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De-escalation of the systemic therapy in advanced colorectal cancer – justified clinical practice from the point of view of efficiency and safety

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Colorectal cancer is one of the most frequent malignant tumours in Poland, making up the third cause of cancer deaths both in women and in men with regards to the frequency of occurrence. The therapy of patients with high-stage colorectal cancer is palliative and should be conducted in a continual manner until the disease progression or unacceptable toxicity of treatment. By definition, palliative care aims at prolongation of the period to the exacerbation of the disease and of the overall survival with simultaneous guarantee of appropriate quality of life to the patients. A long-term use of a multidrug chemotherapy is often connected with the presence of clinically significant toxicity, therefore, de-escalation of systemic treatment is currently the subject of numerous analyses. The studies evaluating the effect of maintenance therapy on patient survival, prove that this kind of treatment makes up a valuable option in the case of patients in whom a good clinical effect is maintained with a concurrent reduction of toxicity of treatment. Especially in the context of the ongoing SARS-CoV-2 pandemic, monotherapy or less aggressive therapy should be discussed with patients.

Key words: advanced colorectal cancer, de-escalation therapy, cetuximab, panitumumab, bevacizumab

Introduction

Colorectal cancer is one of the most frequent tumours in Poland, making up the third cause of cancer deaths in women (7.6%) and in men (8%) with regards to the frequency of occurrence [1]. Thanks to the inclusion of new biological drugs to the classical chemotherapy in patients with metastatic colorectal cancer (mCRC) a significant improvement of the median overall survival (currently 24 months, whilst – after metastasectomy – up to 57 months) [2–5].

However, a large problem which still remains here, is the toxicity of treatment and its effect on the quality of life (QoL). Because the accessibility of chemotherapy infusions in Poland is relatively limited, a condition necessary for the safe therapy is therefore a few days' hospital stay, which is inconvenient for the patients and poses a great burden for the healthcare.

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Additionally, the SARS-CoV-2 pandemic contributed to the search for new solutions aimed at the limitation the contacts with the healthcare system staff to the necessary minimum. That is why, the de-escalation of the treatment of patients with mCRC – the therapy which, by definition, is long and is carried out until the disease progression or unacceptable toxicity – is the subject of debates and analyses.

This paper describes some selected aspects of the embryonal development of the large intestine, as they form the theoretical basis for the diversity of the observed treatment effects. Moreover, the authors present an overview of the research concerning the maintenance therapy and the binding Polish and European recommendations in this area (taking into consideration the recommendations concerning the treatment during the SARS-CoV-2 pandemic).

Embryological and anatomic foundations

Large intestine develops from endoderm. In the 4th week of embryonal life, the head-gut is closed with the oropharyngeal membrane, whilst its caudal part – with the cloacal membrane. As a result of the embryonic folding, the archenteron is divided into three parts: foregut, midgut and hindgut. The organs of the gastro-intestinal system, which are vascularised by the celiac artery, (oesophagus, stomach, duodenum, liver, pancreas, bile ducts) develop from foregut. The small and large intestine, as well as the caecum up till ⅔ length of the transverse colon, are developed from midgut (vascularised by the upper mesenteric artery and innervated by the parasympathetic vagal nerve). The remaining part of the large intestine (from ⅓ of the left transverse colon to the anal canal) develop from hindgut and are vascularised by the inferior mesenteric artery and innervated anatomically by the pelvic plexus (parasympathetic fibres are innervated from the intermediomedial nucleus of the spinal cord on the level of S2–S4) [6, 7].

These embryological differences translate into a diverse characteristics of the cancer developing on the right and on the left side of the large intestine. Right-sided tumours are characterised with slightly poorer prognosis; more frequently they affect women, elderly people or patients with HNPCC. These tumours also have a larger number of mutations in *BRAF, KRAS, PTEN, BRCA1* genes and are more sensitive to immunotherapy. The tumours located on the left side of the intestine, in turn, more frequently affect male patients, younger persons, people with familial adenomatous polyposis and with *APC, TP53, NRAS* mutations [8, 9].

The retrospective analyses of the clinical studies with the use of monoclonal antibodies manifested a different treatment effect depending on the tumour location. The CRYSTAL study revealed that the inclusion of cetuximab into the treatment is not beneficial with respect to progression-free survival (PFS) and overall survival (OS). In the case of left-sided location of the tumour, in turn, the addition of cetuximab to the therapy had a beneficial effect on the prolongation of PFS and OS. In the FIRE-3 study, in the patients with right-sided location, no increase of treatment efficiency was observed after adding cetuximab or bevacizumab to the FOLFIRI (5-fluorouracil + calcium folinate + irinotecan) chemotherapy scheme. However, in the case of the tumours located on the left side, the patients treated with cetuximab lived significantly longer (yet there were no differences with regards to PFS) [10].

