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Impact of new drugs and individualization of treatment approaches in metastatic colorectal cancer

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Some important notices concerning colorectal cancer

Colorectal cancer is one of the most common human neoplasia. If diagnosed in its early stage this malignancy is curable with minimal morbidity and mortality. Unfortunately a significant proportion of patients present in advanced stage of the disease being either locally unresectable or metastatic. The colorectum can be divided in four different regions: ascending colon, transversal colon, descendent and sigmoid colon and the rectum.

From all of these regions metastases can occur either by lymphatic extension or by hematogenous spread or by implantation. In colon carcinoma the cancer cells metastasize through lymphatics along the major arteries, and the metastases reside in lymph nodes of the mesocolon. In rectal cancer there is a predictable course of lymphatic disease that reside at first in the perirectal lymph nodes at the level of primary tumor and afterwards involve the chain that accompany the superior hemorrhoidal veins. Discontinuous or skip metastases are less frequent.

Hematogenous spread occurs via the portal vein system. The first primary site of the hematogenous metastases is usually the liver. Skip metastases to the lungs without metastases in the liver are infrequent in colon cancer and proximal rectal cancer. Due to dual venous drainage, cancer of the distal rectum may spread either to the liver or directly to the lungs, bones, or central nervous system. The liver is the main site of the hematogenous metastatic disease and in about 40% of the autopsy studies liver is the only site involved.

Implantation metastases have been reported with tumor cells shed intraluminally but more often intraperitoneally from tumors involving and penetrating to the serosa. Distal rectal cancer rarely is the cause of peritoneal carcinosis.

Colorectal cancer with metastases in regional lymph nodes may be a curable disease when treated with surgery combined by adjuvant chemotherapy.

Colorectal cancer with a more disseminated abdominal lymphogenous spread or with intraperitoneal dissemination or which has metastatised hematogenicaly has not been considered as a curable disease. Nevertheless, patients with a limited number of liver metastases can be cured with surgery preceded or not by neoadjuvant chemotherapy.

The principal aim of chemotherapy in metastatic colorectal cancer

The principal aim of drug development in metastatic colorectal cancer is targeted to provide symptom relief, to increase the time to progression and to provide a prolonged survival, usually without intent of cure. In managing metastatic colorectal cancer patients we must individually decide whether our main aim is achievement of a response or disease control in general. Response is obviously the main target for patients that are considered for liver resection, and the advent of new drugs along with development of surgical techniques has increased the percentage of patients considered for liver surgery with a curative intent.

5-Fluorouracil: the old and classic drug

Until recently the only effective drug for colorectal cancer was 5-Fluorouracil (5-FU). Several trials have been performed in order to modulate its antitumor activity, since response rates with the single drug were rather low, although a limited percentage of long lasting disease control and long survivals were reported. The only apparently active potentiator of 5-FU activity remained Leucovorin. This was a small but important advance and the leucovorin-5-FU regimen in different dosages remained a standard approach to metastatic colorectal cancer. A further improvement was the introduction of continuous infusional 5-FU such as in so-called deGramont regimen; this regimen appeared to increase activity in comparison to bolus 5-FU administration and decreased toxicities. In fact the different 5-FU regimens were usually well tolerated although the main inconvenience was the infrequent but spectacular occurrence of non-hematological grade IV toxicities associated with bone marrow aplasia. This complication, at first poorly explained, proved to be the consequence of systemic diphosphopyridindexidrogenase (DPD) deficiency. Once resistance to 5-FU developed the only drug that remained for second line options was mitomycin C, a poorly effective and relatively toxic cytotoxic drug.

Changing aspect of colorectal cancer in the last decade

In the last decade the situation of metastatic colorectal cancer has dramatically changed with the advent of four new cytotoxic drugs, two peroral fluoropyrimidines (capecitabine and tegafur-uracil), oxaliplatin, and irinotecan. The addition of these new active drugs in addition to 5-FU gave additional options for combination chemotherapy and sequential treatments that resulted with a significant prolongation of disease control and survival in patients with metastatic colorectal cancer. Nevertheless even in a subcategory of patients treated with these new drugs the best response remained progressive disease. The game was therefore moved to the field of pharmacogenomics and pharmacogenetics. The problem became increasingly acute with the advent of additional two new drugs belonging to the so-called category of biologicals: cetuximab (Erbitux), a monoclonal antibody to the epidermal growth factor receptor (EGFR) and bevacizumab (Avastin), an antibody to VEGF; both drugs added an improvement to the overall efficacy of treatment of metastatic colorectal cancer but added a drastic increase in treatment cost. A question was therefore raised about defining the subcategory of patients who would benefit most from their use. So, the question of predictive markers of response to new drugs, both cytotoxics and biologicals, was raised and investigations were started to find best markers for predicting drug activity, drug toxicity, and drug resistance.

