

SYSTEMIC TREATMENT OF COLORECTAL CANCER

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Summary

Colorectal cancer is the most common type of gastrointestinal cancer. In this article treatment protocols for colon cancer are discussed, including adjuvant and neoadjuvant therapy for resectable disease and chemotherapy for advanced or metastatic colorectal cancer. Surgery is the only curative modality for localized colorectal cancer (stage I-III). Adjuvant chemotherapy is standard for patients with stage III disease. It's use in stage II disease is controversial, with ongoing studies seeking to confirm which markers might identify patients who would benefit. Surgical resection potentially provides the only curative option for patients with limited metastatic disease in liver and/or lung (stage IV disease). Chemotherapy rather than surgery is the standard management for metastatic disease. Biologic agents have a role in the treatment of metastatic disease, with selection increasingly guided by genetic analysis of the tumor.

KEYWORDS: *colorectal cancer, systemic therapy, adjuvant therapy, neoadjuvant therapy*

SISTEMSKO LIJEČENJE RAKA DEBELOG CRIJEVA

Sažetak

Rak debelog crijeva najčešći je zloćudni tumor probavnog sustava. U ovom se radu raspravlja o protokolima koji se primjenjuju u liječenju raka debelog crijeva, uključujući adjuvantnu i neoadjuvantnu terapiju resektabilne bolesti te kemoterapiju uznapredovalog i metastatskog raka debelog crijeva. Kirurgija je jedini kurativni modalitet liječenja lokaliziranog rakadebelog crijeva (stadij bolesti I-III). Adjuvantna kemoterapija predstavlja standard u liječenju bolesnika sa stadij bolesti III. Međutim, njezina uloga kod stadija bolesti II je kontroverzna te se trenutno provode studije koje traže biljege pomoću kojih bi se mogli prepoznati bolesnici koji bi mogli imati koristi od primjene adjuvantne kemoterapije. Kirurška resekcija potencijalno predstavlja jedinu kurativnu mogućnost za bolesnike s bolešću ograničenom na jetru i/ili pluća (stadij IV). U liječenju metastatske bolesti standard predstavlja kemoterapija, prije nego kirurgija. Biološki lijekovi imaju ulogu u liječenju metastatske bolesti, s tim da se njihov izbor sve više temelji na genetskoj analizi tumora.

KLJUČNE RIJEČI: *rak kolorektuma, sistemska terapija, adjuvantna terapija, neoadjuvantna terapija*

Colon and rectal cancer (CRC) is an important public health problem and it is responsible for million of new cancer cases and half a million of deaths worldwide per year^{1,2}. In Europe, 250,000

new patients are recorded yearly, of which 70% are older than 65 years². In order to reduce mortality, optimal diagnostic methods for early diagnosis, appropriate surgical procedure (R0 resection)

and a strategy to select the most appropriate systemic treatment to improve disease control and survival are required.

Patients with stage III (any T, N1, M0, or Any T, N2, M0) and high risk stage II (T3, N0, M0 or T4, N0, M0) colorectal cancer have benefit from adjuvant therapy, which depends on the tumor differentiation, lymphatic, vascular and perineural invasion, clinical presentation with obstruction or perforation of the intestine and the number of removed lymph nodes (12). In terms of the low-risk, following factors may be important in the assessment: p53, K-ras mutation, bcl-2 expression (apoptosis antagonist), transforming growth factor (TGF- α), epidermal growth factor (EGF) and the proliferative index of tumor cell. These prognostic parameters are not yet implemented in every day clinical praxis.

Fluoropyrimidines are basis for adjuvant treatment of colorectal cancer. Results of the NSABP C-01 study have shown the advantage of the addition of adjuvant chemotherapy compared to surgical resection alone (DFS 16%, OS 18%)¹. An orally administered capecitabine is not inferior to fluoropyrimidine infusion protocol (X-ACT study) with the same DFS^{2,3,4}. The addition of oxaliplatin to fluoropyrimidine basis became the standard for stage III disease treatment based on the results of the MOSAIC study (risk reduction 23% after three years and an absolute benefit in OS of 4.2% after six years in the group treated with FOLFOX)^{5,6,7}. Similar results were confirmed in studies NSABP C-07 (FU/LV vs. FLOX) and NO16968 (XELOX)⁸. Adding irinotecan to 5-FU showed no advantage with the deterioration of the toxic profile (CALGB-89803 study, ACCORD and PETACC-3)^{2,9,10}.

