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Stable early onset colorectal cancer: are we in front of a different group in colorectal cancer?

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Background: A small rate of colorectal cancer (CRC) arises in young adults (2−8%). Early-onset is a characteristic of familial and hereditary forms of CRC and certainly many of early-onset CRCs exhibits features similar to those shown in Lynch syndrome (LS) tumours. However, there is a significant rate of these early-onset CRC with different characteristics to those associated to a MMR system deficiency and Microsatellite instabilitiy (MSI).
The aim of this work is to determine familial and clinical defining characteristics of microsatellite stable (MSS) early onset CRC tumours. As we confirm, this group is different from MSI early onset CRC, so we compare it with a cohort of CRC arising in old adult.
Methods: We selected CRC patients diagnosed at an age of 45 years or younger in our institution and a group of patients with CRC at an onset of 65 years or elder in the same period of time. The young adults were classified into two groups according to the tumour microsatellite status and/or the immunohistochemical MMR protein study: those with MSI, reflecting DNA MMR deficiency and those with MSS. We have collected clinicopathological and familial features of both different groups. We compared each one (MSS CRC in young adults and CRC in old patients) in order to characterize MSS group. Statistical analysis was carried out in all comparisons.
Results: We have carried out microsatellite study in early onset CRC, finding 73 stable cases (77%). MSS tumours showed some remarkable differences compared with MSI early onset CRC: elder age of onset (40 vs 36); location of tumour, most frequent at the left colon (81% vs 38%); less mucin production; an important rate of sporadic cases according to the familial history, and a less familial incidence for Lynch syndrome cancers. There was an important presence of polyps in history (42%) and a familial history of other cancers different from Lynch related neoplasm (45%). Early MSS CRC showed differences from CRC of elder as well: More left-sided location (81% vs 62%); medium cellular differentiation (68% vs 23%); less advanced tumors; less synchronous or metachronous CRC (3% vs 18%); less multiple primary cancer (7% vs 28%); more familial aggregation and more Lynch and non-Lynch tumors in family (39% vs 21% and 48% vs 26%). Only statiscally significant values are shown.
Conclusions: MSS early onset CRC are probably related with other carcinogenetic pathways, not only different from those MSI but also with CRC in elder adult.
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NGR-hTNF, a vascular targeting agent (VTA), administered as single agent in patients (pts) with colorectal cancer (CRC) failing standard regimens: a phase II study

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Background: NGR-hTNF is a VTA consisting of TNF-a fused to the tumor-homing peptide NGR, which is able to selectively bind an aminopeptidase N overexpressed on tumor blood vessels.
Methods: CRC pts failing standard therapies received low-dose NGR-hTNF given at 0.8 $\mu g/m^2$ as 1-hour infusion every 3 weeks (q3w; triweekly cohort). Progression-free survival (PFS) was the primary study objective with restaging performed q6w. A 2-stage design was used, with 16 and 27 pts to be recruited. Ultimately, an additional 13 pts were treated with 0.8 $\mu g/m^2$ on a weekly basis (weekly cohort).
Results: In the triweekly cohort, 111 cycles (range, 1−10) were delivered to 33 pts with radiologically-documented progression after last therapy. Pts characteristics were: median age: 65 years (range, 53−79); M/F 16/17; PS 0/1 26/7. Median number of prior lines was 3 (range, 2−5), whereas 8 pts (25%) had received $\geqslant$4 lines and 22 (67%) biologicals. No grade 3−4 drug-related toxicity was observed. Predominant grade 1−2 toxicities were short-lived, infusion-related chills (53%). The median PFS was 2.5 months (95% CI, 2.2−2.8) and the PFS rates at 3 and 4.5 months were 31% and 16%, respectively. The disease control rate was 39% (95% CI, 23−55), with one partial response (3%) and 12 stable diseases (36%). In pts with disease control, the median PFS time was 3.8 months and the 3- and 4.5-month PFS rates were 67% and 42%, respectively. With a median follow-up of 18.4 months (95% CI, 18.3−18.5), the median OS time was 13.1 months (95% CI, 8.7−17.5). The proportions of pts alive at 18 and 24 months were 33% and 25%, respectively. Pts who achieved disease control had a median OS of 15.4 months, while those who did not had 9.3 months. Median OS in pts pretreated with <3 and $\geqslant$3 regimens were 18.6 and 9.3 months ($p = 0.03$), respectively, whereas 1-year survival rates in biological-naïve and prior-biological pts were 72% and 41% ($p = 0.01$), respectively. There was no toxicity exacerbation using the weekly schedule. In this cohort, two patients (15%) had PFS of 10.5 and 11.0 months, which resulted longer than PFS on prior therapy (3.8 and 6.3 months, respectively).
Conclusion: Based on favourable toxicity profile and disease control in heavily pre-treated CRC patients, NGR-hTNF will be further developed in combination with standard chemotherapy.