Capecitabine: the 5-FU prodrug

Capecitabine is a drug from the fluoropyrimidine family of compounds, belonging to the same group as 5-FU. In contrast to 5-FU, capecitabine does not have as native molecule cytotoxic properties. It shares the toxicity profile common to all fluoropyrimidines irrespective of their cytotoxic potential. This toxicity includes low-grade diarrhea, usually low-grade but occasionally troublesome palmo-plantar erythrodysesthesia (so-called hand and foot syndrome) and several other events with low clinical significance. Due to its prolonged administration in clinical practice, during which patients are for usually 14 days exposed to fluoropyrimidines it has additional side effects not usually observed with 5-FU which is usually administered for not more than 5 days successively. This includes interference with vitamin K metabolism and interference with vitamin K dependent factors of the prothrombin complex, and also hemolysis caused by alterations in red blood cell membrane (1). Capecitabine is administered peroraly. Its active principle is in fact 5-FU which is generated from capecitabine by thymidine phosphorylase (TP); this enzyme is present in small quantities in the intestinal wall, is present in insignificant quantities in normal cells, but may be hyperexpresed in cells of breast and colorectal cancers. Thus it is in fact a prodrug, with high bioavailability. When passing through the intestinal wall, a small quantity of 5-FU is generated, usually not enough to cause 5-FU related cytotoxic effects. In the normal cells and cells poor in Thymidine phosphorylase content the prodrug is not converted to its active principle. In cancer cells rich in thymidine phosphorylase the prodrug is metabolized to 5-FU which exerts its action only intracelulary. Capecitabine has an advantage over 5-FU in the fact that its toxicities are less DPD dependent. The result could be that it should be a drug of choice replacing 5-FU in patients with systemic DPD deficiency, since most of toxicities related to DPD deficiency would thus be avoided. However as capecitabine has to be converted to 5-FU in order to be active on cancer cells, and needs hyperexpresion of TP, cancers whose cells are poor in TP have limited possibility of intracellular 5-FU generation and capecitabine may prove poorly effective in such cases.

Oxaliplatin: a DACH platinum effective for colorectal cancer

Oxaliplatin belongs to the third generation of organoplatinum compounds used for treatment of human malignant disease. It belongs to the group of diaminocyclohexanoplatinums (DACH platinums) and is characterized by linkage of the platinum to the DACH ring. DACH ring confers to the cytotoxic drug several new properties. It is hydrophobic and thus the compound once infused into circulation achieves immediately a large distribution volume permitting wide contact with cancers cells. It is also lipophylic and thus passes readily through the cell membrane. Once fixed to DNA in the nucleus of cancer cells, the DACH ring presents a steric hindance to the action of DNA repair mechanisms. The drug makes part of different FolFOX regimens the most widely used being the FolFOX 4 regimen. It has a dose limiting toxicity, the cumulative neurotoxicity which asks for treatment arrest and which usually occurs after a cumulative dose of the drug of 800 mg/m2 has been reached. The intracellular fate of the drug is determined by enzymes of the gluthatione S-transferase superfamily and fast degradation of the drug may interact with its binding to DNA, resulting in poor activity of the drug.

CPT-11: a camptothecine active in colorectal cancer

The third new drug which proved to be a useful addition to the arsenal of drugs active for colorectal cancer is CPT-11 (or campto or irinothecan). It has no cross resistance to either 5-FU or Eloxatin. CPT-11 is in fact a pro drug and its active principle is designated as SN-38. SN-38 is responsible both for the anticancer activity and late toxicities of Irinothecan. SN-38 is the main intracellular metabolite of Irinothecan and its increased level in the plasma due either to individual variabilites or to deficient detoxation is associated to excessive toxicity pattern. SN-38 is inactivated and excreted through the process of glucuroconjugation. Drugs or metabolites that are also excreted by same mechanism tend to prolong the SN-38 half life in the plasma. So, for instance, patients with increased bilirubin levels (bilirubin is also excreted by glucuroconjugation) should not be treated with CPT-11 and the critical bilirubin level has been fixed at 25-50 mmol/L. The native CPT-11 molecule is responsible for early side effects such as early cholinergic diarrhea, as CPT-11 is a cholinergic stimulator; these side effects if excessive can be prevented by anticholinergic such as atropine. SN-38 is responsive for late side effects that are more troublesome and which include a wider range of events including secretory diarrhea and bone marrow toxicity. Degradation of SN-38 is dependent upon activity of different UDP-glucuronosyl transferases and their genetic polymorphisms may be involved both in activity and toxicity of the drug.

