New treatment options for patients with metastatic colorectal cancer in Poland

Introduction

Colorectal cancer is the second most common cancer in Poland and for decades it has been characterised by a growing trend of incidence. According to the National Cancer Registry in 2014, approximately 18,000 new cases were diagnosed (second place in women and third in men) and 11,500 deaths were registered (third place in women and second in men) [1]. It is estimated that at least one in five people, distant metastases are present at the time of the diagnosis. Also, among patients treated radically there is a significant risk of recurrence of the disease — it is more pronounced with more advanced primary process. Annually, the number of patients with non-operative locally advanced or metastatic colorectal cancer is approximately the same as the number of deaths caused by this disease.

Standard management of patients with a good performance status ineligible for radical treatment (metastasectomy) is a systemic palliative treatment [2, 3]. The use of cytostatics and molecular-targeted drugs has significantly increased life expectancy. Today the median overall survival (mOS) of patients participating in phase III clinical trials exceeds 30 months. Cytotoxic drugs of proven efficacy in this indication (fluoropyrimidines, oxaliplatin, irinotecan) have long been reimbursed from public funds in Poland. Restrictions on the use of chemotherapy arise only from clinical considerations: performance status, functional capacity, risk of treatment-related toxicity, or patient preferences. Molecularly-directed drugs, both anti-EGFR and anti-angiogenic agents, are reimbursed to a limited extent by the Ministry of Health drug programs. This is due to the high cost of next-generation therapy, and it is aimed at reducing the treated population to patients who have the greatest chance of obtaining the expected benefit on the basis of clinical trial data.

From 1 July 2017 a new program has been introduced in the treatment of patients with advanced colorectal cancer (Fig. 1) [4]. It allows wider access to biological therapies, and consequently leads to a change in the current strategy for the first-, second-, and third-line of palliative systemic treatment. It is worth mentioning that the initiative to change the shape of the drug program has been introduced through a Ministry of Health initiative, a team with the National Consultant in Clinical Oncology has prepared a new form of drug program. FOLFIRI combined with cetuximab or bevacizumab in the first line and afiblercept in the second line of treatment are now available as therapeutic options. In addition, by changing the eligibility criteria, the population of patients eligible for monotherapy with anti-EGFR antibody used in the third line was increased. Unfortunately, due to the fact that the manufacturers did not make the appropriate refund requests, not all the assumptions were taken into account in the current form of the program. For example, panitumumab plus FOLFOX chemotherapy in the first line is still not reimbursed, and bevacizumab therapy should not be restricted to patients with RAS mutations. Despite this, the new program for treating patients with advanced colorectal cancer actually brings us closer to treatment standards in other countries and facilitates compliance with current medical knowledge.

Key words: colorectal cancer, palliative systemic treatment
Figure 1. Treatment program for patients with metastatic colorectal cancer, applicable from 1 July 2017, including planned additions

First line of treatment

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<thead>
<tr>
<th>FOLFIRI + CETUXIMAB</th>
<th>FOLFIRI + BEVACIZUMAB</th>
<th>FOLFOXIRI + BEVACIZUMAB*</th>
<th>FOLFOX + PANITUMUMAB*</th>
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<tr>
<td>Absent BRAF and RAS mutations</td>
<td>Presence of RAS mutation (criterion introduced by the manufacturer)</td>
<td>Presence of BRAF mutation</td>
<td>Absent BRAF and RAS mutations</td>
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<td>Previous adjuvant chemotherapy with oxaliplatin</td>
<td>The treatment is currently not refunded</td>
<td>The treatment is currently not refunded</td>
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<td>Resection of the primary tumour</td>
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Second line of treatment

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<th>FOLFOX + BEVACIZUMAB</th>
<th>FOLFIRI + AFLIBERCEPT</th>
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<td>No previous adjuvant chemotherapy with irinotecan</td>
<td>No previous chemotherapy with oxaliplatin</td>
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<td>Resection of the primary tumour</td>
<td>Chemotherapy with oxaliplatin and fluoropyrimidine</td>
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<td>Resection of the primary tumour</td>
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Third line of treatment

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<th>CETUXIMAB OR PANITUMUMAB</th>
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<td>Absent BRAF and RAS mutations</td>
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<td>No previous anti-EGFR treatment</td>
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program came from the Department of Drug Policy and Pharmacy of the Ministry of Health, and the new provisions were proposed by a team with the participation of National Consultant in Clinical Oncology. Unfortunately, due to formal reasons (no refund applications submitted in accordance with the program’s provisions), its present shape only partially corresponds to the original assumptions.

