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EDITORIAL

Targeted therapy in first line treatment of RAS wild type colorectal cancer

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Abstract

The debate on the optimal drug combination for treating chemotherapy-naïve patients with metastatic colorectal cancer has recently become particularly heated. The present editorial will review recent data on this topic. The FIRE-3 and PEAK trials have shown a 7.5 to 12 mo survival advantage with the use anti-epidermal growth factor receptor (anti-EGFR) antibodies. The CALGB 80405 has shown no difference between anti-EGFR and anti-vascular endothelial growth factor agents. All three trials have consistently shown a significant increase in objective response rate. These data suggest that there is a subset of metastatic colorectal cancer patients, rigorously selected by molecular profiling, who particularly benefit from an anti-EGFR-based regimen in the first-line setting.

Key words: Colorectal cancer; Bevacizumab; Cetuximab; Panitumumab; RAS

Core tip: Three new randomized head-to-head trials have explored the use of anti-epidermal growth factor receptor and anti-vascular endothelial growth factor targeted agents in chemotherapy-naïve metastatic colorectal cancer patients not carrying activating mutations of RAS proteins.

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HEAD TO HEAD ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR AND ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR AGENTS

The debate on the optimal drug combination for treating chemotherapy-naïve patients with metastatic colorectal cancer (mCRC) has recently become particularly heated[1]. New randomized head-to-head trials have shown a possible survival advantage with the preferential choice of targeted anti-epidermal growth factor receptor (anti-EGFR) over anti-vascular endothelial growth factor (anti-VEGF) agents in

patients not carrying activating mutations of the RAS proteins. However, no "midterm" superiority of either regimen as for progression free survival (PFS) was demonstrated[2-4].

In 2013, at the American Society of Clinical Oncology (ASCO) annual meeting, data from the FIRE-3 trial were first presented by Heinemann *et al*[5]. FIRE-3 (AIO KRK-0306 study) is a randomized phase III study aiming to compare the efficacy of fluorouracil, leucovorin, and irinotecan (FOLFIRI) plus cetuximab with FOLFIRI plus bevacizumab in 592 (nearly 300 patients per arm) KRAS-wild type mCRC patients not pretreated for their metastatic disease. According to presented data, the primary endpoint of objective radiologic response rate (ORR) in the intention to treat (ITT) population was not met, with response rate of about 60% in both arms. Median PFS was also almost identical (about 10 mo). A significant overall survival (OS) advantage, however, was observed for patients treated with first-line FOLFIRI + cetuximab, with an increase of almost 4 mo in median OS (28.8 mo *vs* 25.0 mo, HR = 0.77; *P* = 0.0164). This benefit was even more pronounced according to data presented a few months later, at the end of 2013, at the European Cancer Congress, where results from a sub-analysis excluding patients with other activating mutations in the RAS family genes (all-RAS wild type population) were made available. A 7.5 mo increase in median OS was documented in this subpopulation that is 33.1 mo with FOLFIRI plus cetuximab *vs* 25.6 mo with FOLFIRI plus bevacizumab, HR = 0.70; *P* = 0.011[6]. The study has finally been published in full on Lancet Oncology in September 2014.

FIRE-3 results have been replicated in a smaller phase II randomized trial using another anti-EGFR monoclonal antibody, panitumumab[7]. In the PEAK trial panitumumab plus modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) or bevacizumab plus mFOLFOX6 were administered to 278 patients with previously untreated wild-type KRAS exon 2 (codons 12 and 13) tumors. An extended all-RAS analysis (including exons 2, 3, and 4 of KRAS and NRAS) was pre-planned. In spite of similar PFS (HR = 0.87; *P* = 0.353), a significant OS advantage was noted in favour of FOLFOX + panitumumab, which reached a 12 mo survival gain in the all-RAS wild type population (median OS: 41.3 mo *vs* 28.9 mo, *P* = 0.058). The PEAK study has been published in full on Journal of Clinical Oncology in July 2014.

