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REVIEW ARTICLE

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Is cetuximab in combination with irinotecan as a third-line treatment for advanced colorectal cancer scientifically justified?

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ABSTRACT

Palliative systemic therapy for advanced colorectal cancer involves cytotoxic and molecularly targeted agents, either in combination or as monotherapy. In Poland, patients with *RAS* wild-type tumours can receive epidermal growth factor receptor (EGFR) inhibitors after progression on fluoropyrimidine, irinotecan, and oxaliplatin-based chemotherapy. Monotherapy with cetuximab or panitumumab provides statistically significant survival benefit and improves quality of life. The role of cetuximab and irinotecan in combination, as a more intensive third-line treatment in irinotecan-resistant patients is a matter of controversy. To determine the benefit of this combination we analysed the available literature data (the results of the BOND trial and of two Canadian retrospective studies). In our opinion, the use of cetuximab in combination with irinotecan as the third-line of therapy is not based on reliable scientific evidence.

Key words: cetuximab, irinotecan, colorectal cancer

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Introduction

Colorectal cancer (CRC) is one of the most common cancers in Poland. It represents 10% and 12% of all cancer cases in women and men, respectively. Approximately 17.500 new cases of CRC are diagnosed each year in Poland, and at least 20% of patients have metastatic disease at presentation [1]. Most patients who are not candidates for radical surgery receive systemic therapy. The use of cytotoxic drugs (fluoropyrimidines, oxaliplatin, irinotecan) and molecular targeted agents has significantly improved the prognosis. The median overall survival (OS) reported in phase III clinical trials exceed 30 months. Defining a therapeutic strategy that considers the general patient's condition, comorbidities, symptoms and aggressiveness of the disease as well as patients preferences has become a standard of care. The main aim of the palliative systemic therapy is to use all active agents and to prolong OS without deteriorating the quality of life.

Palliative systemic treatment of advanced colorectal cancer

First- and second-line palliative systemic treatment consists of the administration of a fluoropyrimidine, irinotecan, and oxaliplatin-based chemotherapy. Therapeutic options include the use of multidrug regimens (e.g. FOLFIRI, FOLFOX, CAPOX, FOLFOXIRI), irinotecan or fluoropyrimidine monotherapy. Moreover, an antiangiogenic drug — bevacizumab in combination with FOLFOX chemotherapy regimen — is also accessible in Poland as a second-line therapy. The actual Drug Programme financed centrally resulted in more common use of the FOLFIRI schedule in the first-line therapy of

advanced and unresectable CRC. Patients who received all the above-mentioned therapeutic agents and who remain in good general condition may be qualified for the third-line therapy. In Poland, patients with metastatic colorectal cancer with wild-type *RAS* genes and previously confirmed failure of fluoropyrimidine, irinotecan and oxaliplatin-based chemotherapy are potential candidates for treatment with anti-epidermal growth factor receptor (EGFR) antibody within the Drug Programme. The main goal of this paper is to present and to evaluate the credibility of the data recommending the combined use of cetuximab with irinotecan instead of monotherapy with anti-EGFR monoclonal antibody, in third-line therapy of colorectal cancer.

Monotherapy with anti-EGFR monoclonal antibodies

The recommendations of the American and European scientific societies concerning the third-line systemic therapy of CRC include the use of the anti-EGFR monoclonal antibody in monotherapy or in combination with irinotecan. The benefit of the cetuximab monotherapy in patients without mutations in the exon 2 of the *KRAS* gene, has been proven in a phase III clinical trial. The primary endpoint of this study was OS. The administration of the cetuximab compared to the best supportive care resulted in doubling of the median OS (9.5 *vs*. 4.8 months; $p < 0.001$) and in the improvement of the quality of life [2].

Instead, the administration of the human anti-EGFR monoclonal antibody, panitumumab, did not improve the median OS compared to the supportive therapy alone. This phase III clinical trial reached its primary endpoint and demonstrated a five-week-longer median progression-free survival (PFS). The study failed to demonstrate prognostic benefit, probably due to the latter administration of the antibody to 76% of patients from the control group once the progression of the neoplasm had been confirmed [3, 4].

In 2014, based on the results of the phase III clinical study ASPECT (a non-inferiority type of clinical study), it was proven that both anti-EGFR antibodies have equivalent efficacy concerning OS. No significant differences have been reported in the frequency of the reported side effects; however, patients receiving cetuximab more frequently had a reaction during the infusions of the agent (2% *vs*. 0.5%) and less frequently hypomagnesaemia (3% *vs*. 7%) and grade 3 or 4 skin reactions (10% *vs.* 13%), according to the Common Terminology Criteria for Adverse Events (CTCAE) [5]. Both monoclonal anti-EGFR antibodies have different dosing schedules. Panitumumab is administered at the dose of 6 mg per kilogram every 2 weeks and cetuximab at the dose of 250 mg per square metre weekly (first dose 400 mg/m^2).

