Src Continues Aging: Current and Future Clinical Directions

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Abstract Aberrant activation of members of the Src family of nonreceptor protein tyrosine kinases is common in solid tumor malignancies and may contribute to the development and/or progression of these tumors. As a result, four Src inhibitors are now in more than 50 clinical trials for at least 14 different types of solid tumors. In this review, we briefly discuss the preclinical rationale for Src inhibitors, the development strategies most likely to be successful in the clinic, and the rationale for Src inhibitors in combination with other agents as part of a more comprehensive therapeutic strategy. As the use of Src family inhibitors in clinical trials on solid tumors is in its infancy, further studies on the roles of Src family kinases in tumor progression, chemoresistance, epidermal-to-mesenchymal transition, and other properties of tumor progression will be important in designing the most effective clinical trials using these inhibitors.

Very few molecular targets in oncology have the pedigree of Src: the first oncogene discovered, the first shown to have intrinsic tyrosine kinase activity, and the subject of two Nobel prizes. The virus harboring v-Src, Rous sarcoma virus, was discovered early in the 20th century as a transmissible agent that induced sarcomas in fowl (1). V-Src was then used to show that viral oncogenes originated from normal cellular proto-oncogenes (2). Thus, many of the concepts of proto-oncogenes and their roles in signal transduction and cancer emanated from studies on Src. Nevertheless, until recently, Src was not seriously considered as a target for development of anticancer drugs. With a maturing understanding of the complexities of Src function and the burgeoning number of Src inhibitors entering the clinic, however, Src and its family members have indeed come of age as a potential target for cancer therapy.

Src is the prototypical member of a nine-gene family that includes Yes, Fyn, Lyn, Lck, Hck, Fgr, Blk, and Yrk (3). Src and Src family kinases cooperate in several cellular processes including migration, adhesion, invasion, angiogenesis, proliferation, differentiation, and immune function (for detailed reviews, see refs. 4–6). Based on several lines of promising preclinical research, Src is now being extensively studied in the clinic. This review will touch only briefly on Src functions, focusing instead on the areas of greatest promise and greatest difficulties for moving Src inhibitors from the laboratory to success in the clinic.

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Received 8/2/07; revised 10/2/07; accepted 10/3/07.

Grant support: NIH grants U54 CA 090810 and 5 P20 CA101936 (G.E. Gallick), K12 CA 088084 (S. Kopetz), and T32 CA 09599 (A.N. Shah), and The Eleanor B. Pillsbury Fellowship-University of Illinois Hospital (A.N. Shah).

Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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doi:10.1158/1078-0432.CCR-07-1902

Src Structure and Function

Src family kinases consist of a unique NH_2-terminal region, two Src homology domains (SH2 and SH3), a highly conserved kinase domain, and a COOH-terminal tail containing a negative regulatory tyrosine residue. The phosphorylation of the COOH-terminal tail by COOH-terminal Src kinase (Csk) results in a closed, less active protein conformation. Autophosphorylation in the kinase domain alters the conformation to increase the intrinsic kinase activity. This relative simplicity of regulation belies the fact that Src can be activated by a host of interacting proteins including growth factor receptors, integrins, and G protein–coupled receptors.

Because of their central role in multiple signaling pathways, aberrant Src activity promotes dysregulation of numerous processes, including invasion, migration, proliferation, angiogenesis, and apoptosis (for reviews, see refs. 4, 7). Ironically, these processes are associated primarily with tumor progression and metastasis despite early observations that v-Src was a tumor-initiating oncogene. Biological functions also mediated by Src activity in tumor cells include epithelial-to-mesenchymal transition, which is implicated in cancer progression and development of chemotherapy resistance (8, 9). Further, Src functions in endothelial cells and stromal cells, and elegant recent experiments have shown that Src activation in these cells contributes to dissemination of metastatic tumor cells (10).

Part of the slow acceptance of Src as a drug development target was due to the lack of mutation or gene amplification in the vast majority of tumors. Instead, enzymatic activity increases in the majority of primary tumors, with further increases in synchronous metastases (11). In colorectal carcinoma, increased Src activity correlates with patient survival (12, 13). Although Src activation is prominent in colorectal and breast cancers, overexpression or activation is also seen in most other tumor types (7, 14–17).

