Systemic treatment of colorectal cancer in Serbia: what have we done and what can offer in the new century?

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The treatment of patients with metastatic colorectal cancer (mCRC) has changed dramatically over recent years in Serbia. The more optimal use of 5-fluorouracil (5-FU) in association with leucovorin (LV), the development of new drugs such as oxaliplatin and irinotecan and of the oral fluoropyrimidines, such as capecitabine, have increased therapeutic options and to the improved outcome of patients with mCRC. Throughout our 10-years published papers in international journals, we presented development of chemotherapy for mCRC and improvement in treatment outcome in Serbia. It is shown that combination therapy with 5-FU/LV and oxaliplatin or irinotecan is more active than 5-FU/LV in first line treatment of mCRC. Sequential therapy with FOLFIRI+FOLFOX was the most efficacious combination in comparison to any other 2 drugs combinations. The combination protocols in second line were superior to mono irinotecan and equal to LV5FU2 in terms of time to progression. The oral fluoropyrimidines seems to have an activity comparable to that of i.v. 5-FU/LV. New agents acting on novel targets are under development. Angiogenesis inhibitors, epidermal growth factor inhibitors, COX-2 inhibitors and farnesyl transferase inhibitors might play a role in the future in the treatment of CRC. We will present our first experience with bevacizumab, vascular endothelial growth factor inhibitor.

Key words: metastatic colorectal cancer; chemotherapy; oxaliplatin; irinotecan; bevacizumab.

INTRODUCTION

Approximately 30% of all patients with CRC have metastatic disease at diagnosis, and 50% of early-stage patients will eventually develop metastatic or advanced disease. Chemotherapy is effective in prolonging survival and time to disease progression in patients with metastatic CRC. The paucity of active agents in the treatment of CRC in the past resulted in extensive investigation of 5-fluorouracil (5-FU) and 5-FU-based combinations. This agent has been developed in many different schedules of administration. Modulation of 5-FU anticancer effects with leucovorin (LV) became one of the standard treatment regimens for metastatic colon cancer. Additional pharmacologic strategies to enhance the effectiveness of 5-FU included combination with methotrexate, cisplatin, N-(phosphonomethyl)-L-aspartic acid (PALA), and interferon. Despite these attempts, no survival advantage was established until the advent of the newer cytotoxic drugs irinotecan and oxaliplatin. Additionally, improvement in convenience of drug administration has been achieved with the development of oral fluoropyrimidines for the treatment of metastatic CRC.

CHEMOTHERAPY OF METASTATIC CRC IN SERBIA

The treatment of patients with metastatic colorectal cancer (mCRC) has changed dramatically over recent years in Serbia. In this review, throughout our 10-years published papers in international journals, we present development of chemotherapy for mCRC and improvement in treatment outcome in Serbia.

Our first evaluation of treatment outcome for mCRC patients treated with bolus 5-FU/LV dated from 1993. Response rate was 24% and median survival was 6 months. Cisplatin monotherapy in colorectal cancer was ineffective. Cytarabine has borderline activity in colorectal cancer. In vitro studies on cell lines from human digestive cancers have demonstrated a dose and timing dependent enhancing effect of cytarabine on cisplatin antitumor activity. The aim of the pilot study published in 1996 was to investigate whether this enhancing activity can also be demonstrated in vivo. We have treated 37 patients. The overall response rate was 25% and median survival did not exceed 6 months. Considering treatment outcome with 5-FU/LV and better toxicity profile, we concluded that...
there was no place for further clinical investigation of cisplatin/73ytarabine combination in CRC.

In following years we focused our attention to chronomodulated chemotherapy. To compare the toxicity and efficacy of two schedules with high dose (HD) carboplatin in combination with standard dose 5-FU/LV, and HD carboplatin in combination with HD 5-FU/LV, administered in circadian-dependent time, two consecutive studies were performed. No significant difference in response rate was found in both studies and it was ranged from 28-30%. Median survival was 9 months.

