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EDITORIAL

Epidermal growth factor receptor and metastatic colorectal cancer: Insights into target therapies

Ramon Andrade de Mello, Andrea Marin Marques, António Araújo

Ramon Andrade de Mello, António Araújo, Department of Medical Oncology, Portuguese Oncology Institute, 4200-072 Porto, Portugal
Ramon Andrade de Mello, Department of Medicine, FMUP-Faculty of Medicine, University of Porto, 4200-319 Porto, Portugal
Andrea Marin Marques, Department of Medicine, Centro Hospitalar Médio Ave, 4780 Porto, Portugal
Author contributions: All authors contributed as the same for this manuscript preparation.
Correspondence to: Ramon Andrade de Mello, MD, PhD, Department of Medical Oncology, Portuguese Oncology Institute, Rua Dr. António Bernardino de Almeida, 4200-072 Porto, Portugal. ramondemello@gmail.com
Telephone: +351-22-584000 Fax: +351-22-584010
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Abstract

Colorectal cancer (CRC) has high incidence and mortality worldwide. In 2012, CRC was the second most prevalent cancer among males (9%) and the third among females (8%). In recent decades, standard chemotherapies protocols combining 5-fluorouracil, leucovorin, irinotecan and oxaliplatin were important for improve survival in this set of patients. Further, biological drugs throughout epidermal growth factor receptor (EGFR) pathways showed interesting results in metastatic disease (mCRC) control when in association to standard chemotherapy regimens. Cetuximab and panitumumab are two cornerstones for mCRC treatment and are both approved in Europe and United States based on previous results phase Ⅲ trials. This paper will briefly summarize those anti-EGFR therapies framework in mCRC and discusses some issues in this regard.

Key words: Colorectal cancer; Epidermal growth factor receptor; *KRAS* mutation; Chemotherapy; Cetuximab; Panitumumab

Core tip: Metastatic colorectal cancer (mCRC) remains a challenge for oncologists worldwide. Despite a very aggressive disease profile, mCRC's outcomes are improving toward last decades. Target drugs, such as cetuximab and panitumumab, acquired a main role in this scenario whether phase Ⅲ trials showed interesting results in overall survival and disease control. Thus, we will briefly in this paper discuss some issues and pitfalls concerning this framework.

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INTRODUCTION

Colorectal cancer (CRC) has high incidence and mortality worldwide. In 2012, CRC was the second most prevalent cancer among males (9%) and the third among females (8%)[1]. The survival rates, in advanced CRC remain low; therefore, the development of new therapeutic weapons becomes a real need. Targets therapies through epidermal growth factor (EGF) and its receptor (EGFR) and also KRAS pathways modulation acquired a main role whether in association with standard chemotherapy[2]. Since its discovery, EGFR has been considered a good candidate for targeted cancer therapy[3,4]. It is over expressed in many types of cancers, especially CRC[5].

EPIDERMAL GROWTH FACTOR RECEPTOR

Although EGFR remains a controversial prognostic fac-

Table 1 Mainly clinical trial and target therapies

Study	Design	Median PFS (mo)	Median OS (mo)	Toxicity (grade 3/4)	Genetic analyses	Response rate
PACCE trial[18]	PMAB + Bev/Ox-CT + PMAB + Bev/Iri-CT	10	19.4	Skin rash, diarrhea, infections and pulmonary embolism	*KRAS* status was determined in 82% tumor samples. Mutations were found in 40%	46%
	Bev/Ox-CT + Bev/Iri-CT	11.4	24.5			48%
Peeters *et al*[22]	Panitumumab-FOLFIRI (in the WT KRAS subpopulation)	5.9	14.5[1]	Toxicities associated with anti-EGFR therapy	KRAS status was available for 91% of patients: 597 (55%) with wild-type *KRAS* tumors, and 486 (45%) with mutant *KRAS* tumors	Improved to 35% *vs* 10% with the addition of panitumumab
	FOLFIRI (in the WT KRAS subpopulation)	3.9	12.5[1]			
PRIME study[28]	Wild-type *KRAS* stratum Panitumumab + FOLFOX (4)	9.6	23.9[1]			55%
	FOLFOX(4)	8.0	19.7[1]	Toxicities associated with anti-EGFR therapy	*KRAS* results were available for 1100 (93%)patients	
	Mutant *KRAS* stratum Panitumumab + FOLFOX (4)	7.3	15.5[1]			48% 40%
	FOLFOX (4)	8.8	19.3[1]			40%
COIN trial[29]	Ox and 5FU (arm A) in KRAS wild-type tumours	8.6[1]	17.9[1]	NA	565 (43%) had *KRAS* mutations	57%
	Ox and 5FU plus cetuximab (arm B) in KRAS wild-type tumours	8.6[1]	17.0[1]	Skin rash and gastrointestinal toxic effects		64%
NORDIC-VII[20]	Standard Nordic FLOX (arm A)	7.9[1]	20.4[1]	The regimens were well tolerated	*KRAS* and *BRAF* mutation analyses were obtained in 498 (88%) and 457 patients (81%) respectively	41%
	Cetuximab and FLOX (arm B)	8.3[1]	19.7[1]			49%
	Cetuximab combined with intermittent FLOX (arm C)	7.3[1]	20.3[1]			47%

[1]Without statistical significance. PFS: Progression-free survival; OS: Overall survival; PMAB: Panitumumab; Bev: Bevacizumab; Ox:CT: Oxaliplatin: based chemotherapy; Iri-CT: Irinotecan-based chemotherapy; 5FU: 5-fluorouracil; FOLFOX/FLOX: Fluorouracil, leucovorin and oxaliplatin; FOLFIRI: Fluorouracil, leucovorin and irinotecan; NA: Not applicable.

tor, this expression-stage association may play a crucial role in the decision to initiate an adjuvant treatment toward *KRAS* mutation assessment[6] as it will be discussed below.