Molecular basis for rational use of antitumor drugs in metastatic colorectal cancer

We now know that the new drugs such as oxaliplatin and CPT-11 are more active in colorectal cancer than 5-FU in single drug setting either in relation to response rate and possibly survival benefit. But we also know that there are patients treated with 5-FU that achieve a long survival, in excess of 2 years. We also know that there are patients treated with either oxaliplatin or CPT-11 who do not achieve disease control with these two drugs and whose best response is progressive disease.

So, the question has arisen whether we can or can not predict efficacy of any of the three drugs by any means in order to individualize chemotherapy in a given patient, in order to achieve the optimal result.

Pharamacogenomics and pharmagonetics are starting to give us a clue concerning this particular topic.

Molecular basis for rational use of fluoropyrimidines

It appears that both tumor dihydropyrimidin dehidrogenase (DPD) and thymidine synthetase (TS) are good predictors for 5-FU activity. A significant increase in TS expression score was observed in 5-FU sensitive colorectal cancers compared to 5-FU resistant ones. Although the role of DPD expression in cancer 5-FU sensitivity remained somewhat controversial it now appears that patients with low DPD expression have longer disease free interval or longer disease control with 5-FU than patients with high DPD expression (2). DPD expression in normal cells is a significant factor determining 5-FU toxicities, patients with DPD deficiency in normal cells tending to exhibit life threatening toxicities when treated with 5-FU (3). However the DPD contend in normal and cancer cells in the same individual need not to be identical and there appears to be individuals with adequate DPD content in normal cells and low expression of DPD in cancer cells. By retrograde analysis it has been shown that patients with low tumor DPD and high tumor TS treated with 5-FU only can achieve survival of over 24 months.

The situation might not be identical with peroral fluoropyrimidines. Tegafur-Uracil shares apparently the same pattern with 5-FU concerning cancer cell levels of DPD and TS. Capecitabine could be presumed to be inferior to 5-FU in patients with low TP levels because TP is necessary for conversion of this pro drug into 5-FU that is its active principle. On the other hand, the S-1 compound (combination of tegafur-CDHP and potassium oxonate) is more active than 5-FU in cancers with a high DPD activity due the fact that CDHP is a potent inhibitor of DPD (4).

Thus it appears that, based on the tumor level of DPD, TP, and TS, we can make the choice between different fluoropyrimidines best suitable for a particular patient.

Molecular basis for rational use of oxaliplatin

Members of the glutathione S-transferase (GST) superfamily are important in cellular defense mechanisms. These enzymes attach reduced glutathione to electrophilic groups in a wide variety of toxic compounds, including chemotherapeutic agents. Certain polymorphisms in GSTs are associated with changes in enzyme activity, sensitivity to chemotherapy, and overall patients' survival (5). There are three subclasses of GSTs, designated as P-1, T-1, and M-1. The GST P-1 has been shown to be associated with slower or faster inactivation of oxaliplatin in cancer cells and thus directly related to its activity concerning disease control. There are three variants of GST P-1 differing in only one amino acid residue in the position 105. These three variants determine three phenotypes: the homozygous isoleucine/isoleucine phenotype, the homozygous valine/valine phenotype, and the heterozygous isoleucine/valine phenotype. This genetic polymorphism has been found to have a profound influence on disease control and survival in patients treated with oxaliplatin.

In a retrospective study conducted on patients progressing on 5-FU and subsequently treated with oxaliplatin the impact of genetic polymorphism of GST P-1 on the survival was analyzed. Patients homozygous for the isoleucine/isoleucine phenotype had a median survival of 7.9 months, while those homozygous of the valine/valine phenotype had a median survival of 24.9 months. The heterozygous patients, i.e. those of the isoleucine/valine phenotype had a median survival which was intermediary i.e. 13.3 months.

Thus determination of the GST P-1 might have a crucial impact on choice of patients likely to respond to oxaliplatin and to exclude from this treatment the ones that should have no benefit from it.

