

Status of targeted therapies in the adjuvant treatment of colon cancer

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Abstract: Colon cancer is the 4th most common malignancy with 80% of patients diagnosed with early stage disease that is potentially curable with surgery and the addition of adjuvant chemotherapy in select Stage II and all Stage III patients. Adjuvant chemotherapy with 5-fluorouracil based regimens has been shown to have overall survival benefit in Stage III disease with some benefit shown in certain sub-populations in Stage II disease. In recent years, targeted therapies directed against vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) have shown improved survival in metastatic colon cancer. However, trials of these agents in the adjuvant setting showed no benefit. Reasons for failure of these agents in trials thus far include differences in the molecular biology of macrometastatic versus micrometastatic disease and the lack of biologic predictive markers to target the appropriate patient populations for these agents.

Key Words: Adjuvant therapy; colon cancer; bevacizumab; cetuximab



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Overview of adjuvant therapy in colon cancer

With roughly 100,000 cases diagnosed yearly, colon cancer is the 4th most frequently diagnosed cancer and the 2nd leading cause of cancer related death in the United States (1). Roughly 80% of cases are Stage I-III thus potentially curable with either surgery alone or combination therapy with surgery and chemotherapy (2). The 5-year overall survival (OS) for patients with Stage III colon cancer is 60%, however this decreases to 5% in patients with metastatic disease, underscoring the importance of adjuvant chemotherapy to abolish micrometastatic disease present at the time of curative surgical excision.

Multiple randomized controlled trials have established the benefit of 5-fluorouracil (5-FU) (3-5) and capecitabine (6) based regimens in the adjuvant setting for high-risk Stage II and Stage III colon cancer. 5-FU based adjuvant therapy results in a 5% OS benefit and 10% OS benefit in Stage II and Stage III patients, respectively, at 8 years (4). Two large, multinational, randomized studies [MOSIAC (7) and NSABP C-07 (8)] showed that adding oxaliplatin to 5-FU/leucovorin improves disease free survival (DFS) for Stage II/III colon cancer with decreases in relative recurrence

risk by 20-23% (7-9). An updated subset analysis of the MOSAIC trial, however, questioned the benefit of the addition of oxaliplatin in low risk stage II patients and the elderly (70-75 years of age) (10). Based on available data, the NCCN guidelines currently recommend adjuvant 5-FU +/- oxaliplatin containing regimens for resected high risk Stage II and all Stage III colon adenocarcinoma (11). According to the NCCN, high risk Stage II disease is defined as tumors with poorly differentiated histology (in absence of microsatellite instability), lymphatic, vascular or perineural invasion, bowel obstruction or bowel perforation, close or positive resection margins, or less than 12 lymph nodes examined.

Many questions exist, however, regarding the absolute benefit of adjuvant chemotherapy. For example, most of the adjuvant trials included both Stage II and Stage III patients. Even when patients were sub-divided by stage at time of analysis, data for sub-stages such as Stage IIIA, IIIB and IIIC are pooled. Conceivably, there are differences in the benefit of adjuvant chemotherapy between patient sub-groups however the trials are not powered to detect these subtleties. Differences in adjuvant benefit likely also exist based on gene expression profiling however, to date,

predictive benefits of therapy for a defined high risk group beyond the NCCN criteria for high risk Stage II and Stage III disease have not been established.

Interestingly, not all chemotherapeutic agents have shown benefit in the adjuvant setting. For example, despite proven benefit in metastatic colon cancer (12), irinotecan has not shown benefit in the adjuvant setting. While signals of activity were seen in one trial, overall there were no statistically significant differences in DFS or OS with the addition of irinotecan to 5-FU/leucovorin in the adjuvant setting (13-15). This finding gave an early indication that the mechanism of chemotherapy action might be different in the setting of macrometastatic versus micrometastatic disease, a theme that has pervaded the testing of biologic agents in adjuvant colon cancer as well.

