Editorial

Targeted therapies in colorectal cancer: the dos, don'ts, and future directions

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Submitted Jun 03, 2013. Accepted for publication Jun 25, 2013.
doi: 10.3978/j.issn.2078-6891.2013.040
Scan to your mobile device or view this article at: http://www.thejgo.org/article/view/1281/html

2013 marks 10 years from the approval of the first targeted agent, bevacizumab, in colorectal cancer. Since the FDA approval of bevacizumab (Avastin®), we have seen the sequential approval of cetuximab (Erbitux®), panitumumab (Vectibix®), ziv-aflibercept (Zaltrap®), and regorafenib (Stivarga®). The approval of these angiogenesis and epidermal growth factor receptor (EGFR) targeting agents has been based on benefits in overall survival in metastatic colorectal cancer patients in the first, second, and chemotherapy-refractory settings. In this issue, we review the efficacy data behind the FDA approved targeted agents in colorectal cancer (1,2), their confirmed and suspected mechanisms of resistance (3,4), potential causes of failure in the adjuvant and neoadjuvant settings (5,6), special considerations in the surgical settings (7), and management of associated dermatological toxicities (8).

Progress in angiogenesis targeting in the metastatic setting

As reviewed by Smaglo and Hwang (1), the integration of bevacizumab in the first line treatment of metastatic colorectal cancer has been associated with improved overall survival based on the pivotal randomized phase III clinical trial of irinotecan, bolus 5-FU, and leucovorin (IFL) with or without bevacizumab (9). However, as acknowledged by the authors, there is no other first line phase III randomized clinical trials that indicate an improvement in overall survival of patients with metastatic colorectal cancer when bevacizumab is integrated with other chemotherapy backbones. While the authors indicate some supporting evidence in OS reported on the BICC-C study, one has to acknowledge the limitations of this study as far as design and power (10). The BICC-C study was designed to compare the efficacy of an infusional 5-FU plus irinotecan regimen (FOLFIRI) to IFL, allowing the integration of bevacizumab on both arms in the latter aspects of the study to allow for standard of care changes in the USA. Of concern, a small Greek randomized phase III clinical trial failed to show any improvement in response rate (RR), progression free survival (PFS), and overall survival (OS) when bevacizumab was added to FOLFIRI (11). In addition, the N016966 study randomized untreated metastatic colorectal cancer patients in a 2×2 factorial design to infusional 5-FU plus oxaliplatin (FOLFOX) or capecitabine plus oxaliplatin (XELOX) in combination with bevacizumab or placebo (12). While this study showed a modest improvement in PFS, it failed to show an improvement in OS as a secondary endpoint. Should we integrate bevacizumab with non-IFL chemotherapy backbones in the first-line treatment of metastatic colorectal cancer? While no level-1 evidence exists for an impact of the addition of bevacizumab on OS when added to non-IFL backbones such as FOLFOX, FOLFIRI, XELOX, 5-FU, and capecitabine, there is ample evidence for a robust improvement in PFS with the integration of bevacizumab in the first line therapies when combined with these backbones. These improvements become particularly clinically significant when bevacizumab is added to fluoropyrimidine monotherapy. In addition to the studies reviewed by Smaglo *et al.*, one should place particular attention to the MAX and AVEX phase III clinical trials. On the AVEX first-line phase III clinical trial, elderly patients with metastatic colorectal cancer were randomized to receive capecitabine with or without bevacizumab (13). The RR, PFS, and OS were (19.3% *vs.* 10%; P=0.04), (9.1 *vs.* 5.1 months; P<0.001), and (20.7 *vs.* 16.8 months; P=0.18), respectively, in favor of the bevacizumab arm. The MAX study randomized patients with untreated metastatic colorectal cancer to capecitabine or capecitabine plus bevacizumab or capecitabine plus mitomycin C and bevacizumab (14). The addition of bevacizumab to capecitabine improved the median PFS from 5.7 to 8.5 months for capecitabine plus bevacizumab (HR

for PFS =0.63; P<0.001). Neither the AVEX nor the MAX trials confirmed a statistically significant improvement in OS; however, both studies were not powered for this secondary endpoint.

The above studies strongly support a benefit from adding bevacizumab in the first line treatment of metastatic colorectal cancer in terms of PFS when added to a fluoropyrimidine-based therapy. The delay in progression appears to be more robust when added to fluoropyrimidine-based therapy or less effective combination therapies (IFL) in comparison to the commonly used FOLFOX or XELOX combinations. These data support the integration of bevacizumab in the front line treatment of metastatic colorectal cancer.