Maintenance treatment / chemotherapy de-escalation

The treatment of patients with mCRC has a palliative character and usually does not provide for a possibility of permanent cure. Palliative therapy should prolong PFS and OS, allowing for an appropriate quality of life in the patients. Long-term use of multidrug therapy is often connected with the existence of significant toxicity and deteriorates the quality of life. The concept of the de-escalation of systemic treatment of mCRC was coined many years ago, even before the era of biological drugs. In 2006, the OPTIMOX1 study [11] proved that such way of treatment allowed to reduce toxicity, preserving the treatment efficacy at the same time. In order to reduce neurotoxicity caused by oxaliplatin, the stop-and-go strategy was used. The patients received the FOLFOX treatment regimen (oxaliplatin, 5-fluorouracil, calcium folinate). Group A received treatment continually till the disease progression, whilst group B received 6 cycles of full therapy and then only fluoropyrimidine with calcium folinate was administered in this group (12 cycles; de-escalation), and then the full FOLFOX regimen was resumed (next 6 cycles). In the group with the multidrug chemotherapy (FOLFOX) used in a continual way, PFS was slightly longer, whilst OS was not significantly affected (tab. I). Toxicity grade 3 or 4, as defined by of the National Cancer Institute Common Toxicity Criteria (NCICTC), was observed in 54.4% patients from group A and in 48.7% patients in group B. Moreover, in group A sensory neuropathy grade 3 was diagnosed in 17.9% patients, whilst in group B – in 13.3% ($p = 0.12$). This means that such treatment strategy allowed for the reduction of oxaliplatin neurotoxicity with concurrent maintenance of the therapy efficiency .

The OPTIMOX2 study [12] proved that temporary complete discontinuation of chemotherapy had an adverse effect on the treatment efficacy and that is why it should not be used. The results of treatment in two groups of patients were compared. In one group, after the administration of 6 cycles of the FOLFOX chemotherapy, the treatment was completely discontinued, and then – after the progression of the disease – the therapy was resumed according to the same regimen. In the second group of patients, the treatment was used in a continual way, yet after 6 cycles, de-escalation was used, restricting the number of the administered drugs to two (fluorouracil with calcium folinate), whilst the return to full, multidrug FOLFOX regimen was made only after the disease progression (analogically as in the B arm in the OPTIMOX1 study). The main endpoint of

Table I. A comparison of the most significant clinical studies with maintenance treatment with monoclonal antibodies

