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Anti-angiogenic Agents in Resectable Colorectal Cancer Metastases: A Lebanese Experience

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Abstract

Background: Certain studies demonstrated that the addition of anti-VEGF and anti-EGFR drugs improves the overall survival, progression free survival, and response rate in colorectal cancer patients after resection of their liver metastases in a curative intent. We aimed to assess the benefit of addition of cetuximab to standard chemotherapy in patients with resectable colorectal liver metastases.

Methods: In this research, 11 patients with colorectal cancer and potentially curative liver metastases, who underwent metastasectomy from different Lebanese hospitals were analyzed. Patients received 5-FU, irinotecan, oxaliplatin with either cetuximab or bevacizumab pre and post operation. Response rate was compared between patients retrospectively, whether complete, partial, stable, or no response.

Results: Out of 11 patients, 5 patients had progression free survival for 3 months after surgery, out of which 1 (9%) had a complete response, 2 had partial response, and 2 had a stable disease. No increase in the major side effects or mortality was noted.

Discussion: Our results agree with other studies from different geographic regions. We recommend the addition of a biological agent to the standard systemic chemotherapy, because it is associated with improved overall survival and disease control rate, but further studies are still needed to investigate the influence of KRAS and BRAF mutation status on prognosis and treatment outcome.

Keywords: Colorectal cancer; Liver metastases; Bevacizumab; Cetuximab

Introduction

Colorectal cancer in the most frequently diagnosed cancer in Europe and is one of the leading causes of death due to cancer worldwide. About quarter of the patients with colorectal cancer have metastases at the time of diagnosis. Another quarter will develop metastases after a curative resection of the primary disease. Isolated liver or lung metastases represent a favorable factor because of the possibility of cure after their resection and chemotherapy [1]. The 5 year survival rate after resection of liver metastases is 25% to 40%. However, about 80% of patients are considered unresectable due to involvement of extra hepatic sites [2]. Although there is substantial improvement in survival due to advances in medical treatment and to an increase in surgical resection of metastases, the long term outcome of the patients is still unsatisfactory and further improvements are required [3].

The median survival of patients with metastatic colorectal cancer treated with supportive care is about 6 months. Palliative chemotherapy increases survival to approximately 20 months. The standard chemotherapy regimen for metastatic colorectal cancer is 5-fluorouracil/leucovorin/oxaliplatin (FOLFOX), and 5-fluorouracil/leucovorin/irinotecan (FOLFIRI) [2].

Neoadjuvant chemotherapy is being widely used for multiple reasons:

- Treatment of undetectable microscopic metastases.
- Determination of chemotherapy responsiveness of the tumor to aid in selection of the optimal adjuvant regimen.
- Identification of patients with aggressive disease in whom surgery is inappropriate.
- Downsizing the liver metastasis rendering the unresectable ones resectable [2].

The use of neoadjuvant chemotherapy increases the percentage of patients with resectable colorectal liver metastasis from 25% to 35%; it also improves the long term survival to 40% [4].

Certain studies demonstrated that the addition of antiangiogenic agent, bevacizumab (AVASTIN), with is a fully humanized monoclonal antibody against vascular endothelial growth factor (anti-VEGF) improves the overall survival, progression free survival, and response rate [2]. Bevacizumab promotes tumor shrinkage and inhibits angiogenesis, it also has an effect on the micro metastases [2]. The cellular mechanisms of action of bevacizumab are multifactorial and include inhibition of vascular neogenesis, vascular regression, and normalization of tumor vasculature [5].

The epidermal growth factor receptor EGFR mediates stimulation of cellular proliferation, survival, and motility and may be involved in tumorigenesis. Many anti-EGFR antibodies have shown clinical

efficacy in metastatic colorectal cancer. Cetuximab (ERBITUX), a monoclonal anti-EGFR, was found to increase overall survival and progression free survival when used as a single agent, or in combination with chemotherapy, in patients who are refractory to the usual regimen [6].

