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(Article begins on next page)

Individual patient data meta-analysis of FOLFOXIRI/bevacizumab versus doublets/bevacizumab as initial therapy of unresectable metastatic colorectal cancer

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Running head: FOLFOXIRI/bevacizumab as upfront therapy for mCRC

ABSTRACT

Purpose

Several randomized trials demonstrated that the triplet FOLFOXIRI in combination with bevacizumab is beneficial for metastatic colorectal cancer (mCRC) patients with an increased incidence of adverse events. All trials had primary endpoints other than overall survival (OS), so that a proper estimation of the magnitude of the OS benefit from FOLFOXIRI/bevacizumab versus doublets/bevacizumab is currently lacking. To test OS with higher power compared to single trials, and to explore interaction of treatment effect with main patients' and disease characteristics, we performed an individual patient data (IPD) meta-analysis.

Patients and Methods

Five eligible trials were identified and IPD were collected from all these trials: CHARTA (NCT01321957), OLIVIA (NCT00778102), STEAM (NCT01765582), TRIBE (NCT00719797) and TRIBE2 (NCT02339116). Primary endpoint was OS. Secondary endpoints included progression-free survival (PFS), objective response rate (ORR), R0 resection rate, grade 3/4 adverse events, and subgroup analyses according to main clinical and molecular baseline characteristics.

Results

1697 patients randomized to FOLFOXIRI/bevacizumab (N=846) or doublets/bevacizumab (N=851) were included. Most patients (78%) had ECOG PS 0 and the median age was 61 years. After a median follow-up of 39.9 months, patients assigned to FOLFOXIRI/bevacizumab reported significantly longer OS than those assigned to doublets/bevacizumab (median OS 28.9 vs 24.5 months; HR 0.81 [95%CI 0.72-0.91], $p<0.001$), with no significant heterogeneity among trials ($p=0.39$; $I^2=2\%$). The estimated 5-yr OS was 22.3% vs 10.7% ($p<0.001$). No significant interaction effect between treatment arm and investigated characteristics was demonstrated. Patients assigned to FOLFOXIRI/bevacizumab achieved also longer PFS (median PFS 12.2 vs 9.9 months; HR 0.74 [95%CI 0.67-0.82], $p<0.001$), higher ORR (64.5% vs 53.6%, $p<0.001$), higher R0 resection rate (16.4% vs 11.8%, $p=0.007$), and experienced higher rates of grade 3/4 adverse events, in particular neutropenia (45.8% vs 21.5%; $p<0.001$), febrile neutropenia (6.3% vs 3.7%; $p=0.019$), and diarrhea (17.8% vs 8.4%; $p<0.001$).

Conclusion

The use of FOLFOXIRI/bevacizumab as first-line therapy significantly and meaningfully improves mCRC patients' survival as compared with doublets/bevacizumab, and provides consistent advantages in 5ys-OS, PFS, ORR and R0 resection rate, at the price of an acceptable increase in toxicity.

Introduction

In the last ten years the choice of the first-line therapy of patients with metastatic colorectal cancer (mCRC) has been made more complex by the increased availability of different treatment options. The anti-angiogenic bevacizumab and the anti-EGFR monoclonal antibodies cetuximab and panitumumab (only for patients with *RAS* wild-type tumors) entered the therapeutic scenario, and different intensities of the first-line chemotherapy backbone were investigated, spanning from one to three active cytotoxics.¹⁻⁴

A phase III randomized trial by GONO (Gruppo Oncologico del Nord Ovest) demonstrated the superiority of an intensified regimen, the triplet FOLFOXIRI (irinotecan 165 mg/m², oxaliplatin 85 mg/m², leucovorin 200 mg/m², fluorouracil 3,200 mg/m² 48-hour continuous infusion), over an irinotecan-based doublet as upfront therapy of mCRC patients.⁵ The trial was conducted when the role of targeted agents in this setting had not yet been well established.

