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Chemoembolization Alone or Associated With Bevacizumab for Therapy of Colorectal Cancer Metastases: Preliminary Results of a Randomized Study

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Abstract. *Aim: to assess efficacy and safety of chemoembolization alone (TACE) and followed by bevacizumab (TACE-B) in patients with colorectal liver metastases (CRC-LM) (NCT03732235). Patients and Methods: The study included 30 consecutive patients with CRC-LM. They were informed about the types of treatment available: TACE with irinotecan loaded into polythylene glycol embolics alone or followed by bevacizumab therapy. Each patient underwent self-randomization and 17 chose TACE, whereas 13 chose TACE-B. Results: Tumor response at 3 months was complete response in one (6%) and four (31%) patients, and partial response in two (13%) and six (46%) patients, after TACE and TACE-B, respectively. No complications were observed during TACE. Most TACE-related adverse events were correlated with post-embolic syndrome. Conclusion: The preliminary results of the study showed that the TACE-B is feasible and tolerable. This study will be continued in order accrue a larger number of patients and longer follow-up.*

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Liver metastases are present in more than 50% of patients affected by colorectal cancer (CRC) (1, 2). Surgical resection of liver metastases from colorectal cancer (CRC-LM) is feasible in only 15-20% of cases (3). Median survival at 5 years for those with complete resection (R0) is 25-35%, and recurrence in the liver is frequent (1-3). Despite the introduction of new chemotherapeutic agents and the development of locoregional therapies (embolization, percutaneous ablation, hepatic arterial-directed infusion chemotherapy, internal radiation), there is still a lack of standardized evidence-based protocols for optimal CRC-LM management (3). Transarterial chemoembolization (TACE) with irinotecan-loaded polyethylene glycol embolics has produced interesting results in terms of objective response in CRC-LM treatment (4).

There is wide evidence that CRC is angiogenesis-dependent and that angiogenesis is elevated in CRC compared to non-neoplastic tissue (5-7). Vascular endothelial growth factor (VEGF) is the most important pro-angiogenic factor and is expressed at higher levels in CRC than in non-neoplastic tissues (8-10). The first anti-angiogenic therapy was introduced in 2004 with a humanized murine monoclonal antibody against VEGF called bevacizumab (10, 11). Bevacizumab is approved for the treatment of CRC-LM in combination with fluoropyrimidine-based chemotherapy (12, 13). It is used in normal clinical practice as first-, second- and third-line chemotherapy for CRC-LM and is often associated with chemoembolization.

Expression of VEGF is up-regulated by hypoxia-inducible factor 1 and 2 (HIF1 and HIF2). Chemoembolization induces a hypoxic microenvironment that increases the expression of HIF1 and HIF2, resulting in high VEGF expression and neo-angiogenesis. This may also induce tumor relapse. For this

reason, there is a strong rationale for the association of a biological agent, such as bevacizumab, with hepatic chemoembolization treatment (14).

The aim of this study was to collect data on the treatment of patients with CRC-LM that was refractory to systemic therapies and was treated with TACE alone or in association with bevacizumab, in order to assess tolerability, quality of life and objective responses.

Patients and Methods

Patients. This was a prospective observational study that was approved by the local Institutional Review Board (ClinicalTrials.gov Identifier: NCT03732235). The study included 30 consecutive patients with CRC-LM. They were informed about the types of treatment available: TACE with irinotecan loaded into polythylene glycol embolics alone or TACE followed by bevacizumab therapy (TACE-B). Each patient underwent self randomization as reported in other studies (15): They were informed about the two types of therapies available and were asked to choose the one that they preferred;17 chose TACE, whereas 13 chose TACE-B. Patients were included in the study if they met the following inclusion criteria: Age >18 years, diagnosis of CRC-LM, unresectable disease, no response to standard chemotherapeutic lines, Eastern Cooperative Oncology Group performance status of 0-1, tumor size evaluable according to RECIST version 1.1 (16), liver involvement from 25% to 40%, life expectancy of at least 3 months, normal ranges of routine blood biochemistry assays.

Exclusion criteria were the following: Contraindication to angiographic catheterization, extensive extra-hepatic disease, pregnancy or breast feeding, other severe clinical contraindications.

