Targeting the Epidermal Growth Factor Receptor in Colorectal Cancer

a report by

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A crucial goal in the refinement of systemic cancer therapy is the achievement of high efficacy while minimising side effects. Conventional anticancer drugs target malignant cells to an extent, but are often associated with dose-limiting toxicity. One solution is to improve the specificity of the therapeutic agent based upon knowledge of a specific target. As our understanding of the molecular basis of cancer steadily progresses, the opportunities for the development of such improved treatments rise commensurately. The design of modern drug therapies is informed by the genetic and biochemical mechanisms responsible for the behaviour of malignant cells. One such endeavour includes the development of targeted drugs against the type I transmembrane kinase receptor epidermal growth factor receptor (EGFR). Following a brief outline of EGFR cancer biology, this article will provide an up-to-date synopsis of clinical research efforts attempting to exploit this receptor system in the setting of advanced colorectal cancer.

The Epidermal Growth Factor Receptor Family

EGFR was the earliest of four receptors discovered in the ErbB family of receptor tyrosine kinases.[1,2] Furthermore, it was this receptor that first identified a relationship between an activated oncogene and malignant transformation.[3] This 170kDa glycoprotein comprises an extracellular portion made up of four distinct sub-domains capable of conformational change.[4,5] It is anchored by a single-pass transmembrane domain that connects to a cytoplasmic tail harbouring tyrosine kinase activity.[6] EGFR and its three sibling receptors – HER-2/ErbB2, HER-3/ErbB3 and HER-4/ErbB4 – transduce the effects of at least 11 different peptide ligands, including epidermal growth factor (EGF).[7] Signalling events initiated by such growth factors are involved in normal physiological cellular growth and proliferation, but are critically important in malignant transformation.

The harbinger of growth factor signalling is the extracellular binding of ligands to one or more of these receptors, which induces receptor homo- or hetero-dimerisation or oligomerisation. As a result, phosphorylation of kinase-domain tyrosine residues ensues. These serve as docking sites for various cytoplasmic proteins, which then propagate signalling via second messenger pathways through the cytoplasm. These include Ras/mitogen-activated protein (MAP) kinase, the Src kinase family, Janus kinase (JAK), signal transducer and activator of transcription (STAT), phosphoinositol 3 (PI3), kinase/Akt and other phospholipid metabolism pathways. Via induction of nuclear transcription factors, the end-product of signalling is stimulation of cellular processes such as proliferation, antiapoptosis, growth and migration.[6] Ligand stimulation also leads to increased internalisation of EGFR via endocytic pathways; ultimately, receptors are either recycled or destined for lysosomal degradation.[8] The system is hugely complex in that there are multiple levels of variability and control, which increases system robustness.[9,10] On one level, there are interactions between different receptors and their ligands; on another, receptor–receptor interactions can form oligomer lattices, which in turn force interactions within the second-messenger and output layers.

Overactivation of this signalling mechanism can be due to increased ligand stimulation,[11] receptor overexpression[12] or by mutations leading to constitutive activity or enhanced function,[13] and has been frequently observed in a wide range of epithelial tumour types. Furthermore, such parameters are associated with poorer clinical outcome.[14] Taken together, these factors make EGFR and its receptor family extremely attractive therapeutic targets.

Targeted Therapies

There are two categories of anti-EGFR therapies currently licensed for use: monoclonal antibodies directed against extracellular epitopes of EGFR and small molecular weight tyrosine kinase inhibitors (TKIs). The first successful example of drug abrogation of EGFR signalling in human malignant disease was provided by cetuximab, a chimeric murine-human immunoglobulin (Ig) G1 monoclonal antibody. Others in earlier clinical development include the fully humanised monoclonal antibodies panitumumab (ABX-EGF)[15], matuzumab (EMD72000)[16] and nimotuzumab (h-R3).[17] The mechanism of action of EGFR-directed monoclonal antibodies seems to be multifaceted. Evidence exists suggesting steric hindrance of ligand-binding and dimerisation,[18] antibody-directed cellular cytotoxicity,[19] induction of receptor internalisation and degradation,[20,21] modification of vascular endothelial growth factor (VRGF)[20] and, more recently, the possible blockade of nuclear transfer of EGFR, thus inactivating DNA repair mechanisms.[23–25]

