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World J Gastroenterol 2007 July 28; 13(28): 3806-3815
World Journal of Gastroenterology ISSN 1007-9327

TOPIC HIGHLIGHT

Daniel L Worthley, Dr, *Series Editor*

Metastatic colorectal cancer-past, progress and future

Kathryn Field, Lara Lipton

Kathryn Field, Lara Lipton, Department of Medical Oncology and Clinical Haematology, Western Hospital, Footscray 3011, Victoria, Australia
Correspondence to: Lara Lipton, MBBS, FRACP, Consultant Gastrointestinal Oncologist Western Hospital, Gordon Street, Footscray 3011, Victoria, Australia. lara.lipton@mh.org.au
Telephone: +61-3-83456666 Fax: +61-3-83456445
Received: 2007-05-16 Accepted: 2007-05-28

Abstract

The clinical management of metastatic (stage Ⅳ) colorectal cancer (CRC) is a common challenge faced by surgeons and physicians. The last decade has seen exciting developments in the management of CRC, with significant improvements in prognosis for patients diagnosed with stage Ⅳ disease. Treatment options have expanded from 5-fluorouracil alone to a range of pharmaceutical and interventional therapies, improving survival, and providing a cure in selected cases. Enhanced understanding of the biologic pathways most important in colorectal carcinogenesis has led to a new generation of drugs showing promise in advanced disease. It is hoped that in the near future the treatment paradigm of metastatic CRC will be analogous to that of a chronic illness, rather than a rapidly terminal condition. This overview discusses the epidemiology of advanced CRC and currently available therapeutic options including medical, surgical, ablative and novel modalities in the management of metastatic colorectal cancer.

Key words: Colorectal cancer; Metastases; Chemotherapy; Oncology; Biological therapies

Field K, Lipton L. Metastatic colorectal cancer-past, progress and future. *World J Gastroenterol* 2007; 13(28): 3806-3815

http://www.wjgnet.com/1007-9327/13/3806.asp

INTRODUCTION

In most Western societies, colorectal cancer (CRC) is the second most common cause of cancer-related death[1]. Worldwide, over 500 000 deaths per year are attributable to colorectal cancer[2]. Approximately 35% of patients have stage Ⅳ (M1, metastatic) disease at presentation and 20%-50% with stage Ⅱ or Ⅲ disease will progress to stage Ⅳ. With the introduction of new therapies and improved surgical techniques the death rate continues to decline at approximately 1.8% per year. The five-year survival rate for stage Ⅳ disease overall, remains approximately 10%[1].

The common sites of metastasis are liver, peritoneum and lung. Approximately 50% of patients with stage Ⅳ disease will develop liver metastases[3]. Rectal cancer metastasizes to the lung as commonly as the liver[4]. Cerebral metastases are uncommon; CRC is responsible for around 5% of brain metastases and generally occurs at a late stage in the disease[5,6]. Peritoneal carcinomatosis may occur from transmural spread of the primary malignancy or perforation at diagnosis and is associated with a poor prognosis[7].

DIAGNOSIS

Computerized tomography[8] may be used as part of the diagnostic workup of abdominal symptoms or as part of routine surveillance after curative treatment for stage Ⅱ and Ⅲ colorectal cancer. It has been shown that surveillance CT imaging carries a survival benefit in this setting, compared with less intensive follow-up[4]. The 2005 American Society of Clinical Oncology (ASCO) guidelines recommend annual chest and abdominal CT scans for the first 3 years after primary treatment for patients at moderate to high risk of recurrence and for whom surgical excision of metastases with curative intent would be appropriate[9].

Positron emission tomography (PET) is increasingly utilized when potentially curative resection is under consideration. Combining PET with contrast-enhanced CT, compared with CT alone, increases the likelihood of finding extrahepatic metastases (89% *vs* 64%), new liver metastases after previous liver resection (100% *vs* 50%), and recurrences at the site of resection of the primary tumour (93% *vs* 53%)[10]. PET, particularly when used with CT, aids in accurate selection of patients for resection of metastases.

Serum carcino-embryonic antigen (CEA) is a useful biomarker for surveillance after treatment of stage Ⅱ and Ⅲ colorectal cancer; however, 20% of colorectal cancers do not express CEA[11]. CEA is most sensitive in detecting hepatic metastases, but is less likely to be elevated with isolated pulmonary metastases[9]. The ASCO 2005 guidelines recommend 3 monthly CEA testing for at least 3 years after diagnosis[9].

