Is bevacizumab plus chemotherapy superior to chemotherapy alone in treatment of metastasic colorectal cancer?

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Citation

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Abstract

Colorectal cancer is the third most commonly diagnosed cancer and second leading causes of cancer deaths in the United States. Over the past 12 years, significant progress has been made in the systemic treatment of this malignant condition. The development of targeted biological therapies, such as anti-angiogenesis therapy with bevacizumab, has significantly impacted the survival of patients with cancer. Yet, despite these advances, nearly all patients with metastatic colorectal cancer will succumb to the disease. This review summarizes the results from certain phase-III clinical studies to determine if bevacizumab combined with chemotherapy is superior to chemotherapy alone in treatment of metastatic colorectal cancer. Studies found that the addition of bevacizumab to chemotherapy significantly improves response rates, TTP, PFS and overall survival for first-line mCRC. The reported severe adverse effects were similar to that reported in phase II clinical trials. Bevacizumab plus chemotherapy is superior to chemotherapy alone in treatment of metastatic colorectal cancer and was proven in the phase III randomized controlled clinical studies.

INTRODUCTION

For both men and women, colorectal cancer (CRC) is the third most commonly diagnosed cancer and second leading cause of cancer deaths in the United States each year per data published by the United States National Institute of Health (NIH) (1). In 2008, an estimated 148,810 cases of colorectal cancer were diagnosed and 49,960 people died from this disease (1). While patients who are diagnosed with early-stage disease and undergo surgical resection have a favorable 5-year survival rate of 70-80%, approximately 30% of patients will present with unresectable or disseminated disease and will have a poor prognosis (2). Over the past 12 years, significant progress has been made in the systemic treatment of this malignant condition. Six new chemotherapeutic agents have been introduced, increasing the median overall survival for patients with metastatic colorectal cancer from less than 9 months with no treatment to approximately 24 months (3). The development of targeted biological therapies, such as anti-angiogenesis therapy with bevacizumab, has significantly impacted the survival of patients with cancer. Yet, despite these advances, nearly all patients with metastatic colorectal cancer will succumb to the disease. Some ongoing randomized clinical trials are evaluating these new agents, with the goal of continued progress in prolonging life among patients with metastatic colorectal cancer and increasing cure rates among those with resectable disease (3). This review will summarize the results from certain phase-III clinical studies to determine if bevacizumab combined with chemotherapy is superior to chemotherapy alone in treatment of metastatic colorectal cancer.

BACKGROUND

GENETIC MECHANISM

Angiogenesis is a process involving new blood vessel formation from existing vessels. It is a normal physiological process in growth and development, as well as in wound healing. However, this is also a fundamental step in tumor growth, survival, and metastatic spread. A number of angiogenic factors have been identified including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), angiopoietins, and matrix metalloproteinases (MMPs). VEGF has been demonstrated to be the most potent proangiogenic factor. Studies have shown that the VEGF gene is upregulated in a variety of solid tumors, such as

colorectal cancer, and can be predictive of invasiveness, metastasis, recurrence and prognosis (4). The VEGF exerts its activity by binding to various tyrosine kinase-containing transmembrane VEGF receptors, ultimately stimulating the release of various downstream proteins causing increased endothelial cell proliferation, vascular permeability, migration, survival and angiogenesis. Blocking endothelial cell VEGF activity inhibits tumor angiogenesis, normalizes tumor vasculature, facilitates improved chemotherapy delivery, and prevents the recruitment of progenitor cells from bone marrow, making VEGF an important target for cancer therapy (4).

Bevacizumab is the only United States Food and Drug Administration (FDA) –approved anti-VEGF agent. It is a recombinant humanized monoclonal antibody with high binding specificity to VEGF. It inhibits the binding of VEGF to VEGF receptors thereby inhibiting tumor angiogenesis. In phase I and phase II studies, bevacizumab was well tolerated as a single agent (5,6). Further, the addition of bevacizumab to standard first- and second-line chemotherapy regimens for the treatment of metastatic colorectal cancer seemed to improve overall and progression-free survival times and increase the time to disease progression (5, 6).

COLON CANCER EPIDEMIOLOGY

Approximately 48 cases of colorectal cancer (CRC) are diagnosed per 100,000 people in the United States making it the second leading cause of cancer deaths in the United States each year (NIH). For both men and women, colorectal cancer is the third most commonly malignant neoplasm worldwide (7) although the incidence is higher in men than in women. In addition to the 2008 data mentioned above, about 6% of Americans are expected to develop the disease within their lifetimes (8). Age-specific incidence and mortality rates show that most cases are diagnosed after the age of 50 (8).

