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Overall survival of patients with metastatic *KRAS* wild type colorectal cancer patients treated with anti-EGFR third line monotherapy

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ABSTRACT

Introduction. There is no evidence-based data comparing upfront chemotherapy doublets with anti-EGFR monoclonal antibody with sequential treatment utilizing anti-EGFR monotherapy as a consecutive line of treatment in patients with metastatic colorectal cancer. Here we report real-world survival data for patients with colorectal cancer (CRC) treated with anti-EGFR monoclonal antibody as 3rd line monotherapy.

Material and methods. It was single center retrospective study. We collected retrospectively data of wild-type *KRAS* metastatic CRC patients who have failed oxaliplatin- and irinotecan based therapy and were treated with anti-EGFR monoclonal antibody as the 3. line monotherapy in 2009–2017 in Copernicus Memorial Hospital, Lodz, Poland. Last observation was recorded in February 2020. We calculated median overall survival (since commencement of palliative systemic treatment), median progression free survival and median OSIII (overall survival sine commencement of monotherapy with anti-EGFR agent).

Results. 130 patients were included in the study. 40,6% were females. The median age was 63 years (range 38–83). 57% of patients were initially diagnosed with metastatic/inoperable colorectal cancer. 80 patients were treated with 3. line cetuximab, 50 — with panitumumab. At the moment of data analysis 123 deaths were recorded. OS since start of palliative systemic treatment was calculated for 120 patients and its median was 25,8 months. MPFS since start of anti-EGFR antibody was 4,3 months, mOSIII —10,7 months.

Conclusions. 3rd line treatment of metastatic colorectal cancer with anti-EGFR antibodies is effective. It is good option for patients, who are not fit enough or not willing to have 1st line triplet therapy.

Key words: colorectal cancer, *KRAS* mutation, anti-EGFR antibody, palliative systemic treatment

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Introduction

An anti-epidermal growth factor receptor monoclonal antibody (anti-EGFR MoAb) added on to doublet chemotherapy is currently a first-line, gold standard treatment option for patients with *RAS* wild-type metastatic colorectal cancer (mCRC), allowing for median overall survival (mOS) of about 30 months. In the overall *RAS* wild-type population, the addition of an anti-EGFR MoAb to chemotherapy alone improved progression-free survival (PFS) ($p < 0.001$), and objective response rate (ORR) ($p < 0.001$), with a trend toward longer OS ($p = 0.07$) [1].

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In pivotal trials of chemotherapy doublets, with or without anti-EGFR agents, treatment was continued until progressive disease or unacceptable toxicity. Indeed, in the CRYSTAL trial, discontinuation of combined treatment due to adverse events was observed in 51 out of 599 patients, compared with 28 out of 599 patients treated with chemotherapy alone [2, 3]. There was a statistically significant difference in the toxicity of combined treatment and chemotherapy. More patients treated with cetuximab and FOLFIRI suffered from G3/4 adverse events (79% *vs.* 61% $p < 0.001$), G3/4 diarrhea (15.7% *vs.* 10.5%, $p < 0.008$), and G3/4 skin reactions (19.7 *vs*. 0.2, $p < 0.001$). However, in patients with *KRAS* wild-type (*KRAS* WT) metastatic colorectal cancer in the CRYSTAL study, there were no significant differences in global health status/quality of life (QOL) ($p = 0.12$) and social functioning scores ($p = 0.43$) between the treatment arms [4]. There is no clear data for rechallenge with anti-EGFR MoAb in the case of increased toxicity of combined first-line treatment resulting in treatment discontinuation. Moreover, in Poland, there is no reimbursement for anti-EGFR MoAb if the patient had been previously exposed to the drug, regardless of the reason for discontinuation.

