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Review

Multiple targeted tyrosine kinase inhibition in the clinic: All for one or one for all?

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ABSTRACT

Recent insight into the role of receptor tyrosine kinase function in cancer cells culminated in the design of highly selective tyrosine kinase inhibitors. After proof of concept for the clinical efficacy and tolerability of selective tyrosine kinase inhibitors, it was conceived that most tumours will depend on more than one signalling pathway for their growth and survival. As a consequence, different strategies were pursued to inhibit multiple signalling pathways or multiple steps in the same pathway either by the development of multi-targeted agents or the combination of single targeted drugs. The use of a combination of different compounds will be less convenient to the patient, may result in dosing mistakes and drug-drug interaction should be anticipated. However, this approach will enable the titration of the dose of either agent to optimize target inhibition. The use of multi-targeted agents will circumvent several of the problems of combination therapy. Clinical activity resulting in FDA approval for both BAY 43-9006 and SU11248 has been noted. However, optimal inhibition of several targets might not be feasible at a dose with acceptable toxicity.

1. Introduction

Until recently, systemic treatment of advanced cancer mainly involved cytotoxic drugs directed to targets that were not specific to tumour cells. However, over recent years intensive research efforts have led to important insights into various processes involved in malignant transformation of cells and carcinogenesis. Progress in understanding the key roles of receptor tyrosine kinase function in the signalling pathways that govern fundamental cellular processes and the characterization of both the molecular structure of receptor tyrosine kinases and the main functions of these proteins and their ligands in tumourigenesis initiated a new era with the development of target-specific cancer therapeutics.[1]

Signal transduction in eukaryotic cells is mainly regulated by protein kinases and by modification of their substrate activity they play a crucial role in controlling many important processes in cancer cells. There are more than 90 known protein kinase genes; 58 encode transmembrane receptor TKs distributed into 20 subfamilies, and 32 encode cytoplasmic, nonreceptor TKs in 10 subfamilies.[2] In normal cells, the activity of TKs is tightly regulated. However, malignant transformation might be the result of disturbance of protein kinase signalling by mutations and other genetic alterations.[2] After the tyrosine kinases had been validated as suitable pharmacological targets for anticancer drugs, several small molecules were designed to inhibit the tyrosine kinase domain of the receptor, thereby inhibiting intracellular signalling. At first,

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the agents were designed to be highly selective towards only one tyrosine kinase in order to avoid unexpected toxicities.

2. Single target therapy with tyrosine kinase inhibitors

Gefitinib and erlotinib were among the first targeted drugs to enter clinical studies. Both are small molecules interfering with the ATP binding to the TK domain of the epithelial growth factor receptor-1 (EGFR-1), resulting in inhibition of TK activation and subsequently downstream signalling events. In view of the promising activity observed in the phase I studies in patients with non-small cell lung cancer (NSCLC) as well as on levels of expression of EGFR-1 in this tumour type, EGFR-1 TK inhibitors were initially mainly evaluated in this patient subset.[2] Although EGFR is overexpressed in the majority of NSCLC, response rates were only 9–18%. Yet with erlotinib, statistically significant overall survival benefit was observed versus placebo in patients failing previous chemotherapy (6.7 vs 4.7 months; $P = 0.001$), as well as a benefit in progression free survival (PFS) (2.2 vs 1.8 months; $P < 0.001$).[3] In contrast, and despite a similar response rate, gefitinib did not result in survival benefit. Even when target inhibition could be determined in the tumour, this did not always result in inhibition of phosphorylation of downstream targets. Subsequent subset analysis suggested that female, never-smoker, Asian patients with adenocarcinoma and patients with bronchioalveolar carcinoma were more responsive, yielding greater clinical benefit. This could partly be explained by the following identification of somatic mutations in exon 18 through 21 encoding the TK domain of the EGFR-1 and the observation of a strong correlation between the presence of mutations and response to EGFR-1 TKI. Preliminary data also suggest a strong relation between *EGFR* gene amplification and response to gefitinib in NSCLC.[2,4]