Cetuximab has the ability to increase chemo- and radio-sensitisation even in the face of previous resistance to these treatment modalities.[26,27] Cetuximab is generally well tolerated: the most striking toxicity is skin rash, the presence and intensity of which may predict response and survival.[28] Gefitinib and erlotinib are the most researched of the TKIs in clinical use.[29,30] They are anilinoquinazolines that bind the adenosine tri-phosphate (ATP)-binding pocket of the EGFR kinase domain and hence act intracellularly, impeding second-messenger activation. The most recent EGFR family kinase inhibitor to reach clinical use is lapatinib, a dual TKI of both EGFR and HER-2.[31] However, these drugs may also affect other mammalian kinases; for example, proteomic study of cancer cell lines treated with gefitinib show approximately 30 protein kinases to be targeted.[32] Other small-molecule TKIs that are more specific and bind irreversibly are in pre-clinical development.

Impact on Advanced Colorectal Cancer

Modern chemotherapy regimens using agents such as 5-fluorouracil, irinotecan and oxaliplatin have improved median overall survival from less than one year to over 20 months for patients with advanced colorectal cancer.[33] More recently, it was hoped that the incorporation of targeted

Table 1: Selected Studies of Epidermal Growth Factor-targeted Therapy for Advanced Colorectal Cancer for Non-first-line Use