Molecular basis for rationale use of CPT-11

Although the results are still preliminary there appears to be a relationship between UDP-glucuronosyltransferase (UGT) and activity and toxicity of CPT-11 (6).

The impact of the polymorphism of two members of this family, UGT1-A7 and UGT1-A9 was analyzed in relation to activity and toxicity. Low enzyme activity of the UGT1-A7 genotypes (UGT1-A7 2/2 and UGT1-A7 3/3) was associated with antitumor response and lack of severe gastrointestinal toxicity. In the UGT1-A9 family the UGT1-A9-118 genotype was significantly associated with reduced toxicity and increased response. UGT1-A1 and UGT1-A6 do not appear any impact on activity. However patients who are either homozygous or heterozygous for UGT1-A1- 28 appear to have a significant risk of toxicity by CPT-11.

It appears that determination of UGT1-A7 and UGT1-A9 polymorphism might predict at least toxicity to CPT-11 and perhaps enable us to select patients likely to have a good probability of response to CPT-11 without significant toxicities related to SN-38 (7).

The good and bad prognosis patient with metastatic colorectal cancer

It is perhaps too early to speculate about the prognostic significance of molecular markers in predicting outcome of patients with metastatic colorectal cancer.

Perhaps, it is not.

We could conceive that a patient whose tumor has a high TS content, low DPD content, who is homozygous for the valine/valine phenotype of the GST P-1 and with low enzyme activity of the UGT1-A7 should be a good prognosis patient: its median survival on 5-FU could be over 24 months, on oxaliplatin again over 24 months and this patient would have a good chance of having a therapeutic response to CPT-11 without excessive toxicity.

On the other hand a patient whose tumor has a low TS content and a high DPD content, who is homozygous for the isoleucine/isoleucine phenotype would have a poor chance of response to 5-FU and shall be probably resistant to oxaliplatin. If this patient is in addition homozygous to UGT1-A1- 28 he would have a significant risk for severe toxicity on CPT-11. This patient would be a classic poor prognosis patient even with the most recent drugs.

The biologicals in treatment of colorectal cancer

At the moment there appears to be at least three different targets that could be attacked by available biologicals: the intracellular part of the EGFR, prone to attack by small molecule tyrosine kinase inhibitors; the extracellular part of EGFR that can be blocked by monoclonal antibodies; and the tumor released vascular endothelial growth factor (VEGF) that is critical for the development of specific tumor blood vessels.

Two small molecular weight molecules with selective tyrosine kinase inhibition properties directed to EGFR are available on the market: ZD1839 (Iressa) and OSI-774 (Tarceva). These drugs are orally administered and are reported to induce tumor stabilization in previously treated patients with metastatic colorectal cancer. Addition of these two drugs either to Oxaliplatin or CPT-11 does not appear to increase the specific toxicity of these cytotoxic agents. Unfortunately neither it does add to their activity (8).

A recent advance is represented by bevacizumab (Avastin), a monoclonal antibody against VEGF that has own promising pre clinical and clinical activity in metastatic colorectal cancer, especially in combination with cytotoxic drugs. Addition of bevacizumab to the CPT-11 + 5-FU/LV regimen in previously untreated patients with metastatic colorectal cancer has prolonged survival from 15.6 months (patients treated with CPT-11 + 5-FU/LV only) to 20.3 months. The response rate was also positively affected as well as duration of response in responders, and the drug found its way to neoadjuvant combinations for borderline respectable metastatic liver disease.

Another recent advance is represented by cetuximab (Erbitux), a monoclonal antibody that binds to the extracellular part of EGFR, thus blocking its activity. In combination with CPT-11 a proportion of heavily pretreated patients displayed response or stabilization thus adding a third or fourth treatment line in colorectal cancer. Its activity in first line treatment is under investigation but the results in a defined subpopulation of patients are very promising. Its activity is highly dependent on several molecular markers.

Markers predicting activity of biological agents

At the moment there are no validated biomarkers to predict the efficacy of Bevacizumab in colorectal cancer. In breast cancer there are data that point to the possibility that VEGF genetic variations may be linked to improved survival of patients with breast cancer treated with Bevacizumab and chemotherapy. Patients with genetic variations VEGF-2578 AA and VEGF-1154 A showed better overall survival than those with alternative genotypes (9). Unfortunately no such relation has been proved for colorectal cancer.

