Targeted Drug Therapies and Cancer

K. L. Yim and D. Cunningham

Abstract

With the progress of research in molecular biology and greater understanding of cell signalling systems emerge an increasing array of potential targets for the therapy of cancer. While traditional chemotherapy aims to elicit tumour cell death, it also produces undesirable side effects on physiologically proliferating cells. By isolating cell surface receptors which link specific intracellular secondary messenger pathways, researchers are increasingly able to define the biological network which drives cellular function. Of importance are routes involved in malignant transformation, proliferation, survival and angiogenesis. Thus targeted therapy is directed to specific differential growth processes particular to malignant tumours. The principle mode of action generally involves the "lock-and-key" mechanism and identifying the "Achilles' heel" for drug action. Various targeted agents have been studied and many have translated into significant clinical benefit. This chapter will describe some examples which illustrate the role of this approach in gastrointestinal cancers.

Contents

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1 Cell Signalling Networks and Potential Targets

Examples of potential targets include: (1) cell surface receptors, (2) receptor tyrosine kinase (RTK), (3) intracellular downstream signalling proteins and (4) anti-angiogenic agents.

Targeted therapies may thus be directed towards inhibition of the receptor-intracellular signalling axis via:

1. Inactivation of ligands by preventing binding to receptors triggering signalling pathways.
2. Binding of extracellular receptor domain and interfering with activation by the effector ligand.
3. Inhibition of intracellular tyrosine kinase domain by interrupting phosphorylation and downstream messenger initiation.
4. Disruption of intracellular signalling pathways by disrupting the downstream signal transfer circuit.

Principle of therapy extends to treatments which may also trigger apoptotic pathways and modify inflammation pathways. The range of potential targets is wide but in this chapter clinical data is highlighted to illustrate the translational approach using selected targeted therapies in the management of gastrointestinal cancer (Fig. 1).

2 Targeted Therapies in Gastrointestinal Cancers

2.1 Tyrosine Kinase Cell Receptor Families

2.1.1 EGF Receptor Inhibitor

EGFR is a member of the ErbB family of trans-membrane tyrosine kinase receptors which consists of ErbB1 (HER1, EGFR), ErbB2 (HER2, neu), Erb3 (HER3) and ErbB4 (HER4). Investigation into signal transduction processes involving EGF receptors has linked these receptors to the Ras-Raf-MEK-MAPK, PI3 K-Akt and STAT pathways leading to DNA transcription, cell cycle progression and cellular proliferation. Overexpression of EGFR occurs in a variety of tumours including head and neck, colorectal, pancreatic, lung, breast, kidney, prostate and bladder carcinomas; and HER2 in breast and gastric cancers.

Drugs which target EGFR are monoclonal antibodies (mAb) which competitively bind to the extracelluar domain, inhibiting receptor activation and downstream signalling. Cetuximab and panitumumab are two mAb EGFR inhibitors which are commonly investigated in clinical trials.

