Editorial

FOLFOXIRI plus bevacizumab in the treatment of metastatic colorectal cancer patients with unresectable liver metastases

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Liver is the most common site of metastatic spread from colorectal cancer (CRC) and the only site of metastases in around 20% to 30% of all cases.

For CRC patients with liver-limited metastatic disease, the radical resection of metastases is associated with prolonged overall survival (OS) as compared with non-curative or no liver resection (1,2).

In the last few years, the initial systemic approach for patients with mCRC with metastases confined to the liver has notably changed, thus leading to an increased proportion of patients being or becoming candidate for radical liver surgery, especially among those deemed initially ineligible for radical liver metastasectomy (3). Indeed, the evolution of active systemic treatments and surgical and locoregional interventions, together with their proper and tailored integration in the context of experienced multidisciplinary boards, has substantially contributed to improve the clinical outcome of these selected patients, offering to a proportion of them a chance of cure or, at least, long-term disease-free remission (4).

Despite this rapidly evolving scenario, a consensus about the optimal therapeutic approach for patients with liver-only metastases has not been well-established. This is partially explained by the limited number of trials prospectively conducted in this special population, whose interpretation is biased by the heterogeneity among enrolled patients with different predictive and prognostic factors and the lack of widely accepted criteria on technical/clinical surgical resectability.

Nevertheless, for patients with initially unresectable liver metastases, due to technical/surgical and/or oncological/prognostic factors, when secondary resection is a pursuable objective, the therapeutic choice should be a regimen able to both induce tumour shrinkage and eradicate the micrometastatic disease, in order to make technically feasible locoregional interventions, and/or to prevent disease relapse and achieve a long-term clinical benefit.

To these purposes, the intensified three-drug chemotherapy regimen FOLFOXIRI, including 5-fluorouracil, oxaliplatin and irinotecan, in combination with bevacizumab, is considered a valuable choice when the secondary resection of metastases is a treatment objective, mainly in the case of liver-limited spread (5-7).

The potential role of first-line FOLFOXIRI plus bevacizumab as conversion treatment was prospectively challenged in the phase II OLIVIA study (8), which enrolled 80 patients with liver-limited mCRC deemed initially unresectable according to predefined surgical criteria. As compared to a standard treatment with a two-drug chemotherapy regimen (FOLFOX, 5-fluorouracil, and oxaliplatin) plus bevacizumab, FOLFOXIRI plus bevacizumab increased the overall (R0/R1/R2) resection rate (61% versus 49%, P=0.271)—primary endpoint of the study. Notably, among patients receiving the triplet chemotherapy plus bevacizumab a higher radical (R0) resection rate (54% versus 31%) as well as a markedly improved objective response rate (ORR) (81% versus 62%) were reported, with a substantial benefit also observed

in terms of survival results. The intensified approach did not raise notable safety concerns, with an expected rate of surgery-related adverse events.

Consistently, in a pooled analysis of 205 patients with unresectable liver-limited mCRC, not selected according to the extent of the metastatic spread and/or the potential conversion to resectability, treated with FOLFOXIRI plus bevacizumab in three prospective clinical trials by GONO Foundation, the intensified treatment allowed to achieve remarkable response rate (69%), which translated into a considerable R0/R1 resection rate (36%) and long-term survival outcomes, regardless of clinical and molecular prognostic factors (9).

While data highlighting the added value of the triplet in patients selected according to inclusion criteria of pivotal trials were rapidly increasing (10-12), the primary tumour location clearly emerged as a clinical factor affecting the sensitivity to anti-EGFR antibodies in *RAS* and *BRAF* wild-type tumours (13,14). Based on this evidence, the primary tumour location entered the therapeutic algorithm for upfront treatment of mCRC patients, as one of the major drivers in the current decision-making process, together with patients' clinical conditions and *RAS* and *BRAF* mutational status (15).

In this perspective, independently of the goal of the treatment, the addition of an anti-EGFR antibody to a two-drug chemotherapy regimen is nowadays highly recommendable for patients with left-sided and *RAS* and *BRAF* wild-type tumours, whereas a bevacizumab-based first-line therapy should be preferred for those with right-sided and/or *RAS* or *BRAF* mutated tumours (15). To this regard, an accurate clinical selection of patients candidate to the FOLFOXIRI plus bevacizumab regimen in terms of age and Eastern Cooperative Oncology Group (ECOG) performance status is needed (10,11).

