Short communication

Are current drug development programmes realising the full potential of new agents? Tyrosine kinase inhibitors

Eleanor Gutteridge and John FR Robertson

Professorial Unit of Surgery, Nottingham City Hospital, Hucknall Road, Nottingham, HG5 1PB, UK

Corresponding author: Eleanor Gutteridge, Eleanor.Gutteridge@nottingham.ac.uk

Published: 18 December 2009
This article is online at
http://breast-cancer-research.com/supplements/11/S3/S24

Breast Cancer Research 2009, **11(Suppl 3):**S24
(doi:10.1186/bcr2443)
© 2009 BioMed Central Ltd

The process of drug development is expensive and time consuming, with millions of dollars spent on the testing of new chemical entities [1,2]. Unfortunately many agents that show initial promising activity against a particular biological target will be discarded due to concerns regarding their safety, toxicity and efficacy in humans. There is also a perception that preclinical models may foster unrealistic expectations, and many promising drugs are failing to reach their potential. In addition, reporting of clinical trials may disadvantage certain drugs at an early stage in their development.

The introduction of the tyrosine kinase inhibitors was met with great optimism. Initial agents acted on the erbB signalling pathways. Activation of these pathways lead to the phosphorylation of key downstream signalling elements – such as mitogen-activated protein kinase, AKT, and insulin-like growth factor receptor – known to be involved in cancer progression. Epidermal growth factor receptor (EGFR), a member of the erbB family, is overexpressed in a wide range of common solid tumours (nonsmall-cell lung cancer (NSCLC), 40 to 80%; prostate cancer, 40 to 80%; gastric cancer, 33 to 74%; breast cancer, 14 to 91%; colorectal cancer, 25 to 77%; pancreatic cancer, 30 to 50%; ovarian cancer, 35 to 70%) and overexpression is generally associated with poor prognosis/prognostic factors. Tyrosine kinase inhibitors such as gefitinib (Iressa™; Astra-Zeneca, London, UK) erlotinib (Tarceva™; OSI and Roche-Genentech, Basel, Switzerland) and canertinib (Pfizer, London, UK) block the activation of intracellular tyrosine kinase sites of EGFR, also called erb B1, while lapatinib (Tykerb™; GlaxoSmithKline, Middlesex, UK) blocks the tyrosine kinase sites of EGFR and erb B2 (also called HER2), decrease signal transduction *in vitro* and reduce tumour growth in experimental systems [3].

Phase I clinical trials followed from preclinical experiments, and these trials produce side effect profiles. For example, diarrhoea and rash were the most common side effects encountered with the use of gefitinib. These effects were shown to be dose dependent, and pharmacodynamic and pharmacokinetic studies realised regimes acceptable to most patients [4].

These initial findings led on to phase II clinical trials in NSCLC with gefitinib as monotherapy in heavily pretreated patients. The IDEAL 1 and IDEAL 2 trials randomised patients to gefitinib at a dose of either 250 mg/day or 500 mg/day until disease progression. These studies demonstrated that the efficacy was similar at the two doses but that the side effect profile increased with the 500 mg dose, with a 15% chemotherapy toxicity criteria grade 3 to 4 toxicity [5-7]. Biomarker studies revealed that gefitinib response required EGFR expression although the data were conflicting as regards the level of expression required for response [8].

This encouraging evidence of EGFR-mediated growth suppression led to large multicentre trials in patients with previously treated NSCLC randomised to chemotherapy in combination with gefitinib at 250 or 500 mg or with placebo until disease progression or unacceptable toxicity. Disappointingly there appeared to be no benefit from the addition of gefitinib at either dose to chemotherapy [9,10]. The TRIBUTE trial was a multicentre, randomised, double-blind phase III trial of TARCEVA (erlotinib) plus chemotherapy versus chemotherapy alone for the first-line treatment of advanced NSCLC, and also showed no difference in survival.