Significant improvement in treatment outcome has been achieved introducing irinotecan and oxaliplatin in the chemotherapy of mCRC. Response rate increased up to 50% and overall survival approached 2 years. Results from clinical trials do not allow definitive conclusions about a role of chemoembolization in the treatment of CRC liver metastases. The aim of phase II study published in 2002, was to investigate toxicity and efficacy of chemoembolization for patients with unresectable CRC metastases to the liver after failure to 5-FU based chemotherapy. Secondary endpoint was clinical benefit measurement. The trial results showed that chemoembolization as performed in the study did not appear to bring any benefit. Furthermore, significant liver toxicity compromises the safety of such procedure.

New active drugs, that allowed first, second and third line therapeutic approaches, have dramatically influenced the natural history of ACRC. At present the most important decision in a patient is not "to treat or not to treat with chemotherapy", but to choose the best chemotherapy schedule and sequence in each case. As the number of active drugs for colorectal cancer increases, we continually revisit the question of how best to integrate them. Ideally we should base our decisions on the results of clinical trials but unfortunately these can only explore a limited number of options. The more pressing question seems to be whether specific drugs should be given concurrently in a combination or sequentially, one followed by the next. In our recent studies, with the aim to compare objective patient outcome between different sequential treatments (first-line plus second-line chemotherapy), overall survival was analyzed. 193 patients were assigned to receive 5-FU/LV, irinotecan and oxaliplatin in five different sequential treatment groups (first line+second line): Group A – Mayo Clinic Regimen (MCR)+LV5FU2; B – MCR+irinotecan; C- MCR+FOLFIRI; D – MCR+FOLFOX4; E – FOLFIRI+FOLFOX4. Patients were received chemotherapy until progression in first and second line, respectively. We concluded that sequential therapy with 3 active drugs (FOLFIRI+FOLFOX4) was the most efficacious combination in comparison to any 2 drugs combinations applied in our studies. Regimen that used combination vs. monotherapy as the first line treatment was associated with better OS. The combination protocols in second line were superior to mono irinotecan and equal to LV5FU2 in terms of time to progression.

"NEW DRUGS AVENUE"*

New agents acting on novel targets are under development. Angiogenesis inhibitors, epidermal growth factor inhibitors, COX-2 inhibitors and farnesyl transferase inhibitors might play a role in the future in the treatment of CRC. Randomized trials will determine the impact of these newer agents on survival and quality of life of patients with mCRC.

Angiogenesis inhibitors

Angiogenesis plays an important role in the growth and metastasis of many cancers. The angiogenic drugs can be divided into several categories, including growth factor inhibitors, endothelial cell signal transduction inhibitors, inhibitors of endothelial cell proliferation, inhibitors of matrix metalloproteinases, and inhibitors of endothelial cell survival. CRC has been shown to express elevated levels of the angiogenic factor VEGF (vascular endothelial growth factor). Expression of VEGF in primary tumor tissue is correlated with poor outcome in colon cancer, and plasma levels of VEGF have been correlated with stage, progression of disease, and response to chemotherapy. Some antibodies targeting VEGF have been tested. Among these, bevacizumab (BV), a recombinant humanized monoclonal antibody targeting VEGF, is in further development in CRC. Angiogenesis inhibitors are presented in Table 1.

Epidermal Growth Factor Inhibitors

Tumor growth depends on the activation of cell membrane receptors that control the intracellular signal transduction pathways for proliferation, adhesion, and motility. Epidermal growth factor receptor (EGFR) is a glycoprotein receptor that is expressed on normal epithelium and is sometimes overexpressed in a variety of epithelial tumors, including colorectal carcinoma. The over-expression of EGFR correlates with poor response to treatment, disease progression, and poor survival. Inhibition of EGFR signaling with an EGFR antibody is accompanied by a reduction in the level of DNA-dependent protein kinase and its activity in the nucleus, occasionally resulting in tumor regression. Preclinical data showed that anti-EGF therapies might inhibit tumor growth and proliferation, inducing tumor cell apoptosis. In addition, EGFR blockade enhances the effectiveness of current cytotoxic agents. Cetuximab (C225) and ABX-EGF, among other antibodies targeting EGFR, have been tested in metastatic CRC.

