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COMMENTARY

The Challenge of Metastatic Colorectal Cancer

Esther Uña Cidón

Department of Oncology, Clinical University Hospital, C/Ramon y Cajal s/n, 47005 Valladolid, Spain.
Corresponding author email: aunacid@hotmail.com

Abstract: Colorectal cancer (CRC) is a very common disease with a high rate of mortality around the world, representing the second most frequent cause of cancer-related death. As the majority of patients are diagnosed with advanced cancer with a subsequent low five-year survival rate (10%), it is imperative to develop new strategies to treat this challenging patient population. Traditionally, patients received successive lines of chemotherapy and discontinued the treatment or switched to a different one in the event of disease progression. But despite the therapeutic advances achieved with combination chemotherapy regimens, particularly FOLFOX and FOLFIRI, considerable research has been necessary to further optimize chemotherapy for patients with metastatic colorectal cancer (mCRC). However, progress has been achieved over recent years. The most relevant relates to the approval of several new effective therapeutic drugs, such as monoclonal antibodies, which have greatly improved the outcomes for metastatic disease. The last agent approved has been panitumumab, which has been designed to target the epidermal growth factor receptor molecular pathway involved in the appearance and spread of cancer.

Keywords: colorectal cancer, metastatic colon cancer, panitumumab

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Background

Anyone who treats metastatic colorectal cancer (mCRC) will be happy to read the review by Lindsey and Jimeno,[1] which is focused on panitumumab.

Colorectal cancer (CRC) is a very common disease with a high rate of mortality around the world, representing the second cause of cancer-related death.[2] As the majority of patients are diagnosed with advanced cancer with a subsequent low five-year survival rate (10%), it is imperative to develop new strategies to treat this challenging patient population.[3] Traditionally, patients received succesives lines of chemotherapy and discontinued the treatment or switched to a different one in the event of disease progression. But despite the therapeutic advances achieved with combination chemotherapy regimens, particularly FOLFOX and FOLFIRI, considerable research has been neccesary to further optimize chemotherapy for patients with mCRC.[3] However, considerable progress has been achieved over recent years.[1] The most relevant relates to the approval of several new effective therapeutic drugs, such as monoclonal antibodies, which have greatly improved the outcomes for metastatic disease. These agents have been designed to target the relevant molecular pathways involved in the appearance and spread of cancer, as Drs Lindsey and Jimeno have stated in their article.[1]

Monoclonal Antibodies for Treating mCRC

Bevacizumab

Several monoclonal antibodies have been approved for treating mCRC. The two first approved by the US Food and Drug Administration (FDA) were bevacizumab and cetuximab. The first of these is a humanized monoclonal antibody directed against vascular endothelial growth factor (VEGF), which is a soluble protein that stimulates angiogenesis.[4,5] This agent has been evaluated in combination with chemotherapy and it has been well tolerated, with reversible hypertension and proteinuria representing two of the most common toxicities. Nonetheless, rare yet serious side effects have been observed, such as bowel perforation and serious bleeding or arterial embolic events.[6–8]

Initial studies demonstrated improvements in tumor response rate (RR) and progression-free survival (PFS) when bevacizumab is added to fluorouracil and leucovorin.[9,10] Subsequent randomized trials have shown tha bevacizumab is able to prolong median overall survival (OS) when administered in combination with IFL as a first line or with FOLFOX after the failure of a prior regimen that contains irinotecan.[11,12] Further studies have confirmed improved RR and PFS with the addition of bevacizumab to FOLFIRI or FOLFOX in patients with untreated mCRC.[13,14]

Cetuximab

Cetuximab, a chimeric IgG1 immunoglobulin, has been the first epidermal growth factor receptor (EGFR) inhibitor approved for the treatment of CRC.[1] Cetuximab binds specifically to the extracellular domain of EGFR with a binding affinity greater than that of EGF or TGF, and it competitively inhibits binding of these ligands. This union with EGFR induces receptor internalization and degradation, thus reducing EGFR binding capacity and its potential for downstream growth and survival signaling. This monoclonal antibody produced a significant increase in RR when added to irinotecan in irinotecan-refractory patients.[15] These studies have confirmed a tumor RR of approximately 10% with cetuximab alone and 20% when it is added to irinotecan, indicating cetuximab's ability of overcoming irinotecan resistance in tumor cells.[15] In a study of patients whose disease had progressed on a fluoropyrimidine, irinotecan, and oxaliplatin regimen, weekly cetuximab demonstrated improvements in PFS and OS survival (6.1 vs. 4.6 months) when compared to those treated with best supportive care alone.[16]

Two further studies assessed the addition of cetuximab to first-line regimens. The Cancer and Leukemia Group B CALGB trial has detected an improvement in tumor RR with cetuximab plus either FOLFIRI or FOLFOX.[17] On the other hand, the CRYSTAL trial, which compared FOLFIRI with and without cetuximab, demonstrated improvements in tumor RR (47% vs. 39%) and PFS (median 8.9 months vs. 8.0 months), among patients receiving the two drugs in combination.[18]

All these results have supported the inclusion of cetuximab in first-line treatment protocols, although

it is currently unknown how these regimens compare with treatments containing bevacizumab. To answer this question, several ongoing studies have been designed and we hope to have the results in the near future.