More recently, several phase II and III randomized trials compared the triplet FOLFOXIRI with chemotherapy doublets (FOLFOX or FOLFIRI), both in combination with bevacizumab, demonstrating that the intensification of the upfront chemotherapy was beneficial for mCRC patients at the price of an increase incidence of some hematological and gastrointestinal adverse events.⁶⁻¹² Based on these results, FOLFOXIRI/bevacizumab is included among first-line options in most clinical guidelines and recommendations worldwide.¹⁻³ However, questions are still open about the proper placement of this therapeutic choice in the daily practice.

Firstly, in order to fully appreciate the cost/benefit balance of this option, an accurate estimation of the magnitude of the survival benefit provided by the intensification of the upfront chemotherapy is required to evaluate the acceptability of the additional toxicity. Such estimation

is currently lacking, since all those trials had primary endpoints other than overall survival (OS), and most of them were underpowered to detect a potentially relevant survival effect. Secondly, the identification of clinical and/or molecular characteristics associated with higher benefit from the triplet would be helpful in properly selecting candidate patients. To this regard, FOLFOXIRI/bevacizumab is nowadays often used in patients with BRAF V600E mutated mCRC based on the *post-hoc* subgroup analysis of the TRIBE study, but results of subgroup analyses from other trials are not consistent.^{1,3,7,9,12}

Drawing from these considerations, we conducted a systematic review followed by an individual patient data (IPD) based meta-analysis aimed at providing a robust estimation of the added value of FOLFOXIRI/bevacizumab over conventional doublets/bevacizumab in terms of OS, and at exploring the interaction of treatment effect with main patients' and disease characteristics at baseline.

Patients and Methods

Identification of Studies and Collection of Data

This systematic review and meta-analysis of IPD is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.¹³

The literature search was performed in January 2019 to identify all randomized clinical trials (RCTs) comparing doublet (*i.e.*, FOLFIRI, XELIRI, FOLFOX or XELOX) *versus* the triplet FOLFOXIRI, both in combination with bevacizumab, as first-line treatment of mCRC patients. Search was carried out using PubMed, EMBASE, Medline, Cochrane library, Proceedings of American Society of Clinical Oncology (ASCO), Proceedings of European Society of Medical Oncology (ESMO), without any date restrictions. The following keywords were entered in all the possible combinations: "metastatic colorectal cancer", "first-line", "doublet", "FOLFOX", "FOLFIRI", "XELOX", "XELIRI", "triplet", "FOLFOXIRI", "bevacizumab" and "randomized controlled trial". References of the identified

articles were checked, and principal investigators were asked whether they were aware of other published or unpublished trials.

For all participants enrolled in each of the eligible trials, the following individual patient data at baseline were collected: age, gender, Eastern Cooperative Oncology Group (ECOG) performance status, primary tumor sidedness, time to diagnosis of metastatic disease (synchronous *versus* metachronous), previous adjuvant chemotherapy, surgery on primary tumour, type of metastatic spread (involved organs at baseline), *RAS* and *BRAF* molecular status determined on tissue samples from either primary tumour or related metastases according to procedures of each study, treatment arm (doublets/bevacizumab *versus* FOLFOXIRI/bevacizumab). RECIST response, secondary resection of metastases (yes *versus* no) and outcome resection (R0 *versus* R1 *versus* R2 *versus* palliative resection), first-line progression-free survival (PFS) and OS were also collected.

Study quality

Each study was assessed for quality and potential bias using a structured checklist based on the Method for Evaluating Research and Guideline Evidence (MERGE) criteria.¹⁴ Quality of randomization, blinding, outcome measures, measure assessment, arm comparability, loss to follow-up, and intention to treat analysis were evaluated. An overall quality score was assigned to each study: A (low risk of bias), B1 (low to moderate risk of bias), B2 (moderate to high risk of bias), C (high risk of bias).

Data from each of the included trials were carefully checked and verified for consistency with their original publications or abstracts; discrepancies were discussed and resolved with the authors before setting up the final pooled database used for the planned IPD meta-analysis.

The approval of a formal protocol for the IPD meta-analysis was obtained from the principal investigators of all trials included.

Statistical analysis

All the efficacy analyses were done on an intention-to-treat basis. Safety was assessed in patients who received at least one dose of their assigned study treatment. All the analyses were stratified by trial. All tests were two-sided.

