Review article
UDC: 616.348-006: 616.351-006: 615-085

Systemic therapy for colorectal cancer

Borut ŠTABUC

UNIVERSITY MEDICAL CENTER LJUBLJANA, DEPARTMENT OF GASTROENTEROLOGY, SLOVENIA

Colorectal cancer alone accounts for around 200,000 deaths in Europe and represents a significant health problem. Although about fifty percent of patients are cured by surgery alone, the other half will eventually die due to metastatic disease, which includes approximately 25% of patients who have evidence of metastases at the time of diagnosis. Surgical resection of the primary tumor and regional lymph nodes is the only curative therapy for colorectal cancer. However, adjuvant chemotherapy in stage III for colon cancer following curative resection has been shown to reduce the risk of recurrence by 19-40% and of death by 16-33%. Today, 5-fluorouracil and leucovorin given for six months may represent the best adjuvant treatment available The contribution of levamisole to adjuvant treatment seems to be marginal, if any. The benefit of adjuvant chemotherapy for the patients with Dukes B colon cancer is less clear. A meta-analysis of 1,381 patients with advanced colorectal cancer showed a significant increase in response rate with the bolus 5-fluorouracil and leucovorin versus 5-fluorouracil alone, but no significant difference in median survival. Continuous infusion allows higher doses of 5-FU than rapid bolus infusion and improves response rate, survival and time to progression. Oral fluoropyrimidines (capecitabine and uracil/tegafur [UFT]) are as active as intravenous fluoropyrimidines. Compared to intravenous 5FU, oral fluoropyrimidines have safety advantages, clinical benefits, and are more convenient for patients. Phase III randomized clinical trials in patients with metastatic colorectal cancer demonstrate the significant superiority of combining irinotecan with 5-fluorouracil and leucovorin or oxaliplatin with 5-fluorouracil and leucovorin over the same 5-fluorouracil and leucovorin alone.Several phase II studies have shown that the combination of the oral fluoropyrimidines plus irinotecan or oxaliplatin is very active in metastatic colorectal cancer.Trials with agents acting on novel targets in colorectal cancer are progressing rapidly, including doxifluridine, new inhibitors of thymidylate synthase (ZD9331), oral camptothecins (Rubitecan), multitarget antifolate antimetabolite (Premetrexet), inhibitors of epidermal growth factor receptor (Cetuximab), COX-2 inhibitors (celecoxib) and farnesyltransferaze inhibitors (Zarnestra). However, a few randomized trials failed to show a survival advantage compared with placebo in patients with advanced refractory colorectal cancer.

KEY WORDS: *Colorectal Neoplasms; Antineoplastic Combined Chemotherapy Protocols; Chemotherapy, Adjuvant; Treatment Outcome*

INTRODUCTION

Colorectal cancer is a leading cause of morbidity and mortality with about 340,000 new cases and 190,000 deaths in Europe (1). Although about fifty percent of patients are cured by surgery alone, the other half will eventually die due to metastatic disease, which includes approximately 25% of patients who have evidence of metastases at the time of diagnosis (2).

The prognosis for an individual patient depends mainly on the extent of disease. The TNM as well as the Duke's staging classification is widely used to describe the extent of local disease. Survival is also influenced by other factors, such as surgeon and type of operation, concomitant illness, age, and mode of presentation. The patients presenting as emergencies with obstruction or perforation have worse prognosis. This is reflected in the wide range of survival estimates in the literature for this stage of disease. However, most oncologists would accept an estimate of

Address correspondence to:
Prof. Dr. Borut Štabuc, University Medical Center Ljubljana, Department of Gastroenterology, Japljeva 2, 1525 Ljubljana, Slovenia, Email: borut.stabuc@kclj.si

The manuscript was received: 09. 08. 2003

Provisionally accepted: 30. 09. 2003

Accepted for publication: 01. 12. 2003

40%-50% five-year survival. The overall survival, taking into consideration all patients whether operated on or not, is much lower, being about 20%-25% (3).

5-fluorouracil (5-FU), in use for nearly 40 years, is probably the most active single agent against colorectal cancer. It has been shown to improve both survival (5 vs. 11 months) and quality of life of patients with metastatic disease, compared to best supportive care (4). Leucovorin (LV; folinic acid [FA]) has been extensively studied as a modulator of 5-FU. It acts as a source of reduced folates which optimize the inhibition of thymidylate synthase, the key enzyme in DNA synthesis, by increasing the formation of the stabilized ternary complex between thymidylate synthase, 5-fluorodeoxyuridine monophosphate and reduced folate. LV increases the degree of inhibition of thymidylate synthase (5), depletes cellular thymidine, and induces apoptosis (6). In summary, the infusional 5-FU/LV regimens were less toxic than the monthly 5-FU/LV bolus daily x 5. 5-FU plus LV as bolus IV is generally regarded as the standard treatment for advanced colorectal cancer although it is moderately active. There is no data to distinguish whether high, intermediate or low-dose LV is most advantageous as modulator of 5FU. Recent studies, using 5-FU/LV as a control arm for the comparison to new experimental regimens, resulted in lower response rates than earlier studies. Moreover, in several European countries, different 5-FU/LV infusional regimens are commonly used in advanced colorectal cancer, even though a consensus on dose and regimen has not been reached yet.

