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Targeted therapy in oncology: mechanisms and toxicity

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Citation

Steeghs, N. (2009, November 24). *Targeted therapy in oncology: mechanisms and toxicity*. Retrieved from https://hdl.handle.net/1887/14431

Version:	Corrected Publisher's Version
License:	Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden
Downloaded from:	https://hdl.handle.net/1887/14431

Note: To cite this publication please use the final published version (if applicable).

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Small molecule tyrosine kinase inhibitors in the treatment of solid tumors: an update of recent developments

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Ann Surg Oncol. 2007 Feb;14(2):942-53

Abstract

Small molecule tyrosine kinase inhibitors (TKIs) are developed to block intracellular signaling pathways in tumor cells, leading to deregulation of key cell functions such as proliferation and differentiation. Over 25 years ago, tyrosine kinases were found to function as oncogenes in animal carcinogenesis; however, only recently TKIs were introduced as anti cancer drugs in human cancer treatment. Tyrosine kinase inhibitors have numerous good qualities. First, in many tumor types they tend to stabilize tumor progression and may create a chronic disease state which is no longer immediately life threatening. Second, side effects are minimal when compared to conventional chemotherapeutic agents. Third, synergistic effects are seen in vitro when TKIs are combined with radiotherapy and/or conventional chemotherapeutic agents. In this article, we will give an update of the tyrosine kinase inhibitors that are currently registered for use or in an advanced stage of development, and we will discuss the future role of TKIs in the treatment of solid tumors. The following TKIs are reviewed: Imatinib (Gleevec®/Glivec®), Gefitinib (Iressa®), Erlotinib (OSI-774, Tarceva®), Lapatinib (GW-572016, Tykerb®), Canertinib (CI-1033), Sunitinib (SU 11248, Sutent®), Zactima (ZD6474), Vatalanib (PTK787/ZK 222584), Sorafenib (Bay 43-9006, Nexavar®), and Leflunomide (SU101, Arava®).

Introduction

Conventional chemotherapeutical agents act by creating toxic effects on all dividing cells, frequently resulting in severe damage of normal tissues leading to side efects like myelosuppression, alopecia, or gastrointestinal problems. The optimum goal is to find a treatment modality that specifically kills malignant cells and causes little or no side efects. Targeted therapies were developed to target key elements that play a role in tumor development and tumor growth, with hormonal therapy in breast cancer being the oldest targeted therapy known in oncology. A more recent discovery are the tyrosine kinase inhibitors, developed to block intracellular signaling pathways in tumor cells, leading to deregulation of key cell functions such as proliferation and diferentiation. Over 25 years ago, tyrosine kinases were found to function as oncogenes in animal carcinogenesis. However, only recently, tyrosine kinase inhibitors were introduced as anti cancer drugs in human cancer treatment.[1–3]

Tyrosine kinases (TKs) are enzymes that catalyze the phosphorylation of tyrosine residues. There are two main classes of TKs: receptor TKs and cellular TKs. Receptor TKs have an extracellular ligand binding domain, a transmembrane domain, and an intracellular catalytic domain. The kinase is activated by binding of a ligand (mostly growth factors) to the extracellular domain, leading to dimerization of the receptors and autophosphorylation of the tyrosine residues of the intracellular catalytic domain. This results in an active receptor conformation and activation of signal transduction within the cell. Cellular TKs are located in the cytoplasm, nucleus, or at the intracellular side of the plasma membrane. Tyrosine kinases are involved in cellular signaling pathways and regulate key cell functions such as proliferation, diferentiation, anti-apoptotic signaling, and neurite outgrowth (Fig. 1).[4]

Unregulated activation of TKs, through mechanisms such as point mutations or overexpression, can lead to various forms of cancer as well as benign proliferative conditions.[5] These findings lead to the hypothesis that inhibitors of TKs could have antitumor effects, and many tyrosine kinase inhibitors (TKIs) were subsequently developed.[1,5] Today, there are two main mechanisms to block the activation of a tyrosine kinase. First, the TKI can block the ATP-binding side and prohibit the autophosphorylation of the tyrosine residues, and therefore prohibit the activation of the intracellular signal-transduction pathways. These drugs are usually referred to as small molecule tyrosine kinase inhibitors. Second, a monoclonal antibody can occupy the extracellular ligand domain of the receptor tyrosine kinase and prohibit binding of the actual ligand and, therefore, prohibit activation of the intracellular signal-transduction pathways.