Biologic agents in colon cancer

Anti-VEGF therapy

Vascular endothelial growth factor (VEGF) regulates angiogenesis both in health and disease, and contributes to angiogenesis in malignancy (16). For this reason, bevacizumab (Avastin[®]), a humanized monoclonal antibody to circulating vascular endothelial growth factor A (VEGF-A) was developed. Preclinical studies have shown multiple mechanisms of action for bevacizumab including inhibition of angiogenesis (17) by pruning of existing vessels and normalization of aberrant vessels which is thought to improve delivery of concurrently administered chemotherapy (18). Notably, however, bevacizumab is thought to be cytostatic rather than cytotoxic, which may explain its success only in combination with cytotoxic chemotherapy, rather than as monotherapy (17). Of note, however, the majority of pre-clinical work with bevacizumab has been in models of metastatic disease and the importance of these mechanisms of action are less clear in the adjuvant setting.

Clinically, in 2004, bevacizumab received Food and Drug Administration (FDA) approval for use as first line therapy in metastatic colorectal cancer based on studies showing improved response rate (RR), progression free survival (PFS), and OS when bevacizumab was added to 5-FU containing regimens (19). Soon thereafter, approval for use in the 2nd line metastatic setting was granted, again based on studies indicating improved OS in combination with 5-FU containing regimens (20). In 2013, bevacizumab received an additional indication for continuation therapy at progression of metastatic disease based on data showing improved OS with ongoing bevacizumab use after progression when the chemotherapy backbone was changed (21).

In 2012, two additional anti-VEGF agents received

FDA approval for use in metastatic colorectal cancer. Ziv-aflibercept (Zaltrap[®]) is a recombinant fusion protein with VEGF binding regions that function as decoy receptors binding intra- and extra-vascular VEGF-A such that they cannot bind to their usual receptors. The VELOUR trial showed improved OS with FOLFIRI plus ziv-aflibercept versus FOLFIRI plus placebo in metastatic colorectal cancer that progressed following an oxaliplatin-containing regimen (22). Regorafenib (Stivarga[®]) is an oral tyrosine kinase inhibitor that inhibits VEGF receptors 1 and 3. It is approved for use in the refractory, "last line" setting for patients who have progressed through multiple lines of chemotherapy, based on a modest OS improvement in the CORRECT trial.

Neither of these agents has been tested in the adjuvant setting (23).

Anti-EGFR therapy

The epidermal growth factor receptor (EGFR) regulates signaling pathways involved in cell differentiation, cell proliferation and angiogenesis. Cetuximab (Erbix[®]) is a recombinant chimeric human murine immunoglobulin antibody that binds to and inhibits EGFR. A similar drug, panitumumab (Vectibix[®]), is a fully human monoclonal antibody that inhibits EGFR. By inhibiting EGFR, cetuximab and panitumumab act via multiple mechanisms including G1 cell cycle arrest, induction of apoptosis, inhibition of tumor angiogenesis and activated antibody-dependent cellular toxicity (24). Importantly, the anti-EGFR agents have shown clinical success only in tumors that are KRAS wild type, and not in those with KRAS activating mutations, as these mutations cause constitutive activation of signaling cascades downstream to EGFR (25). Therefore, KRAS mutation status is routinely tested prior to initiation of anti-EGFR therapy. Similarly, the anti-EGFR agents are most effective in tumors that are BRAF wild type (25,26).

Clinically, cetuximab has shown mixed results, with only some trials showing PFS and OS benefit. For example the CRYSTAL trial showed improved PFS with the addition of cetuximab to FOLFIRI in the first line metastatic setting in KRAS wild type patients (27). The PRIME study, an analogous trial with FOLFOX4 with or without panitumumab, also showed improvement in PFS of 1.6 months in the panitumumab group (28).

However, there have been large randomized trials including COIN (29) and NORDIC VII (30) that have shown no benefit with the addition of cetuximab to chemotherapy in the metastatic setting. Reasons postulated for the lack of benefit seen in these trials include

reductions of chemotherapy doses (29) or duration of chemotherapy (30) in the cetuximab groups. Interestingly, sub-group analysis of both trials showed that lack of benefit with the addition of cetuximab was limited to patients receiving either capecitabine or bolus-FU, compared to those receiving infusional 5-FU. The question remains whether one chemotherapy backbone, namely FOLFOX versus FOLFIRI, is more effective in combination with targeted agents. The ongoing Intergroup C80405 trial hopes to answer this question by combining either cetuximab or bevacizumab with physician's choice of chemotherapy backbone- either FOLFOX or FOLFIRI may be chosen. The results of this trial are eagerly awaited.