In contrast to the EGFR TKIs, which until now have only benefited a limited subset of patients, imatinib that inhibits tyrosine kinases of BCR-ABL, cKIT and platelet derived growth factor receptor (PDGFR), has shown major activity both in patients with chronic myelogenous leukemia (CML) and patients with gastrointestinal stromal tumours (GIST). Imatinib was initially described as a selective agent, albeit that it inhibits at least 3 TKs. For CML the relevant inhibition involved bcr-abl. In 95% of the patients with CML a reciprocal translocation between chromosomes 9 and 22 that replaces the first exon of *ABL* with sequences from the *BCR* gene, visualized as the Philadelphia chromosome, represents the key oncogenic event. This can indeed be selectively inhibited by imatinib resulting in a cytogenetic response rate of 60% and complete haematological response in 95%.[5] Likely the other TKs inhibited by imatinib do not play any role, and thus for CML imatinib can be considered targeting only one molecule in the cancer cell.

GISTs are insensitive to conventional chemotherapy and are generally characterized by a gain-of-function mutation of the KIT receptor and, occasionally, of the PDGFR α. Imatinib targets both KIT and PDGF. It yielded approximately 50% objective remissions in GIST, plus an additional 40% long lasting absence of progression.[6,7] This is now known to be a combined effect of inhibiting either KIT or PDGF or both, even with a differential effect on various types of mutations.[8,9] Thus for GIST, imatinib does not selectively target as initially thought.

These data provided the proof of concept for the clinical efficacy and tolerability of the tyrosine kinase inhibitors. However, it was also conceived that it is uncommon that a given tumour will be dependent on just one receptor or signalling pathway for its growth and survival. Second, there is a significant level of compensatory cross-talk among receptors within a signalling network as well as with heterologous receptor systems. As a consequence, increasing efforts are made to develop strategies to inhibit multiple signalling pathways or multiple steps in the same pathway. Two different strategies can be pursued; either the development of multi-targeted agents or the combination of single targeted drugs. The advantages and disadvantages for both strategies will be discussed.

3. Multiple targets therapy

3.1. *Combination of single tyrosine kinase inhibitors*

By combining relatively specific tyrosine kinase inhibitors, the agents will each have low IC_{50} values for their specific target. This enables the exact titration of the optimal concentration of either agent alone with optimal inhibition of the involved targets. As shown in Fig. 1, agents inhibiting several targets, tend to differ in their IC_{50} for each target by factor 10–100.[10–13] In most cases, the spectrum of toxicities will be the sum of the toxicities of either agent alone, which could be a theoretical disadvantage. Despite a lack of interaction, agents can not always be combined at their single agent dose. For instance in the combination gefitinib and RAD001, the dose of RAD001 had to be reduced to 5 mg/day when administered with gefitinib 250 mg/day.[14]

However, concomitant administration of two selective tyrosine kinase inhibitors might result in drug-drug interactions. Several drugs are known to inhibit PGP, or BCRP (i.e. lapatinib), cellular pumps known to be involved in drug absorption and elimination. Since many targeted agents need to be dosed chronically, based on their mechanism of action, they are administered orally for patient convenience. This might also result in an interaction at the level of absorption of those oral agents that are a substrate for these pumps.

In addition, interaction at the level of drug metabolism might occur. CYP3A4 is an enzyme responsible for the metabolism of a wide variety of chemicals, including anti-cancer agents. Several of the currently known tyrosine kinase inhibitors such as erlotinib, gefitinib, SU11248 and ZD6474 are also metabolized by CYP3A4. Recently it was shown for instance, that ZD6474 combined with the CYP3A4 inhibitor itraconazole resulted in a significant increase in ZD6474 exposure, albeit that the 9% increase (90% CI: 1.01–1.18) was not considered clinically relevant.[15] Also CYP3A4 inhibition by ketoconazole yielded no clinical relevant change in the pharmacokinetics and side-effects of sorafenib in healthy volunteers.[16] CYP3A4 induction with rifampin caused a 4-fold reduction in SU11248 plasma exposure and a 2.5-fold reduction in peak plasma concentration compared to SU11248 alone, in both Caucasian and Japanese males.[17] Aside from being a substrate for CYP3A4, erlotinib was shown to be an inhibitor of CYP3A4

