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Original Research

Efficacy of FOLFOXIRI plus bevacizumab in liver-limited metastatic colorectal cancer: A pooled analysis of clinical studies by Gruppo Oncologico del Nord Ovest

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Abstract Secondary resection is a chance of cure for a subgroup of metastatic colorectal cancer (mCRC) patients with unresectable liver-limited disease. Medical treatment has a dual goal: to induce tumour shrinkage and to prevent disease relapse. The aims of the present analysis were to assess the efficacy of FOLFOXIRI plus bevacizumab in this setting, and to investigate whether this regimen could revert the poor prognosis of high-risk patients defined by clinical and molecular factors. We performed a pooled analysis of patients with unresectable and liver-limited mCRC, treated with first-line FOLFOXIRI plus bevacizumab in three prospective clinical trials by Gruppo Oncologico del Nord Ovest. 205 (37.9%) patients with liver-limited disease were selected, out of 541 treated patients. Liver metastases were synchronous, ≥4 and bilobar in 90%, 61%, and 79% of cases, respectively. The largest diameter was >5 cm in 42% of cases, and ≥6 segments were involved in 25%. Seventy-four patients (36.1%) underwent R0 or R1 resection of metastases. R2 resections were performed in 17 cases (8.3%). Having <6 involved segments ($p < 0.001$) and achieving RECIST response ($p = 0.019$) were associated with higher chances of resection. R0/R1 resected patients had significantly longer median progression-free survival (PFS) (18.1 versus 10.7 months, HR: 0.48 [0.35–0.66], $p < 0.001$) and overall survival (OS) (44.3 versus 24.4 months, HR: 0.32 [0.22–0.48], $p < 0.001$) compared with other patients, both in the univariate and multivariate analyses (PFS $p = 0.025$; OS $p < 0.001$). The 5-year PFS and OS rate in R0 resected patients were 12% and 43%, respectively. Neither negative baseline characteristics nor high clinical risk scores or *RAS*/*BRAF* mutations were associated with poor post-resection outcomes. In conclusion, FOLFOXIRI plus bevacizumab demonstrates efficacy in the conversion setting with considerable long-term outcome results independent of clinical and molecular prognostic factors (NCT00719797, NCT01163396 and NCT02271464).

1. Introduction

The optimal integration of systemic treatments and locoregional approaches may lead to cure a subgroup of metastatic colorectal cancer (mCRC) patients [1]. The radical resection of liver metastases may be pursued also in patients initially deemed unresectable, and the rate of patients who may be converted to surgery is notably increasing, thanks to more active systemic regimens, innovative surgical techniques and a widespread multidisciplinary approach [2].

In these patients, the upfront systemic treatment has a dual goal: to shrink the tumour enough to make the surgical resection technically feasible, and to eradicate the micrometastatic disease, to reduce the risk of relapse and to impact on patients' long-term outcome.

To this purpose, the Gruppo Oncologico del Nord Ovest (GONO) studied a combination regimen including the three active cytotoxics, 5-fluorouracil, oxaliplatin and irinotecan (FOLFOXIRI), reporting notable percentages of conversion to resection and considerable results in terms of long-term survival [3–5].

More recently, a phase III trial by the GONO group demonstrated a significant advantage for FOLFOXIRI plus bevacizumab when compared with FOLFIRI plus bevacizumab in terms of response rate, early response, deepness of response, progression-free survival (PFS) and overall survival (OS) in a population of unresectable mCRC patients, not selected with a conversion intent [6–8]. The phase II OLIVIA study randomised patients with initially unresectable mCRC and liver-limited metastases to receive FOLFOXIRI plus bevacizumab or FOLFOX plus bevacizumab, showing a significant increase in R0 resection rate among patients receiving the triplet plus bevacizumab, with remarkable PFS and OS results [9].

In this pooled analysis, we aimed at describing the clinical outcome of mCRC patients with unresectable disease confined to the liver, who received FOLFOXIRI plus bevacizumab as first-line treatment in three prospective clinical trials conducted by the GONO group [8,10,11], and explored the association of baseline and 'on treatment' variables with radical resection following FOLFOXIRI plus bevacizumab. Finally, given that the triplet plus bevacizumab seems an efficacious option especially in poor prognosis patients (i.e. *BRAF* mutant), we asked whether the prognostic impact of negative clinical and molecular factors could be counterbalanced by such an intensive conversion treatment.

2. Methods

2.1. Patients' selection

From July 2007 to March 2015, 541 mCRC patients received first-line FOLFOXIRI plus bevacizumab in three multicenter clinical trials by GONO: the single-arm phase II FOIB study [10] (N = 57), the phase III