MANAGEMENT OF ISOLATED METASTASES

Curative surgery

The 5-year cure rate after resection of liver metastases without extra-hepatic disease is up to 40%, and even more in some series[12]. Improved surgical techniques and chemotherapy response rates have led to an increased number of patients being considered for resection. It is estimated that at least 20% of persons with liver metastases may be suitable to undergo resection with curative intent[13]. The suitability for resection of liver metastases is related to location of disease as resection must leave adequate viable liver (at least 30%), while avoiding major vascular structures as well as absence of extrahepatic disease, usually determined by CT and PET.

Risk factors for reduced survival following hepatic resection include a liver resection margin < 1 cm and multiple versus single metastatic deposits[14]. As an aid to choosing the most appropriate management plan for patients presenting with liver metastases, a computer program (Oncosurge) has been constructed following a comprehensive literature review of treatment options[15]. This tool will be useful for clinicians to assess resectability of patients with liver metastases, in conjunction with discussions in a multidisciplinary setting including experienced hepatobiliary surgeons.

Isolated pulmonary metastases may be considered for surgical resection in patients fit enough for thoracotomy. While operative mortality is just over 1%, 5-year survival rates are approximately 27%[16], with up to 36.9% reported by one series for solitary metastasis (19.3% for 2 metastases and 7.7% for > 2)[17]. One small study comparing 12 patients who underwent pulmonary resection within 3 mo of hepatic resection, to 9 who did not have the lung metastases resected with a 3 year survivals of 60% *vs* 31%[18]. Although small series, these data suggest that pulmonary metastectomy should be considered even after hepatic resection. In retrospective analyses, elevated pre-operative serum CEA was an adverse predictor of survival after pulmonary metastectomy[16,17,19].

The benefit of administering chemotherapy prior to (neo-adjuvant) or after (adjuvant) metastectomy is not yet fully established. Neoadjuvant chemotherapy may downstage tumours to make surgery feasible and more successful and may also aid in control of micrometastatic disease. There have been large studies demonstrating successful resection after neoadjuvant chemotherapy for 15%-20% of liver metastases previously deemed unresectable[20,21]. Disease progression during chemotherapy is indicative of a very poor prognosis regardless of resection[22]. Although complete response of metastases on imaging may occur, without surgery recurrence is the rule. Thus, current practice is to administer 2-3 mo of neoadjuvant combination chemotherapy with repeat imaging to assess response, followed by surgery if appropriate. Upcoming Phase Ⅲ trials of pre- and post-operative FOLFOX4 chemotherapy versus surgery alone, may help to form an evidence base for decisions in this area[23].

Hepatic arterial infusion chemotherapy (HAI)

HAI relies on the preferential blood supply of metastases from the hepatic artery and the dual blood supply of the liver with the portal vein[25]. Higher drug levels are delivered at the sites of metastatic disease. The most common agent used is the 5FU analogue floxuridine (FUDR). The most serious side effects are biliary sclerosis or catheter-related complications, both of which can be fatal[26].

Until recently, trials comparing HAI to systemic chemotherapy for liver metastases had demonstrated improved response rates, but survival benefits were less clear[26-28]. A recent Phase Ⅲ trial of 135 patients comparing HAI (FUDR, leucovorin (LV) and dexamethasone) to systemic chemotherapy (5FU and LV) showed a 24.4 mo *vs* 20 mo (P = 0.0034) median overall survival benefit favouring HAI. Time to extrahepatic progression, conversely, was 7.7 mo *vs* 14.8 mo favouring systemic chemotherapy (P = 0.029) [29]. As more efficacious agents (oxaliplatin, irinotecan) are now used in treatment of metastatic CRC, it is unclear as to whether superiority of HAI in such studies would be maintained when using these newer agents as comparators. A Cochrane review of HAI chemotherapy after resection or ablation of liver metastases secondary to CRC, found no significant overall survival advantage for HAI; as such this is not currently a recommended intervention after liver resection[30].

