

Controversies in colorectal cancer: First line treatment with epidermal growth factor inhibitors and RAS in 2014

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INTRODUCTION

The treatment of metastatic colorectal cancer is one of clinical and multidisciplinary oncology's biggest successes in recent decades. Today, not only does the median overall survival in recent clinical trials consistently exceed 24 months (and 30 months in patients with wild RAS), compared to 6 months or less with supportive treatment alone before the 1990s, but we can also treat patients with metastatic disease confined to the liver with a curative intent.^[1,2] Well trained teams of professionals, including medical, and surgical oncologists, and the use of new drugs are two of the main factors leading to this improvement. Classical chemotherapeutic agents such as fluoropyrimidines, oxaliplatin, and irinotecan, and targeted treatments such as bevacizumab, cetuximab, panitumumab, aflibercept, and regorafenib are part of our current armamentarium.

In this article, we discuss advances and controversies related to the use of epidermal growth factor (EGFR) inhibitors in the treatment of metastatic colorectal cancer. We will not mention erlotinib, a tyrosine kinase inhibitor of EGFR, more than in this introduction, since the small benefit in progression-free survival seen with its use in combination with bevacizumab did not result in improved overall survival in a recently presented randomized clinical trial.^[3] We will focus the discussion on the monoclonal antibodies cetuximab and panitumumab — and especially in the current role of extended testing for mutations in the RAS oncogene.

THE ROLE OF RAS MUTATIONS IN THE TREATMENT OF PATIENTS WITH INHIBITORS OF EPIDERMAL GROWTH FACTOR MONOCLONAL ANTIBODIES

Studies conducted by our research group and others show that the use of biomarkers to help select patients most likely to respond to a therapy not only can make cancer treatment more effective and more cost-effective, but can also reduce clinical trial failures and the cost of developing new drugs.^[4,5] In colorectal cancer, the RAS family of proteins is the most important biomarker in therapeutic selection today. The gene was first described in rat sarcoma (hence its name RAS) and identified as an oncogene in human tumors in 1982. The genes in the RAS family — *KRAS*, *HRAS* and *NRAS* — encode proteins with GTPase activity and have an important role in several cellular signaling pathways involved in the genesis of colorectal malignancies. RAS mutations occur early in the transition from normal to transformed epithelium, in the progression from polyps to invasive carcinoma. This metabolic route is involved in several hallmarks of malignancy, including cell growth, and proliferation, inhibition of apoptosis, invasion, and metastasis.

KRAS AND *NRAS*

In the last 2 years, we have accumulated evidence that not only mutations in *KRAS* exon 2, which we have been testing for several years to select the most appropriate patients for treatment with EGFR inhibitors, but also those in *KRAS* exons 3, and 4, and *NRAS* exons 2, 3, and 4 are important and confer resistance to treatment with cetuximab and panitumumab. In the PRIME study,^[6] of 1183 patients who entered, 512 had wild type *KRAS* exon 2 and were randomized to receive treatment with 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) with or without panitumumab. Of these patients, 17% had mutations in *KRAS* exons 3 and 4 or in *NRAS*. The original results showed better progression-free survival and a trend towards better overall survival with the EGFR inhibitor. With the exclusion of individuals with mutations in extended RAS testing, the results for overall survival became more evident and statistically significant: 20.2 versus 26.0 months, with a hazard ratio (HR) of 0.78, and a $P = 0.02$, compared with 19.7 versus 23.9 months, with a HR of 0.83, and $P = 0.072$ in the original analysis. The European phase 3 study 20050181^[7] randomized patients to receive treatment

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10.4103/0971-5851.138960

with folinic acid, fluorouracil, irinotecan (FOLFIRI) with or without panitumumab and confirmed these findings. Eighteen percent of patients without mutations in KRAS exon 2 had other RAS mutations in extended testing. Results for the primary endpoint—progression free survival—were better with the addition of the monoclonal antibody: 6.4 versus 4.4 months, HR 0.695, in the analysis with extended RAS testing ($P = 0.006$), compared with 5.9 and 3.9 months, HR 0.73 ($P = 0.004$), in the original analysis. The results for overall survival did not reach statistical significance but tended to do so in the extended RAS wild type population.

At the 2014 American Society of Clinical Oncology Annual Meeting, similar results were presented for extended RAS analyzes in the Crystal^[8] and Opus^[9] trials. In the latter, a randomized phase II trial comparing first line treatment with FOLFOX accompanied or not by cetuximab, median progression free survival improved from 5.8 to 12 months (0.53, $P = 0.062$) in wild type RAS patients as compared to the original results which showed an improvement from 7.2 to 7.7 (HR: 0.57, $P = 0.02$) months in KRAS exon 2 wild type patients. Similarly, in the Crystal trial, which compared treatment with FOLFIRI in the first line with or without cetuximab, overall survival improved from 20.2 to 28.4 months (HR: 0.69, $P = 0.0024$) for patients without mutations in extended RAS testing, when compared to an improvement from 20 to 23.5 months (HR: 0.796, $P = 0.0093$) in patients without KRAS exon 2 mutations only.