In this article, we will focus on the small molecule tyrosine kinase inhibitors. The development and registration of new small molecule tyrosine kinase inhibitors is pro-

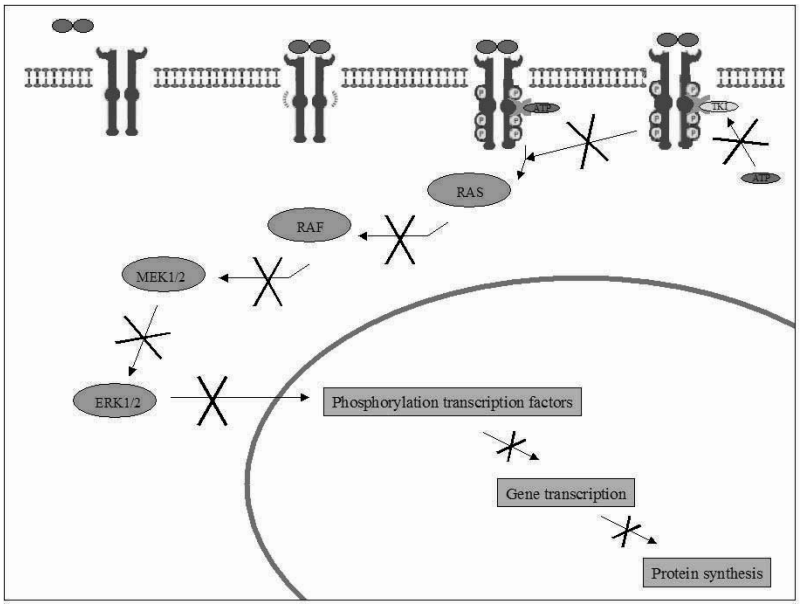

FIG. 1. Tyrosine kinase activation and the MAPK/Erk intracellular signaling pathway; mechanism of action of tyrosine kinase inhibitors (TKIs). The MAPK/Erk intracellular signaling pathway is an example of one of the pathways that can be activated by binding of a ligand (mostly growth factors) to the receptor tyrosine kinase. ATP binds to the tyrosine kinase and auto-phosphorylation takes place, resulting in activation of the MAPK/Erk intracellular signaling pathway. An activated Erk dimer can translocate to the nucleus where it phosphorylates a variety of transcription factors regulating gene expression. Tyrosine kinase inhibitors block the ATP-binding site of the tyrosine kinase and therefore inhibit the activation of the intracellular signaling pathway, resulting in blockage of protein synthesis necessary for proliferation and differentiation of the tumor cells.

ceeding remarkably fast. Therefore, frequent new updates of small molecule tyrosine kinase inhibitors are very relevant for physicians treating cancer patients. In this article, we will give an update of the tyrosine kinase inhibitors that are currently registered for use or in an advanced stage of development, and we will discuss the future role of TKIs in the treatment of solid tumors.

c-KIT Tyrosine Kinase Inhibitors

Imatinib (STI-571, Gleevec® (in US), Glivec® (in Europe))

Imatinib is a small molecule that reversibly competes with ATP for binding to the kinase domain of the c-KIT, c-Abl, and platelet-derived growth factor receptor-β (PDGFR-β) tyrosine kinases. Imatinib was the first commercially available as a small molecule tyrosine

kinase inhibitor, giving astonishing results in patients with chronic myelogenous leukemia (CML) by inhibiting the phosphorylation of the Bcr-Abl TK, and thereby suppressing the proliferation of Bcr-Abl expressing leukemic cells. A phase II study was performed in approximately 1000 patients with CML, with patients in the chronic phase receiving 400 mg of imatinib orally a day, and patients in accelerated phase or blast crisis receiving 600 mg/day. Complete hematological responses were seen in 91% of the patients in chronic phase CML, 53% of patients in accelerated phase CML, and 26% of patients in blast crisis. However, in the late-stages disease, the efects were short lasting, with a recurrence of imatinib-resistant cells within months.[6] In this article, we will focus on the results in solid tumors.

In gastrointestinal stromal tumors (GISTs), imatinib also showed remarkable results.[7,8] Imatinib blocks the c-KIT tyrosine kinase, which is constantly activated in 90% of GISTs by a gain-of-function mutation in the c-KIT proto-oncogene.[9] Approximately 30–50% of GISTs that harbour no c-KIT mutation do have PDGF mutations, and depending on the subtype of the PDGF mutation these GISTs are also sensitive to imatinib. The highest responses were seen in GISTs with exon 11 mutations and, the more rare, PDGF mutations.[9,10] Approximately 5–10% of GISTs are negative for both c-KIT and PDGF mutations. In a phase III trial reported in 2004, 946 patients were randomized for treatment with 400 mg imatinib once daily or 400 mg twice daily.[11] Complete responses were seen in 5 vs. 6%, partial responses in 45 vs. 48%, and stable disease in 32 vs. 32% of patients. At median follow-up of 760 days, 56% in the group receiving imatinib 400 mg once daily showed progression of the disease, compared with 50% of patients receiving 400 mg twice daily. Side effects were frequent but mostly mild. Anemia, edema, fatigue, nausea, pleuritic pain, diarrhea, granulocytopenia, and rash were the most common side effects. These were impressive results for a tumor type that, until recently, was poorly affected by chemo-or radiotherapy and for small molecule TKIs in general. Therefore, studies were initiated to explore the role of imatinib in the adjuvant setting in high risk patients with GISTs. Currently, the results of these studies with adjuvant imatinib in high and intermediate risk GIST are awaited. Resistance to imatinib in GISTs is a well known problem and can be caused by secondary mutations or c-KIT amplification. Therefore, other therapies for GISTs are being explored, like sunitinib (see chapter on sunitinib).[12]