Radiofrequency ablation (RFA)

RFA uses high frequency alternating current creating ionic agitation and heat, resulting in cell death by coagulation necrosis[31]. Percutaneous, laparoscopic, and open surgical techniques may be employed. Patients who are eligible generally have fewer than five metastases, < 5 cm in diameter and clear of major blood vessels[32]. One recent study of 135 patients found a median survival of 28.9 mo after RFA for surgically unresectable liver metastases[31]. RFA can be considered for lung metastases, where thoracotomy is not indicated (surgically unresectable or the patient is medically unfit). Multiple lesions can be treated in one procedure. The RAPTURE trial of RFA for lung metastases from a variety of malignancies, presented 2 year follow-up data in 2005. Of 53 patients with CRC, 72% remain cancer free at 2 years[33]. A Phase Ⅱ study of 55 patients with metastatic CRC undergoing RFA demonstrated a 2-year disease-free survival rate of 57% and median overall survival of 33 mo[34]. The major complication of lung RFA is pneumothorax (up to 43% in one study)[35].

Selective internal radiation therapy (SIRT)

SIR-Spheres® are biocompatible radio-active microspheres containing yttrium-90 which emits beta radiation. This Australian invention[36] delivers up to 40 times more radiation to liver metastases than would be possible using conventional radiotherapy[37], and has shown benefits in liver metastases from both breast and colorectal cancer as well as primary hepatocellular carcinoma (Figure 1) . A hepatic arterial catheter is used to deliver the microspheres, which may be combined with HAI or intravenous

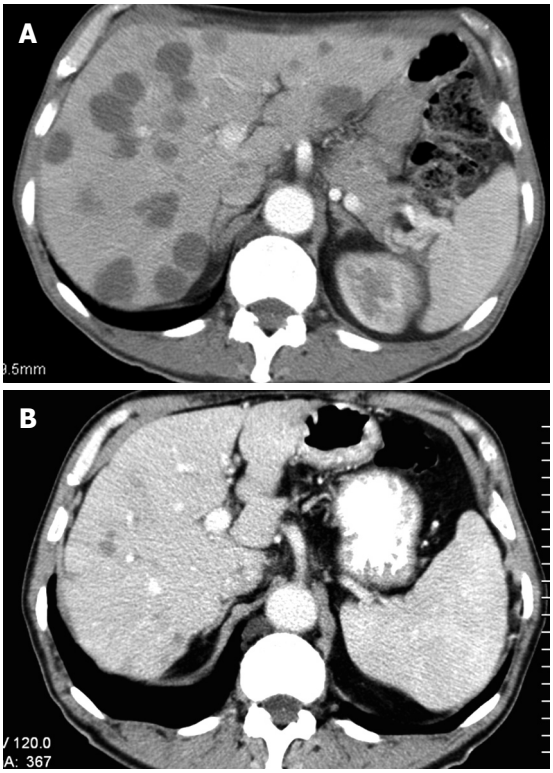

Figure 1 Response of hepatic colorectal cancer metastases treated with SIR spheres. **A**: Pre-treatment; **B**: At 12 wk post after intrahepatic infusion of SIR spheres.

chemotherapy. A Phase Ⅲ trial of 74 patients comparing HAI plus SIRT to HAI alone found a 44% *vs* 17.6% partial and complete response rate ($P = 0.01$), with a 15.9 mo *vs* 9.7 mo time to progression ($P = 0.001$), favouring the combination[38]. This technology appears promising for the future.

SYSTEMIC CHEMOTHERAPY

Please refer to Tables 1 and 2 for details of chemotherapy acronyms, regimens and key Phase Ⅲ trials, which are discussed below.

5-Fluorouracil and calcium leucovorin

The anti-metabolite 5-fluorouracil (5FU) was the mainstay of chemotherapy for metastatic colorectal cancer in the latter half of the 20th century[39]. The addition of intravenous calcium leucovorin (folinic acid, LV) stabilizes the binding of 5FU to thymidylate synthase, enhancing the inhibition of DNA synthesis[40]. Combination therapy was demonstrated in a meta-analysis of nineteen trials to improve response rate and overall survival over 5FU alone[41]. High dose LV does not appear to convey any survival advantage over lower doses[42,43]. The combination provides a median survival of approximately 12 mo compared with 6 mo for supportive care alone[42]. Until the last decade, 5FU and LV were the only active agents in common use for metastatic CRC. Levamisole, an immunomodulatory agent, was initially combined with 5FU-based regimens, but was later abandoned after no survival benefit was shown in the adjuvant setting[44,45].