In breast cancer, activation of the erb family of receptors has been implicated in the development of endocrine resistance, particularly tamoxifen resistance in experimental systems. Additionally, gefitinib may be effective in these tamoxifen-resistant models [11-13].

There have been several clinical trials of gefitinib in patients with breast cancer encompassing different stages of the

EGFR = epidermal growth factor receptor; ER = oestrogen receptor; NSCLC = nonsmall-cell lung cancer.

disease, such as presurgical disease, and there have been neoadjuvant studies as well as phase II and then randomised phase II trials in patients with metastatic disease. Unfortunately the initial results of these studies were often apparently conflicting, with no consistent picture of efficacy.

Initial trials with gefitinib as monotherapy in postmenopausal metastatic oestrogen receptor (ER)-positive breast cancer recruited mainly patients who were heavily pretreated with chemotherapy, and did not select for EGFR positivity; the response rates were poor [14,15]. A study combining gefitinib and herceptin in HER2-positive disease also reported no benefit [16].

In contrast, a phase II clinical trial carried out by our own group in treatment-naïve metastatic disease demonstrated a clear benefit in ER-positive patients (clinical benefit rate, 53%), with the best responses in ER-positive, progesterone receptor-positive tumours [17]. The study recruited patients with advanced disease who were ER-positive and had developed tamoxifen resistance ($n = 27$) or patients who were ER-negative and had received no more than one prior chemotherapy treatment for advanced disease ($n = 27$). The study groups were given a loading dose of gefitinib 1,000 mg on day 1 and then 500 mg/day until disease progression or unacceptable toxicity. The gefitinib responders all expressed EGFR and demonstrated parallel decreases in tumour phosphorylated EGFR, phosphorylated mitogen-activated protein kinase and Ki67 with treatment.

Presurgical studies with gefitinib are difficult to interpret. In a small study, patients with dual EGFR-positive, ER-positive primary breast cancers were randomised to gefitinib with or without aromatase inhibitor anastrazole [18]. The combination regime led to a greater decrease in Ki67 levels and a better tumour response than gefitinib alone. A further presurgical study confirmed the requirement for EGFR expression in the tumour, and suggested that EGFR inhibition may be more effective in ER-positive, progesterone receptor-negative breast cancers [19]. In a randomised neoadjuvant trial of gefitinib and anastrazole versus anastrazole alone in ER-positive, EGFR-negative tumours there was no significant difference in Ki67 levels at 2 or 16 weeks for either combination and there were no statistically significant differences in response rates between the groups [20].

There are also two randomised phase II studies with gefitinib in breast cancer patients. The first study compared gefitinib with or without tamoxifen in ER-positive patients (either endocrine naïve or previously treated with adjuvant tamoxifen (stratum 1) or with adjuvant/metastatic anastrozole (stratum 2)). There was an apparent separation of the progression-free survival curves for the first group, indicating that gefitinib may have a role in preventing or delaying the development of endocrine resistance [21]. The second randomised phase II study in ER-positive, treatment-naïve, metastatic breast cancer randomised between anastrazole versus anastrazole and geftinib – the study reported a median progression-free survival of 14 months for the combination regimen versus 8 months for anastrozole alone [22]. Interestingly the clinical benefit rate in this study was 48% for the combination versus 34% for anastrozole alone; however, the objective response rate was better for anastrazole alone (12%) compared with the combination regime (2%). It is difficult to suggest a rationale where a drug improves clinical benefit rate but shows an apparent opposite effect on objective response

Interestingly, there is evidence to suggest that gefitinib is more effective in certain populations – that is, nonsmokers compared with smokers, Asian compared with Caucasian, and women compared with men [23]. Additionally, two publications report that somatic mutations in the tyrosine kinase domain of the EGFR appear to increase the sensitivity of the mutant receptor to gefitinib [24,25]. A recent paper has also reported that gefitinib alone is significantly more effective than standard chemotherapy in mutation-positive tumours but the reverse is true in mutation-negative lung cancers [26]. These findings highlight the importance of identifying the appropriate population to treat with appropriate predictive biological marker(s)

In summary, trials in metastatic breast cancer have shown no efficacy in heavily pretreated patients. Efficacy has been seen in some clinical studies in Tam-R tumours expressing EGFR, but the level of EGFR expression was not predictive. Randomised phase II clinical trials have failed to demonstrate significant effects when gefitinib was added to tamoxifen, but retrospective analysis has suggested that gefitinib may have been more effect in a hormone-naive subgroup. A small randomised phase II study of anastrozole with or without gefitinib, however, has reported a significant benefit in favour of the combination.