After the presentation of FIRE-3 and PEAK studies that have consistently showed an advantage in choosing an EGFR inhibitor as first-line therapy of wild type mCRC patients, in 2014 the scientific community has been waiting for a third US-based phase Ⅲ trial that compared physician choice chemotherapy (either FOLFOX or FOLFIRI) plus either cetuximab or bevacizumab in the same patient setting: the CALGB 80405 study. Results of CALGB 80405 have been presented at the ASCO annual meeting for the KRAS population and at the European society of medical oncology (ESMO) annual meeting for the all-RAS wild-type population[8].

The CALGB 80405 enrolled > 1100 KRAS wild type patients and, among them, 526 all-RAS wild type patients were assessed for study endpoint in a separate sub-analysis. This study failed to confirm an advantage for cetuximab in OS or PFS. In particular, in the all-RAS wild type population median PFS was about 11 mo for both arms (HR = 1.1; *P* = 0.31) with a median OS of 31-32 mo (HR = 0.9; *P* = 0.40). The CALGB 80405 has not yet published in full in journals.

An intense debate has emerged from these contrasting results. On the whole, it was acknowledged that an exceptionally long survival, not even imaginable a few years ago, was reached with the combined use of monoclonal antibodies plus classic chemotherapy for the treatment of mCRC patients.

For scientists that believe that no meaningful differences exist between EGFR and VEGF inhibitors and between FOLFIRI and FOLFOX in this setting, the choice should be driven by specific toxicity risks and patient-level comorbidities (*e.g.,* risk of perforation and arterial thromboembolic events for bevacizumab, infusion-related reactions and skin alterations for cetuximab, neuropathy for oxaliplatin and diarrhea for irinotecan)[9-12]. More importantly, the choice should follow a deeply informed discussion with the patient about side-effect profiles as well as treatment delivery modalities (*e.g.*, weekly *vs* bi-weekly administration) of the different available schedules and regimens: patient preference should be paramount in the physician decision-making process[13].

However, some researchers overview these data by summing up that in a rigorously molecularly selected patient population (all-RAS wild type) the anti-EGFR agents appear to be superior to anti-VEGF, and a preliminary meta-analysis presented by Gunnar Folprecht at the 2014 ASCO found an overall HR of 0.83, *P* = 0.003, in favour of anti-EGFR agents[14].

A number of biological and methodological explanations have been put forth to illustrate the discrepancy between FIRE-3/PEAK *vs* CALGB 80405 trials: (1) chemotherapy backbones were heterogeneous across the studies, and in particular in the CALGB trial where it was of physician choice. Two third of CALGB patients received the oxaliplatin partner which is thought to be an inferior companion for cetuximab[15]; (2) patient selection laboratory techniques were different across the studies, and this might partly account for discrepant results[16]; (3) even in the presence of similar performances as first-line treatment (similar PFS), responders with anti-EGFR agents might be different from responders with anti-VEGF agents, in that tumor shrinkage might be deeper with cetuximab/panitumumab than with bevacizumab and this would translated in better OS even with no difference in PFS[17]; and (4) a biologically-based difference in effectiveness there might exist depending

on which sequence of the two types of monoclonal antibody is used. It is plausible that many patients who receive EGFR inhibitors in first-line would receive an anti-VEGF agent as second-line and viceversa. There are data that demonstrate a possible reduced activity of anti-EGFR compounds were given after progression on bevacizumab[18,19].

CONCLUSION

In conclusion, even though not conclusive, we believe that these results suggest that there is a subset of mCRC patients who would particularly benefit from an anti-EGFR-based regimen in the first-line setting.

The selection should be primarily based on molecular profile, by excluding patients with activating RAS protein mutations (all RAS wild type population). However, also clinical criteria should be taken into consideration. The trials have consistently shown a significant increase in objective response rate for RAS wild type mCRC patients. In the FIRE-3, after no difference was initially detected in the ITT population, ORR was proven to be significantly higher with cetuximab in the population assessable for response (bevacizumab *vs* cetuximab: 56% *vs* 72%, $P = 0.003$). Similar results were observed in CALGB 80405 trial (ORR = 54% *vs* 67%, $P < 0.01$, respectively). An anti-EGFR agent should be therefore the standard of care in the case an increased chance of tumor shrinkage would be desirable, such as symptomatic patients or patients inoperable upfront but potentially resectable after a so-called conversion therapy.

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