Although most patients are diagnosed at early stages, approximately 20% of patients present with metastatic disease and 30% to 40% of patients with localized disease ultimately develop metastases (9).

In the United States, it was reported that incidence rates declined slightly by 3 percent between 1998 and 2003, after remaining relatively stable 1992 to 1998, following a long-term decline that began in the mid-1980s. In almost all other western countries, however, incidence rates have increased slightly (1). Colonoscopy adopted as a screening test was one of the main reasons for the improvement in the United States.

RISK FACTORS

Age is a major risk factor for sporadic CRC and it is a rare diagnosis before the age of 40. The incidence begins to increase significantly between the ages of 40 and 50, and age-specific incidence rates increase in each succeeding decade thereafter. Secondly, environmental and genetic factors can increase the likelihood of developing CRC. Although inherited susceptibility results in the most striking increases in risk, the majority of CRCs are sporadic rather than familial. Familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC) are the most common of the familial colon cancer syndromes. Together, these two conditions account for fewer than 5 percent of CRC cases (10). Risk factors for sporadic CRC include a personal history of large (>1 cm) adenomatous polyps and villous or tubulovillous polyps; family history of CRC in first-degree relatives or large (>1cm) or histologically advanced colonic adenoma; inflammatory bowel disease; diabetes mellitus and insulin resistance; cholesystectomy; alcohol consumption; obesity and cigarette smoking. Certain protective factors have also been identified, such as a diet high in fruits and vegetables, dietary fiber, folic acid, vitamin B6, calcium, magnesium, physical activity, taking aspirin and NSAIDs, and sulindac, hormone replacement therapy, statins, antioxidants, Omega 3 fatty acids, and garlic consumption (10).

SIGNS AND SYMPTOMS

Early symptoms of colorectal cancer are usually vague, like bleeding, weight loss and fatigue. With disease progression, patients may experience local symptoms, such as hematochezia or melena, abdominal pain, and/or a change in bowel habits including constipation and/or diarrhea, a feeling of incomplete defecation, a reduction in the diameter of stool size and bowel obstruction which causes abdominal pain, bloating and vomiting of stool-like material. Systemic symptoms include unexplained weight loss, fatigue and anemia. Jaundice, epigastric pain, and liver enlargement are usually indications of liver metastases (2).

Approximately 20% of patients have distant metastatic disease at the time of presentation and 30% to 40% of patients with localized disease ultimately develop metastases (1). Regional lymph nodes and liver metastases reflect the most common initial sites of disease spread, but metastases

to other organs, including the lungs, bone, peritoneum and brain, during the course of the disease are common (1).

There are also a variety of unusual presentations of CRC. These include local invasion or a contained perforation causing malignant fistula formation into adjacent organs, such as the bladder or small bowel. This is most common with cecal or sigmoid carcinomas. In the latter case, the condition can mimic diverticulitis. Fever of unknown origin, intra-abdominal, retroperitoneal, abdominal wall abscesses, even Streptococcus bovis bacteremia and Clostridium septicum sepsis may present (2).

SCREENING

Colorectal cancer can take many years to develop and early detection greatly improves the chances of a cure. Screening tests can help identify cancers at an early and potentially treatable stage. Some tests can also prevent the development of colorectal cancer by identifying and removal of adenomatous polyps.

Recommended CRC screening tests are grouped into two categories: a) tests that primarily detect cancer, which include both guaiac-based fecal occult blood testing (gFOBT) immunochemical-based FOBT (FIT) as well as testing stool for exfoliated DNA (sDNA) and, b) tests that can detect cancer and advanced lesions, which include endoscopic examinations and radiologic examinations (ie, flexible sigmoidoscopy (FSIG), colonoscopy, double-contrast barium enema (DCBE), and computed tomography colonography (CT colonography, or virtual colonoscopy) (11).

