Abstract. Targeted biological therapy is becoming a standard in personalized medicine for patients with advanced stages of cancer. Treatment with cetuximab, an anti-epidermal growth factor receptor (EGFR) antibody, represents an example of personalized anticancer therapy for patients with metastatic colorectal cancer and wild (non-mutated) type of the Kirsten rat sarcoma viral oncogene (KRAS). Here the role of cetuximab in treating metastatic colorectal cancer is discussed with a focus on the treatment of hepatic metastases.

The Czech Republic has one of the highest incidence and mortality rates for colorectal cancer (CRC) worldwide (1). In approximately 60% of patients, CRC metastasizes to the liver. Radical resection (R0) of liver metastases from CRC is a prerequisite to successful treatment and, in combination with anti-tumour therapy, provides patients with the prospect of long-term survival (2).

Targeted Biological Treatment with Monoclonal Antibodies

Targeted biological therapy is becoming a standard of personalized medicine for patients with different types of tumors. Two options are currently available in routine clinical practice for patients with metastatic CRC: inhibition of angiogenesis with the anti-vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab, and/or the use of anti-epidermal growth factor receptor (EGFR) antibodies, which inhibit both cell proliferation and angiogenesis. While an effective predictor of treatment success with angiogenesis inhibitors has not been established yet, absence of presence of the Kirsten rat sarcoma viral oncogene (KRAS) gene mutation plays a crucial predictive role in the treatment with anti-EGFR (3).

Cetuximab (Erbitux) is an anti-EGFR antibody of the IgG1 class, targeted against the extracellular domain of the EGFR. The majority of patients with metastatic CRC were shown to have an increased expression of this tyrosine kinase receptor, also known as HER-1 (ERBB1) (4, 5). Cetuximab binds to the EGFR extracellular domain with higher affinity than the two natural receptor-activating growth factors, epidermal growth factor (EGF) and transforming growth factor alpha (TGF-α), and thus acts as a competitive inhibitor of their physiological activity. By binding to EGFR, cetuximab blocks intracellular EGFR signalling and facilitates inhibition of proliferation, angiogenesis and differentiation, stimulation of apoptosis, and blocks release of proteases and their inhibitors, thus inhibiting development of metastases (6, 7). Furthermore, cetuximab inhibits the production of angiogenic factors and stimulates anti-tumour immunity, principally through activation of complement and mediation of complement- and antibody-dependent cell cytotoxicity. In pre-clinical studies, cetuximab showed antitumour effects (in vitro and in vivo) when administered in combination with cytostatic drugs. In addition, the mechanism of overcoming resistance to chemotherapy (mainly to irinotecan), has been described (5, 7-9).

Biomarker testing in patients with metastatic CRC is an example of personalized cancer therapy. For patients with these tumour types, EGFR expression testing was established as a part of disease management at the very beginning (3). Recently, KRAS gene mutation has been shown to play a crucial predictive role in treatment response of metastatic CRC to anti-EGFR therapy. When this gene is mutated, the EGFR
pathway becomes constitutively active, and consequently receptor blockade does not stop tumour cell proliferation. On the contrary, in the case of non-mutated (wt) KRAS gene-bearing tumour cells, the EGFR pathway can be effectively blocked by specific anti-EGFR antibodies, e.g. cetuximab. While the importance of the immunohistochemical determination of EGFR expression has been questioned, the determination of the KRAS status, accomplished by fluorescent in situ hybridization (FISH), has been confirmed as being a prerequisite for the anti-EGFR therapy of metastatic CRC. The large phase III controlled clinical trial, CRYSTAL, has shown that there is no correlation between treatment response and positive or negative immunohistochemical EGFR determination (10). On the other hand, this study, as well as the OPUS study, confirmed the importance of KRAS testing for prediction of treatment response. Meta-analysis of both studies has shown that KRAS status is an independent predictive as well as prognostic factor associated with overall survival and time-to-progression (10, 11). Several other controlled clinical trials had also examined and confirmed the importance of KRAS testing (5). Furthermore, there are several other biomarkers, such as v-raf murine sarcoma viral oncogene homolog B1 (BRAF), phosphatase and tensin homologue deleted on chromosome 10 (PTEN) and other mutations, being currently discussed with regard to their predictive and prognostic role. The post-hoc analysis in the CRYSTAL study showed that the BRAF mutation is not a predictive but a prognostic factor of cetuximab efficacy in the treatment of metastatic CRC. Patients with a mutation of this gene have a poorer disease prognosis, independent of the treatment (10, 11).