The ABX-EGF is a human IgG2 monoclonal anti-body specific to human EGFR. The administration of ABX-EGF without concomitant chemotherapy was shown to be active. Ongoing phase II trials are testing ABX-EGF in metastatic CRC, either alone or in combination with CPT-11, LV, and 5-FU.

Cetuximab (C225) is a chimeric human-murine IgG1 monoclonal antibody that binds selectively to EGFR. C225 induces apoptosis in different cancer cell lines and partially suppresses angiogenesis by inhibiting the pro-
### Table 1

<table>
<thead>
<tr>
<th>Drug</th>
<th>Company</th>
<th>Target</th>
<th>Clinical development</th>
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<tr>
<td><strong>Monoclonal antibodies targeting VEGF-A</strong></td>
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<td>Bevacizumab (Avastin)</td>
<td>Genentech</td>
<td>VEGF-A</td>
<td>Phase I, II, III</td>
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<td>VEGF-Trap</td>
<td>Regeneron</td>
<td>VEGF-A</td>
<td>Phase I</td>
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<tr>
<td>IMC-I-1</td>
<td>Imclone</td>
<td>VEGFR2</td>
<td>Phase I</td>
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<td><strong>Receptor tyrosine kinase inhibitors</strong></td>
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<tr>
<td>SU5416</td>
<td>Sugen/Pharmacia</td>
<td>VEGFR-2</td>
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<tr>
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<td>VEGFR-2, vFGFR, PDDGFR</td>
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<td>VEGFR-2, PDGFR, c-Kit, Flt-3</td>
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<td>VEGFR-1, VEGFR-2</td>
<td>Phase I</td>
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<td>ZD6474</td>
<td>Astra Zeneca</td>
<td>VEGFR-2, EGFR</td>
<td>Phase I, II</td>
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<tr>
<td>CP-547,632</td>
<td>Pfizer</td>
<td>VEGFR-2, EGFR, PDGFR</td>
<td>Phase I</td>
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<td><strong>Inhibitors of endothelial cell proliferation</strong></td>
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<td>ABT-510</td>
<td>Abbott</td>
<td>Endothelial CD-36</td>
<td>Phase I, II</td>
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<td>Entremed</td>
<td>Various</td>
<td>Phase I</td>
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<tr>
<td>Endostatin</td>
<td>Entremed</td>
<td>Variopos</td>
<td>Phase I</td>
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<tr>
<td>TNP-470</td>
<td>TAP</td>
<td>Methionine aminopeptidase,cyclin dependent kinase 2</td>
<td>Phase I</td>
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<tr>
<td>Thalidomide</td>
<td>Grunenthal</td>
<td>Recuction of TNF-a production</td>
<td>Phase I, II, III</td>
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<td><strong>Inhibitors of integrin activity</strong></td>
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<td>Medimmune</td>
<td>Integrin aVaβ3</td>
<td>Phase I, II</td>
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<td>Medimmune</td>
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<td>Merck</td>
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<td>Phase I</td>
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<td><strong>Vascular targeting agents</strong></td>
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<td>Combretastatin A4</td>
<td>Oxigene</td>
<td>Endothelial tubulin</td>
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<tr>
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<tr>
<td>DMXAA</td>
<td>/</td>
<td>Induction of TNF-a</td>
<td>Phase I</td>
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Rosenberg et al. C225 in combination with IFL on the Saltz schedule as first-line treatment for EGFR-positive metastatic CRC resulted in an RR of 44%. No survival data have been reported. Surprisingly, when intensity of EGFR was tested, no correlation between response and the level (1+ to 3+) of EGFR expression was observed. Phase III trials incorporating C225 to standard chemotherapy drugs in CRC patients are ongoing or planned.

