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SYSTEMIC THERAPIES IN COLORECTAL CANCER (SM KAZMI, SECTION EDITOR)

Should Anti-EGFR Agents Be Used in Right-Sided RAS Wild-type Advanced Colorectal Cancer?

Lars Triest[1] · C. Debeuckelaere[1] · T. Vandamme[1] · B. Van Den Heuvel[1] · J. Van Den Brande[1] · K. Papadimitriou[1] · M. Rasschaert[1] · H. Prenen[1] · M. Peeters[1]

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Abstract

Purpose of Review Colorectal cancer is the third most common cancer worldwide with a high mortality rate at the advanced stages of the disease. Treatment options are dependent on the stage of the disease, patients' performance status, and the specific molecular makeup of the tumor. Adding an anti-epidermal growth factor receptor monoclonal antibody (anti-EGFR mAb) to conventional chemotherapy in molecularly selected patients (i.e., RAS wild-type) leads to a survival advantage. We aim to review the latest evidence on the influence of primary tumor location (PTL) on treatment response to chemotherapy combined with an anti-EGFR in patients with metastatic colorectal cancer (mCRC).

Recent Findings Colon cancer arising on the left side versus the right side of the colon portrays different outcomes, emerging PTL as an important characteristic in understanding the outcomes for patients with colorectal cancer. Patients with right-sided tumors have a worse prognosis than those with left-sided tumors. Primary tumor location may also be predictive of treatment benefit from targeted therapy with an anti-EGFR or anti-VEGF in the treatment of RAS wild-type mCRC. Although no benefit in overall survival (OS) has been demonstrated, available data up to now can endorse the use of an anti-EGFR in right-sided RAS wild-type advanced colorectal cancer if the therapy goal is tumor shrinkage (given the higher objective response rate). However, the majority of data on PTL has been obtained through retrospective analysis of clinical trials where PTL was neither part of the stratification nor pre-planned subgroup analysis, rendering it susceptible to recall bias.

Summary There is a great necessity to improve our understanding of the molecular and histological variability in left versus right-sided colon cancer and its impact on future targeted therapy.

Keywords Metastatic colorectal cancer (mCRC) · Targeted therapies · EGFR (epidermal growth factor receptor) · Anti-EGFR mAb · Panitumumab · Cetuximab · Bevacizumab · Chemotherapy · Left-sided · Right-sided · Sidedness · RAS wild-type · Primary tumor location (PTL) · Prognostic · Predictive · First-line · Overall survival (OS) · Progression-free survival (PFS) · Objective response rate (ORR) · BRAF mutation · Microsatellite instability (MSI)

Introduction

Colorectal cancer is the third leading cause of cancer and cancer-related death, with more than 1.3 million new diagnoses and 649,000 deaths in 2012 [1, 2].

The last two decades, the clinical outcome for patients with metastatic colorectal cancer has significantly improved due to new systemic therapies, ablative techniques, and increasing referral to surgery [3].

Colorectal cancer, originating from the epithelial tissue of the colon, may develop either on the left side or the right side from the colon. Depending on this location, CRCs behave differently in terms of therapy response, disease progression, and overall survival.

Numerous studies have shown that patients with left-sided CRC have a significantly better prognosis (overall survival (OS), progression-free survival (PFS), and disease-free survival (DFS)) than tumors originating on the right side of the colon in all CRC stages [4], although other studies found that

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✉ Lars Triest
lars.triest@uza.be

[1] Departement of Oncology, Antwerp University Hospital, Wilrijkstraat 10, 2650 Edegem, Belgium

disease laterality was not associated with long-term OS or cancer-specific survival (CSS) in early-stage resected colon cancer [5].

Differing outcomes between left and right-sided colorectal cancer may be explained by difference in embryological origin, physiological function, microbiome composition, and chromosomal and molecular characteristics between the two entities [6•].

Right-sided CRC patients are more frequent female and elderly with high microsatellite instability, RAS and BRAF mutations, and CpG island methylator phenotype (CIMP)-high and these tumors generally have a mucinous histology. Left-sided CRC patients are more frequent male and present predominantly chromosomal instability pathway-related mutations, such as KRAS, APC, PIK3CA, and p53 mutations, and these tumors demonstrate more polypoid-like morphology [7].

Epidermal growth factor receptor plays an important role in colon cancer oncogenesis and is regarded as an important target for cancer therapy.