The improvement in OS from the targeting of vascular endothelial factor (VEGF) in the second-line treatment of metastatic colorectal cancer is more definitively established in combination with contemporary chemotherapy. Smaglo and Hwang review the OS benefit data from both TML and VELOUR studies, establishing a role for the continuation of bevacizumab with second-line oxaliplatin or irinotecan-based chemotherapy and a role for the addition of ziv-aflibercept to second-line FOLFIRI chemotherapy (1). However, the clinical benefits were modest with less than 2 months improvement in OS (15,16).

Last, regorafenib, a small molecule tyrosine kinase inhibitor targeting VEGF receptors and Tie-2 amongst other tyrosine kinases, in patients who failed all standard agents (including bevacizumab and anti-EGFR agents in *KRAS* wild type) has been recently approved based on a statistically significant improvement in OS of 6 weeks when compared to placebo (17).

The clinical benefits associated with bevacizumab, ziv-aflibercept, and regorafenib in metastatic colorectal cancer in terms of OS have been modest and are associated with significant cost to society and patients. These agents should only be used within their label indications and based on current supporting evidence, as reviewed by Smaglo and Hwang (1). Moving forward, we can only foresee a substantial clinical benefit from these agents as we better understand their true mechanisms of activity and associated mechanisms of resistance. The mechanisms of resistance to VEGF targeting can be complex. Clarke and Hurwitz provide a comprehensive review of VEGF axis related resistance, the role non-VEGF modulators of angiogenesis in resistance, and the significance of the stroma in the response to angiogenesis targeting (3). The Clark and Hurwitz article gives further insight as to the potential role of biomarkers in identifying patients least likely to benefit from angiogenesis targeting (3). Unfortunately, none of the current putative biomarkers is supported by ample clinical evidence and significant progress is still needed in this area.

Anti-EGFR therapy: work in progress on the appropriate patient selection

Since the approval of cetuximab and panitumumab in the metastatic colorectal cancer in 2004 and 2006 respectively, significant progress has been made in defining mechanisms of resistance to anti-EGFR therapy and in improving patient selection. In this issue, Harlaldsdottir and Bekaii-Saab provide a comprehensive review on the role of anti-EGFR therapies in colorectal cancer (2). Both monoclonal antibodies, when administered as monotherapy, have been associated with favorable outcomes in patients with chemotherapy-refractory *KRAS* wild type colorectal cancer (18,19). Indeed, the OS of patients with chemoresistant disease and *KRAS* wild type disease is doubled when compared to best supportive care in patients treated with cetuximab monotherapy. Similar advantages in OS are expected from the integration of panitumumab monotherapy (10). Panitumumab monotherapy has been noted to be equivalent to cetuximab monotherapy in a recent phase III clinical trial (ASPECCT) in patients with *KRAS* wild-type patients (http://www.amgen.com/media/media_pr_detail.jsp?releaseID=1816635). The estimated hazard ratio on the ASPECCT trial was 0.966 (95% CI: 0.839-1.113) favoring the panitumumab arm.

Both agents have been associated with an improvement in OS in the first line treatment of metastatic colorectal cancer. In an updated analysis of the PRIME study investigating FOLFOX + panitumumab *vs.* FOLFOX chemotherapy, panitumumab-treated patients with exon 2 *KRAS* wildtype metastatic colorectal cancer experienced a statistically significant 4.4-months improvement in OS (P=0.027) (20). Similarly, the addition of cetuximab to FOLFIRI has been associated with a statistically significant 3.5-months improvement in OS in the first line setting when limiting the analysis to patients with *KRAS* wild type metastatic colorectal cancer (21). Improvements in PFS and RR have also been documented from the integration of cetuximab and panitumumab in the second line treatment of KRAS wild type (panitumumab) metastatic colorectal cancer (22-24). However, an improvement in OS from anti-EGFR therapy integration in the second-line therapy has yet to be demonstrated. The lack of an OS benefit could be attributed to cross-over to anti-EGFR therapy in the salvage setting. At this time, the integration of anti-EGFR therapy (cetuximab or panitumumab) can be considered in combination with chemotherapy in the first (panitumumab + FOLFOX, cetuximab + FOLFIRI), second-line (panitumumab + FOLFIRI, cetuximab + irinotecan), or subsequent chemo-resistant settings (panitumumab or cetuximab monotherapy, or cetuximab plus irinotecan). Given the ASPECCT data and the similar improvements

with these agents in the first and later settings, it is not unreasonable to use cetuximab or panitumumab interchangeably. In contrast to anti-angiogenesis therapies, there is no supportive data on the continuation of anti-EGFR therapy beyond progression and therefore a re-challenge with these agents is not considered a standard approach at this time.

