Background: Unresectable colorectal liver metastases can be resected after response to chemotherapy. The use of neoadjuvant chemotherapy with or without targeted monoclonal antibodies increases the proportion of resectable liver metastases and conferred a long term survival of 40%. Methods: The current ongoing studies regarding neoadjuvant treatment strategies aiming to increase a proportion of patients with resectable liver metastases is going to be presented. Results: Perioperative chemotherapy with FOLFOX4 is compatible with major liver surgery and reduces the risk of events of progression free survival in resected patients. The results of the CELIM study confirm a favourable long-term survival for patients with initially suboptimal or unresectable colorectal liver metastasis who respond to conversion therapy and undergo secondary resection. The New EPOC randomised trial does not support the addition of cetuximab to chemotherapy and surgery for operable colorectal liver metastasis in KRAS exon 2 wild-type patients. Conclusion: The ability of anti–epidermal growth factor receptor agents to increase response rate and resection when added to chemotherapy has been clearly shown in a number of trials. The resection rates are higher with chemotherapy plus Cetuximab, in general, a conversion is contributes to the better overall survival. Key words: colorectal cancer, metastasis, cure

INTRODUCTION:

Generally, metastatic colorectal cancer represents an incurable situation for which only palliative options (e.g.: best supportive care, palliative chemotherapy) should be considered. However, there are specific circumstances where an attempt at metastasectomy may be possible and where five-year survivals may reach 40 percent. Such treatment requires involvement of a multidisciplinary team that should include a hepatobiliary surgeon, thoracic surgeon, and oncologist. The epidermal growth factor receptor (EGFR) and the vascular endothelial growth factor (VEGF) or its receptor (VEGFR) represents a very important molecular target in patients with advanced colorectal cancer (mCRC), which has been proved in several clinical studies. However, the benefit from anti-EGFR monoclonal antibodies such as cetuximab or panitumumab has been shown only in patients with wild-type K-RAS. The mutational status of K-RAS had no prognostic effect in patients receiving best supportive care (BSC) alone, indicating its role as a predictive biomarker for anti-EGFR antibody efficacy, thus including the genetic testing for somatic mutations in K-RAS in patients with mCRC as a routine clinical practice also in S3-quideline. 

Patients and Methods:

The S-3 Guidelines from June 2013 suggest that the liver metastasis, potentially R0- resectable should be resected with the suggestion grade A and level of evidence of 3b. The German experts defined the resectability of liver metastasis according to modified Fong-score if the extrahepatic metastasis are not present, if less that 70% of liver tissue is involved, if less than 3 liver veins and less than 7 liver segments are involved, when no liver insufficiency od Child-B or Child – C Liver cirrhosis is present and no severe diseases are present. The ESMO also defined the groups of liver metastasis according to their resectability. The first randomised data regarding the role of perioperative chemotherapy in resectable liver metastasis have been published from the EORTC study showing significant better overall survival (OS) in patients with perioperative chemotherapy. Adam et al showed that the chemotherapy leads to downsizing of the tumour making it resectable and improving
the OS and disease free survival (DFS) in these patients. In addition in a number of patients (4-9%) achieved a complete pathological remission 11. The overall response rate in phase III studies and in big number of patients has been described in couple of studies from 38 to 66% (Table 1). The results of different Phase II Studies in “only liver” patients are also promising (response rate from 57-78% of patients) (Table 2). In the Cetuximab in neoadjuvant treatment of unresectable colorectal Liver Metastases (CELIM) study, patients were randomized to receive either FOLFOX/cetuximab or FOLFIRI /cetuximab 3. The results have shown that the patients who underwent R0 resection achieved better median OS than those who did not. The median DFS for R0 resected patients was 9.9 months and the 5-year OS rate was 46.2%, being probably the most important result of this trial, confirming in a multicentre, randomized study the value of intensive “conversion chemotherapy”. Of those patients defined as not-resectable before the study treatment, 34% finally underwent R0 resection and an additional 12% underwent R1 resection. Increase response rates and higher resection rates have been described in patients with K-RAS wild-type tumours who received cetuximab plus FOLFIRI or FOLFOX in both the CRYSTAL and OPUS studies, which enrolled patients with both only-liver and non-liver limited metastasis 4.

