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PRO AND CON DISCUSSIONS

FOLFOXIRI plus bevacizumab as standard of care for first-line treatment in patients with advanced colon cancer

THE CASE FOR FOLFOXIRI PLUS BEVACIZUMAB AS STANDARD OF CARE FOR FIRST-LINE TREATMENT IN PATIENTS WITH ADVANCED COLON CANCER (PROF. CERVANTES)

The first therapeutic decision is of paramount importance in any patient with an advanced solid tumor and should be made after considering many clinical features related to the patient condition and to the extension and biology of the tumor, as well as the tolerance profile of the drug or combinations of drugs to be used. This principle is of particular importance when considering the first treatment approach in patients with advanced colon cancer. We may witness very different clinical presentations at different ages with diverse organ involvement in individuals with varying clinical conditions. On the other hand, we agree that advanced colon cancer behaves as an aggressive disease able to lead to extensive tumor dissemination and therefore needing more intensive therapeutic strategies.

FOLFOXIRI, a triplet drug combination including 5-fluorouracil, folinic acid, oxaliplatin and irinotecan, was developed by a group of investigators at the University of Pisa led by Prof. Alfredo Falcone in combination with bevacizumab (Bev) and was tested for the first time in a randomized phase III trial published in 2014 and carried out in a multicenter academic setting. That trial took progression-free survival (PFS) as the primary endpoint and was designed to test the hypothesis that FOLFOXIRI could decrease the risk of progression by 25% relative to FOLFORI plus Bev as standard of care. The study was carried out by the Italian Gruppo Oncologico Nord Ovest (GONO) and reported its primary endpoint in the *New England Journal of Medicine*.[1] FOLFOXIRI plus Bev showed a significant prolongation of PFS from 9.7 months in FOLFIRI plus Bev to 12.1 months [hazard ratio (HR) 0.75; $P = 0.003$] as well as a significant increase in response rate from 53% in the control arm to 65% ($P = 0.006$). One year thereafter, the same investigators reported a significantly increased overall survival (OS) observed in the experimental arm at a median follow-up of 48.1 months.[2] Median survival in patients randomized to the triplet reached 29.8 months, while in the standard doublet it stayed at 25.8 months (HR 0.80; $P = 0.03$). These data obtained in a multicenter setting supported the superiority of the triplet combination plus Bev in terms of response rate, PFS and OS, despite a counterbalance of more episodes of grade 3-4 toxicity, mainly neurotoxicity, stomatitis, diarrhea and neutropenia. However, no excess of toxic deaths was observed in the triplet combination arm.

One of the principles accepted in the early days of chemotherapy development was the potential superiority of combination chemotherapy over single agent or even two drug combinations, administering in the same schedule several drugs with different mechanisms of action to overcome intrinsic or acquired resistance and also different toxicity profiles to allow better tolerability. This seems to be accomplished in the case of FOLFOXIRI plus Bev. However, the authors faced several criticisms on the optimal strategy to deliver the three most active cytotoxic agents for advanced colon cancer treatment. To further validate the role of this upfront intensive treatment, the GONO group designed another randomized phase III study comparing again FOLFOXIRI plus Bev and reintroduction after progression with a more sequential approach starting with modified FOLFOX6 plus Bev followed upon progression by FOLFIRI plus Bev in the treatment of patients with metastatic colorectal cancer (mCRC) (TRIBE2). Median PFS after two treatments was 19.2 months starting with the triplet and reintroducing it after first progression compared with 16.4 months when the sequential FOLFOX followed by FOLFIRI strategy is applied (HR 0.74; $P = 0.0005$).[3] Perhaps more importantly, median OS was 27.4 months in the experimental group and 22.5 months in the control group (HR 0.82; $P = 0.032$). This increment in median OS in almost 5 months is clinically very relevant and is similar to the one observed in the previous phase III study.[2]

Another evidence, supporting the superiority of FOLFOXIRI plus Bev versus doublets plus Bev as initial therapy of mCRC, comes from an individual patient data meta-analysis of five different trials designed on this strategy including 1697 patients, in which better responses and prolonged PFS and OS are observed in those randomized to the triplet combination.[4] Another phase III trial carried out by Spanish investigators selected advanced colorectal cancer patients with three or more circulating tumor cells detected, who were randomized to FOLFOXIRI plus Bev versus FOLFOX plus Bev. A significant improvement in PFS was also confirmed for the triplet arm (PFS 12.4 versus 9.3 months; HR 0.64; $P = 0.017$).[5]

Currently, FOLFOXIRI plus Bev is recommended as an alternative option in first-line treatment for patients with good performance status presenting with advanced colorectal cancer by the European Society for Medical Oncology

(ESMO) and American Society of Clinical Oncology (ASCO) clinical practice guidelines.[6,7]

THE CASE AGAINST FOLFOXIRI PLUS BEVACIZUMAB AS STANDARD OF CARE FOR FIRST-LINE TREATMENT IN PATIENTS WITH ADVANCED COLON CANCER (PROF. PRAGER)

Treat smart, not hard!

The merit of the chemo—triplet regimen FOLFOXIRI goes back to the year 2007 as the GONO published data from a clinical phase III study, which compared FOLFOXIRI with FOLFIRI in first-line mCRC treatment.[8] The same study group further confirmed the superiority of the triplet in the TRIBE[1] and TRIBE-2[3] studies, each of which combined Bev to chemotherapy in both treatment arms.