Author	Year	Phase	Regimen	Regimen	Regimen	N	CR%	PR%	SD%	DCR%	PD%	TTP	MS	PFS	Notes
Jonker[35]	2007	III	Cetux	BSC		287							6.1m		HR (for MS): 0.77 (p=0.005)
				BSC		285							4.6m		HR (for TTP): 0.68 (p<0.001)
Saltz[36]	2004	II	Cetux			57	0	9	37	46			6.4m		
Lenz[37]	2006	II	Cetux			346		11.6		43.4			6.6m	1.4m	
Mirtsching[38]	2004	II	Cetux			29	0	11	46	57	43	72d			Mean SD duration: 109d
Meyerhardt[39]	2006	Retro	Cetux			24	0	16	56	72				5.1m	Previous TKIs + chemo
Cunningham[34]	2004	II	Cetux			111	0	10.8	21.6	32.4		1.5m	6.9m		PR comparison: p=0.0074
			Cetux	Irinotecan		218	0	22.9	32.6	55.5		4.1m	8.6m		TTP comparison: p=0.001
Gebbia[77]	2006	Retro	Cetux	Irinotecan		60		20		50			6m	3.1m	
Vincenzi[78]	2006	Retro	Cetux	Irinotecan		55	0	25.4	38.2	63.6		4.7m	9.8m		
Cassano[79]	2007	II	Cetux	Irinotecan		24		8.6	26	34.6	65.4	3m	7m		
Wilke[80]	2006	II	Cetux	Irinotecan q1,2,3w		1,123							9.2m		12w rate=61%; 24w rate=34%
Cianci[81]	2006	II	Cetux	Irinotecan		57		14	24.6	38.6	40.4	4m	8m		
Tahir[82]	2006	II	Cetux	Irinotecan		22		18	41	59	41	24w			
Teoh[83]	2007	Retro	Cetux	Irinotecan		7				43				3m	Duration of SD:16m vs 2.5m
				Cape	Mitimicin c	11				36				3m	Favouring cetux + irinotecan
Sobrero[41]	2007	III	Cetux	Irinotecan		648							10.71m	3.98m	MS comparison: p=0.712
				Irinotecan		650							9.99m	2.56m	PFS comparison: p<0.0001
Koo[84]	2006	Retro	Cetux	FOLFIRI		31		25.8	32.2	58	35.5	2.9m	12.7m		
Souglakos[85]	2006	II	Cetux	Oxali	Cape	40	2.5	17.5	27.5	47.5		3m	9m		
Grothe[86]	2005	II	Cetux	Oxali	Cape	15		27	27	54	46				
Jennis[42]	2005	III	Cetux	FOLFOX4		45		22	49	71	29			4.4m	Stopped early as oxali became
				FOLFOX4		49		8	57	65	27			4.1m	routine first line
Chan[87]	2007	II	Cetux	Celecoxib		12		8.3	33						
Saltz[43]	2005	II	Cetux	Beva	Irinotecan	40		35	43	78	18				
			Cetux	Beva		35		23	54	77	17				
Souglakos[44]	2007	II	Cetux	Beva		14	0	7	14	21					TTP: 2.4m; acceptable toxicity
Geva[88]	2006	Retro	Cetux	Any chemo		49		12.2 (14.3FR)	24.5	51		1.9m	3.6m		
Tai[89]	2006	II	Cetux	FOLFOX or FOLFIRI		48	31.3	33.3		77.1					ORR: 65%
Levi[90]	2006	II	Cetux	Chrono irinotecan or oxali		45		29.7	35	65	35				Amplified EGFR: poorer RR/ survival
Van Cutsem[46]	2007	III	Panitu	BSC		231		10						8w	HR (for PFS): 0.54 (p<0.0001)
				BSC		232		0						7.3w	No difference in overall survival
Humblet[47]	2006	II	Panitu	BSC		174	1	9	32	41	57			8.1w	Crossover patients following BSC
Berlin[45]	2006	Review	Panitu	BSC		615	0–1	8–13	21–32	29–43					Review of five studies
Rothenberg[48]	2005	II	Gefitinib	250 or 500mg		110		1					6.3m	1.9m	4m PFS:13%; EGFR not inactivated
Mackenzie[49]	2005	II	Gefitinib	750mg		24			33	33					13% stopped due to toxicity
Townsley[91]	2006	II	Erlotinib			31			39	39	61	123d			Pre- and post-tumour Bx: decreased pEGFR, pERK
Keilholz[92]	2005	II	Erlotinib			40		5	32.5	37.5	62.5				
Fields[93]	2005	II	Lapatinib			86		1(6FR)	6	13		8w	42.9w		Low activity
Hofheinz[50]	2006	I–II	Gefitinib	FOLFIRI AIO											Stopped early; no advantage
Veronese[51]	2005	II	Gefitinib	FOLFIRI		13		8	54	62					Excess toxicity: 77% dose reductions
Kuo[52]	2005	II	Gefitinib	FOLFOX4		27		36	48	84			12m		Better than FOLFOX4 alone
Kindler[94]	2005	I–II	Gefitinib	250 and 500mg	Oxali	14			38 and 17	55					Inactive, therefore phase II not done
Meyerhardt[53]	2006	II	Erlotinib	Cape	Oxali	32		25	44	69			14.7m	5.4m	Well-tolerated

Beva = bevacizumab; BSC = best supportive care; cape = capecitabine; cetux = cetuximab; CR = complete response; d = day; DCR = disease control rate; HR = hazard ratio; m = month; MS = median survival; N = number of patients in study; ORR = overall response rate; oxali = oxaliplatin; panitu = panitumumab; PD = progressive disease; PFS = progression-free survival; PR = partial response; retro = retrospective data series; RR = response rate; SD = stable disease; TKI = tyrosine kinase inhibitor; TTP = time to progression; w = weeks.

therapy into these regimes would afford further gains in efficacy while adding minimal toxicity. Clinical proof of this principle was provided by a randomised phase II study (BOND) in which patients received either cetuximab plus irinotecan or cetuximab alone following previous treatment with irinotecan.[34] The observation of significantly improved median time to progression (4.1 versus 1.5 months) favouring combination treatment led to US Food and Drug Administration (FDA) approval of cetuximab for this indication in 2004. Since then, there has been a multitude of studies incorporating EGFR-targeted therapies, which have met with varying degrees of success.

