Acta Oncologica, 2010; 49: 278–286

informa
healthcare

REVIEW ARTICLE

Cetuximab and chemoradiation for rectal cancer–is the water getting muddy?

ROB GLYNNE-JONES, SUZY MAWDSLEY & MARK HARRISON

Mount Vernon Cancer Centre, Northwood, Middlesex, UK

Abstract

The epidermal growth factor receptor (EGFR) inhibitor cetuximab has been successfully combined with radical radiotherapy in head and neck cancer. In colorectal cancer, increased response rates are achieved by cetuximab and panitumumab within standard chemotherapy schedules, but not in chemoradiation regimens. This review examines the clinical evidence and potential mechanisms for an interaction when EGFR inhibitors are added to fluoropyrimidine-based chemoradiation in rectal adenocarcinoma. *Methods.* This review was compiled by searching PubMed and Medline for English language articles published until 2009 with established search strategies, supplemented by hand searching of abstracts from the proceedings of relevant international meetings. The primary outcome measure was pathological complete response (pCR). *Results*. Only 13 publications and three presentations in abstract of 13 phase I/II trials of preoperative chemoradiation with cetuximab in rectal cancer were identified. A total of 316 patients were identified who received cetuximab in combination with radiotherapy and 5-fluorouracil or capecitabine preoperatively. One hundred and thirty eight of these patients received either additional irinotecan or oxaliplatin. One study with panitumumab with safety but no efficacy results was identified, and two studies with gefinitib. The pCR rate ranged from 0–20%. The overall pooled pCR for cetuximab based chemoradiation was 9.1% (29/316). The rate of G3/G4 gastrointestinal toxicity, in terms of diarrhoea, varied from 5–30%, with an overall pooled rate of 47/313 (15%). *Discussion.* Potential reasons for the disappointing results of EGFR inhibition with fluoropyrimidine-based preoperative chemoradiation include a less critical role of repopulation in rectal adenocarcinoma using a non-curative radiation dose; or antagonistic effects on 5FU-based chemoradiation and oxaliplatin, if some cells arrest in G1 or G2-M and fail to pass through S phase. *Conclusion.* Cetuximab combined with fluoropyrimidine-based chemoradiation is not currently recommended. A better understanding of the mechanisms involved in combinations of chemotherapy and radiotherapy might allow more effective future scheduling of biological and chemical agents in combination with radiation.

Randomised phase III trials of neoadjuvant preoperative chemoradiation (CRT) in resectable rectal cancer [1–3] show the addition of 5FU to preoperative radiation increases the pCR rate over radiotherapy alone [4], and improves loco-regional control [2,3], but has not extended disease-free survival (DFS) or overall survival (OS). Phase II studies of chemoradiation consistently use pCR as the primary endpoint of novel combinations of oxaliplatin and irinotecan to demonstrate efficacy. The overall pathological complete response (pCR) rate of 3 157 patients included in a review of 77 phase II and phase III was 13.5%, and the use of two cytotoxic drugs in combination with radiation increased the pCR rate [5]. Recent efforts to improve outcome of chemoradiotherapy further have focussed on adding biological strategies to avoid overlapping toxicities.

EGFR regulates cellular growth, survival, proliferation and differentiation. Inhibitors of the receptor include the monoclonal antibodies cetuximab and panitumumab. Clinical studies in colorectal cancer have confirmed the efficacy of these agents in irinotecan refractory patients in terms of response rate and progression free survival [6], and have shown a significant benefit in response rates and progression free survival for the addition of cetuximab to FOLFIRI [7,8]. However, these results have not been replicated in the COIN study, where cetuximab

Correspondence: Rob Glynne-Jones, Mount Vernon Centre for Cancer Treatment, Northwood, Middlesex HA6 2RN, UK. E-mail: Rob.glynnejones@nhs.net

(Received 30 October 2009; accepted 2 December 2009)

ISSN 0284-186X print/ISSN 1651-226X online
DOI: 10.3109/02841860903536010

was added to oxaliplatin and 5FU or capecitabine in the first-line setting [9], apart from a small improvement in response rate from 55 to 59% in patients with wild type K-ras.

A landmark randomised phase III study in patients with locally advanced head and neck cancer showed that cetuximab in combination with radical radiotherapy significantly improved overall survival [10] compared to radiation alone. Many mechanisms for this advantage have been proposed [11], including inhibition of repopulation during the latter phase of radiotherapy. Accelerated treatments improve outcome only in head and neck cancers, which have high EGFR expression [12].

This review aims to examine the current evidence from phase I/II and phase III randomised trials of preoperative cetuximab and fluoropyrimidine-based CRT in rectal adenocarcinoma, to test whether additive effects and increased efficacy in terms of the early alternative endpoint of pathological complete response are achieved. Also, we aimed to assess if irinotecan or oxaliplatin was a more effective partner with cetuximab and radiotherapy.

Methods

The information used to produce this review was compiled by searching PubMed and Medline for English language articles published until October 2009 with established search strategies, supplemented by hand searching of abstracts from the proceedings of the American Society of Clinical Oncology and other international meetings. The primary outcome measure was pathological complete response. Secondary outcome measures included acute toxicity, local recurrence (LR), disease free survival (DFS) and overall survival (OS), a negative circumferential margin, R0 resections and node positivity following chemoradiation. The search strategy employed the key words – EGFR inhibition, cetuximab, complete pathological response, preoperative, synchronous, concurrent, irradiation, radiotherapy, chemoradiation, radiochemotherapy, combined modality, adenocarcinoma, and rectal cancer.

Results

A total of only 13 reports of 10 phase I/II trials of preoperative chemoradiation with cetuximab in rectal adenocarcinoma were identified–four (see Tables I and II) reported the phase I [13] and phase I/II components of the same patient group [14–16]. In addition we found two studies integrating gefitinib [17,18] and one integrating panitumumab [19] (see

Table I. Published papers and abstracts documenting pCR in preoperative chemoradiation studies using cetuximab.