Study	Intervention	ITT	mPFS (months)	HR PFS (95% CI)	mOS (months)	HR OS (95% CI)
OPTIMOX1 [11]	FOLFOX4 continual treatment *vs.* 6 FOLFOX7 cycles ⟶ 12 5FUL/LV cycles ⟶ FOLFOX7	311 *vs.* 309	9 *vs.* 8,7	1.06 (0.89–1.2)	19.3 *vs.* 21.2	0.93 (0.72–1.11)
OPTIMOX2 [12]	6 FOLFOX7 ⟶ 5FU/LV cycles *vs.* 6 FOLFOX7 cycles ⟶ follow-up	98 *vs.* 104	8.6 *vs.* 6.6	0.61 no data	23.8 *vs.* 19.5	0.88
PRODIGE-9 [21]	12 FOLFIRI cycles + bevacizumab ⟶ bevacizumab *vs.* 12 FOLFIRI cycles + bevacizumab ⟶ follow-up	247 *vs.* 247	9.2 *vs.* 8.9	0.91 (0.76–1.09)	21.7 *vs.* 22	1.07 (0.88–1.29)
CAIRO3 [22]	6 CAPOX cycles + bevacizumab ⟶ capecitabine + bevacizumab *vs.* 6 CAPOX cycles ⟶ follow-up after PD (PFS1) CAPOX + bevacizumab until PD (PFS2)	279 *vs.* 279	11.7 *vs.* 8.5	0.67 (0.56–0.81)	25.9 *vs.* 22.4	0.89 (0.73–1.07)
VELVET [24]	1–6 i FOLFOX7 cycles + aflibercept ⟶ 5FU/LV/capecitabine + aflibercept	48	9.3 (8.3–12.5)	–	22.2 (18.2–24.7)	–
SAPPHIRE [25]	6 FOLFOX6 cycles + panitumumab ⟶ FOLFOX6 + panitumumab, continual treatment *vs.* 6 FOLFOX6 cycles + panitumumab ⟶ 5FU/LV + panitumumab	56 *vs.* 57	9.1 *vs.* 9.3	0.93 (0.60–1.43)	not reached	1.41 (0.69–2.88)*
VALENTINO [26]	8 FOLFOX4 cycles + panitumumab ⟶ 5FU/LV + panitumumab *vs.* 8 FOLFOX4 cycles + panitumumab ⟶ panitumumab	117 *vs.* 112	12 *vs.* 9.9	1.51 (1.11–2.07)	–	1.13 (0.71–1.81)
MACRO-2 [27]	FOLFOX6 + cetuximab ⟶ cetuximab *vs.* FOLFOX6 + cetuximab, continual treatment	129 *vs.* 64	9 *vs.* 10	1.19 (0.80–1.79)	23 *vs.* 27	1.24 (0.85–1.79)
COIN-B [28]	FOLFOX + cetuximab 12 weeks ⟶ Interval till PD *vs.* FOLFOX + cetuximab 12 weeks ⟶ cetuximab	64 *vs.* 66	3.1 *vs.* 5.8	–	16 *vs.* 17.5	–
MACBETH [29]	FOLFOXIRI + cetuximab ⟶ cetuximab *vs.* FOLFOXIRI + cetuximab ⟶ bewacizumab	59 *vs.* 57	13.3 *vs.* 10.8	0.73 (0.46–1.17)	37.5 *vs.* 37	0.98 (0.52–1.87)
Jiang et al. [30]	9–12 FOLFIRI cycles + cetuximab ⟶ follow-up *vs.* 9–12 FOLFIRI cycles + cetuximab ⟶ irinotecan + cetuximab (M1) *vs.* 9–12 FOLFIRI cycles + cetuximab ⟶ 6–12 irinotecan cycles + cetuximab ⟶ cetuximab (M2)	28 *vs.* 44 *vs.* 25	6.1 (M1) *vs.* 8.7 (M2)	–	–	–
NORDIC-7.5 [32]	8 FLOX cycles + cetuximab ⟶ cetuximab	152	8.0	–	23.2	–
Chan et al. [31]	2–12 FOLFOX / FOLFIRI cycles + cetuximab ⟶ cetuximab	15	6.8	–	17.0	–

CI – confidence interval; HR – hazard ratio; ITT – intention-to-treat; mOS – median overall survival; mPFS – median progression-free survival; FOLFOX: 5-fluorouracil + calcium folinate + oxaliplatin; 5FU/LV – 5-fluorouracil + calcium folinate; FOLFIRI – 5-fluorouracil + calcium folinate + irinotecan; CAPOX – capecitabine + oxaliplatin; FOLFOXIRI – 5-fluorouracil + oxaliplatin + oxaliplatin; Nordic FLOX – 5-fluorouracil (bolus) + calcium folinate + oxaliplatin; * – estimated value

the study was the duration of disease control (DDC). Median DDC was 13.1 months in the patients treated in a continual way and 9.2 months in the patients in whom the therapy was temporarily suspended (p = 0.46). Median PFS and median OS were longer in the group treated in a continual way (tab. I), whereas elective complete discontinuation of chemotherapy had a negative effect on the efficiency of treatment.

The results of metanalysis carried out by Berry et al. [13] clearly show that de-escalation does not deteriorate the treatment results only when the maintenance chemotherapy is continued and not when the systemic treatment is completely discontinued.

Biological therapy of high stage colorectal cancer

The first biological agent which was added to the ILF regimen (irinotecan, fluorouracil, calcium foliate) and which confirmed its efficacy in the third phase study was bevacizumab [14]. This drug is an IgG subclass humanised antibody, specific for vascular endothelial growth factor (VEGF). It manifests an antiangiogenic effect by means of inactivating all the VEGF isoforms and improves the penetration of cytostatic drugs into the tumour by means of decreasing the pressure inside it [15]proliferative processes. Numerous regulators of angiogenesis have been identified and characterized over the last decades. Among these, vascular endothelial growth factor (VEGF. In the group of patients in whom bevacizumab was added to their chemotherapy, OS was about 5 months longer in comparison to the group of patients treated with chemotherapy alone (20.3 *vs.* 15.6 months). Another antiangiogenic drug introduced to therapy was aflibercept. It binds with VEGFA and VEGFB, blocking their ability of connecting to the receptor. In the second line of treatment, in combination with the FOLFIRI chemotherapy, aflibercept contributed to the prolongation of the median PFS by about 2 months, whilst to the median OS – by 1 month [16].

