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Young-onset colorectal cancer: treatment-related nausea, vomiting and diarrhoea

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ABSTRACT

Objectives Early-onset colorectal cancer (EO-CRC) incidence is increasing, raising a clinical challenge. Clinicians tend to treat EO-CRC patients with more intensive regimens despite the lack of survival benefits, based on an age-related bias. Limited evidence is available regarding treatment-related toxicities in this peculiar subset of patients.

Methods We performed a literature search in MEDLINE/PubMed, EMBASE and Scopus, looking for reporting of nausea, vomiting and diarrhoea occurring in patients with EO-CRC, defined by age lower than 50 years old at initial diagnosis, while receiving anticancer treatment.

Results 2318 records were screened and 9 full-text articles were considered eligible for inclusion for a total of 59 783 patients (of whom 8681 EO-CRC patients). We found nausea and vomiting occurring at higher incidence among EO-CRC compared with older patients, while no difference was reported as for diarrhoea. Peritoneal involvement, age younger than 40, female gender, suboptimal adherence to guidelines and oxaliplatin might represent potential risk factors for increased nausea and vomiting in patients with EO-CRC.

Conclusion EO-CRC patients experience more nausea and vomiting but equal or less diarrhoea compared with older patients. Adherence to clinical guidelines is recommended, and more data are warranted to assess if an enhanced antiemetic approach might be required, particularly in case of specific risk factors.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Patients with early-onset colorectal cancer (EO-CRC) often receive more intensive cytotoxic regimens without achieving survival benefits, while few data are available on toxicities experienced by this peculiar patients' population.

WHAT THIS STUDY ADDS

⇒ Unexpectedly, patients with EO-CRC suffer more nausea and vomiting compared with older patients. Oxaliplatin, peritoneal involvement, age younger than 40, female gender and a low body mass index might play a role as potential risk factors of increased nausea and vomiting.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Based on this initial data, dedicated studies are warranted to define if enhancing primary antiemetic prophylactic might be an option to improve treatment tolerability in young patients with CRC.

INTRODUCTION

In the USA, colorectal cancer (CRC) recently became the first and second cause of cancer death among adult male and female between 20 and 50 years of age, respectively. This is the epidemiological consequence of a steady CRC incidence increase by 1%–4% per year, which has been reported worldwide since the early 90s.[1]

Early-onset CRC (EO-CRC) commonly defines CRCs diagnosed in adults earlier than 50 years of age, based on the empirically predefined age screening cut-off.[1] Most of EO-CRC are sporadic and usually occur in the left side of the colon or rectum, with peculiar clinicopathological features.[1] EO-CRC patients prognosis is harshly debated and no clear-cut data emerged due to wide heterogeneity of data available mainly in terms of stages and treatments provided.[1] Despite these partial data, based on an age-related bias, clinicians are prone to treat EO-CRC patients with more aggressive medical

regimens.[2] Furthermore, very little is known on the toxicity burden experienced under treatment by this subset of patients.

Here, we review the available literature to address the burden of nausea, vomiting and diarrhoea experienced by patients with EO-CRC receiving standard CRC treatments. We focused on these toxicities given their prevalence and impact on patients' quality of life.

MATERIALS AND METHODS

The purpose of this systematic review is to evaluate the burden of nausea, vomiting and diarrhoea occurring in patients with EO-CRC undergoing systemic medical treatments.

We reviewed MEDLINE/PubMed, EMBASE and Scopus for citation from December 1962 to March 19th, 2023. The Medical Subject Headings terms used for the search in PubMed were (young[Title/Abstract] OR early onset)[Title/Abstract] AND (Gastrointestinal[Title/Abstract] OR nausea[Title/Abstract] OR vomiting[Title/Abstract] OR diarrhea[Title/Abstract] OR diarrhoea)[Title/Abstract] AND (colorectal adenocarcinoma[Title/Abstract] OR colorectal[Title/Abstract] OR CRC[Title/Abstract] OR colon[Title/Abstract] OR rectal)[Title/Abstract]. The Medical Subject Headings used for the search both in EMBASE were (young:ab,ti OR 'early onset':ab,ti) AND ('gastrointestinal':ab,ti OR nausea:ab,ti OR vomiting:ab,ti OR diarrhea:ab,ti OR diarrhoea:ab,ti) AND ('colorectal adenocarcinoma':ab,ti OR colorectal:ab,ti OR crc:ab,ti OR colon:ab,ti OR rectal:ab,ti). The Medical Subject Headings terms used for the search in Scopus were TITLE-ABS-KEY ((young OR early AND onset) AND (gastrointestinal OR nausea OR vomiting OR diarrhea OR diarrhoea) AND (colorectal AND adenocarcinoma OR colorectal OR crc OR colon OR rectal).