Several mechanisms lead to increased Src activity in tumors. Src is downstream in signaling from a number of growth factor receptors including epidermal growth factor receptor (EGFR), platelet-derived growth factor receptor, and vascular

endothelial growth factor receptor (3, 18). In many tumor types, overexpression of these receptors, their ligands, or both is common (19). Overexpression of other Src binding partners, including focal adhesion kinase, also activate Src (20), as do physiologic processes such as cellular stress, including that induced by chemotherapy.

The Transition of Src Inhibitors to the Clinic

Currently, four compounds have sufficient potency and acceptable toxicity for development as Src family inhibitors. Three compounds, dasatinib, bosutinib, and AZD0530, are small-molecule competitive inhibitors of ATP binding and are also inhibitors of Abl and BCR-Abl, and a fourth, KXO1, inhibits binding of selective Src substrates. Although initially selected for its ability to inhibit Src, dasatinib has been approved by the Food and Drug Administration for the treatment of imatinib-refractory chronic myelogenous leukemia based, in part, on a 95% complete hematologic response rate for chronic-phase chronic myelogenous leukemia (21). As a result of this approval, the side effect profile of dasatinib has been the best described. Pleural effusions occur in 35% of chronic myelogenous leukemia patients in one study and were a prominent toxicity in one phase I study in patients with solid tumors (22). Despite the fact that grade 3 or 4 neutropenia and thrombocytopenia were seen in 45% and 35% of chronic myelogenous leukemia patients, respectively, myelosuppression has not been prominent in studies of dasatinib in patients with solid tumors (21, 22). Mild peripheral edema and hypocalcemia have also been reported (21).

There is not a convincing overlap in the toxicity profiles seen with the various agents, suggesting that many of the side effects may be agent specific. Phase I trials of other Src inhibitors have also been fairly well tolerated (23, 24). Dose-limiting toxicities for these Src family kinase inhibitors have included diarrhea and fatigue.

Guided by preclinical investigations, clinical development has proceeded with trials with inhibitors as single agents and with multiple combinations, including growth factor receptor inhibitors, traditional cytotoxic chemotherapy, and hormonal therapies (Fig. 1). More than 50 trials of Src inhibitors are currently ongoing or soon to open (Table 1; for all publicly available trials at the time of this review, see Supplementary Table S1).

Single-agent trials and preclinical rationale. As single agents, Src inhibitors are undergoing investigation in most major tumor types, including breast, lung (non–small-cell and small-cell), colorectal, pancreatic, prostate, and renal cell carcinomas, as well as in less common tumor types such as mesothelioma, melanoma, and sarcoma based on preclinical evidence of Src activation in these tumors (25–27). For example, in a breast cancer murine model, treatment with bosutinib reduced the volume of mammary fat pad tumors compared with untreated controls (28). A prostate murine model showed reduction in the growth of primary prostatic tumors after treatment with AZD0530 (29). In some cell lines, however, the effects of Src inhibitors on cell proliferation seem to be independent of Src inhibition and, instead, may be the result of inhibition of other tyrosine kinases (30, 31).

Despite this initial broad approach to exploring the action of Src as a single agent, most preclinical reports suggest that Src inhibitors affect proliferation in only a small subset of cell lines or animal tumors (32–34). For these reasons, as single agents, Src inhibitors would be predicted to have modest benefit in most tumors, a prediction supported by the initial results from single-agent phase I studies, in which radiographic tumor regression has not been seen. Instead, the best reported responses have been stable disease in a variety of tumor types,

