytopenia	NR
Gemcitabine and dasatinib or gemcitabine, dasatinib and cetuximab in refractory solid tumors ⁷⁰	25	1/18 PR 8/18 SD	Neutropenia, bilirubin, vomiting	4 reported: neutropenia (Gr 3; GDC; n=1) elevated alanine transaminase (Gr 3; GD; n=2) pneumonitis (Gr 5; GDC, n=1)
Cetuximab and dasatinib in advanced solid tumors (CA180-049) ⁷¹	25	9/17 (53) SD	Headache	3 reported: headache (n=2) nausea
Dasatinib and docetaxel in metastatic CRPC (CA180-086) ⁷³	16	13/31 (42) PR 3/31 (10) uPR 5/31 (16) SD 18 weeks	Fatigue, dysgeusia, GI disorders	None occurred
Dasatinib and capecitabine in advanced breast cancer (CA180-004) ⁷⁵	40	6/27 (22) PR 5/27 (19) uPR 9/27 (33) SD	Fatigue (or asthenia), GI toxicities, hand-foot syndrome, pleural effusion	4 reported: headache pneumonia (n=2) diarrhea (all Gr 3)
Erlotinib and dasatinib for patients with recurrent NSCLC (CA180-080) ⁷⁸	9	5/8 (63) SD	Skin rash, diarrhea, pleural effusions	NR
Dasatinib and erlotinib in recurrent malignant glioma (00002272) ⁸⁰	15	3/6 (50) SD		Fatigue (Gr 4)
Cetuximab and dasatinib combined with FOLFOX chemotherapy in metastatic colorectal cancer (CA180-048) ⁸²	12	2/8 (25) PR	Hypophosphatemia, neutropenia, anemia	Fatigue (Gr 3)

Abbreviations: BID, twice daily; CRPC, castration-resistant prostate cancer; FOLFOX, 5-fluorouracil, leucovorin, oxaliplatin; GD, gemcitabine and dasatinib; GDC, gemcitabine, dasatinib and cetuximab; GI, gastrointestinal; Gr, Grade; NR, not reported; NSCLC, non small cell lung carcinoma; PR, partial response; QD, once daily; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease; uPR, unconfirmed PR

Table 3

Results from phase 2 clinical trials of dasatinib in patients with solid tumors.

Treatment and study population	Treated patients, n	Key efficacy data Response (evaluable patients, n); n (%)
Dasatinib in metastatic CRPC (CA180-085) ^{54,72}	47 (BID)	RECIST (24): 12 (50) SD PSA (43): 1 (2) uNTX (39) / BAP (44): 32 (82) / 28 (63) Bone scan at Week 12 (40): 21 (53) SD
	48 (QD)	RECIST (20): 1(5) PR; 10 (50) SD PSA (43): 1 (2) uNTX 40% (43) / BAP (44): 22 (51) / 26 (59) Bone scan at Week 12 (40): 25 (63) SD
Dasatinib and docetaxel in metastatic CRPC (CA180-086) ⁷⁴	46	RECIST (31): 13 (42) PR; 3 (10) uPR; 5 (16) SD 18 weeks PSA (43): 1 (2) uNTX 35% (34) / BAP (32): 17 (50) / 24 (75) Bone scan at Week 6 (39): 11 (28) improvement
Dasatinib in patients with advanced 'triple-negative' breast cancer (CA180-059) ⁷⁶	44	RECIST (43): 2 (5) PR; 2 (5) SD 16 weeks
Dasatinib in advanced estrogen/progesterone receptor-positive or HER2/neu-positive breast cancer (CA180-088) ⁷⁷	70	RECIST (69): 3 (4) PR; 6 (9) SD 16 weeks
Dasatinib in recurrent NSCLC (MDA-2006-0593) ⁷⁹	16	RECIST (16): 1 (6) PR; 6 (38) SD
Dasatinib in recurrent glioblastoma multiforme (RTOG-0627) ⁸¹	26	RECIST (26): 1 (4) PR ; 2 (8) SD
Dasatinib in HNSCC (2006-0571) ⁸³	15	RECIST (15): 1 (7) SD 12 weeks
Dasatinib in advanced melanoma (YALE-HIC-0608001765) ⁸⁴	25	RECIST (25): 1 (4) uPR; 3 (12) PR

Abbreviations: BAP, bone alkaline phosphatase; BID, twice daily; CRPC, castration-resistant prostate cancer; HNSCC, head and neck squamous cell carcinoma; NSCLC, non small cell lung carcinoma; PR, partial response; PSA, prostate-specific antigen, QD, once daily; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease; uNTX, urinary N-telopeptide; uPR, unconfirmed PR