Presurgical and neoadjuvant studies do not provide a consistent picture of what type of tumours were sensitive to gefitinib or what tissue markers reflect or predict biological effects. Clinical studies do not correlate well with biological studies except that, in general, EGFR expression is required to see any biological activity.

More recently, lapatinib – a tyrosine kinase inhibitor that targets not only EGFR (erb B1) but also erb B2 (HER2) receptor tyrosine kinase signalling – has been studied. Following promising preclinical results [27], a phase III randomised, double-blind trial of lapatinib and placebo versus lapatinib and letrozole in ER-positive, treatment-naïve metastatic breast cancer ($n = 1,286$) has shown a benefit in clinical benefit rate and progression-free survival in the HER2-positive subpopulation. There was no significant effect from the addition of lapatinib in the much larger HER2-negative subpopulation, suggesting that lapatinib acts at least in large part through the inhibition of the tyrosine kinase on the HER2.

The current spectrum of preclinical models only partially reflects the true heterogeneity of breast cancer, and as clinicians we must be aware of the limitations of results from these model systems. Clinical trials are still essential to the development of new generations of biological agents but traditional large clinical trials may not be the best way of evaluating agents that have a target expressed in only a minority of breast cancers. We must strive to have a better understanding of tumour biology. This involves identifying not only a therapy and the target it might hit, but also the biological markers that predict and measure efficacy (or not) of treatment. This needs to be highlighted not simply in large randomised trials that compare very heterogeneous tumour types, but in individual cancers or at least small groups of tumours that can be characterised biologically.

Competing interests

The authors declare a potential conflict of interest in that JFRR has received honoraria and research grants from AstraZeneca.

Acknowledgement

This article has been published as part of *Breast Cancer Research* Volume 11 Suppl 3 2009: Controversies in Breast Cancer 2009. The full contents of the supplement are available online at http://breast-cancer-research.com/supplements/11/S3.