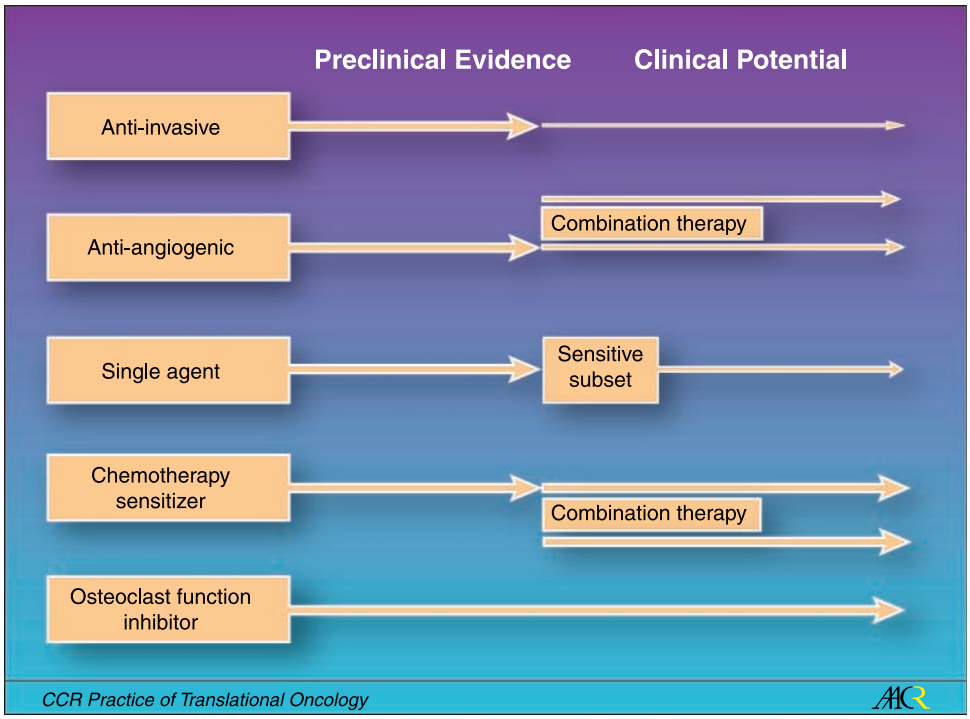

Fig. 1. Preclinical evidence and predicted clinical potential for Src inhibitors. Strong preclinical data support Src inhibition in multiple antitumor and anti-invasive functions. As a result, numerous clinical trials with Src inhibitors are in progress. Based on preliminary clinical results, properties of Src inhibitors, and past successes and/or failures with protein tyrosine kinase inhibitors, preclinical success will not translate into equivalent clinical success. The thickness of the lines for clinical potential represents the authors' predictions about clinical efficacy; the thicker the line, the more clinical promise.

Table 1. Strategies for use of Src inhibitors in clinical trials

Single agents
Colorectal, pancreatic, small-cell and non–small cell lung, breast, prostate, mesothelioma, hepatocellular, ovarian, head and neck, glioblastoma, sarcoma, melanoma, and nonmelanomatous skin cancer
Combination with Her family
Colorectal, non–small cell lung, pancreatic
Combined with cytotoxics
Colorectal, ovarian, breast, pancreatic, prostate, melanoma
Targeting established bone metastases
Breast, prostate
Combined with hormonal agents
Breast

NOTE: Details on all public trials using Src inhibitors available at the time of this review are provided in Supplementary Table S1.

including breast, colon, non–small cell lung, and pancreatic tumors (23).

As single agents, however, Src inhibitors have been shown to be potent inhibitors of bone resorption by inhibiting osteoclast function. Functional deletion of Src in mice leads to osteopetrosis due to inhibition of osteoclast bone resorptive function (35). In a study of healthy volunteers, serum markers of osteoclastic bone resorption were reduced in a dose-dependent manner after treatment with a Src inhibitor (24). Clinical trials are ongoing to determine the effect of Src inhibitors alone or in combination with a bisphosphonate on previously established bone metastases in breast cancer.

Combination with cytotoxic and biological therapies. Followowing other lines of preclinical investigation, many current trials are exploring the potential benefit of Src inhibitors in combination with chemotherapeutics and biologics targeting the EGFR family. Src activation has been associated with resistance to chemotherapy, including paclitaxel, oxaliplatin, and gemcitabine (36, 37). For example, in a metastatic murine model, Src was activated after oxaliplatin treatment and the combination of oxaliplatin and a Src inhibitor produced synergistic cytotoxicity (38). Src inhibitors may overcome this resistance through inhibition of the antiapoptotic Akt pathway, although the precise mechanism(s) remains unknown (39, 40). Similarly, 5-flurouracil–resistant cell lines are resensitized by a Src inhibitor, an effect that seems to be mediated by modulation of thymidylate synthase (41).