Circulating endothelial cell monitoring in metastatic colorectal cancer patients treated with first line bevacizumab based combinations has been studied in at least one randomized phase II study in order to establish a possible relation to response. The results indicate that the base line and end-of-cycle 1 circulating endothelial cell levels may predict tumor control in patients with metastatic colorectal cancer starting Bevacizumab- including chemotherapy (10). However, results require further validation and at the moment circulating endothelial cell level should not be used as a predicting factor in clinical practice.

The predictors of activity for cetuximab are far better known. Their use in clinical practice is mandatory. The EGFR membrane density has been shown to be irrelevant to decision whether to apply Cetuximab or not. Moreover even tumors that appear to be EGFR negative with available techniques have the potential to respond to Cetuximab in both first line and salvage setting. The interpretation of this finding may be that binding of the drug to even minimal amount of EGFR, undetectable with available techniques, may have impact on cancer cell survival.

The situation with K-Ras and BRAF markers are clearer. Both molecular factors are involved more or less directly in the EGF signaling pathway. In the presence of wild type K-Ras and BRAF blocking EGFR directly interferes with the pathway. If either of them is mutated the signaling pathway bypasses the usual sequence and blockade of EGFR is ineffective, and in consequence, the effect of cetuximab is wiped out.

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OP 2

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Chemoradiation with capecitabine and mitomycin c in preoperative treatment of locally advanced rectal cancer

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Background

In recent years, several reports of preoperative chemoradiation in respectable locally advanced rectal cancer have been published. These reports showed an interesting rate of negative pathologic specimens (9%-29%), an increased proportion of sphincter-saving surgical procedures (up to 66- 85% of patients) and low incidence of acute toxicity (2- 19%) (1,2). The rationale for combining cytotoxic agents and radiotherapy is based on ability of some drugs to act as enhancer of radiotherapy (2).

The purpose of this study was to evaluate toxicity and treatment results of preoperative capecitabine plus mitomycin C and radiation therapy in patients with locally advanced rectal cancer.

Material and methods

From October 2006 to April 2008, an open-label, nonrandomized, phase II study was conducted in the Institute for Oncology and Radiology of Serbia. The primary endpoint of this study was to evaluate the pathological complete response (pCR). Secondary endpoints were clinical response and toxicity.

Inclusion criteria were: minimum age of patients 18 years, histological confirmed, locally advanced stage II (T3/ T4, N0, M0) and stage III (T3 /T4, N1/2, M0) rectal adenocarcinoma of up to 16 cm from the anocutaneous line; no pretreatment except formation of an artificial anus (e.g. due to immanent intestinal obstruction); ECOG (Eastern Cooperative Oncology Group) status ≤ 2; sufficient bone marrow, liver and, renal function.

Patients were assessed at baseline by digital rectal examination, total colonoscopy with biopsy of the rectal tumor and determination of the distance between the lower edge of the tumor and the anocutaneous line, pelvic NMR, abdominal CT, transrectal ultrasonography, chest X ray.

Preoperative radiochemotherapy was started in the same day. Capecitabine 825 mg/m^2/d p.o., on days 1-35, splitting the total daily dose into 2 separate dose; mitomycin C: 7 mg/m^2 IV, on days I and 29 as a two-hour infusion in 500 ml glucose 5%.

Radiotherapy began on day 1 of chemotherapy after administration of mitomycin C; it is performed conventional at a daily dose of 1.8 Gy, at the reference point according to ICRU 50/62 once per day and five times per week, in 25 fractions over a period of 5 weeks, until a total reference dose of 45 Gy was reached. Radiotherapy was delivered with high-energy photons (15, 18 MeV) on linear accelerators.

Five to six weeks after preoperative treatment, before surgery, restaging was performed. Treatment response was evaluated after 5-6 weeks after radiochemotherapy completion according to the RECIST criteria (3). NCI-CTC criteria were used for toxicity grading (4).

Dependent of tumor stages determined by histopathology, after surgery, patients received adjuvant therapy according to hospital routine practice.

After operation, standardized histopathological examination was done with assessment of tumor regression in accordance with a tumor regression grading method established by Dworak (5): grade 0: no regression; grade 1: minimal regression; dominant tumor mass with obvious fibrosis and vasculopathy; grade 2: moderate regression; fibrotic changes dominate with few tumors cell nests easily to locate; grade 3: good regression; very few isolated tumor cells that are hard to find under the microscope, in predominantly fibrotic tissues and pools of mucus. Grade 4: complete regression: no tumor cells, only fibrotic tissue. Responses were thus defined as complete (grade 4), major (grades 3 and 2), or minor (grade 1).

Follow-up procedures were performed every 3 months within the first 2 years and every 6 months in years 3-5.

