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SYSTEMIC THERAPY FOR COLORECTAL CANCER – OVERVIEW OF RECENT TRIALS

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Summary

Colorectal cancer (CRC) is the most common malignancy of the gastrointestinal tract worldwide, and also one of the leading causes of cancer-related mortality, accounting for more than 600000 deaths every year. Depending on the stage of the disease some patients who were surgically treated for CRC with curative intent require adjuvant chemotherapy (fluorouracile-based), which reduces the risk of recurrence and death in patients with stage III CRC, but its role in stage II is still controversial. Pathogenesis of CRC is a result of two different genetic pathways: chromosomal instability (CIN), and inactivation of mismatch repair (MMR) genes. Stage II patients with deficient MMR tumor status do not benefit from adjuvant therapy and should receive surgery alone. For patients with metastatic CRC optimal sequence of chemotherapy regimens and targeted therapy is still debated. Epidermal growth factor receptor (EGFR) has been validated as a therapeutic target in several human tumors including CRC. Recently it has been reported that activating mutations in exons 2, 3, and 4 of both KRAS and NRAS all predict a lack of response to EGFR trageted agents. Recent studies suggest BRAF is another prognostic and potential predictive biomarker of CRC. It is necessary to indentify new prognostic and predictive markers, to acquire maximal benefit from every therapy line and to improve prognosis of these patients.

***Keywords*:** colorectal cancer; personalized medicine; chemotherapy; targeted therapy; biomarkers.

Colorectal cancer (CRC) is the most common malignancy of the gastrointestinal tract worldwide, and also one of the leading causes of cancer-related mortality [1], accounting for more than 600,000 deaths every year [2]. Treatment options include surgery, chemotherapy, immunotherapy and radiotherapy. In localized disease, primary

surgery is the most widely used primary treatment, and these patients are treated with curative intent. Depending on the stage of the disease, some of these patients require adjuvant (fluoropirimidine-based) chemotherapy, which reduces the risk of recurrence and death in patients with stage III CRC, but its role in stage II is still controversial. Sargent et al. have collected individual patient data from 18 trials and more than 20,800 patients to investigate efficacy of adjuvant therapy in patients with stage II and III CRC [3]. According to their results, adjuvant chemotherapy for colon cancer (CC) provides significantly longer progression-free survival (PFS) and overall survival (OS), what reflects the curative role of chemotherapy in the adjuvant setting. In stage II, 72.2% of patients who underwent surgery and received adjuvant chemotherapy were alive at 8 years follow-up, in contrast to 66.8% of patients who received surgery alone. In stage III, 53% of patients who underwent surgery and received adjuvant chemotherapy and 42.7% of patients who received surgery alone were alive at 8 years follow-up.

Pathogenesis of CRC is a result of two different genetic pathways. Chromosomal instability (CIN) involves changes in number and structure of chromosomes and accounts for 85% of CRC cases, and inactivation of mismatch repair (MMR) genes, which take part in the repair od incorrectly connected DNA fragments, results in microsatelite instability (MSI) and accounts for 15% of CRC cases. MMR tumor status can be defficient (dMMR), with high content of MSI (MSI-H), and profficient (pMMR), with low-stable content of MSI (MSS i MSI-L). Previous retrospective and obsvervational studies showed that dMMR phenotype (in contrast to CIN-tumors) is associated with lower stage of the disease, right-sided tumor localization, high grade, mucinous/medullar type, more favorable prognosis, and lower efficacy of adjuvant fluorouracile-based adjuvant chemotherapy. Sargent et al. analyzed data from 7,803 stage II and III patients enrolled in 17 trials [4]. In adjuvant setting, 571 (7.3%) of these patients received surgery alone, 3878 (49.7%) 5-fluorouracil (5- FU) monotherapy, 2299 (29.5%) 5-FU and oxaliplatin, and 1055 (13.5%) 5-FU and irinotecan. Results have confirmed prognostic utility of MMR status in stage II CC, since dMMR tumor status was shown to be strongly associated with improved OS (90% of dMMR-positive patients who did not receive adjuvant chemotherapy were alive at 5-year follow-up). Based on these results, determination of tumor MMR status should be a routine test in all stage II CC patients, if adjuvant treatment is considered, since atients with dMMR tumor status do not benefit from adjuvant therapy and should receive surgery alone. Impact of MMR status on the outcome in stage III patients was also confirmed, but altering the management based on the MMR status was not recommended. Hence, determination of MMR tumor status should not be a routine test in these patients – all stage III patients should receive adjuvant

chemotherapy. In patients who were treated with fluorouracil- based adjuvant chemotherapy, prognostic value of MMR status was attenuated in both stage II and stage III patients compared to patients who received surgery alone, and after disease recurrence MMR status was no longer prognostically significant in the sense of OS in neither stage II nor stage III patients.