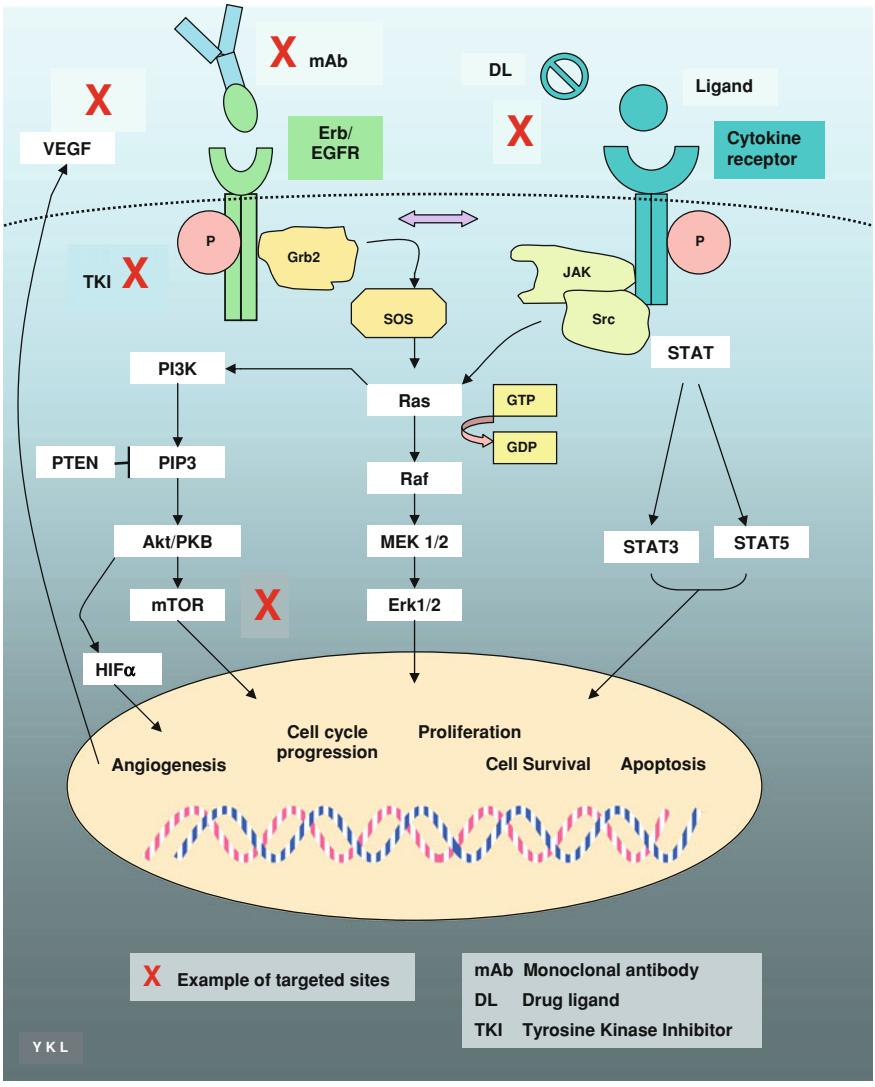

Fig. 1 Simplified example of cell surface receptors and their interaction with intracellular signalling pathways

EGFR inhibitors have been investigated in several large phase III metastatic colorectal cancer (mCRC) trials, initially in the chemo-refractory setting and more recently as part of first-line therapy. However, activating somatic *KRAS* mutation occurs in around 40% of cases and commonest mutations occur in codons 12, 13 and 61 (approximately 82, 17 and 8%, respectively) (Edkins et al. 2006). Subgroup analyses of the major randomised EGFR-therapy trials demonstrate lack of clinical benefit in tumours with *KRAS* mutation due to the evasion of upstream

EGFR blockade (Karapetis et al. 2008). This highlighted the importance of an intact receptor-signalling axis and illustrates the proof of concept in targeted therapies.

The synergistic effect of cetuximab when used in combination with chemotherapy was first reported in the BOND trial which compared single agent cetuximab with cetuximab in combination with irinotecan for patients who had progressed on irinotecan-based regimens. Significant improvement in response rate (22.9 vs. 10.8%), median time to progression (4.1 vs. 1.5 months) and median survival (8.6 vs. 6.9 months) (Cunningham et al. 2004) was achieved, demonstrating the ability of cetuximab to reverse irinotecan-resistance and also for monotherapy activity in patients resistant to conventional lines of treatment. In the EPIC (Sobrero et al. 2008) trial, cetuximab was used in combination with irinotecan in the second-line treatment of patients with mCRC. Compared to irinotecan alone, statistically significant improved response rate and progression-free survival (PFS) were achieved (16.4 vs. 4.2% and 4.0 vs. 2.6 months, respectively), reinforcing the concept of reversal of chemo-resistance. However, there was no difference in overall survival (OS). This may have been due to treatment cross over between the arms.

The importance of *KRAS* mutation emerged from subsequent trials. When treatment with cetuximab monotherapy plus best supportive care (BSC) was compared to BSC alone, patients with *KRAS* wild-type (wt) tumours had significantly better median OS (9.5 vs. 4.8 months, $p < 0.0001$) and median PFS (3.7 vs. 1.9 months, $p < 0.0001$) (Karapetis et al. 2008) with EGFR therapy. Similar improvement in PFS but not OS was also found in *KRAS* wt patients treated with panitumumab monotherapy versus BSC (3.0 vs. 1.8 months, $P < 0.001$) (Amado et al. 2008).

Subsequent trials incorporated EGFR-targeted therapy with combination chemotherapy in the first-line treatment of patients with mCRC. The CRYSTAL trial (Van Cutsem et al. 2009a) randomised 599 chemotherapy-naïve patients with mCRC to FOLFIRI with cetuximab versus 599 patients to FOLFIRI alone. Treatment with EGFR inhibition led to an improved hazard ratio for PFS in patients with *KRAS* wt (0.68; 95% CI, 0.50–0.94) but not *KRAS* mutant (mt) tumours. The OPUS trial randomised 337 patients to cetuximab in combination with FOLFOX-4 versus FOLFOX-4 alone. Benefit was again limited to the *KRAS* wt, but not *KRAS* mt group confirming an improved chance of response (ORR = 61 vs. 37%; odds ratio = 2.54; $p = 0.011$) and a lower risk of disease progression (HR 0.57; $p = 0.0163$) in favour of anti-EGFR therapy.