	No of pts*	Cetuximab	Capecitabin	5FU	Oxaliplat	Irinotecan	RT dose	PCR**	R0***	Good TRG***
Chung 2006 [51]	20	Yes		Yes	No	No	50.4 Gy /28#/38	2/17 **(12%)**	17/17 **(100%)**	NS
Machiels 2007 [52]	40	Yes	Yes		No	No	45 Gy/25#/33	2/40 (5%)	>2 mm 27/40 **(73%)**	Few cells only 10/40 **(25%)**
Rodel 2008 [20]	48	Yes	Yes		*Yes*	No	50.4 Gy /28#/38	4/48 **(8%)**	42/45 **(93%)**	Good (>50%) 10/45 **(21%)**
Hofheinz 2006 [13]	20	Yes	Yes		No	Yes	50.4 Gy /28#/38	5/20 (25%)	18/20 **(90%)**	6/20 **(30%)**
Horisberger 2009 [16]	50	Yes	Yes		No	**Yes**	50.4 Gy /28#/38	4/50 **(8%)**	50/50 **(100%)**	30/50 **(60%)**
Bertolini 2008 [53]	40	Yes		Yes	No	No	50 Gy/25#/ 33–50.4 Gy/28#/38	3/40 **(7.5%)**	36/38 **(95%)**	Dworak 8/38 **(21%)**
Hong 2007 [22]	10	Yes	Yes	**No**	No first 10 pts only	Yes	50.4 Gy /28#/38	2/10 **(20%)**	10/10 **(100%)**	2/10 **(20%)**
Cabebe 2008 [21]	23	Yes	Yes			No	50.4 Gy /28#/38	4/23 **(17%)**	NS	NS
Eisterer 2009 [54]	**28**	**Yes**	**Yes**		No	**No**	45 Gy/25#/33	**0/28 (0%)**	NS	NS
Velenik 2009 [55]	**37**	Yes	Yes	**No**	**No**	No	45 Gy/25#/33	3/37 **(8.1%)**	NS	**TRG3 7/37 (18.9%)**
Total	**316**	**Yes-all**					**45–50.4 Gy**	**29/316 (9.1%)**		

*number entering study; **number having had surgery; ***using tumour regression grading not yp (various systems used). NS, not specified; RT, radiotherapy; PCR, pathological complete response; R0 resection, curative resection; TRG, tumour regression grade; (NB The terms Tmic and TRGs remain unvalidated surrogate endpoints, and the lack of consistency in their reporting, hinders their interpretation; as a measure of response within rectal cancer trials).

Table III). There were no published phase III trials or meta-analyses. We therefore retained only 10 studies with cetuximab (see Table I). In eight of the 10 studies oral capecitabine was partnered with radiation (256 patients) and in two studies a prolonged venous infusion of 5FU (60 patients). In three studies cetuximab was partnered with capecitabine as a single agent with radiation. In total 58 patients received additional oxaliplatin [20,21], and 80 patients in three studies received additional Irinotecan [13,16,22]. The pCR rate in the 10 retained studies with a total of 316 patients ranged from 0 to 20%. Twenty nine of three hundred and sixteen achieved a pCR giving an overall pCR rate of 9.1%. In the irinotecan containing studies, the pCR was 11/80 (13.8%). In the main oxaliplatin containing study the pCR rate was 4/48 (8%). In the 10 trials integrating cetuximab, an R0 resection varied from 90–100% with an overall pooled rate of 173/185 (93.5%). Good regression following chemoradiation ranged from 21 to 60%. Only two papers gave information on nodal downstaging, which occurred in 8/19 patients (42%) [13], and 24/37 (65%) [16]. There was no long-term data provided in terms of LR, DFS or OS from any of the reported studies.

The rate of G3/G4 acute gastrointestinal toxicity, in terms of diarrhoea, varied from 5–30% in the cetuximab studies, with an overall pooled rate of 47/313 (15%).

Discussion

The addition of cetuximab to fluoropyrimidine-based CRT schedules suggest an overall pooled pCR of 9.1%, compared with an overall pCR rate of 13.5% seen with fluoropyrimidine-based chemoradiation schedules in a recent review [9], and 13.1% overall from the results of randomised trials using fluoropyrimidine-based chemo-radiation (Table VI). In these randomised phase III studies, the pCR rate with radiotherapy alone has consistently been in the region of 4–5% [2,4,23]. The rate with CRT ranges between 8% and 17% (see Table IV). A pooled pCR of 8.5% for preoperative chemo-radiotherapy with the addition of cetuximab appears to be a rate which falls between that achieved with radiotherapy alone and that with fluoropyrimidine-based chemoradiation.

The heterogeneity of the data presented in this present review makes it difficult to draw firm conclusions. The eligibility criteria for inclusion in phase I/II studies are wide and permissive in terms of initial stage. The studies are few with small numbers of patients, and there are no large phase III studies. There are also limitations of the use of pCR as an endpoint, since the confidence intervals for achieving a pCR in such small studies must be very wide. The potential for achieving a pCR depends on the case-mix and clinical stage of patients on entry to any study [24,25]. Also as pathologists become more

Table II. Published papers and abstracts documenting toxicity and surgical morbidity in preoperative chemoradiation studies using cetuximab.

	No of pts*	Cetuximab	Oxali	Irinotecan	RT dose	G3/G4 diarrhoea	SEPSIS	Anastom Leak	Reoperation
Chung 2006 [51]	20	Yes	No	No	50.4 Gy/28#/38	**2/20 (10%)**	NS	NS	NS
Machiels 2007 [52]	40	Yes	No	No	45 Gy/25#/33	6/40 **(15%)**	5/40 **(12.5%)**	NS	5/40 (12.5%)
Rodel 2008 [20]	48	Yes	Yes	No	50.4 Gy/28#/38	9/48 **(19%)**	2/48 **(4%)**	5/48 **(11%)**	5/48 **(11%)**
Hofheinz 2006[13]	20	Yes	No	Yes	50.4 Gy/28#/38	2/10 **(20%)**	2/20 **(10%)**	3/20 **(15%)**	NS
Horisberger 2009 [16]	50	Yes	No	Yes	50.4 Gy/28#/38	15/50 **(30%)**	NS	8/50 **(16%)**	NS
Bertolini 2008 [53]	40	Yes	No	No	50 Gy/25#/33–50.4 Gy/28#/38	3/40 **(7.5%)**	1/40 **(5%)**	1/40 **(5%)**	1/40 **(5%)**
Hong 2007 [22]	10	Yes	No	*Yes*	50.4 Gy /28#/38	1/40 **(5%)**	NS	NS	NS
Cabebe 2008 [21]	23	Yes	first 10 pts	No	50.4 Gy /28#/38	4/23 **(17%)**	NS	NS	NS
Eisterer 2009 [54]	28	Yes	No	No	45 Gy/25#/33	4/28 **(15%)**	NS	NS	NS
Velenik 2009 [55]	37	Yes	No	No	45 Gy/25#/33	4/37 **(11%)**	NS	NS	NS
Total	**316**				45–50.4 Gy	47/313 **(15%)**			

*number entering study; **number having had surgery; ***using tumour regression grading not yp. NS, not specified in paper; RT, radiotherapy; G3/G4, grade 3 and grade 4 toxicity.

