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Chemotherapy options for metastatic colorectal carcinoma; First, second, third line...

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ABSTRACT

For almost 40 years, the only option for patients with unresectable metastases was treatment with 5-fluorouracil. In the last decade, new drugs became available that changed attitude toward treatment of metastatic CRC, as well as the prognosis for some patients although the "story" of 5-FU is not finished yet. Irinotecan, oxaliplatin and oral fluoropyrimidines produces higher response rates, longer symptom control and longer survival for the majority of the patients with unresectable metastases. Neoadjuvant chemotherapy is particularly interesting, because according to the results of some studies, it actually allows curative resections of previously unresectable liver metastases. This paper deals with the current status of chemotherapy of metastatic CRC, and some dilemmas about that issue. Also, we report results of third line chemotherapy of metastatic CRC patients treated at the Institute for Oncology and radiology of Serbia (IORS).

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INTRODUCTION

Approximately 25% to 40% of CRC patients at the time of diagnosis already have advanced disease. Additional 50% of patients, who were considered cured with operation, will also develop metastases in the months or years after surgery.
For almost 40 years, the only option for patients with unresectable metastases was 5-fluorouracil. In the last decade, new drugs became available that changed attitude toward treatment of metastatic CRC, although it is still incurable disease for majority of patients. New drugs produce higher response rates, longer survival and symptom control. Neoadjuvant chemotherapy is particularly interesting, because in some studies, it actually allows curative resections of previously unresectable liver metastases.
This paper deals with the current status of chemotherapy of metastatic CRC, and some dilemmas about that issue.
Also, we report results of third line chemotherapy of metastatic CRC patients treated at the Institute for Oncology and radiology of Serbia (IONS).

5-fluorouracil

5-fluorouracil (5-FU) was extensively studied in various modes of application with different bio-modulating agents and there are few dilemmas left about this drug.
Five randomized trials compared chemotherapy given immediately on diagnosis of advanced or recurrent disease with chemotherapy delayed until symptoms occurrence. The results suggested that early treatment increases median survival from median five to ten months, while the symptom free survival increases from median two months to ten months (1-4).
As a single agent given in bolus 5-FU produces only 10% responses. Low response rate (RR) was attributed to its very short plasma half-life. Addition of biomodulators, such as folinic acid (FA, leucovorin), levamisol or metotrexate, resulted in doubling of RR up to 24% (5,6).
Meta-analysis of nine randomized trials, comparing 5-FU alone vs. 5-FU-FA, confirmed better responses with addition of FA, although with little effect on overall survival, except for the responding patients (5).
The other mode to prolong tumor cells exposure to 5-FU is continuous IV administration of 5-FU. Meta-analysis of six randomized trials confirmed higher response rates (22% vs. 14%) and better toxicity profile for continuous IV administration of 5-FU (7). Several infusional regimens are developed, with different doses of 5-FU and LV, that can be given weekly or bimonthly, and all have similar activity. The choice of the particular regimen is left to the individual preferences of the physicians (8,9). However, survival is only marginally prolonged with infusional regimens while, all optimizations of 5-FU-FA action, resulted in modest increase of response rates up to 24%.
Although infusional regimen, are now the standard treatment in Europe, and lately in the USA, in many countries bolus Mayo regimen is still the therapy of choice in every day clinical practice. In countries like ours, the main reason for that is the lack of infusional pumps, and inconveniences related to the implantation of central venous catheter.

Irinotecan

Irinotecan (CPT-11) is a potent inhibitor of topoisomerasa I, which causes inhibition of DNA replication. As a single agent, irinotecan was used in various dose and schedules. The two most frequently used doses are 350 mg/m^2, once in 3-week intervals, and 100-125 mg/m^2, weekly during 4 weeks, and than 2 weeks rest.
Several phases II/III studies confirmed efficacy of irinotecan as a single agent (RR 24-29%, first line; 11-23%, second line) (10) and after those studies irinotecan was combined with bolus or infusional 5-FU, in previously untreated patients. In the European phase III trial, irinotecan was combined with infusional 5-FU, either AIO (irinotecan 80mg/m^2) or DeGramont (irinotecan 250 mg/m^2). The investigational arms were compared to infusional 5-FU-LV. The