Methods

From December 2010 to June 2016, patients were enrolled from three different hospitals in Lebanon. All adult patients with resectable colorectal liver metastases who underwent resection of the primary tumor site, with or without extra-hepatic distant metastatic disease were considered and studied retrospectively (Table 1).

Patients	Age	Sex	ECOG performance status	Site of primary tumor	Surgery of primary tumor	Extrahepatic metastases
Patient 1	60	Female	1	rectum	yes	no
Patient 2	35	Male	0	Right colon	yes	no
Patient 3	50	Female	0	Right colon	yes	no
Patient 4	72	Female	1	Sigmoid	yes	no
Patient 5	79	Male	1	Right colon	yes	no
Patient 6	67	Male	0	Rectum	yes	no
Patient 7	74	Male	1	Sigmoid	yes	no
Patient 8	65	Male	1	Sigmoid	yes	Lung
Patient 9	54	Female	0	Rectosigmoid	yes	no
Patient 10	74	Male	1	Rectosigmoid	yes	no
Patient 11	54	Male	0	Right colon	yes	no

Table 1: Demographic and clinical characteristics of patients.

Inclusion criteria

- Histologically confirmed diagnosis of colorectal adenocarcinoma was needed in all patients.
- Patients should have resectable colorectal liver metastases; there was no limit to the number of metastases.
- ECOG performance status should be 2 or less.
- All patients had adequate liver and renal function, no significant cardiovascular disease, no current therapeutic anticoagulation, and no active infection.

Exclusion criteria

- Patients with uncontrolled medical comorbidity likely to interfere with treatment or assessment of response.
- Patients with another previous or current malignant disease were excluded.
- Patients with any disorder affecting the patient's ability to consent or comply with medications were not included in the study.

The chemotherapy regimen was oxaliplatin (alkylating agent) with 5 FU (antifolate) plus or minus anti-angiogenic agent bevacizumab or cetuximab, or irinotecan (anti-topoisomerase inhibitor) with 5 FU plus or minus bevacizumab or cetuximab pre and post op. Treatment was given every 2 weeks. The feasibility of surgical resection of metastatic sites was routinely assessed and strongly recommended when feasible. The treatment was interrupted and then resumed after surgery.

The primary end point was progression free survival at 3 months post op. Secondary end points were response rate and overall survival.

Assessment of response was done with CT scans repeated every 8 weeks. Progression free survival was calculated from the day of starting the treatment to the first observation of disease progression or death due to any cause. The overall survival was calculated from the day of treatment till the death or the last date known to be alive (Table 2).

Number of patients		11
Median age, years		62.2
Sex	Male, (%)	63.6
	Female, (%)	36.4
ECOG Performance status		0-1
Patients with primary tumor resected, (%)		100
Histology, adenocarcinoma, (%)		100
Prior adjuvant chemotherapy, (%)		100
Extra-hepatic metastasis, (%)		9

Table 2: Patient demographics.

Treatment

Eligible patients received bevacizumab 5 mg/kg by IV infusion over one and a half hour for the first infusion and then half an hour for the remaining cycles or cetuximab loading dose 400 mg/m^2 as a 2 hour infusion then a maintenance dose of 250 mg/m^2 over 1 hour. Irinotecan was administered also by IV infusion each dose over one

and a half hour. 5 FU was administered on variable time infusions depending on the patient's regimen. Oxaliplatin was administered by IV infusion over 2 hours.

Study evaluation

Evaluation included a complete history, physical examination, routine blood tests, and CT scans of the chest and abdomen to evaluate the extent of the disease. A multidisciplinary team of oncologists, surgeons, radiologists and anesthesiologists confirmed that the patient was eligible for the surgery. Response rate was evaluated by serial follow-up PET scans on CT scans.

Surgical technique

Liver metastasectomy was planned at least 4 weeks after the last chemotherapy session. For patients who received preoperative chemotherapy, sessions ranged from 4 to 29, and postoperative from 1 to 19 where the first was started after a minimum of 4 weeks after the surgery. Patients were assessed before surgery by a minimum of cardiologist and pulmonary physician for pre op clearance. During surgery, all visible liver metastases were completely resected with a negative margin in all patients.