Therefore, current experts’ statements recommend cetuximab to be used only for patients with metastatic CRC expressing (wt) KRAS. In the Czech Republic, EGFR expression testing is still required (12), mainly by health care providers and is, therefore, maintained in the guidelines of the Czech Society of Clinical Oncology. However, the National Comprehensive Cancer Network (NCCN) guidelines clearly state that no patient should be denied treatment with anti-EGFR antibodies solely upon negativity of the immunohistochemical EGFR determination.

The Role of Cetuximab in the Treatment of Metastatic CRC

The efficacy of cetuximab in treatment of chemorefractory metastatic CRC has been shown in numerous clinical studies. The phase II BOND (Bowel Oncology with erbitux aNtiboDy) study played a crucial role in the development of this monoclonal antibody. In two randomized parallel arms, cetuximab monotherapy was compared to a combination of cetuximab with irinotecan in patients with EGFR-positive metastatic CRC refractory to irinotecan. Combined therapy led to an improvement in treatment response (23% vs. 11%), improved time-to-progression (4.1 vs. 1.5 months) and median survival (8.6 vs. 6.9 months) (8). Based on the results of this study, cetuximab was licensed and launched in clinical practice as part of treatment regimens for patients with metastatic CRC, first in the USA and, subsequently, in Europe. In the Czech Republic, cetuximab has been available since 2005. Cetuximab monotherapy was compared to best available supportive care in heavily pretreated patients with metastatic CRC, after the failure of fluoropyrimidines, irinotecan and oxaliplatin (NCIC CO.17 trial) and results proved the therapeutic efficacy of monotherapy with cetuximab for this subset of patients. Furthermore, results of the randomized phase III trial EPIC (the Erbitux Plus Irinotecan in Colorectal Cancer) confirmed the efficacy of cetuximab in combination with irinotecan for patients with metastatic CRC refractory to oxaliplatin. In addition, some other studies, e.g. LABEL (Latin American erBitux prE-Licence study), MABEL (Monoclonal Antibody er-Bitux in a European pre-Licence study), EVEREST (Evaluation of Various Erbitux Regimens by means of Skin and Tumour biopsies), and the 045 study provided similar results to those of the BOND study (13-17). Altogether, these studies provided innovative data not only with respect to objective parameters of treatment response, but also with respect to safety of biological treatments and patient quality of life (13-17).

Efficacy of cetuximab as the first line treatment for metastatic CRC was evaluated in two pivot randomized clinical trials: the phase III CRYSTAL (Cetuximab combined with iRinotecan in first line therapY for metaStatic colorectal cancer) study and the phase II OPUS (Oxaliplatin and Cetuximab in First-Line Treatment of Metastatic Colorectal Cancer) study (11, 18). Both studies showed that addition of cetuximab to standard chemotherapy [(FOLFIRI) and (FOLFOX), respectively] was significantly more effective compared to standard chemotherapy alone. Explorative analyses have shown that treatment efficacy is highly significant in patients with (wt) KRAS only, while in patients with mutated KRAS, cetuximab provides no additional benefit. Increased efficacy was evident mainly through a higher treatment response rate and reduced risk of disease progression in comparison to the carriers of mutated KRAS. In the OPUS study, cetuximab was added to the FOLFOX4 regime for 337 patients. The results showed that adding cetuximab to the FOLFOX4 regime increased the treatment response rate by 65% in patients with (wt) KRAS and improved median progression-free survival by 7%. Risk of progression was reduced by 43%. Overall survival was 22.8 months on the combination treatment with cetuximab and 18.5 months with chemotherapy alone.