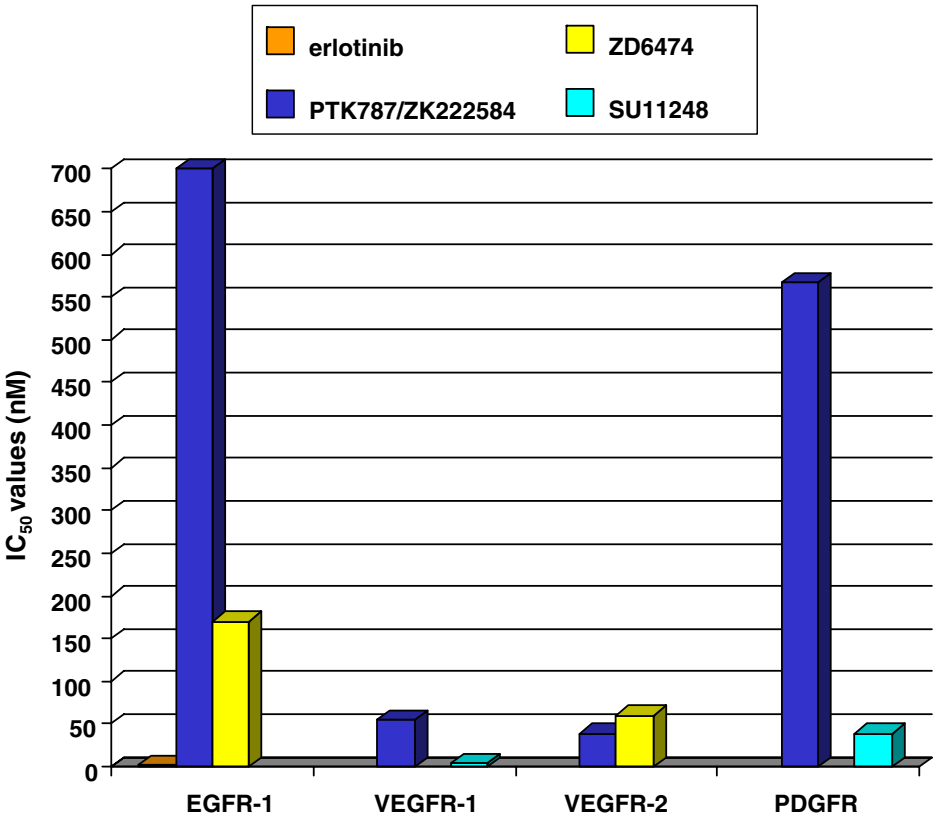

Fig. 1 – IC_{50} values in nM for several small molecule tyrosine kinase inhibitors.

activity *in vitro*, while in contrast gefitinib was able to induce CYP3A4 activity. Clinical CYP3A4 activity can be assessed by the erythromycin breath test, correlating with hepatic CYP3A4 activity, and by assessing the pharmacokinetics of oral midazolam, reflecting both intestinal and hepatic CYP3A4 activity.[18] Erlotinib decreased exposure to midazolam in patients (24% on day 8 and 30% on day 14), as compared to baseline. In contrast, the erythromycin breath test showed minimal effect of erlotinib on the excretion of CO_2. Although a wide inter-patient variability has to be taken into account, these preliminary data do not suggest a clinically relevant inhibitory effect of erlotinib on CYP3A4 activity. The possible induction of CYP3A4 activity by gefitinib was quantified by a change in urinary cortisol metabolite 6-β-hydroxycortisol after cortisol administration[19] in 21 patients before the start of treatment and on day 15 and day 29 after start of treatment. The urinary 6-β-hydroxycortisol versus free cortisol ratio was 7.4 ± 4.63, 7.31 ± 4.21 and 12.60 ± 10.02 (mean ± SD) before treatment, and on day 15 and day 29, respectively, suggesting induction of CYP3A4 during treatment with gefitinib. However, the trough concentration of gefitinib in plasma did not change significantly between day 15 and day 29. Yet, the results caution that when gefitinib is administered in combination with other agents metabolized by CYP3A4, the possibility of drug-drug interactions should be taken into account.[19]

Apart from the potential of drug-drug interaction there is another practical problem in combining new agents. In choosing the drugs to combine, pharmaceutical companies will obviously prefer to combine agents from their own development pipeline, rather than using agents from competitors. Thus the conceptually most optimal combination may practically not be applicable in early drug development.