The American Cancer Society recommends that CRC screening for average-risk adults should start at age 50 with one of the following options: a) annual gFOBT or FIT; b) sDNA; c) FSIG every 5 years; d) colonoscopy every 10 years; e) DCBE every 5 years; or f) CT colonography every 5 years. More intensive surveillance is recommended for individuals at higher risk for CRC, which include individuals with a) a history of adenomatous polyps; b) a personal history of curative-intent resection of CRC; c) a family history of either CRC or colorectal adenomas diagnosed in a first-degree relative before age 60 years; d) a history of inflammatory bowel disease of significant duration; e) a known or suspected presence of 1 of 2 hereditary syndromes, specifically hereditary nonhyphenpolyposis colon cancer or familial adnomatous polypsis (11).

DIAGNOSIS

CRC may be suspected from one or more of the symptoms and signs described above or may be asymptomatic and discovered by routine screening of average and high-risk subjects. The most commonly used diagnostic methods include (12):

a) Colonoscopy is the single best diagnostic test in symptomatic individuals. The vast majority of colon and rectal cancers are endoluminal adenocarcinomas that arise from the mucosa and the colonoscopy is the best since it can localize lesions throughout the large bowel, biopsy mass lesions, detect synchronous neoplasms, and remove polyps.

b) The air contrast barium enema (BE), supplemented with flexible sigmoidoscopy, is also used to evaluate symptomatic patients, but the diagnostic yield of this combination is less than that of colonoscopy for the evaluation of lower tract symptoms.

c) A double-contrast BE or CT colonography can provide a radiographic diagnosis in whom the colonoscopy is not able to reach the tumor for technical reasons (e.g., partially obstructing cancer, tortuous colon, poor prep). Further, abdominal and pelvic CT scans can demonstrate regional tumor extension, regional lymphatic and distant metastases, and tumor-related complications.

d) A contrast-enhanced MRI may identify more hepatic lesions than can be visualized by CT and potentially narrow the available therapeutic options for patients with suspected liver metastases.

e) Both transrectal or endorectal ultrasound (EUS) and MRI with or without an endorectal coil can demonstrate the various layers of the rectal wall, but the EUS is less expensive and less time consuming. The addition of EUS-guided fine needle aspiration (FNA) biopsy also improves the accuracy of N staging.

f) A variety of serum markers have been associated with CRC, particularly carcinoembryonic antigen (CEA), and carbohydrate antigen (CA) 19-9. However, these markers have a low diagnostic ability to detect primary CRC due to significant overlap with benign disease and low sensitivity for early stage disease.

DIFFERENTIAL DIAGNOSIS

The majority of CRCs are adenocarcinomas. Many conditions can cause signs or symptoms that are similar to

CRC, including other malignancies and a multitude of benign lesions such as hemorrhoids, diverticulitis, infection, or inflammatory bowel disease. A direct evaluation of the total colonic mucosa is necessary to exclude carcinoma with certainty (12).

STAGING

Initial staging usually involves a colonoscopy, abdominal and pelvic CT scan and a chest X-ray. The final stage of a colorectal cancer frequently depends upon the findings during surgery and pathologic staging. Pathologic stage represents the most important prognostic factor for patients with colorectal cancer. The tumor-node-metastasis (TNM) system, as defined by the American Joint Committee on Cancer, is the most commonly used staging system and is based on depth of invasion of the bowel wall, extent of regional lymph node involvement, and presence of distant site of disease. The depth of tumor invasion defines the T stage and increases from T1 (invasion of the submucosa) to T4 (invasion into the serosa or adjacent structures). Pathologic review of surrounding lymph nodes defines the 3N categories: N0 (no lymph nodes involved), N1 (1-3 lymph nodes involved), and N2 (>3 lymph nodes involved). In general, the extent of a colorectal cancer can be considered as either localized (stage I to III) or advanced (stage IV) (12).

Current guidelines recommend the identification of 12 or more lymph nodes in the resected specimen because the examination of fewer regional lymph nodes has been linked with poorer outcome in patients with node-negative and node-positive disease. The examination of fewer lymph nodes may reflect a less complete surgical procedure or an inadequate inspection of the pathologic specimen, mistakenly leading to understaging of the tumor and the subsequent omission of beneficial adjuvant therapy (9).

TREATMENT

Treatment of CRC depends on the severity or stage of disease. Treatment modalities include surgery, radiotherapy, chemotherapy, and adjuvant therapy. Surgery is the only curative modality for localized colon cancer. Surgery also provides a potentially curative option for selected patients with limited metastatic disease in liver and/or lung. Furthermore, even patients who are not candidates for a curative resection can benefit from surgical palliation for symptoms of obstruction and bleeding from the primary tumor (13).