Table III. Studies with panitumumab and gefitinib chemoradiation.

	No of pts*	Fluoropyrimidine	Biol Agent	RT dose	G3/G4 diarrhoea	PCR**	Good TRG***
Czito 2006 [17]	6	Capecitabine 650 mg/m^2 bid	Gefitinib	50.4 Gy/28#/38	**16%**	**0/6**	No data
Valentini 2008 [18]	33	5FU 225 mg/m^2 PVI +	Gefitinib	50.4 Gy/28#/38 +10 Gy IORT	**12.8%**	10/33	7/33 (21%)
Star-02 Fabio 2009 [19]	51	5FU 225 mg/m^2 PVI + **Oxaliplatin**	Panitumumab	50.4 Gy /28#/38	**32%**	No data	No data
Total	**90**				**22/90**	**10/39**	**7/33**

RT, radiotherapy; PCR, pathological complete response; R0 resection, curative resection; TRG, tumour regression grade.

thorough, and work rigorously to an agreed technique, the pCR is likely to more difficult to achieve compared to historical controls [26]. Hence, more recent studies tend to have lower rates of pCR. Comparisons between phase II trials are statistically invalid, but pCR rates observed with the same chemoradiotherapy regimens without cetuximab, [27,28] are higher (see Tables III, IV and V for details). The only phase III trial using capecitabine and oxaliplatin reported a pCR rate of 18.8% for a combination of capecitabine, oxaliplatin and 50.4 Gy [29].

An R0 resection in the cetuximab trials varied from 90–100% with an overall pooled rate of 173/185 (93.5%). These data compare with a range of 81–98%, and with a pooled rate of 220/238 (92.8%) from recently published phase II preoperative chemoradiation trials of capecitabine and oxaliplatin in rectal cancer. There is a range of 96–100% with a pooled rate of 58/59 (98%) from trials of capecitabine and irinotecan chemoradiation. One group used a histological margin of 2 mm with and without cetuximab 27/40 (73%) and 30/40 (75%) respectively. It is not statistically valid to compare phase II studies, but the results appear similar with the addition of cetuximab. Data on tumour regression grading is also pooled and ranges for good regression from 21 to 60%.

The side-effects of cetuximab include an acneiform rash and diarrhoea, which could still prove a problem of overlapping toxicity with pelvic radiation. A trial integrating cetuximab with cisplatin, 5FU and radiation in head and neck cancer was terminated early because of unexpected adverse effects [30]. In rectal cancer the crude rate of G3/G4 gastrointestinal toxicity, in terms of diarrhoea, does not appear increased by the addition of cetuximab to chemoradiation, although this effect has been observed in randomized clinical trials of chemotherapy in patients with metastatic colorectal cancer [31,32]. The overall rate of G3/G4 gastrointestinal toxicity, in terms of diarrhoea, in the cetuximab studies was 47/313 (15%) and compares with a range of 8–30% with a pooled rate of 48/297 (16%), from chemoradiation trials of capecitabine and oxaliplatin, and a range of 11–42% with a pooled rate of 16/71 (22.5%) from chemoradiation trials of capecitabine and irinotecan.

A large multinational randomised phase II study EXPERT-C (NCT00383695) has compared neoadjuvant therapy comprising oxaliplatin, capecitabine, and chemoradiotherapy with or without cetuximab in 164 patients [40]. The study has completed in July 2008, and results may throw more light on combinations of cetuximab and chemoradiation in the clinical

Table IV. Studies documenting pCR in preoperative chemoradiation studies using capecitabine and oxaliplatin.

	No of pts*	Capecitabine	Oxaliplatin	RT dose	PCR**	R0 resection	Good TRG***
Gerard 2009 [56] (phase III)	291	800 mg/m^2 bid	YES	50.4 Gy/28#/38	54/291 (18.8%)	282/291 (94%)	NS
Aristu 2008 [57]	20	825 mg/m^2 bid	YES	various	4/20 **(20%)**	17/20 **(85%)**	11/20 **(55%)**
Fakih 2008 [58]	25	725 mg/m^2 bid	YES	50.4 Gy/28#/38	6/25 **(24%)**	NS	6/25 **(24%)**
Hospers 2007 [59]	22	1000 mg/m^2 bid	YES	50.4 Gy/28#/38	2/21 **(10%)**	18/22 **(81%)**	1/22 **(5%)**
Koeberle 2008 [60]	60	825 mg/m^2 bid	YES	45 Gy/25#/33	6/60 **(10%)**	*59/60* **(98%)**	8/60 **(13%)**
Machiels 2005 [61]	40	825 mg/m^2 bid	YES	45 Gy/25#/33	5/40 **(12.5%)**	>2 mm 30/40 **(75%)**	*6/38* **(15.8%)**
Rodel 2003 [62]	32	825 mg/m^2 bid	YES	50.4 Gy/28#/38	6/31 **(19%)**	*29/32* **(91%)**	*12/31* **(39%)**
Rodel 2007 [63]	110	825 mg/m^2 bid	YES	50.4 Gy/28#/38	17/104 **(23%)**	*98/104* **(95%)**	NS
Total	**600**			**45–50.4 Gy**	100/592 **(16.9%)**	*380/395* **(96%)**	44/196 **(22.4%)**

NS, not specified in paper; RT, radiotherapy; PCR, pathological complete response; R0 resection, curative resection.

Table V. Published papers documenting pCR in preoperative chemoradiation studies using capecitabine and irinotecan.