Advanced Chemoresistant Disease

Table 1 summarises selected published studies of EGFR-targeted drugs in second- and subsequent-line treatment of advanced colorectal cancer. All

Table 2: Published Phase II and III Studies using Epidermal Growth Factor-targeted First-line Therapy for Advanced Colorectal Cancer

Author	Year	Phase	Regimen	Regimen	Regimen	N	CR%	PR%	ORR%	SD%	DCR%	PD%	TTP	Notes
Pessino[54]	2006	II	Cetux			37	1	3	4	35	39		2m	
Sastre[55]	2006	II	Cetux			39	2.6	12.8	15.4	38.5	54	46.2		Elderly study: all >70yrs old
Rougier[95]	2004	II	Cetux	FOLFIRI		23	0	46	46	41	87		10.9m	
Rosennberg[96]	2002	II	Cetux	IFL		25	0	44	44	20	64			
Schoffski[97]	2002	II	Cetux	IFL		13	0	31	31	8	39			
Raoul[98]	2003	II	Cetux	FOLFIRI		21	0	43	43	52	95	5	183d	
Folprecht[99]	2006	II	Cetux	IFL		21			67	29	96		9.9m	MS: 33m
Van Laethem[100]	2003	II	Cetux	FOLFIRI		23	0	67	67	22	89	11		
Van Cutsem[56]	2007	III	Cetux	FOLFIRI		608	0.5	46.4	46.9	37.4				PFS: 8.9m (HR: 0.85; p=0.0479)
				FOLFIRI		609	0.3	38.4	38.7	46.7				PFS: 8m
Venook 80203[57]	2006	III		FOLFIRI		61			36					Study stopped early
			Cetux	FOLFIRI		59			44					Replaced by SWOG 80405
				FOLFOX		60			40					Adding cetux increases OPR
			Cetux	FOLFOX		58			60					from 38 to 52% (p=0.029)
Tai[89]	2006	II	Cetux	FOLFOX4 or FOLFIRI		28	28.6	32	63	14.3	77.8	21.4		
Cartwright[101]	2007	II	Cetux	Irinotecan	Cape	55	4	36	40	40	80	20		Duration of response: 8.8m
Bennouna[102]	2007	II	Cetux	Irinotecan	UFT/LV	31	6	35	41	16	57			
Heinemann[103]	2007	II	Cetux	Irinotecan	Cape	33			42		91			
			Cetux	Oxali	Cape	29			66		93			
Sufferlein[104]	2005	I–II	Cetux	FUFOX		41			54–71					
Diaz Rubio[105]	2005	II	Cetux	FOLFOX		42	9	63	72	23	95			PFS:10.2m
Tabernero[106]	2004	II	Cetux	FOLFOX4		20	5	76	81	17	98	2		
Dakhil[107]	2006	II	Cetux	FOLFOX6		66 EGFR+	6	57	63	30	93			Overall TTP: 8m
		II	Cetux	FOLFOX6		13 EGFR-	7.7	46	54	23	77			
Colucci[108]	2006	II	Cetux	FOLFOX4		22		73	73	23	95	5		
Helbing[109]	2006	II	Cetux	XELOX		37		53	53		82			
	2006	II	Cetux			37		33	33		82			
Ocean[110]	2007	II	Cetux	FOLFOX6	Beva	58	5	50	55					PFS: 9.6m; acceptable toxicity
Berlin[58]	2007	II	Panitu	IFL		19			46		74			PFS: 5.6m; MS: 17m
			Panitu	FOLFIRI		24			42		79			PFS: 10.9m; MS: 22.5m
Zampino[59]	2005	II	Gefitinib	FOLFOX6		39		74.4		23.1		2.6		
Nakhoul[60]	2006	II	Erlotinib	Cape		6		17	17	17	34	66		Quite toxic
Spigel[111]	2006	II	Erlotinib	Beva	FOLFOX4	21	14	43	57	38	95	5		MS:12.4m; PFS:10.9m toxicity: four possible treatment deaths
Tournigand[112]	2007	II	Erlotinib	Oxali/5FU	Beva	38								Feasibility study: grade 3–4 toxicity: 70%
Vincent[113]	2007	II	Erlotinib	Cape		22	0	27	27	27	54			Grade 3 diarrhoea: 20%
				Cape		15	0	13	13	33	46			
			Erlotinib			13	0	0	0	46	46			