Despite the improvements in OS in the first line treatment of *KRAS* wild type patients, there has been limited integration of these agents in the first-line treatment in the US. This is in part related to the associated dermatological toxicities with these agents, especially when used for protracted periods. A comprehensive review on the dermatological toxicities and their management is presented by Urban and Anadakt in this issue (8).

A better understanding of the mechanisms of resistance to anti-EGFR therapy may help better select for appropriate patients or lead to novel approaches to complement EGFR targeting (25). In this issue, Shaib *et al.* detail some of the potential mechanisms of resistance to anti-EGFR therapy (4). In addition to the markers detailed in the Shaib article, there is an increased interest in non-exon 2 *RAS* mutations as markers of resistance to anti-EGFR therapy. Indeed, the exclusion of *NRAS* mutations and non-exon 2 *KRAS* mutations on the PRIME study has been recently associated with further improvement in OS in the panitumumab arm compared to chemotherapy alone (26 *vs.* 20.2 months, P=0.043) (26). The exclusion of *NRAS* and non-exon 2 *KRAS* mutations (in addition to exon 2 mutations) has been similarly associated improvements in PFS and OS on the first line PEAK study (19). A trend to a worsened outcome was noted with the addition of panitumumab on both the PRIME and PEAK study in *NRAS* and non-exon 2 *KRAS* mutations, suggesting that this group of patients does not benefit—and may be potentially harmed—from anti-EGFR therapy (26,27). Of note, the exclusion of *NRAS* and non-exon 2 *KRAS* mutations results in the additional exclusion of approximately 15% of exon 2 *KRAS* wild-type patients, therefore enriching further for good responders to anti-EGFR therapy. If confirmed across other anti-EGFR studies, these findings may lead to an increased integration of anti-EGFR therapies in the front-line treatment of a molecularly-appropriate patient population.

Targeted therapies in the adjuvant and neoadjuvant treatment of targeted therapies

Contrary to the benefits of targeted therapies in the metastatic colorectal cancer, no benefits have yet to be associated with anti-angiogenesis therapy or anti-EGFR therapy in the adjuvant treatment or neoadjuvant treatment of primary colorectal cancer. Nelson and Benson review the data for bevacizumab and cetuximab in the adjuvant treatment of stage III colon cancer (5). As noted by the authors, the lack of benefit from two phase III clinical trials investigating bevacizumab and two phase III clinical trials investigating cetuximab close the case on the integration of these biological therapies in earlier stages of colorectal cancer. A comprehensive review of by Glynn-Jones *et al.* on the neoadjuvant integration of bevacizumab or anti-EGFR therapies on rectal cancer leads to the same conclusion (6). More recently, the EPOC study reported on the combination chemotherapy (FOLFOX or FOLFIRI) with or without cetuximab as a neoadjuvant treatment in patients with resectable metastatic liver metastases (28). The study was closed as per the recommendations of the Independent Data Monitoring Committee after noting a harmful effect of cetuximab on progression free survival. These results suggest a lack of benefit from the anti-EGFR therapy in resectable *KRAS* wild type tumors, whether localized or metastatic. The evidence of discordance between the benefits from anti-EGFR and anti-VEGF therapies in the metastatic setting and resectable settings are poorly understood at this point and may denote a complex interaction between these agents, microscopic/macroscopic disease, and the stroma. The identification of additional potential markers of resistance to anti-EGFR therapy (*NRAS*, *HRAS*, non-exon 2 *RAS)* will mandate the re-analysis of the anti-EGFR adjuvant and neo-adjuvant trials in hopes of identifying a molecular subgroup of patients that may benefit from these agents.

Surgical considerations

The reader is referred to the review by Luu *et al.* on the integration of targeted therapies in the neoadjuvant treatment of surgical cancers (7). As noted by Luu *et al.*, several studies have suggested an increased resectability of hepatic metastasis, particularly with anti-EGFR therapies. Therefore, strategies that improve response rates, including the integration of anti-EGFR therapies should be strongly considered in the unresectable, potentially resectable metastatic colorectal cancer population. However, one should not integrate targeted therapies routinely in the resectable metastatic patient population due to the lack of evidence of benefit and in light of the potential harm reported on the EPOC study.