	No of pts*	Capecitabine	Irinotecan	RT dose	PCR**	R0 resection	Good TRG***
Hoffheinz 2005 [64]	19	500 mg/m^2 bid	YES	50.4 Gy/28#/38	4/19 **(21%)**	NS	5/19 **(26%)**
Klautke 2006 [65]	28	750 mg/m^2 bid	YES	55. Gy/31#/42	4/28 **(14%)**	24/25 **(96%)**	3/28 **(11%)**
Willeke 2007 [66]	36	500 mg/m^2 bid	YES	50.4 Gy/28#/38	5/34 **(14%)**	34/34 **(100%)**	9/34 **(26%)**
Total	83				**13/83 (15.6%)**	58/59 **(98%)**	17/83 **(20.4%)**

RT, radiotherapy; PCR, pathological complete response; R0 resection, curative resection; TRG, tumour regression grade.

setting in locally advanced rectal cancer. There are three other ongoing or recently closed phase II trials registered in the http://clinicaltrials.gov website: NCT00297128 a study of preoperative chemoradiation with capecitabine and cetuximab by the Austrian Breast & Colorectal Cancer Study Group; NCT00795301 A study of radiotherapy in rectal cancer using oxaliplatin, capecitabine with or without cetuximab from Singapore; NCT00689702 cetuximab, capecitabine and radiotherapy in neoadjuvant treatment of patients with rectal cancer (XERT), and a British study EXCITE which combines radiation with capecitabine, irinotecan and cetuximab, and finally a Phase II study from Vanderbilt-Ingram Cancer Centre of Cetuximab, 5FU and Radiation as neoadjuvant therapy for patients with locally advanced rectal cancer.

In the first-line metastatic setting there appears an advantage when cetuximab is added to regimens containing irinotecan [7], but not always oxaliplatin [9]. The least promising results in the chemoradiation studies have been seen with the combination of capecitabine, oxaliplatin, radiation and cetuximab. Interestingly, there was a trend for inferior results in the COIN study for the combination of oxaliplatin, cetuximab and capecitabine, [9], compared to 5FU.

There may be differences between integrating cetuximab with radiotherapy alone in comparison with 5FU- based chemoradiation, although the combination of cetuximab and capecitabine is clearly active in wild type K-ras patients and doubles the response rates from 24 to 48% over capecitabine alone [32].

There could also be a difference for a rectal adenocarcinoma, where 45–50 Gy is not considered as a radical curative dose, but sufficient for microscopic disease. Repopulation may be less crucial in a preoperative setting, when surgery is scheduled, than in squamous carcinomas of the head and neck. Repopulation does not appear to be a major issue in adenocarcinoma of the rectum, since neither overall treatment length nor a treatment interruption appear to impact on local control [33]. Repopulation may also be less crucial in the presence of a continuous exposure to 5FU, or capecitabine chemoradiation.

In advanced colorectal cancer treated with cetuximab there is a low chance to benefit from therapy, when K-ras mutations at codons 12 and 13 have been observed [17,34,35]. However the recent results of the large UK COIN study have not confirmed a benefit in terms of PFS or OS from the addition of cetuximab to oxaliplatin based chemotherapy in patients who have wild type K-ras over 5FU and oxaliplatin alone [9].

In addition, the proportion of patients with rectal cancer (as opposed to colon cancer) with mutant K-ras varies between 30% [36] and 40% [37]. In a recent preoperative chemoradiation study using cetuximab, K-ras mutant type was found in 9/39 (23%) patients. Only one of these nine K-ras mutant patients (11%) demonstrated a good pathological regression (TRG3 and 4) compared to 11/30 (37%), ($p=0.12$) in patients with wild-type K-ras [38]. In contrast,

Table VI. Published papers of randomised single agent fluoropyrimidine-based chemoradiation documenting pCR.

Trial	Patient numbers	Chemo	RT Dose	pCR	OS
NSABP RO3 [67]	267	FUFA	50.4 Gy/28#/38 days	15%	5 year 74%
CA0/ARO/AIO-94 [1]	394	120 hour 5FU infusion	50.4 Gy/28#/38 days	8%	4 year 74%
Polishstudy [68,69]	157	FUFA	50 Gy/25#/33 days	16%	4 year 66%
FFCD 9203 [2]	375	FUFA	45 Gy/25#/33 days	11.4%	5 year 66%
EORTC 22921 [3,4]	505	FUFA	45 Gy/25#/33 days	13.4%	5 year 65%
ACCORD 12/0405 Prodige 2 [29]	295	capecitabine	45 Gy/25#/33 days	13.8%	NS
STAR-01 [70]	379	PVI 225 mg/m^2/day	50.4 Gy/28#/38 days	15.8%	NS
All	2372			312/2372 13.1%	

[ ], reference number; FUFA, 5FU and folinic acid; RT, radiotherapy; PCR, pathological complete response; OS, overall survival.

K-ras status did not significantly influence response in a Belgian study using cetuximab prior to and concurrent with capecitabine [39].

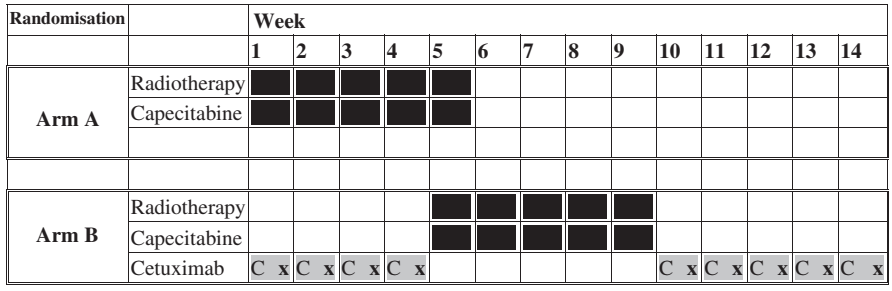
Cell cycle effects seem crucial to achieve these additive effects, because cells which fail to progress through S phase in the presence of 5FU do not accumulate additive effects with radiation [40,41]. 5FU is S-phase specific and acts by inhibiting thymidylate synthase and the synthesis of thymidine nucleotides required for DNA replication, thus preventing cell division. Additive effects can normally be observed by the addition of 5FU to radiation at concentrations, which on their own are non-cytotoxic and when tumour cells have become resistant to 5FU. The hypothesis generated to explain these findings is that these additive effects with 5FU and RT occur in cells, which are provoked into an inappropriate progression through S-phase in the presence of 5FU, arising from a disordered S-phase checkpoint [42]. This is supported by evidence demonstrating that if S-phase entry is blocked resulting in G1 arrest or the progression to S-phase is inhibited; no additive effects are observed from the combination of 5FU and radiation. If S-phase entry is blocked, producing G1 arrest or progression to S-phase is inhibited, additive effects are not observed from the combination of 5FU and radiation [42]. Similarly acquired resistance to 5FU appears to work via cell cycle delay in the G1 and G1/S boundary [43]. High EGFR expression appears to be linked to high Ki-67 and PCNA [44] and studies suggest that both Ki-67 and PCNA predict for an improved response to chemoradiation in rectal cancer.