Please see Table 1 *for guide to abbreviations.*

patients had received one or more lines of chemotherapy demonstrating at least partial chemo-refractory disease. Compared with best supportive care, a recently published randomised phase III study by the National Cancer Institute of Canada (NCIC) demonstrated that cetuximab significantly increases median survival from 4.6 to 6.1 months.[35] The response rate to cetuximab was 6.6%. These results are reasonably consistent with earlier phase II trials of cetuximab monotherapy, in which response rates – including mimimal responses – ranged from 9 to 11.6%, with approximately one-third of patients achieving disease stabilisation. Median overall survival and progression-free survival were approximately 6.5 and 1.4 months, respectively.[36–38] Interestingly, in a small restrospective data series of patients who had received previous TKI with chemotherapy, cetuximab led to a higher rate of disease control, with 72% accomplishing stable disease or partial response accompanied by a progression-free survival of over five months.[39] From this, a strategy of sequential targeting of EFGR may be feasible, accepting the caveats implied by a small sample size. In a large safety analysis,[40] cetuximab monotherapy was generally well tolerated: the most frequent adverse events were rash (all grades, 83%; grade 3 or 4, 8.6%), malaise (all grades, 49%; grade 3 or 4, 10.4%) and fever (grade 1 or 2, 33%). Myelosuppression, diarrhoea and alopecia were rare.

Combinations of cetuximab and chemotherapy following chemotherapy resistance have also been tested. A large, randomised phase III trial (EPIC) of 1,298 patients showed increased responses (16.4 versus 4.2%) and modest prolongation of progression-free survival (3.98 versus 2.56 months; p<0.0001) when cetuximab was added to irinotecan.[41] However, overall survival was similar in both arms (10.7 versus 9.99 months). A second phase III study planned to assess the addition of cetuximab to FOLFOX4 as subsequent-line therapy[42] stopped early owing to the evolution of oxaliplatin-containing regimes in routine first-line treatment. Numerous single-arm phase II studies have been conducted evaluating cetuximab with chemotherapy (see *Table 1*). Average response rates and disease control rates were approximately 24 and 55%, respectively. In many of these studies, there was no correlation between responsiveness and number of lines of previous chemotherapy treatment. The side-effect profile of cetuximab with irinotecan chemotherapy includes rash (all

grades: 81%, grade 3 or 4: 12.7%), malaise (all grades: 73%, grade 3 or 4: 15.8%) and diarrhoea (all grades: 72%, grade 3 or 4: 22.3%) and there was no marked enhancement of toxicities beyond that which would have been expected from monotherapy with either agent.[40]

Two reported studies have addressed the use of the anti-VEGF monoclonal antibody bevacizumab in combination with cetuximab and chemotherapy.[43,44] Responses and disease control rates are 35 and 78%, respectively, and the combinations had acceptable toxicity. Though patient numbers are small, there is an indication of higher efficacy by the addition of bevacizumab; much larger randomised trials to test this concept are required.