Panitumumab

The last monoclonal antibody introduced in the therapeutic arsenal to treat this disease has been panitumumab, which also targets the EGFR.

As Lindsey and Jimeno have explained in their article, panitumumab has shown similar single agent activity to cetuximab in mCRC under a biweekly administration schedule. In an initial study, 9% of patients whose cancers had progressed after treatment with fluorouracil and either irinotecan or oxaliplatin experienced a tumor response to this agent.[19] Other studies, such as the trial by van Cutsem et al[20] in which 463 patients whose disease progressed after fluoropyrimidine-irinotecan-oxaliplatin regimens, were treated with either single-agent panitumumab or the best supportive care. The patients given panitumumab demonstrated an improved PFS when compared with best supportive care (median, 8.0 vs. 7.3 weeks), similar to the improvement previously reported with cetuximab. But OS was not significantly different between both groups. This fact has been explained by the crossover from the best supportive care alone to panitumumab after progression, which could confound the results. An exploratory analysis excluding crossover data has been done and supports this hypothesis.[20]

Based on the positive results as a monotherapy in advanced line, additional studies have been performed to evaluate panitumumab as a part of a combination regimen. The PACCE study[21] (Panitumumab Advanced Colorectal Cancer Evaluation) compared bevacizumab and oxaliplatin-based or bevacizumab and irinotecan-based regimens with and without panitumumab at a dose of 6 mg/kg every two weeks. Interim data have shown shorter PFS (8.8 vs. 10.5 months) and increased grade 4 toxicity in the panitumumab, oxaliplatin and bevacizumab group. Because of these results, the PACCE study was stopped. Additional results from each arm of treatment demonstrated a median PFS of 10 months with panitumumab versus 11.4 months with the standard therapy with a similar RR (46% versus 48%). The irinotecan group showed at PFS of 10.1 months in the panitumumab group and 11.7 with the standard therapy, without any significant difference in RR. In both analyses, it was demonstrated that significant intolerable adverse events increased in the panitumumab groups, so the use of panitumumab in combination with bevacizumab was not recommended.[21]

The combination of panitumumab with FOLFOX for first-line treatment has been investigated in a randomized study where 1,183 patients were randomized to FOLFOX4 with panitumumab every two weeks versus FOLFOX4 alone. Patients with wild-type KRAS status (see below) in the panitumumab group shown a median PFS of 9.6 months and a RR of 55% compared to a PFS of 8 months and a RR 48% in patients with unmutated KRAS treated with FOLFOX4 alone.[22]

Other combinations with different chemotherapy regimens are ongoing. Studies evaluating panitumumab as part of combination therapy in the second-line setting have also been performed. Patients in the combination arm with wild-type KRAS were found to have a longer PFS of 5.9 months compared to 3.9 months in the monotherapy group. OS was also significantly increased in the FOLFIRI/panitumumab group[23] with 14.5 versus 12.5 months in the wild-type KRAS group. No significant difference in PFS or OS was noted in patients with KRAS mutations.

The combination of panitumumab and XELOX in the second-line, or its use as part of combination chemotherapy in the third-line setting, are presently being studied. On the other hand, there is an important point to evaluate: neoadjuvant therapy. This field is also being studied. A small retrospective study of CRC patients treated with FOLFOX and panitumumab or cetuximab prior to resection of liver metastases was performed. The results were encouraging, with a partial response in 10 of 12 patients (83%) and stable disease in the remaining two patients. The authors have concluded that although the study is small, a pre-operative combination of panitumumab with FOLFOX and an EGFR inhibitor is associated with a high response rate and may increase resectability rates.[24] Others combinations are being studied in patients with unresectable liver metastases.

All these data are promising, although there is still the need to determine the best timing or combination, or the optimal sequence of administration to use in patients with mCRC. On the other hand, all these benefits have to be weighted against their side effects, mainly because only a subset of patients' tumors treated with cetuximab or panitumumab will respond to these drugs.

The most important adverse events related to these drugs are acneiform rash, hypomagnesemia and infusion reactions.[1] The relevance of these secondary effects is related not only to the patient´s quality of life, but to the ability to predict their response to anti-EGFR.

In this way, the presence and grade of an acneiform rash have been positively associated with an improved RR among patients with mCRC.[1] Although this fact is very important, there are some patients with this toxicity who do not experience a response to these treatments.

This fact has lead to further research to identify predictive markers of response and outcome, particularly with these new biologic agents, and prospective clinical trials will be required to validate these markers.

Potential Predictive Tumor Characteristics

Two such tumor characteristics have emerged from initial studies:[25,26] EGFR copy number as determined by fluorescence *in situ* hybridization (FISH), and KRAS gene mutation status. Among patients treated with cetuximab or panitumumab, a high EGFR gene copy number determined by FISH has been associated with higher tumor RR, and prolongation of disease-free survival and OS.

In contrast, patients with tumors having mutations in KRAS appear to be relatively resistant to treatment with cetuximab or panitumumab, with lower RRs and poorer survival. These and other molecular features may help define a subset of patients who will derive benefit from treatment with an EGFR inhibitor.