Thus slowing down the cell cycle time may increase the amount of time available for DNA repair prior to mitosis, and thus could increase the potential for resistance to both 5FU and radiation. The use of cetuximab prior to or concurrently with radiation might therefore abolish fluoropyrimidine-based radiosensitisation, if only a small proportion of cells arrest in G0/G1 or G2/M. High EGFR expression appears linked to high Ki-67 and PCNA, demonstrating increased rates of cell turnover [45]. This study showed that significant decreases in proliferation with the addition of 5FU, which were not seen with radiation alone. This finding also suggests that 5FU does not recruit quiescent cells into proliferation. Other authors also suggest that elevated tumour proliferation is associated with improved outcomes with chemoradiation in rectal cancer [46–48].

Cetuximab can lead to G1 or G2/M cell cycle arrest, and if only a small proportion of cells within the tumour are affected, this decrease in proliferation could impact on the chance of achieving a pCR. This hypothesis is supported by the evidence from one of the cited studies, which suggests that cetuximab up-regulated several genes involved in proliferation (PIK31, CGREF1 and PLAGL1) with a reduction in Ki-67 [39]. This process might also affect oxaliplatin, which is mainly active in S phase, but would be less likely to be impacted by irinotecan.

Pre-clinical data suggests that the sequencing of chemotherapy, EGFR inhibition and radiation may be clinically significant**,** and that the sequence of oxaliplatin followed by cetuximab may be more effective than cetuximab prior to oxaliplatin [49]. Better efficacy might be achieved by integrating cetuximab in the latter portion of the radiotherapy, or following chemoradiation. This strategy has already been proposed when integrating anti-metabolites such as gemcitabine with EGFR inhibitors and radiation [50]. In the light of all these results above, in the UK we have amended the protocol of an ongoing funded phase I/II study (XERXES), to compare a schedule of capecitabine based chemoradiation with a cetuximab sandwich approach (see Figure 1). Finally, better selection for the potential efficacy of EGFR inhibition by molecular markers could be appropriate in the future [38].

Early endpoints in terms of efficacy at the level of the primary tumor (eg, pCR), may not 'per se' be coupled to longer-term endpoints such as DFS and OS. Phase III randomised studies are the best way



CX = weekly Cetuximab

Figure 1. Diagram of trial schedule

to define the advantages of a novel treatment. Sadly, the pharmaceutical industry is unlikely to commit resources to a large costly undertaking without the promise of increased efficacy (such as an increase in pCR rate) demonstrated in phase II trials, which we have yet to deliver.

Conclusions

Integration of targeted drugs such as cetuximab into preoperative chemoradiation schedules in rectal adenocarcinoma is attractive in principle. However, the results of chemoradiation clinical trials with cetuximab, as discussed above, on the early clinical endpoint of pCR are at best disappointing. Cetuximab if delivered concurrently with radiation could potentially abolish additive effects of 5FU, by inhibiting proliferation. However, the combination may yet reproduce the results achieved when cetuximab has been combined with radiation alone in studies of head and neck cancer.

More rationally designed preclinical and translational studies (with recognised negative predictive factors such as k-ras mutations, b-raf mutatations, and EGFR gene copy numbers) might therefore help select out inappropriate patients, and determine the optimal sequence of such chemotherapy and biological triple combinations. Only then can we move on to perform large randomised phase III trials.

Declaration of interest: Dr Glynne-Jones has sat on advisory boards for Pfizer, Merck, Sanofi-Aventis, Roche, Astra-Zeneca and has had research funding in the last three years from Merck-Serono. The other authors report no conflicts of interest.

References

[1] Sauer R, Becker H, Hohenberger W, Rodel C, Wittekind C, Fietkau R, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004;351: 1731–40.

[2] Gerard JP, Conroy T, Bonnetain F, Bouché O, Chapet O, Closon-Dejardin MT, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-T4 rectal cancers: Results of FFCD 9203. J Clin Oncol 2006;24: 4620–5.

[3] Bosset JF, Collette L, Calais G, Mineur L, Maingon P, Radosevic-Jelic L, et al. Chemotherapy with pre-operative radiotherapy in rectal cancer. N Engl J Med 2006;355: 1114–23.

[4] Bosset JF, Calais G, Mineur L, Maingon P, Radosevic-Jelic L, Daban A, et al. Enhanced tumoricidal effect of chemotherapy with preoperative radiotherapy for rectal cancer: Preliminary results of EORTC 22921. J Clin Oncol 2005;23: 5620–7.

[5] Hartley A, Ho KF, McConkey C, Geh JI. Pathological complete response following preoperative chemoradiotherapy in rectal cancer: Analysis of phase II/III trials. Br J Radiol 2005;78:934–8.

[6] Cunningham D, Humblet Y, Siena S, Khayat D, Bleiberg H, Santoro A, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan refractory metastatic colorectal cancer. N Engl J Med 2004;351:337–45.

[7] Van Cutsem E, Köhne CH, Hitre E, Zaluski J, Chang Chien CR, Makhson A, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med 2009;360:1408–17.

[8] Sobrero AF, Maurel J, Fehrenbacher L, Scheithauer W, Abubakr YA, Lutz MP, et al. EPIC: Phase III trial of cetuximab plus irinotecan after fluoropyrimidine and oxaliplatin failure in patients with metastatic colorectal cancer. J Clin Oncol 2008;26:2311–9.