However, not all patients have a good response to anti-EGFR monoclonal antibodies, and given the risks for adverse effects associated with their use and their substantial cost, there is particular interest in identifying predictors of treatment benefit or lack thereof[2]. Genetic alterations may explain the resistance to anti-EGFR therapies[7]. In current clinical practice, *KRAS* mutation (codon 12 and 13) is mainly responsible for primary resistance to the EGFR target drugs, particularly cetuximab and panitumumab[8]. Thus the advantages of anti-EGFR monoclonal antibody treatment of colorectal cancer may be limited to *KRAS* wild-type patients[9].

METASTATIC COLORECTAL CANCER

Currently, we know that many monoclonal antibodies has been approved by Food and Drugs Administration (FDA) and European Medicine Agency for the treatment of mCRC: cetuximab and panitumumab in KRAS wild-type patients[5,9] and bevacizumab for those harbor codon 12 or 13 mutation[10,11]. These drugs are used in association with chemotherapy in patients with mCRC or maintenance therapies in chemorefractory tumors (Table 1). In overall, current guidelines advocate the use of the following regimens as initial standard chemotherapy for mCRC: fluorouracil, leucovorin, and oxaliplatin-based chemotherapy (FOLFOX), fluorouracil, leucovorin, and irinotecan-based chemotherapy (FOLFIRI), capecitabine plus oxaliplatin (CapeOx or XELOX)[12,13], and fluorouracil, leucovorin, oxaliplatin and irinotecan-based chemotherapy (FOLFOXIRI)[14]. The addition of a biological agent, such as anti-vascular endothelial growth factor (bevacizumab)[15] or anti-EGFR (cetuximab or panitumumab), in KRAS wild-type, will depends on patients KRAS profile, fitness and related- clinical co-morbidities.

However, we should be aware for the toxicity profile. Most common anti-EGFR adverse events[16] are the skin acneiform rash, xeroderma, hypomagnesemia, diarrhea and nausea[17]. Hecht *et al*[18] assessed panitumumab plus bevacizumab versus regular chemotherapy (oxaliplatin and irinotecan-based) as first line treatment for mCRC and showed no outcomes benefit, but only increase in toxicity profile, particularly diarrhea, infections and pulmonary embolism[19]. The increased in the toxicity can be explicated by dual-pathway inhibition in combination with chemotherapy[18]. In this study the patients were

enrolled onto one of two cohorts per investigator arm: a fluorouracil, leucovorin, and oxaliplatin-based chemotherapy (FOLFOX) cohort or a fluorouracil, leucovorin, and irinotecan-based chemotherapy (FOLFIRI) cohort, each with bevacizumab. Anyway, panitumumab given with FOLFOX or with FOLFIRI in the absence of bevacizumab appears to be well tolerated in other studies.

Tveit *et al*[20] evaluated in mCRC patiens the efficacy of cetuximab plus bolus fluorouracil/folinic acid and oxaliplatin, administered continuously or intermittently as first line regimen. This study did not show significant benefit compared with the FOLFOX regime. For another hand in third-line treatment of patients with chemotherapy-refractory mCRC, cetuximab provides a substantial prolongation of progression-free-survival (PFS) and overall survival[21]. Similarly, panitumumab plus FOLFIRI has shown significantly improved in PFS and was well-tolerated as second-line treatment in patients with wild-type *KRAS* mCRC[22].

Plus, the combination of cetuximab plus FOLFIRI as first-line chemotherapy in wild-type *KRAS* tumors also can reduce the risk of progression of mCRC as compared with FOLFIRI alone[23]. Moreover, we should note that the toxicity of FOLFIRI plus cetuximab combination was superior to FOLFIRI regimen alone (notably skin reactions). Notwithstanding, patients with *KRAS* wild-type locally advanced rectal cancer with the addition of cetuximab to chemoradiation regimen based on irinotecan plus capecitabine showed no benefit compared to the use of chemoradiation alone[24]. Further, in spite of we have focused our attention to *KRAS* mutations; there are others biomarkers that are also implicated in colorectal cancer outcomes, such as *BRAF* mutation. *BRAF*-mutant tumors have worse prognosis[25]. Recently *BRAF* inhibitor, vemurafenib, was approved by the FDA for treatment of patients with *BRAF*-mutant metastatic melanoma[26]. It is expected that in the near future other *BRAF* inhibitors are developed and maybe directed to mCRC.

CONCLUSION

In summary, the most recent studies aim to demonstrate not only the efficacy and safety of the target molecules discussed above, in particular cetuximab and panitumumab, but also how these new agents act in conjunction with conventional chemotherapy. Currently, mCRC molecular profile assessments acquired a main role for oncologists worldwide due to the possibility of personalizing treatments approaches for mCRC patients and thus improve survival outcomes as well as quality of life[27-29]. In addition, the choice to use bevacizumab, cetuximab or panitumumab in association with standard chemotherapy (FOLFOX or FOLFIRI) for mCRC framework run toward patients fitness, acceptable toxicities profiles, survival outcome and mainly pharmaco-economic evaluation of those drugs in this setting.

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