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Evaluation of the efficacy of chemotherapy with capecitabine and oxaliplatin in patients with disseminated colorectal cancer. The impact of primary cancer focus on treatment efficacy

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ABSTRACT

Introduction. Colorectal cancer is an increasingly common cancer, and due to the possibility of using many drugs and combination therapy, it bears the hallmarks of a chronic disease. Improving the quality of life is important.

Material and methods. The following analysis applies to the oxaliplatin and capecitabine (CAPOX) regimen in a group of 305 patients. This chemotherapy was used as part of palliative treatment lines I, II or III.

Results. The work proved the effectiveness of the scheme despite the reduction of drug doses in about 50% of patients, and toxicity grade 3 was only present in 5% (grade 4 complications were not observed). The group of patients in which CAPOX was used as the first treatment line was considered representative, and the effectiveness of the treatment depending on the location of the primary tumour was evaluated.

Conclusion. Differences in overall survival of patients after stratification were observed relative to the location of the primary tumour. Survival was longer in patients with left-sided primary tumour compared to right-sided localisation and was, respectively, 20.4 (95% CI, 17.5–23.4) and 12.1 months (95% CI, 10.5–13.8) ($P = 0.014$).

Key words: metastatic colorectal cancer, oxaliplatin, capecitabine, primary tumour location

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Introduction

Palliative chemotherapy has been used in patients with generalised colorectal cancer (CRC) for many years. At the time of diagnosis, a generalised disease is found in approximately 15–20% of patients.

Even after radical surgery (R0 resection), approximately 50% of patients will develop metastatic lesions, including 30–35% having only liver metastases. In this cohort, 10–25% are eligible for surgical treatment, and 75–90% of patients will be offered palliative chemotherapy. The use of chemotherapy allows objective response to be obtained in 50% of

cases in imaging tests, and extended progression-free survival (PFS) to 10 months and overall survival (OS) to 20–24 months [1].

In about 15–20% of patients, generalised colorectal cancer is an asymptomatic or slow-growing disease; therefore, aggressive treatment is not required [2]. It should be emphasised that the quality of life of patients receiving palliative treatment, apart from the toxicity of treatment, is significantly influenced by the frequency and length of hospitalisation.

Currently, an important argument in choosing a treatment regimen is patients' quality of life, which includes — among others — the frequency and route of drug admini-

Table 1. Characteristics of patients in the observed group

Treatment line	First-line treatment	Second-line treatment	Third-line treatment	
Number of patients	222	66	17	
Gender	Male 183 (60%)	Female 122 (40%)		
Age	Mean 64.4	Range 32–87	≥ 65 years 146 (48%)	< 65 years 159 (52%)
Prior adjuvant treatment	YES 139 (46%)	NO 166 (54%)		
WHO performance status	0–1 278 (91%)	2 27 (9%)		

stration. The generalised stage of colorectal cancer often requires lengthy treatment, and the use of oral medications significantly improves the comfort of such treatment. These regimens include: CAPOX, XELIRI, and capecitabine alone.

The CAPOX regimen includes capecitabine and oxaliplatin. Capecitabine is administered orally at a dose of 1000 mg/m² twice daily for 14 days, and oxaliplatin is administered on the first day of the cycle at a dose of 130 mg/m² as a two-hour intravenous infusion. The cycle is repeated every 21 days.

Nonetheless, the most common therapeutic option proposed for patients with stage IV colorectal cancer is systemic treatment, which improves the quality of life and often extends the survival. The most commonly used anticancer drugs (in monotherapy or multi-drug regimens) for colorectal cancer include fluorouracil, irinotecan, oxaliplatin, capecitabine, bevacizumab, aflibercept, cetuximab, panitumumab, and regorafenib. The main goal is to achieve the greatest effectiveness with the least toxicity of treatment.

A regimen containing a combination of capecitabine and oxaliplatin is used in the first-, second-, or third-line treatment, depending on the genetic characteristics.

Currently, the growing importance of primary tumour location in the biology of colorectal cancer is underlined. The location of the primary tumour on the right side is associated with a worse prognosis. More and more publications are devoted to the impact of tumour location on response to targeted therapy with anti-epidermal growth factor receptor (EGFR) or anti-vascular endothelial growth factor (VEGF) antibodies, while there is little data on the effect of tumour location on the effectiveness of chemotherapy.

