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Letter to the Editor

Treatment options after regorafenib failure in metastatic colorectal cancer

Dear Editor,

We read the last paper by Dr. Eraslan E et al[1], recently published on Eur Rev Med Pharmacol Sci and titled "Treatment options after regorafenib failure in metastatic colorectal cancer"; very hot topic in the "re-challenge strategy approach" in pre-treated metastatic colorectal cancer (mCRC) patients and in good performance status (PS).

We know, thanks to advances in knowledge of the molecular profile, prognostic and predictive factors to response to medical treatment, that mCRC patients live longer with a median overall survival (OS) significantly improved[2-7].

In fact, from the late 1990s the median OS for m-CRC patients have increased from about 12 months[2], for those treated with a 5-fluorouracil (5-FU)-based chemotherapeutic regimens, to approximately 18 months with the addition of irinotecan and oxaliplatin[4]. The advent of target biologic drugs, next to the results obtained with chemotherapy alone, has increased the OS of mCRC to more than 24 months, median[3].

Moreover, also a more aggressive surgery approach[8], for resectable metastatic disease and the use of tailored treatment as gamma-knife radiosurgery and/or other loco-regional treatments, have significantly contributed to improve further the OS in mCRC patients.

In this paper, Eraslan et al[1] compared the role of rechallenge chemotherapy (RCH) vs. best supportive care (BSC) in mCRC patients after standard chemotherapy and subsequent Regorafenib (RGR) treatment.

The results obtained, in terms of OS, were significantly favourable in the setting of patients treated with RCH chemotherapy: 7.5 and 1.2 months, respectively RCH chemotherapy and BSC group (p< 0-001), while, about time to progression (TTP), no difference has been highlighted between two groups.

The clinical and tumour characteristics were similar between two groups especially for median age at diagnosis, gender, localization of primary tumour, metastatic disease localization and previous chemotherapy treatment received.

The following variables were significantly different between two groups: PS, albumin, CEA and Ca 19.9 serum level and they were worse about PS and higher values for laboratory parameters in the BSC group and according to the authors variables might be suspected as poor prognostic factors for OS.

Interesting to note that, 22 patients (84.6%) received RCH chemotherapy as 4th line treatment and 1 as 5th line treatment, with Grade 3-4 toxicities observed in only 15.4% of patients, and without toxic death.

Unfortunately, data on OS, TTP and toxicity are missing in elderly population ($\geq$ 70 years old) and this aspect could represent a bias of selection in a setting of patients of particular interest for clinical characteristics, toxicities, and response rates (RRs) to oncological treatment.

Moreover, we know that CRC has a high incidence in elderly population and, in our opinion exclude them from this kind of study represent a bias of selection.

Elderly cancer patients are often underrepresented in clinical trials due to only chronological age, despite many studies have already demonstrated[9] similar results in terms of efficacy and safety between young and elderly cancer patients, especially in the fit.

Very interesting is the hypothesis about the role of RGR as chemo-sensitizing agent, most likely due to a multikinase inhibitor effect on signalling pathways that targets a broad spectrum

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of angiogenic and stromal kinases. Marks et al[10] described that the combination of RGR and 5-FU had a synergistic anticancer activity on CRC cells with KRAS, BRAF, and P53 mutations as well as mismatch repair-deficient cells *in vitro* suggesting that RGR treatment may advantage to overcome chemotherapy resistance.

We encourage this type of study, considering the wide availability of new drugs and more knowledge about mCRC[11]; we agree to treat, after 3rd line of treatment, mCRC patients in good PS and at the same time we strongly suggest to consider also the so called "frail patients", as elderly and HIV-positive mCRC in this kind of clinical trials[12,13].

Conflict of interest

The Authors declare that they have no conflict of interests.

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