However, no significant survival benefit from the addition of cetuximab to FOLFOX was seen in the UK MRC COIN trial (Adams 2009). Early data suggested a trend to inferior survival in patients with *KRAS* mt tumours treated in the cetuximab combination arm. Together with a significantly shortened PFS in the subgroup of patients with *KRAS* mt tumours from the OPUS trial, this suggests a possible negative interaction between oxaliplatin and anti-EGFR-targeted therapy not seen with irinotecan-based combination chemotherapy (see Sect. 3).

Resection of liver-only metastases in CRC improves survival (Giacchetti et al. 1999; Adam et al. 2004). In patients with unresectable hepatic metastases, cetuximab was shown to increase response rate when added to FOLFIRI (59.3%) (Van Cutsem et al. 2009a). However, when added to FOLFOX, overall response rate of up to 85% was achieved in the randomised phase II CELIM trial, leading to a resection rate of 40%. Activity in *KRAS* wt tumours was 79% with cetuximab. In the UK, the use of cetuximab combined with chemotherapy in patients with liver-only metastases has been approved by NICE.

2.1.2 HER2 Receptor Inhibitor

It is estimated that between 6 and 35% of oesophageal and gastric malignancies overexpress HER2. In the first phase III prospective randomised ToGA trial (Van Cutsem et al. 2009b) investigating HER2 inhibition in locally advanced or metastatic gastroesophageal and gastric adenocarcinomas, histological samples were found to be HER2 positive in 22.1% of 3,807 patients (Bang et al. 2009). A modified HER2 score was used and HER2 positivity was defined as IHC 3+ and/or FISH positive.

Five hundred and ninety two patients with HER2 positive tumours were randomised to receive 3-weekly fluoropyrimidine (5-fluorouracil or capecitabine) with cisplatin alone or in combination with trastuzumab. Results were in favour of the trastuzumab arm showing a significant improvement in OS of 2.4 months (13.5 vs. 11.1 months, respectively) with no unexpected adverse events or difference in symptomatic congestive cardiac failure. Results of this trial suggest the benefit of anti-HER2 targeted therapy as a treatment option in the management of these patients.

2.1.3 IGFR-1 Receptor Inhibitor

Another class of tyrosine kinase transmembrane receptor is the IGF-1R which is activated by IGF-1 and 2 ligands. It is structurally similar to the insulin receptor and share the IRS-1 and 2 substrate transmission proteins. However, IGF-1R has been shown to trigger the Ras-Raf-MEK-MAPK and PI3 K-Akt pathways leading to a wide range of cellular activity including growth, differentiation and survival. IGF-1R is known to be overexpressed in gastric, colorectal and pancreatic cancers leading to increased risk of metastases and worse clinical outcome.

In gastric cancer, a positive correlation between overexpression of IGF-1R and rate of nodal metastases in gastric cancer was found (Guo et al. 1995). IGF-1R is also implicated in the pathogenesis of colorectal cancers (Guo et al. 1995; Zecevic et al. 2006). The risk of developing bowel malignancy is known to be increased in patients with acromegaly. This is associated with high growth hormone and IGF-1 levels. IGF-1 may be overexpressed in up to two-thirds of colorectal cancer and can independently affect tumour progression (Scartozzi et al. 2009).

Various IGF-1R receptor antibodies and tyrosine kinase inhibitors (TKI) have been developed and are undergoing clinical trials. In vitro study using IR3 antibody directed to IGF-1R in gastric carcinoma resulted in a reduction of cell colony count (Pavelic et al. 2002). In colorectal cancer, a current phase II/III trial investigates anti-IGFR antibody MK-0646 in conjunction with cetuximab and irinotecan.

This combination was found to be tolerated and further results on PFS and correlation with *KRAS* status is pending (Watkins et al. 2009). In pancreatic cancer, a dose-response relationship was found in cell line studies when treated with single agent IGF-1R antibody and synergistic effect was observed when IGF-1R blockade was combined with gemcitabine and panitumumab (Beltran et al. 2009).