Imatinib is also designated as orphan drug for the treatment of dermatofibrosarcoma protuberans (DFSP), based on case reports of this rare tumor type, in cases that can not be managed with surgery alone.[13,14] The cutaneous malignant mesenchymal tumor dermatofibrosarcoma protuberans is typically associated with a translocation between chromosomes 17 and 22, involving the platelet-derived growth factor-β (PDGF-β) gene, forming a ring chromosome. Imatinib inhibits the growth of these tumor cells by inhibiting PDGFR tyrosine kinase.

Imatinib's activity in advanced aggressive fibromatosis (desmoid tumor) and, to a lesser extent, in advanced chordoma may also be based on PDGFR-β inhibition. In a recently published article, 3 out of 19 desmoid patients demonstrated a partial response, with 4 additional patients showing stable disease for more than one year.[15] In a multicenter phase II trial, 51 patients with advanced aggressive fibromatosis were treated with imatinib 300 mg po BID. At the time of analysis, 45 patients were evaluable. Median time to treatment failure was 6.8 months. Remarkably, in only 1 of 22 available tumor specimens a PDGFR mutation was found.[16] In chordoma patients, the effect was often less clear on CT-scan, but in some cases clearly by subjective improvement of complaints.[17] Recent clinical studies suggest that there might also be an effect of imatinib in glioblastoma multiforme and malignant gliomas by inhibiting PDGFR tyrosine kinase.[18–21]

Imatinib inhibited growth of small-cell lung cancer (SCLC) cells in vitro by inhibiting c-KIT; however, there was no objective tumor response in SCLC patients in vivo. This was probably caused by the fact that there was no c-KIT mutation detectable in most of the patients.[22,23] This was also seen in other tumor types, like uterine leiomyosarcomas.[24]

EGFR/Her1 and Her2 Tyrosine Kinase Inhibitors

The Her-family of tyrosine kinases consists of four members: Her1 (Human Epidermal Growth Factor Receptor: EGFR, erbB1), Her2 (erbB2), Her3 (erbB3), and Her4 (erbB4). After binding of a receptor-specific ligand homodimeric or heterodimeric complexes are formed. Her-kinase activation deregulates growth, desensitises cells to apoptotic stimuli, and regulates angiogenesis.[25] Overexpression of EGFR and Her2 is a factor of poor prognosis in a variety of malignancies, including breast cancer, ovarian cancer, and lung cancer.[26,27]

Gefitinib (Iressa®)

Gefitinib was the first commercially available EGFR TKI and is now registered for use in Asia and the United States in second-or third line therapy for advanced non-small-cell lung cancer (NSCLC). Two phase II trials evaluated the efficacy of gefitinib in patients with advanced NSCLC: IDEAL (Iressa® Dose Evaluation in Advanced Lung Cancer)-1 and IDEAL-2. IDEAL-1 included 210 patients in Europe, Australia, South Africa, and Japan who had previously received one or two chemotherapy regimens, with at least one containing platinum. IDEAL-2 included 216 patients in the United States who had failed two or more prior chemotherapy regimens containing platinum and docetaxel. Patients were

randomized for continuous treatment with 250 or 500 mg gefitinib monotherapy once daily orally.

IDEAL-1 showed that gefitinib dosage of 250 and 500 mg/day were equally efective, with an objective tumor response of 18% and 19% respectively.[28] The objective tumor response rate in IDEAL-2 was 12% in the 250 mg/day gefitinib patients and 9% in the 500 mg/day patients.[29] The difference in response was most likely caused by the worse performance status in IDEAL-2, a higher number of previous chemotherapy regimens in IDEAL-2, and the Japanese origin of a subset of patients in IDEAL-1 (which later became correlated with an higher number of activating mutations in the EGFR gene).[30] Overall survival was 18.5 (IDEAL-1) and 16.3 (IDEAL-2) months in patients with complete or partial response, 8.5 and 9.4 months in stable disease, and 3.8 and 4.2 months in progressive disease. Most reported side effects were cutaneous and gastrointestinal complaints. Since the use of gefitinib became more widespread, a more serious side effect, pulmonary fibrosis, was noted in approximately 1% of patients.[31,32] The recommended dose for use was established at 250 mg/day while this was equally effective and better tolerated.

