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review

Advances in the treatment of metastatic colorectal carcinoma

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Background. *In most cases, metastatic colorectal cancer is incurable; however, the prognosis and survival of these patients have significantly improved in the last 6 years. A few years back, the only efficient drug for colorectal carcinoma, 5-fluoruracil, yielded the mean survival of 10 months, whereas today, the survival rates of 20 months or more may be obtained by using new cytostatics. In the last six years, five new drugs were registered for the treatment of metastatic colorectal cancer. These are three cytostatics (capecitabine, irinotecan, oxaliplatin) and two target drugs (cetuximab and bevacizumab).*

Conclusions. *A combined treatment assures a better quality of life, and longer remissions and overall survival. The combination of cytostatics and target drugs improves particularly the mean survival rate, which may be longer than 30 months. These combinations of drugs used together with surgical treatment of lung and liver metastases may result in complete remission. An important research achievement of this year is the determination of KRAS mutations. The KRAS gene is the first biomarker that predicts how well patients will respond to certain combination of treatment.*

Key words: metastatic colorectal cancer; chemotherapy; targeted therapy; KRAS

Introduction

Only seven years ago, the treatment of metastatic colorectal cancer was based on a single agent, *i.e.* 5-fluorouracil (5-FU). This agent yielded a response rate of 20%, time to disease progression of four months, and mean survival of 10-11 months. From 2000 onwards, these values have doubled by applying new cytostatics and, by adding target drugs, they have trebled. Currently, the response rate in the first-line treatment of metastatic disease is >45%, the time to progression around 8 months, the survival around 20 months, and by adding the target drugs, it may be longer, often more than 3 years. With successful surgery of liver metastases, a 50% five-year survival may be obtained, while some authors have reported about 30% ten-year survival.

Given these new achievements, a new concept of the second- and third-line treatment of the patients with the metastatic colorectal cancer could be adopted; the real-

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ity we are witnessing today, only five years back appeared to be almost inaccessible. The second-line chemotherapy yields response rates of ~20%, time to progression of 4 months and mean survival of ~10 moths.

Taking into account the new biomarker, *i.e.* the determination of KRAS gene mutation, 60%-80% response rates may be achieved in the patients with non-mutated KRAS gene if chemotherapy is applied in combination with cetuximab. Several research studies have confirmed that better response rates improve the chances of the liver surgery for colorectal metastases.

In stage IV patients, treatment plans are made separately for each individual patient because the treatment mainly depends upon the size and location of the primary, the number and location of metastases, the performance status of a patient, and the liver and renal function.

In the treatment of these patients, we follow the basic treatment guidelines. In the patients with large tumours, obstructing the lumen and thus posing a serious risk for ileus, we recommend the resection of the primary tumour of the colon or rectum, or the preoperative irradiation of the rectal tumour before the resection.[1] If solitary metastases are detected in the lung or liver, they should be excised in the first place; in the patients with multiple metastases in one or more organs, the systemic treatment with chemotherapy is recommended if the patient's physical condition allows it.

Resectable metastatic disease

In the patients with the metastatic disease invading only the liver or the lung, surgery as the treatment option should be carefully considered. If radical resection of metastases is performed immediately after they have been detected, the disease recurs in ~80% of cases; this speaks in favour of the systemic treatment which could reduce the risk of the disease recurrence. It, however, appears that the best treatment approach would be to apply at first the systemic treatment which would indicate whether the disease is chemosensitive; if so, surgery would follow after the response to treatment was obtained. The results of the Phase III EORTC Trial on GI Group, published in 2008, confirm the benefits of such an approach.[2] In this trial, the patients preoperatively and postoperatively received 6 cycles of chemotherapy. This treatment scheme may pose a risk for the potentially curable patients who may experience early progression of the disease due to the systemic treatment. However, since in the patients receiving standard treatment in combination with chemotherapy, the percentage of early disease progressions is rather low, estimated at ~10%, the potential benefit of this treatment scheme outweighs the risk of early disease progression.[2,3]