The aim of this work is to shift new treatment options together with the reasons for their introduction and an indication of where the program adopted provisions differ from those originally developed.

First line of palliative systemic treatment

The basis of systemic treatment of the first line is chemotherapy. Most commonly used is the combination of fluoropyrimidine with irinotecan or oxaliplatin. It allows 30–50% objective response to treatment, and median progressive-free survival (mPFS) of 7–9 months [5]. Monotherapy with fluorouracil or capecitabine is better tolerated but less effective, especially with regard to responses and mPFS. Responses are achieved in approximately 25% of patients, and mPFS has a value of about five months [6]. Fluoropyrimidine monotherapy is commonly used in patients with low performance status, the presence of comorbid conditions, or when, due to the expected toxicity, multidrug chemotherapy is abandoned. In order to improve the effectiveness of palliative treatment, molecular-targeted drugs are added to the cytostatics.

The new Ministry of Health program introduces the possibility of using cetuximab with FOLFIRI chemotherapy in the first-line of treatment [4]. This treatment, compared with chemotherapy used alone, in the population of patients with wild-type RAS genes, increases the rate of responses (66% vs. 39%, p < 0.001) and prolongs OS (median 28.4 vs. 20.2 months, HR = 0.69; 0.54–0.88; p = 0.0024). The disadvantage of combination therapy is the higher incidence of side effects, especially skin toxicity. In the CRYSTAL study patients receiving cetuximab were observed more frequently to have severe skin rash (16% vs. 0%), diarrhoea (16% vs. 11%), neutropenia (28% vs. 25%), and hypersensitivity during infusion (2.3% vs. 0%) [7].

The novelty compared to the previous provisions is the obligation to exclude V600E mutation in the BRAF gene when qualifying for treatment with anti-EGFR drugs. The incidence of this mutation is 5–10%. This limitation is a result of two meta-analyses evaluating the predictive value of this mutation. In the first of them, on the basis of 463 carriers of the mutation BRAF gene
involved in 10 II- and III-phase trials, it was shown that cetuximab and panitumumab had no effect on the OS in this population (hazard ratio = 0.91; 95% CI 0.62–1.34, p = 0.63), PFS (HR = 0.88, 95% CI 0.67–1.14, p = 0.33) or response rate (HR = 1.31; 95% CI 0.83–2.08, p = 0.25) [8]. The second meta-analysis of 351 patients also showed no effect of anti-EGFR antibodies on the prognosis. Interpretation of this publication hinders the lack of significant difference between the results obtained in the population with wild-type and mutated BRAF (p = 0.43) [9].

A new therapeutic option available from July 1 this year is the combination of FOLFIRI regimen with bevacizumab in first-line treatment [4]. According to the program the following are eligible: patients with KRAS or NRAS activating mutations who have previously received adjuvant chemotherapy containing oxaliplatin. The value of bevacizumab in the first line of treatment raises some doubts. However, a meta-analysis of the first line of treatment, published in 2012, showed a prolongation of OS following the addition of bevacizumab to irinotecan-containing chemotherapy (HR = 0.78, 95% CI 0.68–0.89, p = 0.0002) [10]. It is worth noting that the combination of oxaliplatin with anti-VEGF antibody did not improve the prognosis. Only two contradictory studies are included in the analysis of irinotecan. Decisive were results from Hurwitz et al. [11], who found that the addition of bevacizumab to the IFL chemotherapy was associated with an increase in mOS of almost five months (20.3 vs. 15.6 months, HR = 0.66; p < 0.001). In patients receiving bevacizumab, the following adverse events were more frequently reported: hypertension (22.4% vs. 8.3%), proteinuria (26.5% vs. 21.7%), and thromboembolic complications (19.4% vs. 16.2%). The FOLFIRI scheme included in the Ministry of Health program is more effective and less toxic than IFL. Furthermore, the combination of FOLFIRI or bevacizumab received approximately 27% of the patients participating in the CALGB/SWOG 80405 study, which demonstrated similar efficacy of the combination of chemotherapy with bevacizumab as with cetuximab. However, the small size of the analysed group makes it impossible to draw conclusions [12].