Anti-EGFR monoclonal antibodies, panitumumab and cetuximab, targeting the extracellular domain of the EGFR, thereby blocking the RAS/RAF/MAPK pathway activation, added to chemotherapy improve outcome for metastatic colorectal patients. KRAS and NRAS, both oncogenes downstream of EGFR and essential components of the EGFR signaling cascade, have an established role as predictive biomarkers of benefit from anti-EGFR mAb treatment. Activating mutations in exons 2, 3, and 4 of KRAS and NRAS oncogenes (representing approximately 50% of mCRC tumors) are negative predictive biomarkers for anti-EGFR mAb treatment, thus rendering EGFR mAbs ineffective in this specific population [8].

Therapeutic regimens and treatment approaches may not be similarly effective across left- and right-sided colorectal cancer, making tumor sidedness an interesting parameter for clinical use.

Primary tumor location may not only be prognostic but may also have a predictive role in RAS wild-type mCRC.

Hereby, we review the latest data on predictive effects of primary tumor location on OS, PFS and objective response rate (ORR) and its prognostic value in patients with RAS wild-type mCRC.

Primary Tumor Location Predictive for Treatment Response?

Venook et al. published in 2016 a retrospective subgroup analysis from the CALGB/SWOG 80405 trial [4], presenting the results of 1137 treatment-naïve patients with KRAS wild-type mCRC randomized to treatment with first-line mFOLFOX or FOLFIRI with either bevacizumab or cetuximab. Patients with right-sided tumors treated with cetuximab had a median OS of 16.7 months compared with 36 months in patients with left-sided tumors (HR = 1.98 [95% CI 1.60–2.46]; $p < 0.001$). Right-sided tumors treated with bevacizumab had a median OS of 24.2 months compared with 31.4 months for those with left-sided tumors (HR = 1.32 [95% CI 1.05–1.65]). These data suggested that treatment with cetuximab benefited more patients with left-sided tumors and bevacizumab improved outcomes for patients with right-sided tumors.

A retrospective analysis of the FIRE-3 and CRYSTAL trials by Tejpar et al. found similar results, confirming that patients with left-sided tumors derived more benefit from first-line FOLFIRI treatment with cetuximab (versus FOLFIRI or FOLFIRI plus bevacizumab, respectively) compared with right-sided CRC. [9]

A reanalysis of the NCIC CO.17 trial showed a significant benefit of adding cetuximab to best supportive care in patients with chemotherapy-refractory KRAS wild-type disease in the distal colon. Little benefit was observed among patients with right-sided colon cancer [10].

The study by Wang et al. [11] also revealed that the addition of cetuximab to first-line or second-line chemotherapy significantly improved ORR, PFS, and OS in left-sided mCRC. These improvements were not seen in patients with right-sided tumors, treated with cetuximab.

A possible association between tumor sidedness and treatment efficacy of panitumumab in first-line mCRC patients with RAS wild-type primary tumors was investigated by Boeckx and colleagues [12]. In this paper, data from two panitumumab trials were retrospectively analyzed, including the PRIME trial comparing panitumumab plus FOLFOX versus FOLFOX alone and the PEAK trial comparing panitumumab plus FOLFOX versus bevacizumab plus FOLFOX. The results confirmed that in RAS wild-type patients, right-sided primary tumors were associated with worse prognosis than left-sided tumors, regardless of first-line treatment received. RAS wild-type patients with left-sided tumors derived greater benefit from panitumumab-containing treatment than chemotherapy alone or combined with bevacizumab. Due to the relatively low number of patients, no final conclusion could be drawn for RAS wild-type patients with right-sided mCRC but higher response rates (RR) were seen in these patient groups if they were receiving panitumumab compared with comparator treatments.

To date, the largest data set on the predictive effect of tumor sidedness was presented in the ESMO analysis by Arnold and colleagues [13]. In this retrospective analysis, which pooled data from six randomized trials (CRYSTAL, FIRE-3, CALGB 80405, PRIME, PEAK, and 20050181), chemotherapy plus EGFR antibody (experimental arm) was compared with chemotherapy or chemotherapy plus bevacizumab (control arms). A significant predictive benefit was demonstrated for

chemotherapy plus EGFR antibody therapy in patients with left-sided tumors (HRs = 0.75 [0.67–0.84] and 0.78 [0.70–0.87] for OS and PFS, respectively). There was a nonsignificant trend towards benefit for right-sided tumor patients treated with chemotherapy with or without bevacizumab (HRs = 1.12 [0.87–1.45] and 1.12 [0.87–1.44] for OS and PFS, respectively). For ORR, there was a trend (p value = 0.07) towards a greater benefit for chemotherapy plus EGFR antibody therapy in the patients with left-sided colon cancer (OR = 2.12 [1.77–2.55]) compared with those with right-sided tumors (OR = 1.47 [0.94–2.29]).