Results

The study included 49 patients. The median follow-up was 18 months (range 6- 29 months). All 49 enrolled patients were analyzed for clinical response, histopathological response, toxicity, overall survival, and disease-free survival. The median age was 52 years, with the baseline ECOG status 0 or 1. The T3 stage at diagnosis was in 34 (69.4%) patients and T4 in 15 (30.6%) patients. Positive lymph nodes were diagnosed in 28 (57.1%) patients. In all patients tumor was localized in distal (36 patients) and middle third part (13 patients) of rectum.

Confirmed objective clinical tumor response was seen in 40 (82%) patients (95%CI 0.69-0.90) calculated on an intention-to-treat basis. Complete response was noticed in 10 (20.4%) patients, partial

response in 30 (61, 2 %) patients and stabile disease in 9 (18, 4%) patients. No patient showed disease progression.

After evaluation on chemoradiotherapy, all patients underwent surgery. R0 resection was performed in 46 patients (93.9%) and R1 in 3 patients (6.1%).

Histopathological complete response was seen in 8 (16%, 95%CI 0.09-0.29) patients, major response was noticed in 24 (49%) patients and minor response in 14 (29%) patients. Histopathological response was not seen in 3 (6%) patients. Out of 49 patients, who underwent surgery, 24 patients (49%) had positive lymph nodes (20 patients had pN1 and 4 patients had pN2).

Tumor regression grade was assessed in all patients. Tumor regression rate are presented in Table 1.

Table 1. Incidence of tumor regression rate determined by histopathology

Mitomiycin C/Capecitabine/Radiotherapy		
	No. of cases N=49	%
Grade 4	8	16.3
Grade 3	6	12.2
Grade 2	18	36.7
Grade 1	14	28.7
Grade 0	3	6.1

Tumor downstaging was noticed in 26 (53.1%) patients.

Almost all patients received >90% of planned dose intensity for both drugs (capecitabine 92%, rang 69-108; mitomycin C 94%, range 54-105). Out of 49 patients, toxicity grades 1-4 were diagnosed in 35 (71.4%) patients. Radiotherapy was temporarily interrupted in one patient due to diarrhea grade 3 for 7 days and all patients completed radiotherapy. Chemotherapy was definitely stopped in 2 (4.1%) patients. Hematological toxicity was noticed in 14 (28.6%) patients, and nonhematological in 33 (67.3%) patients. The most common non-hematological side effects were dermatitis noticed in 29 (59.2%) patients and diarrhea in 15 (30.6%) patients. One-year disease-free survival was 93.3%, and two-year disease-free survival was 82%. One-year survival was 97.7%. Overall, 5 of 49 patients relapsed.

Discussion

Searching through literature (Medline), we did not find published clinical study that investigated preoperative radiotherapy combined with capecitabine and mitomycin C. There are some studies which investigated combinations of 5-FU and mitomycin C in preoperative settings combined with radiotherapy. Our results showed that preoperative radiotherapy with capecitabine/mitomycin had clinical tumor response rate of 82%, pCR of 16%, and downstaging rate of 53 %, with very acceptable treatment tolerance.

In FUMIR study (6), 83 patients were treated with mitomycin C, 10 mg/m2 day 1, plus 24h continuous infusion IV 5-FU 1000mg/m2 days 1-4, and concurrent radiotherapy with tumor dose of 37.8 Gy, conventionally fractionated 1.8 Gy per day, 5 times per week. Almost all patients, 98%, had T3 tumors. Response rate was 77% and pCR 8%. Tumor downstaging was reported in 57% of patients. Hematological toxicity grade 3/4 was noticed in 12% of patients. Treatment was temporarily interrupted in 11% due to acute complications. One of recent studies which investigated combination of 5-FU and mitomycin C in neoadjuvant settings was published by Chau and coauthors (7) 36 patients received protracted venous infusion 5-FU (300mg/m2/day for 12 weeks) with mitomycin (7 mg/m2/day IV bolus every 6 weeks) and beginning on week 13, 5-FU was reduced to 200 mg/m2/day and combined with concomitant radiotherapy with 50.4 Gy. Postoperatively, patients received 12 weeks of mitomycin and 5-FU at the same preoperative doses. There was no grade 3 and 4 hematological toxicity. Nine patients (25%) had grade 3 and 4 nonhematological toxicity such as diarrhea, stomatitis, infection, and hand-foot syndrome. Response rate was 81%. Pathological CR was find in one patient, 25 patients (74%) had down-staging of their primary tumor on histological examination. Preoperative radiotherapy with capecitabine/mitomycin in our study showed higher pCR rate and favorable toxicity profile (especially hematological toxicity) in comparison to results obtain in studies that combined preoperative radiotherapy with 5-FU/mitomycin.