It should be pointed out that reducing the population of patients who may receive bevacizumab only to RAS gene mutation carriers has no rationale. On the contrary, data are available suggesting that the lack of KRAS mutations may be a weak favourable predictor for anti-VEGF antibody therapy. A meta-analysis by Petrilli et al. [13] published in 2013 with the data from 2266 patients (46% were carriers of the mutation KRAS), indicated that bevacizumab combined with chemotherapy in patients with wild type of KRAS gene, as compared to the carriers of the mutation, increases the OS (HR = 0.65; 95% CI 0.46-0.92; p = 0.01), PFS (HR = 0.85; 95% CI 0.74–0.98, p = 0.02) and increases the response rate (55% vs. 48%, OR 1.42, p = 0.02). Subsequent meta-analyses provided similar results [14, 15].

The original program design did not include the presence of activating mutation in KRAS and NRAS. The manufacturer of bevacizumab is responsible for the introduction of this criterion (a reimbursement application for such a population was made several years ago).

Another significant requirement for bevacizumab combined with FOLFIRI is the prior use of adjuvant chemotherapy with oxaliplatin. It is worth explaining that the reason was to allow the use of bevacizumab in those patients currently unable to receive this antibody in the second line of treatment. Both in the previous and the current drug program, prior oxaliplatin therapy is the exclusive criterion for application of bevacizumab with FOLFOX regimen in the second-line treatment. Currently, depending on whether or not patients receive oxaliplatin-containing adjuvant treatment, they may receive an anti-VEGF antibody in the first or second line of treatment.

The most common BRAF V600E mutation is a recognised unfavourable prognostic factor. The median overall survival in BRAF mutation carriers may be up to three times lower compared to patients with a wild-type gene (10.4 vs. 34.7 months, p < 0.001) [16]. BRAF mutations do not coexist with KRAS mutations [17]. This means that the introduction by the manufacturer of the criterion of presence of RAS mutation as a condition of bevaczumab therapy essentially prevents the use of this drug in the first line in patients with BRAF mutations.

An attempt to improve treatment outcomes in patients with the BRAF mutation is the addition of bevacizumab to FOLFOXIRI regimen. The results of TRIBE study suggest that patients with BRAF mutations may benefit from such a procedure, but the limitations of this analysis are very small in the study population (28 carriers of the BRAF mutation) [18]. The initial design of the program was — despite the sketchy clinical data pointing to the merits of such a procedure — the possibility of using FOLFOXIRI chemotherapy with bevacizumab in patients with BRAF mutations. However, this requires the manufacturer to submit the appropriate reimbursement request.

An important gap in the new drug program is the lack of first-line chemotherapy with FOLFOX and panitumumab due to the fact that the manufacturer failed to file a refund claim. Based on the PRIME study analysis it was demonstrated that the combination leads to an improved prognosis of patients with RAS wild type genes. It was shown that mOS were 26.0 and 20.2 months, respectively (HR = 0.78; 95% CI 0.62–0.99; p = 0.04), whereas mPFS medians 10.1 and 7.9 months (HR = 0.83, 95% CI 0.58–1.10, p = 0.004) [19]. The original design of the program assumed such an opportunity.
Second line of palliative systemic treatment

The cytostatics used in the first line of treatment determine the choice of the second line. The efficacy of FOLFIRI, FOLFOX, or XELOX regimens are comparable. Irinotecan monotherapy is used in patients with low performance status or with contraindications to the use of fluorouracil. The addition of anti-angiogenic drugs improves outcome.

