Significance of Tyrosine Kinase Inhibitors in the Treatment of Metastatic Breast Cancer

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Key Words

Metastatic breast cancer · Tyrosine kinase inhibitor · Her-2/neu · Anti-angiogenesis · Intracellular kinase pathways

Summary

Preclinical and clinical trials suggest that tyrosine kinase inhibitors (TKI) could supplement current therapies in metastatic breast cancer (MBC). HER-2 inhibition is still a main focus. Numerous agents targeting the epidermal growth factor receptors EGFR and HER-2 are currently tested after previous trastuzumab treatment. Lapatinib targets HER-2 and EGFR. As monotherapy, clinical activity was low. Combined with cytotoxic agents, lapatinib showed good activity (overall response rate (ORR) 24–27%) and moderate toxicity. Neratinib, a pan-ErbB TKI, showed an ORR of 26%. Neratinib combined with trastuzumab was well tolerated and active (ORR = 27%). After bevacizumab's proof-of-concept studies, anti-angiogenesis remains of importance. Sunitinib inhibits the vascular endothelial growth factor receptor (VEGFR), the platelet-derived growth factor receptor (PDGFR), c-kit and the colony-stimulating factor 1 (CSF-1) receptor. Monotherapy is tolerated and moderately active in MBC. Combination trials are ongoing. Toxicities of docetaxel ± sunitinib were manageable (ORR 72.2%). Pazopanib targets VEGFR, PDGFR and c-kit. Pazopanib ± lapatinib was superior in combination (progression-free survival (PFS) = 27% vs. 19%). Axitinib has similar targets. Combined with docetaxel, it was superior compared to placebo (ORR 40% vs. 23%), with manageable toxicity. Imatinib inhibits PDGFR and c-kit. As monotherapy, it showed no clinical activity. Combination trials with chemotherapy are ongoing.

Schlüsselwörter

Mammakarzinom, metastasiertes · Tyrosinkinase-Inhibitor · Her-2/neu · Anti-Angiogenese · Kinasesignalwege, intrazelluläre

Zusammenfassung

Vorklinische und klinische Studien zeigen, dass Tyrosinkinase-Inhibitoren (TKI) Standardtherapien beim metastasierten Mammakarzinom (MBC) ergänzen könnten. HER-2 ist als Therapieziel unverändert interessant. Etliche neue zielgerichtete Substanzen richten sich gegen die epithelialen Wachstumsfaktorrezeptoren EGFR und HER-2 und werden, nach vorhergehender Trastuzumab-Therapie, gerade in klinischen Studien getestet. Lapatinib inhibiert HER-2 und EGFR. Als Monosubstanz hatte es nur eine niedrige Aktivität. Kombiniert mit zytotoxischen Substanzen zeigte Lapatinib eine gute Aktivität (Gesamt-Response-Rate (ORR) 24–27%) und moderate Toxizitäten. Neratinib, ein Pan-ErbB-TKI, zeigte eine ORR von 26%. Kombiniert mit Trastuzumab wurde es gut toleriert und war aktiv (ORR = 27%). Nach den positiven Bevacizumab-Studien bleibt die Anti-Angiogenese im Blickpunkt. Sunitinib hemmt den vaskulären endothelialen Wachstumsfaktorrezeptor (VEGFR), den Plättchen-Wachstumsfaktorrezeptor (PDGFR), c-kit und den Kolonien stimulierenden Faktor 1 (CSF-1)-Rezeptor. Die Monotherapie wurde vertragen und war mäßig effektiv. Kombinationsstudien laufen gerade. Die Toxizitäten von Docetaxel ± Sunitinib waren akzeptabel (ORR 72.2%). Pazopanib hemmt VEGFR, PDGFR und c-kit. Pazopanib ± Lapatinib war in der Kombination überlegen (progressionsfreies Überleben (PFS) = 27% vs. 19%). Axitinib hat ähnliche Targets und war mit Docetaxel dem Placeboarm überlegen (ORR 40% vs. 23%), bei akzeptablen Nebenwirkungen. Imatinib blockt PDGFR und c-kit. Als Monotherapie hat es keine klinische Aktivität. Kombinationsstudien mit Chemotherapeutika laufen aktuell.

Introduction

Treatment options for advanced breast cancer include chemotherapy, antiestrogen interventions, and antibody-mediated therapies. Despite the success of these strategies, there is a persistent need for novel and improved therapeutic approaches. Substantial preclinical and indirect clinical evidence has shown that tyrosine kinase inhibitors (TKIs) add potential value to current treatment regimens. This review will focus on novel TKI therapies in the field of metastatic breast cancer (MBC).