Many studies have shown that Src inhibitors have antiangiogenic effects (42–45). Previous studies of agents targeting the tumor vasculature suggest that, in most tumors, antiangiogenic agents are effective only in combination with cytotoxic chemotherapy. Similarly, the antiangiogenic properties of Src inhibitors are likely best used in combination with other cytotoxic agents.

Combination with EGFR inhibitors. Several trials are exploring the combination of EGFR inhibitors and Src inhibitors based on several lines of research (reviewed in ref. 46). EGFR can activate Src independently of ligand binding; conversely, Src preferentially phosphorylates EGFR at a site that promotes survival. In cells dependent on EGFR for survival, especially cells with EGFR mutations or gene amplification, Src inhibition induces apoptosis (47–49). Combined treatment with Src inhibitors and EGFR inhibitors has been shown to be synergistic (50). Similarly, resistance to cetuximab, an EGFR-directed antibody in clinical use, is associated with Src activation, and Src inhibition results in resensitization (51). This interaction may also extend to other members of the Her family, including Her2, and a trial of a Src inhibitor in combination with a dual EGFR and Her2 inhibitor is ongoing (52).

Combination with hormonal therapy. Many of the same Src modulations occur with antiestrogen therapies. Elevated Src levels have been shown to be associated with tamoxifen resistance, and treatment with a Src inhibitor prevented or reversed the development of this resistance (53, 54). Two phase II studies are exploring the combination of these antiestrogen agents and Src inhibitors in randomized trials in breast cancer.

Antimetastatic applications. As discussed above, numerous studies have shown that Src activation promotes metastasis. For example, cells overexpressing Csk (inactivating Src family kinase activity) lose the ability to invade through Matrigel *in vitro* and to develop metastases *in vivo* (55). Similarly, a carcinoma cell line expressing a dominant negative Src was able to form primary tumors but did not recapitulate the metastatic phenotype of the parental cell line in a murine model (34). Several *in vivo* preclinical studies have shown that pharmacologic inhibitors inhibit development of lymph node and distant metastases (28, 29, 56, 57).

Unfortunately, exploiting an anti-invasive or antimetastatic property of a drug remains difficult (58). For the majority of early-stage tumors, patient outcome is driven by subclinical metastases present at the time of diagnosis and surgery, without a clear window where a patient could obtain benefit from an agent that prevents tumor migration and invasion. As yet, the ability of Src inhibitors to suppress outgrowth of these established subclinical metastases has not been tested.

Conclusion

Several questions remain in the development of Src inhibitors. Can we identify a subgroup of tumors that will be uniquely susceptible to treatment with Src inhibitors? When administered alone or in combination regimens, are Src functions too ubiquitous to be inhibited without unacceptable toxicity in patients? Are there easily assayed and validated biomarkers that will predict success for Src inhibitors? Given that subclinical metastases may already be established at the time of diagnosis, is there a role for an agent with an anti-invasive and antimetastatic phenotype in the clinic? Finally, how will we apply the knowledge gained from ongoing research on the interaction of Src and other targets of interest, including urokinase plasminogen activator receptor, insulin-like growth factor receptor, and c-Met? As yet, we cannot answer these questions. The ability of Src inhibitors to overcome resistance to standard therapies, the early but anecdotal success of Src inhibitors in combination regimens, and the tolerable toxicity profile in most chronic

myelogenous leukemia patients provide hope that Src inhibitors in biologically relevant combination with other anticancer agents will find their way as standard treatments for at least some tumors. The next few years will provide many answers on whether Src inhibitors will find a role in cancer treatment, just in time for the centennial anniversary of the discovery of Rous sarcoma virus. This coming of age of Src has indeed been a long time in coming.

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