Although much was expected from the application of biological therapy, it is not justified in the adjuvant treatment. Results of the AVANT study in which bevacizumab was added to FOLFOX4 protocol showed no significant clinical benefit with more side effects¹¹. Similar results were confirmed with FOLFOX6 protocol (NSABP C-08)¹². No clinical benefits were shown when cetuximab was added to FOLFOX4 protocol in K-RAS wild subtype patients in PETACC-8 study¹³. Answers to questions, such as why drugs which are effective in metastatic disease are not effective in adjuvant treatment and what factors affect their ineffectiveness in micrometastatic environment,

may be clarified by studies currently in progress: QUASAR2, E5202, INT NO 147. Also, optimum time of application of adjuvant therapy remains unclear: six-months or three-months therapy. Answer to that question may be provided by the results of six ongoing clinical trials¹⁴.

Since 2004 neoadjuvant treatment of rectal cancer became a standard after results of two important clinical studies for T3, T4, or N + (positive regional lymph nodes) rectal cancer were announced. NSABP R-03 study showed that preoperative chemoradiotherapy compared to postoperative insignificantly improves five-year progression-free survival (65% vs. 53%) and insignificantly improves five-year survival rate (75% vs. 66%) with no effect on the incidence of local recurrence (11%). Pathological complete response was around 15%^{15,16,17,18}. On the contrary CAO/ARO/AIO-94 study, after eleven years of follow-up, showed a lower incidence of local recurrence (7.1% vs. 10%), a higher incidence of sphincter preservation (39% vs. 20%) and less acute and chronic toxicity in comparison with postoperative chemoradiotherapy, without significant difference in five-year survival (59%) and occurrence of distant metastases^{15,19,20}.

Usefulness of the adjuvant chemotherapy was confirmed by Sweden population study published in 2013. Study included 2400 patients with stage III rectal cancer, of whom 79% had received preoperative radiotherapy (90% short-course, 25 Gy in 5 fractions of 5 Gy), and after surgery 42% of patients continued adjuvant chemotherapy with 5-FU/LV (DeGramont protocol) for 12 cycles. Study showed significant benefit of adjuvant chemotherapy with five-year survival rate of 65.8% vs. 45.6% without chemotherapy, while reducing the risk of death by 35%. Patients with tumors located more than 10 cm above the anocutaneous line, patients between 50 and 60 years, and patients younger than 70 years have benefited the most from adjuvant chemotherapy²¹. Completely conflicting results were given by the EORTC 22921 study published in 2014. That study included 1011 patients with stage III rectal cancer who received preoperative radiotherapy (45 Gy in 25 fractions) with or without 5-FU/LV chemotherapy, which was or was not continued with postoperative adjuvant therapy with 5-FU/LV for another 4 cycles. The results showed that adjuvant chemotherapy based on fluoropyrimidine after preoperative ra-

diotherapy with or without concomitant chemotherapy does not affect recurrence-free survival and overall survival. This study, therefore, does not support the application of adjuvant chemotherapy after preoperative radiotherapy or radiochemotherapy. New researches, that will confirm or disprove this opinion, need to be conducted, and results are expected from five ongoing studies^{22,23}. The questions how to accurately identify patients who are optimal candidates for preoperative chemoradiotherapy, which chemotherapy drug will be most effective and during which period of time should that drug be used, remains. Controversy of ideal preoperative approach also remains due to the fact that neither short-course irradiation nor long-course chemoradiation showed statistically significant difference in overall survival, incidence of distant metastases and local disease control, except definitive difference in the costs of treatment. Optimal moment for surgical procedure after chemoradiotherapy is still undefined^{27,28}.

Patients with stage II are treated better thanks to early screening and improved surgical techniques. The five-year survival rate is around 90%. Further progress can be achieved by analyzing 12 genes (OncotypeDX), but without predictive significance for the usefulness of adjuvant treatment^{29,30,31}. Similar results were obtained by ColoPrint test which analyzes 18 prognostic genes^{32,33}. Both tests have confirmed their independence in relation to the standard TNM classification.