Table 1 Common chemotherapy regimens for metastatic colorectal cancer

Regimen	Description	Cycle length
5FU Mayo[93,94]	5-FU 425 mg/m^2/d D1-5 LV 20 mg/m^2/d D 1-5	4 wk
5FU Roswell Park[45]	5-FU 500 mg/m^2/d weekly × 6 LV 500 mg/m^2/d weekly × 6	8 wk
LVFU2[95] (de Gramont)	5FU 400 mg/m^2 bolus D1 and D2 LV 200 mg/m^2 D1 and D2 5FU 600 mg/m^2 CIVI 22 h D1 and D2	2 wk
LV5FU2 (AIO)[96]	LV 500 mg/m^2 D1 weekly × 6 5FU 2300-2600 mg/m^2 CIVI 24 h D1 weekly × 6	8 wk
Capecitabine[48]	1250 mg/m^2 BD, D1-14	3 wk
FOLFOX4[53]	Oxaliplatin 85 mg/m^2 D1 LV 200 mg/m^2 D1 and D2 5FU 400 mg/m^2 D1 and D2 5FU 600 mg/m^2 CIVI 22 h D1 and D2	2 wk
FOLFOX6[97]	Oxaliplatin 100 mg/m^2 D1 LV 400 mg/m^2 D1 5FU 400 mg/m^2 D1 5FU 2400-3000 mg/m^2 CIVI 46 h (D1, D2)	2 wk
bFOL[98]	Oxaliplatin 85 mg/m^2 D1, D15 LV 20 mg/m^2 D1, D8, D15 5FU 500 mg/m^2 D1, D8, D15	4 wk
FUFOX[99]	Oxaliplatin 85 mg/m^2 D1, 15, 29; LV 20 mg/m^2 D1, 8, 15, 22, 29; 5FU 500 mg/m^2 D 1, 8, 15, 22, 29	8 wk
FLOX[100]	Oxaliplatin 85 mg/m^2 D1 wk 1, 3, 5 5FU 500 mg/m^2 bolus weekly wk 1-6 LV 500 mg/m^2 bolus weekly wk 1-6	8 wk
FOLFIRI[63]	Irinotecan 180 mg/m^2 D1, LV 200 mg/m^2 D1 and D2, 5FU 400 mg/m^2 bolus D1 and D2, 5FU 600 mg/m^2 CIVI 22h D1 and D2	2 wk
IFL[62]	Irinotecan 100-125 mg/m^2 weekly × 4 wk LV 20 mg/m^2 weekly × 4 wk, 5FU 400-500 mg/m^2 bolus weekly × 4 wk	6 wk
XELOX[54]	Oxaliplatin 130 mg/m^2 D1 Capecitabine 1 g/m^2 BD D1-14	3 wk
CAPOX[55]	Capecitabine 1 g/m^2 BD D1-14 Oxaliplatin 70 mg/m^2 D1, D8	3 wk
XELIRI[64]	Irinotecan 200-250 mg/m2 D1 Capecitabine 1 g/m^2 BD D1-14	3 wk
CAPIRI[65]	Capecitabine 1 g/m^2 BD D1-14 Irinotecan 100 mg/m^2 D1, D8	3 wk
FOLFOXIRI [91,101]	Irinotecan 125-175 mg/m^2 D1 Oxaliplatin 85-100 mg/m^2 D1 LV 200 mg/m^2 D1 5FU 400 mg/m^2 bolus D1 5FU 3200 mg/m^2 CIVI 48 h	2 wk

D1: day 1; LV: leucovorin; CIVI: continuous intravenous infusion; BD: twice daily; d: daily.

Despite numerous documented regimens employing either bolus or infusional 5FU, minimal overall survival advantages have been shown for any one although the response rate and progression free survival appear better with infusional schedules, and one meta-analysis suggested a slight survival advantage for infusional over bolus 5FU (12.1 *vs* 11.3 m, $P = 0.04$)[46]. The side effect profiles differ; infusions of 5FU cause more diarrhoea and hand-foot syndrome (erythema, dryness and cracking of palms and soles) while bolus 5FU carries a higher incidence of haematological toxicity. 5FU/LV is used alone in patients who are intolerant or have contra-indications to more complex regimens.

