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Low rate of bleeding and absence of perforation in metastatic colorectal cancer [mCRC] patients with unresected primary tumor receiving bevacizumab and chemotherapy

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Abstract

Purpose: palliative resection of the primary tumor in asymptomatic patients with mCRC remains controversial. Whereas adding bevacizumab to chemotherapy significantly improved survival rates, it might increase risk of bleeding in patients with non-operated primary tumor. **Objectives:** to retrospectively analyze the safety of upfront bevacizumab and chemotherapy for mCRC patients with unresected primary tumor. **Methods:** medical records were reviewed to identify all mCRC patients admitted between 1/07 and 1/10, with minimally/non-symptomatic and unresected primary tumor, and treated with bevacizumab and chemotherapy. **Results:** eighteen consecutive patients were identified. First-line chemotherapy regimen was oxaliplatin-based in eleven patients and irinotecan-based in seven. Median follow-up was 396 days. Ten patients presented with primary tumor bleeding, none of which had symptom worsening. There were no new cases of gastrointestinal bleeding. Bevacizumab was discontinued in three cases due to persistent grade II proteinuria in one, grade III perianal fistula in other and pelvic abscess requiring surgical intervention in the remainder. **Conclusions:** in selected cases, minimally/non-symptomatic patients with mCRC could be managed with the use of antiangiogenic therapy. Prospective trials are still needed to further investigate the actual role of surgery in this setting.

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Introduction

Excluded non-melanoma skin cancers, colorectal cancer is the fourth most common malignant neoplasm in Brazil. Approximately 27,000 new cases of colorectal cancer are diagnosed every year, for an estimated incidence of 13 new cases/100,000 women and 15 new cases/100,00 men.[1] According to a hospital-based registry, 24% of patients are diagnosed with metastatic disease at the time of first presentation.[2]

In the setting of metastatic colorectal cancer (mCRC), surgical resection with or without adjuvant therapy is the standard approach for patients who have potentially curable disease.[3] For patients in whom complete resection is not possible, the main goals of management are maintenance of quality of life and prolongation of survival.[4] The role of palliative resection of primary tumor in relatively asymptomatic patients is debatable,[3] since it can lead to major morbidity and mortality, potentially delaying the benefits of systemic therapy.[5]

Despite recent advances in chemotherapy, that yielded median survival times in the range of 15 months, nearly all patients with mCRC will die from their disease.[6] In the need for more effective and better tolerated therapies, inhibition of vascular endothelial growth factor signaling pathway began to be studied, since this angiogenic factor was shown to be overexpressed in near half of colorectal cancers and its increased expression was associated with more advanced disease and worse prognosis.[7]

In the last few years, phase III trials demonstrated that the combination of chemotherapy and bevacizumab, a recombinant humanized monoclonal antibody against vascular endothelial growth factor, resulted in statistically significant and clinically important improvement in survival among patients with mCRC.[6, 8] As a direct consequence of these data, adding bevacizumab to chemotherapy is now considered a standard first-line approach for stage IV disease, irrespective of the genetic status of the tumor.[9]

However, due to its antiangiogenic properties, bevacizumab was associated with an increased risk of hypertension, bleeding and gastrointestinal perforation in early clinical studies.[7, 10] In spite of the relatively low incidence of serious treatment-related adverse events observed in late phase III clinical trials,[6, 8, 11] the safety of administering bevacizumab to patients with unresected colorectal cancer remained to be further studied, since rates of adverse events were not separately reported in this subgroup of patients at special risk for bleeding and perforation.

Therefore, the aim of our study was to retrospectively analyze the safety and tolerability of upfront bevacizumab in combination with chemotherapy for the treatment of mCRC patients with unresected primary tumor, in the setting of routine clinical practice.