A significant progress in the systemic treatment of mCRC was made together with the introduction of the antibodies directed against epidermal growth factor receptor (EGFR): panitumumab and cetuximab. Panitumumab is an IgG2 subclass human antibody, whilst cetuximab is a chimeric monoclonal antibody. These drugs manifest affinity to EGFR and prevent EGFR from binding ligands, by inhibiting the pathway of the EGFR/RAS/RAF/MEK signal transduction to the cell nucleus [17, 18]. The presence of mutation in the *KRAS* or *BRAF* gene results in permanent activation of this pathway, irrespectively of the EGFR activation. Mutations in the *KRAS* gene occur in about 30–40% colorectal cancer patients [19]. In these people, the drugs against EGFR are ineffective. The PRIME study [3] proved that adding the therapy directed against EGFR to the FOLFOX chemotherapy in the patients without mutation in *RAS* genes allowed to prolong their survival to more than 2 years (26 *vs.* 20.2 months in the group treated with chemotherapy alone). The study performed by Van Cutsem et al. [20] confirmed that the FOLFIRI chemotherapy combined with cetuximab used in the first line of treatment is more efficacious in comparison with chemotherapy alone.

Maintenance therapy with bevacizumab

In the third phase study, PRODIGE-9 [21]phase III, randomized controlled trial, we compared the tumor control duration (TCD in patients untreated earlier for mCRC, induction chemotherapy with FOLFIRI regimen was used in combination with bevacizumab, and then the patients with response to the treatment were assigned to the arm with maintenance therapy with bevacizumab (5 mg/kg every 2 weeks) or to the group with follow-up alone. At the moment of progression, the patients received 8 cycles of FOLFIRI + bevacizumab, and then they continued maintenance treatment or follow-up in accordance with earlier randomisation. Such a sequence of treatment was continued till the moment of disease progression during chemotherapy. The primary endpoint in this study was DDC. Median DDC was in both arms of the study was 15 months, and no significant differences between PFS and OS were found (tab. I).

The CAIRO3 study [22] phase 3, randomised controlled trial, we recruited patients in 64 hospitals in the Netherlands. We included patients older than 18 years with previously untreated metastatic colorectal cancer, with stable disease or better after induction treatment with six 3-weekly cycles of capecitabine, oxaliplatin, and bevacizumab (CAPOX-B evaluated the efficiency of maintenance therapy with capecitabine with bevacizumab (*vs.* follow-up) after the administration of 6 CAPOX chemotherapy cycles (capecitabine, oxaliplatin). At the moment of disease progression (PFS1), the patients received CAPOX treatment again, combined with z bevacizumab until the next progression (PFS2 – primary endpoint). In the arm which used only the maintenance therapy, the PFS2 prolongation was observed with good treatment tolerance (tab. I). Solely the hand-foot syndrome (HFS) was more frequent in the group using the maintenance therapy. This allowed the authors of the study to conclude that the maintenance therapy with capecitabine with bevacizumab is effective and does not have a negative effect on the patients' quality of life.

The metanalysis performed by Ma et al. [23] confirmed that in maintenance therapy bevacizumab is effective in combination with chemotherapy.

Maintenance therapy with aflibercept

The data concerning maintenance therapy with aflibercept is very limited. In one arm, second phase VELVET prospective study [24], the patients, previously untreated for mCRC received FOLFOX with aflibercept (1–6 cycles), and then maintenance therapy with fluoropyrimidine with aflibercept (4 mg/kg every 2 weeks) until the disease progression or the occurrence of toxicity. At the moment of progression, therapy with oxaliplatin was resumed. The primary endpoint was PFS

after 6 months. After this period, 67.4% patients (n = 33) did not experience the disease progression, whilst median PFS was 9.3 months (95% CI: 8.3–12.5), also 23% patients developed G3/G4 arterial hypertension.