Table 2 Key phase Ⅲ trials in metastatic colorectal cancer

Author/trial	*n*	Arms	RR (%)	TTP (mo)	OS (mo)
Van Cutsem[48]	602	Capecitabine	18.90	5.2	13.2
		5FU/LV Mayo	15.00	4.7	12.1
			(P NA)	(*P* = 0.65 NS)	(*P* = 0.33 NS)
De Gramont[53]	420	FOLFOX4	50.70	9	16.2
		LV5FU2	22.30	6.2	14.7
			(*P* = 0.0001)	(*P* = 0.0003)	(*P* = 0.12 NS)
Hochster TREE-1[56]	147	FOLFOX	41	8.7	19.2
		bFOL	20	6.9	17.9
		CapeOx	27	5.9	17.2
			(P NA)	(P NA)	(P NA)
Hochster TREE-2[56]	213	FOLFOX + bevacizumab	52	9.9	26
		bFOL + bevacizumab	39	8.3	20.7
		CapeOx + bevacizumab	46	10.3	27
			(P NA)	(P NA)	(P NA)
Fuchs BICC-C[a][66]	430	FOLFIRI	46.60	7.6	23.1
		mIFL	41.90	5.8	17.6
					(*P* = 0.10)
		CAPIRI	38	5.5	18.9
			(P NA)	(P NA)	(*P* = 0.19 NS)
Fuchs BICC-C 2[66]	117	FOLFIRI + bevacizumab	54.40	9.9	NR
		mIFL + bevacizumab	53.30	8.3	18.7
			(P NA)	(P NA)	
Saltz[62]	683	IFL	39	7	14.8
		5FU/LV (Mayo)	21	4.3	12.6
			(*P* < 0.001)	(*P* = 0.004)	(*P* = 0.04)
		Irinotecan			
Douillard[63]	387	FOLFIRI	35	6.7	17.4
		LV5FU2 (AIO)	22	4.4	14.1
			(*P* =0.005)	(*P* < 0.001)	(*P* = 0.031)
Tournigand[88] GERCOR	220	FOLFIRI ⩾ FOLFOX6	56	8.5	21.5
		FOLFOX6 ⩾ FOLFIRI	54	8	20.6
			(*P* = NS)	(*P* = 0.26 NS)	(*P* = 0.99 NS)
Goldberg[89] N9741	795	FOLFOX4	45	8.7	19.5
		IFL	31	6.9	15
			(*P* = 0.002)	(*P* = 0.0014)	(*P* = 0.0001)
		IROX	35	6.5	17.4
			(*P* = 0.03)	(*P* = 0.001)	(*P* = 0.09 NS)
Colucci[90]	360	FOLFIRI	31	7	14
		FOLFOX4	34	7	15
			(*P* = 0.60 NS)	(*P* = NS)	(*P* = 0.28 NS)
Ross[71]	200	Mitomycin C + infusional 5FU	54	7.9	14
		Infusional 5FU	38	5.4	15
			(*P* = 0.024)	(*P* = 0.033)	(*P* = NS)
Souglakos *et al*[91]	283	FOLFOXIRI	43	8.4	21.5
		FOLFIRI	33.6	6.9	19.5
			(*P* = 0.168 NS)	(*P* = 0.17 NS)	(*P* = 0.337 NS)
Falcone[92]	244	FOLFOXIRI	66	9.8	22.6
		FOLFIRI	41	6.9	16.7
			(*P* = 0.0002)	(*P* = 0.0006)	(*P* = 0.032)
Hurwitz[24]	813	IFL + bevacizumab	44.8	10.6	20.3
		IFL	34.8	6.2	15.6
			(*P* = 0.004)	(*P* < 0.001)	(P < 0.001)
Giantonio[78] ECOGE 3200	822	FOLFOX4 + bevacizumab	22	7.2	12.9
		FOLFOX4	9	4.8	10.8
				(*P* < 0.0001)	(*P* = 0.0018)
		Bevacizumab	Discontinued		
Cunningham[81] BOND-1	329	Cetuximab + irinotecan	22.9	4.1	8.6
		Irinotecan	10.8	1.5	6.9
			(*P* = 0.007)	(*P* < 0.001)	(*P* = 0.48 NS)
BOND-2[102]	74	Cetuximab + irinotecan + bevacizumab	38	8.5	n/a
		cetuximab + bevacizumab			
			23	6.9	n/a
Peeters[87]	463	Panitumumab		Improved PFS	Approx 6.5 m both arms
		BSC		(HR 0.54 *P* < 0.0001)	(*P* = NS)

NS: Not significant; BSC: Best supportive care; NA: Not available. aIn the BICC-C trial all arms were also randomized to +/- celecoxib, which neither improved efficacy nor toxicity of chemotherapy.