The primary endpoint was OS, defined as the time from study randomization to death due to any cause. Secondary endpoints included PFS, defined as the time from study randomization to the first evidence of disease progression, or death from any cause; objective response rate (ORR), defined as the percentage of patients who experienced partial or complete response according to the version of RECIST criteria adopted in each trial; rate of R0 surgery of metastases (*i.e.*, resection with no macroscopic or microscopic residual tumor), defined as the percentage of patients out of the total number of included patients, undergoing a R0 resection of metastases; rate of treatment-related grade 3 or 4 adverse events, defined as the percentage of patients experiencing grade 3 or 4 all-cause adverse events out of the total number of patients eligible for toxicity analysis. Pre-specified subgroup analyses of OS and PFS were performed in order to explore the consistency of the treatment effect on the outcome according to key baseline patients' and disease characteristics, including age, gender, ECOG performance status, liver-only disease, primary sidedness, *RAS* and *BRAF* status, and the combined evaluation of *RAS* and *BRAF* status and primary sidedness.

The median duration of follow-up and its interquartile range (IQR) was calculated for the entire study cohort according to the reverse Kaplan-Meier method. Distributions of time-to-event variables for OS and PFS were estimated with the use of the Kaplan-Meier product-limit method. The log-rank test stratified by trial was used as primary analysis for comparisons between treatment groups. The heterogeneity among studies was quantified through the Higgins I^2 index. Subgroup analyses were performed by means of an interaction test to determine the consistency of the treatment effect according to specified baseline characteristics.

The ORR, the proportion of patients undergoing a R0 resection of metastases, and the toxicities were compared using the Mantel-Haenszel χ^2 test stratified by trial for combining two-by-two tables.

All statistical analyses on individual patient data were performed with SPSS for Windows, version 25.0. Trial-level meta-analysis, in order to obtain plots for each trial and calculate the heterogeneity among studies, was performed using the Review Manager (RevMan 5.3) software.

Results

Of the 758 entries returned by our search strategy, five eligible trials were identified: TRIBE (NCT00719797), OLIVIA (NCT00778102), CHARTA (NCT01321957), STEAM (NCT01765582), and TRIBE2 (NCT02339116).^{6-10,12} One trial (METHEP-2, NCT01442935) was excluded because a triple regimen other than FOLFOXIRI (*i.e.*, FOLFIRINOX) was used.¹⁵ Main characteristics of each study are listed in Table 1, and their detailed eligibility criteria and results have been previously reported.^{6-10,12,16}

In all studies, most of the evaluation criteria for the MERGE checklist were fulfilled, with overall quality score B1 (all included studies were of sufficiently high quality to consider the risk of bias as low to moderate).

Overall, 1705 (95%) patients of the 1797 initially randomized were eligible for the meta-analysis (92 patients were excluded because they had received an alternating treatment with doublets, named sequential FOLFOXIRI, in the STEAM trial). IPD were available for 1697 (99.5%) patients were included in the meta-analysis (8 patients randomized in the CHARTA study had no available data and were excluded from the intention-to-treat population of the trial). Inclusion criteria were not the same among the 5 trials. The OLIVIA trial randomized only patients with disease confined to the liver, while the TRIBE2 trial included only patients who had not received an oxaliplatin-containing adjuvant therapy (Table 1). In all eligible studies an induction phase was planned, with

a duration ranging from 4 to 6 months, followed by maintenance with a fluoropyrimidine (5-fluorouracil/leucovorin or capecitabine) and bevacizumab until disease progression, patient's refusal, unacceptable adverse events, or consent withdrawal (Table 1).