TACE and TACE-B procedures. Tumor arterial perfusion was assessed by diagnostic angiography before TACE. TACE was performed using 2 ml of LifePearl® with 100 micron diameter (Terumo Europe NV, Leuven, Belgium) that were loaded with irinotecan (100 mg) as previously described (4, 13). Infusion was performed at fixed speed of 1 ml/minute for a median time of 12 minutes. A second TACE was performed after 30 days.

For the TACE-B group, bevacizumab therapy was started 15 days after the first TACE at a concentration of 5 mg/kg, and was repeated every 2 weeks for a total of eight cycles.

Assessment of objectives. The baseline data collected for each patient included: medical history; weight; height; blood pressure; performance status; routine complete blood chemistry; tumor parameters [carbohydrate antigen 19-9 (CA 19-9), carcinoembryonic antigen (CEA) and VEGF]; tumor assessment by computed tomographic scan of the thorax, abdomen and pelvis; fluorodeoxyglucose positron-emission tomography/computed tomography with scan or liver ultrasound contrast agent (Sonovue). RECIST criteria version 1.1 (13) was used to monitor tumor response (at 3, months) from abdominal and pelvic computed tomographic imaging. The CEA level was monitored at 1, 3, 6 months after TACE.

National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 3.0 was used to classify adverse events (16).

Statistical analysis. The data analysis of the whole sample was performed using the median for continuous data; proportions are expressed as percentages. Significance of continuous variables was assessed with chi-square and Student's t-test ($p<0.05$). Overall survival (OS) was analyzed with the Kaplan–Meier method, and significance was computed with the log rank test, significance was established as $p<0.05$.

Results

Patients. The study included 30 patients affected by unresectable CRC-LM that were non-responsive to systemic therapy. Seventeen were treated with TACE alone and 13 with TACE-B. Fifteen (50%) patients were males and 15 (50%) females. The median patient age was 72.5 (range=50-87) years (Table I).

Tumor response. Tumor responses at 3 months after TACE and TACE-B were complete response in one (6%) and four (31%), partial response in two (13%) and six (46%), stable disease in eight (50%) and two (15%), and progressive disease in five (31%) and one (8%), respectively. The corresponding disease control rates were 69% and 92% for TACE and TACE-B, respectively; the difference was statistically significant ($p<0.01$).

Median follow-up was 6 (range=1.3-6) months. The CEA level consistently decreased from baseline to 1, 3 and 6 months (Table I) in all patients.

Survival. Median overall survival (OS) was 12 (range=7-22 months) (Figure 1), time to progression was 4.5 (range 3-9) months and median progression-free survival was 6 (range=3-18) months for the TACE-B group. Median OS was 5.8 (range=1.5-7.7) months (Figure 1), median time to progression was 2.9 (range=1.5-6.4) months and median progression-free survival was 4 (range=1.5-7.7) months in the TACE group. OS and progression-free survival were statistically greater ($p<0.01$) in the TACE-B than in the TACE group.

Tolerability. No complications were observed during TACE. Most TACE-related adverse events were correlated with post-embolic syndrome and were of mild or moderate intensity. Pain (grade 2) was observed in 14 (47%) patients, and was resolved in 2-5 days. Transaminase rise was observed in 10 (33%) patients and was of grade 2-3 intensity. No thromboembolic effects were observed.

Bevacizumab-related adverse events were increased blood pressure (grade 2) in two (16%), fever (grade 2) in two (16%) and skin rash (grade 2) in four (31%) patients.

Discussion

TACE is an occlusive procedure that closes medium-caliber vessels feeding the tumor. Tumors need neovascularization in order to obtain oxygen and nutrients for their growth and development. Bevacizumab creates an insufficient blood

Table I. *Characteristics of study population.*

Characteristic	Value
Gender, n (%)	
Male	15 (50%)
Female	15 (50%)
Age, years	
Median (range)	72.5 (50-87)
Tumor size, mm	
Median (range)	50 (5-110)
Tumor nodules, n (%)	
1-2	7 (23%)
3-5	14 (47%)
>5	9 (30%)
CEA, U/ml	
Baseline, median (range)	400 (110-932)
At 1 Month, median (range)	250 (70-800)
At 3 Months, median (range)	212 (40-763)
At 6 Months, median (range)	135 (45-245)
Chemotherapy lines, n (%)	
1	4 (13%)
2	11 (37%)
3	8 (27%)
>3	7 (23%)