Materials and Methods

Study population

Medical records of patients admitted to the Medical Oncology Department of AC Camargo Hospital between January, 2007 and January, 2010 were retrospectively reviewed in order to identify all cases who met the following criteria: biopsy-proven colorectal cancer, stage IV disease with synchronous distant metastasis, no previous surgical procedure directed to primary tumor or metastases other than biopsy and/or endoscopic examinations, minimal or no symptoms related to the primary tumor, upfront treatment with bevacizumab and triple-drug chemotherapy, follow-up at our institution.

Treatment characteristics

Chemotherapy regimens used in combination with bevacizumab consisted of FOLFOX6 [oxaliplatin 100 mg/m2, folinic acid 400 mg/m^2 and bolus 5 fluorouracil 400 mg/m^2 on day 1, followed by 48-hour infusion of 5 fluorouracil 2400 mg/m^2, every 2 weeks], FOLFOX 4 (oxaliplatin 85 mg/m^2 on day 1, folinic acid 200 mg/m^2 on day 1 and 2, bolus 5 fluorouracil 400 mg/m^2 on day 1, followed by 22-hour

infusion of 5 fluorouracil 600 mg/m^2, every 2 weeks) or FOLFIRI (irinotecan 180 mg/m^2 on day 1, folinic acid 400 mg/m^2, bolus 5 fluorouracil 400 mg/m^2 on day 1 and 2, followed by 48-hour infusion of 5 fluorouracil 2400 mg/m^2, every 2 weeks). Bevacizumab 5 to 10 mg/Kg was administered over 30- to 90-minute infusion on day 1, every 2 weeks.

Data collection and statistical analysis

Data collection included patients characteristics [age at presentation, sex and race], presence of comorbidities, sites of primary and metastatic tumors at presentation, type and duration of systemic treatment, occurrence of bevacizumab-related adverse events, and vital status at last follow-up. Follow-up was calculated from first chemotherapy to last follow-up. Toxicity was assessed according to the National Cancer Institute's Common Toxicity Criteria version 2.0 [http://ctep.cancer.gov]. Continuous variables were summarized by medians. Categoric variables were summarized by counts and percentages. All study procedures were conducted under the approval of Institutional Research Ethics Committee and in accordance with the Helsinki Declaration of 1975, as revised in 1983.

Results

Patients' characteristics

Eighteen consecutive patients were identified on the basis of study criteria (10 males and 8 females). Median age at presentation was 55 years (range, 28 to 76 years). Sites of primary tumor were the rectum in twelve patients (66.6%), the left sigmoid colon in four (22.2%), the transverse colon in one (5.6%), and the right sigmoid colon in one (5.6%). All patients had liver metastases, six presented with pulmonary metastases, two had lymph node involvement, and one had peritoneal metastases. Metastatic disease involved one site in eleven patients, two sites in five patients, and three sites in two patient. Seven patients presented with hypertension and eleven with primary tumor bleeding. Table 1 depicts demographic and clinical characteristics in detail.

Systemic treatment

First-line chemotherapy regimen was oxaliplatin-based in ten patients (55.5) and irinotecan-based in 8 (44.5%). Median interval between diagnosis and start of chemotherapy was 27 days (range, 3 to 125 days). Median number of bevacizumab infusions was 14 (range, 3 to 45). Three patients received radiotherapy concomitantly to fluoropyrimidine-based chemotherapy.

Treatment outcomes

After a median follow-up was 396 days (range, 42 to 980 days), five patients died from mCRC, 12 still are on systemic therapy, and one lost to follow-up after 613 days. Among ten patients with primary tumor bleeding at presentation, symptom ceased after treatment initiation in seven (70.0%) and no episodes of symptom worsening were reported in the three remainder. There were no new cases of gastrointestinal bleeding. Two patients developed grade 1 epistaxis, both of which had gastrointestinal bleeding that stopped after the start of systemic therapy.

During treatment with bevacizumab, hypertension was successfully controlled in all seven patients who initially presented with this comorbidity, none of them requiring modification of antihypertensive treatment. There were no cases of worsening hypertension. One patient developed grade I hypertension after treatment initiation and was successfully managed with ACE inhibitor. Table 2 details selected treatment characteristics and outcomes.