The aim of the study was to evaluate the effectiveness of chemotherapy with capecitabine and oxaliplatin in patients with generalised colorectal cancer and to compare treatment results depending on the tumour's original location.

Material and methods

We carried out a retrospective analysis of consecutive patients diagnosed with generalised colorectal cancer

treated at the Colon Cancer Clinic and the Gastrointestinal Cancer Clinic between March 2008 and April 2011. The inclusion criteria included: histopathological diagnosis of colorectal adenocarcinoma, good general condition (WHO 0–2), locally advanced or metastatic colorectal cancer, the use of chemotherapy according to CAPOX scheme (I, II, or III line), and the presence of a measurable lesion. Table 1 presents the characteristics of 305 patients included in the analysis.

On average, six CAPOX cycles were used in each treatment line. A retrospective analysis of response to CAPOX treatment was performed (including disease control rate [DCR], time to progression [TTP], and overall survival), taking into account dose reductions and treatment toxicity. A retrospective analysis of clinical outcome in patients with metastatic colorectal cancer depending on the location of the primary tumour was also made. This analysis included only the group of patients treated with the CAPOX regimen in the first and second line of treatment.

Results

There were no statistically significant differences in disease control rates (DCR) between the analysed groups. In the entire study group, regardless of the treatment line in which the CAPOX regimen was used, DCR was 75.9%; in individual lines: I — 77.3% (n = 167), II — 72.2% (n = 47), and III — 69.2% (n = 9) (P = 0.604).

Table 2 presents the distribution of response to the treatment according to the RECIST 1.1 criteria.

The median overall survival (OS) in the first-line treatment is 19.3 months (95% CI, 17.06–23.5), in the second-line treatment 14.2 (95% CI, 11.61–17.83), and in the third-line treatment 13.96 (95% CI, 11.78–16.73).

There was no grade 4 haematological or non-haematological toxicity in the study group. Grade 3 leukopaenia and neutropaenia were only observed in patients receiving CAPOX regimen in third-line treatment (5.9% — grade 3 leukopaenia, 2.9% — grade 3 neutropaenia). A statistically significant difference in complications

Table 2. Assessment of response to treatment with the CAPOX regimen in individual treatment lines

Treatment line	Complete response (%)	Partial response (%)	Stable disease (%)	Progressive disease (%)
First-line treatment	4.2	35.2	38	22.6
Second-line treatment	4.6	24.6	43.1	27.7
Third-line treatment	0	7.7	61.5	30.8

Table 3. Results of treatment of metastatic colorectal cancer with the CAPOX regimen (capecitabine + oxaliplatin) depending on the primary tumour location

	Right side	Left side	Total
DCR (%)	68.3	76.7	74.7
Median PFS (months, 95% CI)	3.9 (3.4–4.5)	4.2 (3.9–4.5)	4.1 (3.9–4.4)
Median OS (months, 95% CI)	12.0 (10.0–14.0)	18.7 (16.4–21.1)	16.9 (14.9–18.8)
First-line mOS [(months, 95% CI)	12.1 (10.5–13.8)	20.4 (17.5–23.4)	19.3 (15.6–23.1)
Second-line mOS (months, 95% CI)	7.2 (6.2–8.2)	16.1 (12.0–20.1)	14.2 (11.3–17.1)

CI — confidence interval; DCR — disease control rate; OS — overall survival; PFS — progression-free survival

according to the treatment line was found only in case of leukopaenia after CAPOX used in third-line treatment ($P < 0.001$). Grade 3 vomiting occurred in 0.9% of patients in first-line treatment and 1.5% in second-line. Grade 3 hand-foot syndrome was observed in 0.5% of patients in first-line treatment. Grade 3 sensory neuropathy was found in 2.8% of patients in first-line treatment and 3% in second-line treatment.