These phase I/II studies, including our study, suggest higher pCR compared with 5-FU based chemoradiotherapy alone. However, some studies have shown that increased pCR leads an increase in acute toxicity, and data on long-term toxicity are not yet available (8,9). Phase III trials are necessary to determine whether these novel combination regimens, including capecitabine/mitomycin regimen, offer an advantage compared with 5-FU based combined modality protocols. Regarding these different possibilities and combinations of cytotoxic drugs, the future challenge in the treatment of advanced rectal cancer is to identify and select patients for the appropriate treatments according to predictive and prognostic molecular markers and further investigations with monoclonal antibodies.

Conclusion

Preoperative chemoradiation with capecitabine and mitomycin C appeared to be effective treatment combination with safety application and low toxicity. Further phase III studies are necessary.

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News in treatment of peritoneal carcinomatosis from colon cancer by cytoreductive surgery and hyperthermic perioperative intraperitoneal chemotherapy

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Peritoneal involvement in colorectal cancer occurs in approximately 30% of patients. Approximately 8% of patients are diagnosed with synchronous peritoneal dissemination at the time of primary colorectal surgery and 25% of patients have recurrence confined to the peritoneal cavity (1).

Systemic chemotherapy treatment alone is no longer appropriate for patients with limited peritoneal dissemination from a primary or recurrent colon cancer. The surgical management of peritoneal surface malignancies of colonic origin with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) has been clearly defined and continues to improve.

Better surgical techniques that include peritonectomy procedures, standardized methods to deliver intraoperative hyperthermic intraperitoneal chemotherapy and better patient selection criteria, have resulted in a significant improvement in survival and in morbidity and mortality of the surgical management of this particular group of stage IV colon cancer patients.

Sugarbaker and colleagues (1990) proposed cytoreductive surgery and perioperative intraperitoneal chemotherapy as a definitive treatment for peritoneal dissemination from appendiceal neoplasms and diffuse malignant peritoneal mesothelioma (2-4). Better surgical techniques that include peritonectomy procedures, standardized methods to deliver intraoperative hyperthermic intraperitoneal chemotherapy and better patient selection criteria, along with the strong treatment rationale and superior results when compared to historical controls, have lead to the establishment of numerous treatment centers in the United States and Europe. Over the last decade, an increasing number of international treatment centers have published their prospective results using cytoreductive surgery and HIPEC in the management of peritoneal surface malignancies of colorectal origin. In 2003, the Dutch group conducted a randomized controlled trial comparing systemic chemotherapy with cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy and this trial clearly demonstrated the superiority in survival of the combined treatment group (5). In 2004, a multi-institutional registry study from 28 international treatment centers showed that the median survival was 19 months and 3-year survival was 39% after cytoreductive surgery and HIPEC for 506 patients with colorectal peritoneal carcinomatosis (6).[1]

An analysis of evidence indicates improvement of survival and potential for cure in patients with low volume metastatic adenocarcinoma of colonic origin limited to the peritoneal cavity using cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC). However, as pointed out by Yan et al in a recent systematic review of the quality of evidence in 14 rigorously selected series, there were 2 randomized controlled trials, one randomized comparative study, and 11 observational studies without control groups, including one multi-institutional study (7). In addition, the indications for, the technique of HIPEC, the drugs used and the degree of heat, vary among physicians using these methods of treatment.

Preoperative evaluation

Long-term survival can only be achieved by cytoreductive surgery and HIPEC when a complete cytoreduction is accomplished. Proper patient selection remains a crucially important aspect in the treatment of patients with peritoneal dissemination from colorectal cancer. Review of the data in multiple series shows that those patients that have an incomplete removal of their peritoneal dissemination have a median survival of about 6 months and therefore these patients do not benefit from a surgical procedure (8,9).

Once a patient has been diagnosed with colorectal cancer with peritoneal involvement, the work-up usually includes a complete colonoscopy as well as a CT scan of the chest, abdomen, and pelvis with maximum oral and intravenous contrast to evaluate the extent of peritoneal dissemination. A PET scan can be considered if there is any question of extra-abdominal disease. Review of two published series trying to address the diagnostic accuracy of the CT scan as an imaging modality can be summarized by stating that the detection of peritoneal carcinomatosis by CT scan is only moderately useful and that it has severe limitations in detecting small peritoneal implants, especially in the small intestine. In addition, CT scan was considered of limited value in selecting colorectal patients with peritoneal carcinomatosis, who will not benefit from cytoreductive surgery with HIPEC (10,11).