Analysis from only the FIRE-3 trial [14] data on patients with right-sided RAS wild-type tumors suggested that these patients may benefit more from chemotherapy plus bevacizumab compared with the addition of cetuximab in terms of OS (HR = 1.31, $p = 0.27$) and PFS (HR = 1.44, $p = 0.11$), but not for ORR.

The predictive relevance of primary tumor location in later-line treatment was examined in different studies.

An analysis of the PICCOLO trial [15] revealed that the addition of panitumumab to irinotecan as second-line or third-line therapy equally benefitted left-sided and right-sided tumors regarding the PFS, rendering the question if better objective predictive biomarkers are needed instead of primary tumor location as predictive marker for treatment selection in this population of metastatic colon cancer patients.

However, this finding is likely attributable to patient selection in later-line studies (patients with initially poor prognosis are naturally excluded).

Other analyses, however, concluded that adding cetuximab to second- or third-line chemotherapy generally benefited patients with left-sided colon cancer, regarding the OS and PFS [11, 16].

Primary Tumor Location Prognostic for Survival?

The meta-analysis by Holch and collaborators [17], combining 13 first-line randomized controlled trials and one prospective pharmacogenetic study investigated the prognostic relevance of PTL in patients with metastatic colorectal cancer. Right-sided mCRC was associated with a significantly worse prognosis compared with left-sided tumors (HR for OS = 1.56 [1.43–1.70]; $p < 0.0001$). Overall survival in patients with right-sided colon cancer was generally poor and remained below 20 months in several studies investigating chemotherapy with and without targeted therapy.

The previous mentioned retrospective ESMO analysis [13] including 2159 patients (515 with right-sided and 1644 with left-sided tumors) with unresectable RAS wild-type mCRC in six randomized trials showed a significantly worse prognosis (OS, PFS, ORR) for patients with right-sided colon cancer in both the pooled control and experimental arms.

The largest dataset available to date in order to answer the question if PTL is prognostic from survival outcomes from Petrelli et al. [18••] In this meta-analysis of 66 studies, including more than 1.4 million patients with a median follow-up of 65 months, a significant prognostic impact of tumor site on OS was found with a 20% reduced risk of death for cancers arising on the left side (HR = 0.82 [0.79–0.84]; $p < 0.001$). This finding was independent of stage, race, adjuvant therapy, year of study, number of participants, and quality of included studies.

However, primary tumor location may not be prognostic in patients with localized disease [19]. The population-based retrospective cohort study by Karim et al. [5] on cancer-specific survival and overall survival among 6391 patients with localized (stages I–III) colon cancer in the Ontario Cancer Registry revealed no difference in OS (HR 1; 95% CI [0.92–1.08]) or CSS (HR 1; 95% CI [0.91–1.10]). Furthermore, in contrast with the observation that tumor sidedness is associated with response to anti-EGFR therapy in the metastatic setting; in the localized setting, there was no association with responsiveness to adjuvant chemotherapy.

Discussion

Metastatic colorectal cancer is a genetically heterogeneous disease, where tumors arising from different sides of the colon (left versus right) have different clinical outcomes.

Primary tumor location plays a significant role in prognostication for mCRC, with left-sided tumors having improved outcomes. All the described trials above showed better treatment outcomes, including a greater OS, PFS, and ORR in patients with left-sided tumors compared with those with right-sided tumors [18••].

Potential explanations could be that tumor sidedness correlates with embryologic origin, biologic, molecular, and immunologic differences between right- and left-sided colorectal cancer translating into significant clinical differences, with relevant implications in metastatic patients' management [20].

According to the ESMO consensus guidelines [3], tumor characteristics, patient characteristics, treatment characteristics, and treatment goals (disease control versus tumor volume reduction) are for the moment the main drivers for treatment decision-making in first-line therapy for mCRC.

Anti-EGFR mAbs have been proven to add a survival advantage to chemotherapy in the setting of patients with extended RAS wild-type metastatic colorectal cancers [21, 22].