References

1. DiMasi JA, Hansen RW, Grabowski HG: **The price of innovation: new estimates of drug development costs.** *J Health Econ* 2003, **22:**151-185.
2. DiMasi JA: **The value of improving the productivity of the drug development process: faster times and better decisions.** *Pharmacoeconomics* 2002, **20(Suppl 3):**1-10.
3. Sirotnak FM, Zakowski MF, Miller VA, Scher HI, Kris M: **Efficacy of cytotoxic agents against human tumor xenografts is markedly enhanced by coadministration of ZD1839 (Iressa), an inhibitor of EGFR tyrosine kinase.** *Clin Cancer Res* 2000, **6:**4885-4892.
4. Baselga J, Rischin D, Ranson M, Calvert H, Raymond E, Kieback DG, Kaye SB, Gianni L, Harris A, Bjork T, Averbuch SD, Feyereislova A, Swaisland H, Rojo F, Albanell J: **Phase I safety, pharmacokinetic, and pharmacodynamic trial of ZD1839, a selective oral epidermal growth factor receptor tyrosine kinase inhibitor, in patients with five selected solid tumor types.** *J Clin Oncol* 2002, **20:**4292-4302.
5. Baselga J, Yano S, Giaccone G, Nakagawa K, TamuraT, Douillard J, Nishiwaki Y, Vansteenkiste JF, Kudou S,Rischin D, Eek RW, Averbuch S, Macleod A, Feyereislova A, Dong R-P, Fukuoka M: **Initial results from a phase II trial of ZD-1839 (IRESSA) as second and third line monotherapy for patients with advanced non-small cell lung cancer (IDEAL-1).** In *Program and abstracts of the 2001 AACR-NCI-EORTC International Conference – Molecular Targets and Cancer Therapeutics.* October 29-November 2, 2001; Miami Beach, Florida. Abstract 630A
6. Kris MG, N.R., Herbst RS, Lynch TJ Jr, Prager D, Belani CP: **A phase II trial of ZD1839 ('Iressa') in advanced non-small cell lung cancer (NSCLC) patients who had failed platinum- and docetaxel-based regimens (IDEAL 2) [abstract 1166].** In *Proceedings of the 38th Annual Meeting of the American Society of Clinical Oncology*; 2002.
7. Natale R, SA, Maddox A, Hammond L, Thomas R, Gandara D, Gerstein H, Panella T, Cole J, Jahanzeb M, Kash J, Hamm J, Langer C, Saleh M, Stella P, Heyes A, Helms L, Ochs J, Averbuch S, Wolf M, Kay A: **Improvement in symptoms and quality of life for advanced non-small-cell lung cancer patients receiving ZD1839 ('Iressa') in IDEAL 2 [poster 1167].** In *Proceedings of the American Society of Clinical Oncologists*; 2002.
8. Bailey LR, Kris M, Wolf M, Kay A, Averbuch S, Askaa J, Janas M, Schmidt K, Fukuoka M: **Tumor EGFR membrane staining is not clinically relevant for predicting response in patients receiving Gefitinib (Iressa, ZD1839) monotherapy for pretreated advanced non-small-cell lung cancer: IDEAL 1 and 2.** *Proc Am Assoc Cancer Res* 2003, **44:**1362.
9. Herbst RS, Sandler AB: **Overview of the current status of human epidermal growth factor receptor inhibitors in lung cancer.** *Clin Lung Cancer* 2004, **6(Suppl 1):**S7-S19.
10. Giaccone G, Herbst RS, Manegold C, Scagliotti G, Rosell R, Miller V, Natale RB, Schiller JH, Von Pawel J, Pluzanska A, Gatzemeier U, Grous J, Ochs JS, Averbuch SD, Wolf MK, Rennie P, Fandi A, Johnson DH: **Gefitinib in combination with gemcitabine and cisplatin in advanced non-small-cell lung cancer: a phase III trial – INTACT 1.** *J Clin Oncol* 2004, **22:**777-784.
11. Gee JM, Harper ME, Hutcheson IR, Madden TA, Barrow D, Knowlden JM, McClelland RA, Jordan N, Wakeling AE, Nicholson RI: **The antiepidermal growth factor receptor agent gefitinib (ZD1839/Iressa) improves antihormone response and prevents development of resistance in breast cancer in vitro.** *Endocrinology* 2003, **144:**5105-5117.
12. Massarweh S, Osborne CK, Jiang S, Wakeling AE, Rimawi M, Mohsin SK, Hilsenbeck S, Schiff R: **Mechanisms of tumor regression and resistance to estrogen deprivation and fulvestrant in a model of estrogen receptor-positive, HER-2/neu-positive breast cancer.** *Cancer Res* 2006, **66:**8266-8273.