In large phase III studies, INTACT-1 and-2, gefitinib in combination with chemotherapy in previously untreated NSCLC patients did not show improved efficacy over chemotherapy alone.[33,34] A placebo-controlled phase III trial randomizing NSCLC patients in second-or third-line treatment for treatment with gefitinib 250 mg/day or placebo plus best supportive care also did not show any survival benefit.[35]

In the approval of gefitinib, the EGFR status of the tumor was not included in selecting patients for treatment. Patient characteristics that were associated with responsiveness to EGFR inhibitors were histologic features of adenocarcinoma, female sex, no history of smoking, and Asian ancestry. The EGFR level in immunohistochemical staining does not predict response to EGFR inhibiting therapies and does not correlate with poor survival.[36–38] Recent studies reported an activating mutation in the tyrosine kinase side of the EGFR gene in NSCLC that seemed predictive for response to gefitinib treatment.[39–41] For future use of gefitinib, it will be highly important to select those patients that are likely to benefit from this EGFR-TKI, while non-selection is probably the main cause of the disappointing results of gefitinib.

Phase II studies with gefitinib monotherapy or combination therapy have been conducted in many tumor types, including esophageal carcinoma, metastatic breast cancer, prostate cancer, head and neck cancer, colorectal cancer, renal cell carcinoma, and ovarian carcinoma.[42–53] In EGFR expressing colorectal cancer (CRC), the monoclonal antibody cetuximab has been proven active.[54,55] Therefore, beneficial effects of EGFR TKIs were expected. However, recent trials showed no effect of gefitinib in CRC patients. Of the 115 gefitinib treated patients, only one patient obtained a partial response, progression

free survival was 1.9 months, and median survival 6.3 months. No significant changes in biological indicator of EGFR pathway activation were detected.[52] However, a second phase II trial reported partial responses in 78% of patients treated with gefitinib in combination with fluorouracil and oxaliplatin (FOLFOX-4).[56] Many trials with gefitinib for various tumor types are still ongoing.

Erlotinib (OSI-774, Tarceva®)

Erlotinib is an EGFR TKI with proven efficacy in monotherapy phase II trials in NSCLC, ovarian cancer, pancreatic cancer, head and neck squamous cell cancer, and primary glioblastoma.[57–59]

A survival benefit of erlotinib compared with best supportive care was reported in previously treated NSCLC patients.[60] Patients with stage IIIB or IV NSCLC were randomly assigned in a 2:1 ratio to receive oral erlotinib, at a dose of 150 mg daily, or placebo. The response rate was 8.9 percent in the erlotinib group and less than 1 percent in the placebo group. Progression-free survival was 2.2 months and 1.8 months, respectively. In contrast to the trial with gefitinib,[35] the study comparing erlotinib with best supportive care[60] did show improved survival for erlotinib treated patients. The trials were similarly designed; however, the strict inclusion criterion describing refractory disease in the gefitinib trial may have resulted in a different patient population. After the publication of these trials, clinicians favored the use of erlotinib over gefitinib. However, a trial directly comparing the two drugs was never started.

In phase III trials (TALENT and TRIBUTE) in NSCLC patients, there was no additional benefit of erlotinib in combination with chemotherapy, compared to chemotherapy alone.[61,62] Erlotinib is registered for the second-and third-line treatment of patients with advanced NSCLC after failure of at least one prior platinum treatment.

Since late 2005, erlotinib is also registered for advanced pancreatic cancer. A Phase III trial in 569 chemotherapy-naıve patients with advanced pancreatic cancer reported an improval in 1-year survival from 17% to 24% when erlotinib 100 mg daily was added to gemcitabine 1000 mg/m^2/week, compared to gemcitabine alone.[63] Median overall survival increased from 5.9 months to 6.4 months. EGFR status was not an entry criterion; however, tumor samples are being evaluated for EGFR expression by immunohistochemistry. Current studies in pancreatic cancer patients focus on combination with chemotherapy, radiotherapy, and other targeted therapies, or on maintenance therapy of erlotinib.

A phase II study of erlotinib in patients with advanced biliary cancer showed a potentially beneficial efect of erlotinib. Progression free survival at 6 months was 17% and partial responses were seen in 3 of 42 patients.[64] Earlier, the same author reported

a phase II study of erlotinib in hepatocellular cancer patients. Progression free survival at 6 months was 32%, and partial responses were seen in 3 of 38 patients.[65] Phase II trials in metastatic colorectal carcinoma patients with erlotinib alone or in combination with chemotherapy showed promising results.[66,67] Erlotinib 150 mg orally daily, in combination with bevacizumab 10 mg/kg intravenously every 2 weeks, was evaluated in 63 patients with metastatic clear-cell renal carcinoma, which resulted in a median survival of 11 months and 1-year pro-gression-free survival of 43%. Treatment was well tolerated; skin rash and diarrhea were the most frequent treatment-related toxicities.[68]

The most frequent reported adverse events in erlotinib treatment are skin rash and diarrhea. The incidence of interstitial lung disease in patients receiving erlotinib was equal to that in gefitinib, approximately 1%.[69,70]

Lapatinib (GW-572016, Tykerb®)

Lapatinib is an EGFR and Her2 tyrosine kinase inhibitor.[71] Phase I studies in trastuzumab refractory breast cancer and NSCLC demonstrated clear tumor responses.[72] In a phase II study in 86 patients with metastatic colorectal cancer, effects of lapatinib were minor, with 1 partial response, 5 minor responses, and 5 patients with stable disease.[73] Reported adverse events were diarrhea and skin rash.