DISCUSSION:

Only a couple of years ago, the patients with metastatic colorectal cancer have been regarded as incurable. The 5 year OS rate of almost 45% in patients receiving an intensive “conversion chemotherapy” together with liver surgery and R0 resection is the most important result in the last decade in the field of metastatic colon cancer. The finding that patients with unresectable liver metastasis can become resectable after responding to chemotherapy and have a better long term outcome than chemotherapy alone 5 has led to the introduction of the concept of “conversion or downsizing chemotherapy”. It has been also shown that the response of chemotherapy correlates with a resection rate, thus indicating that the prior chemotherapy or the combination with immunotherapy has a central role in the conversion chemotherapy.

Cetuximab, the anti-EGFR antibody improves both the overall survival and response rate when combined with chemotherapy in patients whose tumours are without K-RAS mutation. The addition of bevacizumab, an antibody by VEGFR to oxaliplatin-based chemotherapy significantly improved PFS in this first-line trial in patients with MCRC, however overall survival differences did not reach statistical significance 5,6. In addition, it has been shown that treatment continuation until disease progression may be necessary in order to optimize the contribution of bevacizumab to therapy. It has been also shown that there was no increased bleeding risk in patients receiving bevacizumab and concomitant anticoagulation therapy compared with control group of patients. The similar results have been also obtained in randomized, phase 3 study in elderly patients in combination with capecitabine (AVEX 16).

Panitumumab, anti EGFR antibody have shown that panitumumab-FOLFOX4 was well tolerated and significantly improved PFS in patients with WT K-RAS tumors and underscores the importance of KRASTesting for patients with mCRC (PRIME Study) 10. The new AIO Study (PanaMa) which has been also initiated in our oncological center (OZN) has the aim to compare in the multicenter randomised study the effect of panitumumab in patients with mCRC.

SUMMARY

DA LI METASTAZIRANI KOLOREKTALNI KARZINOM MOŽE DA SE IZLĲEĬ?

Uvod: Primarno neresektabilne metastaze kolorektalnog karcinoma u jetri mogu se resecuri posle primene citostatike terapije. Primena neoadjuvantne (periopterative) citostatske terapije u kombinaciji sa monoklonskim antitelima povećava procenat resektabilnosti metastaza jetre i omogućava dugogodišnje preživljavanje od 40%.

Metode: U ovom preglednom radu su prikazane aktuelne randomizirane studije čiji je cilj omogućavanje resektabilnosti metastaza kolorektalnog karcinoma u jetri.

Rezultati: Perioperativna citostatska terapija prema protokolu FOLFOX4 je kompatibilna sa resekcijom metastaza i produžava DFS kod resecuranih pacijenata. Rezultati Crystal, OPUS i CELIM studije potvrđuju dugogodišnje preživljavanje kod pacijenata sa primarno neresektabilnim metastazama kolorektalnog karcinoma u jetri koji su odgovorili na perioperativnu kombinovanu citostatsko/immunološku terapiju. Efekat kombinovane primene cetuximab-a i bavazizumab-a sa citostatikom terapijom se vidi kod tumora sa KRAS kodon 12/16/61 wild-tip ekspresijom.

Zaključak: Multidisciplinarni pristup bolesniku sa metastazama kolorektalnog karcinoma u jetri omogućava posle primene perioperativne kombinovane citostatsko/immunološke terapije resektabilnost metastaza i dugogodišnje preživljavanje. Optimalna kombinacija je predmet više studija sa ciljem da se poveća resektabilnost metastaza kod bolesnika sa kolorektalnim karcinomom.

Ključne reči: kolorektalni karcinom, metastaze, leenje

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