Capecitabine (Xeloda®)

This oral pro-drug is converted to 5FU in three enzymatic steps including thymidine phosphorylase, a tumour-associated angiogenic factor, theoretically resulting in increased concentration at the site of metastases[47]. Capecitabine is at least equivalent in efficacy to bolus 5FU in metastatic colorectal cancer[48]. The toxicity profile is similar to infusional 5FU with diarrhoea and hand-foot syndrome of some degree in up to 50%-60% of clinical trial subjects[49], often requiring a dose reduction. Although many patients prefer to use an oral form of chemotherapy rather than attending hospital for intravenous 5FU-based chemotherapy, compliance must be assured when such therapy is used.

Tegafur is an oral 5FU pro-drug given in combination with uracil (UFT) and oral leucovorin. Phase Ⅲ data comparing UFT/LV with bolus 5FU/LV in previously untreated metastatic CRC demonstrated equivalent overall survival (12.4 m *vs* 13.4 m, $P = 0.630$ NS) with less diarrhoea and myelosuppression than bolus 5FU[50].

Oxaliplatin (Eloxatin®)

This platinum-based agent works by forming platinum-DNA adducts, thus blocking DNA replication[51]. Although it has minimal single-agent activity, it is synergistic with 5FU in the treatment of metastatic CRC[52]. A large Phase Ⅲ trial of 420 patients compared FOLFOX4 to LV5FU2 (Table 1) and demonstrated improved response rate (50.7% *vs* 22.3%, $P = 0.0001$) and progression-free survival (9.0 mo *vs* 6.2 mo, $P = 0.0003$), but overall survival was not statistically significantly different[53], possibly attributable to patients in the control arm later receiving oxaliplatin, thus obscuring any survival benefit. Newer trials have combined capecitabine with oxaliplatin (CAPOX or XELOX), with phase Ⅱ data demonstrating a 19.5 mo median overall survival[54,55]. TREE-1 (Table 2), a small Phase Ⅲ trial, compared CAPOX and two other regimens combining oxaliplatin with 5FU and found equivalent overall survival (OS) in each arm[56].

Oxaliplatin's main toxicity is sensory peripheral neuropathy of two types-an acute, temporary cold related dysaesthesia; and a chronic cumulative persistent sensory neuropathy which is dose-limiting and may be irreversible[57]. Up to 90% of patients experience some form of acute neurotoxicity[58] and 10%-15% chronic neuropathy[59]. While most fully recover after a median time of 13 wk[60], in the MOSAIC study which employed the FOLFOX4 regimen, 29% of patients still had some degree of neurotoxicity 12 mo after cessation of therapy[57].

Irinotecan (CPT11, Camptosar®)

Irinotecan, a camptothecin derivative, inhibits Topoisomerase I, impeding DNA uncoiling causing double-stranded DNA breaks[61]. A Phase Ⅲ trial of 683 patients compared IFL (Table 1) with single agent irinotecan or bolus 5FU/LV (Mayo regimen). Response rate, progression free survival and median overall survival (14.8 mo *vs* 12.6 mo, $P = 0.04$) were all improved with IFL[62]. Another Phase Ⅲ trial randomized 387 patients to FOLFIRI versus LV5FU2 (Table 1). This trial also demonstrated a higher overall survival (median 17.4 mo *vs* 14.1 mo, $P = 0.031$), favouring the irinotecan arm[63]. The combination of capecitabine with irinotecan (CAPIRI or XELIRI) in Phase Ⅱ studies suggest comparable activity to FOLFIRI with a 16-19 mo median overall survival[64,65]; however, recent data from a phase Ⅲ trial found a trend towards superior response rate and overall survival with FOLFIRI over CAPIRI (OS 23.1 m *vs* 18.9 m $P = 0.19$ NS)[66]. The main dose-limiting side effect is diarrhoea, experienced in over 50% of patients in these studies. This was of Grade 3 or 4 severity in 22%-44% of those treated.