Panitumumab is a fully humanised anti-EGFR monoclonal antibody. When used alone in advanced chemo-resistant colorectal cancer, response rates vary from 8 to 13% and disease control is attained in 29–43% of patients.[45–47] One randomised phase III trial has demonstrated a small, significant prolongation of progression-free survival (8 versus 7.3 weeks; hazard ration (HR) 0.54; p<0.0001) compared with best supportive care,[46] which has led to FDA approval for the use of panitumumab in chemo-resistant disease. The lack of any observable difference in overall survival in this study may be in part due to 76% of the control group crossing over to receive panitumumab. Further trials of the use of this antibody in combination with chemotherapy are awaited. Trials in this setting investigating TKIs are small and the available data are limited: monotherapy with gefitinib, erlotinib or lapatinib appears to have poor activity with only 1–5% of patients responding. One study using serial biopsies showed that EGFR inactivation was not achieved by gefitinib at 250 or 500mg.[42] A high-dose study of gefitinib (750mg) led to stable disease in 33% of patients, but at the expense of higher toxicity with over half of patients requiring dose reductions or discontinuation of therapy.[49] Toxicity issues continue to be problematic when TKIs are combined with chemotherapy. In combination with irinotecan, one study reported lack of efficacy and stopped dose escalation because of toxicity,[50] and another study demonstrated excessive toxicity with diarrhoea, dehydration and neutropaenic sepsis being common.[51] In contrast, however, when gefitinib was combined with a 5-fluorouracil-based oxaliplatin-containing regimen, treatment was better tolerated and about 30% achieved partial response among 69% of patients with overall disease control.[52,53] Further trials are required to assess this treatment combination.

First-line Advanced Disease

Table 2 summarises selected studies of EGFR-targeted therapies in chemo-naïve patients. Two small phase II studies of cetuximab monotherapy have been performed: objective responses were observed in 4–15% and disease control rates ranged from 39 to 54%.[54,55] The latter study importantly demonstrated tolerability and efficacy in an elderly population of patients over the age of 70, providing a feasible therapeutic option for some patients who may not withstand conventional cytotoxics.

The combination of cetuximab and chemotherapy has been tested in a large phase II trial (CRYSTAL).[56] One thousand, two hundred and seventeen patients were randomised to receive either FOLFIRI or cetuximab. Progression-free survival – the primary end-point – was marginally but significantly higher in favour of the combination group (8.9 versus 8 months, HR 0.85; p=0.0479). More patients who received cetuximab responded to treatment (46.9 versus 38.7%; p=0.0038) and went on to have liver surgery with curative intent (6 versus 2.6%; p=0.0034). Data for overall survival and quality of life analyses are awaited. The combination was well tolerated with skin rash (grade 1–3, 18.7%; grade 4, 0%) accounting for most of the additional toxicity observed. The only other published phase III data in the first-line setting are in part provided by the CALGB 80203 study,[57] in which chemotherapy (FOLFIRI or FOLFOX) was used with or without cetuximab. Preliminary results show a significant increase – from 38 to 52% – in responses, but the study was stopped early and replaced by CALGB 80405, which is still recruiting; this latter study randomises between cetuximab or bevacizumab or both in combination with chemotherapy.

> Clearly, EFGR-targeted therapies, especially monoclonal antibodies, have proved to be active agents and provide possible further valuable treatment options in the management of advanced colorectal cancer.

In proceeding phase II trials of cetuximab with chemotherapy in the first-line setting, objective response rates averaged 56% (range 31–81%) and disease control was achieved in about 84% of patients (see *Table 2*). More phase III trials are required to ascertain the optimal chemotherapy regimens for coupling to cetuximab and, importantly, to further define the degree of clinical benefit. At this time, one small phase II trial has been published testing panitumumab with irinotecan-containing chemotherapy.[58] Disease control was achieved in approximately 76% of patients with median survival of approximately 20 months. Limited data are available regarding the efficacy of TKIs with chemotherapy in this setting. One study showed encouraging response rates for gefitinib in combination with FOLFOX6 chemotherapy,[59] but another has shown excessive toxicity with capecitabine.[60]