In the single-center FORBES trial, Shen and colleagues evaluated the added value of combining bevacizumab with a modified schedule of first-line FOLFOXIRI (mFOLFOXIRI) with reduced dose of irinotecan in molecularly selected mCRC patients (16).

While the impact of combining bevacizumab with different chemotherapy regimens, including fluoropyrimidine monotherapy and oxaliplatin- or irinotecan-containing doublets has been largely investigated (17-21), no randomized comparison of FOLFOXIRI with or without bevacizumab was available when the FORBES trial was planned.

Though in the absence of a prospective randomized comparison, the absolute benefit from adding bevacizumab to FOLFOXIRI in terms of survival was previously estimated, by adopting a propensity score-adjusted model, to minimize as more as possible this relevant bias (22). In a population not selected according to both the extent of the disease and tumour mutational profile, patients treated with FOLFOXIRI plus bevacizumab in the TRIBE study (10) reported longer progression-free survival (PFS) and OS, than those treated with the triplet alone in a previous phase III trial (23), with a magnitude of benefit similar to the relative impact of adding bevacizumab to less intensive chemotherapy backbones.

The same question challenged in the FORBES trial has been addressed also by the AIO-CELIM-2 (24), investigating the added value of combining bevacizumab to first-line FOLFOXIRI as compared to FOLFOXIRI alone, in mCRC patients with *RAS* or *BRAF* mutated unresectable liver-limited disease. However, the study was prematurely terminated due to the slow accrual, and no significant differences were observed with regard to the primary endpoint ORR.

Looking at the main results provided by the FORBES trial, they appear hardly comparable to previous findings, even indirectly, due to some methodological and conceptual limitations.

The non-randomized design and the treatment assignment based on patients' preferences and not stratified according to well-known prognostic factors are arguable and responsible for a clear imbalance between treatment groups in terms of baseline number of liver metastases.

Also, the primary endpoint of the study—the percentage of patients achieving no evidence of disease (NED), including clinical complete responses, surgical radical (R0) resections with or without local ablative treatments, or macroscopically complete ablation of all visible tumour masses—is unusual and still not validated as a surrogate of long-term benefit. Moreover, additional information defining a high standard of documentation of the baseline extent of disease spread—number of involved liver segments, uni- or bilobar liver involvement—would be helpful for better characterising and comparing the study population with those of other similar trials. Similarly, currently missing information include post-resection/local procedure morbidity data that are relevant when a conversion treatment is investigated.

More recently, the phase III CAIRO5 study prospectively confirmed the added value of an intensified regimen as conversion therapy in the subgroup of patients with

unresectable liver-only disease and right-sided and/or *RAS* or *BRAF* mutated tumours (25). This trial was designed to verify the superiority of FOLFOXIRI plus bevacizumab versus a two-drug chemotherapy regimen [FOLFOX or FOLFIRI (5-fluorouracil and irinotecan), by patient preference] plus bevacizumab in 219 patients with liver metastases deemed unresectable by a liver expert panel of surgeons and radiologists based on predefined criteria. The triplet chemotherapy plus bevacizumab provided a significant PFS advantage—primary endpoint—as compared with doublets plus bevacizumab [10.6 versus 9.0 months (HR =0.77; 95% CI: 0.60–0.99); P=0.038]. In addition, ORR (52% versus 31%; P<0.001) and R0/R1 resection rate with or without ablation was significantly improved (51% versus 37%; P=0.02). The adoption of FOLFOXIRI plus bevacizumab in this setting was independently correlated to an increased risk of postoperative complications (26).

In conclusion, results of the FORBES trial are quite consistent with the available body of evidence about the role of the triplet plus bevacizumab in the setting of liver-limited mCRC, and though acknowledging above reported limitations strengthen the importance of choosing the best upfront therapy especially when conversion to resectability is a clinically relevant objective of the systemic therapy.

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