Her-2/neu-Targeted Therapies

Led by the success of trastuzumab's HER-2 blocking capabilities in breast cancer, epidermal growth factor receptor (EGFR) inhibition with an emphasis on HER-2 inhibition continues to be an area of focus in the treatment of breast cancer patients. A plethora of new agents directed towards the EGFR and HER-2 pathway have been introduced and continue to demonstrate promising results. These agents are currently studied in clinical trials for patients with MBC, after progression on or after trastuzumab treatment.

Lapatinib

Lapatinib is a novel oral reversible TKI belonging to the 4-anilinoquinazoline class that targets the kinase domain of both HER-2 and EGFR and has demonstrated clinical benefit in patients with HER-2-positive breast cancer. Lapatinib has been tested as a single agent in the second-line setting, in inflammatory breast cancer, and in patients suffering from brain metastasis. Additionally, clinical trials in combination with different cytotoxic agents have been performed. Sufficient data from first-line metastatic or adjuvant trials are not yet available.

Monotherapy in Second-Line MBC

Several studies investigated lapatinib monotherapy in second-line MBC. A phase II study evaluated the efficacy and safety of lapatinib in patients with HER-2-positive breast cancer that progressed during prior trastuzumab therapy. 78 women were treated with single-agent lapatinib 1,200 or 1,500 mg once daily. Tumor response according to Response Evaluation Criteria in Solid Tumors (RECIST) was assessed every 8 weeks. Independent review response rates (complete response (CR) or partial response (PR)) were 5.1%, and clinical benefit rates (CBRs) (CR, PR, or stable disease (SD) for ≥ 24 weeks) were 9.0%, respectively. Median time to progression (TTP) was 15.3 weeks, and median overall survival (OS) was 79 weeks. The most common treatment-related adverse events were rash (47%), diarrhea (46%), nausea (31%), and fatigue (18%). Overall, single-agent lapatinib showed clinical activity with manageable toxic effects in HER-2-overexpress-

ing breast cancer that progressed on previous trastuzumab-containing therapy [1].

Inflammatory Breast Cancer

In cases of aggressive inflammatory breast cancer with HER-2 overexpression, treatment options after anthracycline or taxane and trastuzumab treatment are limited. Lapatinib (1,500 mg once daily) was assessed in a phase II study (EGF103009) with 126 patients with relapsed or refractory HER-2+ inflammatory breast cancer. No patient had a CR. 49 patients (39%; 95% confidence interval (CI) 30–48%) had a PR. Median progression-free survival (PFS) was 14.6 weeks (95% CI 12.1–16.0 weeks), with a median duration of response of 20.9 weeks (12.7–32.1). The likelihood of response to lapatinib was not affected by previous treatment with trastuzumab. 130 (92%) of 141 patients had at least 1 adverse event; 45 (32%) had serious adverse events, the most common were dyspnoea (8 patients) and pleural effusion (6). 5 patients had fatal adverse events that were possibly treatment related. Cardiac events occurred in a low incidence [2].

Brain Metastasis

Brain metastases develop in one third of patients with advanced HER-2+ breast cancer. Effective therapy for patients with central nervous system (CNS) progression after cranial radiation is extremely limited. 242 patients, most of them heavily pretreated with prior chemo- and or hormonal therapy, were included in the EGF105084 trial to further evaluate the CNS activity of lapatinib after trastuzumab treatment and cranial radiation. The study was amended to allow patients who progressed on lapatinib the option of receiving lapatinib plus capecitabine. CNS objective responses to lapatinib were observed in only 6% of patients. Of the 50 evaluable patients who entered the lapatinib plus capecitabine extension, 20% experienced a CNS objective response. This study confirms the modest CNS antitumor activity of lapatinib. Additional responses were observed with the combination of lapatinib and capecitabine [3].

Lapatinib in Combination with Chemotherapy

As single agent, the activity of lapatinib was only moderate; it appeared to be necessary to investigate the clinical activity in combination with chemotherapy.