Predictive Markers

Earlier studies relied upon positive immunohistochemical (IHC) staining for EGFR as an inclusion criterion logically based upon it being the putative target. However, this practice has ceased since the discovery that tumour EGFR positivity does not correlate with response to EGFR-targeted therapy.[61–63] It is thought that EGFR detection by IHC and its interpretation may not be wholly representative in that even low levels of expression, which are regarded as negative staining, may still be important biologically. Furthermore, other targets and mechanisms of action, such as abrogation of VEGF, might be responsible for efficacy. Following on from the examples set by HER-2 overexpression and trastuzumab sensitivity in breast cancer[64] and EGFR mutations and TKI sensitivity in lung cancer,[65] the identification of useful predictive markers for colorectal cancer is a keen pursuit. However, EGFR mutations seem to be rare in colorectal cancer; other candidate markers under investigation include EGFR copy number (by FISH), expression of p21, p53, VEGF, cyclooxygenase (COX)-2, pAkt1, cyclin-D1 and gene polymorphisms.[66–70] With regard to these, studies have yielded mixed results. Furthermore, co-expression of HER-2, HER-3 and HER-4 with EGFR and their respective ligands might also play a part in drug-sensitivity. A molecular marker remains to be established as a significant predictive tool. Recent evidence has emerged for mutations in K-ras to predict for non-response to cetuximab. Among 37 colorectal tumour specimens from patients treated with cetuximab, mutant K-ras was found in 46% and

precluded tumour response.[71] A similar study of 59 patients showed that mutant K-ras was associated with disease progression and significantly decreased time to progression.[72]

A physical predictive marker observed in the clinic is acneiform skin rash, which appears over the head, neck and trunk. Intriguingly, its presence appears to strongly correlate with response and survival.[28,73] This is not altogether surprising given the high expression of EGFR in skin. The occurrence of skin rash as a potential surrogate marker for response led to the design of a phase I/II study of cetuximab dose escalation (EVEREST study).[74] Patients being treated with cetuximab and irinotecan with grade 1 or lower skin toxicity were randomised to either continuation at the same dose of cetuximab (250mg/m^2/week) or to cetuximab dose escalation (500mg/m^2/week). The latter group exhibited heightened responses (30 versus 13%).

Future Perspectives

Clearly, EGFR-targeted therapies, especially monoclonal antibodies, have proved to be active agents and provide possible further valuable treatment options in the management of advanced colorectal cancer. Nonetheless, there are several ongoing challenges for the enhancement of their use. For cetuximab, the optimal dose in a given individual is uncertain and may depend on rash development as a surrogate marker. More convenient fortnightly dosing might retain the efficacy of the present weekly schedule as suggested by a recent pharmacokinetic study.[75] The optimal incorporation of these drugs in combination with conventional cytotoxics is yet to be fully defined. Furthermore, studies are required to explore how EGFR-specific therapies can be used synchronously or sequentially or in conjunction with other targeted drugs. For example, in a multitargeted approach, a kinase inhibitor might be combined with monoclonal antibodies against both EGFR and VEGF in an attempt to further increase efficacy. Owing to a lack of detailed knowledge of how different signalling systems interact, stringent phase III trials incorporating molecular analyses are necessary to test these ideas. For example, panitumumab was recently withdrawn from the PACCE trial, which randomises between chemotherapy and bevacizumab with or without panitumumab. An interim analysis revealed a significant difference in progression-free survival favouring the control arm.[76] Evidently, the coupling of some targeted drugs may be counterproductive. Finally, in accordance with the philosophy of making therapy more 'targeted' and not least in helping to circumvent the problem of the prohibitive financial cost of these drugs, effective criteria for patient selection are desperately needed. Additional trials are needed incorporating genomic and tumour profiling and pharmacogenomics to search for useful predictive biomarkers. Further understanding of the molecular biology of EGFR and other tumour signalling systems and mechanisms of action of targeted agents may provide answers to such questions in time. ■

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