There was a statistically significant increase in the frequency of oxaliplatin dose reduction in subsequent treatment lines (I — 53.5%, II — 69.7%, III — 82.4%; $P = 0.008$) as well as drug withdrawal (I — 12.5%, II — 16.7%, III — 35.3%; $P = 0.034$). No similar difference was found for capecitabine, for which dose reduction rates were similar in all treatment lines (I — 56%, II — 66%, III — 58.8%).

The clinical benefit obtained in the study did not depend on the chemotherapy line in which CAPOX regimen was used in patients with stage IV colorectal cancer.

We did not observe any relationship between the results of CAPOX treatment and primary tumour location in patients treated in the first line (Tab. 3). The percentage of patients achieving disease control was 68.3% for right-sided and 74.7% for left-sided tumour location ($p = 0.188$).

Similarly, the median progression-free survival (PFS) did not differ and was for right-sided and left-sided location 3.9 (95% CI, 3.4–4.5) and 4.2 months (95% CI, 3.9–4.5; $P = 0.443$), respectively. Median PFS for the whole cohort was 4.1 months (95% CI, 3.9–4.4) and was shorter than in published randomised clinical trials for CAPOX regimen (7.1–10.3 months for CAPOX in first-line treatment; 4.7 months for CAPOX in second-line treatment) [3, 4]. The reason for the differ-

ence between our results and data from clinical trials is uncertain, but it is probably due to patient selection for randomised trials.

Median OS in the study population was 16.9 months (95% CI, 14.9–18.8). This value is similar to the results obtained in randomised clinical trials, in which (depending on the study) it was from 16.0 to 24.6 months, average 17–19 months [3, 4]. In one study with use of CAPOX regimen in second-line treatment the median OS was 11.9 months, compared to 14.2 months (95% CI, 11.3–17.0) in an analogous group in our population [6].

However, we observed a statistically significant difference in overall survival for patients stratified according to the primary tumour location. If the tumour was located on the right side of the colon, the median OS was 12.1 months (95% CI, 10.5–13.8), compared to 20.4 months (95% CI, 17.5–23.4) for the disease with left-sided location ($P = 0.014$). In one retrospective study of patients with metastatic colorectal cancer receiving polychemotherapy without targeted drugs, results similar to ours were achieved: for right and left-sided disease the median OS was 13.0 and 17.8 months, respectively [6].

Based on this data, it is difficult to determine whether this difference in OS is to any extent the result of differences in the effectiveness of CAPOX regimen in these two subgroups. It has been reported in many studies, however, that the difference in overall survival is certainly greatly influenced by the more aggressive course of right-sided colorectal cancers [7, 8]. Poorer prognosis of colorectal cancers located on the right side was also confirmed in the group of patients receiving CAPOX regimen in second-line treatment [9].

Discussion

Currently, there are many data related to the effectiveness and toxicity of chemotherapy, but it is worth emphasising the effectiveness of the CAPOX regimen with a significant dose reduction. No grade 4 toxicity was observed, and grade 3 only in 5% of patients.

Particularly interesting is the importance of primary tumour location in the biology of colorectal cancer, and this observation is discussed below. In this context right-sided tumours (proximal to the splenic flexure) and left-sided tumours (distal to this structure) are distinguished.

The biological explanation for differentiating these locations is, among others, distinct embryogenesis of right and left segments of the large intestine (developing from the middle and posterior intestine, respectively), separate vascularisation (superior and inferior mesenteric artery, respectively), and differences in the intestinal microbiome and alternative carcinogenesis pathways occurring in these sections (right-sided cancers more often develop from serrated adenomas or traditional serrated polyps harbouring *BRAF* mutations and/or microsatellite instability; left-sided cancers typically evolve from classic adenomas with *APC* gene mutations) [8].

The distinction between these locations of colorectal cancers also has great prognostic justification. The results of several studies and meta-analyses indicate that cancers located on the left side have a lower risk of death (relative risk in the large meta-analysis 0.82, 95% CI 0.79–0.84) regardless of the presence of other prognostic factors (e.g. clinical stage, chemotherapy, cancer histology, and *BRAF* mutation) [8]. Attention is also paid to the predictive significance of primary tumour location, which can be of great importance when choosing the method of palliative therapy. In patients with left-sided tumours, unequivocal benefit from using anti-EGFR antibodies (e.g. cetuximab, panitumumab) has been proven; in turn, in patients with a primary tumour located on the right side, the use of anti-VEGF antibodies (e.g. bevacizumab) is preferred [11].