In Poland, the public payer has financed bevacizumab with FOLFOX4 chemotherapy in the second line since 2012 [4]. Qualification criteria and exclusions from the program have not changed. Treatment may be used in patients who have not previously received oxaliplatin-containing regimen. This record is a duplication of the inclusion criterion for the third-phase study that demonstrated the value of the anti-VEGF antibody. Bevacizumab added to second-line chemotherapy FOLFOX4 increases mOS by two months (12.9 vs. 10.8 months, HR = 0.75, p = 0.0011), mPFS by 2.5 months (7.3 vs. 4.7 months, HR = 0.61, p = 0.0001), and the response rate (23% vs. 9%, p = 0.0001) [20].

The new program introduces the reimbursement of aflibercept plus FOLFIRI chemotherapy in second-line treatment [4]. Documentation of the ineffective palliative treatment with fluoropyrimidine and oxaliplatin is required. It should be emphasised that for the above-mentioned reasons, in the current drug program there is no first-line combinations of panitumumab with FOLFOX in the first line. Consequently, aflibercept will be used in a very limited population (patients receiving oxaliplatin chemotherapy alone). Based on the results of the VELOUR study, the addition of aflibercept to FOLFIRI chemotherapy slightly improves OS (median 13.5 vs. 12.1, HR = 0.82, 95.34% CI 0.71–0.94; p = 0.0032), PFS (6.9 vs. 4.7; HR = 0.76; 95% CI 0.66–0.87; p = 0.0001) and response rate (20% vs. 11%; p = 0.0001) [21]. Grade 3, or 4, adverse events were reported in 84% of patients receiving aflibercept and 63% receiving placebo. Most common were neutropenia (37% vs. 30%), diarrhoea (19% vs. 8%), hypertension (19% vs. 2%), stomatitis (14% vs. 5%), and infectious complications (12% vs. 7%). Due to the severity of adverse events 27% of patients stopped treatment with aflibercept (in the control arm 12%).

The third line of palliative systemic treatment

In the third line of treatment, chemotherapy — aside from trifluridine/tipiracil — is of marginal importance. Molecular targeting drugs that improve the prognosis are panitumumab, cetuximab, and regorafenib. The value of anti-EGFR antibodies in patients with wild-type RAS and BRAF genes is not in doubt. In 2008, cetuximab was shown to improve OS (median 9.5 vs. 4.8 months, p < 0.001) and improve the quality of life when compared to best supportive care [22]. On the other hand, the ASPECTCT study confirmed the similar efficacy of panitumumab [23].

In Poland, both anti-EGFR antibodies are currently reimbursed in the third line of treatment (cetuximab also in the first line). Anti-EGFR antibodies used in monotherapy are available in individuals who have not received them before [4]. Analogously to first-line treatment, the need to exclude mutations in the BRAF gene was introduced. The required parameters of the blood morphology and renal and hepatic parameters were changed. The new criteria are platelet count ≥ 0.75 × 10^5/mm^3, absolute neutrophil count ≥ 1000/mm^3, haemoglobin concentration ≥ 8.0 g/dL, total bilirubin not exceeding three times the upper limit of normal (except for Gilbert syndrome), and creatinine concentration not exceeding twice the upper limit of normal. That gives an opportunity to use cetuximab or panitumumab also in patients in whom, as result of prior chemotherapy or advanced malignancy, deteriorated function of certain organs can be observed.

Summary

The new program for treating colorectal cancer — despite the fact that it significantly differs from the original proposal — extends the treatment options for patients with metastatic colorectal cancer according to current medical knowledge. There is the possibility to use cetuximab and bevacizumab in first-line treatment and aflibercept in the second line. Currently, a more rational and systematic approach to the clinical situation can be planned for systemic sequencing using both antiangiogenic and anti-EGFR antibodies. It is hoped that the recently submitted reimbursement application will allow to fund panitumumab in the first line, and that manufacturer of bevacizumab will soon submit the reimbursement request in line with the original design of the program.

References


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