Still, there are data for OS benefits with anti-EGFR MoAb monotherapy in the third-line of treatment when compared with best supportive care (BSC). On the other hand, in pivotal trials of first-line chemotherapy combined with anti-EGFR antibody, only about 30% of patients who had received chemotherapy alone were treated with targeted agents in further lines. So, we cannot assume that using monoclonal antibodies as first-line treatment is better than in a sequential schedule. Unfortunately, to date, there are no evidence-based data comparing upfront triplet therapy with sequential treatment utilizing anti-EGFR MoAb monotherapy as a consecutive line of treatment, and, as a matter of fact, we should not expect such data. Investigators, patients, and pharmaceutical companies are determined to incorporate targeted agents into treatment schedules as soon as possible. Moreover, considering increased toxicity affecting patients treated with anti-EGFR MoAb combined with first-line chemotherapy, they are more willing to test strategies of de-escalating treatment intensity in the maintenance setting or intermittent strategies after triplet induction regimens. Maintenance therapy may include cytotoxics, targeted agents, or a combination of chemotherapy and targeted therapy [5–8]

Here we report real-world survival data for patients with metastatic colorectal cancer treated with anti-EGFR MoAb as third-line monotherapy.

Material and methods

We collected retrospective survival data of 130 metastatic colorectal cancer patients with the wild-type *KRAS* gene, treated with anti-EGFR agent monotherapy as third-line treatment from 2009 to 2017 in the Nicolaus Copernicus Memorial Hospital, Łódź, Poland. Before 2013, patients with *wild*-type *KRAS exon 2 status* were eligible for this treatment. From November 2013, patients were also screened for *KRAS* mutations in exons 3 and 4, along with *NRAS* mutations in exons 2, 3, and 4, and for *BRAF* mutations before starting targeted therapy (78 patients). All patients had failed oxaliplatin and irinotecan-based therapy before starting anti-EGFR treatment. Panitumumab was administered at a dose of 6 mg/kg every 14 days, and cetuximab was administered at a dose of 400 mg/m^2 (initial dose), followed by 250 mg/m^2 weekly or 500 mg/m^2 every 14 days.

Data were collected from medical files and pathology reports including age, sex, tumor histology, tumor location, number and location of metastases, type of treatment, and its timing. The clinical stage was determined according to the 7th edition of the American Joint Committee on Cancer (AJCC) staging system. During targeted therapy, the response to anti-EGFR treatment underwent radiological evaluation every 12 weeks. The response rate to anti-EGFR treatment was determined according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. We calculated median overall survival as the time from the start of palliative systemic treatment until death or the last follow-up. Progression-free survival was defined as the time from the first dose of the anti-EGFR agent until the date of progression, death, or last follow-up, and overall survival III (OS III) was defined as the time from the first dose of the anti-EGFR agent until the date of death or last follow-up. The study adhered to the principles of the Declaration of Helsinki and acquired ethical approval from the Ethics Committee of the Medical University of Łódź.

A control group was a cohort of unselected patients diagnosed with advanced colorectal cancer and treated with palliative chemotherapy from 2009 to 2017 in the Nicolas Copernicus Memorial Hospital, Łódź, Poland.

Results

Patients' characteristics are presented in Table 1, part 1. Fifty-seven percent of patients were initially diagnosed with TNM IV colorectal cancer. Fifty-two patients were checked only for *KRAS* exon 2 status. Eighty patients were treated with third-line cetuximab, fifty were treated with panitumumab. During data analysis, 123 deaths were recorded. OS since the start of palliative systemic treatment was calculated for 120 patients, and its median amounted to 25.8 months. In comparison, mOS of unselected colorectal cancer patients receiving palliative sys-

Table. 1. Part 1. Characteristics of patients (*KRAS* Exon 2 WT) treated with an anti-EGFR monoclonal antibody in the third line; **Part 2.** Characteristics of patients (*KRAS* exon 2 WT, mutated or not checked) who underwent palliative systemic treatment in the same oncologic center from 2008 to 2012

Feature	Part 1. 1130 Patients *KRAS* Exon 2 WT, treated with anti–EGFR monoclonal antibody in 3rd line		Part 2. 288 patients (*KRAS* exon 2 WT, mutated or not checked) who underwent palliative systemic treatment in the same oncologic center (2008–2012)	
Age	38–83 Med. 63 Average 62.8		33–85 Med. 63 Average 62.6	
	Patients number	**%**	**Patients number**	**%**
Sex				
Female	58	40.6	120	41.6
Male	85	59.4	168	58.4
Resection of primary tumor	86	66	187	64.9
Palliative surgery	33	26.2		
No surgery	40		101	35.1
Localization of primary tumor				
Rectum	46	35	126	43.8
Left side	60	46	112	38.9
Right side	24	18	48	16.7
Multiple/simultaneous tumors (%)	2		2	0.7
Grading				
G1	3		26	9
G2	94		193	67
G3	19		32	11.1
Unknown	14		37	12.8
Primary metastatic cancer	74	57	167	58.0
Liver metastases	98	73.1	130	45.1
Patients treated with anti-EGFR agent		100	61	21.2
Patients treated with bevacizumab	8	6	0	
Treated with ≥ 4 lines of systemic treatment	21		15	5.2
***KRAS* mutated**			74	25.7
***KRAS* gene WT**			94	32.6
***KRAS* gene unknown status**			120	41.7
Med. OS (months)	25.8		15.6	