Unresectable metastatic disease potentially put in remission

The patients who fall into this group have the metastatic disease so severely spread in the liver or the lung that it is unresectable. The primary aim of the systemic treatment of these patients is to reduce the size of the metastases in order to facilitate the radical resection. In selecting the systemic therapy, it should be noted that, after the radical resection, the survival rates of these patients may be the same as those of the patients with resectable disease, *i.e.* 30-50%. The neoadjuvant systemic treatment can downstage the disease to the extent allowing radical resection. This approach is effective in 15% of patients. As the neoadjuvant treatment aims at reducing the tumour mass as much as possible, the most effective combinations of cytostatics are selected,

e.g. FOLFIRI (irinotecan / 5-fluorouracil / Calcium folinate) and FOLFOX (oxaliplatin / 5-fluorouracil / Calcium folinate). The two combinations are equally effective. Several research studies have proved that better response to treatment increases the chances for liver surgery.[4] In order to improve the response rate, the combinations with target drugs are also used. The addition of cetuximab to standard chemotherapy significantly improves the response to chemotherapy, thereby doubling the number of liver metastases resections in comparison to the use of standard neoadjuvant chemotherapy alone.[5] Recently published research studies on KRAS gene mutations have proved that, by determining the mutations of the KRAS gene, it is possible to identify the patients who can most benefit from the use of cetuximab; these are the patients with KRAS wt (wild type / non-mutated) gene. In these studies, the absence of KRAS mutation proved to be a prognostic factor for the response to treatment, time to disease progression, and survival.[6] The response rates of this group of patients were higher by 40-60% than of the group of patients treated with standard chemotherapy. The patients in whom higher resectability rates of liver metastases are obtained by neoadjuvant chemotherapy, have a significantly longer survival. The five- and ten-year survivals of 40% and 25%, respectively, are comparable with the survivals of the patients with primary resectable liver metastases, which is indeed an important achievement in the treatment of metastatic colorectal cancer.[7] At ESMO 2008, a randomized multicentric trial was presented which was performed on the use of the combination of cetuximab with FOLFOX or FOLFIRI applied in the patients with the wild type KRAS gene and with primary unresectable liver metastases. The results of this trial are most encouraging; with the obtained response rate of 80%, R0 resection was possible in 34% of patients.[8] With the addition of bevacizumab, an agent that belongs to the group of the inhibitors of angiogenesis, to the irinoitecan-based chemotherapy (IFL treatment scheme), the response to treatment was obtained in 48% of patients, whereas the addition of bevacizumab to the FOLFOX or XELOX regimens did not improve the response rate.[9-11]

Unresectable metastatic disease

In the majority of patients with stage IV colorectal metastatic cancer, the disease is unresectable and metastasizing in more than one organ, thus not allowing the radical surgical treatment. The standard treatment for these patients is systemic chemotherapy or chemotherapy in combination with target drugs. From the last ten years of practicing the treatment of stage IV patients, a number of important conclusions were drawn:

- Chemotherapy with fluoropyrimidines is better than the best supportive care because it yields a longer survival and better quality of life.
- The sooner the treatment is started, the better the outcome for the patients.
- The combination of calcium folinate and 5-FU is more effective than 5-FU alone.
- The infused 5-FU infusion is better than bolus.
- Chemotherapy combining two agents is more effective in the first-line treatment than monotherapy, but it also has more toxic effects.
- Treatment with polychemotherapy with the addition of target drugs is more effective than polychemotherapy alone; moreover, it also yields a longer survival.
- The second-line systemic treatment is more effective than the best supportive care;[12,13] the same applies also to the third-line treatment.

The application of these new issues in clinical practice cannot always be a clear-cut practice because it should bear in mind that the most effective treatment modality is not always the best option for a particular patient. Therefore, in selecting the treatment modality, the following factors should be considered:
– age
– performance status
– tumour-associated symptoms
– size and invasion of metastases
– treatment line
– associated diseases.