Unfortunately, there are very little data available on the impact of colorectal cancer location on response to chemotherapy, including fluoropyrimidines. Based on experimental data, it appears that fluorouracil may be more active in right-sided cancers due to the higher expression of thymidine phosphorylase and lower expression of gamma-glutamyl hydrolase, which promotes higher folic acid levels in cancer cells and higher fluoropyrimidine cytotoxicity [12]. Thymidine phosphorylase is also required to convert the prodrug capecitabine to the active form, fluorouracil [13]; thus, it appears that a higher level of this enzyme in right-sided tumours [14] may contribute to higher capecitabine activity. However, there is no direct evidence confirming this hypothesis.

The negative prognostic value of right-side location of colorectal cancer persists regardless of the treatment used [6, 7]. This does not mean, however, that patients with right-sided tumours do not benefit from chemotherapy; probably the opposite is true: in stage III cancers, adjuvant treatment with fluorouracil or capecitabine with oxaliplatin has a relatively greater benefit in terms of disease-free survival (DFS) in patients with right-sided cancer [15, 16].

Unfortunately, there are also scarce data on the impact of tumour location on chemotherapy results for stage IV cancers. In one study, Negri et al. did not observe differences in objective response rate (ORR) between originally left- and right-sided cancers during treatment with fluorouracil alone or in combination with mitomycin and interferon, although right-sided location was associated with 1.6-times higher risk of death [17].

In the FIRE-1 study comparing FuFIRI (irinotecan, fluorouracil infusion, leucovorin) and mIROX (irinotecan, oxaliplatin) regimens in the first-line treatment, it was found that using the FuFIRI regimen leads to a higher ORR in patients with primary left-sided tumour (33% and 47% for right-sided and left-sided cancer, respectively); however, such differences were not observed for the mIROX regimen (ORR 40% for both locations) [18]. A tendency towards longer OS was also observed when the FuFIRI scheme was used for left-side primary tumour location and the mIROX scheme for right-sided cancer, but these results did not reach statistical significance [18]. Unfortunately, there are no such studies for chemotherapy regimens currently most commonly used in first- and second-line palliative treatment (FOLOX/CAPOX, FOLFIRI/XELIRI), especially taking into consideration the fact that these regimens are nowadays frequently associated with biological drugs for which the location of the primary tumour is a strong predictive factor (i.e. as described above).

An additional issue is the molecular differences between right- and left-sided cancers, which can affect the response to chemotherapy. Particularly important are the differences in the occurrence of microsatellite instability-high (MSI-H) and *BRAF* gene mutations, which are more frequent in cancers originally located on the right side. In the presence of *BRAF* gene mutation (18.4–22.4% of right-sided cancers and 1.3–7.8% of left-sided cancers), which is a poor prognostic factor, patients do not benefit significantly from chemotherapy with fluoropyrimidine, oxaliplatin, or irinotecan [19–22]. In turn, the presence of MSI-H, which is typical for sporadic *BRAF* mutant cancers (52% of patients with *BRAF* mutation also indicate MSI-H), are found in about 5% of metastatic colorectal cancers, almost exclusively right-sided [7]. Tumours with MSI-H are characterised by markedly reduced sensitivity to fluoropyrimidines,

as seen in preclinical studies [22, 23] and confirmed in a number of clinical studies [24–27]. Similarly, the lack of efficacy of fluoropyrimidines is observed in CpG island methylator phenotype (CIMP) cancers, and this is typical for sporadic MSI-H cancers and in cancers of mucocellular histology, which is a manifestation of MSI-H presence [7, 28]. In summary, primary right-sided cancers show a number of molecular features such as MSI-H, CIMP, and *BRAF* mutations that promote resistance to fluorouracil and capecitabine. Molecular aberrations responsible for reduced effectiveness of fluoropyrimidines are found in the absolute minority of right-sided cancers. It remains an open question to what extent these relationships can be extrapolated to all right-sided colorectal cancers.

Conflict of interest

The authors report no conflicts of interest.

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