RANDOMIZED COMPARISONS BETWEEN EPIDERMAL GROWTH FACTOR INHIBITORS AND BEVACIZUMAB WITH CHEMOTHERAPY IN THE FIRST LINE TREATMENT OF PATIENTS WITH METASTATIC COLORECTAL CANCER

Three studies presented in the last 12 months compared bevacizumab with EGFR inhibitors added to chemotherapy in the first-line treatment of patients with metastatic colorectal cancer. Two of these clinical trials, FIRE 3^[10] and PEAK,^[11] but not yet Cancer and Leukemia Group B (CALGB) 80405,^[12] also corroborated the results of extended RAS testing. In the FIRE3 study, 592 KRAS exon 2 wild type patients were randomized to receive FOLFIRI with bevacizumab or cetuximab. There were no statistically significant differences in the primary outcome analysis, objective response rate, or in progression free survival. Results for overall survival, however, showed a clinically relevant and statistically significant improvement with cetuximab: 28.7 versus 25 months with bevacizumab (HR: 0.77, 95% confidence interval [CI]: 0.62-0.96, $P = 0.017$). These results were even more marked in the analysis of 342 patients with wild type RAS in extended testing. The absolute difference in overall survival increased to 7.5 months (25.6 months with bevacizumab and 33.1 months with cetuximab, HR: 0.70, $P = 0.011$).

Researchers in the randomized phase II PEAK trial allocated patients to treatment with FOLFOX in combination with bevacizumab or panitumumab. In the main analysis, there was no statistically significant difference in progression-free survival but overall survival was better with panitumumab (34.2 vs. 24.3 months with bevacizumab, HR: 0.63, $P = 0.009$). These clinical results were even more significant when patients with mutations in KRAS exons 3 and 4 and NRAS were also excluded. For the 170 patients with wild type RAS in extended testing, overall survival improved from 28.9 months with the VEGF inhibitor to 41.3 months with the EGFR inhibitor. There was also a statistically significant difference in progression-free survival (13 months vs. 9.5 months, HR: 0.65, 95% CI: 0.44-0.96, $P = 0.029$).

Cancer and Leukemia Group B80405 was initially designed as a 3-arm study randomizing patients to treatment with chemotherapy, investigator choice of FOLFOX or FOLFIRI, in combination with cetuximab, bevacizumab or both. As clinical trials showed that the combination of targeted agents could be harmful, the third arm was dropped from the study. The trial was further amended to include only KRAS exon 2 wild type patients. Investigators enrolled 1137 patients. There were no statistically significant differences in overall survival (29 months with bevacizumab and 29.9 months with cetuximab) or progression free survival (10.4 months with cetuximab and 10.8 months with bevacizumab). Unfortunately, results with extended RAS testing have not yet been reported, hampering our ability to make a final determination if chemotherapy treatment with EGFR inhibitors is superior to treatment with bevacizumab.

CHEMOTHERAPY AND CETUXIMAB: WHAT IS (ARE) THE BEST PARTNER(S)?

With negative results in some of the trials that included oxaliplatin chemotherapy regimens, such as COIN in the United Kingdom, and preliminary preclinical studies suggesting negative interactions of the same agent with cetuximab, one of the big questions in the last few years has been which drug or drugs can or cannot be used in combination with cetuximab. We performed a meta-analysis^[13] testing the interaction, the appropriate statistical method for this kind of comparison, between clinical research outcomes and the use of cetuximab with oxaliplatin, irinotecan, and fluoropyrimidines in continuous infusion, oral or bolus. Results of our study showed that there was no significant interaction with oxaliplatin and irinotecan but there was a significant interaction with the fluoropyrimidine schemes. Those studies in which patients received cetuximab with a fluoropyrimidine in infusional regimens showed clinical benefit with the monoclonal antibody, while those that used fluoropyrimidines by bolus or oral administration

did not show a significant benefit. Thus, cetuximab should not be used in combination with 5FU bolus regimens or capecitabine, only with infusional regimens such as FOLFOX or FOLFIRI. Results of the CALGB 80405 trial confirm some of these findings, showing that there were no differences in results with the use of FOLFOX or FOLFIRI.

USE OF CETUXIMAB IN PATIENTS WITH RESECTABLE METASTATIC LIVER DISEASE

The EPOC^[14] trial evaluated the addition of cetuximab to chemotherapy in the treatment of patients with liver-only resectable metastatic disease. One-hundred and twenty-eight *KRAS* exon 2 wild-type patients were randomized to chemotherapy alone and 129 to chemotherapy with cetuximab. Progression-free survival was significantly shorter in the chemotherapy plus cetuximab group than in the chemotherapy alone group (14.1 vs. 20.5 months, HR: 1.48, $P=0.030$). These results are in line with those of the PETACC8 and N0147 trials, which did not show any benefit with cetuximab in the adjuvant therapy of patients with resected stage III colon cancer, suggesting that the agent is only beneficial for patients with unresectable metastatic disease.

CONCLUSION

Approximately, 55% of patients with metastatic colorectal cancer have mutations in *KRAS* or *NRAS* and these patients should not be treated with cetuximab or panitumumab as they do not derive benefit - and may in some cases be harmed-with the use of EGFR inhibitors. Two of three studies comparing chemotherapy with cetuximab or panitumumab to bevacizumab in first-line, especially in patients without RAS mutations in extended testing, suggested a consistent benefit in relation to overall survival, but not in progression-free survival, but the third study did not show any differences in patients without *KRAS* exon 2 mutations. For now, patients with wild type RAS in extended testing can receive treatment with chemotherapy-containing infusional fluorouracil and either oxaliplatin or irinotecan - with bevacizumab, cetuximab or panitumumab. We eagerly await the results of extended RAS testing for the CALGB 80405 study to help clarify if EGFR inhibitors are superior to bevacizumab when combined to chemotherapy in the first line treatment of wild type patients or not. Cetuximab does not seem to be of benefit in the treatment of patients with resectable metastatic disease.

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How to cite this article: Junior Gd. Controversies in colorectal cancer: First line treatment with epidermal growth factor inhibitors and RAS in 2014. *Indian J Med Paediatr Oncol* 2014;35:140-2.
Source of Support: Nil. **Conflict of Interest:** None declared.