EUR. J. ONCOL., vol. 19, Suppl n. 1, pp. 33-35, 2014

Bevacizumab beyond progression: Pros

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Bevacizumab targets the vascular endothelial growth factor (VEGF) to inhibit angiogenesis. The combination of bevacizumab with fluoropyrimidine-based chemotherapy is an effective treatment for patients with metastatic colorectal cancer (mCRC), and it is currently a standard treatment in the first-line (1–3) and in bevacizumab-naïve second-line settings (4).

The optimal duration of bevacizumab therapy is crucial to maximising potential treatment benefits for patients. Angiogenesis is a complex and multifactorial process, but several preclinical data suggest that VEGF is continuously expressed during tumour growth and it continues to be expressed throughout tumour progression, facilitating angiogenesis, even as secondary signalling pathways emerge (5). Data from preclinical models demonstrated that longer exposure to anti-VEGF monoclonal antibodies lead to delayed tumour growth, extended survival in established tumours in both cell transplants and genetic tumour models and prevented regrowth of a subset of residual tumours following cytoablative therapy (6).

Results of two non-randomised observational cohort studies (BRITE and ARIES) showed a correlation between the use of bevacizumab beyond progression to first-line therapy and substantial improvement in overall survival in advanced colorectal cancer (7, 8).

Two randomized trials were conducted to verify the hypothesis that continued antiangiogenic treatment might be clinically effective without cumulative toxicity despite the development of resistance to chemotherapy: the multinational ML18147 trial (9) and the Italian BEBYP trial (10).

The ML18147 trial (9) was a prospective, intergroup, randomised, open-label, phase 3 study in 220 centres in 15 countries. Patients with unresectable, histologically confirmed metastatic colorectal cancer progressing up to 3 months after discontinuing first-line bevacizumab plus chemotherapy were randomly assigned in a 1:1 ratio to second-line chemotherapy with or without bevacizumab 2.5 mg/kg per week equivalent (either 5 mg/kg every 2 weeks or 7.5 mg/kg every 3 weeks, intravenously). The choice between oxaliplatin-based or irinotecan-based second-line chemotherapy depended on the first-line regimen (switch of chemotherapy). Patients were excluded if they had a diagnosis of progressive disease for more than 3 months after the last bevacizumab administration and, first-line progression-free survival of less than 3 months, and if they were given less than 3 months (consecutive) of first-line bevacizumab. From February, 2006, and June, 2010, 409 (50%) patients were assigned to bevacizumab plus chemotherapy and 411 (50%) to chemotherapy alone. Median follow-up was 11.1 months in the bevacizumab plus chemotherapy group and 9.6 months in the chemotherapy alone group. The overall survival (primary end-point) was significantly improved for bevacizumab plus chemotherapy, with a median survival of 11.2 months for bevacizumab plus chemotherapy versus and 9.8 months for chemotherapy alone (HR= 0.81, 95% CI 0·69–0·94; unstratified log-rank test p=0.0062). The continuation of

bevacizumab with second-line chemotherapy improved also the progression free survival, median progression-free survival was 5.7 months in the bevacizumab plus chemotherapy group and 4.1 months in the chemotherapy group (HR=0.68, 95% CI 0·59–0·78; unstratified log-rank p<0·0001). Response rate was low in both arms and it was not improved by bevacizumab (5% for patients treated with bevacizumab plus chemotherapy with versus 4% of patients treated with chemotherapy, p=0.31). In a post-hoc analysis, 68% patients achieved disease control in the bevacizumab plus chemo therapy group versus 54% in the chemotherapy alone group (p<0·0001). Pre-specified subgroup analyses were generally consistent with the primary findings. Although differences were noted in HRs for overall survival in men and women, there was no evidence of treatment by sex interaction in the Cox model (p>0.05). The exploratory subgroup analysis according to KRAS status (n=616) showed that there is no evidence to suggest differences between the overall population and subgroups based on KRAS mutational status. The safety profile of bevacizumab plus chemotherapy was consistent with previously reported data in bevacizumab naïve patients and did not show substantial differences in toxicity between the two treatment groups. The findings of the ML 18147 trial demonstrate that maintenance of VEGF inhibition with bevacizumab plus standard second-line chemotherapy beyond disease progression has clinical benefits in patients with metastatic colorectal cancer, while maintaining an acceptable safety profile.

The BEBYP trial (10) was a prospective, intergroup, randomised, open-label, phase 3 study conducted in 19 Italian centres. Patients with unresectable, histologically confirmed colorectal adenocarcinoma with progressive disease after or during first-line therapy with fluoropyrimidine, FOLFIRI, FOLFOX plus bevacizumab, or more than 3 months after the last dose of FOLFOXIRI plus bevacizumab, were randomized to receive a second line chemotherapy (FOLFIRI or mFOLFOX-6 depending on first-line) with or without bevacizumab. The original study design was to detect a HR for PFS of 0.70 in favour of bevacizumab required a total of 262 patients. Accrual started on April, 2008, and was stopped prematurely on May, 2012, because of the notice of TML study results and because of a slow accrual rhythm due to bevacizumab supply limitation. A total of 185 patients were randomized. Median follow-up was 30.4 months. The continuation of bevacizumab with second-line chemotherapy improved the progression free survival (primary and point), with a median progression-free survival of 6.7 months in the bevacizumab plus chemotherapy group and 5.0 months in the chemotherapy group (HR=0.66, 95%CI 0.49-0.89; unstratified log-rank p=0.0065). A trend toward longer overall survival was observed with bevacizumab plus chemotherapy, with a HR=0.75, 95%CI 0.54-1.06; unstratified log-rank test p=0.11. Response rate (21% versus 18%) and disease control rate (72% versus 61%) were not improved by bevacizumab. Subgroup analyses were consistent with the primary findings in all sub-groups. Safety profile was consistent with previously reported data. The findings of the BEBYP trial, although with some difference due to dissimilar inclusion criteria, and with the limitations of a less powered trial, confirmed that maintenance of VEGF inhibition with bevacizumab plus second-line chemotherapy beyond disease progression is associated with significant clinical benefits in patients with metastatic colorectal cancer, while maintaining an acceptable safety profile.

The biological concept of continued benefit associated with VEGF inhibition with bevacizumab after disease progression is also supported by results from 2 recent trials. In the phase 3 VELOUR (11) study, aflibercept (an antiangiogenic recombinant fusion protein that blocks the activity of VEGFA, VEGFB and PlGF) was added to FOLFIRI treatment in patients who had tumour progression on oxaliplatin-based first-line treatment. Aflibercept improved outcomes to almost the exact extent as bevacizumab in the ML18147 study, independent of whether patients had been given bevacizumab in first-line treatment. In the CORRECT trial (12) treatment with regorafenib (an orally administered multikinase inhibitor with potent inhibitory activity VEGFR1, VEGFR2 and VEGFR3 was beneficial in patients with colorectal cancer progressing after receiving all approved standard treatments. Notably, all patients in CORRECT had been given bevacizumab in an earlier treatment line.

Taken together, these data suggest that prolonged duration of anti-VEGF treatment is associated with improved outcome in patients with metastatic colorectal cancer. Moreover, these results lead to a new second-line treatment option for patients with metastatic colorectal cancer who have progressed on bevacizumab plus standard first-line chemotherapy, while maintaining an acceptable safety profile.

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