combined therapy was significantly better, with RR 35% vs. 22%, time to progression (6.7 vs. 4.4 months) and survival (17.4 vs. 14.1 months) (11).
Quality of life analysis, (EORTC QLQ-C30) also showed that quality of life was not negatively affected in patients treated with combinational therapy.
In the other large phase III trial conducted in the USA, comparisons were done between irinotecan 125 mg/m^2 with or without bolus 5-FU-FA, to bolus 5-FU-FA as a standard treatment (12). The response rate was significantly better for combined chemotherapy (RR 39% vs. 21%) with longer time to progression (7 vs. 4.3 months) and longer survival (14.3 vs. 12.6 months).
The results of these trials led to approval of irinotecan in many countries for first and second line treatment of metastatic CRC (13).
The objective anti-tumor activity of irinotecan was consistent through all studies, with additional 40% to 70% of patients with disease stabilization. Patients with disease stabilization also had benefits of chemotherapy that is translated in to a longer survival and better quality of life comparing to patients with progressive disease.

Oxaliplatin

Oxaliplatin (LOHP) is the third generation platinum compounds, and also has a significant influence on the treatment of metastatic CRC. Although as a single agent it has a moderate activity (10% second line; 24% first line), this drug has synergistic activity with 5-FU and favorable toxicity profile.
Two large randomized trials that compared oxaliplatin, 5-FU-FA vs. 5-FU-FA alone, confirmed better response for combinational arm, but without effect on overall survival. In the De Gramont study, the RR was 51% for oxaliplatin arm compared to 23% for 5-FU-FA arm and the progression free interval also was better for combination (14).
In the other study, chronomodulated 5-day 5-FU with or without oxaliplatin also confirmed higher RR (53% vs.16%), and significantly prolonged time to progression (8.7 vs. 6.1 months) for the combinational arm, but also without effects in overall survival (19.4 vs. 19. 9 months) (15).
The latter trial is important because, in the oxaliplatin arm, almost 30% of patients with initially unresectable liver metastases had tumor shrinkage, and underwent salvage surgery. That confirmed that concept of neoadjuvant chemotherapy could be very effective in some selected patients.

Sequential administration of irinotecan and oxaliplatin

To find out whether irinotecan is more efficient over oxaliplatin, or vice versa, several studies were performed. In the USA Intergroup study N9741, previously untreated, metastatic CRC patients were randomized between three regimens: bolus 5-FU-FA+irinotecan (IFL), infusional 5-FU-FA+oxaliplatin (FOLFOX 4), and the combination of irinotecan+oxaliplatin.
In this study, FOLFOX regimen was superior to the other two arms, in terms of RR, time of tumor progression and survival. However, in the FOLFOX regimen, infusional 5-FU was used, while in the IFL regimen 5-FU was given as bolus and it had already been proved that infusional 5-FU was more efficient that bolus 5-FU.
Also, more that 50% of the patients in the FOLFOX received second-line chemotherapy consisting of irinotecan, while only 20% of patient treated with IFL received oxaliplatin based second-line chemotherapy (16). The main reason for those differences in administration of second-line treatment was because oxaliplatin at that time was not commercially available in the US.
In the phase III study (GERCOR), conducted in France, two sequences of chemotherapy were compared in previously untreated metastatic CRC patients. In one arm, patients received FOLFIRI until progression and than treatments were continued with FOLFOX, and in the other arm FOLFOX was given until progression and than continued with FOLFIRI (17).
The two sequences did not differ significantly, in terms of RR, time to progression, or overall survival in the first-line treatment. Analyzing those endpoints in the second-line treatment, the FOLFOX-FOLFIRI seemed to be slightly more efficient than the reverse sequence. Median survival in this study was over 20 months in both arms.
However, it can be concluded, that current results confirmed equal activity of both drugs in metastatic colorectal cancer patients (18).

Oral fluoropyrimidines

Three oral fluoropyrimidines are currently available: uracil/tegafur (UFT) capecitabine, and eniluracil. Several large randomized trials confirmed that oral fluoropyrimidines have similar efficacy as bolus 5-FU, in the first-line treatment of metastatic CRC patients.
Two studies compared UFT-leucovorin, with 5-FU-FA, and RR, time to progression and the survival were not different. (19,20). Van Cutsem and Hoff, also confirmed similar results of capecitabine versus bolus 5-FU-FA (21,22).
Eniluracil is withdrawn from further studies because the trend to lower activity of the combination of eniluracil, 5-FU-FA versus 5-FU-FA alone was registered.
Although there are no significant differences in the activity compared to bolus 5-FU-FA, oral fluoropyrimidines have some toxicity and quality of life advantages over intravenous 5-FU, and many patients prefer oral route to chemotherapy.