Mitomycin C

This antineoplastic antibiotic, isolated from *Streptomyces caespitosis*, is activated to become an alkylating agent in vivo, cross-linking and inhibiting DNA synthesis and function[67]. It demonstrates single-agent activity in metastatic CRC[68,69], but is accompanied by a significant risk of neutropenia and a small risk of haemolytic-uraemic syndrome[70]. A randomised study of 200 patients showed a 54% *vs* 38% response rate in patients receiving mitomycin C and infusional 5FU, compared with 5FU alone ($P = 0.024$); overall survival was equivalent[71]. Irinotecan added to mitomycin C, in 41 patients who had progressed on 5FU, showed a median overall survival of 11.9 mo[72]. More recently, a phase Ⅱ study of 36 patients demonstrated efficacy for mitomycin C and capecitabine in irinotecan-refractory metastatic CRC, with a 15.2% response rate and median overall survival of 9.3 mo[73].

Targeted therapies

Inhibitors of circulating growth and angiogenic factors, their cell surface receptors, and corresponding intracellular tyrosine kinases are increasingly used combined with or as an alternative to chemotherapy. For metastatic CRC, two agents have entered routine clinical practice: the monoclonal antibodies bevacizumab and cetuximab.

Bevacizumab (Avastin®)

Bevacizumab is a humanised monoclonal antibody targeting vascular endothelial growth factor (VEGF), an angiogenic factor over-expressed in approximately 50% of colorectal cancers[74]. The antibody-bound form of VEGF is unable to bind to its cell surface receptor, preventing activation of an intracellular tyrosine kinase pathway which regulates cell proliferation, angiogenesis, and cell survival[75]. Bevacizumab in combination with chemotherapy, is now regarded as appropriate 1st-line therapy for metastatic CRC. After a preliminary Phase Ⅱ study suggested that bevacizumab had efficacy in combination with 5FU/LV in metastatic CRC[76], a Phase Ⅲ trial with 813 previously untreated patients randomized to IFL +/- bevacizumab further demonstrated activity. A significant overall survival advantage was seen favouring the experimental arm (20.3 mo *vs* 15.6 mo, $P < 0.001$)[24]. An analysis of 3 trials using 5FU/LV +/- bevacizumab demonstrated a 17.9 mo *vs* 14.6 mo ($P = 0.008$) overall survival advantage with the combination compared with 5FU-based treatment alone[77]. In the three arm ECOG 3200 study, FOLFOX4 +/- bevacizumab was compared

with bevacizumab alone in 822 patients with previously treated metastatic CRC. The bevacizumab-alone arm was discontinued due to inferiority at an interim analysis. An overall survival advantage (12.9 mo *vs* 10.8 mo, $P = 0.0024$) as well as significant response rates and progression-free survival benefits were seen in the FOLFOX4 plus bevacizumab arm[78]. The TREE-2 study (Table 2) added bevacizumab to three different oxaliplatin-containing regimens and found improved response rates and time to progression when added to all three[56]. The toxicities of bevacizumab when added to chemotherapy alone include hypertension (22% *vs* 8.3% overall and 11% *vs* 2% requiring treatment), bleeding or thrombosis, in particular arterial thrombotic events (CVA, AMI, TIA, angina), were increased (5% *vs* 2.5%), proteinuria in 26% and gastro-intestinal perforation in 1.5% or 6/393[24]. VEGF is involved in wound healing, which may explain the last complication.

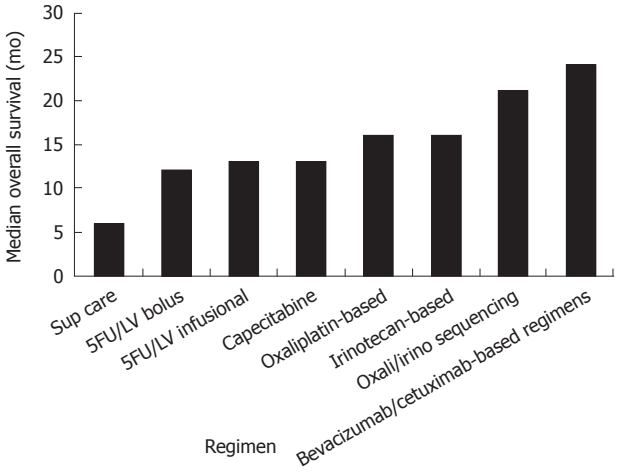

Figure 2 Survival benefits of chemotherapy regimens in metastatic colorectal cancer.