VEGF or EGFR targeting in the first line treatment of metastatic colorectal cancer

There is still no clear consensus as to which targeted

therapy approach is optimal in the first line treatment of metastatic colorectal cancer. The CALGB 80405 clinical trial has completed accrual more than 1 year ago and is expected to report its results in the upcoming year. On this study, patients with *KRAS* wild type metastatic colorectal cancer were assigned to FOLFOX or FOLFIRI with further randomization to bevacizumab or cetuximab. Meanwhile, the FIRE-3 study, a randomized phase III clinical trial of FOLFIRI plus bevacizumab or FOLFIRI plus cetuximab in KRAS wild type metastatic colorectal cancer was recently reported at ASCO 2013. The primary endpoint on this study was RR while PFS and OS constituted secondary endpoints. The study failed to show superiority of FOLFIRI plus cetuximab over FOLFIRI plus bevacizumab in the intent to treat population but showed a significant improvement in RR in the response-assessable population. While PFS were superimposable, an OS survival advantage of 3.8 months (28.8 *vs.* 25 months) emerged in favor of the cetuximab arm (29). At this time, it is unclear if the discordance between the OS and PFS results were related to post-progression therapies or due to a favorable impact of anti-EGFR therapy on the depth of response (results awaited). These findings certainly boost the positioning of anti-EGFR therapy in the first line treatment of metastatic colorectal. Further validation on the CALGB 8045 will be eagerly awaited. In addition, further analysis of the FIRE-3 data in light of the all wild type *RAS* data presented on the PEAK and PRIME studies will also be needed.

The dos, don'ts, and future progress

Reported clinical trials over the last decades have clearly established a role for anti-angiogenesis and anti-EGFR targeting in the treatment of metastatic colorectal cancer. These agents should be considered in the context of the data reviewed above and elaborated upon in the accompanying reviewed articles. Do consider the addition of bevacizumab to systemic chemotherapy in the front line treatment of metastatic colorectal cancer. When appropriate, do consider carrying bevacizumab or using ziv-aflibercept (with FOLFIRI) in the second line settings. Do consider the use of regorafenib as a last line of treatment in metastatic colorectal cancer but only in good performance status patients (ECOG 0-1). Be cognizant of the potential toxicities of this agent and its limited clinical efficacy. Do consider cetuximab or panitumumab in the first line treatment (or beyond) of metastatic colorectal cancer, especially when response matters, and only in *KRAS* wild type patients. Do not integrate biological therapy in the adjuvant or neoadjuvant treatment of localized or resectable metastatic colorectal cancer. A positive impact on resectability or recurrence has never been documented in those settings. While the use of bevacizumab as an adjunct to chemotherapy in resectable metastatic colorectal cancer has not been associated with harmful oncological outcomes, support for this strategy is lacking and potential associated toxicities are a reality. The integration of anti-EGFR and bevacizumab in resectable metastatic colorectal liver metastases as a neoadjuvant strategy should be discouraged until further supportive data are generated.

We can only see further progress from continuing the path towards offering the appropriate medicine to the appropriate patients. Considerable strides have occurred in narrowing the anti-EGFR candidate population. If the "all" *RAS* mutant population is excluded, we anticipate that only 45% of patients would be eligible for anti-EGFR therapy. Excluding *BRAF* mutants would identify only a 35% of metastatic colorectal cancer patients with the best potential response to anti-EGFR inhibition. We recognize that the aggregate of these markers requires further retrospective prospective validation across other completed randomized studies; such results would be eagerly awaited. We would hope that similar progress would be made on identifying markers of benefit to anti-angiogenesis therapies. The identification of markers of response and resistance will not only be essential to apply individualized therapies but also to identify novel pathways for drug development in colorectal cancer.

Acknowledgements

Disclosure: The author has served as a consultant for BMS, AMGEN, and ONYX pharmaceuticals and serves on the Speakers Bureau for Genentech and Bayer pharmaceuticals.

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Cite this article as: Fakih M. Targeted therapies in colorectal cancer: the dos, don'ts, and future directions. J Gastrointest Oncol 2013;4(3):239-244. doi: 10.3978/j.issn.2078-6891.2013.040