IGF-1R also interacts with other receptors involved in malignant transformation including EGFR and VEGF. A study on surgical specimens demonstrated correlation between membrane-dominant dominant EGFR/cytoplasmic-dominant IGF receptor with lower grade and prognosis, and cytoplasmic-dominant EGFR/membrane-dominant IGF receptor with higher grade and worse prognosis. In addition, IGF-1R and EGFR overexpression was also more frequent in liver metastases compared to pancreatic primaries (Ueda et al. 2006).

2.2 VEGF Inhibitor

With tumour cell proliferation, angiogenesis is essential for continued growth. This process is mediated by the VEGF family of circulating angiogenic ligands (VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E and placenta growth factor PlGF). The ligands exert its effect on corresponding VEGF receptors VEGF-R1 (migration, invasion), VEGF-R2 (proliferation, survival) and VEGF-R3 (lymphangiogenesis). These processes are not only involved in inflammation and wound healing, but are also activated in malignant angiogenesis. In addition, VEGF plays an important role in the orchestration of tumour survival including inhibition of apoptosis, migration and invasion.

Bevacizumab is an antibody to VEGF-A. Curbing the development of tumour blood vessels, it also normalises vessel blood flow through vasoconstriction, reducing hypoxia and expression of HIF-1. It was one of the earliest to be studied in colorectal cancer improving median survival from 15.6 to 20.3 months when used in combination with first-line 5-fluorouracil and irinotecan (Hurwitz et al. 2004). A recent Cochrane analysis showed overall benefit of bevacizumab (Wagner and Moehler 2009). Although it has little efficacy as monotherapy, improvement in PFS and OS was evident when used in combination with chemotherapy. The benefit of anti-VEGF therapy was also found in patients $\geq$65 years old (Kabbinavar et al. 2009). Allowing for heterogeneity in treatment duration and chemotherapy platform using oxaliplatin-based regimens, improvement in HR for PFS (0.61; 95% CI 0.45–0.83) and OS (0.81; 95% CI 0.73–0.90) was demonstrated in the first-line setting. The value of continuing bevacizumab beyond progression was suggested by the observational BRiTE study. Although not randomised, median OS rates were 12.6 months in patients who stopped treatment, 19.9 months in those who continued chemotherapy without bevacizumab and 31.8 months in those who continued chemotherapy with bevacizumab (Grothey et al. 2008). In the second-line setting, a large trial using FOLFOX with bevacizumab demonstrated a in HR for PFS (0.61; 95% CI 0.51–0.73) and OS (0.75; 95% CI 0.63–0.89) (Giantonio et al. 2007).

However, early data on bevacizumab in the adjuvant scenario showed it to be of little advantage. The NSABP-C08 phase III trial comprising of 2,672 patients with stage II or III colorectal cancer did not demonstrate benefit in terms of PFS after a year of anti-VEGF treatment in addition to FOLFOX (Wolmark et al. 2009).

2.3 Small Molecule TK Inhibitor

Signal transduction occurs at the intracellular domain when the receptor is triggered by their complementary ligand. This leads to downstream phosphorylation of substrate proteins and subsequently activates the network of signal transduction pathways which regulate important cell functions. TKI block this key activation process and were the forerunners of targeted therapy in cancer.

2.3.1 Imatinib

Kit and PDGFR display extensive structural homology and are members of the type III tyrosine kinase receptor family. TKIs which act on these sites were among the earliest described and provided the initial proof of concept. STI-571 (Imatinib mesylate) has binding activity to sites including Kit, Bcr-Abl and PDGF domains. It was tested in advanced GIST tumours which express the kit (Hirota et al. 1998) mutation. Early studies showed a response rate exceeding 80% and median PFS of over 24 months could be achieved. The commonest mutation occurs at the exons 11 (70%) and 9 (15%) but other sites including exons 13, 14, 17 as well as PDGFRA (exons 12, 18) (Heinrich et al. 2003) have been reported. Exon 11 encodes for the intracellular autoinhibitory juxta-membrane domain, while exon 9 encodes for the distal part of the extracellular domain. In addition, exons 13/14 and 17 encode for the drug/ATP binding pocket and activation loop, respectively. Differential mutations at these sites predict for objective response—71.7% for exon 11 versus 44.4% for exon 9, as well as clinical outcome where presence of exon 11 mutation led to a 5-year recurrence-free survival of 89 $\pm$ 10%, but only 40 $\pm$ 8% if other mutations were found ($p = 0.03$) (Singer et al. 2002). Doubling the dose of imatinib to 800 mg improved PFS for patients with exon 9 mutation (Verweij et al. 2004; Van Glabbeke et al. 2007). Secondary mutations in exons 13/14 and 17/18 led to resistance. Clinical observation suggested that abrupt withdrawal of the drug could result in accelerated progression. This may reflect heterogeneity of the tumour where previously imatinib sensitive malignant clones encounter resurgence.