Maintenance therapy with panitumumab

In order to evaluate the efficacy and possibilities of de-escalation of chemotherapy in combination with panitumumab, the second phase study – SAPPHIRE [25] was conducted. Initially, all the patients received 6 cycles of chemotherapy with FOLFOX regimen in combination with panitumumab, and then, in one group (arm A) the full treatment regimen was continued, whilst in the other group (arm B), the therapy was de-escalated (to fluorouracil with calcium folinate in combination with panitumumab). Maintenance therapy was connected with a similar efficiency after 6 treatment cycles in comparison with the full FOLFOX regimen with panitumumab (PFS 9.1 *vs.* 9.3 months). Temporary suspension of oxaliplatin treatment allowed for the decrease of the frequency of clinically significant neurotoxicity (≥G2; in arm A and arm B: 57.4% *vs.* 9.3% respectively).

In the second-phase study, VALENTINO [26], the efficacy of the use panitumumab in monotherapy as maintenance treatment was evaluated. Initially all the patients received 8 cycles of the FOLFOX chemotherapy in combination with panitumumab. In the next stage, the therapy was de-escalated. One group of patients received fluorouracil with calcium folinate in combination with panitumumab, whilst the other – panitumumab in monotherapy. The rate of 10-month survival and median PFS treated with panitumumab fluorouracil and calcium folinate were significantly higher in comparison with panitumumab in monotherapy (with slight increase of toxicity).

The results of the above studies justify the use of maintenance therapy with the use of panitumumab in combination with fluorouracil and calcium folinate – also as an efficient form of treatment de-escalation.

Maintenance therapy with cetuximab

The MACRO-2 study evaluated the efficiency and safety of the treatment according to the FOLFOX regimen with the use of cetuximab followed by cetuximab in monotherapy every week (arm A) in comparison with the continual treatment with FOLFOX chemotherapy in combination with cetuximab (arm B). The patients, on average, received 1–8 cycles of induction treatment. After 9 months of follow-up, the non-inferiority of the compared regimens was evaluated with respect to the time to progression ($p < 0.1$) and no differences were observed in median PFS, median OS and in objective response rate (ORR) – tab. I. Serious adverse events (SAEs) were reported in 20% patients (n = 25) in arm A and in 25% (n = 17) in arm B [27]. The results of the study confirmed the same value of the continual treatment in comparison with maintenance therapy.

In the COIN-B study, the patients who had already received FOLFOX chemotherapy with cetuximab for 12 weeks were randomly divided into a group in which the treatment was completely suspended and the group in which maintenance therapy with cetuximab was continued (1 x week). At the moment of progression, the treatment with FOLFOX regimen with cetuximab or with FOLFOX chemotherapy only was reintroduced for 12 weeks and then it was discontinued again (or cetuximab alone was used). The primary endpoint of the study was failure-free survival (FFS). Median FFS was 12.2 months (95% CI: 8.8–15.6) in the group with discontinued treatment in comparison with 14.3 months (95% CI: 10.7–20.4) in the group with continual treatment. Median OS and median PFS in the intention-to-treat (ITT) group are presented in table I. Some adverse effects were similar in both groups. According to the authors of the study, maintenance therapy with cetuximab guaranteed a better treatment effect than interrupted treatment, in spite of the lack of statistical significance [28].

Cremolini at al. [29] in turn, conducted a retrospective second phase study with randomisation (MACBETH) which evaluated the effect of maintenance treatment with cetuximab (arm A) or bevacizumab (arm B) after an induction chemotherapy (up to 8 cycles) with FOLFOXIRI regimen (fluorouracil, calcium folinate, oxaliplatin, irinotecan) + cetuximab. The study did not reach the predicted endpoint which was the improvement of the 10-month period to the disease progression from 50% to >70%. Median OS and median PFS were comparable in both arms of the study (tab. I). Also the adverse effects were comparable, with the exception for the skin toxicity, which was more frequently observed in arm A (20% *vs.* 3%, $p = 0.03$). Although the endpoint was not reached, the authors concluded that an intensive induction treatment followed by maintenance therapy with a biological drug was effective.

In a retrospective analysis carried out by Jiang et al. [30], the patients received the FOLFIRI chemotherapy + cetuximab and were either assigned to the control group or continued maintenance treatment with cetuximab with irinotecan (M1 – the first group with maintenance therapy). After 6–12 cycles of maintenance therapy, the patients with treatment response (n = 21) were assigned to the second group (M2) with maintenance therapy with cetuximab in monotherapy continued till the disease progression, death or unacceptable toxicity. The primary endpoint was the failure-free survival (FFS) period which was 12.7 months (95% CI: 6–19.4) in M1 group in comparison with 3 months (95% CI: 2.6–3.4) in the control group. Median PFS is presented in table I. The authors of the study observed that maintenance therapy with cetuximab prolongs FFS and is well tolerated by the patients.

