Chemotherapy of advanced colorectal cancer: when do we have to stop?

Davorin Radosavljević
Institute for Oncology and Radiology of Serbia, Belgrade

Introduction

Colorectal cancer is one of the leading causes of death from cancer worldwide, both in men and women. The incidence in Serbia is around 40 ASR-W (age-standardised rate on world population) in male and around 20 in women. Numerically, it accounts more than 4000 deaths annually from colorectal cancer, about 2500 plus 1600 in men and women, respectively, according to data from 2009. Surgery is the therapy of choice, both in colon and rectal cancer, reserved for early stages of disease, i.e. for stages I – III, without detectable metastases. Inoperable disease recurrence and metastatic disease are the broad field for systemic treatment – cytotoxic chemotherapy is used most often, together with biological, targeted therapy, and more recently, with immunological therapy.

Surgery alone may cure one half of resected patients; adjuvant chemotherapy adds to the cure rate, but up to 30% of resected patients will develop metastatic disease. Metastatic disease has been seen in 30% patients at presentation, having metastases dominantly in liver. Surgical treatment of locally advanced rectal cancer is of greater value if it follows preoperative radiation or radio-chemotherapy. In oligometastatic disease surgery may also be valuable, but usually after combined, radio-chemotherapy approach.

Metastatic colorectal cancer should be treated with systemic therapy, where backbone is cytotoxic combination therapy, based on fluoropyrimidines. Two cytotoxic drugs of the most proven and equal value are platinum derivative oxaliplatin and topo I inhibitor irinotecan. Given with fluoro-pyrimidines (5FU or capecitabine) and leukovorine, they form the most popular and most useful regimens FOLFOX and FOLFIRI.

Advances in tumour biology resulted in enrichment of our armamentarium for systemic treatment of colorectal cancer: monoclonal antibodies against vascular endothelial growth factor receptor (VEGFR) and against epithelial growth factor receptor (EGFR), bevacizumab/afibreccept and cetuximab/panitumumab, respectively, when added to cytotoxic backbones, may add to response, and translate this biological effect into better progression-free survival (PFS) and overall survival (OS). Biomarker for patient selection for EGFR inhibition is RAS antigen, giving that only patients having wild-type of RAS antigen may benefit from those drugs (cetuximab and panitumumab). Contrary, patients with mutations in RAS antigen would have harmful effects after receiving those drugs. So far there is no predictive biomarker for VEGF inhibition. BRAF antigen mutation is associated with worse prognosis for these patients.

Key words: advanced colorectal cancer, palliative chemotherapy, communication, adverse events, quality of life
Chemotherapy backbones with bevacizumab is typically used in first or less frequently in second line of systemic treatment, afibertec® has been registered with FOLFIRI for second-line treatment. EGFR inhibitors are active equally in all chemotherapy lines, and may be applied as mono-therapy or in combination with chemo backbones.

In third line of treatment, one of previously used regimens may be repeated, if patient has not progressed on it, or regorafenib12, multi-targeted TKI (tyrosine kinase inhibitor), or the most recent drug here, TAS-10215 which consists of the cytoxin trifluridine and the thymidine phosphorylase inhibitor tipiracil may be given.

It is not complicated to start with chemotherapy, regimens should be chosen according to above-mentioned characteristics. The postulate of treatment continuum, meaning that patient should receive the whole spectrum of available active drugs against metastatic colorectal cancer, is based on better results of treatment if patient has been treated in that manner. That is how the overall survival was significantly improved over the last 10-15 years, starting from 10-14 months with fluoropyrimidines only, through 18-20 months with backbone chemo-doubllets (with oxaliplatin or irinotecan), 24-26 months with antibodies added to chemo-doubllet (bevacizumab, cetuxumab/panitumumab) to 30+ months with molecular (RAS testing), more precise patient selection16,17 or use of more aggressive regimens (chemo-triplets +/- biological agents)18. This impressive improvement in overall survival is among the best in clinical oncology of solid tumours.

Various treatment strategies have been developed aimed at achieving the best sequence of applied chemotherapy regimens: maintenance phase, after achieving the best response, treatment holiday to prevent treatment toxicity, pre-planned pauses in chemotherapy course, re-challenge with the previously effective regimen and some others19,20,21,22,23,24. The best sequence means that the right regimen will be applied at the right moment, taking into account a lot of patient and tumour features: performance status, comorbidities, age, patient preferences, stage of disease, disease symptoms, number and distribution of metastases, aggressive or indolent course of disease.

Typically, there are several situations where patients or doctors decide to stop the treatment. On the doctors’ side, recommendations say: discontinue therapy if obvious disease progression occurred, or toxicity of treatment is unacceptable. Patients may decide to stop the treatment if they feel that such treatment is not beneficial for them, or also without any explicit explanation. Usually, such decision is not hard to make, however, sometimes there is much hesitation and indecisiveness in attempt to prolong specific oncological treatment and maintain patient belief in favourable treatment outcome.

Generally speaking, it is much easier to change one treatment for another than to tell the patient that there are no more therapies for him/her, and that palliative and supportive measures will be the only therapy approach for them.

Let us consider firstly the doctor’s side: who are the patients which are not the right candidates for starting chemotherapy? Predominately these are the patients with poor performance status, ECOG 3 or 4, due to disease burden, and patients with significant comorbidities and health conditions that do not permit chemotherapy administration.