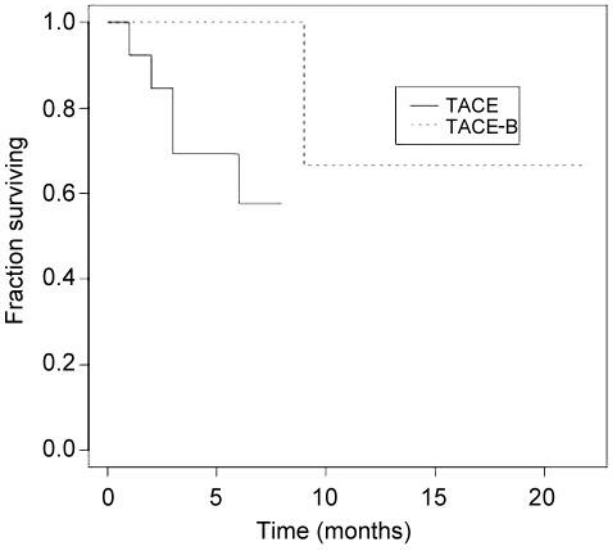

Figure 1. *Kaplan–Meier curve of survival according to therapy with transarterial chemoembolization with irinotecan (TACE) alone and combined with bevacizumab (TACE-B).*

afflux to the tumor by the biomolecular mechanism of anti-angiogenesis. The association of TACE with bevacizumab creates a double antiangiogenic attack.

TACE can be associated with several anti-angiogenic factors (bevacizumab, aflibercept and regorafenib) in targeted therapy (17). This association can increase tumor responses and duration, and improve quality of life.

Very few studies have focused on the association of TACE with bevacizumab, and they were performed in HCC (18-20).

Bevacizumab has been used with proven results in association with irinotecan, as bolus followed by infusional 5-fluorouracil and leucovorin (FOLFIRI) and with irinotecan, bolus fluorouracil and leucovorin, resulting in increased partial response and objective response rates, and reduction of mortality risk in patients with CRC-LM (19, 20).

In the present study, we collected data on 30 patients affected by CRC-LM whose disease was refractory to previous chemotherapy and who were treated with TACE alone or followed by intravenous bevacizumab. Median OS was 12 months (range=7-18 months) and 5.7 (range=1.5-7.7) months in the TACE and TACE-B groups, respectively. The median OS of the TACE-B group [12 (range=7-22) *vs*. 5.8 (range=1.5-7.7) months for TACE alone] was comparable to that previously reported for patients with CRC-LM treated with TACE alone [14 (range=1.3-25) months] (21). Many patients included in this study received more than two lines of chemotherapy, this may have influenced OS and reduced their life expectancy.

The disease control rates of 69% and 92% for TACE and TACE-B, respectively, were comparable to the 78% reported by another study treating CRC-LM with TACE and leucovorin, fluorouracil and oxaliplatin (FOLFOX) (22).

The results of this study showed that TACE-B was well tolerated and associated with mainly grade 1-2 adverse events that were resolved in a few days, in agreement with previous studies (9, 10).

The main limitations of this report were the small number of patients enrolled and the number of centers involved. Further randomized multicentric studies with a larger number of patients are necessary to confirm these data on the association of TACE with angiogenesis inhibitors in for the treatment of refractory CRC-LM.

In conclusion, the results of our study suggest that the combination of TACE with intravenous bevacizumab is effective, feasible, and well-tolerated by patients with CRC-LM and may potentially have more benefits concerning tumor response and survival than TACE alone.

Conflicts of Interest

All Authors declare they have no conflicts of interest in regard to this study.

Authors' Contributions

Giammaria Fiorentini performed the bevacizumab treatment and supervised the study. Donatella Sarti collected and analyzed the data, including table and graph production, wrote the article. Stefano Guadagni supervised the study and reviewed the article. Michele

Nardella, Riccardo Inchingolo, Massimiliano Nestola, and Alberto Rebonato performed the TACE treatments.

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