Cetuximab is FDA approved for use in KRAS wild type tumors in combination with chemotherapy for metastatic disease in both the first and second line settings. It is also approved as monotherapy after failure of both irinotecan and oxaliplatin containing regimens. Panitumumab has similar indications, and is primarily used in patients intolerant to cetuximab due to hypersensitivity reactions.

Biologics in the adjuvant setting

Given the success of the addition of biologic agents to chemotherapy in the metastatic setting, multiple studies were attempted to investigate possible benefit of these agents in the adjuvant setting. Success of the anti-VEGF and anti-EGFR agents in the adjuvant setting was thought by some to be a foregone conclusion, looking to the adjuvant use of 5-FU and oxaliplatin as historical examples. However, it is important to note that drugs with clinical success in the metastatic setting do not always show success adjuvantly, with irinotecan being a key example of a surprise failure in the adjuvant setting (13-15).

Adjuvant bevacizumab

Two large randomized phase 3 trials investigated the use of bevacizumab with FOLFOX in the adjuvant setting. The NSABP (National Surgical Adjuvant Breast and Bowel Project) C-08 trial included 2,672 patients with resected stage II and III colon cancer (31). The standard therapy arm received mFOLFOX6 for a planned 12 cycles, and the experimental arm received the same with the addition of bevacizumab 5 mg/kg every two weeks for a year. Overall, this was a negative study. At a median follow up of 3 years, the DFS was 75.5% for the standard arm and 77.4% for the bevacizumab arm [hazard ration (HR) 0.89, 95% confidence interval (CI), 0.76-1.04, P=0.15]. Exploratory analysis found that there was a DFS benefit in favor of the bevacizumab group prior to 15 months of follow-up (HR 0.61; 95% CI,

0.48-0.78, P<0.0001), however this effect disappeared with longer follow up.

The AVANT (bevacizumab plus oxaliplatin-based chemotherapy as adjuvant treatment for colon cancer) trial (32) was a multi-center, international trial that randomized 2,867 patients with resected stage III colon cancer to mFOLFOX4 for a planned 12 cycles versus mFOLFOX4 with bevacizumab 5 mg/kg every 2 weeks for 12 cycles followed by bevacizumab 7.5 mg/kg every 3 weeks for 8 additional cycles versus XELOX with bevacizumab 7.5 mg/kg every 3 weeks for 8 cycles followed by 8 additional cycles of bevacizumab monotherapy. There was no significant difference in 3-year DFS or 5-year OS between the three groups. In fact, there were numerically more relapses and deaths due to disease progression in the two bevacizumab containing arms, though these differences did not reach statistical significance. Similar to the NSABP trial, there was a decreased risk of relapse in the bevacizumab groups in the first 12 months of follow-up, however an increase in later relapses resulted in no overall differences between the groups.

Much has been made of the indication of transient benefit in the bevacizumab groups in both the NSABP and the AVANT trials. Specifically, relapse risk was decreased by 39% in the first 15 months in NSABP C-08 and by 37% in the first 12 months in the AVANT trial. However, in both cases, excess relapses after bevacizumab was discontinued resulted in no differences in DFS with longer follow-up. One explanation is that existing metastasis, too small to be seen on imaging, were maintained at a small size while exposed to bevacizumab, however had rebound growth upon discontinuation of anti-VEGF therapy. Another possibility is ascertainment bias noting that neither of these trials was placebo controlled. Regardless, the long term follow-up data showing no difference in DFS in either trial and even the concerning trend toward worse outcomes with bevacizumab in the case of the AVANT trial, indicate that adjuvant bevacizumab therapy is not appropriate clinical care for patients at this time.

The completed and ongoing trials studying bevacizumab in the adjuvant treatment of colon cancer are summarized in *Table 1*. QUASAR2 is an ongoing phase III international trial comparing capecitabine with capecitabine plus bevacizumab for the adjuvant treatment of stage II and III colorectal cancer (35). The primary endpoint is 3-year DFS. The study has fully accrued and study completion is anticipated in July 2014.