When are the patients not the candidates for continuation of systemic treatment? Above all it is unacceptable toxicity of chemotherapy; usually it means CTC grades 3 or 4, especially if experienced toxicity is non-haematological. These may be acute, like allergic reactions to a drug, or subacute, like skin toxicity to cetuxumab/panitumumab or hand-foot syndrome due to use of capcetabine; it also may be cumulative, like oxaliplatin-induced peripheral neuropathy, which typically occurs after 4-6 months of oxaliplatin-based treatment. Depending on the grade of adverse event(s) and patients’ self-reported experiences, doctors should decide about the discontinuation or modification of treatment. Naturally, the discontinuation may also be temporary, especially after grade 3 adverse events, and after recovery the patient may continue treatment in reduced doses. There is established set of recommendations for dose reduction depending on severity of adverse events. We are also witness to raised knowledge about treatment of these adverse events: today we have recommendations how to treat mucositis, diarrhoea, hand-foot syndrome, aceniform rash, peripheral neuropathy. By applying these auxiliary treatments, we could shorten period of recovery, and allow treatment continuation, or become assured that treatment should definitely be stopped. Situations described above are very frequent and doctors should follow the recommendations.

Patients with potentially resectable liver metastases who receive perioperative conversion therapy must be re-evaluated regularly in order to prevent the overtreatment of resectable patients as the maximal response is expected to be achieved after 12-16 weeks of therapy in most patients12,25. The regimens applied in this indication are usually chemo-doublet with either EGFR or VEGF inhibitor, or even triplet. Liver toxicity of those agents is naturally of particular interest, in order to avoid difficulties in subsequent surgery; numerous reports have demonstrated an association between irinotecan and steatohepatitis as well as between oxaliplatin and sinusoidal dilation. The amount of chemotherapy can be optimized so that the patient derives the most potential benefit while suffering the least possible toxicity. Finally, great caution should be used in patients at risk for nonalcoholic steatohepatitis (NASH). Specifically, careful thought should be given to hepatectomy in obese, diabetic, and alcoholic patients who received preoperative chemotherapy26.

Chemotherapy for metastatic epithelial tumours, including colorectal cancer, rarely, if ever, cures patients. Palliative chemotherapy accounts for most of the work of
everyday oncology, but some of its achievements, especially in prolonging survival must be respected: more than six months of added survival could be as important as an increased rate of cure.

Particularly sensitive situation is when doctor should decide about termination of specific, systemic treatment. The most frequent reason is disease progression, but after confirmation of this disease state, doctor should talk with patient and explain that his/her disease could not be controlled anymore with chemotherapy. The truth is that we do not treat the tumor but the patient, and that supportive measures will also help, but the majority of patients invests their belief solely in the strength of systemic treatment to cure their cancer disregarding the value of supportive treatment. That sensitive aspect is of great importance, especially for further communication between patient and doctor, and for patient’s active role in measures of palliative medicine. Moving on to third or fourth-line chemotherapy may be easier than discussing hospice care with patients, as the patient and family may be less upset, and they may even prefer not to discuss the issue with the oncologist.25

There are a few facts that make the use of chemotherapy in end-of-life phase more complicated than it was in the past: on the one hand, the chemotherapy is increasingly available and better tolerated and on the other hand, patients with cancer are generally willing to undergo aggressive treatment with major adverse events for very small chance of benefit, which is generally different from what their doctors would choose. Palliative chemotherapy is increasingly given near death: in the two weeks before death, more than 20% of patients receiving Medicare who had metastatic disease started a new chemotherapy regimen.26 In Italy, 23% of patients with incurable cancer received chemotherapy within 30 days of death.27

The largest study of comparison between patients who received hospice care and no chemotherapy versus those who did not receive hospice care but had chemotherapy showed that survival was marginally longer for hospice care metastatic colon cancer patients, but there was no difference in breast or prostate cancer patients survival.28 Thus, it seems reasonable not to recommend chemotherapy to the patients who are eligible for hospice: chemotherapy in these patients produces adverse events, precipitates hospitalizations and emergency department visits, may require additional supportive care with colony-stimulating factors making detrimental effects on patient overall quality of life. The median length of stay in hospice has declined from 29 days in 1995 to 26 days in 2005, with one-third being admitted to hospice in the last weeks of life and for 10% of patients this was done during the last day of life (http://www.nphco.org).

In conclusion, the need for better communication between metastatic colorectal patient and doctor should be stressed, giving both sides the opportunity for discussing detailed treatment plan and especially the transition from chemotherapy to palliative measures.

SUMMARY

HEMOTERAPIJA UZNAPREDOVALOG KOLOREKTALNOG KARCINOMA: KADA SE MORAMO ZAUSTAVITI?


Ključne reči: uznapreovali kolorkeletalni karcinom, palijativna hemoterapija, komunikacija, neljepi efekti, kvalitet života

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List of abbreviations:
ASR-W - age-standardised rate on world population
SFU – five fluorouracil
FOLFOX – 5FU-leucovorin-oxaliplatin combination regimen
FOLFIRI – 5FU-leucovorin-irinotecan combination regimen
VEGF – vascular endothelial growth factor receptor
EGFR – epithelial growth factor receptor
PFS – progression-free survival
OS – overall survival
RAS – R-Karsten Sarcoma Virus
BRAF – V-RAF murine sarcoma viral oncogene homolog B
TKI – tyrosine kinase inhibitor
ECOG – Eastern Cooperative Oncology Group
CTC – Common Toxicity Criteria