Inclusion criteria were the following: full-text articles of studies reporting on or reviewing nausea, vomiting and/or diarrhoea occurring in patients with CRC diagnosed earlier than 50 years of age and treated with systemic medical regimens. The exclusion criteria were: publications written in language other than English, the inclusion of patients older than 50 years of age and/or younger than 18 among EO-CRC population. Full-text selection and data extraction was carried out by two reviewers with inter-rater agreement (MP and GM). Data concerning clinical study type, prevalence and severity of nausea, vomiting and diarrhoea, and treatment regimens administered were reviewed to look for differences between patients with EO-CRC and their older counterpart. Finally, collected data, table and manuscript were then reviewed by other authors ahead of submission.

RESULTS

Out of 2318 screened, 38 records were identified through database searching (PUBMED, EMBASE and SCOPUS) plus 3 additional records by manual searching through bibliographies of selected manuscript (online supplemental figure 1). Nine records were eligible for inclusion, all being full-text articles[3–11] accounting for a total of 59 783 patients of whom 8681 patients with EO-CRC) (table 1). Most of the studies included CRC only patients. However, some of the studies were included despite considering also other tumour types provided that the burden of nausea, vomiting and diarrhoea were described separately from non-CRC histology.[6 8]

Nausea and vomiting in EO-CRC

The incidence of nausea in patients with EO-CRC was reported significantly higher as compared with the older counterpart in all the studies dealing this topic.[3–7 9–11]

In the adjuvant setting, a post hoc analysis on 16 349 patients from the IDEA trial described a higher incidence of nausea and vomiting in EO-CRC.[3] Importantly, one study did not report any difference in nausea, vomiting or diarrhoea incidence considering 50 years of age as upper limit cut-off, while confirmed the same trend presented in other studies with a higher incidence of nausea and vomiting in the subset of EO-CRC younger than age 40 (10% vs 7%, OR 0.64, p 0.04).[5]

In the metastatic setting, Blanke *et al*[4] reported a higher prevalence of grade 3 or higher nausea in EO-CRC. In addition, in TRIBE and TRIBE2 trials EO-CRC had a higher risk of nausea and vomiting.[9] The authors suggested that these results might be related to a higher percentage of females among the youngers.[9] A similar but not-statistically significant higher rate of any grade nausea (43% vs 32%, p=0.249) and vomiting (26% vs 16%, p=0.226) has been described in EO-CRC patients with advanced *RAS* wild-type mCRC treated with FOLFOX plus panitumumab within the Valentino clinical trial.[10] Similarly, Meng *et al*, dividing in three age subgroups patients treated with first line FOLFOX (<50 yars vs 50–65 years vs >65 years), identified differences in incidence of nausea/vomiting (69.3% vs 57.6% vs 60.4%, p=0.019), and the EO-CRC group had also earlier onset of nausea/vomiting (1.0 vs 2.1 vs 2.6 weeks, p=0.012).[11]

In a population of both non-metastatic and metastatic CRC patients, similar findings were obtained with patients with EO-CRC being more likely to report nausea and vomiting.[6] Finally, in one study female gender and age lower than 50 were significantly associated with the onset of gastrointestinal toxicities.[7]

Diarrhoea in EO-CRC

Differently from data concerning nausea and vomiting, patients with EO-CRC were found to suffer same or less diarrhoea compared with their older counterpart both in the adjuvant and the metastatic setting.[3 8–11]

Table 1 Published studies discussing gastrointestinal toxicities in early-onset colorectal cancer (EO-CRC) patients retrieved through our systematic review process.