[9] Maughan T, Adams RA, Smith CG, Seymour MT, Wilson R, Meade AM, et al. Addition of cetuximab to oxaliplatin based combination chemotherapy in patients with Kras wild-type advanced colorectal cancer (ACRC); a randomised superiority trial (MRC COIN). Eur J Cancer 2009;(Suppl)7;4 (abstract 6LBA).

[10] Bonner JA, Harari PM, Giralt J, Azarnia N, Shin DM, Cohen RB, et al. Radiotherapy plus cetuximab for squamous cell carcinoma of the head and neck. N Engl J Med 2006;354: 567–78.

[11] Baumann M, Krause M, Dikomey E, Dittmann K, Dörr W, Kasten-Pisula U, et al. EGFR targeted anticancer drugs in radiotherapy: Preclinical evaluation of mechanisms. Radiother Oncol 2007;83:238–48.

[12] Eriksen JG, Steiniche T, Overgaard J; Danish Head and Neck Cancer study group (DAHANCA). The influence of epidermal growth factor receptor and tumor differentiation on the response to accelerated radiotherapy of squamous cell carcinomas of the head and neck in the randomized DAHANCA 6 and 7 study. Radiother Oncol 2005;74:93–100.

[13] Hoffheinz R-D, Horisberger K, Woernle C, Wenz F, Kraus-Tiefenbacher U, Kähler G. Phase I trial of cetuximab in combination with capecitabine, weekly irinotecan and radiotherapy as neoadjuvant therapy for rectal cancer. Int J Radiat Oncol Biol Phys 2006;66:1384–90.

[14] Mai SK, Hoffheinz R, Treschl A. Correlation of minimal tumor dose and histopathological regression of rectal cancer after neoadjuvant combined radio-chemo-immunotherapy–Results of a prospective Phase I/II study (Cetuximab Capiri-RT). Int J Radiat Oncol Biol Phys 2008;72:S263.

[15] Erben P, Horisberger K, Muessle B, Müller MC, Treschl A, Ernst T, et al. mRNA expression of platelet-derived growth factor receptor-beta and C-KIT: Correlation with pathologic response to cetuximab-based chemoradiotherapy in patients with rectal cancer. Int J Radiat Oncol Biol Phys 2008;72: 1544–50.

[16] Horisberger K, Treschl A, Mai S, Barreto-Miranda M, Kienle P, Ströbel P, et al. MARGIT (Mannheimer Arbeitsgruppe für Gastrointestinale Tumoren). Cetuximab in combination with capecitabine, irinotecan, and radiotherapy for patients with locally advanced rectal cancer: Results of a phase II MARGIT trial. Int J Radiat Oncol Biol Phys 2009;74: 1487–93.

[17] Czito BG, Willett CG, Bendell JC, Morse MA, Tyler DS, Fernando NH, et al. Increased toxicity with gefitinib, capecitabine, and radiation therapy in pancreatic and rectal cancer: Phase I trial results. PROC ASCO GI 2006:116a.

[18] Valentini V, De Paoli A, Gambacorta MA, Mantini G, Ratto C, Vecchio FM, et al. Infusional 5-fluorouracil and ZD1839 (Gefitinib-Iressa) in combination with preoperative radiotherapy in patients with locally advanced rectal cancer: A

phase I and II trial (1839IL/0092). Int J Radiat Oncol Biol Phys 2008;72:644–9.

[19] Di Fabio F, Pinto C, Maiello E, Pini S, Latiano T, Aschele C, et al. Safety analysis of starpan (Star-02) study with Panitumumab, 5-Fluorouracil, oxaliplatin and concurrent radiotherapy in locally advanced rectal cancer. Eur J Cancer 2009;7(Suppl): 335 (abstract 6045).

[20] Rodel C, Arnold D, Hipp M, Liersch T, Dellas K, Iesalnieks I, et al. Phase I-II trial of cetuximab, capecitabine, oxaliplatin, and radiotherapy as preoperative treatment in rectal cancer. Int J Radiat Oncol Biol Phys 2008;70:1081–6.

[21] Cabebe EC, Kuo T, Koong M, Welton M, Shelton A, Kunz PL, et al. Phase I trial of preoperative cetuximab in combination with oxaliplatin, capecitabine, and radiation therapy for locally advanced rectal cancer. J Clin Oncol 2008;26(Suppl) 645s (abstract 15019).

[22] Hong YS, Kim DY, Lee KS, Lim SB, Choi HS, Jeong SY, et al. Phase II study of preoperative chemoradiation (CRT) with cetuximab, irinotecan and capecitabine in patients with locally advanced resectable rectal cancer. J Clin Oncol 2007; 25:18S, 174s (abstract 4045).

[23] Boulis-Wassif S, Gerard A, Loygue J, Camelot D, Buyse M, Duez N, et al. Final results of a randomised trial on the treatment of rectal cancer with pre-operative radiotherapy alone or in combination with 5 fluorouracil followed by radical surgery. Cancer 1984;53:1811–8.

[24] Rödel C, Martus P, Papadoupolos T, Füzesi L, Klimpfinger M, Fietkau R, et al. Prognostic significance of tumour regression after preoperative chemoradiotherapy for rectal cancer J Clin Oncol 2005;23:8688–96.

[25] Glynne-Jones R, Anyamene N. Just how useful an endpoint is complete pathological response after neoadjuvant chemoradiation in rectal cancer? Int J Radiat Oncol Biol Phys 2006;66:319–20.

[26] Sebag-Montefiore DJ, Rutten H, Rullier E, Peters M, Brown G, Van Cutsem E et al. Three-year survival results of CORE (Capecitabine, Oxaliplatin, Radiotherapy, and Excision) study after postoperative chemotherapy in patients with locally advanced rectal adenocarcinoma. 2009 ASCO Gastrointestinal Cancers Symposium (abstract 447).

[27] Rödel C, Liersch T, Hermann RM, Arnold D, Reese T, Hipp M, et al. Multicenter phase II trial of chemoradiation with oxaliplatin for rectal cancer. J Clin Oncol 2007;25:110–7.