OS — overall survival

temic treatment in the same Oncologic Center from 2008 to 2012 was 15.6 months. This group is characterized in Table 1, part 2. Median progression-free survival (mPFS) since the start of anti-EGFR antibody treatment amounted to 4.3 months, mOSIII — 10.7 months. Sixteen percent of patients with progression during/after anti-EGFR monotherapy had further lines of anticancer treatment.

Discussion

The efficacy of third-line anti-EGFR treatment reported in our study was similar to data reported in pivotal clinical trials. According to Karapetis et al., in patients with wild-type *KRAS* tumors, treatment with cetuximab compared to supportive care alone significantly improved overall survival [median, 9.5 *vs.* 4.8 months;

hazard ratio for death, 0.55; 95% confidence interval (CI), 0.41 to 0.74; $p < 0.001$] and progression-free survival (median, 3.7 months *vs.* 1.9 months; hazard ratio for progression or death, 0.40; 95% CI, 0.30 to 0.54; $p < 0.001$) [9]. Van Cutsen et al. [10] reported that mPFS (8 weeks) favored panitumumab monotherapy over BSC, with no difference in OS. However, *KRAS* mutational status was not verified, and most patients in the BSC group crossed over to panitumumab treatment. After *KRAS* status ascertainment, it was revealed that WT *KRAS* patients had longer overall survival (HR, 0.67) and progression-free survival (HR 0.45) [11].

Median overall survival of 25.8 months in our patients exposed to sequential treatment with an anti-EGFR agent seems to be impressive, especially compared with poor survival of unselected patients treated in the same hospital within a similar period which was 15.6 months.

Real-world data on overall survival associated with biweekly versus weekly cetuximab administration among metastatic colorectal cancer (mCRC) patients in the United States showed that medians of OS were 29 and 23 months, respectively, for the first-line treatment. For third-line treatment, they were both almost 13 months [12].

Unfortunately, there are drawbacks resulting from the retrospective character of our study. The selection of patients is the most significant issue. During first and second-line treatment, most patients in poor condition and with rapid progression of cancer either died or were redirected to receive supportive care. It is worth noticing that only 58.3% of patients from the control group were screened for *KRAS* mutations. At that time, when anti-EGFR antibodies were reimbursed only in the third line, genetic testing usually was performed before the anticipated treatment. Ninety-four patients in the control group had *KRAS* gene WT, and 61 of them were treated with anti-EGFR antibodies. Again, 33 patients were not able to start the targeted treatment [13].

Moreover, more than 40% of patients in our study were screened only for *KRAS* exon 2 mutations. Nowadays anti-EGFR antibodies are indicated for patients with WT *KRAS*, *NRAS,* and *BRAF* genes. Finally, there are currently other active agents available for the treatment of colorectal cancer (bevacizumab, regorafenib, aflibercept, trifluridine, and tipiracil), which were mostly unavailable to the patients in our study. Only 8 out of 130 patients included in the study (6%) had been treated with bevacizumab combined with Folfox in the second line. No patient from the control group was treated with an anti-VEGF antibody. It seems that antiangiogenic treatment had a negligible impact on the observed differences in outcomes.

Conclusions

Results of the third-line anti-EGFR antibodies monotherapy in metastatic colorectal cancer patients treated in our center are in accordance with the results of clinical trials. The monotherapy is a good option for patients who are not fit enough for, or not willing to have first-line triplet therapy.

Conflict of interest

Maja Habib-Lisik — lecture fee from Amgen and Merck.

The other authors declare no conflict of interest.