The group of patients with potentially resectable metastases should be especially pointed out (liver, lungs). In that group of patients any active protocol could be applied. The order of administration of chemotherapy is not clearly defined. There are several possible approaches (neoadjuvant or perioperative therapy or liver resection first). Perioperative therapy should be based on protocols for metastatic disease for a total time of six months. Caution is needed when applying the protocol based on oxaliplatin and irinotecan due to the potential hepatotoxicity^{34,35,36}. The addition of bevacizumab to irinotecan showed higher effectiveness than to oxaliplatin, but the overall results were modest^{37,38,39}. Cetuximab in addition to standard FOLFIRI protocol showed the highest effectiveness in the overall response and the percentage of R0 resection, but showed no impact on overall survival, which was confirmed by a meta-

analysis^{40,41,42}. Radiographic examination is required every two months during the course of treatment, and planned surgical procedure should be performed as early as possible after achieving resectability⁴³.

Although by definition metastatic disease is incurable, in the last decade, we have witnessed great progress in the treatment of patients with metastatic colorectal cancer (mCRC). In addition to the therapy based on 5-fluorouracil as the sole active drug, now we have a whole range of new available drugs including irinotecan, oxaliplatin, capecitabine, and biological drugs such as bevacizumab, panitumumab, regorafenib and ziv-aflibercept. With the development of a multidisciplinary approach to treatment (surgery, radiofrequency ablation, CyberKnife, radioembolisation), certain percentage of patients with metastatic disease can be potentially cured.

Metastases will occur in about 50-60% of patients with CRC, mostly in the liver. Seventy percent of these patients were initially unresectable, 10% were resectable and 20% borderline resectable. 8% of partially resectable patients will become resectable and potentially curable by using chemo +/- biological therapy⁴⁴. In summary, only 4% of patients will ultimately be treated with curative surgery, while others will be treated with some form of systemic therapy. Chemotherapy +/- biological therapy makes the basis of treatment of unresectable patients with the primary goal of long-term survival and preservation of quality of life.

Today we no longer talk about certain lines of treatment, but the continuity of treatment. The choice of treatment depends on the characteristics of the patients and the available therapeutic options. For now there is no clear stand about which chemotherapy regimen should be used as first line treatment. Recommended protocols are FOLFIRI, FOLFOX, CapeOx, infusion FU/LV or capecitabine and FOLFOXIRI.

Studies have shown that the initiation of treatment with FOLFOX protocol is as effective as treatment with FOLFIRI protocol⁴⁵. In the U.S., 70% of patients starts treatment with FOLFOX while in Croatia, as well as in the rest of Europe, most of patients usually start with FOLFIRI. Certain differences in the protocols can be found in the profile of side effects (peripheral sensory neuropathy vs. alopecia and diarrhea).

Problem of neuropathy can be mitigated by using the so-called “stop-and-go” approach. OP-TIMOX1 study showed that the FOLFOX protocol can be administered in a way to have intervals without the use of oxaliplatin and that it will not affect the patients overall survival⁴⁶. A practical recommendation is to limit the use of oxaliplatin to three months or less, in the purpose of preventing or reducing the side effects, and to continue with maintenance therapy up to 6 months or until disease progression. In the case of neuropathy, oxaliplatin therapy may be continued only after the withdrawal of symptoms to a level very close to complete absence of symptoms.

Infusion 5-fluorouracil+leucovorin or capecitabine (-/+ bevacizumab) are therapies of choice in patients with poor general condition and patients who are not able to withstand the aggressive forms of treatment⁴⁷. We should point out the population of patients older than 70 years in which addition of bevacizumab led to prolongation of PFS (9.1 vs. 5.1 months; AVEX study)⁴⁸.

In order to get answers to questions, which protocol should we begin treatment with, should we add biological therapy, what type of biological therapy should we add, how to position the surgical procedure and maintenance therapy, great attention is paid to potential biomarkers. Appropriate biomarker could define groups of patients who will respond best to treatment, as well as those who will not benefit from the treatment at all and it would reduce the toxicity and treatment costs. Talking about the origin of biomarkers of tumor tissue, it remains unclear whether we should refer to the characteristics of the primary tumor or metastasis when choosing the right therapy. Gerlinger and colleagues published an interesting paper in which they pointed out intratumour heterogeneity in the same person who underwent biopsy of multiple metastatic site⁴⁹. This research has opened up a whole series of questions about the type and time of drug administration based on the status of biomarkers. Positive examples of defining biomarkers from the primary tumor site are the applications of cetuximab and panitumumab.