[28] Willeke F, Horisberger K, Kraus-Tiefenbacher U, Wenz F, Leitner A, Hochhaus A, et al. A phase II study of capecitabine and irinotecan in combination with concurrent pelvic radiotherapy (CapIri-RT) as neoadjuvant treatment cancer. Br J Cancer 2007;96:912–7.

[29] Gerard JP, Azria D, Gourgou-Bourgade S, Martel-Laffay I, Hennequin C, Etienne P, et al. Randomized multicenter phase III trial comparing two neoadjuvant chemoradiotherapy (CT-RT) regimens (RT45-Cap versus RT50-Capox) and in patients (pts) with locally advanced rectal cancer (LARC): Results of the ACCORD 12/0405 PRODIGE-2. J Clin Oncol 2009;27:18S part II of II, 797s (abstract LBA 4007).

[30] Pfister DG, Su YB, Kraus DH, Wolden SL, Lis E, Aliff TB, et al. Concurrent cetuximab, cisplatin and concomitant boost radiotherapy for locally advanced, squamous cell head and neck cancer: A pilot phase II study of a new combined modality paradigm. J Clin Oncol 2006;24:1072–8.

[31] Adams RA, Meade AM, Madi A, Fisher D, Kay E, Kenny S, et al. Toxicity associated with combination oxaliplatin plus fluropyrimidine with or without cetuximab in the MRC COIN trial experience. Br J Cancer 2009;100:251–8.

[32] Rivera F, Gravalos C, Massuti B, Puente J, Marcuello E, Valladares M, et al. Cetuximab plus capecitabine as first-line treatment for elderly patients with advanced colorectal cancer (mCRC). Final analysis of activity and survival according to KRAS status – the TTD-06-01 Spanish Cooperative Group trial. Eur J Cancer 2009;7(Suppl);215 (abstract 0-4004).

[33] Brierley JD, Keane TJ, Cummings B, Hao Y. The absence of an adverse effect of prolongation of radiation treatment of primary rectal adenocarcinoma. Clin Oncol (R Coll Radiol) 1996;8:97–101.

[34] Bokemeyer C, Bondarenko I, Makhson A, Hartmann JT, Aparicio J, de Braud F, et al. Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. J Clin Oncol 2009;27: 663–71.

[35] Kohne C-H , Grunberger T, Bechstein W, Hartmann J, Lang H, Lordick F, et al. Results from the CELIM Study: Cetuximab Plus FOLFOX6 or Cetuximab Plus FOLFIRI as neoadjuvant treatment for nonresectable colorectal cancer liver metastases. Ann Oncol 2009;20(Suppl 7):vii23 (abstract 22).

[36] Luna-Pérez P, Segura J, Alvarado I, Labastida S, Santiago-Payán H, Quintero A. Specific c-K-ras gene mutations as a tumour-response marker in locally advanced rectal cancer treated with preoperative chemoradiotherapy. Ann Surg Oncol 2000;7:727–31.

[37] Jonsson M, Ekstrand A, Edekling T, et al. Experiences from treatment-predictive KRAS testing; high mutation frequency in rectal cancers from females and concurrent mutations in the same tumour. BMC Clin Pathol 2009;9:1–5.

[38] Bengala C, Betelli S, Bertolini F, Salvi S, Chiara S, Sonaglio C, et al. Epidermal growth factor receptor gene copy number, K-ras mutation and pathological response to preoperative cetuximab, 5-FU and radiation therapy in locally advanced rectal cancer. Ann Oncol 2009;20:469–74.

[39] Debucquoy A, Haustermanns K, Daemen A, Aydin S, Libbrecht L, Gevaert O, et al. Molecular response to cetuximab and efficacy of preoperative cetuximab-based chemoradiation in rectal cancer. J Clin Oncol 2009;27:2751–7.

[40] Huang SM, Harari PM. Modulation of radiation response after epidermal growth factor receptor blockade in squamous cell carcinomas: Inhibition of damage repair, cell cycle kinetics, and tumor angiogenesis. Clin Cancer Res 2000;6: 2166–74.

[41] Lawrence TS, Blackstock AW, McGinn C. The mechanism of action of radiosensitisation of conventional chemotherapeutic agents. Semin Radiat Oncol 2003;13:13–21.

[42] Lawrence TS, Davis MA, Tang H-Y, Maybaum J. Fluorodeoxyuridine-mediated cytotoxicity and radiosensitisation require S phase progression. Int J Radiat Biol 1996;70: 273–80.

[43] Guo X, Goessi E, Collie-Duguid ESR, Cassidy J, Wang W, O'Brien V. Cell cycle perturbation and acquired 5-fluorouracil resistance. Anticancer Res 2008;28:9–14.

[44] Rego R, French AJ, Smyrk TC, Foster DJ, Sargent H, Windschitl MJ, et al. Epidermal growth factor receptor expression in colon cancer with defective DNA mismatch repair. ASCO Gastrointestinal Cancers Symposium Program/proceedings 2007:294 (abstract 422).

[45] Willett CG, Warland G, Cheek R, Coen J, Efird J, Shellito PC, et al. Proliferating cell nuclear antigen and mitotic activity in rectal cancer: Predictor of response to preoperative irradiation. J Clin Oncol 1994;12:679–82.

[46] Rödel C, Grabenbauer GG, Papadopoulos T, Bigalke M, Günther K, Schick C, et al. Apoptosis as a cellular predictor for histopathologic response to neoadjuvant radiochemotherapy in patients with rectal cancer. Int J Radiat Oncol Biol Phys 2002;52:294–303.

[47] Rau B, Sturm I, Lage H, Schneider U, Hauptmann S, Wust P, et al. Dynamic expression profile of p21WAF1/CIP1 and Ki67 predicts survival in rectal cancer treated with preoperative radiochemotherapy. J Clin Oncol 2003;21: 3391–401.

[48] Nyati MK, Morgan MA, Feng FY, Lawrence TS. Integration of EGFR inhibitors with radiochemotherapy. Nat Rev Cancer 2006;6:876–85.

[49] Morelli P, Cascone T, Troiani T, De Vita F, Orditura M, Laus G, et al. Sequence-dependent antiproliferative effects of cytotoxic drugs and epidermal growth factor receptor inhibitors. Ann Oncol 2005;(Suppl 4):iv61–iv68.