Irinotecan combined with cetuximab in patients with resistance to irinotecan

Preclinical studies

The *in vitro* and *in vivo* studies in animal models preceded the use of the combination of the topoisomerase I inhibitor and epidermal growth factor signalling pathway inhibitor in humans. The results of the study, in which the combination of irinotecan and cetuximab was administered to thymus-deprived mice with the xenograft of human CRC cells, were published in 2002. The study proved that the combination of these two drugs results in the inhibition of the growth of tumours resistant to irinotecan [6]. However, the study did not prove any effect of cetuximab monotherapy on cancer cells in mice, which is contradictory to the results reported in humans. The influence of the observed inhibition of tumour growth on OS also remains unknown. The real toxicity cannot be assessed based on the preclinical studies.

Prospective clinical studies

During the years 2001–2002 a prospective BOND trial was carried out to evaluate the combination of irinotecan and cetuximab. A total of 329 patients with metastatic CRC, previously treated with irinotecan, were enrolled into the study. In all patients sampling of the primary tumour or of the metastases proved the EGFR expression. This criterion resulted from the fact that valuable predictive markers for anti-EGFR therapy were unknown at that time. The population of that study differed from the patients recently qualified for the cetuximab administration in the third-line therapy, due to the unknown status of the *RAS* genes mutations. Moreover, about one fifth (21%) of patients enrolled into the study previously received only one line of chemotherapy, and oxaliplatin was used only in 63% of patients. The accredited definition of the irinotecan resistance aroused some controversies at the time of the study. Primarily, the patients who had progressed on irinotecan or during the three months after completion of the therapy were enrolled into the study. However, after the intervention of the Swedish Drugs Evaluating Agency, the time criterion of the progression was changed from three months to four weeks after the completion of the irinotecan therapy. The study population was also extended from 225 to 300 patients, to assure the appropriate power of the applied statistical tests in the group of patients meeting the new criterion of

irinotecan resistance. The overall response rate (ORR) was the main endpoint of the study. This fact seems very controversial because the ORR is considered much less important than the OS and quality of life in the evaluation of the further lines of palliative systemic therapy. In the experimental arm 23% of patients achieved partial remission of the disease compared to 11% in the control group ($p = 0.007$). No complete remissions have been observed. However, in the group completing the new criterium of resistance no statistically significant difference in the response rate between the two study arms has been reported (25% *vs.* 14%, $p = 0.07$). In patients receiving combined therapy, the PFS was longer (median 4.1 *vs*. 1.5 months, $p < 0.001$) but there was no benefit in OS (HR = 0.91; 95% CI 0.68–1.21; $p = 0.48$). Half of the patients in the control group received irinotecan after progression, but the ORR in this group was only 4% and median PFS barely reached 1.4 months. The efficacy of irinotecan administered after progression in patients primarily treated with cetuximab monotherapy was small, so it cannot explain the lack of OS difference. Patients receiving chemotherapy combined with cetuximab experienced more frequent adverse events of CTCAE grade 3 or 4 (65% *vs*. 44%, $p < 0.001$). The frequency of diarrhoea, defined as at least seven loose stools per day, was 10 times higher (21% *vs*. 2%, $p < 0.001$) [7]. Unfortunately, the quality of life in both treatment arms was not compared in the BOND study. This should be considered as an important disadvantage of this study because the toxicity of the combined therapy was significantly higher and the combination of irinotecan and cetuximab did not improve OS.

The predictive value of mutations in codon 12 and 13 of the *KRAS* gene (subsequently some other mutations in exons 2, 3, and 4 of *KRAS* and *NRAS* genes) for anti-EGFR therapy with monoclonal antibodies, was proven four years after the publication of the BOND study. That is why, according to the actual knowledge, 50% of patients enrolled into the study were harbouring *RAS* genes mutations. This means that 50% of patients in the control arm received a drug with placebo-like activity, while all patients in the experimental group received chemotherapy, which could be active in some of them. If the patients had been qualified to the study following the actual criteria, significantly higher efficacy of the cetuximab monotherapy would have been expected.

Retrospective studies

Due to the significant limitations of the BOND study and the lack of data derived from prospective studies carried out in populations of patients molecularly selected based on the *RAS* genes status, the results of the retrospective studies often constitute the basis for the use of the combination of irinotecan and cetuximab. The most important of these are two retrospective Canadian studies.