In patients with either transmural invasion or positive perirectal lymph nodes, the addition of radiation therapy (RT) and chemotherapy after surgical resection of the primary tumor can enhance both local control and cure rates.

Patients with inoperable metastatic colorectal cancer are usually treated with systemic chemotherapy (14). However, some patients with stage IV disease (particularly those with liver-limited metastases) can be surgically cured of their disease. Even selected patients with initially unresectable liver metastases may become eligible for resection if the response to chemotherapy is sufficient.

For most patients with advanced CRC, systemic chemotherapy will be palliative and not curative, and the treatment goals are to prolong overall survival and maintain quality of life (QOL) for as long as possible.

There are now five different classes of drugs with significant antitumor activity: Fluoropyrimidines (5-fluorouracil [5-FU] which is usually given with leucovorin [LV], capecitabine, UFT), irinotecan oxaliplatin cetuximab (Erbitux) and panitumumab (Vectibix), two therapeutic monoclonal antibodies (MoAbs) directed against the epidermal growth factor receptor (EGFR) bevacizumab (Avastin), a MoAb targeting vascular endothelial growth factor (VEGF) (14, 15).

The available evidence supports initial combination chemotherapy for most patients with metastatic CRC (mCRC), particularly those who have limited liver metastases that might become potentially resectable. Initial combination therapy is also preferred for patients with nonoperatable mCRC, for whom the palliative treatment strategy should aim at maximizing the number of patients to be exposed to as many active agents as possible. This is best achieved by using well-established combination doublets (ie, FOLFOX (oxaliplatin day1, leucovorin and fluorouracil day1 and day2), XELOX (Xeloda and oxaliplatin), or FOLFIRI (irinotecan, fluorouracil, and folinic acid)) as the chemotherapy backbone, which would then only require one additional step to have all three active agents included in the treatment algorithm (eg, FOLFOX followed by FOLFIRI, or FOLFIRI followed by FOLFOX).

For the vast majority of patients with incurable mCRC, rationally designed doublet combinations, such as FOLFOX, XELOX, or FOLFIRI, should be considered the standard chemotherapy backbone for first-line palliative therapy. As first-line therapy, FOLFOX and FOLFIRI have similar

efficacy, and the decision to use one or the other should mainly be based on the expected toxicity profile of both regimens.

Bevacizumab is a humanized monoclonal antibody that targets vascular endothelial growth factor-A (VEGF-A), a member of a family of VEGF-receptor-activating ligands. CRC was the first malignancy for which clear evidence for efficacy of an anti-VEGF strategy was obtained in randomized trials. The addition of bevacizumab to chemotherapy has significantly improved response rates, TTP (time to progression), and overall survival. This development was promoted by the relatively open FDA labeling rule that allowed bevacizumab to be used as part of first-line therapy in combination with an IV 5-FU-based regimen, which, by definition, included FOLFOX.

In clinical practice, cetuximab is the recommended medicine for inhibiting the epidermal growth factor receptor (anti-EGFR) and the preferred MoAb when used in combination with chemotherapy. However, for monotherapy, there is no strong preference over one another between cetuximab and panitumumab.

Both of the therapeutic MoAbs, cetuximab and anitumumab, which target EGFR, have been well documented. In cross-trial comparisons, comparable single agent activity in patients with mCRC that is refractory to both oxaliplatin and irinotecan-based regimens has been noted (15). But there is no convincing evidence to establish cetuximab as a component of front-line therapy in unselected patients. In the US, the FDA-approved use of cetuximab requires a patient to have failed irinotecan-based chemotherapy; the use of cetuximab in combination with irinotecan as second-line therapy after failure of FOLFOX is considered “off-label.”

Now, clinical trials which compared a combination of combined chemotherapy with or without cetuximab/bevacizumab as last-line therapy in patients with chemorefractory metastatic CRC are ongoing (15).

Although the long-term prognosis is poor for patients with unresectable mCRC, palliative chemotherapy can relieve symptoms, improve quality of life (QOL), and prolong survival. The optimal way to combine and sequence all of these agents has not yet been established. In general, exposure to all active agents is more important than a specific sequence of administration.

PROGNOSIS

In patients with resectable colorectal cancer, several other pathologic and clinical features have been identified that are associated with an increased risk for tumor recurrence. These include poorly differentiated histology, lymphovascular invasion, perineural invasion, T4 tumor penetration, bowel perforation, clinical bowel obstruction, and an increased preoperative plasma level of carcinoembryonic antigen (16).