The above data stress the importance of studying pharmacokinetics when combining new agents, in order to evaluate a possible drug-drug interaction. They also point to the fact that developing a combination of agents, despite its potential for individual titration, creates many hurdles. Finally from a regulatory point of view this approach will be challenging.

4. Multitargeted drug

The administration of a single compound targeting multiple tyrosine kinases avoids possible drug-drug interactions and is more convenient and less complex for the patient. Presently, several small molecule multiple tyrosine kinase inhibitors have entered clinical trials.

Although severe and unexpected toxicities were predicted by some, the actual administration of multitargeted TKIs resulted in a manageable toxicity profile. Dose limiting toxicities observed in the phase I clinical trials tend to correlate to the targets inhibited. For instance ZD6474 is an orally administered competitive inhibitor of the ATP-binding site of the VEGFR-2 tyrosine kinase and also inhibits EGFR-1 tyrosine kinase at sub-micromolar concentrations.[12] Dose limiting toxicity in the phase I study consisted of diarrhoea and rash, reflecting the inhibition of EGFR-1, and hypertension, linked to the inhibition of VEGFR-2.[20] SU11248, an indolinone, selectivity targets VEGF2, cKit, Flt-3, and PDGF beta at sub-micromolar concentration, in decreasing order of potency.[10]

The adverse-event profile consisted of hypertension and asthenia, associated with inhibition of VEGF and VEGFRs, skin toxicity also attributed to a direct anti-VEGFR and/or PDGFR effect on dermal endothelial cells, and reversible hair depigmentation associated with modulation of tyrosinase-related protein 1 genes and tyrosinase, related to the Kit signalling pathway.[21] Importantly, there is some evidence now that these agents can also be safely combined with certain cytotoxic drugs.[22]

Administration of a multitargeted TKI disables exact titration of inhibition of the separate targets which might constitute a possible draw-back of this approach. Whether administration of the drug at the recommended dose yielded optimal inhibition of the targets was evaluated both for SU11248 and ZD6474.

In the phase I multiple dosing studies of SU11248 dose levels between 30 mg every other day and 75 mg daily were studied.[23–25] The recommended dose for further studies was defined as 50 mg/day for 4 weeks, followed by 2 weeks rest. Pharmacodynamic evaluation during the phase I study revealed a correlation between drug exposure and an increase in plasma VEGF levels and decrease in soluble VEGFR-2 levels. Plasma levels of soluble Kit decreased in patients with a GIST achieving tumour reduction but not in patients whose disease failed to regress.[26] In the single dose escalation study in acute myeloid leukaemia patients dose levels up to 350 mg were studied.[27] Inhibition of foetal liver tyrosine kinase receptor 3 (Flt-3) phosphorylation was apparent in 50% of Flt-3 wild type patients and in 100% of Flt-3-mutant patients. Strong inhibition of Flt-3 phosphorylation in >50% of the patients, the primary end point of the study, was reached with 200 mg and higher doses, also resulting in inhibition of downstream signalling pathways. However, toxicity will prevent prolonged dosing at these higher doses, preventing optimal inhibition of this particular target.

During the first phase II study on orally once daily ZD6474 performed in patients with previously treated metastatic breast cancer, patients started at 100 mg, which was subsequently increased to 300 mg in absence of grade 3–4 QTc prolongation at the 100 mg dose.[28] Diarrhoea was the most commonly reported side-effect with 4.5% of the patients at the 100 mg dose level and 37.5% at the 300 mg dose level experiencing $\geqslant$ grade 2 Diarrhoea. Rash was reported by 26% of the patients but no grade 3 or 4 rash was observed. Interestingly, hypertension requiring treatment was not reported, while the steady state ZD6474 plasma concentrations for individual patients exceeded the projected IC_{50} for inhibition of VEGF-stimulated human umbilical vascular endothelial cell (HUVEC) proliferation in 90% of patients treated at 100 mg and in 100% of the patients treated at 300 mg. In contrast, only one patient treated at 100 mg achieved a steady-state concentration above the projected IC_{50} for inhibition of EGFR-stimulated HUVEC proliferation, while 60% of the patients did so at 300 mg. However, these IC_{50} values are based on *in vitro* inhibition of VEGF- and EGF-stimulated HUVEC proliferation and do not reflect the heterogeneity of the tumour. Tumour perfusion, studied by DCE-MRI was not affected by treatment. Although the majority of the patients achieved plasma concentrations above the IC_{50} for VEGF inhibition, the lack of effects on blood pressure combined with the lack of effect on tumour perfusion studied with DCE-MRI in this phase II study all suggest insufficient inhibition of VEGF during treatment with ZD6474. The lack of high-grade rash suggests suboptimal inhibition of EGFR as well.[28] In addition, no antitumour activity was observed in this patient population.