New drugs for the treatment of metastatic CRC at the IORS

At the Institute for Oncology and Radiology of Serbia (IORS), irinotecan has been administered since 1997 (23), oxaliplatin and capecitabine two years later. Since that time, dozens of patients received irinotecan as a single or combined second-line therapy, but third-line therapy was seldom used until oxaliplatin became available. The main criteria in making decision about second and third line therapy were made upon patients' performance status, absence of major organ failure signs, and patients' motivations for treatment continuation.
We are presenting results of sequential treatment of metastatic CRC patients treated at the IORS in the last three years (24).

PATIENTS AND METHODS

In the last three years 84 metastatic CRC patients with performance status (PS) 0-1, after failure to 5FU-LV, were treated with second-line chemotherapy: irinotecan+/-5FU-LV, oxaliplatin+5FU-LV, DeGramont 5FU-LV, or capecitabine. Eventually, disease progressed in all patients but 32/84 (38%) retained PS 0-1. Twenty-two patients could not afford further treatment, and continued with best supportive care. Ten patients (11.9%) 6 females, 4 males, median 52.5 years were treated with third-line therapy, and they were analyzed separately. Depending on previous treatment, as third-line was administered: irinotecan+/-5-FU-LV (4 patients), oxaliplatin+5FU-LV (4 patients), and capecitabine (2 patients). All patients had PS 0-1, bilirubin, creatinine, and hemoglobin level within grade 0-1 WHO. Five patients had bulky liver metastases (> 5 cm).

RESULTS

Median number of chemotherapy cycles in third-line was 3.5 (1-6). Best response was stabilization of disease in 6 patients, 1 had rapid progression, and 3 patients were not evaluable for response (beginning of treatment, evaluation to be done). Toxicity was mild, except for patients on irinotecan (diarrhea grade 2). Median survival was 21 months (9-36+m). Despite dare prognosis of metastatic CRC, approximately one-third of patients reported in this study, retained good performance status without organ failure, even after second-line chemotherapy. It seems that in well-selected patients, third-line chemotherapy could be beneficial, prolonging the time of disease control.

DISCUSSION

After 40 years, it seems that "one-drug-show" with 5-fluorouracil is finally over. Still, debate continues because the future role of 5-FU is not completely defined yet. Some authors suggest that the only future of 5-FU is in the combination with other, newer drugs, with non-overlapping mechanisms of actions. On the other hand, other authors point out that there are insufficient data whether all patients have to be treated in the first line with combined 5-FU based chemotherapy, or some can be treated first with 5-FU-FA, and after progression with other combinations. Drugs given in the first line do affect the number of available chemotherapy combinations, but it is not known whether that may influence the length of survival.

Irinotecan and oxaliplatin in combination with 5-FU increase response rates up to 40%-50% of patients (12). The higher RR does correlates with longer survival and longer time of symptoms controls (16). Nevertheless, it is still not quite clear whether combination with irinotecan or oxaliplatin should be used in all patients as a first line therapy, or the same outcome of the disease could be achieved with sequential use of those drugs after failure on 5-FU-FA. Also, there are no clear recommendations which of these drugs should be used first. The results of current randomized trials make sequence choice of drugs for second or third line therapy less debatable, and dependent mostly on the physicians and patient's preferences considering toxicity profile of the therapy and performance status of the patient. Survival of the patients with unresectable metastases of colorectal carcinoma can definitely be influenced with chemotherapy. Untreated patients have a median survival of 5 months, 5-FU-FA prolongs survival up to 12 months, and oxaliplatin and irinotecan prolong survival in selected patients up to 20 months. Also, significant symptomatic improvement is registered in 90% of patients with partial response, and in 65% of patients with stable disease (25). That is not age dependent, and many elderly patients have the same benefits of chemotherapy as those who are younger (26).

Since there are many differences among the patients, the same stage of the disease does not mean the presence of the same symptoms, performance status, probability for response and survival. Therefore, careful treatment planning for the individual patient is necessary to achieve the best responses, symptom control and survival.

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