Adjuvant cetuximab

The United States National Cancer Institute Intergroup Study N1047 trial evaluated 2,686 patients with resected

Table 1 Adjuvant trials with biologic agents in colon cancer

Trial	Cancer stage	Treatments	3 years disease free survival	
			%	P value
NSABP C-08 (31)	II/III	mFOLFOX 6 vs.	75.5%	0.15
		mFOLFOX 6 + bevacizumab	77.4%	
AVANT (32)	III	FOLFOX 4 vs.	76%	--
		FOLFOX 4 + bevacizumab vs.	73%	0.07
		XELOX + bevacizumab	75%	0.04
NCCTG N-0147 (33)*	III	mFOLFOX 6 vs.	74.6%	0.08
		mFOLFOX 6 + cetuximab	71.5%	
PETACC-8 (34)	III	FOLFOX 4 vs.	78.0%	0.91
		FOLFOX 4 + cetuximab	75.1%	
Ongoing trial				
QUASAR2 (35)	II/III	Capecitabine vs. Capecitabine + bevacizumab		

*results reported for KRAS WT only

stage 3 colon cancer, randomized to either mFOLFOX6 for 12 cycles or mFOLFOX6 with cetuximab at the standard dosing of 400 mg/m² on day 1 of cycle 1, then 250 mg/m² on day 8 of cycle 1 and days 1 and 8 of subsequent cycles (33). The trial was halted at interim analysis when, at a median follow up of 28 months, no benefit was seen with the addition of cetuximab regardless of KRAS or BRAF status. The 3-year DFS was 74.6% in the mFOLFOX6 group versus 71.5% in the mFOLFOX6/cetuximab group in patients with wild-type KRAS. In sub-group analysis, those ages 70 or older actually had decreased 3-year OS with the addition of cetuximab (86.2% vs. 72.5%, P=0.03). No evaluated sub-group showed any benefit from the addition of cetuximab.

Of note, the patients in the cetuximab arm received fewer cycles and lower doses of chemotherapy compared to patient in the mFOLFOX6 arm. Specifically, fewer patients in the cetuximab group were able to complete at least 6 cycles of chemotherapy (80% vs. 89%, P<0.001) and fewer received all 12 cycles (67% vs. 79%, P<0.001), though dosage intensity in the cycles given were similar between the groups.

The Pan-European Trials in Alimentary Tract Cancer (PETACC8) trial was presented at the European Society for Medical Oncology (ESMO) 14th World Congress on Gastrointestinal Cancer in 2012 and similarly showed no benefit to adding cetuximab to chemotherapy in the adjuvant setting (34). This phase 3 trial of 2,559 resected stage III colon cancer patients compared FOLFOX4 alone to FOLFOX4 with cetuximab. The interim analysis of the 1,602 KRAS wild-type patients after 39.6 months follow up showed no significant difference in DFS between the

groups (78% FOLFOX4 alone, 75% cetuximab). Sub group analysis and long-term interim analysis are planned in the next few years.

The completed and ongoing trials studying cetuximab in the adjuvant treatment of colon cancer are summarized in *Table 1*.

Pathophysiology of macrometastasis versus micrometastasis

So why the failure of two classes of biologic agents- anti-VEGF and anti-EGFR- in the adjuvant setting despite success in metastatic disease? One explanation may be the differing pathophysiology of macrometastatic versus micrometastatic disease. Different genes, pathways and molecules may be required for a cell to establish itself as a metastatic foci (micrometastatic disease) rather than flourish as a metastatic mass. Micrometastasis may simply have different molecular features than macrometastasis and thus respond differently to biologic agents (36,37). Some have proposed that micrometastasis may actually grow faster than macrometastasis (Gompertz's principle) (38), making them more responsive to cytotoxic chemotherapy than to biologic therapies widely thought to be cytostatic (17).

The evolution of a tumor with malignant potential to a tumor that actualizes that potential by establishing metastatic foci is complicated. Certainly the ability to create a new blood supply for tumor growth - angiogenesis- is required. Also required is the ability to make the epithelial-mesenchymal transition (39). Cell-cell adherence must initially be reduced allowing migration and spread (40)

but later cells must have an analogous mesenchymal to epithelial transition to re-gain cell-cell adherence to make a stable metastasis (41). EGFR is thought to have a significant role in the epithelial-mesenchymal transition of metastatic cells (42).