Authors, ref.	Country	Study setting/study type	Total n of participants (cases; controls)	EO-CRC age cut-off (years of age)	Gender F/M (%)	Control cohort	Treatment provided	Main results
Raimondi *et al*, 2022[10]	Italy	Adv./post hoc analysis of Valentino trial	229 (35;194)	<50	34/66	Yes	FOLFOX plus panitumumab first-line treatment	► EO-CRC experienced higher rate of any grade nausea (43% vs 32%, p=0.249) and vomiting (26% vs 16%, p=0.226).
Meng *et al*, 2022[11]	USA	Adv./post hoc analysis of 3 clinical trials (NCT00272051; NCT 00305188; NCT00364013)	1223 (179;1044)	<50, 50–65, >65	40/60	Yes	FOLFOX	► EO-CRC (<50 yo vs 50–65 years vs >65 years) had higher incidence of nausea and vomiting (69.3% vs 57.6% vs 60.4%, p=0.019). ► Lower incidence of severe diarrhoea in EO-CRC pts (6.1% vs 9.1% vs 13.0%, p=0.02).
Antoniotti *et al*, 2022[9]	Italy	Adv./post hoc analysis of TRIBE and TRIBE2 studies	1187 (194; 993)	< 50	42/58	Yes	FOLFOXIRI+bevacizumab or doublets+bevacizumab	► EO-CRC had lower risk of diarrhoea (9% vs 14%, p=0.04) and higher of nausea and vomiting (69% vs 57%, p<0.01; 44% vs 32%, p<0.01). ► Among pts receiving FOLFOXIRI/bevacizumab, the incidence of G3-G4 GI adverse events (mucositis, nausea, diarrhoea) was not significantly different in EO-CRC.
Fontana *et al*, 2021[3]	International	Adj./post hoc analysis of the IDEA cohort	16349 (1564; 14785)	< 50	43.6/56.4	Yes	CAPOX or FOLFOX (3 or 6 months)	► Higher incidence of nausea/vomiting (58,2% vs 44,8% p<0.0001; 22,3% vs 16.1% p<0.0001) but not diarrhoea (42.1% vs 39.4% p=0.3765) in pts with EO-CRC.
Perl *et al*, 2016[8]	Israel	Adj. and Adv./ retrospective cohort	50 pts with GI malignancies (80% were CRC pts) (40; 0)	< 40	52/48	No	Surgery, chemotherapy, radiotherapy, combined modality	► Diarrhoea and abdominal pain significantly increased during-treatment administration (p<0.05) in EO-CRC pts.
Suzuki *et al*, 2016[7]	Japan	N.S./retrospective	179 (22; 157)	< 50	39/61	Yes	FOLFOX, XELOX, FOLFIRI	► Female (OR 2.870, 95% CI 1.139 to 7.228; p=0.025)* and age <50 (OR 4.277; 95% CI 1.472 to 12.424; p=0.008) were risk factors for CINV.
Sanford *et al*, 2014[6]	USA	Adj and Adv./ multicentric prospective study	1544 breast cancer and 718 CRC (37; 681)	< 40	48/52	Yes	N.S.	► EO-CRC pts had more nausea (adjusted OR 2.59, 95% CI 1.02 to 6.59 p<0.05), while G3-G4 diarrhoea, vomiting or mucositis were not significantly different.
Hubbard *et al*, 2012[5]	International	Adj./post hoc analysis of 10 randomised phase III trials	33574 (5,817†; 27 757)	< 40 and < 50‡	45/55	Yes	Fluorouracil-based monotherapy and combination chemotherapy	► EO-CRC <40: more nausea and vomiting (10% vs 7%, OR 0.64 p 0.04), but no difference in diarrhoea (15% vs 16%, p>0.05).
Blanke *et al*, 2011[4]	International	Adv./post hoc analysis of 9 phase III trials	6284 (793; 5491)	< 50	36.5/63.5	Yes	Fluorouracil-based monotherapy and combination chemotherapy	► More G3 nausea (10% vs 7%; p=0.01); rarer severe diarrhoea (11% vs 14%; p=0.001) in patients with EO-CRC.

*Reported as a potential factor influencing a higher gastrointestinal symptoms incidence in EO-CRC cohort.

†Number of patients included in the younger than 50 years of age cohort.

‡Two cohorts of patients with EO-CRC were studied. Nausea grading is reported according to Common Terminology Criteria for Adverse Events (CTCAE).