2.3.2 Sunitinib

Sunitinib is a TKI with activity against Kit (CD117), PDGF-Rβ and VEGFR. In patients with GIST who progress on imatinib, sunitinib has shown to be effective as second line therapy (Demetri et al. 2006, 2009; Heinrich et al. 2008). Although it demonstrated in vitro activity in wild-type, exons 11 and 9 mutated tumours, benefit in clinical trials translated into the exon 9 group. This is

postulated to be due to dimerisation of the receptor as a distinct mechanism of activation compared to exon 11 mutations (Dibb et al. 2004; Yuzawa et al. 2007). However, clinical trials will be required to test sunitinib TKI naïve GIST to exclude selection bias.

2.3.3 Sorafenib

Sorafinib is active against Raf kinase, PDGFR, VEGF receptor 2 and 3 kinases and c-Kit. Targeting signalling through the Ras-Raf-MAPK-Erk pathway, it has been studied in a phase III trial (Llovet et al. 2008) in advanced hepatocellular carcinoma (HCC). Patients were randomised to receive sorafenib or placebo. In the treated group, a significant improvement in median OS and median time to radiological progression was found (10.7 vs. 7.9 months, 5.5 vs. 2.8 months, respectively).

A separate analysis of signalling pathway proteins in HCC tumour samples show activation of Erk pathway correlated with low levels of nuclear β-cat and high levels of *p*-mTOR, distinguishing them from normal liver parenchyma. Better survival of 6 months or more in patients treated with sorafenib was linked to tumours with a high level of nuclear *p*-Erk with low level of *p*-Akt and *p*-GSK3β in tumour cells. In addition, high levels of VEGFR, *p*-Erk and *p*-Src in endothelial cells were associated with high microvessel density and micrometastases (Ji et al. 2009).

2.3.4 Erlotinib

Erolitnib was the first targeted therapy to show survival benefit in a phase III trial involving advanced pancreatic cancer. Compared to gemcitabine alone, it led to a modest but statistically significant improvement in survival at 12 months (23 vs. 17%) and HR for OS (0.82; 95% CI, 0.69–0.99, $p = 0.038$) (Moore et al. 2007).

However, interesting questions remain relating to the mechanism of action. *KRAS* mutation was found in 79% of patients in the trial and analysis of subgroups shows advantage irrespective of EGFR expression, given variation in laboratory testing techniques. One hypothesis is anti-EGFR therapy targets EGFR expressing endothelial cells in the tumour microenvironment stimulated by EGF-like peptides expressed at high levels in pancreatic cancer (Bruns et al. 2000; Normanno and De Luca 2007; Salomon et al. 1995). Although erlotinib may play a part in angiogenesis, it may be an early indirect effect on cellular proliferation that limits the condition conducive to VEGF production. This may explain the negative results in large phase III clinical trials where the addition of bevacizumab to gemcitabine and erlotinib did not result in OS benefit (Vervenne et al. 2008; Van Cutsem et al. 2009c). An on-going phase I/II TARGET trial addresses the efficacy and safety of gemcitabine and capecitabine together with erlotinib and bevacizumab.

2.3.5 Gefitinib

Overexpression of EGFR has been found to be a negative prognostic factor in oesophageal carcinoma (Yacoub et al. 1997). Several non-randomised phase II trials investigating gefitinib in patients with advanced oesophageal carcinoma

demonstrated an overall response rate between 30 and 58% (Janmaat et al. 2006; Ferry et al. 2004, 2007). Currently the UK COG trial is underway randomising patients between gefitinib and placebo in patients with relapsed advanced oesophageal cancer.

3 Network Interactions and Resistance to Targeted Therapies

The interaction of various signalling networks suggests that tumours may escape interruption of downstream signalling by TKI through by-passing blocked channels. This re-routing of messaging system enables continued progression despite disabling a known target. The interplay of signalling pathways is more elaborate than initially thought and appears to contribute to tumour progression and resistance to therapy.