The failure of biologic agents in the adjuvant setting supports the theory that micrometastasis behave differently than clinically apparent foci of metastatic disease. One theory is that micrometastatic disease may develop early resistance mechanisms to anti-angiogenic therapy such as increased invasiveness (43) or upregulation of pro-angiogenic mechanisms (44). Others hypothesize that tumor cell dormancy develops in the presence of adjuvant therapy, with tumor re-growth occurring once the biologic and chemotherapeutic agents are no longer present (45). Thus the early benefit of anti-VEGF agents seen in some of the adjuvant trials is lost once bevacizumab is discontinued when cells that were quiescent start to proliferate again (46).

Some preclinical and animal model data raise concerns that anti-VEGF therapies may actually select for a more aggressive tumor type with enhanced angiogenic capabilities (43,44,46,47). For example, in a mouse lung cancer model, cells treated with anti-VEGF agents exhibited 50-60% regression of tumor vasculature, however returned to pre-treatment vascularization levels with 7 days of removal of the anti-VEGF receptor drug (48). Similarly, Paez-Ribes *et al.* report that in mouse models of both pancreatic neuroendocrine carcinoma and glioblastoma, VEGF inhibitors concurrently exhibit anti-tumor effects and promote heightened invasiveness of tumor with increased lymphatic and distant metastasis (43). Indeed, induction of tumor hypoxia and an inflammatory state caused by anti-angiogenic agents may promote malignancy (43,47). Other animal models, however, have shown that treatment and subsequent discontinuation of anti-VEGF therapy resulted in tumor re-growth at a slower rate than control-treated animals, speaking against a so-called rebound growth effect (18).

Despite the above theoretical concerns, no clinical studies have indicated that exposure to biologic agents select for more aggressive tumors or promote tumor invasiveness. For example, a study in patients with glioblastoma multiforme treated with the pan-VEGF receptor tyrosine kinase inhibitor, cediranib, showed no rebound angiogenesis when the drug was withheld (49). And in multiple large, randomized clinical trials with bevacizumab in multiple disease types including renal cell carcinoma (50), breast cancer (51), and lung cancer (52), there have been no indications of re-bound tumor effect after withdrawal of bevacizumab.

Conclusions

New chemotherapy drug development has traditionally started with testing agents in the refractory, advanced disease setting, followed by the first line metastatic setting with only drugs with success in advanced disease advancing to testing in the adjuvant setting. However the assumption that drugs successful in macrometastatic disease will also be effective in micrometastatic disease (adjuvant setting) is increasingly being questioned, particularly in the era of biologic agents. In colon cancer, the benefit of cytotoxic agents such as 5-FU, capecitabine, and oxaliplatin did indeed translate to the adjuvant setting for most patient sub-groups. However, irinotecan showed no benefit in the adjuvant setting and bevacizumab and cetuximab even had trends towards worse outcomes when used adjuvantly. The importance of large-scale clinical trials of drugs in the exact settings in which they will be used cannot be overstated. An interesting concern is the idea that agents unsuccessful in the metastatic setting may show efficacy in the adjuvant setting. However, acting on this possibility would involve changing the paradigm of how we currently move new drugs through clinical trials with no current examples of such a drug at present.

Where do we go from here in the adjuvant treatment of colon cancer and other malignancies in the biologic era? Perhaps new classes of biologic agents such as inhibitors of insulin growth factor, MEK, PI3kinase or BRAF may be more successful. Or perhaps anti-VEGF or anti-EGFR therapies have a role, but we have to identify the correct patient population, with predictive markers. While plasma levels of VEGF-A or VEGFR-1 or 2 were not predictive of bevacizumab benefit in the AVANT trial (32), other studies have shown early signals. For example, genetic variations in the VEGF receptor genes may predict clinical response to bevacizumab in breast cancer (53). Similarly, the vascular normalization index in glioblastoma multiforme may predict response to the anti-VEGF tyrosine kinase inhibitor, cediranib (54). As additional targeted therapies are developed, validated biologic predictive markers must be determined to ensure these drugs are used in the patient population in which they are most likely to succeed. Additionally, it is imperative to understand the micro- and macro-environments in which these drugs function, and the differences in these environments in the adjuvant and metastatic settings. Finally, questions of optimal chemotherapeutic backbone must be addressed. Until then, the biologic agents will retain their clear role only in the metastatic disease setting for colorectal cancer.

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