Adj, Adjuvant setting; Adv, Advanced/metastatic setting; CINV, chemotherapy-induced nausea or vomiting; F, female; G, grade; GI, gastrointestinal; LO-CRC, later-onset colorectal cancer; M, male; n, number; Neoadj, neoadjuvant; N.S., not specified; Prosp, prospective; Pts, patients; ref, reference; Retro, retrospective.

In one study conducted in the adjuvant setting, any grade diarrhoea during treatment was observed in 37% of patients with EO-CRC younger than 40 years (control cohort not available).[8] In the same setting, [4] while in the IDEA trial cohort no increased in diarrhoea incidence was noticed among patients with EO-CRC.[3]

Moreover, even in the advanced setting when receiving a triplet combination, patients with EO-CRC had a lower risk of diarrhoea.[9] Similarly, Meng and *et al*[11] found lower incidence of severe diarrhoea (6.1% vs 9.1% vs 13.0%, p=0.02) in patients with EO-CRC treated with first line FOLFOX. Also from the Valentino trial, no significant differences in any grade diarrhoea (54% vs 52%, p=0.855) were reported.[10]

DISCUSSION

In our review, we found that patients with EO-CRC suffer more nausea and vomiting compared to older patients receiving systemic anticancer treatments. Data available in retrieved articles did not allow us to precisely define the impact of each specific anticancer regimen on nausea and vomiting. However, given its prevalence of administration and its emetogenicity, oxaliplatin might be regarded as a potential risk factor of increased nausea and vomiting in patients with EO-CRC.[12]

Nausea and vomiting represent a multifactorial symptom and the primary cause is often difficult to assess. Accordingly, all but one articles retrieved do not differentiate its cause.[7] Indeed, there are several potential causes leading to an increased burden of nausea and vomiting in patients with EO-CRC, which might also be differently prevalent from older patients. First, EO-CRC patients more frequently receive more intense cytotoxic combinations, including multiple drugs with moderate emetogenic potential, and this might explain more nausea and vomiting.[2 12] Second, it should be noted that the reported higher prevalence of peritoneal involvement in EO-CRC, particularly in patients with mucinous or signet-ring CRC, might impact on the burden of nausea and vomiting.[1 2] Third, the burden of nausea and vomiting in EO-CRC has been reported to increase among those younger than 40 years of age,[5 6] which has been postulated to be potentially related to psychological consequences and emotional stress of a cancer diagnosis at a very young age. Moreover, it has been reported that younger female patients, particularly if with low body mass index according to data from a CRC population ranging between 40 and 65 years of age, might suffer more nausea and vomiting.[7 13] Finally, based on data from other young patients with cancer cohorts not limited to EO-CRC, physicians suboptimal adherence to international guidelines for the management of nausea and vomiting treating younger patients might represent an additional risk factor.[14] Indeed, based on an age-related bias, patients with EO-CRC might be expected to better tolerate medical systemic treatments and consequently be undertreated for side effects. However, according to data available so far in the literature, this attitude should be discouraged. Indeed, we suggest patients with EO-CRC to be treated for nausea and vomiting as stated in European Society of Medical Oncology (ESMO) and American Society of Clinical Oncology (ASCO) guidelines for the overall cancer population.[12]

Differently from nausea and vomiting, we found that the burden of diarrhoea experienced by patients with EO-CRC is overall comparable or lower to the older counterpart.[3] Thus, diarrhoea does not emerge as a specific issue among the gastrointestinal toxicity burden experienced by patients with EO-CRC.

Our review has some limitations such as the few data available on this topic and the heterogeneity of records retrieved hampering the drawing of definitive conclusion. Most of the studies retrieved are secondary analysis of randomised clinical trials whose first aim was not to address EO-CRC specific outcomes, leading to the lack of a proper matched control population. Moreover, the lack of grading for nausea, vomiting and diarrhoea in most of the studies retrieved hampered the understanding of the actual impact of these toxicities on EO-CRC patients quality of life (QoL). Accordingly, towards any clinical implementation more data are mandatory.

In conclusion, given the limited amount of data on this topic in this specific subset of patients, nausea and vomiting in patients with EO-CRC should be managed as recommended in the ASCO and ESMO clinical guidelines for the general CRC population. Further dedicated and prospective studies are warranted to define if enhancing primary antiemetic prophylactic might be an option to improve treatment tolerability and QoL in patients with EO-CRC.

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