An international, multicenter, randomized, open-label phase III trial in patients with documented HER2 overexpressing refractory advanced or metastatic breast cancer treated with lapatinib in combination with capecitabine versus capecitabine alone was recently stopped after the interim analysis. At the time of interim analysis, 392 patients had been enrolled in the study, of which 321 were included in the analysis (161 in the combination arm and 160 in the monotherapy arm). Median time to progression in the combination arm was 8.5 months, compared with 4.5 months in the capecitabine alone arm.[74] The addition of lapatinib to capecitabine resulted in such a striking increase in time to progression that this combination will probably be used by clinicians as standard of care in patients with advanced HER2positive breast cancer that failed on trastuzumab. However lapatinib is not yet registered for use in this, or any, indication.

In a phase III trial, patients with advanced renal cell carcinoma (RCC) who failed prior cytokine therapy were randomized to receive oral lapatinib 1250 mg OD or hormone therapy. At the time of the analysis, 417 patients were randomized. In the general study-population, median time to progression and median overall survival did not difer between the two groups. In the EGFR overexpressing patients, median time to progression was 15.1 months in the lapatinib treated patients, vs. 10.9 weeks in the hormone therapy treated patients. The reported median overall survival was 46.0 vs. 37.9 weeks.[75]

Phase II results on the use of lapatinib in breast cancer patients with brain metasta-

ses, locally advanced squamous cell carcinoma of the head and neck, biliary carcinoma, and hepatocellular carcinoma have recently been reported at the 2006 ASCO Annual Meeting (http://www.asco.org).

Canertinib (CI-1033)

Canertinib is a tyrosine kinase inhibitor that non-selectively inhibits all members of the Her-family. This might result in a broader spectrum of anti tumor activity. In phase I studies, reported adverse events were diarrhea, rash, anorexia.[76] In a phase II study in patients with platinum-refractory or recurrent ovarian cancer, canertinib did not show activity in unscreened patients.[77] Studies in breast cancer and NSCLC are currently ongoing.

Vascular Endothelial Growth Factor Tyrosine Kinase Inhibitors

The Vascular Endothelial Growth Factor (VEGF) family belongs to the platelet-derived growth factor (PDGF) superfamily and consists of VEGF-A, -B, -C, -D, -E, and the placenta growth factor (PlGF). VEGF-A (normally referred to as VEGF) is the most potent endothelial growth factor. It contributes to tumor angiogenesis and presumably to tumor growth and haematogenous spread of tumor cells.[78] Moreover, VEGF-A protects endothelial cells from apoptosis and contributes to the maintenance of the vascular system.[79,80]

Most of the VEGF Receptor (VEGFR) kinase inhibitors under investigation inhibited multiple kinases not involved in angiogenesis, resulting in diverse side efects. New VEGFR kinase inhibitors are being developed to selectively target a small subset of protein kinases, and therefore minimalize the side-efects.

Sunitinib (SU 11248, Sutent®)

Sunitinib is an orally available inhibitor of VEGFR, PDGFR, c-KIT, and FLT-3 kinase activity. In a phase II study in patients with immunotherapy refractory metastatic renal cell carcinoma treated with sunitinib (6-week cycles: 50 mg orally once daily for 4 weeks, followed by 2 weeks of), 40% of patient showed a partial response and 27% stable disease.[81] When the results were combined with a second study with an identical patient population, the total evaluable patient population was 168 patients. Objective responses were seen in 42% and stable disease of 3 or more months in 24%. Median progression

free survival was 8.2 months.[82] These response rates were much higher than seen with any other systemic treatment in RCC. The main adverse effects were fatigue, diarrhea, nausea, dyspepsia, stomatitis, and bone marrow abnormalities. Motzer reported the results of a phase III study comparing sunitinib (6-week cycles: 50 mg orally once daily for 4 weeks, followed by 2 weeks off) to IFN-α (6-week cycles: subcutaneous injection 9 MU given three times weekly) as first line therapy for metastatic renal cell cancer patients. There was a statistically significant improvement in median progression free survival (47.3 vs. 24.9 weeks) and objective response rate (24.8% vs. 4.9%) for sunitinib over IFN-α.[83] Sunitinib might therefore now be considered the new standard first-line treatment for advanced kidney cancer.