The results of one arm studies with maintenance therapy with cetuximab are summarised in table [31, 32]. The subject literature describes a few clinical cases which confirm the efficiency of monotherapy with cetuximab following a previous induction chemotherapy [33, 34].

Polish and foreign recommendations

The national diagnostic and therapeutic guidelines concerning the treatment of the patients with colorectal cancer, published in 2020, emphasise that treatment de-escalation may be considered, although its value has not been confirmed by prospective randomised studies. In particular, this strategy must be taken into consideration in the case of toxicity (oxaliplatin-induced polyneuropathy). Monotherapy with biological agents may shorten the time to disease progression, so it should not be applied as a standard treatment after a few cycles of chemotherapy, but only when there are grounds for it (permanent control of the disease confirmed in imaging diagnostics, accompanied by increasing side effects of cytostatic drugs or the patient's exhaustion with the intensity of treatment) [35].

According to the recommendations of the European Society for Medical Oncology (ESMO,) in the patients with mCRC treatment should not be discontinued. Active maintenance therapy with fluoropyrimidine and a biological agent should remain a standard. The limited data concerning the treatment with anti-EGFR antibodies in monotherapy do not permit for definite conclusions here. Each decision about the de-escalation of treatment should be discussed with the patient [36, 37].

Maintenance therapy during the SARS-CoV-2 pandemic

General recommendations concerning the patients treated palliatively in the period of COVID-19 pandemic stipulate that the treatment should be continued. However, in order to guarantee the patient safety, it is advised to modify the treatment regimens (e.g. the use of oral or metronomic therapies or de-escalation).

The published standpoint of the experts of the Polish Society of Clinical Oncology concerning the treatment of patients with palliative therapy during the SARS-CoV-2 pandemic, provides for the possibility of discontinuance of chemotherapy in the persons in whose case:

- a good disease control is maintained,
- the intervals between treatment have been maximally prolonged, or
- intravenous infusions have been given up and replaced with the oral treatment with capecitabin.

In the patients treated within the drug programmes of the Ministry of Health, the experts recommend the use of chemotherapy with a biological agent in 4-week intervals. However, the experts emphasise that monotherapy with an anti-EGRF or anti-VEGF agent is less effective than its combination with cytostatic drugs.

Moreover, all the patients with a period of G3 neutropenia during the therapy, should, according to the CTCAE, receive prophylactic treatment with granulocyte colony-stimulating factor (G-CSF). This recommendation applies also to the patients receiving chemotherapy connected with the risk of developing neutropenic fever (10–20%) [38, 39]. In patients with mCRC this risk varies between 3 and 14% for the chemotherapy with FOLFIRI regimen and 0–8% for the FOLFOX regimen respectively [40].

The recommendations of the ESMO experts are consistent with the recommendations of the national experts. They propose prophylactic use of G-CSF in the treatment schemes connected with the risk of developing neutropenic fever and maintenance therapy with capecitabine instead of long-hour fluorouracil infusions. Moreover, the treatment should be conducted on an outpatient basis [41, 42].

Conclusions

The studies which evaluate the effect of maintenance treatment on the effectiveness of therapy measured with OS and PFS show that this strategy works in the mCRC patients who have a persistent good clinical effect with concurrent reduction of clinically significant adverse effects. This allows for a good quality of life in the patients, accompanied with treatment efficacy. It must be stressed, however, that a complete interruption in the therapy (and, in case of progression, its resumption) worsens the results and is not justified. The treatment should be carried out till the moment of disease progression or unacceptable toxicity. However, the study results quoted here, allow to recommend the de-escalation of the therapy and maintaining the anti-EGFR/anti-VEGF treatment with fluoropyrimidine. In selected patients with unacceptable marrow toxicity, monotherapy with a targeted anti-EGFR agent could be applied. Antiangiogenic agents should be used in connection with fluoropyrimidine. The currently binding drug programme provides for the possibility of interrupting chemotherapy (in the case of persistent response to the first-line treatment confirmed in two consecutive imaging examinations) and the use of biological agent alone (in the case of bevacizumab, monotherapy is possible only in the second line of treatment) or the continuation of chemotherapy with fluoropyrimidine in combination with a biological drug, on condition of a systematic evaluation of the treatment response. In the case of disease progression, the patients may receive the treatment which they have had so far (provided that they still meet the qualification criteria) [43]. On account of the ongoing pandemic, de-escalation is justified in the light of the Polish and international recommendations. Each time, however, such treatment should be considered individually with an active participation of the patient in the decision making process.

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