In a phase III trial ($n = 399$), patients were randomly assigned to receive either combination therapy (lapatinib at a dose of 1,250 mg per day continuously plus capecitabine at a dose of 2,000 mg/m² of body surface area on days 1 through 14 of a 21-day cycle) or monotherapy (capecitabine alone at a dose of 2,500 mg/m² on days 1 through 14 of a 21-day cycle). The primary end point was TTP. The analysis of TTP revealed superiority in the combination therapy group. The hazard ratio (HR) for the TTP was 0.57 (95% CI 0.43–0.77; $p < 0.001$), with 82 events in the combination therapy group and 102 events in the monotherapy group. The median TTP was 6.2 months in the combination therapy group as compared

Fig. 1. Kaplan-Meier estimates of TTP (A) (5 patients with competing risk were censored for purposes of generating the Kaplan-Meier curve) and OS (B) in an intention-to-treat population by an independent review committee.

with 4.3 months in the monotherapy group. The combination showed a trend toward improved survival (HR: 0.78, 95% CI: 0.55–1.12, $p = 0.177$) and fewer cases with CNS involvement at first progression (4 vs. 13, $p = 0.045$) (fig. 1). These data are not yet fully mature; based on results from an interim analysis, the trial was finished prematurely. The overall response rate (ORR) was 24% in the combination therapy group compared with 14% in the monotherapy group, corresponding to an odds ratio of 1.9 (95% CI 1.1–3.4; $p = 0.017$) in favor of the combination therapy group. The most common adverse events were diarrhea, hand-foot syndrome, nausea, fatigue, vomiting, and rash. Diarrhea and rash occurred more frequently in the combination therapy group.

Lapatinib plus capecitabine is superior to capecitabine alone in women with HER-2-positive advanced breast cancer that has progressed after treatment with regimens that included an anthracycline, a taxane, and trastuzumab [4, 5].

Lapatinib was also tested in combination with chemotherapies. In a trial with an unselected patient population (HER-2/neu negative and unknown), it was evaluated in conjunction with taxanes. In a phase III randomized double-blind study (EGF30001) of 580 patients, lapatinib 1,500 mg daily combined with paclitaxel 175 mg/m² was compared with paclitaxel 175 mg/m² alone as first-line treatment for patients with MBC, irrespective of HER-2 status. The ORR was 35% vs. 25% in favor of the combined group. However, TTP and OS were not significantly different between the two arms except in a subgroup of patients with HER-2-positive advanced breast cancer. As expected, there was a significantly greater toxicity profile in the combination group over the paclitaxel monotherapy group, with alopecia, nausea, vomiting, rash and diarrhea being the most common events. In combination with chemotherapies, lapatinib showed a low incidence of adverse cardiac effects [6].

Lapatinib in Combination with Trastuzumab

The EGF104900 phase III study treated patients with lapatinib ± trastuzumab and found that patients treated with both drugs had a significantly improved median PFS (12 weeks vs.

8.1 weeks), a 27% reduction in risk of disease progression ($p = 0.008$), an increased CBR (24.7% vs. 12.4%), and a trend for improved survival. This trial was a proof-of-concept study showing an advantage for the combination of lapatinib with trastuzumab [7].

Neratinib

Neratinib (HKI-272) is an oral irreversible pan-ErbB receptor TKI. In an ongoing phase II study, the preliminary objective response rate was 26% in patients with Her-2+ MBC. Another study assessed the safety and preliminary efficacy of the combination of neratinib plus trastuzumab. In part 1 (dose escalation), patients received neratinib 160 or 240 mg daily plus trastuzumab 4 mg/kg intravenous (IV) loading dose, then 2 mg/kg weekly. In part 2, patients received weekly trastuzumab with neratinib 240 mg daily. 45 patients were enrolled in parts 1 and 2. The most common adverse events were diarrhea (91%), nausea (51%), anorexia (40%), vomiting (38%), and asthenia (27%). No cardiac events were reported. The objective response rate was 27% (95% CI 13–46%); median PFS was 19 weeks (95% CI 15–32 weeks). Neratinib plus trastuzumab was well tolerated with no significant or unexpected toxicities, and demonstrated clinical activity [8].

Hormonal Resistance-Reversing Agents

The majority of breast cancers in postmenopausal women express estrogen and/or progesterone receptors. These breast cancers carry a better prognosis than hormone receptor-negative patients, and they can often be treated with hormonal therapy alone. However, hormone resistance ultimately becomes a major treatment barrier and cytotoxic chemotherapy becomes a necessity. There is evidence that estrogen receptor-positive breast cancers become resistant to hormonal therapy by up-regulating other signaling pathways involved in tumor proliferation such as EGFR, HER-2, mitogen-activated

protein kinase (MAPK) and phosphatidyl inositol 3-kinase (PI3K)/Akt. Novel strategies have now been employed to overcome this resistance by the addition of new signal transduction-inhibiting agents to standard hormonal agents. The combination of the aromatase inhibitor letrozole ± lapatinib served as proof of concept in a recent phase III study. The combination improved the median PFS to 8.2 (vs. 3.0) as well as the CBRs [9].