Results

From December 2010 till June 2016, 11 patients with colorectal cancer and liver metastases potentially curable by resection were enrolled into the retrospective study. The median age was 62.2 years and the majority of patients had an ECOG performance status 0-1, where about two third (63.6%) of them were males.

Out of 9 patients, 11 were assessed for response to chemotherapy post-op, 2 patients (18.18%) lost to follow-up. 1 patient (9%) had complete response and 2 patients (18.18%) had partial response with an overall response rate of 27.18%. 2 patients (18.18%) had a stable disease. Thus the disease control rate was 45.36%. 4 patients (36.3%) had a progressive disease. So 45.3% had progression free survival 3 months after surgery (Table 3).

Response	Number of patients	Percentage (%)
Complete	1	9
Partial	2	18.18
Stable	2	18.18
Progressive	4	36.3
Lost follow-up	2	18.18

Table 3: Tumor response to chemotherapy postop.

Discussion

The management of metastatic colorectal cancer patients after surgical resection of metastases is still debated. In these patients the current NCCN guidelines recommend 2 to 3 months pre op chemotherapy FOLFOX or FOLFIRI with anti-angiogenic agent if normal wild KRAS gene, and possible post op chemotherapy such that the total doesn't exceed 6 months of chemotherapy. On the first hand, many studies proved some deleterious effect of the biologic therapy on the overall survival of patients with metastatic colorectal cancer [7]. In the trial of Kemeny et al. the addition of bevacizumab to hepatic arterial injection (HAI) and systemic chemotherapy didn't improve survival, also it was associated with increased biliary toxicity [8]. Also in a retrospective study by Turan et al. there was no survival benefit of adding bevacizumab to chemotherapy and no difference between the various chemotherapy regimens was seen [9]. Primrose et al. in the new EPOC randomized controlled trial did not recommend the combination of cetuximab and systemic chemotherapy (oxaliplatin, 5FU, and irinotecan) due to non-significant increase in response and shorter progression free survival in wild type KRAS exon 2 patients receiving both chemotherapy and cetuximab (14.1 months) compared to chemotherapy alone (20.5 months) [4]. On the other hand, Masi et al. in their phase 2 trial comparing FOLFOXIRI regimen alone or in combination with bevacizumab, showed that the combination of FOLFOXIRI and bevacizumab was feasible. It was associated with an overall response rate of 77% and disease control rate of 100% [3]. In addition, Gruenberger et al. concluded in their study that the addition of bevacizumab plus XELOX (capecitabine and oxaliplatin) allowed potentially curative resection in approximately 95% of patients without increase in the rate of surgical complications [2]. Stein et al. proved that the systemic chemotherapy pre and post op in combination with EGFR or VEGF antibodies has reduced recurrence and prolonged survival in initially clearly resectable metastatic colorectal cancer [1]. Moreover, in a study conducted by Wong et al. neoadjuvant capecitabine and oxaliplatin plus bevacizumab resulted in a high response rate for patients with colorectal cancer with liver only metastasis with poor-risk features not selected for upfront resection and converted 40% of patients to resectability [10].

Our data demonstrates that the addition of a biologic agent, bevacizumab or cetuximab, to the standard chemotherapy regimen (oxaliplatin, 5-FU, irinotecan) in the preoperative period, and in the postoperative period was associated with improved survival and promising efficacy. The percentage of disease control rate was 45.36%, 3 months post op; while a progression of the disease in 36.3% with no increase in the major operative complications.

This high level of efficacy may be due to the fact that all patients included in our study had good performance status and the small sample size of this trial may have affected the results. Our study has several limitations, the major weakness is the small number of patients included. Furthermore, the patients were not evaluated for the KRAs and BRAF mutations which are very important in the evaluation of colorectal cancer prognosis and treatment strategies.

In summary, we recommend the addition of a biological agent to the standard systemic chemotherapy, because it is associated with improved overall survival and disease control rate according to our study, but further studies are still needed to investigate the influence of KRAS and BRAF mutation status on prognosis and treatment outcome.

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