However, in the year 2023, the one-size-fits-all approach might not be any longer the best option for most of our patients:

Firstly, we have learned from pre-clinical, translational and most importantly clinical studies that molecular characterization of the individual colorectal tumor as well as location of the primary tumor allows stratification of treatments, which leads to an increase in efficacy and spares unnecessary toxicities. Thus, RAS/BRAF wild-type (wt) mCRC has superior therapeutic sensitivity toward anti-epidermal growth factor receptor (EGFR) antibodies plus chemotherapy doublets as shown in four prospective randomized clinical phase II or III trials (CALGB80405,[9] FIRE-3,[10] PEAK[11] and PARADIGM[12]). In this context, the abovementioned GONO study group has recently demonstrated via the phase III trial TRIPLETE that in this predefined RAS wt/BRAF wt patient population FOLFOXIRI was not superior when compared to FOLFOX in mCRC patients when combined with panitumumab, in terms of response rates (76% for the experimental arm versus 73% for the chemo doublet; HR 0.87; confidence interval (CI) 0.56-1.34; $P = 0.526$) or median PFS (12.7 months in the experimental group versus 12.3 months in the control group; HR 0.88; 95% CI 0.70-1.11; $P = 0.277$), but was associated with significant higher toxicities.[13] In addition, the subgroup of mismatch repair deficient/microsatellite instability-high (dMMR/MSI-h) patients should be offered immunotherapy as a standard treatment instead of a more toxic chemo combination (Keynote-177[14]). In addition, BRAF V600-mutated mCRC seems also not to gain benefit from FOLFOXIRI plus Bev when compared to doublets plus Bev (HR 1.11; 95% CI 0.75-1.73) as the meta-analysis by Cremolini et al., which was recently published, suggests.[4]

Secondly, the benefit of adding Bev to FOLFOXIRI has never been demonstrated in prospective randomized trials and remains elusive. Various studies such as TRIBE[1] and TRIBE-2,[3] STEAM,[15] CHARTA[16] and OLIVIA[17] have only compared chemo doublets plus Bev versus triplets plus Bev.

Thirdly and probably most important for patients, FOLFOXIRI + Bev bears a significant higher toxicity. As noted by the abovementioned meta-analysis, the administration of FOLFOXIRI/Bev was associated with a significantly higher incidence of grade 3 or 4 neutropenia (45.8% versus 21.5%; $P < 0.001$), febrile neutropenia (6.3% versus 3.7%; $P = 0.019$), mucositis (5.1% versus 2.9%; $P = 0.024$), nausea (5.5% versus 3.0%; $P = 0.016$) and diarrhea (17.8% versus 8.4%; $P < 0.001$).[4] In addition, the highly pre-selected patient population of younger and fit patients being treated in the FOLFOXIRI plus Bev trials with a median age of ∼60 years does not necessarily reflect the real-world setting of stage IV colorectal cancer patients.

Finally, considering the option of a smart treatment stratification according to patient's and tumor characteristics, FOLFOXIRI + Bev might only be the favorable treatment choice in the RAS mut and/or right-sided primary patients, especially if the patient is a candidate for a secondary resection. At least in this subgroup downsizing by induction FOLFOXIRI + Bev qualified for curative-intent local therapy as suggested by the CAIRO-5 trial.[18] While the rate of successful local treatment was higher, OS data are still pending.

With the introduction of novel targeting treatment concepts such as BRAF inhibitors for BRAF V600-mutated tumors, upcoming KRAS G12C inhibitors, Her-2-targeting concepts as well as blocking agents for FGFR or TRK fusions, the group of patients with an urgent need for a toxic chemo—triplet combination is dropping. Many of these molecular targeting concepts are currently tested in clinical studies in the first-line setting for advanced colorectal cancer and mCRC.

In summary, FOLFOXIRI ± Bev is an effective treatment and might be considered for a subgroup of fit patients, who might not yet have a smarter choice of treatment.

RESPONSE BY PROF. CERVANTES

I concur with most of the comments by Prof. Prager. The good point is that we have diverse treatment options for patients with advanced colorectal cancer in first line and obviously a single size doesn't fit all. In fact, in the meta-analysis previously cited,[4] the authors underlined the fact that only a minority (20%) of RAS wt and left-sided tumors were accrued across the five different trials selected, indicating a potential preference for anti-EGFR-based therapies. Moreover, what the TRIPLETE trial is telling us is that when panitumumab is associated with a chemotherapy backbone, staying with FOLFOX provides similar outcomes in response rates and in PFS than combining it with FOLFOXIRI, with a substantial increase in gastrointestinal toxicity and therefore, it should not be used in this setting.

Another important fact to optimize the clinical use of FOLFOXIRI plus Bev is to remember that no patients over 75 years of age were treated in any of the studies and patients between 70 and 75 years were eligible only if they presented performance status 0. Safety should be one of our priorities when selecting an intensive treatment strategy, and a preventive and quick access for patients to supportive care has to be guaranteed.

Recognizing some very specific subtypes of advanced colon cancer such as dMMR/MSI-h could certainly avoid any first-line chemotherapy as primary option, including triplets,

in favor of immunotherapy. At the moment, treatment options for other molecular subtypes of low prevalence are only recommended after first-line chemotherapy progression, but this may change in the future when targeted agents could show improved efficacy in future trials. Oncology is moving forward very rapidly. All advances we are witnessing are based upon innovative trial designs with new and more efficacious drugs mostly in selected or enriched populations of patients. However, we should not forget that in some instances using intensive chemotherapy schedules, like FOLFOXIRI, may also be a smart option.

RESPONSE BY PROF. PRAGER

I could not agree more with Prof. Cervantes' statement that we have diverse treatment options. By the detection of potential actionable molecular aberration in mCRC, a stratified systemic treatment approach is favorable; thus, a molecular characterization should be considered at baseline to choose the best option for the individual mCRC patient. In this context, FOLFOXIRI plus Bev might be one of the candidates, if the molecular and patient characteristics suggest a more aggressive but efficient treatment approach. So treating hard might be smart under certain conditions.

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