Microsatellite instability and loss of heterozygosity at chromosome 18q are the two best-defined molecular prognostic markers. Microsatellite instability results from mutations or promoter hypermethylation of mismatch repair genes leading to errors in DNA replication and changes in short, repeated sequences of DNA. Patients with tumors possessing a high degree of microsatellite instability have a more favorable prognosis than those whose tumors are microsatellite stable (17). Loss of heterozygosity at chromosome 18q has been reported in approximately 50% of colon cancers and has been associated with worse prognosis (18).

As the cancer stage advances from stage I to stage IV as defined by American Joint Committee on stages of cancer, the 5-year overall survival rates decline dramatically: stage I, greater than 90%; stage II, 70% to 85%; stage III, 25% to 80%; and stage IV, 10% (19).

METHODS

A systemic search was conducted through PubMed in MD Anderson Cancer Center library using MeSH terminology “Colorectal Neoplasms”, “bevacizumab”, “Clinical Trial”, combined with “and”. Thirty-seven articles were found through this search. Only full text English articles published after 2007 were selected for this review.

In order to select the best articles the following inclusion and exclusion criteria were used. The only inclusion criterion was that the patients’ diagnosis was histologically confirmed as colorectal cancer that was advanced or metastatic. The only exclusion criterion was that the patients have no previous exposure to bevacizumab.

Finally, three original clinical trial phase III reports were chosen for this review, because all the trials were randomized controlled studies that compared treatment efficacy of combined bevacizumab with chemotherapy to chemotherapy alone in treatment of advanced stage

colorectal colon cancer. These are some of the best studies which provided level I clinical evidence proving that bevacizumab plus chemotherapy is superior to chemotherapy alone in treatment of metastasis colorectal cancer.

DISCUSSION OF RESEARCH PAPERS

The first study entitled "Bevacizumab in combination with Oxaliplatin, Fluorouracil, and Leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the eastern cooperative oncology group study E3200" is a multi-institutional, cooperative group, open-label, randomized phase III study by Giantonio, et al (20). In this study, a total of 829 patients with metastatic colorectal cancer patients previously treated with a fluoropyrinidine and irinotecan were enrolled into the study between November 2001 and April 2003 from 221 sites in the United States and South Africa. The patients were randomly assigned to one of three treatment groups: oxaliplatin (85mg/m^2, day1), fluorouracil (400mg/m^2 IV bolus followed by 600mg/m^2 IV, day1 and day2) , and leucovorin (200mg/m^2, day1 and day2) (FOLFOX4) with bevacizumab (10mg/kg, day1), 286 patients; FOLFOX4 without bevacizumab, 291 patients; or bevacizumab alone, 243 patients. Treatment assignment was balanced by sex, age, ECOG (the Eastern Cooperative Oncology Group) performance status, and prior radiation therapy exposure. The overall survival, with additional determinations of progression-free survival, response, and toxicity was determined.

All the patients' diagnosis was histologically confirmed as colorectal cancer that was advanced or metastatic and measurable as defined by the Response Evaluation Criteria in Solid Tumors (RECIST). Prior chemotherapy with irinotecan and a fluoropyrimidine for advanced disease was required, and the previous use of oxaliplatin or bevacizumab was not permitted. A history of hypertension was allowed provided that blood pressure readings were maintained below 150/100 mmHg on a stable antihypertensive regimen. Those patients with a history of major surgery within 28 days, radiotherapy within 14 days, a hypersensitivity to recombinant murine monoclonal antibodies, or a thrombotic or hemorrhagic event within 6 months of study entry, and those requiring therapeutic anticoagulation were excluded from the study.

Eligible patients were randomly assigned in a 1:1:1 ratio to receive FOLFOX4 in combination with bevacizumab; FOLFOX4 without bevacizumab; or bevacizumab alone. Random assignment was stratified on the basis of prior radiation therapy and Eastern Cooperative Group (ECOG) performance status. Treatment in all three arms of the study was administered every 14 days as one cycle of therapy. A baseline radiographic tumor evaluation was required within 4 weeks before study registration. Tumor assessment was performed after every fourth cycle of therapy. Patients without progressive disease were allowed to continue in the study. All patients were followed for disease progression and death.