Of the 1697 included patients, 851 patients (50.1%) were assigned to the doublets/bevacizumab group and 846 (49.9%) to the FOLFOXIRI/bevacizumab group. Patient's demographic, clinical, and molecular characteristics are listed in Table 2. Among patients allocated in the doublets/bevacizumab group, 595 (69.9%) received treatment with FOLFOX/bevacizumab and 256 (30.1%) with FOLFIRI/bevacizumab. Altogether, the median age of the pooled population was 61 years (IQR 53-67); most patients had an ECOG performance status of 0 (78.3%) and presented with synchronous metastases (84.7%). The 34.8% of patients had a right-sided primary tumour, and 32.7% had liver-limited disease. Out of 1316 patients with available data, *RAS* and *BRAF* mutations were reported in the 65% and 9% of cases, respectively. No relevant differences between the two groups were evident, except for a significantly higher percentage of patients with a right-sided primary tumor (37.3% *versus* 32.3%, $p=0.036$) and liver-only disease (35.6 *versus* 29.9%, $p=0.012$) in the FOLFOXIRI/bevacizumab compared to the doublets/bevacizumab group (Table 2).

After a median follow-up of 39.9 months (IQR 30.1-49.9) (40.8 months in the doublet/bevacizumab group and 38.9 months in the FOLFOXIRI/bevacizumab group), 1118 (66%) of 1697 patients had died [591 (69%) in the doublets/bevacizumab group and 527 (62%) in the FOLFOXIR/bevacizumab group]. Median OS was 28.9 months (95% CI 27.3-30.4) in the FOLFOXIRI/bevacizumab group and 24.5 months (95% CI 23.0-25.9) in the doublets/bevacizumab group (HR 0.81 [95% CI 0.72–0.91]; $p<0.001$ at log-rank test stratified by trial, Figure 1A). The estimated 5-years OS was 22.3% (95% CI 18.0%-26.6) in the FOLFOXIRI/bevacizumab group and 10.7% (95% CI 8.0-15.8) in the doublets/bevacizumab group ($p<0.001$). No significant

heterogeneity among the five trials ($p=0.39$; $I^2=2\%$, Figure 1B) was detected. Treatment effect was consistent across all analysed clinical and molecular subgroups (Figure 2).

A total of 1489 (88%) patients experienced first-line disease progression [761 (89%) in the doublets/bevacizumab group and 728 (86%) in the FOLFOXIRI/bevacizumab group]. Median PFS was 12.2 months (95% CI 11.6-12.8) in the FOLFOXIRI/bev group and 9.9 months (95% CI 9.5-10.3) in the doublets/bev group (HR 0.74 [95% CI 0.67–0.82]; $p<0.001$ at log-rank test stratified by trial, Figure 3A). No significant heterogeneity among the five trials was observed ($p=0.19$; $I^2=35\%$, Figure 3B). Treatment effect was consistent across all analysed clinical and molecular subgroups (Supplementary Figure 1).

Among the 1695 (99.9%) of 1697 patients evaluable for RECIST response, 545 (64.5%) of 845 in the FOLFOXIRI/bevacizumab group and 456 (53.6%) of 850 in the doublets/bevacizumab group achieved an objective response (OR 1.57 [95% CI 1.29-1.91]; $p<0.001$ at Mantel-Haenszel test stratified by trial). There was no evidence of heterogeneity among the five trials ($p=1.00$; $I^2=0\%$; Supplementary Figure 2).

Secondary surgery for metastases was performed with a radical curative intent (*i.e.*, R0 resection) for 139 patients (16.4%) in the FOLFOXIRI/bevacizumab group and 100 patients (11.8%) in the doublets/bevacizumab group (OR 1.48 [95% CI 1.12-1.95]; $p=0.007$ at Mantel-Haenszel test stratified by trial, Supplementary Figure 3). No evidence of heterogeneity among the five trials was observed ($p=0.33$; $I^2=13\%$).

A sensitivity analysis explored the survival difference between treatment arms in patients who underwent R0 resection or not following the upfront therapy. There was no significant interaction between treatment arm and the achievement of R0 resection in terms of OS ($p=0.667$). In patients with R0 resection, median OS was 64.0 months with FOLFOXIRI/bevacizumab and 52.6 months

with doublets/bevacizumab (HR 0.79 [95%CI 0.50-1.24]), while in other patients median OS was 25.7 and 22.3 months respectively (HR 0.84, [95%CI 0.74-0.95]) (Supplementary Figure 4).

