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Antitumour treatment

Biologic therapies in the metastatic colorectal cancer treatment continuum – Applying current evidence to clinical practice

Marc Peeters [a,*], Timothy Price [b,c]

[a] Department of Oncology, Antwerp University Hospital, Wilrijkstraat 10, 2650 Edegem, Belgium
[b] Haematology/Medical Oncology Unit, The Queen Elizabeth Hospital/University of Adelaide, Woodville, SA 5011, Australia

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ABSTRACT

More therapeutic options are now available than ever before for patients with metastatic colorectal cancer (mCRC) and, as such, treatment decisions have become more complex. A multidisciplinary approach is, therefore, required to effectively manage these patients. In the past few years, many trials have reported on the value of combining biological agents, such as those targeting vascular endothelial growth factor A and epidermal growth factor receptors, with chemotherapy. However, despite the plethora of information now available, the optimal treatment strategy for patients with mCRC remains unclear. Indeed, the propensity of investigators to conduct clinical trials utilising a variety of chemotherapy backbones combined with the increased complexity of retrospectively incorporating analyses of genetic mutation status (e.g. *KRAS* and *BRAF*) have led to conflicting results for seemingly similar endpoints, particularly overall survival. As a result, guidelines that have been developed, whilst having some similarities, have distinct differences in terms of suggested therapeutic combinations. Therefore, here, we review and distil the currently available data reported from phase III trials of biologic agents in the first-, second- and third-line mCRC settings.

Introduction

Approximately 60–70% of patients with colorectal cancer (CRC) receive a biological agent targeting the vascular endothelial growth factor A (VEGF-A) or epidermal growth factor receptor (EGFR) over their treatment course. Bevacizumab (F. Hoffmann-La Roche Ltd., Basel, Switzerland) is indicated combined with intravenous 5-fluorouracil [5-FU]-based chemotherapy for the first-/second-line treatment of patients with metastatic CRC (mCRC)[1,2] and is the only currently available anti-VEGF-A agent.

The two EGFR inhibitors (EGFRIs) indicated for mCRC, are the chimeric monoclonal antibody (mAb) cetuximab (Merck KgaA, Darmstadt, Germany) and the fully human mAb panitumumab (Amgen Inc., Thousand Oaks, CA, USA). Both cetuximab and panitumumab are indicated as monotherapy in patients with wild-type (WT) *KRAS* tumours who are refractory to or have progressed following initial chemotherapy and are also recommended in combination with chemotherapy.[3–5]

In recent years, a plethora of new data have been published shedding light on the efficacy of these targeted agents in mCRC; including the consequence of chemotherapy backbone choice, and the relative importance of patient selection through biomarker analysis. These data have sometimes been conflicting, or at least inconsistent, resulting in a challenging environment in which physicians are required to make treatment choices. This is potentially further complicated by the fact that current treatment guidelines for mCRC differ around the world.[6,7] Here, we attempt to take an evidence-based approach to provide meaningful guidance for physicians assessing optimal treatment strategies in different mCRC settings and patient groups.

Key phase III first-line trials incorporating bevacizumab

AVF2107g: IFL ± bevacizumab

AVF2107g was a randomised, placebo-controlled trial comparing irinotecan, leucovorin, and 5-fluorouracil (IFL) alone with IFL/bevacizumab in 813 patients with mCRC.[8] At the time the study was designed, IFL was a standard of care in the US but has since been superseded by more efficacious infusional fluoropyrimidine-based regimens including irinotecan or oxaliplatin. Addition of bevacizumab significantly improved progression-free survival (PFS), overall survival (OS) and ORR (Table 1).[8] Tumour *KRAS* status was retrospectively assessed in 28% of patients;[9] results suggested that bevacizumab was active irrespective of *KRAS* status, but a

* Corresponding author. Tel.: +32 3821 3954; fax: +32 3825 0564.
E-mail addresses: Marc.Peeters@uza.be (Marc Peeters), Timothy.Price@health.sa.gov.au (T. Price).
[c] Tel.: +61 8 8222 6865; fax: +61 8 8222 7054.

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Table 1
Efficacy data from key phase III first- and second-line trials of bevacizumab.

	First-line trials																Second-line trial		
	AVF2107g[8,9]			BICC-C[11]						NO16966[12]			AGITG MAX[14,15]				ECOG E3200[2]		
	IFL	IFL + B	HR (*p*-value)	mIFL	FOLFIRI	HR (*p*-value)	mIFL + B	FOLFIRI + B	HR (*p*-value)	XLX/ FLX	XLX/ FLFX + B	HR (*p*-value)	C	CB	CBM	HR[a] (*p*-value)	FLX	FLX + B	HR (*p*-value)
Median PFS, months																			
Overall	6.2	10.6	0.54 (<0.001)	5.9	7.6	1.51(0.004)	8.3	11.2	(0.28)	8.0	9.4	0.83 (0.002)	5.7	8.5	8.4	0.63[a] (<0.001)	4.4	7.3	0.61 (<0.0001)
WT *KRAS*	7.4	13.5	0.44 (<0.0001)	–	–	–	–	–	–	–	–	–	5.9	8.8	8.8	0.66[b] (0.006)	–	-	-
MT *KRAS*	5.5	9.3	0.41 (0.0008)	-	-	-	-	-	-	-	-	-	6.2	8.2	8.2	0.65[b] (0.06)	-	-	–
Median OS, months																			
Overall	15.6	20.3	0.66 (<0.001)	17.6	23.1	(0.09)	19.2	Not yet reached	(0.007)	19.9	21.3	0.89 (0.077)	18.9	18.9	16.4	0.88[a] (0.314)	10.8	12.9	0.75 (0.0011)
WT *KRAS*	17.6	27.7	0.58 (0.04)	–	–	–	–	–	–	–	–	–	20.0	19.8	19.8	0.61[b] (0.38)	–	–	–
MT *KRAS*	13.6	19.9	0.69 (0.26)	–	–	–	–	–	–	–	–	–	22.8	17.6	17.6	1.15[b] (0.57)	–	–	–
ORR, %																			
Overall	35	45	(0.004)	43	47	NS	53	58	NS	38[c]	38[c]	(0.31)	30.3	38.1	45.9	(0.16)[a]	9	23	(<0.0001)
WT *KRAS*	37	60	(0.006)	–	–	–	–	–	–	–	–	–	27.1	41.0	44.7	–	–	–	–
MT *KRAS*	41	43	(0.86)	–	–	–	–	–	–	–	–	–	48.5	24.2	45.8	–	–	–	–

B, bevacizumab; FLX, FOLFOX; C, capecitabine; CB, capecitabine + bevacizumab; CBM, capecitabine + bevacizumab + mitomycin; HR, hazard ratio; NS, not significant; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; XLX, XELOX.

[a] HR and *p*-value for C vs CB.

[b] HR and *p*-value for C vs CB and CBM.

[c] By independent response review committee.