However, current trials show that efficacy is not necessarily improved by combining targeted drugs. For example, two CRC trials using VEGF together with EGFR-directed mAbs and chemotherapy demonstrate a detrimental effect on survival (Hecht et al. 2009; Tol et al. 2009). Apart from increased toxicity, combining targeted agents worsened survival especially in patients with *KRAS* mt tumours as confirmed on meta-analysis (Zhou et al. 2009). The choice of chemotherapy platform may also have a negative impact. In the OPUS trial where FOLFOX-4 was used in combination with cetuximab, patients with *KRAS* mt tumours had a trend to reduced median PFS compared to FOLFOX-4 alone (5.5 vs. 8.6 months, HR 1.83; 95% CI, 1.095–3.056, $p = 0.192$) (Bokemeyer et al. 2009). A negative effect of reduced median PFS was again seen when FOLFOX was added to panitumumab in the PRIME study (7.3 months in chemotherapy-only arm vs. 8.8 months for combination treatment; HR 1.29; 95% CI, 1.04–1.62, $p = 0.0227$) (Douillard 2009). Early results from the COIN study (Adams 2009) investigating FOLFOX or CAPOX in combination with cetuximab suggested a worse outcome with the capecitabine combination. These trials indicate a negative interaction between targeted agents and oxaliplatin or capecitabine. The mechanism of interaction is of considerable interest and remains to be elicited.

Forty to seventy percentage of *KRAS* wt tumours do not benefit from EGFR inhibition. The varied permutation and interaction between signalling pathways is only beginning to be understood. In a report investigating chemorefractory mCRC found mutations in *KRAS*, *BRAF* and *NRAS* were mutually exclusive and occur independently in over 47% of cases (Lambrechts et al. 2009). *BRAF* wt also conferred a significantly better PFS and OS. Mutation in *BRAF* and *NRAS* occurred in 9.8 and 5% of *KRAS* wt CRC tumours, respectively. Best outcome was associated with *KRAS/BRAF/NRAS* wt. Twelve percentage carried the independent PI3 K mutation but this was not correlated with tumour response or outcome. In advanced gastric cancer, however, *KRAS* and *BRAF* status was not predictive of response to cetuximab (Stella et al. 2009). In addition, mutation rates of *KRAS*

were lower compared to colorectal tumours at 11.4 and 2.3%, respectively. Similarly *KRAS* mutation was found in only 12% of cholangiocarcinoma and did not impact on treatment response to EGFR inhibition (Gruenberger et al. 2009).

Interaction between receptors may also impact on prognosis. In a study of 66 patients with mCRC receiving irinotecan and cetuximab, partial response rate was 50% in *KRAS* wt and IGF-R1 tumours but 5% with a co-existent IGF-R1 mutation. A statistically significant difference in time to tumour progression was also found (11 vs. 3.2 months). Thus IGF-R1 status is implicated as a predictive factor for resistance in tumours treated with anti-EGFR therapy (Scartozzi et al. 2009).

Mutations in exons 13/14 may be coexpressed with exon 17 in GIST tumours. Although both are involved in signal transduction, they occur in distinct parts of the pathway. The former involves changes in the ATP binding site and the latter in the ATP activation loop. However, they are linked by a common primary mutation (V560D). Thus stopping treatment directed at one arm of the mutational defect due to development of a second defect at the first sign of resistance may also disinhibit activity in the second mutational site leading to rapid tumour growth. For example, although tumours resistant to imatinib due to secondary mutation in exons 13/14 were sensitive to second-line sunitinib, this mutation was coexpressed as a mutation in exon 17 (V560D) which was not susceptible to either drugs (Heinrich et al. 2008). Therefore removing collateral inhibition may result in tumour flare.

4 Conclusion

The role of targeted treatment in cancer has developed rapidly in recent years. With greater understanding of the biology of various cancers, new drugs have been developed and tested in the clinical setting demonstrating efficacy and extending the treatment paradigm beyond that of traditional chemotherapy. Current data bridging in vitro studies and clinical trials demonstrate the mechanism of action of targeted therapy is more than just a proof of concept in translational cancer research. However, understanding the interplay between numerous receptor-signalling pathways has presented to us a bigger challenge than simply addressing individual targets. More research is warranted both to greater understand the basic molecular biology of cancer as well as to develop further randomised clinical trials in addressing the potential of targeted therapy in this era of biological treatment in cancer.