One patient developed persistent grade II proteinuria requiring bevacizumab discontinuation after 45 infusions of the monoclonal antibody. Bevacizumab was also discontinued two other patients, after 3 and 8 infusions, due to pelvic abscess requiring surgical intervention and grade III perianal fistula, respectively.

Discussion

Most patients diagnosed with mCRC are submitted to primary tumor resection, but only a small percentage of them undergo surgery for tumor-related symptoms or as part of a potentially curative approach.[12] Performance status, the existence of comorbid disease, the anatomical location of the primary tumor, and the extent of distant metastases are among the considerations that generally influence the decision to perform primary tumor resection in asymptomatic patients with mCRC.[3, 13] Nevertheless, surgical resection of the primary tumor for patients who present with incurable mCRC still remains controversial.[13] Immediate resection is often indicated in order to prevent complications, which could later result in an urgent surgery frequently associated with higher mortality. On the other hand, since most patients will never develop symptoms, the majority of them could be spared from unnecessary operations, minimizing the risk of delaying or precluding systemic therapy.[14]

Several small retrospective studies found a significant survival advantage in favor of palliative resection of primary tumor in asymptomatic mCRC patients.[3, 15-17] Using the larger Surveillance, Epidemiology, and End Results database, Cook and co-workers observed that, in all age groups, the 17,658 mCRC patients undergoing primary tumor resection had higher median and 1-year survival rates when compared with the 9,186 patients who did not undergo resection ($p<0.001$).[13]

However, the possible benefits of primary tumor resection in asymptomatic stage IV colorectal patients were accompanied by a 20.0% to 30.2% postoperative complication rate and a postoperative mortality rate that ranged from 3.4% to 11.2%.[3, 12, 18] In addition, resection of asymptomatic primary tumors has not shown to reduce the incidence of life-threatening tumor-related complications.[12] No significant differences in the incidence of peritonitis, intestinal hemorrhage, fistula formation and bowel obstruction were found among 82 patients who received initial treatment with chemotherapy and without resection of the primary tumor, when compared to 280 patients who had undergone surgery.[4]

It's also important to consider that selection bias and unaccounted clinical factors may explain the survival benefit reported in the aforementioned studies.[12] Indeed, retrospective data showed that patients with resected disease were more likely to be young,[13] to have a significantly higher frequency of right colon cancers,[3, 13] to have metastatic disease restricted to the liver or only one other site apart from the primary tumor,[3] and to have fewer than three metastases.[19]

The type of systemic treatment is also likely to have influenced the results favoring surgery in older series. As opposed to patients treated with fluoropyrimidine-only conventional chemotherapy, researchers from the Memorial Sloan-Kettering Cancer Center evaluated 233 consecutive patients with unresected primary colorectal cancer and synchronous metastatic disease who received oxaliplatin- or irinotecan-based, triple-drug chemotherapy, with or without bevacizumab, between 2000 and 2006. The vast majority of the patients (93%) never required surgical palliation of their primary tumor. Moreover, the use of bevacizumab was not associated with an increased intervention rate. These findings seems to support the nonoperative initial management of the asymptomatic primary tumor, in those patients with synchronous mCRC and without overt obstruction or hemorrhage.[14]

With all the limitations inherent to small retrospective series, our study confirmed the results found by Poultsides and colleagues, demonstrating an extremely low rate of grade 1 bleeding and absence of bowel perforation in mCRC patients with unresected primary tumor receiving bevacizumab and triple-drug chemotherapy. It's worth to note that our study also included patients with grade I bleeding at presentation, which did not translate into an increased risk of serious hemorrhage during antiangiogenic therapy, although these results should be interpreted with extremely caution. Both in our series, in which rectal cancer patients accounted for 66.6% of the study population and none of them required surgical intervention, and in Poultsides' study, location of the primary tumor in the rectum, as opposed to the colon, was not associated with a higher incidence of urgent surgery.[14] Additionally, our study suggested that, in the daily practice, hypertension can be successfully managed during bevacizumab treatment, as previously indicated in phase III trials.