References

1. Pietrantonio F, Cremolini C, Petrelli F, et al. First-line anti-EGFR monoclonal antibodies in panRAS wild-type metastatic colorectal cancer: A systematic review and meta-analysis. Crit Rev Oncol Hematol. 2015; 96(1): 156–166, doi: 10.1016/j.critrevonc.2015.05.016, indexed in Pubmed: 26088456.
2. Van Cutsem E, Köhne CH, Láng I, et al. Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status. J Clin Oncol. 2011; 29(15): 2011–2019, doi: 10.1200/JCO.2010.33.5091, indexed in Pubmed: 21502544.
3. Van Cutsem E, Köhne CH, Hitre E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med. 2009; 360(14): 1408–1417, doi: 10.1056/NEJMoa0805019, indexed in Pubmed: 19339720.
4. Láng I, Köhne CH, Folprecht G, et al. Quality of life analysis in patients with KRAS wild-type metastatic colorectal cancer treated first-line with cetuximab plus irinotecan, fluorouracil and leucovorin. Eur J Cancer. 2013; 49(2): 439–448, doi: 10.1016/j.ejca.2012.08.023, indexed in Pubmed: 23116683.
5. Pietrantonio F, Morano F, Corallo S, et al. Maintenance Therapy With Panitumumab Alone vs Panitumumab Plus Fluorouracil-Leucovorin in Patients With RAS Wild-Type Metastatic Colorectal Cancer: A Phase 2 Randomized Clinical Trial. JAMA Oncol. 2019; 5(9): 1268–1275, doi: 10.1001/jamaoncol.2019.1467, indexed in Pubmed: 31268481.
6. Modest DP, Rivera F, Bachet JB, et al. Panitumumab-based maintenance after oxaliplatin discontinuation in metastatic colorectal cancer: A retrospective analysis of two randomised trials. Int J Cancer. 2019; 145(2): 576–585, doi: 10.1002/ijc.32110, indexed in Pubmed: 30614531.
7. Yuan M, Wang Z, Zhao Y, et al. Cetuximab Can Be an Effective and Low-Toxicity Maintenance Treatment Drug in Patients With Metastatic Colorectal Cancer: A Real-World Study of Zhejiang Cancer Hospital. Front Pharmacol. 2021; 12: 632076, doi: 10.3389/fphar.2021.632076, indexed in Pubmed: 34122063.
8. Aranda E, García-Alfonso P, Benavides M, et al. Spanish Cooperative Group for the Treatment of Digestive Tumours (TTD). First-line mFOLFOX plus cetuximab followed by mFOLFOX plus cetuximab or single-agent cetuximab as maintenance therapy in patients with metastatic colorectal cancer: Phase II randomised MACRO2 TTD study. Eur J Cancer. 2018; 101: 263–272, doi: 10.1016/j.ejca.2018.06.024, indexed in Pubmed: 30054049.
9. Karapetis CS, Khambata-Ford S, Jonker DJ, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. N Engl J Med. 2008; 359(17): 1757–1765, doi: 10.1056/NEJMoa0804385, indexed in Pubmed: 18946061.
10. Van Cutsem E, Peeters M, Siena S, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J Clin Oncol. 2007; 25(13): 1658–1664, doi: 10.1200/JCO.2006.08.1620, indexed in Pubmed: 17470858.
11. Amado RG, Wolf M, Peeters M, et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol. 2008; 26(10): 1626–1634, doi: 10.1200/JCO.2007.14.7116, indexed in Pubmed: 18316791.
12. Agg H, Han Y, Cui Z. Real-world data on overall survival associated with biweekly versus weekly cetuximab among metastatic colorectal cancer (mCRC) patients in the United States. J Clin Oncol. 2021; 39(3_suppl): 33–33, doi: 10.1200/jco.2021.39.3_suppl.33.
13. Krakowska M. Ocena wyników systemowego leczenia chorych na zaawansowanego raka jelita grubego w Regionalnym Ośrodku Onkologicznym w Łodzi w latach 2008-2012. Doctoral thesis. https://eds.s.ebscohost.com/eds/detail/detail?vid=1&sid=77238185-d2e6-40de-90ab-952de8bcbe66%40redis&bdata=Jmxhbmc9cGwmc2l0ZT1lZHMtbGl2ZSZzY29wZT1zaXRl#AN=UML.jc18110057&db=cat03792a.