Metastatic disease: which systemic treatment is most appropriate?

So far, no definite suggestion has been made which of the twin therapies to select, FOLFIRI or FOLFOX. Several randomized trials which compared the two treatment regimens confirmed that they were equally effective and also showed that the survivals were comparable. Thus, either of the twin therapies can be recommended as the first- or second-line treatment. Also the toxicity of the two treatment regimens is comparable, except that the specter of toxicity is different; the most typical toxic effect of FOLFOX is neurotoxicity, while FOLFIRI typically causes diarrhoea and alopecia. The FOLFOX-associated neurotoxicity may be severe; it is cumulative and occurs in late treatment cycle, the FOLFIRI-associated toxicities develop in the earliest treatment cycles, already after the first completed cycle.[14-18]

As the FOLFOX regimen has been designated as the adjuvant treatment of the patients with the stage III colorectal cancer, medical oncologists will in no time start receiving the patients with the disease progression after the completed chemotherapy. It is, therefore, obvious why the FOLFIRI scheme in combination with biological drugs will become a treatment of choice in the first-line treatment of metastatic colorectal cancer.

New target drugs

In Europe, and consequently in Slovenia, two new anticancer target drugs were registered in recent years; these are cetuximab which was approved in June 2004, and bevacizumab, approved in January 2005.

Cetuximab is a chimeric monoclonal antibody that targets the extracellular domain of the epidermal growth factor receptor (EGFR).[19] EGFR is overexpressed in 60%-80% of colorectal tumours. Several preclinical and clinical trials have confirmed the efficiency of cetuximab applied as monotherapy or, in the FOLFIRI non-responsive patients, in combination with FOLFIRI regimen. In a clinical phase III trial on cetuximab, the improvement of the disease-free survival, but no increase in the toxicity of chemotherapy, was observed in the FOLFIRI non-responsive patients treated with cetuximab plus FOLFIRI regimen. The adverse effects of treatment with cetuximab are allergic and skin reactions that can be managed.[19] It was also proved that the patients with grade II skin reactions are more likely to respond to treatment.[19,20] The efficiency and safety of cetuximab applied in combination with irinotecan in the patients refractory to chemotherapy was demonstrated also in the multicentric studies MABEL[21] and LABEL.[22] Most valuable data were provided also by the recent studies that were followed by phase II trials, which all support the comparability and consistency of the obtained results. A phase III randomised study on cetuximab NCIC CO.17 proved that cetuximab is the only biological drug which assures efficiency, safety and better quality of life of the

patients in whom all other treatment potentials have been exhausted. The patients who were treated with weekly doses of cetuximab (monotherapy) had significantly longer survival and better quality of life than the patients who were receiving the best supportive care.[23] The results of the EPIC phase III clinical trial are noteworthy, too. In this trial, the patients in whom oxaliplatin-based chemotherapy failed were receiving either the irinotecan-based chemotherapy or a combination of irinotecan and cetuximab. In the patients who had received cetuximab, a fourfold improvement of response rate, a significantly longer time to disease progression and improved quality of life were observed.[24] The results of two randomized studies (CRYSTAL and OPUS), in which the patients treated for metastatic colorectal cancer were receiving cetuximab in the first-line treatment, revealed that the mutations on the KRAS gene have a predictive value for prognosticating the efficiency of treatment with target agents targeting EGFR. Hence, these mutations are the first biomarkers that will be of great help in selecting a proper treatment that will assure a better response to treatment, longer survival and better quality of life to each individual colorectal cancer patient.[5,6]

The overexpression of vascular endothelial growth factor (VEGF) is an important mediator of angiogenesis in colorectal cancer as well as in a number of other cancers. Bevacizumab is a recombinant human antibody against VEGF. A combined treatment of the patients with colorectal cancer has proved to be most effective. By adding bevacizumab to chemotherapy, the response rate to treatment has increased by 10% and the survival by 5 months. On account of these favorable results, bevacizumab in combination with chemotherapy has become a treatment doctrine in the USA as well as in Europe. The most frequent adverse effects of the treatment with bevacizumab are proteinuria, hypertension, and thromboembolic disorders.[9]