The CRYSTAL study involved 1198 patients. Combined treatment with cetuximab and FOLFIRI (5-fluorouracil, folic acid, irinotecan) provided the following benefits: one-year
survival was achieved by 43% of patients compared to 25% treated with FOLFIRI, two-year survival was achieved by 51% of patients compared to 44% treated with FOLFIRI. Overall survival of patients on combination treatment with cetuximab was 23.5 months (20.0 months on chemotherapy alone, \( p=0.0094 \)). The risk of disease progression was reduced by 30% when cetuximab was used. The treatment response rate was nearly two-fold higher. Treatment response of patients with (wt) KRAS increased from 43% to 59%, i.e. by 37% (\( p=0.0025 \)), risk of progression decreased by 32% and relative risk of death decreased by 16%. The FOLFIRI plus cetuximab combination shifted the median overall survival, for patients with (wt) KRAS, beyond the 24-month threshold. In patients with hepatic-only metastases, cetuximab plus FOLFIRI provided a 77% response rate. The CRYSTAL study thus became a pivotal study upon which the European Medicines Agency (EMEA) approved the use of cetuximab as the first line treatment of metastatic CRC. In the Czech Republic, reimbursement of cetuximab as the first line for metastatic CRC treatment was approved in July 2011.

Meta-analysis of the CRYSTAL and OPUS studies was designed to evaluate OS (overall survival), PFS (progression-free survival) and RR (response rate) in 482 patients with (wt) KRAS and metastatic CRC. The results suggested that with the cetuximab/chemotherapy combination, the risk of death was reduced by 19% (\( p=0.0062 \)) compared to patients on chemotherapy alone. For patients on the combined regimen, the risk of progression was reduced by 34% (\( p=0.0001 \)). Combination treatment also provided nearly a two-fold increase in the treatment RR (\( p=0.0001 \)) (11, 18).

Some contradictory data appeared when the final results of the COIN study were published early in 2011. The COIN study evaluated the addition of cetuximab to a standard oxaliplatin-based chemotherapy (19). This randomized phase III study compared continual administration of oxaliplatin plus modified de Gramont’s regimen (OxMdG) and xeloda plus oxaliplatin (XELOX) regimens without cetuximab (arm A), with cetuximab (arm B), and intermittent administration of OxMdG (quasi-XELOX)/ XELOX regimens (12-week treatment and then upon progression, arm C) in patients with metastatic CRC. A total of 2445 patients were included. The primary objective was to evaluate OS in (wt) KRAS patients. Analysis did not show any benefit of adding cetuximab to the oxaliplatin-based regimen, neither in OS (17.0 vs. 17.9 moths, \( p=0.68 \)) nor disease-free survival (8.6 months in both arms, \( p=0.6 \)). This result contravenes the findings from the CRYSTAL and OPUS studies, both showing a benefit from adding cetuximab to chemotherapy regimens (to the FOLFIRI in the CRYSTAL and to FOLFOX in OPUS) with respect to disease-free as well as OS (the difference in OS in the OPUS study did not reach statistical significance). Intermittent administration of oxaliplatin was not beneficial (19, 20). Possible synergistic toxicity is perceived as a possible reason for these conflicting results. Prognostic and predictive significance of BRAF, neuroblastoma RAS viral (v-ras) oncogene homolog (NRAS), the phosphatidylinositol 3-kinase catalytic subunit (PIK3CA) and others has been evaluated in the COIN study too, with results confirming their negative prognostic but not predictive impact (20).