These findings emphasize potential problems that can be encountered with the administration of a multitargeted TKI, yielding intolerable toxicity at plasma concentrations that are required for optimal target inhibition. It also underscores the importance that in further development, we will have to accept some toxicity of these agents, and that they will have to be administered on a more chronic base at MTD or close to MTD. Moreover, the focus of the major determinant TKI within multitargeted TKIs may come as a surprise. This is exemplified in the recent development of BAY 43-9006 (sorafenib), designed as a C-RAF targeted agent, but likely yielding its major activity through VEGFR-2, and possibly PDGFR-β, Flt-3 and c-kit. These results again show that sometimes a compound has hidden potentials.[29]

Yet, despite these limitations of the multitargeted TKIs, clinical activity has been observed in patients with several tumour types. Results are especially promising both in renal cancer and GIST patients. The clinical activity of BAY 43-9006 was evaluated in a phase II randomized discontinuation trial, in which 484 patients with advanced solid tumours were treated, especially patients with colorectal, renal cell cancer and melanoma.[30,31] Data for 202 patients with renal cell carcinoma revealed that after the 12-week run-in phase, 65 patients had a <25% change in tumour volume from baseline and were entered into the randomized phase of the study. Median progression-free survival after randomization was 23 weeks for patients on BAY 43-9006 versus 6 weeks for patients on placebo ($P = 0.0001$). A phase III study in patients who had received one prior systemic treatment for advanced renal cancer versus placebo was subsequently initiated. Analysis of the progression free survival yielded a doubling of the median progression free survival from 12 to 24 weeks ($P < 0.00001$).[32,33] Median survival for patients receiving placebo was 14.7 months, where the median survival for patients treated with BAY 43-9006 has not been reached. Based on these data, BAY 43-9006 was approved by the FDA for the use in patients with renal cell cancer.

Also in renal cancer patients, two phase II studies on SU11248 given daily for 4 weeks, followed by 2 weeks off treatment were performed, and yielded investigator assessed response rates of 40% with a median duration of response of more than 10 months and a median time to progression of 8.7 months, which compared favourably with the median time of 2.5 months on placebo treatment.[34,35] A phase III trial of SU11248 versus interferon-α for first-line treatment of renal cancer patients has meanwhile been initiated.

Early data on a phase III study in GIST in 312 patients, in which administration of SU11248 was randomized against placebo in a 2:1 randomisation, resulted in a more than 4-fold increase in median time to progression (hazard ratio 0.335, $P < 0.00001$) from 1.5 to 6.3 months.[36] Recently the FDA approved SU11248 for both indications; for the treatment of GIST in patients who progressed on or with intolerance to imatinib and an accelerated approval for the treatment of patients with advanced renal cell carcinoma.

These data indicate that multitargeted TKIS shown promising activity in tumour types for which classic chemotherapy and immunotherapy is of no or limited value.

5. Conclusion

Although proof of concept has been provided for selective tyrosine kinase inhibitors, data accumulate that for most tumours significant levels of cross talk exists within and between signalling networks, necessitating the combined inhibition of multiple targets in order to establish tumour growth inhibition. Combination of selective tyrosine kinase inhibitors has the advantage of the possibility to titrate the dose of either agent to optimize target inhibition. However, drug-drug interaction must be anticipated and studied. The use of a combination of different agents will also be less convenient to the patient and can result in more dosing mistakes. The use of multi-targeted kinase inhibitors will circumvent this problem. Clinical activity has been noted, resulting in FDA approval of BAY 43-9006 and SU11248 for the treatment of patients with renal cell cancer and the latter also for the treatment of patients with GIST. However, optimal inhibition of several targets might not be feasible at a dose with acceptable toxicity. Further investigations are needed to optimize both strategies.

Conflict of interest statement

None declared.

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