The efficiency of bevacizumab was tested on 923 patients with metastatic colorectal cancer included in the randomized phase III AVF2107 clinical study. The study compared a placebo in combination with irinotecn plus 5-FU/LV (IFL regimen) versus bevacizumab and IFL regimen versus bevacizumab plus 5-FU/LV. The primary aim of the study was to evaluate the overall survival. The secondary aims were to evaluate the disease-free survival, overall response rate and duration of the response.[9] As soon as the safety and efficiency of the combination of IFL regimen plus bevacizumab was confirmed and approved, the recruitment of patients for the third group was closed. Altogether 813 patients were included in the study groups 1 and 2; the group that received bevacizumab in combination with chemotherapy had longer overall survival (20.3 months) than the group treated with chemotherapy alone (15.5 months). The combination of cetuximab and irinotecan plus 5-FU/LV prolonged the time to disease progression by 4.4 months.

In the second-line treatment, bevacizumab was tested in two large international phase III studies, NO16966 and E3200. The NO16966 study showed a significantly longer time to disease progression in the patients who were receiving bevacizumab in addition to chemotherapy (XELOX or FOLFOX regimen). The patients who were receiving bevacizumab until the disease progression particularly benefited from this therapy.[25]

In the E3200 study, J. Giantonio *et al*. assessed the efficiency of bevacizumab (10 mg/kg) in combination with the FOLFOX4 regimen in 829 patients with advanced colorectal cancer who underwent prior therapies. The patients were randomized into three study groups by the following

treatment regimens: FOLFOX 4 plus bevacizumab, FOLFOX 4 alone, bevacizumab alone. The agents were applied in two-week treatment schedules. Bevacizumab in combination with FOLFOX 4 statistically significantly improved the disease-free survival (7.3 months vs. 4.7 months, $p<0.0001$) and objective response to treatment (22.7% vs. 8.6%). The results of the study also showed that the overall survival of the patients treated with the combination of bevacizumab and the FOLFOX 4 regimen was by 2.1 months longer than that of the patients treated with the FOLFOX 4 regimen alone. The time to disease progression was also longer, while the death risk was reduced by 24%.[25,26]

In October 2008 the results of the BriTE study, an American research study performed on a large cohort of patients with metastatic colorectal cancer treated with bevacizumab plus chemotherapy in the first-line treatments, were presented. The study included 1,953 patients from 49 countries. The aim of the study was to assess the efficiency of bevacizumab after the disease progression in the patients in whom the cetuximab therapy was not discontinued after the disease progression. The patients with the disease progression were randomized in three study groups: the patients with no further therapy, the patients receiving further therapies without cetuximab, and the patients treated with cetuximab plus chemotherapy. The median overall survival was 25.1 months and the mean time to disease progression was 10 months. One of the most important conclusion of this study was that the patients treated after the disease progression with cetuximab plus chemotherapy had the longest median survival (31.8 months, $p<0.001$).[27]

Conclusions

In the most recent years, five new agents, capecitabine, irinotecan, oxaliplatin, cetuximab and bevacizumab were registered. Their different combinations in the treatment of patients with metastatic colorectal cancer improved the efficiency of treatment, quality of life of patients, and survival rates. Before the use of these agents in clinical practice, the mean survival of colorectal cancer patients was 11 months; with the introduction of the new agents, the survival may be longer than three years or even five years if the treatment with new agents is combined with careful surgical excision of colorectal cancer liver metastases. Among the important advances in the study of a cancer cell was the determination of the KRAS gene mutation which appeared to be the first biomarker to predict the response to treatment with target drugs. We believe that the further development of this area will play a fundamental role in selecting the appropriate treatment regimen for each individual patient.

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