Dear Editor

from the pivotal phase III randomized clinical trial\(^1\), we know that aflibercept in combination with fluoroouracil, leucovorin and irinotecan (FOLFIRI) conferred a statistically significant survival benefit over FOLFIRI in patients with metastatic colorectal cancer (mCRC) previously treated with oxaliplatin for both overall survival (OS) (p=0.0032) and progression free survival (PFS) (p<0.0001). Qi et al.\(^2\), in a systematic review and meta-analysis including 15 trials with 4451 patients treated with aflibercept in second-line for mCRC, have reported incidences of all-grade and high-grade hypertension of 42.4 % (95% CI: 35.0-50.3) and 17.4 % (95% CI: 13.7-21.9), respectively; the use of aflibercept in cancer patients was associated with a significantly increased risk of all-grade (OR=4.47, 95% CI: 3.84-5.22, p<0.001) and high-grade (OR=4.97, 95% CI: 3.95-6.27, p<0.001) hypertension.

More recently, Salgado Fernández et al.\(^3\) have reported a safety analysis from a named patient program provided early access to aflibercept to mCRC patients in Spain before its commercialization (89 patients). Patients have received a median of 6 cycles of FOLFIRI plus aflibercept. Grade $\geq$3 hypertension was reported in 3.4% of patients, confirming results from VELOUR trial\(^1\). Syed et al.\(^4\) have reported a review concerning the use of aflibercept in metastatic colorectal cancer. They concluded that the addition of aflibercept significantly prolonged PFS and significantly increased the objective response rate (ORR) compared with FOLFIRI alone. In addition, the most common reported grade 3 or 4 adverse events with aflibercept plus FOLFIRI included neutropenia, diarrhea and hypertension.

In this report we retrospectively analyzed our experience with the incidence of hypertension during the administration of aflibercept in combination with FOLFIRI in second-line treatment for mCRC patients treated with prior oxaliplatin regimens; we have also analyzed the presence of a possible relationship between the value of hypertension immediately before starting the administration of aflibercept and the development of hypertension.

A retrospective analysis of consecutives patients with diagnosis of mCRC and treated aflibercept in combination with FOLFIRI in second-line treatment at the Medical Oncology Unit of Mater Salutis Hospital, Legnano (Italy) between November 2013 and November 2014 was performed. All informations were obtained from case history and reviewed the patient's medical history. Follow-up time (FUT) was define as the time patients have been followed at Our Institution. Overall Survival (OS) was estimated starting from the first day of the first cycle of chemotherapy to the last visit or patient’s death date, censoring surviving patients at the time of last follow-up.

We evaluated 5 female (100.0%) patients. Median follow-up time (FUT) was 19.08 months (range: 16.41-106.45). At the last FUT 1 patient (20.0%) was deceased. Median OS was 20.03 months (range: 17.27-106.94). Median age was 60 years (range: 39-68). Four patients (80.0%) underwent surgery for primary site. All patients (100.0%) had liver as site of metastases. First-line treatment was 5-fluorouracil, leucovorin and oxaliplatin (FOLFOX) in 3 patients (60.0%) and capecitabine and oxaliplatin (XELOX) in 2 patients (40.0%). Concerning second-line treatment, 4 patients (80.0%) showed partial response (PR) and 1 patient (20.0%) complete response (CR) as best response to treatment. Mean number of cycles were 11 (range: 8-12); a total of 54 cycles were considered. Hypertension was the most common side effect: grade III in 2 cases (40.0%), grade II in 1 case (20.0%) and grade I in 1 case (20.0%); only 1 patient (20.0%) had hypertension (well controlled side effect: grade III in 2 cases (40.0%), grade II in 1 case (20.0%) and grade I in 1 case (20.0%); only 1 patient (20.0%) had hypertension (well controlled by beta-blockers) as comorbidities before starting treatment, which has not developed hypertension after treatment with aflibercept. The only other comorbidity reported was the presence of post-ischemic cardiac disease (about 10 years before), actually with normal ejection fraction, in treatment with acetylsalicylic acid, which has not developed hypertension after treatment with aflibercept. The mean value of systolic and diastolic blood pressure before each cycle was 130 (range: 100-170) and 90 (range: 60-110), respectively. The trend of the values of systolic and diastolic blood pressure relating to each course of therapy for each patient are shown in Figure 1. At the $\chi^2$-test, there was no statistical significance difference between the systolic (p=0.287) and diastolic (p=0.599) blood pressure before starting the administration of aflibercept and the development of hypertension.
We can confirm that the use of aflibercept is associated with an increased risk of developing all-grade and high-grade hypertension [2-4]; based on our experience, we can affirm that there was no relationship between the systolic and diastolic blood pressure before starting the administration of aflibercept and the development of hypertension.

We know the limit of a retrospective experience and the small size of the cohorts (this might explain the different incidence of hypertension than the incidence reported in the previous trial1,3 and the fact that data coming from a single Institution could reflect only the habits of that particular set of physicians; on the contrary, report like the above, though the analysis of not selected case study, are able to evaluate treatment patterns in a real-world clinical practice, also in relation to the littleness of data in the literature. In facts, the data presented are not currently defined in the literature. Other larger experiences are needed to corroborate our findings.

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References