[50] Shewach DS, Lawrence TS. Antimetabolite radiosensitizers. J Clin Oncol 2007;25:4043–50.

[51] Chung KY, Minsky B, Schrag D, O'Reilly D, D'Adamo E, Hollywood M, et al. Phase I trial of preoperative cetuximab with concurrent continuous infusion 5-Fluorouracil and pelvic radiation in patients with local-regionally advanced rectal cancer. J Clin Oncol 2006;24:18S, 161s (abstract 3560).

[52] Machiels JP, Sempoux C, Scalliet P, Coche JC, Humblet Y, Van Cutsem E, et al. Phase I/II study of preoperative cetuximab, capecitabine and external beam radiotherapy in patients with rectal cancer. Ann Oncol 2007;18:738–44.

[53] Bertolini F, Chiara S, Bengala C, Antognoni P, Dealis C, Zironi S, et al. Neoadjuvant treatment with single agent cetuximab followed by 5-FU, cetuximab and pelvic radiotherapy: A phase II study in locally advanced rectal cancer. Int J Radiat Oncol Biol Phys 2009;73:466–72.

[54] Eisterer WM, De Vries A, Oefner D, Greil R, Rabl H, Tschmelitsch J, et al. Neoadjuvant chemoradiation therapy with capecitabine plus cetuximab and external beam radiotherapy in locally advanced rectal cancer (LARC) ABCSG trial R03. J Clin Oncol 2009;27;15S (part I of II), 195s (abstract 4109).

[55] Velenik V, Ocvirk J, Oblak I, Anderluh F. Neoadjuvant cetuximab, capecitabine, and radiotherapy (RT) in locally advanced resectable rectal cancer: Results of a phase II trial. J Clin Oncol 2009;27 (abstract e15029).

[56] Gerard JP, Azria D, Gourgou-Bourgade S, Martel-Laffay I, Hennequin C, Etienne P, et al. Randomized multicenter phase III trial comparing two neoadjuvant chemoradiotherapy (CT-RT) regimens (RT45-Cap versus RT50-Capox) and in patients (pts) with locally advanced rectal cancer (LARC): Results of the ACCORD 12/0405 PRODIGE-2. J Clin Oncol 27:2009;18S part II of II (Suppl), 797s (abstract LBA 4007).

[57] Aristu JJ, Arbea L, Rodriguez J, Hernández-Lizoain JL, Sola JJ, Moreno M, et al. Phase I-II trial of concurrent capecitabine and oxaliplatin with preoperative intensity-modulated radiotherapy in patients with locally advanced rectal cancer. Int J Radiat Oncol Biol Phys 2008;71:748–55.

[58] Fakih MG, Bullarddunn K, Yang GY, Pendyala L, Toth K, Andrews C, et al. Phase II study of weekly intravenous oxaliplatin combined with oral daily capecitabine and radiotherapy with biologic correlates in neoadjuvant treatment of rectal adenocarcinoma. Int J Radiat Oncol Biol Phys 2008; 72:650–7.

[59] Hospers GA, Punt CJ, Tesselaar ME, Cats A, Havenga K, Leer JW, et al. Preoperative chemoradiotherapy with capecitabine and oxaliplatin in locally advanced rectal cancer. A phase I-II multicenter study of the Dutch Colorectal Cancer Group. Ann Surg Oncol 2007;14:2773–9.

[60] Koeberle D, Burkhard R, Von Moos R, Winterhalder R, Hess V, Heitzmann F, et al. Phase II study of capecitabine and oxaliplatin given prior to and concurrently with preoperative pelvic radiotherapy in patients with locally advanced rectal cancer. Br J Cancer 2008;98:1204–9.

[61] Machiels JP, Duck L, Honhon B, Coster B, Coche JC, Scalliet P, et al. Phase II study of preoperative oxaliplatin, capecitabine and external beam radiotherapy in patients with rectal cancer: The RadiOxCape study. Ann Oncol 2005;16: 1898–905.

[62] Rodel C, Grabenbauer GG, Papadopoulos T, Hohenberger W, Schmool HJ, Sauer R, et al. Phase I/II trial of capecitabine, oxaliplatin, and radiation for rectal cancer. J Clin Oncol 2003;21:3098–104.

[63] Rodel C, Liersch T, Hermann RM, Arnold D, Reese T, Hipp M, et al. Multicenter phase II trial of chemoradiation with oxaliplatin for rectal cancer. J Clin Oncol 2007;25:110–7.

[64] Hofheinz RD, von Gerstenberg-Helldorf B, Wenz F, Gnad U, Kraus-Tiefenbacher U, et al. Phase I trial of capecitabine and weekly irinotecan in combination with radiotherapy for neoadjuvant therapy of rectal cancer. J Clin Oncol 2005;23: 1350–7.

[65] Klautke G, Kuchenmeister U, Foitzik T, Ludwig K, Prall F, Klar E, et al. Concurrent chemoradiation with capecitabine and weekly irinotecan as preoperative treatment for rectal cancer: Results from a phase I/II study. Br J Cancer 2006; 94:976–81.

[66] Willeke F, Horisberger K, Kraus-Tiefenbacher U, Wenz F, Leitner A, Hockhaus A, et al. A phase II study of capecitabine and irinotecan in combination with concurrent pelvic radiotherapy (CapIri-RT) as neoadjuvant treatment of locally advanced rectal cancer. Br J Cancer 2007:96:912–7.

[67] Roh MS, Colangelo LH, O'Connell MJ, et al. Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R03. J Clin Oncol 2009;27:5124–30.

[68] Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Kryj M. Long-term results of a randomised trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. Br J Surg 2006;93:1215–23.

[69] Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Pudełko M, et al. Sphincter preservation following preoperative radiotherapy for rectal cancer: Report of a randomized trial comparing short-term radiotherapy vs. conventionally fractionated radiochemotherapy. Radiother Oncol 2004;72:15–24.

[70] Aschele C, Pinto C, Rosati G, Luppi G, Bonetti A, Miraglia S, et al. Preoperative (FU)-based chemoradiation with and without weekly oxaliplatin in locally advanced rectal cancer; pathologic response analysis of the Studio Terapia Adjuvante Retto (STAR)-01 randomized phase III trial. J Clin Oncol 2009;27:18S (part II of II), 804s (abstract CRA 4008).