Use of the EGFR inhibitor is indicated in patients with wild-type KRAS exon 2, which was clearly confirmed by meta-analysis of 14 randomized clinical trials⁵⁰. In remaining 40% of patients there is a mutation of codon 12 and 13 of exon 2 so anti-EGFR therapy has no effect. Anti EGFR ther-

apy will, however, be useful in only 13 to 17% of patients with the wild-type KRAS exon 2^{51,52}. The PRIME study (FOLFOX +/- panitumumab as initial treatment) showed that in 17% of patients who don't have mutation in KRAS exon 2 there is an additional KRAS mutation outside of exon 2 (exon 3-4%; exon 4 -6%) and NRAS (exon 2 -3%; exon 3 -4%)⁵³. According to some literature data NRAS mutation can be found in 2.6% of cases of colon cancer⁵⁴. These findings require a change in current terminology and now we won't be able to talk about KRAS but RAS mutation (which is already applied in the approval of panitumumab in Europe). There is a clear need to introduce the analysis of RAS mutations in standard practice so we could isolate a small group of patients who will respond well to therapy. For now, there is no standardized test for determining RAS mutations but it can be determined in well-equipped laboratories in Croatia. In patients with wild-type KRAS, who have progressed after or during chemotherapy based on irinotecan/oxaliplatin, the use of panitumumab prolongs time to disease progression comparing to best supportive care⁵¹. BRAF mutation that occurs in 4-14% of patients with CRC who do not show KRAS exon 2 mutations should also be mentioned. BRAF mutation is associated with poor prognosis, but it is not predictive of efficacy of panitumumab⁵³. However, for now there is not enough data on the use of anti EGFR therapies based on BRAF mutation.

CRYSTAL study, in which cetuximab was added to FOLFIRI protocol as initial treatment for mCRC, showed prolongation in overall survival⁵⁵. OPUS and COIN studies have shown no benefit from the addition of cetuximab to FOLFOX/CapeOX protocol neither in the time to disease progression nor in the overall survival^{56,57}. Results of direct comparison between adding cetuximab or bevacizumab to FOLFIRI protocol in first line of treatment were expected with special interest. The answer was partly given by FIRE-3 study which showed prolongation of overall survival in KRAS wild-type group who received cetuximab despite surprisingly equal overall response and time to disease progression^{58,59}. The results are a bit confusing, but very important to daily practice, although there are complaints about the lack of an independent data processing and the small number of patients who received a second line therapy.

Despite initial optimism, for now we are not able to confirm circulating VEGF-A as a biomarker of efficacy of bevacizumab. Anti VEGF therapy is standard treatment for patients with mCRC as an addition to FOLFIRI or FOLFOX protocol^{60,61,62}. It has been proven that discontinuation of bevacizumab does not cause “rebound” phenomenon^{63,64}. Use of bevacizumab is indicated after progression on first-line of treatment regardless of previous application of bevacizumab. Studies TML and BE-BYP justify continuation of bevacizumab therapy together with other chemotherapeutic partner after progression due to extension of overall survival, and the E3200 study justifies the application of bevacizumab in the second line of therapy when it was not used in the first line^{65,66,67,68}. VELOUR study has shown that the application of ziv-aflibercept with FOLFIRI after progression on oxaliplatin provides a small (1.4 months) but statistically significant difference in overall survival⁶⁹. Ziv-aflibercept is a recombinant fusion protein that functions according to the principle of the trap for VEGF and prevents angiogenesis. It should be applied only in combination with FOLFIRI protocol in patients who haven't received it previously. Application of ziv-aflibercept is associated with therapy disruptions in 26% of patients due to adverse events (nausea, infections, diarrhea, high blood pressure).

Regorafenib is a tyrosine kinase inhibitor structurally very similar to sorafenib. The CORRECT study showed small but statistically significant difference in overall survival compared to the best supportive care in patients previously treated with standard therapies⁷⁰.

Although recent studies with regorafenib (CORRECT), ziv-aflibercept (VELOUR) and extended application of bevacizumab (TML) showed similar modest improvement in overall survival of 1.4 months, it still represents an additional step in extending the lives of patients with mCRC's.

Patients should be additionally informed about the effectiveness of physical activity and healthy eating on treatment outcome (CALGB 89803)^{71,72,73}.

These findings suggest a smaller clinical significance of classical TNM classification, the need for further genetic analysis, a personalized approach to the treatment and above all, better organized preventive actions.

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