Gefitinib

Gefitinib is an oral small-molecule selective EGFR TKI. As a single agent, it was found to have little antitumor activity in breast cancer. However, its activity in combination therapy has shown more potential. Gefitinib was evaluated in combination with anastrozole in a phase II multicenter, double-blind, randomized trial to investigate its efficacy on reversing resistance to hormone therapy. In this trial, 94 women with newly diagnosed hormone receptor-positive MBC were randomized to receive anastrozole 1 mg daily in combination with either gefitinib 250 mg daily or placebo, with the primary end point of the study being PFS. The results of the study showed a superior PFS in the gefitinib group when compared with placebo (14.5 months vs. 8.2 months). The CBR also favored the gefitinib group when compared with placebo (49% vs. 34%). Treatment-related adverse events were generally mild and well tolerated but were seen twice as often in the gefitinib arm when compared with the placebo arm. Especially EGF-specific toxicities as diarrhea and skin rash were seen. It was concluded that the combination of anastrozole plus gefitinib is well tolerated and shows increased antitumor activity when compared to anastrozole alone in this group of MBC patients [10]. These results are promising and demand further studies of this combination.

Angiogenesis Inhibition

Led by the success of bevacizumab's vascular endothelial growth factor receptor (VEGFR) blocking capabilities in breast cancer, angiogenesis inhibition with an emphasis on VEGFR-2, fibroblast growth factor receptor (FGFR)-2, and platelet-derived growth factor receptor (PDGFR) inhibition continues to be an area of focus. Numerous new agents, many TKIs, directed towards angiogenic pathways are currently studied in clinical trials for patients with MBC.

Sunitinib

Sunitinib is an oral, multitargeted TKI that inhibits VEGFR, PDGFR, stem cell factor receptor (c-kit) and colony-stimulating factor-1 receptor. Sunitinib is already part of standard

therapies in other solid tumors, as in renal cancer. It is also currently being investigated in a broad clinical study program for efficacy and tolerability.

Monotherapy

In 2008, Burstein et al. [11] published results of a phase II, open-label, multicenter study, which evaluated sunitinib monotherapy in patients with MBC. 64 patients previously treated with an anthracycline and a taxane received sunitinib 50 mg/day in 6-week cycles (4 weeks on, then 2 weeks off treatment). The primary end point was objective response rate. 7 patients achieved a PR (median duration, 19 weeks), giving an ORR of 11%. 3 additional patients (5%) maintained SD for ≥6 months. Median TTP and OS were 10 and 38 weeks, respectively. Notably, responses occurred in triple-negative tumors and HER-2-positive, trastuzumab-treated patients. 33 patients (52%) required dose interruption during ≥1 cycle, and 25 patients required dose reduction (39%). 36 patients (56%) had dose modifications due to adverse events. Grade 3/4 neutropenia was reported in one third of the patients (34%). There were no episodes of neutropenic fever. The higher incidence of neutropenia reported here may be due to the heavily pretreated nature of the study population. Transient episodes of grade 3 thrombocytopenia and leukopenia were also observed. The most common other adverse events were fatigue, nausea, diarrhea, mucosal inflammation, and anorexia. Most adverse events were mild to moderate (grade 1 to 2) in severity and were effectively managed with dose delays or reductions. No patient was considered to have discontinued due to adverse events. It was concluded that sunitinib is well tolerated and moderately active as a single agent in patients with heavily pretreated MBC [11].

Combination with Chemotherapy

Aiming to increase clinical efficacy further, ongoing studies are exploring the use of sunitinib in combination with other agents in a variety of breast cancer patient populations and settings. In a phase II trial (n = 22), the combination of sunitinib and docetaxel was manageable, but showed grade IV neutropenia in 11 patients (50%). Overall, it showed promising activity as a first-line treatment for advanced breast cancer. The objective response rate among patients with evaluable disease was 72.2% (n = 13). One phase III randomized study (SUN1064) is currently ongoing. In this study, first-line sunitinib plus docetaxel is compared to docetaxel alone in patients with advanced breast cancer and MBC [12].

A similar clinical setting was chosen for a phase I clinical trial with sunitinib and paclitaxel. Treatment of patients (n = 21) with advanced breast cancer in the first-line setting with the combination of sunitinib and paclitaxel was generally well tolerated. Adverse events observed were those commonly reported with paclitaxel or sunitinib treatment. Most adverse events were mild or moderate in severity. The most common grade 3 adverse events were fatigue and diarrhea. The com-

bination of paclitaxel and sunitinib showed promising activity as a first-line treatment for advanced breast cancer. The objective response rate among patients with measurable disease was 38.9%, including 2 patients with CR [13]. A phase III trial, sunitinib plus paclitaxel vs. bevacizumab plus paclitaxel, has recently been stopped as sunitinib combined with paclitaxel was unable to meet the primary end point of superior PFS compared to the combination of bevacizumab and paclitaxel.