13. Shou J, Massarweh S, Osborne CK, Wakeling AE, Ali S, Weiss H, Schiff R: **Mechanisms of tamoxifen resistance: increased estrogen receptor-HER2/neu cross-talk in ER/HER2-positive breast cancer.** *J Natl Cancer Inst* 2004, **96:**926-935.
14. Albain K, Elledge R, Gradishar WJ, Hayes DF, Rowinsky E, Hudis C, Pusztai L, Tripathy D, Modi S, Rubi S: **Open-label, phase II, multicenter trial of ZD1839 ('Iressa') in patients with advanced breast cancer.** *Breast Cancer Res Treat* 2002, **76(Suppl 1):**S96.
15. von Minckwitz G, Jonat W, Fasching P, du Bois A, Kleeberg U, Luck HJ, Kettner E, Hilfrich J, Eiermann W, Torode J, Schneeweiss A: **A multicentre phase II study on gefitinib in taxane- and anthracycline-pretreated metastatic breast cancer.** *Breast Cancer Res Treat* 2005, **89:**165-172.
16. Arteaga CL, O'Neill A, Moulder SL, Pins M, Sparano JA, Sledge GW, Davidson NE: **A phase I–II study of combined blockade of the ErbB receptor network with trastuzumab and gefitinib in patients with HER2 (ErbB2)-overexpressing metastatic breast cancer.** *Clin Cancer Res* 2008, **14:**6277-6283.
17. Gutteridge E, Agrawal A, Nicholson R, Cheung KL, Robertson J, Gee J: **The effects of gefitinib in tamoxifen resistant and hormone insensitive breast cancer: A phase II study.** *Int J Cancer* 2009.
18. Polychronis A, Sinnett HD, Hadjiminas D, Singhal H, Mansi JL, Shivapatham D, Shousha S, Jiang J, Peston D, Barrett N, Vigushin D, Morrison K, Beresford E, Ali S, Slade MJ, Coombes RC: **Preoperative gefitinib versus gefitinib and anastrozole in postmenopausal patients with oestrogen-receptor positive and epidermal-growth-factor-receptor-positive primary breast cancer: a double-blind placebo-controlled phase II randomised trial.** *Lancet Oncol* 2005, **6:**383-391.
19. Slamon D: **Report of the BCIRG 103/Study 219.** ASCO; 2006.
20. Smith IE, Walsh G, Skene A, Llombart A, Mayordomo JI, Detre S, Salter J, Clark E, Magill P, Dowsett M, *et al.*: **A phase II placebo-controlled trial of neoadjuvant anastrozole alone or with gefitinib in early breast cancer.** *J Clin Oncol* 2007, **25:**3816-3822.
21. Osborne K, Neven P, Dirix L, Mackey J, Robert J, Underhill C, Gutierrez C, Magill P, Hargreaves L: **Randomized Phase II study of gefitinib (IRESSA) or placebo in combination with tamoxifen in patients with hormone receptor positive metastatic breast cancer [abstract 2067].** *Breast Cancer Res Treat* 2007, **106(Suppl 1):**155.
22. Cristofanilli M, Valero V, Mangalik A, Rabinowitz I, Arena FP, Kroener JF, Curcio E, Watkins C, Magill P: **A phase II multicenter, double-blind, randomized trial to compare anastrozole plus gefitinib with anastrozole plus placebo in postmenopausal women with hormone receptor-positive (HR^+) metastatic breast cancer (MBC) [abstract 1012].** *J Clin Oncol* 2008, **26(Suppl):**44s
23. Paez JG, Janne PA, Lee JC, Tracy S, Greulich H, Gabriel S, Herman P, Kaye FJ, Lindeman N, Boggon TJ, Naoki K, Sasaki H, Fujii Y, Eck MJ, Sellers WR, Johnson BE, Meyerson M: **EGFR**

mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science* 2004, **304:**1497-1500.
24. Sorscher SM: **EGFR mutations and sensitivity to gefitinib.** *N Engl J Med* 2004, **351:**1260-1261; author reply 1260-1261.
25. Chang KL, Lau SK: **EGFR mutations in non-small cell lung carcinomas may predict response to gefitinib: extension of an emerging paradigm.** *Adv Anat Pathol* 2005, **12:**47-52.
26. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, Sunpaweravong P, Han B, Margono B, Ichinose Y, Nishiwaki Y, Ohe Y, Yang JJ, Chewaskulyong B, Jiang H, Duffield EL, Watkins CL, Armour AA, Fukuoka M: **Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma.** *N Engl J Med* 2009, **361:**947-957.
27. Johnston SR, Leary A: **Lapatinib: a novel EGFR/HER2 tyrosine kinase inhibitor for cancer.** *Drugs Today (Barc)* 2006, **42:**441-453.