References

Adam R et al (2004) Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. Ann Surg 240:644–657

Adams R (2009) Intermittent versus continuous oxaliplatin-based combination chemotherapy in patients with advanced colorectal cancer: a randomised non-inferiority trial (MRC COIN). Eur J Cancer Suppl 7:10

Amado RG et al (2008) Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol 26:1626–1634
Bang Y et al (2009) Pathological features of advanced gastric cancer (GC): relationship to human epidermal growth factor receptor 2 (HER2) positivity in the global screening programme of the ToGA trial. J Clin Oncol (Meeting Abstracts) 27:4556
Beltran PJ et al (2009) AMG 479, a fully human anti-insulin-like growth factor receptor type I monoclonal antibody, inhibits the growth and survival of pancreatic carcinoma cells. Mol Cancer Ther 27:5800–5807
Bokemeyer C et al (2009) Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. J Clin Oncol 27:663–671
Bruns CJ et al (2000) Blockade of the epidermal growth factor receptor signaling by a novel tyrosine kinase inhibitor leads to apoptosis of endothelial cells and therapy of human pancreatic carcinoma. Cancer Res 60:2926–2935
Cunningham D et al (2004) Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med 351:337–345
Demetri GD et al (2006) Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet 368:1329–1338
Demetri GD et al (2009) Molecular target modulation, imaging, and clinical evaluation of gastrointestinal stromal tumor patients treated with sunitinib malate after imatinib failure. Clin Cancer Res 15:5902–5909
Dibb NJ, Dilworth SM, Mol CD (2004) Switching on kinases: oncogenic activation of BRAF and the PDGFR family. Nat Rev Cancer 4:718–727
Douillard J (2009) Randomized phase 3 study of panitumumab with FOLFOX4 compared to FOLFOX4 alone as first-line treatment for metastatic colorectal cancer: the PRIME trial. Eur J Cancer Suppl Abstr 10LBA 7:6
Edkins S et al (2006) Recurrent KRAS codon 146 mutations in human colorectal cancer. Cancer Biol Ther 5:928–932
Ferry DR et al (2004) Phase II trial of gefitinib (ZD1839) in advanced adenocarcinoma of the oesophagus incorporating biopsy before and after gefitinib. J Clin Oncol (Meeting Abstracts) 22:4021
Ferry DR et al (2007) A phase II study of gefitinib monotherapy in advanced esophageal adenocarcinoma: evidence of gene expression, cellular, and clinical response. Clin Cancer Res 13:5869–5875
Giacchetti S et al (1999) Long-term survival of patients with unresectable colorectal cancer liver metastases following infusional chemotherapy with 5-fluorouracil, leucovorin, oxaliplatin and surgery. Ann Oncol 10:663–669
Giantonio BJ et al (2007) Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. J Clin Oncol 25:1539–1544
Grothey A et al (2008) Bevacizumab beyond first progression is associated with prolonged overall survival in metastatic colorectal cancer: results from a large observational cohort study (BRiTE). J Clin Oncol 26:5326–5334
Gruenberger B et al (2009) K-ras status and response in patients with advanced or metastatic cholangiocarcinoma treated with cetuximab plus gemcitabine-oxaliplatin (GEMOX): a single center phase II study. J Clin Oncol (Meeting Abstracts) 27:4586
Guo YS et al (1995) Insulin-like growth factor-II expression in carcinoma in colon cell lines: implications for autocrine actions. J Am Coll Surg 181:145–154
Hecht JR et al (2009) A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. J Clin Oncol 27:672–680
Heinrich MC et al (2003) PDGFRA activating mutations in gastrointestinal stromal tumors. Science 299:708–710

Heinrich MC et al (2008) Primary and secondary kinase genotypes correlate with the biological and clinical activity of sunitinib in imatinib-resistant gastrointestinal stromal tumor. J Clin Oncol 26:5352–5359

Hirota S et al (1998) Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science 279:577–580

Hurwitz H et al (2004) Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 350:2335–2342

Janmaat ML et al (2006) Predictive factors for outcome in a phase II study of gefitinib in second-line treatment of advanced esophageal cancer patients. J Clin Oncol 24:1612–1619

Ji Y et al (2009) Analysis of signal pathway activation in hepatocellular carcinoma: association with clinical outcomes to sorafenib in Chinese patients. J Clin Oncol (Meeting Abstracts) 27:e15529

Kabbinavar FF, Hurwitz HI, Yi J, Sarkar S, Rosen O (2009) Addition of bevacizumab to fluorouracil-based first-line treatment of metastatic colorectal cancer: pooled analysis of cohorts of older patients from two randomized clinical trials. J Clin Oncol 27:199–205

Karapetis CS et al (2008) K-ras mutations and benefit from cetuximab in advanced colorectal cancer. N Engl J Med 359:1757–1765

Lambrechts D et al (2009) The role of KRAS, BRAF, NRAS, and PIK3CA mutations as markers of resistance to cetuximab in chemorefractory metastatic colorectal cancer. J Clin Oncol (Meeting Abstracts) 27:4020

