Cancer Treatment Reviews 36 (2010) 492–500

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Hot Topic

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

John Araujo *, Christopher Logothetis [1]

Genitourinary Center, M.D. Anderson Cancer Centre, Houston, TX, USA

ARTICLE INFO

Article history:
Received 22 December 2009
Received in revised form 2 February 2010
Accepted 6 February 2010

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

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 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.

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 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

* Corresponding author. Address: Genitourinary Center, M.D. Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 428, Houston, TX 77030, USA. Tel.: +1 713 792 2830; fax: +1 713 792 1654.
E-mail addresses: johna@mdanderson.org (J. Araujo), clogothe@mdanderson.org (C. Logothetis).
[1] Tel.: +1 713 563 7210; fax: +1 713 792 1654.

0305-7372/$ - see front matter © 2010 Published by Elsevier Ltd.
doi:10.1016/j.ctrv.2010.02.015

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.

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, i.e., 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, i.e., 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