1674 (98.6%) out of 1697 patients were included in the safety analysis (23 patients, 15 in the doublets/bevacizumab arm and 8 in the FOLFOXIRI/bevacizumab arm, did not receive any dose of the assigned treatment and were excluded). As compared to doublets/bevacizumab, the administration of FOLFOXIRI/bevacizumab was associated with a significantly higher incidence of the following grade 3 or 4 adverse events: neutropenia (45.8% versus 21.5%, $p<0.001$), febrile neutropenia (6.3% versus 3.7%, $p=0.019$), nausea (5.5% versus 3.0%, $p=0.016$), mucositis (5.1% versus 2.9%, $p=0.024$) and diarrhea (17.8% versus 8.4%, $p<0.001$). No significant increase in the rate of toxic deaths was reported (2.3% versus 1.4%, $p=0.277$) (Figure 4).

Discussion

The present meta-analysis of IPD from five randomized trials provides robust confirmation of the survival benefit from FOLFOXIRI/bevacizumab compared with doublets/bevacizumab as initial therapy of unresectable mCRC. The advantage achieved with FOLFOXIRI/bevacizumab is not only statistically significant but also clinically meaningful: a reduction in the risk of death of 19% is reported, with a 4.4 months absolute difference in median OS, and, notably, a 11.6% relative increase in the estimated 5ys-OS rate that reaches 22.3% with the triplet plus bevacizumab. The consistent benefit observed in terms of PFS, ORR, and radical resections corroborates OS results. Therefore, our findings provide a reliable answer to one of the most frequently reported concerns with regard to the upfront use of the three cytotoxics: the short-term effect of the intensified regimen in the first part of the therapeutic route of affected patients, not followed by a coherent long-term benefit. In particular, present results should be reassuring about the worry that the exposure to the three drugs may somehow impair the efficacy of subsequent therapies, thus not translating into a relevant survival advantage. Results of another randomized study comparing

FOLFOXIRI/bevacizumab and FOLFOX/bevacizumab as upfront treatment of mCRC with at least 3 circulating tumor cells detected at baseline were recently presented and are consistent with findings from our meta-analysis [ref].

With the aim of improving the estimation of the cost/benefit balance of the upfront use of FOLFOXIRI/bevacizumab, the price of the intensified chemotherapy backbone in terms of toxicity cannot be neglected. A higher incidence of grade 3 and 4 gastrointestinal (diarrhea, mucositis, nausea) and hematological (neutropenia and febrile neutropenia) adverse events was confirmed with no increase in bevacizumab-related toxicities or in fatal events. The overall incidence of febrile neutropenia was 6%, thus below the threshold for recommending the routine use of G-CSF as primary prophylaxis.¹⁷ Notably, results are consistent among different trials conducted in different geographic areas. Unfortunately, quality of life data are missing for most of the trials included in the present metanalysis. However, in the CHARTA study, no impairment of quality of life as assessed by means of the EORTC QLQ C30 was reported during FOLFOXIRI/bevacizumab as compared with FOLFOX/bevacizumab.

To minimize the impact of toxicity and maximize treatment efficacy, an appropriate selection of candidate patients is mandatory. Even if the enrollment of patients with ECOG performance status 2 was allowed in TRIBE, TRIBE2 and CHARTA study, the 99% of patients included in the present meta-analysis had ECOG performance status of 0 or 1 and the median age was 61 years old. In the TRIBE, TRIBE2 and STEAM trial patients older than 75 years old were not eligible and for those between 70 and 75 an ECOG performance status of 0 was required. The same criteria should be adopted in the daily practice to identify patients suitable for the intensified regimen. A pooled analysis of the TRIBE and TRIBE2 study also evidenced higher rates of grade 3 and 4 diarrhea and neutropenia among patients > 70 years old, thus underlining that the higher efficacy of the triplet should be carefully balanced with the higher risk of clinically relevant toxicities in this subgroup.¹⁸

Identifying disease characteristics associated with higher benefit from the intensification of the upfront chemotherapy would be helpful to draw the portrait of the ideal candidate to FOLFOXIRI/bevacizumab and therefore to select suitable patients based on a personalized estimation of the cost/efficacy balance. Nevertheless, among investigated subgroups, no clinical or molecular characteristics associated with higher benefit from the intensified regimen were identified.