In rectal cancer (RC), fluoroupirimidine- based radiochemotherapy is nowadays a standard preoperative treatment for locally advanced disease, with continuous infusion of 5-FU being equally efficient to peroral capecitabine. Adjuvant chemotherapy for rectal cancer shoud be optimized, since up to 30% of these patients who are treated with preoperative radiochemotherapy and subsequent mesorectal excision (TME) ultimately develop distant metastases, irrespective of the application of adjuvant chemotherapy. In CC, fluoropirimidine-based monochemotherapy is a standard in high- risk stage II patients, and FOLFOX or CapeOx are preffered in stage III. To integrate the most effective treatment of stage II and III rectal cancer, in a clinical trail by German Rectal Cancer Study Group a total of 637 patients were randomly assigned to preoperative radiotherapy (tumor dose (TD) =50.4 Gy) plus infusional 5-FU (1 g/m^2 on days 1-5 and 29-33), followed by TME and 4 cycles of bolus 5-FU (500 mg/m^2 for 5 days) or preoperative radiotherapy (TD =50.4 Gy) plus infusional 5-FU (250 mg/m^2 on days 1-14 and 22-35) and oxaliplatin (50 mg/m^2 on days 1, 8, 22, and 29), followed by TME and subsequent 8 cycles of adjuvant FOLFOX6 regimen [5]. Results showed that adding oxaliplatin to 5-FU-based neoadjuvant chemoradiotherapy and adjuvant chemotherapy in locally advanced rectal cancer significantly improved DFS. In contrast to these results, several other trials showed that adding an oxaliplatin to fluorouracile-based preoperative chemoradiotherapy does not improve tumor regression (there is no radiosenstizing effect). In a study by Schmoll et al., in capecitabine plus radiotherapy arm minimal, moderate, good, and complete tumor regression were achieved in 22%, 37%, 20%, and 13% of patients, respectively, and in capecitabine plus oxaliplatin and radiotherapy arm in 16%, 40%, 22%, and 15% of patients, respectively [6]. Not only that tumor regression was not improved, patients' compliance was also significantly compromised due to toxicitiy in a study arm with added oxaliplatin. After TME in these patients, the first study arm continued to receive capecitabine alone, and the second arm received capecitabine and oxaliplatin, same as in the preoperative setting. Again, no difference in PFS was observed, and thus preoprative fluoropirimidine-based monochemotherapy remains the standard treatment in this setting for rectal cancer, however, adjuvant oxaliplatin-based chemotherapy (FOLFOX regimen) improves 3-year PFS in patients with residual T3-4 and/or N1-2 disease, after completed chemoradiotherapy and curative rectal cancer resection [7]. Results regarding OS in this setting are still awaited.