The recent interest in primary sidedness as a potential driver of treatment choices was raised by post hoc analyses of head-to-head trials of first-line chemotherapy doublets plus either bevacizumab or an anti-EGFR.

Regarding the predictive value of primary tumor location on the treatment benefit from the addition of an anti-EGFR agent, the data showed the greatest benefit in those patients who had left-sided primary tumors, as seen in the first-line PRIME and CRYSTAL trials where patients received chemotherapy plus an EGFR antibody versus chemotherapy alone.

Data on OS confirmed that patients with left-sided tumors receiving chemotherapy plus an anti-EGFR had superior results, compared with right-sided colorectal cancer patients receiving the same therapy. Concerning response and PFS, most data demonstrated a better outcome for patients with left-sided RAS wild-type tumors treated with chemotherapy plus an anti-EGFR. Limited benefit was noticed if EGFR antibody treatment was added to chemotherapy in the patients with a primary right-sided tumor except for data from the CRYSTAL trial in terms of ORR but not for OS or PFS.

Thus, conventional chemotherapy plus an anti-EGFR has mostly higher treatment effects in left-sided versus right-sided tumors. This could possibly be explained by previous observations that an EGFR inhibitor-sensitive phenotype appears to be more prevalent in left-sided tumors, whereas right-sided colon cancers appear to be more heterogeneous and only a subset of them are sensitive to anti-EGFR agents [23]. Translational research showed that specific genetic features and expression profiles according to primary tumor location were present, suggesting that different pathways to tumorigenesis in right- and left-sided advanced colorectal cancer may underlie clinical differences [24••, 25]. The efficacy of bevacizumab can be linked to a lower systemic inflammatory status and a higher expression of pro-angiogenic factors, both of which appear to characterize patients with right-sided tumors [26].

All this previous data suggests that primary tumor location has an impact on therapy responsiveness to most therapies in mCRC (on bevacizumab, cetuximab, panitumumab, and even conventional chemotherapy). But, results from the all the above described studies should be interpreted with care. Firstly, given the fact that they were derived retrospectively from prospective randomized controlled trials renders them subject to inherent biases. Secondly, retrospective analysis happened on data drawn from trials which included mCRC patients initially independently of RAS status and can be associated with selection biases and thus hypothesis generating. Thirdly, the interstudy heterogeneity with imbalances in certain baseline characteristics between treatment arms and the absence of upfront stratification according to RAS mutation status and primary tumor location, and the absence of data on other mutational analysis (e.g., BRAF mutation) makes it difficult to use this data in order to support a change in actual clinical practice. Fourthly, there are analytical limitations imposed by relatively small sample sizes in some patients' subgroups, resulting in insufficient power, thus requiring further validation in a larger, external cohort.

Before data can be really used to support a change in clinical practice, additional research and future prospective trials are needed, taking mutational and gene expression signatures into account, next to the PTL, further refining our understanding of the molecular subtypes of mCRC in order to improve outcomes and identify patients who may benefit from a certain (targeted) therapy. To date, mutational profiling is limited and does not capture all known mutations in colorectal cancer. For example, additional research can possibly uncover the subset of patients with RAS wild-type right-sided mCRC who may derive benefit from anti-EGFR therapy.

A more refined use of biomarkers can advance clinical trial design, drug development, and patient outcomes.

A plethora of tools will become available to clinicians in the near future, and we must now learn how to use these tools in order to improve the outcomes for patients with metastatic colorectal cancer.

Conclusions

In clinical practice, based on our current knowledge, patients with RAS wild-type left-sided tumors benefit most from anti-EGFR therapy combined with chemotherapy in the first-line treatment of metastatic colorectal cancer, especially if tumor response is wanted.

For patients with RAS wild-type right-sided tumors, associated with a worse prognosis, therapy with chemotherapy alone or probably chemotherapy plus bevacizumab may be preferred if the treatment goal is prolongation of survival end-points. If the treatment goal is tumor shrinkage, EGFR antibodies remain an option in these right-sided mCRC patients, given the higher ORR.

Further research on biomarkers is necessary in order to identify a potential subgroup of patients with right-sided mCRC who might benefit more from anti-EGFR.

Given the fact that no data is available on a specific treatment sequence, there is no reason to avoid EGFR antibody treatment in later lines in cases of disease progression, treatment intolerance, or chemorefractory setting independent of primary tumor location.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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