Overall survival was defined as the time from random assignment to death from any cause, censoring patients who had not died at the date last known alive. Progression-free survival was defined as the time from random assignment to progression, censoring patients without progression at the date of last disease assessment. Cases without evidence of progression dying within 4 months of the last disease assessment were counted as events of progression at the time of death. Second primary colon or rectal cancers were considered events as of the date of diagnosis.

The addition of bevacizumab to FOLFOX4 resulted in a statistically significant improvement in overall survival. At a median follow-up of 28 months, patients treated with bevacizumab in combination with FOLFOX4 had a median survival of 12.9 months compared with 10.8 months for those treated with FOLFOX4 alone (hazard ratio = 0.75; P = .0011). The median survival for those treated with bevacizumab alone was 10.2 months. In addition, the combination of bevacizumab and FOLFOX4 resulted in a statistically significant improvement in progression-free survival compared with those treated with chemotherapy alone (7.3 v 4.7 months; hazard ratio for progression = 0.61; P < .0001). The median progression-free survival for patients treated with bevacizumab alone was 2.7 months.

The occurrence of any grade 3 or 4 adverse event was greater for those individuals treated with the combination of FOLFOX4 plus bevacizumab compared with patients treated with chemotherapy alone (75% v 61%). For the individuals treated with FOLFOX4 plus bevacizumab, there were higher rates of grades 3 or 4 neuropathy, hypertension, bleeding, and vomiting when compared with those who received FOLFOX4 without bevacizumab. The majority of the bleeding events in the patients treated with FOLFOX4 in combination with bevacizumab were from the GI tract. The grade 4 bleeding event required an intervention to achieve hemostasis. There were no significant differences in the

incidence of adverse events leading to treatment discontinuation or in 60-day all-cause mortality rates. Bevacizumab as a single agent was associated with a 36% overall incidence of grade 3 or 4 toxicity.

The significance of these findings extends beyond the demonstration of effective second-line therapy for this disease. The improvement in median overall survival by 2 months in the current study is of particular importance, because an equal if not greater gain may be expected by adding bevacizumab to first-line treatment with FOLFOX4.

The authors concluded that antiangiogenic therapy with bevacizumab in combination with the oxaliplatin-based regimen FOLFOX4 prolongs survival for patients with previously treated metastatic colorectal cancer. These findings add to the existing experience for bevacizumab in colorectal cancer, suggesting that improvements in clinical outcome do not appear to be limited to a single chemotherapy regimen. Moreover, the gain in survival duration demonstrated by the addition of bevacizumab to second-line therapy with FOLFOX4 supports the use of this combination as initial treatment of metastatic colorectal cancer.

Another study reported by Grothey, et al. in Journal of Clinical Oncology is entitled “Bevacizumab beyond first progression is associated with prolonged overall survival in metastatic colorectal cancer: results from a large observational cohort study (BRiTE) (21). It is a prospective observational cohort study (OCS) in an effort to evaluate the safety and effectiveness of bevacizumab in combination with chemotherapy in a large, community-based patient population with previously untreated mCRC which was conducted at 248 study sites in 49 states in the US.

Between February 2004 and June 2005, 1,953 patients with mCRC who had been previously untreated were included in this BRiTE study with no specific exclusion criteria, of which, 1,445 patients had experienced progressive disease (PD). Of the patients with documented PD, 253 received no post-PD treatment, 531 received post-PD treatment without bevacizumab (no BBP, the use of bevacizumab beyond first progression), and 642 received post-PD treatment with bevacizumab. There was no difference between these three groups in terms of age, ethnicity, site of primary tumor, first-line chemotherapy, and exposure to three active chemotherapy agents including 5-FU, irinotecan, and oxaliplatin. There were no protocol-specified treatments or assessments. All aspects of patients’ treatments over time, including specific chemotherapy agents and/or combinations, and the dose, schedule, and duration of bevacizumab treatment, including BBP, were determined by a physician. Post-PD treatment was defined as any systemic anticancer therapy, including cytotoxic and/or biologic agents. Patients who discontinued bevacizumab within 28 days after first PD were considered not exposed to BBP. Gaps in bevacizumab or chemotherapy administration of less than 28 days were considered continuous treatment. Measure of clinical outcomes were based on physician determination and included time to progression from the date of initiation of first-line treatment to first PD; overall survival (OS) from the date of initiation of first-line treatment to death.