Epidermal growth factor receptor (EGFR) has been validated as a therapeutic target in several human tumours including CRC. Previous studies have shown that anti-vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab in non-selected patients and EGFR inhibitors cetuximab and panitumumab in patients with KRAS (exon 2) wild-type tumors improve OS (median survival > 24 months) when given with chemotherapy. Ten percent of these patients survive more than 5 years. Prevalence of KRAS exon 2 wild-type mutation is approximately 40%, and it is a predictor of EGFR inhibitors' efficacy. Activating mutations in KRAS exon 2 have long been known to blunt the response to EGFR-targeted agents in metastatic CRC. Lately, more extensive genetic testing for RAS gene mutations beyond routine analysis of exon 2 is becoming a new standard of care, to pinpoint which patients stand to benefit from anti-EGFR therapy in the treatment of metastatic CRC, since it was reported that activating mutations in exons 2, 3, and 4 of both KRAS and NRAS all predict a lack of response to panitumumab in the second-line setting, corroborating similar recent findings from the PRIME and PEAK trials regarding panitumumab's efficacy in the first-line setting [8, 9]. In PRIME trial, statistically significant benefit in OS was shown with addition of panitumumab to FOLFOX regimen in „all- RAS" wild-type patients, when compared to KRAS exon 2 wild-type patients, what is in accordance with results that show no benefit of panitumumab being added to FOLFOX regimen in patients with KRAS exon 2 wild-type and other RAS mutation present. These results were also confirmed in PEAK trial, in which bevacizumab and panitumumab were directly compared, both in combination with FOLFOX6 regimen. When looking at the original KRAS exon 2 wild-type patients only, there was no statistically significant difference in PFS between study arms (p=0.35), although prolonged OS was observed in the panitumumab arm (34.2 vs. 24.3 months, p=0.009), however, in the „all-RAS" wild-type patients both PFS and OS were prolonged in the panitumumab study arm. Again, there was no benefit of addition of panitumumab to FOLFOX regimen in patients with KRAS exon 2 wild-type and other RAS mutations. Similar results were reported in FIRE-3 trial, in which FOLFIRI plus cetuximab showed benefit in OS over FOLFIRI plus bevacizumab of 3.7 months in KRAS exon 2 wild-type patients and 7.5 months in „all-RAS" wild-type patients [10]. In contrast, benefit in OS in CALGB/SWOG 80405 clinical trial was also in favor of the FOLFOX regimen plus cetuximab versus FOLFOX plus bevacizumab, but difference did not reach statistical significance. Expanded „all-RAS" analysis of KRAS and NRAS exons 2, 3, and 4 is crucial for the optimal selection of first-line therapy in CRC. According to ASPECCT trial, panitumumab is not less effective than cetuximab in chemorefractory patients in terms of OS [11].

Another investigated marker in CRC is BRAF [12, 13]. BRAF mutation is a poor prognostic factor. Van Cutsem and colleagues concluded that lacking randomised tri-

als in this specific molecular subgroup, FOLFOXIRI plus bevacizumab might be a reasonable option for the first-line treatment of BRAF mutant metastatic CRC patients.

To conclude, optimal sequence of chemotherapy regimens and targeted therapy in patients with metastatic CRC is still debated. It is necessary to indentify new prognostic and predictive markers to acquire maximal benefit from every therapy line, to improve prognosis of these patients.

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Sažetak

Sustavna terapija raka debelog crijeva – pregled novih kliničkih studija

Rak debelog crijeva (CRC) najučestalija je maligna neoplazma gastrointestinalnog trakta, te je sa preko 600.000 smrti godišnje jedan od vodećih uzroka smrtnosti od zloćudnih bolesti. Ovisno o stadiju bolesti, neki od bolesnika koji su kirurški liječeni radi raka debelog crijeva s ciljem izlječenja zahtijevaju primjenu adjuvantne kemoterapije (bazirane na fluorouracilu) koja smanjuje rizik povrata bolesti i smrti u III. stadiju bolesti, no njena uloga u stadiju II još je uvijek nedovoljno jasna. Patogeneza u CRC rezultat je dvaju različitih molekulsko-genskih mehanizama: kromosomske nestabilnosti (CIN) te inaktivacije gena koji sudjeluju u popravku pogrešno spojenih fragmenata DNA (MMR). Na temelju provedenih istraživanja, u bolesnika stadija II u kojih je prisutan deficijentan MMR status ne postoji dobit od primjene adjuvantne terapije te je u toj skupini bolesnika kirurško liječenje dostatno. U bolesnika s metatastatskim CRC još uvijek nema konsenzusa o optimalnom redoslijedu kemoterapijskih protokola i ciljane biološke terapije. Receptor za epidermalni čimbenik rasta (EGFR) potvrđen je kao terapijski cilj u više humanih tumora, uključujući CRC. Odnedavno, istraživanja su pokazala da aktivirajuće mutacije na eksonima 2, 3 i 4 KRAS i NRAS gena dovode do izostanka odgovora na ciljanu terapiju usmjerenu na EGFR. BRAF je još jedan od istraživanih biljega u raku debelog crijeva, te je pokazano da je povezan sa lošijom prognozom. Potrebna su daljnja istraživanja i identifikacija novih prognostičkih i prediktivnih biljega kako bi se postigla maksimalna učinkovitost svake terapijske linije te poboljšala prognoza ovih bolesnika.

***Ključne riječi*:** rak debelog crijeva; personalizirana medicina; kemoterapija; ciljana terapija; biomarkeri.

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