Overall, only a minority (20%) of patients included in our meta-analysis had a left-sided *RAS* and *BRAF* wild-type tumor as a consequence of the increased use of anti-EGFR monoclonal antibodies in the first-line therapy of these patients in the last years, so that the combination of a chemotherapy doublet with an anti-EGFR remains a preferred option in these patients.¹⁻³ The association of three-drugs regimens with anti-EGFRs and the added value of the intensified chemotherapy backbone when compared with upfront doublets is currently under investigation in randomized trials.¹⁹⁻²¹

In the last years, the use of FOLFOXIRI/bevacizumab has been often considered the preferable option in *BRAF* V600E mutated tumors with the aim of rapidly counteracting the intrinsic biologic aggressiveness of these tumors at poor prognosis.^{1,3} This recommendation was based on the results of the subgroup analysis of the phase 3 TRIBE study showing a higher magnitude of benefit from FOLFOXIRI/bevacizumab compared with FOLFIRI/bevacizumab in the *BRAF* mutated subgroup, though in the absence of a significant interaction effect between treatment arm and *RAS* or *BRAF* mutational status.⁷ These results consistently corroborated previous findings from a prospective phase 2 study of FOLFOXIRI/bevacizumab in patients with *BRAF* V600E mutated mCRC, providing encouraging signals of activity for this regimen.²² However, more recent results of the TRIBE2 study did not confirm the suggestion of the previous TRIBE trial,¹² and the present meta-analysis further challenges the role of the triplet plus bevacizumab in *BRAF* mutated tumors, since

no increased benefit from the intensified approach is evidenced in this subgroup. The different comparator arm (FOLFIRI/bevacizumab in the TRIBE study *versus* FOLFOX/bevacizumab in all the other trials) may explain these results.

Another decision driver that affects the choice of the intensity of the first-line therapy is the treatment aim: in potentially resectable patients an active upfront treatment is crucial not to miss the opportunity to convert the disease to surgical resectability.¹⁻³ Consistently with these considerations, FOLFOXIRI/bevacizumab is often considered a valuable choice only when the secondary resection of metastases is a pursuable treatment objective, mainly in the case of liver-limited spread.^{23,24} The OLIVIA trial actually confirmed the efficacy of FOLFOXIRI/bevacizumab in this specific setting.⁸ However, most of patients included in trials investigating this option and included in the present meta-analysis were not selected based on the extent of the metastatic spread and/or the potential conversion to resectability. In an exploratory sensitivity analysis no interaction effect was found between treatment arm and the achievement of R0 resections, thus confirming that the benefit from FOLFOXIRI/bevacizumab is not limited to patients undergoing radical resection of their lesions, and indirectly demonstrating that the survival benefit reported with FOLFOXIRI/bevacizumab is not only due to the higher rate of patients converted to R0 resection.

In conclusion, based on the results of our meta-analysis, FOLFOXIRI/bevacizumab is a valuable upfront option able to provide a clinically meaningful survival benefit to unresectable mCRC patients with an ECOG performance status of 0 or 1. Younger patients, with right-sided and/or *RAS* mutated tumors, independently of the conversion intent, may be the best candidates to this approach. Obviously, the personalized estimation of the cost/benefit balance of chemotherapy intensification should take into account patient-related characteristics including personal beliefs, attitudes and expectations.

Figures' legend

Figure 1. Overall survival curves by treatment arm (A). Forest plot of treatment effect on overall survival (B)

Figure 2. Treatment effect on overall survival within main clinical and molecular subgroups

Figure 3. Progression free survival curves by treatment arm (A). Forest plot of treatment effect on progression free survival (B)

Figure 4. Odds ratios of most frequent grade 3 or 4 adverse events

Supplementary Figure 1. Treatment effect on progression free survival within clinical and molecular subgroups

Supplementary Figure 2. Forest plot of treatment effect on objective response rate

Supplementary Figure 3. Forest plot of treatment effect on R0 resection rate

Supplementary Figure 4. Overall survival curves by treatment arm in patients achieving (A) or not (B) R0 resection of metastases.

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