Although still not using bevacizumab as part of the upfront treatment, Muratore et al. also found that a very low rate of complications related to the non-resected colorectal tumor, among 35 patients treated with a more modern, oxaliplatin-based chemotherapy (FOLFOX6). Fifteen of them (42.9%) were down-staged to surgery, none of which developed complications related to the primary tumor during chemotherapy. Of the 20 remainder, only one (2.8%) developed clinical signs of intestinal occlusion and required urgent colostomy, 5.6 months from chemotherapy initiation.[20] Furthermore, two other retrospective studies have failed to show any survival advantage in favor of immediate surgery for patients with asymptomatic mCRC, even though triple-drug chemotherapy and antiangiogenic agents were not used in both studies.[18, 19]

Conclusions

Our data is consistent with the view that upfront, modern, triple-drug chemotherapy, in combination with bevacizumab, is a safe approach for patients with unresected primary colorectal cancer and synchronous metastases. No major complications related to the primary tumor were observed. Although our data comes from a limited number of patients, there is a lack of prospective controlled trials in the literature on this subject. Therefore, in selected cases, asymptomatic or minimally symptomatic patients with mCRC could be managed without immediate surgery, even with the use of antiangiogenic therapy. Prospective trials are still needed to further investigate the actual role of primary tumor resection for asymptomatic mCRC patients.

Acknowledgments

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Table 1. Baseline patients' characteristics.

Patient	Sex	Age [years]	Primary tumor location	Sites of metastatic disease	Hypertension	Primary tumor bleeding
#1	female	58	transverse colon	Liver and lungs	no	no
#2	female	75	rectum	Liver and lungs	yes	yes
#3	male	53	rectum	Liver	no	yes
#4	male	53	rectum	Liver	no	yes
#5	female	55	rectum	Liver	no	yes
#6	female	70	rectum	Liver and lungs	yes	yes
#7	female	48	left colon	Liver	yes	no
#8	female	55	rectum	Liver	no	yes
#9	male	43	left colon	Liver	no	yes
#10	male	58	rectum	Liver	yes	yes
#11	female	60	left colon	Liver, lungs and peritoneum	yes	no
#12	male	28	rectum	Liver	no	no
#13	male	71	rectum	Liver and lungs	no	yes
#14	male	29	left colon	Liver	no	yes
#15	male	52	right colon	liver, lungs and lymph nodes	no	no
#16	male	61	rectum	Liver	no	yes
#17	male	51	rectum	Liver and lymph nodes	yes	no
#18	female	76	rectum	Liver	yes	no

Table 2. Treatment characteristics and selected safety results.

Patient	CT regimen	Number of bevacizumab infusions	Follow-up [days]	Hypertension [worst grade]*	Bleeding [worst grade]*
#1	FOLFOX6	20	423	0	0
#2	FOLFOX6	4	345	0	1
#3	FOLFIRI	6	535	0	1
#4	FOLFOX4	15	678	0	0
#5	FOLFIRI	10	523	0	1
#6	FOLFOX6	5	288	0	1
#7	FOLFOX6	22	522	0	0
#8	FOLFIRI	15	369	1	1
#9	FOLFOX6	19	613	0	0
#10	FOLFOX6	20	635	0	0
#11	FOLFOX6	45	980	0	0
#12	FOLFIRI	14	637	0	0
#13	FOLFOX6	14	267	0	0
#14	FOLFOX6	9	121	0	0
#15	FOLFOX6	20	321	0	0
#16	FOLFIRI	3	290	0	0
#17	FOLFIRI	8	284	0	0
#18	FOLFIRI	4	42	0	0

*According to the National Cancer Institute's Common Toxicity Criteria version 2.0.

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