EGFR tyrosine kinase inhibitors reduce EGFR phosphorylation, leading to cell cycle arrest and apoptosis of cells expressing EGFR. ZD1839 (Iressa) is a potent oral anilinoquinazoline inhibitor of EGFR tyrosine kinase that blocks EGF-induced growth of tumor cells in culture. The drug has been tested in patients with solid tumors known to express or overexpress EGFR. The most common adverse events were diarrhea and acne-like skin rash. Anti-
tumor activity was most evident among non-small-cell lung cancer patients.

Preclinical studies have shown an enhanced growth inhibitory effect of ZD1839 combined with several chemotherapeutic agents that are active in CRC including raltitrexed, CPT-11, and oxaliplatin.

OSI-774 (Tarceva) is another oral EGFR inhibitor that has been investigated in CRC. OSI-774 at 150 mg given orally daily in 16 metastatic CRC patients previously treated with Irinotecan and 5-FU given either in combination or sequentially has been reported in abstract form27. The preliminary efficacy results were disappointing since none of the 13 evaluable patients had a radiologic response. A number of other strategies targeting the EGFR pathway in CRC are being developed28.

**COX-2 Inhibitors**

Cyclooxygenase (COX) is an enzyme that catalyses the synthesis of prostaglandins. COX-1 and COX-2 are the two isoforms, inhibited by nonsteroidal anti-inflammatory drugs (NSAIDs)29. COX-1 is constitutively expressed in a number of cell types, whereas COX-2 is an inducible enzyme whose expression and activity are up-regulated in response to a variety of cytokines, growth factors, and tumor promoters29,30. Cyclooxygenase 2 (COX-2) is overexpressed in 71% to 85% of CRCs31,32. Two potent COX-2 inhibitors, celecoxib and rofecoxib, are undergoing intense testing in different types of cancers including CRC.

Celecoxib has been further studied in patients with CRC. Blanke et al33 recently reported a phase II trial combining celecoxib with IFN in patients with untreated advanced CRC. A disappointing 28% partial RR in a group of 18 evaluable patients was observed. Lin et al34 reported a retrospective analysis of 67 patients taking either capecitabine and celecoxib or capcitabine alone as first- or second-line treatment of CRC. In this small retrospective study, celecoxib appeared to attenuate capcitabine-induced hand-foot syndrome, and the efficacy results suggested an improved TTP. Randomized trials in CRC are planned or underway to investigate the addition of celecoxib to either XELIRI or FOLFIRI regimens.

**Farnesyltransferase Inhibitors**

Farnesyltransferase is an enzyme that transfers farnesyl isoprenoid to proteins associated with cell membranes. Farnesyltransferase inhibitors (FTIs), which were developed as a strategy to attack Ras-dependent cancers, can inhibit malignant cell growth and tumor formation. Secretion of VEGF, synthesized by many tumors, can be partially suppressed by FTIs. As a single-agent therapy, FTIs may be efficacious against premalignant lesions and may have the capability to block the growth of micrometastasis after primary site therapy. In addition, FTIs can potentially function as radiosensitizers and chemotherapy-enhancing agents35. A randomized trial with the FTI R115777 (Zarnestra) compared to placebo in 368 patients with previously treated metastatic CRC showed disappointing results36. The overall survival was not statistically different (5.7 months for the FTI arm and 6.1 months for the placebo arm). The signal transduction cascades are complex, and the relative importance of Ras is unclear.

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* Some data in the "New drug avenue" chapter has been adapted from: Coutinho AK. Metastatic colorectal cancer: systemic treatment in the new millennium. Cancer Control 2003; 10(3):224-238.