While initial studies attempted to detect EGFR on the surface of tumor cells by immunohistochemical techniques, subsequent retrospective analysis found no correlation between EGFR expression, as assessed by immunohistochemistry (IHC), and clinical outcome.[27] Therefore, the need for other predictive factors has become imperative in order to avoid unnecessary toxicities and waste of resources.

KRAS mutations occur in about 45% of primary CRC, and such mutations have been demonstrated to be predictors of resistance to anti-EGFR monoclonal antibodies. In the presence of specific mutations of the KRAS gene, the Ras protein is constitutively activated and subsequent signaling events are not regulated and independent from EGFR control.[2,27]

Several studies carried out in patients with mCRC have shown resistance to cetuximab in the presence of KRAS mutations (point mutations in codons 12 and 13).

In this way, the recent addition to this therapeutic arsenal, panitumumab, which is the first human monoclonal antibody directed against EGFR, has shown inefficacy in patients diagnosed with mCRC with KRAS mutations and therefore this drug was approved for the treatment of patients with wild-type KRAS who have proven to be resistant to chemotherapy.

A new problem has emerged with this mutational analysis. Where should we determine the mutational KRAS status: at the primary tumor or at the metastasis? In all these studies, the mutational analysis was conducted almost exclusively on primary tumors.[1] It has been shown that primary CRCs may differ from their metastases in terms of EGFR, assessed by IHC. Although it is well known that KRAS mutations occur in the first stages of CRC progression, additional data have demonstrated that the frequency of KRAS mutations in lymph node metastases is higher than in the related primary CRC. The study by Santini et al[28] which tried to verify if the point explained above is right, have concluded that the detection of KRAS mutations in either primary or metastatic tumors from patients with CRC is concordant, and this evaluation could be used as predictor of response to cetuximab and panitumumab.

With these results in mind, we have to consider why some patients with wild-type KRAS continue without responding to these monoclonal antibodies. As Drs Lindsey and Jimeno have explained, other parts of the EGFR signaling pathway have been evaluated as possible contributing factors. One of these potential factors is BRAF that acts as a downstream effector of KRAS. Mutation of this gene has resulted in pathway activation similar to that of induced by KRAS.

Several retrospective analyses have been carried out on patients with metastatic CRC after they were treated with cetuximab or panitumumab to evaluate the effect of BRAF mutation. The mutation was found in several patients with wild-type KRAS and none of them responded to this treatment, and their PFS and OS were shorter when compared to patients with wild-type BRAF.[1] When sorafenib, which is an RAF inhibitor, was added to an anti-EGFR monoclonal antibody, the RR was improved in BRAF-mutated cells.[29] Further trials will be necessary to assess this combination.[30]

The study published by Laurent-Puig et al[31] tried to discriminate the role of different biomarkers as predictive factors in mCRC. They evaluated tumors from 173 patients retrospectively. All but one of the patients received a cetuximab-based regimen as second-line or greater therapy. KRAS and BRAF status, EGFR amplification and the expression of PTEN were assessed. In the 116 patients with KRAS wild-type tumors, BRAF mutations ($n = 5$) were weakly associated with a lack of response ($P = 0.063$) but strongly associated with a shorter PFS ($P < 0.001$) and OS ($P < 0.001$). Negative PTEN expression was found in 19.9% of cases and was associated with a shorter OS ($P = 0.013$). In te multivariate analysis, BRAF mutation and PTEN expression status were associated with OS. The authors concluded that BRAF status and cytoplasmic expression of PTEN were associated with outcome measures in wild-type KRAS patients treated with a cetuximab-based regimen.

Although these are very interesting results, subsequent studies in clinical trials will be required to confirm the clinical utility of these biomarkers.

On the other hand, as Lindsey and Jimeno have noted, specific mutations of the *PIK3CA* gene are considered to be oncogenic in cellular models, and are thought to be associated with metastasis and decreased apoptosis. Sartore-Bianchi et al[32] explored the relevance of *PIK3CA* mutation. They carried out a retrospective analysis of 110 patients with mCRC who had previously been treated with panitumumab or cetuximab therapy. Of the 15 patients with *PIK3CA* mutations, none demonstrated an objective tumor response to EGFR inhibitor therapy, and an overall trend of decreased PFS was observed. Others (e.g. Prenen et al) detected a 20% response to cetuximab in mCRC patients with *PIK3CA* mutations.[33]

With all these data, it is clear that the era of pharmacogenomics has been widely heralded and it will represent the start of a new approach to cancer care. As Lindsey and Jimeno have concluded, panitumumab is a very important new therapy in CRC not only due to its demonstrated activity but also its generally good tolerability. Also panitumumab has had an important role in the development of biomarker science to predict subgroups of patients who are likely to benefit from these treatments.

Readers are recommended to refer colleagues to this review by Lindsey and Jimeno and to use it as a reference when treating mCRC patients.

Disclosure

This manuscript has been read and approved by the author. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The author and peer reviewers of this paper report no conflicts of interest. The author confirms that they have permission to reproduce any copyrighted material.

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