Pazopanib

Pazopanib is an oral, multitargeted inhibitor targeting all isoforms of VEGFR, PDGFR and c-kit. It has already shown to be efficacious in metastatic renal cell cancer (RCC) [14]. A randomized study compared pazopanib 400 mg daily plus lapatinib 1000 mg daily to lapatinib 1500 mg daily alone in patients with untreated HER-2-positive advanced breast cancer or MBC in the first-line setting [15]. The progressive disease rate was higher in the lapatinib alone group when compared to the combination group (27% vs. 19%). The ORR also favored the combination group (44%) when compared to the lapatinib monotherapy group (30%). The most common adverse effects in the combination group were diarrhea, rash and nausea. Liver function abnormalities were also more common in the combination group. This was the first phase II trial to evaluate the combination of two TKI in first-line HER-2-positive MBC patients [15].

Axitinib

Axitinib is an orally active TKI that inhibits VEGFR 1 and 2 and also PDGFR and c-kit. Its activity in breast cancer was demonstrated in a randomized double-blind phase II study of axitinib 5 mg twice daily in combination with docetaxel 80 mg/m² or placebo. 168 previously untreated patients with MBC were randomized in this study, and the results showed a significant ORR in favor of the axitinib group when compared to placebo (40% vs. 23%). In addition, TTP favored the axitinib group when compared to placebo (9 vs. 6.3 months). The most common adverse events in the combination arm were diarrhea, nausea, alopecia, fatigue and stomatitis. It was concluded that the combination of axitinib and docetaxel is tolerable and has potential antitumor activity for MBC in the first-line setting [16]. Further studies using axitinib in breast cancer are ongoing.

Imatinib

Imatinib mesylate (Gleevec) inhibits several protein tyrosine kinases, including PDGFR and c-kit, which are preferentially

expressed in tumor cells. The activity of imatinib mesylate in MBC was tested with overexpression of PDGFR or c-kit. 13 patients were treated with imatinib administered orally at 400mg twice a day (800 mg/day), until disease progression. All patients demonstrated PDGFR- β overexpression and none showed c-kit expression. No objective responses were observed among the 13 patients treated in an intention-to-treat analysis. All patients experienced disease progression, with a median TTP of 1.2 months. 12 patients died, and the median OS was 7.7 months. No patient had a serious adverse event.

PDGFRs are pivotal in peritumoral vasculature, stroma, and bone. In another study, signaling through PDGF- β receptors was shown to increase interstitial fluid pressure and therefore to affect the tumor cells' chemosensitivity. Inhibition of this pathway by imatinib can enhance drug delivery to the tumor. In vitro evidence from another study suggested that inhibition of the PDGF pathway would decrease the concentration of VEGF and other proangiogenic molecules. In conclusion, results indicated that targeting PDGFR with imatinib mesylate monotherapy in MBC is ineffective [17]. Further studies with a careful selection of patients with PDGFR and/or c-kit overexpression are ongoing. In a phase I/II study, concomitant administration of chemotherapy (vinorelbine) is performed [18].

Conclusions

In recent years there have been significant advances in the treatment of all types of cancer, but in particular breast cancer. These accomplishments have been led by the arrival of targeted therapies including hormonal inhibitors, antibodies inhibiting HER-2 and angiogenesis (VEGF) and now additionally TKIs for several targets. Until today, lapatinib is the only TKI that is approved and is part of standard treatment protocols in MBC. Further promising agents will be incorporated in the treatment of specific groups of MBC patients and could be part of successful treatment regimens in the future. With increasing tumor resistance to chemotherapy or endocrine therapy in MBC, it is of vital importance to continue to apply these novel therapies to current treatment standards and to continue to search for new therapies. The role of most of these biologic and targeted agents is thus far undefined. The relatively safe toxicity profile and convenience of these agents often makes them more attractive when compared to conventional cytotoxic chemotherapy. It is now imperative for researchers and clinicians to establish specific defined molecular targets and optimal patient populations. In the future, additional clinical trials have to establish the efficacy and tolerability of these novel agents in combination or as monotherapy in detail. This is important to develop new strategies in the treatment of breast cancer.

Conflict of Interest

Christoph Mundhenke has received an unrestricted research grant for translational research from Novartis Oncology, Germany. Christian Schem has received an unrestricted research grant for translational research from Pfizer Oncology, Germany.

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