In January 2006, sunitinib was not only approved by the FDA for advanced renal cell carcinoma, but also for imatinib-resistant and imatinib-intolerant GIST. This was based on the early results of a phase III trial in patients with documented progression of GIST on imatinib.[84,85] Patients were treated with a starting dose of 50 mg sunitinib once daily for four weeks, followed by 2 weeks off treatment, in repetitive 6-week cycles (N = 207) or placebo (N = 105). Due to the positive results found at a planned interim analysis, the trial was unblinded and all patients started treatment with sunitinib. Partial response was seen in 6.8% of sunitinib treated patients, compared to 0% in the placebo group. Stable disease for more than 22 weeks occurred in 17.4%, compared to 1.9%. Time to progression was significantly longer in the sunitinib treated patients, 27.3 weeks compared to 6.4 weeks. The most common non-hematological adverse events were fatigue, diarrhea, nausea, sore mouth, and skin discoloration.

From a biological point of view, continuous dosing of sunitinib seems more logical. A study in 28 patients with advanced imatinib-resistant GIST explored the continuous daily 37.5 mg dosing regimen, which was feasible and associated with similar tolerability as is seen with intermittent sunitinib dosing.[86]

Sunitinib showed a potentially beneficial efect in previously treated advanced NSCLC and unresectable neuroendocrine tumors in phase II studies.[87,88]

Zactima (ZD6474)

Zactima is an orally available, small molecule, dual VEGF receptor-2 (VEGFR-2) and EGFR tyrosine kinase inhibitor. Zactima has the potential to directly inhibit tumor cell proliferation and survival by blocking EGFR and inhibit tumor angiogenesis by blocking VEGF activity. Zactima inhibits VEGF signaling and angiogenesis in vivo and shows broad-spectrum antitumor activity in a range of histologically diverse tumor xenograft models.[89] In phase I trials, dose limiting toxicities were diarrhea, hypertension, thrombocytopenia, and prolongation of the cardiac QT interval. Phase II assessment of zactima is now in

progress in a variety of tumor types in single and combination regimens.[90,91] In early reports of two phase II studies of zactima in combination with docetaxel or carboplatin and paclitaxel for NSCLC, zactima did not significantly increase toxicity compared to chemotherapy alone.[92] In the study reported by Heymach, patients with locally advanced or metastatic (stage IIIB/IV) NSCLC after failure of first-line platinum-based chemotherapy were randomized to treatment with zactima 100 mg orally once daily plus docetaxel (75 mg/m^2 i.v. infusion every 21 days) (N = 42), zactima 300 mg orally once daily plus docetaxel (N = 44), or docetaxel alone (N = 41). Median progression free survival was higher in the combination therapy treated groups (19 vs. 17 vs. 12 weeks respectively).[93] This resulted in the initiation of a phase III evaluation of zactima plus docetaxel in second-line NSCLC.

In a double-blind, randomized phase II trial, 168 patients with NSCLC were randomized for initial treatment with zactima 300 mg or gefitinib 250 mg. Zactima demonstrated a significant prolongation of progression free survival versus gefitinib (11.0 vs. 8.1 weeks). Overall survival was not significantly diferent (median 6.1 and 7.4 months, respectively).[94]

Zactima shows also promising evidence of clinical activity in patients with hereditary medullary thyroid carcinoma. Of 15 evaluable patients, 3 had partial responses and 10 stable disease.[95]

Vatalanib (PTK787/ZK 222584 (PTK/ZK))

Vatalanib is an oral inhibitor of a number of kinases including VEGFR-1 and VEGFR-2 as well as the platelet-derived growth factor receptor (PDGFR). It clearly demonstrated an anti-tumor efect in several solid tumor types. Adverse events were lightheadedness, fatigue, transaminase elevation, hypertension, nausea, and vomiting.[96] Dynamic contrast-enhanced molecular resonance imaging (DCE-MRI) in patients with advanced colorectal carcinoma and liver metastases showed a vatalanib dose-dependent reduction of vascular permeability and blood flow in the liver metastases.[97] A phase III study (CONFIRM-1, Colorectal Oral Novel Therapy for the Inhibition of Angiogenesis and Retarding of Metastases in First-line) showed no beneficial effects of adding vatalanib to chemotherapy (oxaliplatin/5fluorouracil/leucovorin (FOLFOX4)) in metastatic colorectal cancer patients.[98] A second phase III study in 855 pretreated patients with metastatic colorectal carcinoma (CONFIRM-2, Colorectal Oral Novel Therapy for the Inhibition of Angiogenesis and Retarding of Metastases in Second-line) demonstrated a significant improvement in progression free survival when vatalanib 1250 mg qd was added to FOLFOX. Overall survival was the same in both treatment arms.[99] Combination and monotherapy trials are currently also conducted in other tumor types.