The first study, published in 2013, included 178 patients with resistant to irinotecan and oxaliplatin metastatic CRC, in whom the mutations in codon 12 and 13 of the *KRAS* gene had been excluded. The study compared the efficacy and toxicity of panitumumab monotherapy (141 patients) and of the combination of irinotecan with cetuximab (37 patients) administered as third-line therapy [8]. It is evident that patients with worse performance status and older age were qualified to the monotherapy arm, while persons younger and in better general condition entered the combined therapy group. Patients with performance status 2–3 in the ECOG (Eastern Cooperative Oncology Group) scale constituted 23% of the population receiving panitumumab and only 3% of the group treated with the combined therapy. Performance status is the most important prognostic and predictive factor and shorter OS in patients receiving panitumumab monotherapy as compared to patients treated with the combine therapy (7.7 *vs*. 8.3 months, $p = 0.03$) is not surprising. However, in the multivariate analysis the type of therapy had no impact on the prognosis (HR = 1.28; 95% CI 0.77–2.14; $p = 0.34$). The only factor correlated with OS was the general performance status (ECOG 2–3 *vs*. 0–1: HR = 3.37; 95% CI 2.08–5.45; $p < 0.01$). No data on the quality of life or on the toxicity of the therapy were collected.

The results of the most recent retrospective analysis were published in March 2017 [9]. Data concerning 1081 patients with wild type *KRAS* gene CRC, treated with a combination of cetuximab and irinotecan or with panitumumab monotherapy between the years 2009 and 2012, were obtained from the Canadian Cancer Registry. The majority (74%) of patients received panitumumab and remaining ones received a combination of cetuximab and irinotecan. Prolongation of OS (median 8.8 *vs*. 5.9 months, $p < 0.001$) and of the time to treatment discontinuation (median 3.5 *vs*. 2.8 months, $p < 0.001$) was shown in patients receiving the combination of cetuximab and irinotecan. Panitumumab was more often administered to elderly patients, while the combination of cetuximab with irinotecan was given to younger ones. Unfortunately, the authors did not present any data concerning performance status which is the most important prognostic factor. One may speculate that similarly to the previously cited analysis, the combination of cetuximab and irinotecan was more frequently used in patients in very good or good performance status, and panitumumab alone was administered to patients with performance status 2 or 3 according to the ECOG scale. No attempt to include the influence of the aforementioned factor on the prognosis is preclusive of drawing any conclusions on the real impact of the two-drug therapy on OS.

Toxicity was analysed based on the frequency of emergency room or hospital admissions from the beginning of the anti-EGFR therapy up to 30 days after its completion, as well as on the mortality during the 14 and 30 days after the administration of the last dose of the drug. In patients receiving panitumumab the death rate in the 30 days after the administration of the last dose of anti-EGFR antibody was two times higher, especially in the younger subset of patients (< 65 years of age). No difference was observed concerning all other mentioned parameters. Frequent death in the first month post therapy in patients receiving panitumumab alone may suggest that the therapy had been started in persons with initially worse prognosis, resulting mostly from the worse performance status. The authors of the review emphasise that the combined therapy did not result in a higher toxicity, but the data concerning the side effects are insufficient because they include no detailed information (e.g. concerning the haematological toxicity or the diarrhoea incidence). The quality of life could not be accessed due to the character of the study.

In the discussion, the authors indicate that the median OS rates presented in their paper are similar to the ones shown in the BOND study, in which, *nota bene*, no significant difference in OS was proven, and suggest that this correspondence confirms the clinical value of the retrospective analyses. Regrettably, we cannot agree with this conclusion because in the presented analysis patients were selected based on *KRAS* gene status, while in the BOND study, as previously mentioned, the *KRAS* status was unknown. The median OS in patients receiving panitumumab alone (5.9 months) should be compared to the results shown in the other phase III clinical trials carried out at that time, involving patients with wild-type *KRAS* gene. In the ASPECCT study, enrolling patients between the years 2010 and 2012, the median OS was 10.4 months [5]. Such a big difference is not surprising and may be explained by the selection into the clinical trials of patients in good performance status and without significant comorbidities. That is why a group with similar prognosis to the patients from the ASPECCT study are not the patients treated with panitumumab alone, but the 24% of subjects qualified for the combined therapy with irinotecan and cetuximab. In this group, the median OS reached 8.8 months, which can be regarded as close to the median reached in the ASPECCT study. The comparison of these data represents another argument that the difference in OS shown in the analysis by Jerzak et al. results probably only from the worse performance status of patients qualified for panitumumab monotherapy [9].

Summary

The use of a combination of cetuximab and irinotecan in third-line therapy in patients with advanced CRC is a matter of significant controversy. This option is still included in the recommendations of scientific societies, mostly for historical reasons (the first registration of cetuximab as the combination with irinotecan). However, we should remember that the clinical value of this modality has not been prospectively evaluated in an appropriately selected patient population. The BOND study, the results of which constitute a scientific basis for combined cetuximab and irinotecan therapy, was in fact a negative study, even for its primary, clinically barely important endpoint (ORR) in the group of patients selected by the actualised definition of the irinotecan resistance. In this study, no positive impact of the combined therapy on the prognosis was shown, and quality of life was not evaluated, but the higher rate of side effects was proven (including severe diarrhoea). The results of the retrospective analyses are conflicting and difficult to interpret. Despite the efforts undertaken in Poland aimed at fostering combined therapy, the authors of this review challenge (based on the current clinical evidence) the validity of the combination of cetuximab and irinotecan.

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