Cetuximab (Erbitux®)

This chimeric monoclonal antibody, targeting the extracellular domain of the epidermal growth factor receptor (EGFR or HER-1), has demonstrated activity in metastatic CRC. Although the EGFR gene is over-expressed or upregulated in 60%-80% of colorectal cancers[79], cetuximab response in CRC appears independent of EGFR expression[80,81]. In a phase Ⅱ study (128 patients) adding cetuximab to irinotecan after failure of irinotecan alone, a 22.5% response rate was obtained[82]. In the BOND-1 study of 329 participants refractory to irinotecan, randomised to cetuximab and irinotecan or cetuximab alone, a significantly higher response rate and median time to progression for the combination was seen, although overall survival was no different[81]. The above trials explored the use of cetuximab in previously treated patients. Its role in 1st-line treatment; and also in combination with oxaliplatin-based regimens, is yet to be fully elucidated. The main side effect is an acneiform skin rash in up to 89%[83]; the degree of skin reaction may correlate with response rate[80,84]. Diarrhoea is relatively common; and allergic reactions may occur, possibly related to the mouse component of the antibody[85].

Panitumumab

This antibody also targets the EGFR, but in contrast to cetuximab, it is derived from the XenoMouse, a transgenic mouse which produces fully humanized antibodies[86]. A Phase Ⅲ trial comparing panitumumab with best supportive care in 463 patients with CRC after progression on irinotecan and oxaliplatin, showed 8% *vs* 0% partial responses and 28% *vs* 10% with stable disease. No overall survival benefit has been seen to date[87]. Rash of some degree occurs in over 90% of patients, and hypomagnesaemia in 38% of patients in this trial, but allergic reactions appear uncommon.

Which agent and which combination?

Decisions as to the best choice of therapy are based on performance status, co-morbidities, and the preferences of the individual. The optimal combination and sequencing of therapeutic agents in the metastatic setting is unknown. A randomized study of FOLFIRI followed by FOLFOX6 at progression, or the reverse sequence, demonstrated equivalent time to first progression (8.5 mo *vs* 8.0 mo $P = 0.26$) and median overall survival (21.5 mo *vs* 20.6 mo, $P = 0.99$)[88]. A Phase Ⅲ study in 795 persons compared FOLFOX4 with IFL and IROX (irinotecan and oxaliplatin). All outcome measures were better for the FOLFOX4 regimen with median survival 19.5 mo (*vs* 15 mo for IFL $P = 0.0001$ and 17.4 mo for IROX$P = 0.09$ NS)[89]. Because oxaliplatin was not available commercially in the US at the time, the difference in overall survival may have been accentuated by differential access to second-line treatment for those in the two arms of the trial. Additionally, only the FOLFOX4 arm used infusional 5FU, which may have contributed to its advantage. In fact, phase Ⅲ data from a study of 360 persons comparing FOLFIRI and FOLFOX4 (both using infusional 5FU), demonstrated no difference in response rate, time to progression and OS between the two arms[90]. A recent Phase Ⅲ study comparing FOLFOXIRI (Tables 1 and 2) to FOLFIRI in 283 participants demonstrated more toxic side effects but no difference in outcomes with the triple combination[91]. A further phase Ⅲ trial compared FOLFOXIRI with FOLFIRI in 244 persons and found a statistically significant overall survival advantage of 22.6 mo *vs* 16.7 mo ($P = 0.032$) for the triplet arm with increased but manageable toxicities[92]. In practice, most fit patients will receive a number of therapeutic agents for management of metastatic disease, including 5FU, capecitabine, irinotecan, oxaliplatin, cetuximab and bevicuzimab, as overall survival benefits continue to improve (Figure 2).

CONCLUSION

The management of metastatic colorectal cancer in the twenty-first century is becoming increasingly complex, with the development of innovative new therapies and further scope for combinations of active agents. In addition, there have been significant advances in surgical and other

ablative and local techniques, and it seems certain that targeted therapies will become a major component of the management of colorectal cancer Overall, these gains in the last decade are beginning to impact on survival and quality of life for people affected with this devastating disease, and there is hope that terminal metastatic colorectal cancer may one day become a rarity.

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