Sorafenib (Bay 43-9006, Nexavar®)

Sorafenib is a novel oral Raf-1 kinase, platelet-derived growth factor receptor (PDGFR) and VEGFR kinase inhibitor with antitumor efects in colon, pancreas and breast cancer cell lines and in colon, breast and non-small-cell lung cancer xenograft models.[100] A phase I study in 69 patients with refractory solid tumors reported promising results.[101] Dose limiting toxicities were hematological toxicity, diarrhea, fatigue, hypertension, and skin rash. In a recent phase II randomized discontinuation trial in patients with metastatic renal cell carcinoma, sorafenib showed anti-tumor activity and was well tolerated.[102,103] An interim analysis of a phase III trial randomizing 769 patients with advanced RCC to sorafenib 400 mg bid or placebo reported an improvement of progression free survival from 12 weeks to 24 weeks in sorafenib treated patients compared to placebo.[104] Updated results reported at the ASCO 2006 meeting showed a survival benefit for sorafenib over placebo (median overall survival of 19.3 months vs. 15.9 months).[105] Sorafenib was granted FDA fast track approval in December 2005.

Phase III trials in stage III or IV melanoma and in advanced hepatocellular carcinoma, and phase II trials in multiple tumor types are currently ongoing.

It has previously been suggested that rash commonly associated with EGF-pathway inhibitors could be predictive of treatment outcome, and that the onset of rash could be used for optimal dose titration.[106] This might also be effective in treatment with sorafenib, as it is an inhibitor of Raf kinase, which is a downstream effector molecule of the EGFR signaling pathway. A recent report combining data from four phase I trials supported this hypothesis. Patients receiving sorafenib dosed at or close to the recommended dose of 400 mg bid, and experiencing skin toxicity and/or diarrhea, had a significantly increased time to progression compared with patients without such toxicity.[107] Blood pressure has also been reported as a possible biomarker in patients treated with sorafenib and other VEGF inhibitors.[108,109]

Platelet-Derived Growth Factor Tyrosine Kinase Inhibitors

Platelet-derived growth factor (PDGF) and its tyrosine kinase receptor (PDGFR) have been implicated in the pathogenesis of a number of tumor types and play an important role in various cellular functions, including growth, proliferation, diferentiation, and angiogenesis.[110] Multiple PDGFR kinase inhibitors have been evaluated in human solid tumors; many are not specific for PDGF and act on a number of tyrosine kinase receptors. Examples are imatinib B-Raf, VEGFR, PDGFR), and leflunomide (SU101; PDGFR, EGFR, FGFR).[111]

Leflunomide (SU101, Arava®)

Leflunomide is a small molecule inhibitor of the PDGFR tyrosine kinase and partially inhibits EGFR and the fibroblast growth factor receptor (FGFR). Leflunomide is an immunomodulatory agent that is indicated in adults for treatment of active rheumatoid arthritis. It has demonstrated broad-spectrum antitumor activity in preclinical studies. A multicenter phase II study in hormone refractory prostate cancer patients treated with leflunomide showed partial responses in 1 of 19 patients, a prostate-specific antigen decline greater than 50% in 3 of 39 patients, and improvement in pain in nine of 35 evaluable patients. The patients received a 4-day i.v. loading dose of SU101 at 400 mg/m^2 for 4 consecutive days, followed by 10 weekly infusions at 400 mg/m^2. Despite the detection of PDGFR overexpression in 80% of the metastases and 88% of the primary tumors, these were disappointing results.[112] The most frequently reported side effects with leflunomide were asthenia, nausea, anorexia, and anemia.

A phase III randomized study of leflunomide versus procarbazine for patients with glioblastoma multiforme in first relapse, and a phase II/III randomized study of leflunomide with mitoxantrone and prednisone versus mitoxantrone and prednisone alone in patients with hormone refractory prostate cancer have just finished recruiting. Results have not yet been reported.

Tyrosine Kinases As A Target: Success Or Failure?

Imatinib (Gleevec®/Glivec®) was the first small molecule TKI that was successfully developed. The results of imatinib in GIST, a tumor that is poorly afected by chemotherapy and radiotherapy, were astonishing and lead to a boost in research of small molecule tyrosine kinase inhibitors in solid tumors. The results of these investigations in other solid tumors were not as astonishing, although substantial efects were seen in many diferent tumor types.

There are multiple reasons for this more modest efect in other solid tumors. First, most tumor cells harbor multiple genetic defects, and inhibiting one tyrosine kinase might not be sufficient. Second, inhibiting tyrosine kinases leads to a stop in cell division, and lack of further growth is therefore the maximum achieved goal. Third, inhibiting an intracellular signaling pathway by a TKI can be overcome by tumor cells by redirecting the signals through other pathways. Fourth, tumor cells can become resistant to TKIs, mostly due to new mutations in the tyrosine kinase, drug efflux mechanisms, receptor down-regulation, and loss of TK-inhibitory pathways.