The role of abdominal laparoscopy in the pre-treatment evaluation of peritoneal carcinomatosis

Garofalo et al. achieved full laparoscopic Peritoneal Cancer Index assessment in 96/97 cases, while only 2/96 cases were under staged. There was a good correlation between the open successive surgery data and the laparoscopic Peritoneal Cancer Index. There was no mortality and no neoplastic colonization at the trocar port site. Patients with massive involvement of their small bowel or mesentery by staging laparoscopy should be considered not amenable for peritonectomy. They considered laparoscopy a useful tool in peritoneal surface malignancies. It allows direct visualization even of small cancer nodules and provides a reliable assessment of the feasibility of peritonectomy (12).

A group of French investigators also evaluated the role of explorative laparoscopy to evaluate candidates for complete resection of peritoneal carcinomatosis combined with hyperthermic intraperitoneal chemotherapy (HIPEC). Eleven patients planned to undergo a cytoreductive surgery + HIPEC underwent an explorative laparoscopy. Laparoscopic evaluation was successful in all 11 patients (13). The conclusion was that laparoscopic scoring of peritoneal carcinomatosis is accurate to assess the complete resectability of peritoneal carcinomatosis in patients for which there is inadequate or contradictory information concerning disease extent.

Variables associated with the increased chances of having a complete cytoreduction

Complete cytoreduction means that no macroscopic residual disease was left after the operative procedure. The following are clinical and radiographic variables that are usually associated with the increased chances of achieving a complete removal of an entire tumor greater than 2.5 mm:

(1) ECOG performance status two or less;
(2) No evidence of extra-abdominal disease;
(3) Up to three small, resectable parenchymal hepatic metastases;
(4) No evidence of biliary obstruction;
(5) No evidence of ureteral obstruction;
(6) No evidence of intestinal obstruction at more than one site;
(7) Small bowel involvement: no evidence of gross disease in the mesentery with several segmental sites of partial obstruction;
(8) Small volume disease in the gastro-hepatic ligament (14).

Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

Cytoreductive surgery will include peritonectomy procedures in order to remove all visible tumors. If a complete cytoreduction, CC-0/CC-1, by the completion of cytoreduction score or a R0/R1 by the R scoring system is achieved, then the patients will undergo hyperthermic intraperitoneal chemotherapy (HIPEC) with mitomycin C (15– 35 mg/m^2) with a target intraperitoneal temperature of 39–42^{0}C for 60–120 min. Whether an open or closed method for the chemotherapeutic perfusion is used, and whether or not early post-operative intraperitoneal chemotherapy (EPIC) with 5 days of 5-FU is used, will be the surgeon's preference. In those patients with symptomatic ascites in whom an adequate cytoreduction could not be achieved, HIPEC could be performed at the discretion of the surgeon with the intention of palliating the intractable ascites. Although mitomycin C is the most commonly used drug, oxaliplatin is being used more frequently with very promising results.

Survival

There are two prospective randomized controlled trials (RCT), one non-randomized comparative study and numerous observational studies regarding clinical an oncological outcome of patients with peritoneal carcinomatosis arising from CRC. Verwaal et al. reported a disease- specific survival of 22.2 months after additional CRS and HIPEC vs. 12.6 months after standard systemic treatment with 5-FU and leucovorin (8,15).[8,2] In patients with complete macroscopic cytoreduction (CCR-0/1), median survival was 48 months and 5-year survival rate was 45%, respectively. The second RCT was closed after inclusion of only 35 patients during a 4-year accrual period. The 2-year survival rates were 60% in both arms (16).[3] In the comparative study published by Mahteme et al., the median survival in the HIPEC group was 32 months vs. 14 months in the control group. 5-year survival rates were 28% and 5% respectively (17). In the observational studies, the overall median survival ranged from 15 to 32 months and from 28 to 60 months after complete macroscopic cytoreduction (CCR0-1), respectively (18).

Conclusion

The current evidences suggest that cytoreductive surgery combined with perioperative intraperitoneal chemotherapy is associated with an improved survival, as compared with systemic chemotherapy for peritoneal carcinomatosis from colorectal carcinoma.

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