What is the case of the contradictory general results of the COIN study has not been clarified. However, there was a clear bias in the protocol therapy, when the dose of capecitabine was unilaterally reduced by 15% in the subgroup of patient randomized to cetuximab plus XELOX, while it remained unchanged in the subgroup randomized for XELOX-only. This disparity in drug exposure refers to 19% of patients in the cetuximab plus XELOX subgroup. With regard to the fact that almost twice as many patients were treated with XELOX than with the OxMdG regime, the unbalanced drug exposure could significantly influence the final therapeutic outcomes. Finally, it should be noted that post-hoc explorative analyses of the COIN study data have shown significant treatment benefit of cetuximab, with significant reduction of the progression risk in the subgroup of patients treated with cetuximab plus OxMdG (quasi-FOLFOX) and subgroups with single organ metastatic affliction and/or liver metastases only. Finally, the frequency of G3 gastrointestinal toxicity of cetuximab in combination with oxaliplatin was not significantly different compared to a safety report from a previous clinical trial, where cetuximab was used in combination with either FOLFOX or XELOX regimes (12, 18).

The Role of Cetuximab in the Treatment of Liver Metastases from CRC

Liver metastases gradually develop in 50-75% of patients with locally-advanced CRC. At present, radical surgical resection (R0) is the only hope for potential cure, or at least significant improvement in OS of these patients. Just under one fourth of all patients with hepatic metastases are indicated for surgical management. The disease is found primarily unresectable in the remaining 75% of patients. However, resectability, and thus an improvement in long-term survival, may be achieved in another 15-40% of patients by using chemotherapy followed by surgery. A specialised multidisciplinary team (oncologist, radiologist, liver surgeon, internal medicine specialists) plays a crucial role here. When this collaboration is well-functioning, five-year survival may be achieved in more than 50% of patients with hepatic metastases (21, 22). An optimal approach to first line treatment of metastatic CRC has not been established. However, it is recommendable that anticaner treatment followed by resection when tumour downsise is used for patients with primarily unresectable liver metastases (23).

Objective RR of more than 50% and up to 24-month median survival may be achieved with neoadjuvant (induction) systemic treatment with modern oxaliplatin or irinotecan-based
chemotherapy regimens added to 5-fluorouracil and leucovorin or capecitabine (24). An addition of targeted biological treatment to conventional chemotherapy continues to increase the objective RR and OS. An optimal induction regimen should have minimal toxicity. Adverse hepatotoxicity of conventional chemotherapeutics is well-recognized (25, 26). Targeted biological treatment should, therefore, have minimal effect on the liver parenchyma. Monoclonal antibody cetuximab fulfills these criteria (27, 28). The efficacy of cetuximab in patients with unresectable hepatic metastases and wild type KRAS was confirmed in the multicentric randomised CELIM study (29). The study enrolled a total of 111 patients with unresectable hepatic metastases. Unresectability criteria in this study were as follows: five and more metastatic lesions; technical unresectability; infiltration of the hepatic vessels; infiltration of both hepatic arteries or infiltration of both branches of the portal vein. In these patients, a combination of cetuximab with FOLFIRI and FOLFOX 6 was evaluated. A significant reduction of 79% in the size and spread of metastases, enabled resection of metastases in 43% of patients (radical R0 resection was achievable in 34% of patients). The POCHER study, where induction treatment with cetuximab was administered in combination with an intensive chronomodulation conventional chemotherapy with irinotecan, 5-fluorouracil, leucovorin and oxaliplatin (FOLFIRINOX), also showed efficacy of cetuximab as an induction treatment for CRC hepatic metastases. A total of 43 patients with primarily unresectable liver metastases were included. Radical R0 resection was achieved in 60% of patients, median OS was 37 months, and two-year survival 68%. Higher toxicity associated with this intensive therapy required dose reduction but was then bearable by the patients (30).

**Conclusion**

In patients with confirmed (wt) KRAS gene, monoclonal anti-EGFR antibody cetuximab represents a targeted biological therapy as a new standard of personalised medicine for patients with metastatic CRC.

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