However, TKIs do have numerous good qualities. First, in many tumor types, they tend to stabilize tumor progression and may create a chronic disease state which is no longer immediately life threatening. Second, side efects are minimal when compared to con-

Table 1. Tyrosine kinase inhibitors: currently registered or in clinical development for solid tumors

Agent	Target receptors	Development stage
Imatinib (STI-571, Gleevec®)	c-Abl, PDGFR-b, c-KIT	Licensed for GIST, (CML) Orphan drug request for DFSP
Gefitinib (Iressa®)	EGFR	Licensed for 2d- or 3rd line NSCLC (Asia, United States)
Erlotinib (OSI-774, Tarceva®)	EGFR	Licensed for 2d- or 3rd line NSCLC, advanced pancreatic cancer
Lapatinib (GW-572016, Tykerb®)	EGFR, Her-2	Phase I/II/III
Canertinib (CI-1033)	EGFR, Her-2, Her-3, Her4	Phase I/II
Sunitinib (SU11248, Sutent®)	PDGFR, VEGFR, KIT, FLT-3	Licensed for advanced RCC, and imatinib-resistant/-intolerant GIST
Zactima (ZD6474)	VEGFR, EGFR	Phase I/II/III
Vatalanib (PTK787)	VEGFR, PDGFR, C-KIT	Phase II/III (colorectal carcinoma)
Sorafenib (BAY43-9006, Nexavar®)	c-Raf-1, B-Raf, VEGFR, PDGFR	Licensed for advanced RCC, Phase II/III (melanoma, HCC)
Leflunomide (SU101, Arava®)	PDGFR (EGFR, FGFR)	Phase II/III (prostate cancer, GBM)

PDGFR: platelet-derived growth factor receptor, GIST: gastrointestinal stromal cell tumor, CML: chronic myelogenous leukemia, DFSP: dermatofibrosarcoma protuberans, EGFR: epidermal growth factor receptor, NSCLC: non-small-cell lung cancer, VEGFR: vascular endothelial growth factor receptor, RCC: renal cell carcinoma, HCC: hepatocellular carcinoma, FGFR: fibroblast growth factor receptor, GBM: glioblastoma multiforme

ventional chemotherapeutic agents. Third, synergistic efects are seen in vitro when TKIs are combined with radiotherapy and/or conventional chemotherapeutic agents.[113–117] If studies in vivo confirm these results, one should consider studying the effects of reducing chemotherapy dose, which might lead to fewer side effects with equal efficacy. One of the mechanisms of synergy between these drugs and chemotherapy is the increase of drug uptake due to decrease of interstitial fluid pressure by PDGF inhibition.[1–3]

The TKIs that are currently registered or in advanced stages of clinical development are shown in Table 1.

Future directions

The identification of patients who are likely to benefit from inhibition of specific tyrosine kinases will become highly important. An important issue is the high costs of small

molecule tyrosine kinase inhibitors, up to $30,000 per patient per year.[1] Patients should be selected based on genetics of their cancer cells, as is proven to be effective in NSCLC patients, where only patients with a mutation in the EGFR receptor showed a favorable response to gefitinib.

Alterations should be made to the conventional phases of drug-development. Maximum tolerated dose (MTD) can no longer be the only end-point in phase I studies, since TKIs have limited side efects and MTD might never be reached. Instead, phase I studies should aim at identifying the maximum biological active dose, i.e. the dose that creates the maximum target inhibition. In phase III studies, selection of the study population should be made based on biogenetics of the tumor, and investigations should also include pharmacodynamic analysis of target inhibition. In previous large phase III trials in unselected patients, TKIs were incorrectly judged to be inefective, and research of an efective drug has incorrectly been stopped. Instead of response rate, other endpoints should be chosen, like time to progression, while with tyrosine kinase inhibitors it might take some time before stabilization of the disease occurs.

Most small molecule tyrosine kinase inhibitors lack substantial benefit when given as monotherapy. Therefore combination therapies based on synergy, combining multiple small molecule TKIs (like gefitinib and sunitinib in RCC trials), combining a small molecule TKI with an antibody TKI (like erlotinib and bevacuzimab in CRC trials, and lapatinib and trastuzumab in breast cancer trials), or combining a TKI with conventional chemotherapy and/or radiotherapy are more likely to be efective.

In the near future, preclinical studies will hopefully be able to identify more activated tyrosine kinases, as overexpression of a target is not a guarantee for treatment success. Molecular markers for toxicity, response and survival, such as the various mutations in GISTs are needed. Future treatment regiments are likely to include multiple tyrosine kinase inhibitors, based on biogenetics of the tumor cells, in combination with chemotherapy, radiotherapy, and other anticancer agents. Hopefully, this will improve the prognosis of patients with several solid tumors by giving a complete or partial tumor response or by creating a chronic stable state in which the disease is no longer immediately life threatening.

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