The median OS for the overall BRiTE group was 25.1 months (95% CI, 23.4 to 27.5 months). The median OS was longer for the BBP group (31.8 months, 95% CI, 27.9 to NA months) compared with the no-BBP groups (19.9 months, 95% CI, 18.0 to 22.0 months). Similarly, survival beyond first progression (SBP) was longer for the BBP group (19.2 months, 95% CI, 16.8 to 20.7 months) than the no-BBP group (9.5 months, 95% CI, 8.4 to 11.2 months). Patients who received no post-PD treatment had shorter median OS and SBP despite a similar first-line time to progression (TTP).

There was a similar improved survival associated with use of post-PD therapy within 2 months of PD. Furthermore, there was a greater improvement in survival in the BBP group compared with the no-BBP group when therapy was initiated for both within 2 months of PD. The median SBP associated with BBP started within 2 months of PD was 16.8 months (95% CI, 14.7 to 19.6 months) compared with 9.2 months (95% CI, 8.3 to 11.2 months) for patients who started chemotherapy without bevacizumab within 2 months of PD.

After the analysis was adjusted for other important prognostic factors such as baseline ECOG PS (Eastern Cooperative Oncology Group performance status), baseline albumin levels, baseline alkaline phosphatease levels, site of primary tumor, first-line TTP, best first-line response, BBP maintained a statistically significant effect on SBP compared with no BBP (HR, 0.49; 95% CI, 0.41 to 0.58; $p<0.001$).

A series of sensitivity analyses was performed to address the contribution of observed variability in the treatment patterns of bevacizumab and chemotherapy to the effect of BBP on survival. Compared with the ones in the no-BBP group,

patients in the BBP group who received bevacizumab continuously from first-line into post-PD demonstrated significantly improved SBP (adjusted HR, 0.51; 95% CI, 0.42 to 0.62). After excluding patients who initiated post-PD therapy more than 2 months after first-PD, the HR associated with BBP compared with no BBP was 0.51 (95% CI, 0.42 to 0.63). In an analysis that reclassified BBP as post-PD therapy with any use of bevacizumab, the HR associated with BBP compared with no BBP was consistent at 0.53 (95% CI, 0.45 to 0.63).

In all the sensitivity analyses performed, the HRs for the survival comparison between the BBP and no-BBP groups resulted in HRs that ranged from 0.46 to 0.53.

The incidence of most bevacizumab-associated adverse effects described in the BRiTE study, including arterial thromboembolic events, grades 3 to 4 bleeding, and GI perforation, were similar in the no post-PD treatment, no-BBP and BBP groups. There was a higher incidence of new or worsening hypertension in the BBP group compared with the no-BBP group or with the overall BRiTE population (19.2% v 24.6%), which may due to longer exposure to bevacizumab in the BBP group.

Besides promising findings in this study, there are some limitations. First, patients are not randomly assigned to the treatment groups being compared. The authors used multivariate analyses to adjust for possible confounding factors and found the effect of BBP on survival as independent from such pre- or post-treatment variables, although some residual confounding as a result of the timing of, or errors in, measurement of prognostic variables is possible. Another potential limitation is that actual administration dates for bevacizumab and chemotherapy were not collected, and consequently, misclassification of BBP may have occurred. However, such misclassification would have likely produced more similar groups and would have biased the effect toward the no-BBP group. Analysis that examined all of these potential biases was performed, and minimal effect was noted on the observed association.

In summary, the use of BBP in this BRiTE study is one possible explanation for the longer-than-expected median OS observed in the study population, and it suggests that traditionally defined tumor progression may not indicate a loss of clinical benefit from bevacizumab. Continued suppression of the VEGF pathway may be important to maximize the clinical benefit from bevacizumab in mCRC.

Another report published in The Journal of Clinical Oncology by Saltz, et al. in April 2008 evaluated the effect on PFS of bevacizumab versus placebo when combined with oxaliplatin-based chemotherapy (XELOX or FOLFOX4) in a randomized phase III study in metastatic colorectal cancer patients (22).

Inclusion criteria for this study were patients age> 18 years; histologically confirmed mCRC; one or more measurable lesions which were not amenable to curative resection; ECOG performance status < 1; life expectancy longer than 3 months; no prior systemic therapy or previous treatment with oxaliplatin or bevacizumab. Exclusion criteria were pregnant or breast-feeding women; clinically significant cardiovascular disease; clinically detectable ascites; use of full-dose anticoagulants or thrombolytics; known CNS metastases; serious nonhyphenhealing wound, ulcer, or bone fracture; clinically significant bleeding diathesis or coagulopathy; and proteinuria > 500mg/24 hours.