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Phase I study of first-line sunitinib (SU) plus modified FOLFOX6 (mFOLFOX6) in Japanese patients (pts) with metastatic colorectal cancer (mCRC)

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Background: SU is an oral multitargeted tyrosine kinase inhibitor of VEGFRs, PDGFRs, KIT, FLT3, CSF-1R and RET and is approved for advanced RCC and imatinib-resistant GIST. SU has recently shown activity in combination with mFOLFOX6 in pts with previously treated advanced solid tumours. We report preliminary findings of a phase I, open-label, Pfizer-sponsored study of the safety/efficacy of two schedules of SU plus mFOLFOX6 in Japanese pts with previously untreated mCRC (ClinicalTrials.gov: NCT00631410).
Methods: Pts in Arm A received SU 37.5 mg/day for 4 weeks, then 2 weeks off; and pts in Arm B received SU 50 mg/day for 2 weeks, then 2 weeks off. mFOLFOX6 was given as: oxaliplatin 85 mg/m^2 and L-leucovorin 200 mg/m^2 2-hr IV infusion, then IV bolus 5-FU 400 mg/m^2 and 46-hr infusion of 5-FU 2,400 mg/m^2 on days 1 and 2 of each cycle, repeated every 2 weeks. Adverse events (AEs), objective tumour responses by RECIST, and plasma concentrations of SU and its active metabolite (SU12662) were evaluated.
Results: Of 12 pts enrolled (6 pts/arm), median age was 64 years (range 55−70) in Arm A and 65 (56−77) in Arm B. Mean dose intensity of SU across a total of 27 and 36 cycles in Arms A and B, respectively, was 59% and 90%; for oxaliplatin, 53% and 64%; for 5-FU bolus, 33% and 54%. 4/6 and 3/6 patients required sunitinib dose reductions in Arms A and B, respectively. To date, 10/12 pts (83%) discontinued: due to AEs (1 pt in Arm A, 2 in Arm B), progressive disease (3 per arm) or other (1 pt in Arm A). Grade (G) 3/4 AEs were similar between arms: all pts experienced G3/4 neutropenia (100% in each arm; 50% G4 in arm A, 33% G4 in Arm B), thrombocytopenia (83% Arm A; 67% Arm B), and leukopenia (67% in each arm). Other all-cause, mainly G1/2, AEs in $\geqslant$50% of pts included anorexia, nausea, fatigue, diarrhoea, vomiting and hand–foot syndrome. Plasma concentrations of SU and SU12662 were not affected by mFOLFOX6 from 0−24 hours post-dose. There were 8 partial responses (PRs; objective response rate 67% in both arms). Overall, 10 patients achieved $\geqslant$ stable disease as best response (other patients had progressive disease and indeterminate response, respectively).
Conclusions: Both schedules of first-line SU plus mFOLFOX6 showed preliminary activity with 8 PRs. Higher dose intensity was achieved in Arm B, though dose reductions or modifications were needed in both arms to optimize tolerability; most AEs were clinically manageable.