Llovet JM et al (2008) Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 359:378–390

Moore MJ et al (2007) Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 25:1960–1966

Normanno N, De Luca A (2007) Erlotinib in pancreatic cancer: are tumor cells the (only) target? J Clin Oncol 25:5836–5837

Pavelic K, Bukovic D, Pavelic J (2002) The role of insulin-like growth factor 2 and its receptors in human tumors. Mol Med 8:771–780

Salomon DS, Brandt R, Ciardiello F, Normanno N (1995) Epidermal growth factor-related peptides and their receptors in human malignancies. Crit Rev Oncol Hematol 19:183–232

Scartozzi M et al (2009) Correlation of insulin-like growth factor 1 (IGF-1) expression and clinical outcome in K-RAS wild-type colorectal cancer patients treated with cetuximab-irinotecan. J Clin Oncol (Meeting Abstracts) 27:4017

Singer S et al (2002) Prognostic value of KIT mutation type, mitotic activity, and histologic subtype in gastrointestinal stromal tumors. J Clin Oncol 20:3898–3905

Sobrero AF et al (2008) EPIC: phase III trial of cetuximab plus irinotecan after fluoropyrimidine and oxaliplatin failure in patients with metastatic colorectal cancer. J Clin Oncol 26:2311–2319

Stella G et al (2009) KRAS and BRAF mutational status as response biomarkers to cetuximab combination therapy in advanced gastric cancer patients. J Clin Oncol (Meeting Abstracts) 27:e15503

Tol J et al (2009) Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. N Engl J Med 360:563–572

Ueda S et al (2006) Potential crosstalk between insulin-like growth factor receptor type 1 and epidermal growth factor receptor in progression and metastasis of pancreatic cancer. Mod Pathol 19:788–796

Van Cutsem E et al (2009a) Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med 360:1408–1417

Van Cutsem E et al (2009b) Efficacy results from the ToGA trial: a phase III study of trastuzumab added to standard chemotherapy (CT) in first-line human epidermal growth factor receptor 2 (HER2)-positive advanced gastric cancer (GC). J Clin Oncol (Meeting Abstracts) 27:zLBA4509

Van Cutsem E et al (2009c) Phase III trial of bevacizumab in combination with gemcitabine and erlotinib in patients with metastatic pancreatic cancer. J Clin Oncol 27:2231–2237

Van Glabbeke MM et al (2007) Comparison of two doses of imatinib for the treatment of unresectable or metastatic gastrointestinal stromal tumors (GIST): A meta-analyis based on 1, 640 patients (pts). J Clin Oncol (Meeting Abstracts) 25:10004

Vervenne W et al (2008) A randomized, double-blind, placebo (P) controlled, multicenter phase III trial to evaluate the efficacy and safety of adding bevacizumab (B) to erlotinib (E) and gemcitabine (G) in patients (pts) with metastatic pancreatic cancer. J Clin Oncol (Meeting Abstracts) 26:4507

Verweij J et al (2004) Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. Lancet 364:1127–1134

Wagner AD, Moehler M (2009) Development of targeted therapies in advanced gastric cancer: promising exploratory steps in a new era. Curr Opin Oncol 21:381–385

Watkins DJ et al (2009) A phase II study of the anti-IGFR antibody MK-0646 in combination with cetuximab and irinotecan in the treatment of chemorefractory metastatic colorectal cancer. J Clin Oncol (Meeting Abstracts) 27:4127

Wolmark N et al (2009) A phase III trial comparing mFOLFOX6 to mFOLFOX6 plus bevacizumab in stage II or III carcinoma of the colon: Results of NSABP Protocol C-08. J Clin Oncol (Meeting Abstracts) 27:LBA4

Yacoub L, Goldman H, Odze RD (1997) Transforming growth factor-alpha, epidermal growth factor receptor, and MiB-1 expression in Barrett's-associated neoplasia: correlation with prognosis. Mod Pathol 10:105–112

Yuzawa S et al (2007) Structural basis for activation of the receptor tyrosine kinase KIT by stem cell factor. Cell 130:323–334

Zecevic M et al (2006) IGF1 gene polymorphism and risk for hereditary nonpolyposis colorectal cancer. J Natl Cancer Inst 98:139–143

Zhou Z, Walsh WV, Bathini VG, Piperdi B (2009) Anti-VEGF and anti-EGFR monoclonal antibodies (Mabs) in the first-line therapy for metastatic colorectal cancer: a meta-analysis. J Clin Oncol (Meeting Abstracts) 27:e15012