Between February 2004 and February 2005, a total of 1,401 patients were randomly assigned in the 2x2 factorial (bevacizumab v placebo) part of this study using an interactive voice response system. Randomization was stratified by region, ECOG performance status, liver as a metastatic site, alkaline phosphatase level, and number of metastatic sites. Baseline demographic and clinical characteristics were well balanced between treatment arms.

Bevacizumab or placebo was administered before oxaliplatin at a dose of 7.5mg/kg on day 1 of a 3-week cycle when given with XELOX or 5mg/kg on day 1 of a 2-week cycle when given with FOLFOX4. XELOX consisted of oxaliplatin 130mg/m^2 on day 1, capecitabine 1000mg/m^2 bid from day 1 to day 14. The FOLFOX4 was given as described above. Treatment was continued until disease progression or for 48 weeks. Tumor assessment was made by CT or MRI within 28 days of when treatment started and repeated every 6 weeks and at the end of treatment. Response evaluation criteria in solid tumor guidelines were used to define all responses.

Overall, 699 patients comprised the bevacizumab-containing arms and 701 comprised the placebo-containing arms. PFS (progression free survival) was significantly increased with bevacizumab compared with placebo when combined with oxaliplatin-based chemotherapy (HR, 0.83; 97.5% CI, 0.72 to 0.95; p=.0023), the median PFS duration was 9.4 months with bevacizumab plus chemotherapy versus 8.0 months

with placebo plus chemotherapy. Using the prespecified secondary analysis of on-treatment PFS, the median on-treatment PFS was 10.4 months with chemotherapy plus bevacizumab versus 7.9 months with chemotherapy plus placebo (HR, 0.63; 97.5% CI, 0.52 to 0.75; p<.0001).

Using general PFS definition, statistical superiority of bevacizumab versus placebo was evident in the XELOX subgroup (HR, 0.77; 97.5% CI, 0.63 to 0.94; p=.0026), bur did not reach the significance level in the FOLFOX4 subgroup (HR, 0.89; 97.5% CI, 0.73 to 1.08; p=.1871). Using the on-treatment PFS definition, significant results were evident in both the XELOX (HR, 0.61; 97.5% CI, 0.48 to 0.78; p<.0001) and FOLFOX4 subgroups (HR, 0.65; 97.5% CI, 0.50 to 0.84; p=.0002).

Median OS was 21.3 months with bevacizumab plus chemotherapy and 19.9 months with placebo plus chemotherapy. But this difference did not reach statistical significance (HR, 0.89; 97.5% CI, 0.76 to 1.03; p=.077). Response rate (RR) was similar in the bevacizumab plus chemotherapy versus placebo plus chemotherapy groups (47% versus 49%; odds ratio, 0.90; 97.5% CI, 0.71 to 1.14; p=.31).

The overall incidence of grade 3 or 4 adverse events felt to be potentially related to bevacizumab was 16% in the bevacizumab containing arms and 8% in the placebo-containing arms. The most common were thromboembolic events, grade 3 or 4 hypertension and bleeding. In general, the addition of bevacizumab caused no clinically relevant aggravation of grade 3 or 4 chemotherapy-related toxicity.

This study confirmed that bevacizumab improves PFS when combined with chemotherapy for first-line mCRC, which is consistent with reports from other phase III trials. The safety profile of bevacizumab documented in this trial was similar, too but the observed trend in an improvement in OS did not reach statistical significance, which may be explained by a shorter treatment duration in the bevacizumab arms. Adjust for preprogression alterations to study therapy using the predefined on-treatment PFS analysis showed PFS benefit offered by bevacizumab was considerably larger than placebo arms, suggesting that the duration of bevacizumab therapy is important, and that treatment until PD may be necessary to maximize the clinical benefit derived from bevacizumab therapy.

CONCLUSION

In conclusion, the addition of bevacizumab to chemotherapy significantly improves response rates, TTP, PFS and overall survival for first-line mCRC. The reported severe adverse effects were similar to that reported in phase II clinical trials. Bevacizumab plus chemotherapy is superior to chemotherapy alone in treatment of metastatic colorectal cancer and was proven in the above reports with randomized controlled clinical studies.

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