ROLE OF ADJUVANT THERAPY IN COLON CANCER

5-FU alone or in combination with LV or Levamisole is the most frequently used chemotherapy regimen in patients with resectable colon cancer of stage T3/4 N1/2 M0. In stage III colon cancer, adjuvant chemotherapy following curative resection has an established role and has been shown to reduce the risk of recurrence by 19%-40% and of death by 16%-33%. The benefit of adjuvant chemotherapy for patients with stage II colon cancer is less clear (7). While some studies have shown that the relative benefit is similar to that seen in stage III disease, the absolute improvement in survival is small because of the relatively good prognosis of this group. Patients with stage II colon cancer should be selected for adjuvant chemotherapy in prospective trials or according to the individual circumstances. A number of clinico-pathological features are known to be associated with a poor prognosis, including perforated or obstructed tumors, stage T4 tumors, poorly differentiated tumors, extra-mural vascular invasion and mucinous differentiation.

Moertel et al. showed a 5-year disease-free survival rate in colon cancer patients stage III of 61% in the 5FU/Levamisole group, 44% in the antihelminthic drug levamisole alone group and of 44% in those patients receiving no adjuvant chemotherapy (8). The Intergroup trial included 1,296 patients with colon cancer (325 stage II; 971 stage III). The patients were randomized to follow-up alone or post-operative levamisole 50 mg 8-hourly for 3 days every 2 weeks and 5-FU at a dose of 450 mg/m2 daily for 5 days, followed 28 days later by weekly 5-FU at the same dose for a total of 48 weeks. During the 6.5 years follow-up period, levamisole plus 5-FU decreased the risk of cancer recurrence by 40% ($p<0.0001$) and the mortality rate by 33% ($p<0.007$) compared with observation alone or levamisole alone. For the group of stage II patients, chemotherapy was associated with an insignificant improvement in disease-free survival (79% vs. 71% at 7 years; $p=0.1$), and with no difference in overall survival (9).

Two studies have demonstrated a survival advantage for the combination of 5-FU and LV as adjuvant therapy for colon cancer. The IMPACT investigators (8) randomized a total of 1,526 patients in three separate trials between surgery alone and post-operative 5-FU (370-400 mg/m^2) plus LV (200 mg/m^2), both given daily for 5 days every 4 weeks for 6 cycles. The hazard ratio for death was 0.76 in favor of the treated group after adjustment for other prognostic variables ($p=0.018$). A subgroup analysis demonstrated no significant event-free or overall survival advantage for the patients with stage II tumors.

A North Central Cancer Treatment Group (NCCTG) trial (10) used a similar schedule of 5-FU (425 mg/m^2) and LV (20 mg/m^2). Three hundred and seventeen patients were included, the majority of whom had stage III tumors. Five-year survival was 74% in the chemotherapy arm and 63% in the control arm ($p=0.02$). Following the results of these trials, a consensus was established that 5-FU based chemotherapy should be considered for all patients with resected stage III colon cancer. Subsequent studies have compared regimens, seeking to determine the optimal duration of adjuvant chemotherapy, and the best agents to employ.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) C-03 trial compared a weekly schedule of 5-FU (500 mg/m) and LV (500 mg/m^2) for 6 weeks of every 8-week cycle with MOF chemotherapy. Both regimens were given for about a year in total. This demonstrated a significant advantage in three-year disease-free and overall survival for the 5-FU+LV treated patients (2).

The NSABP C-04 study compared the same regimen of 5-FU+LV either with or without oral levamisole, with a third arm assigned to a combination of 5-FU and levamisole given according to the Intergroup schedule described above. Again each regimen was continued for one year. There was no significant difference in disease-free or overall survival between the three arms, but a significant survival advantage for 5-FU+LV over 5-FU+levamisole ($p<0.05$) was observed.

The Intergroup regimen of 5-FU+levamisole was also compared with a three drug combination of 5-FU (370 mg/m^2) and LV (20

mg/m^2) each given daily for 5 days every 4 to 5 weeks plus levamisole 50 mg three times daily for 3 days every 2 to 3 weeks. In this study, performed by the NCCTG and the National Cancer Institute of Canada Clinical Trials Group (NCICCTG), the patients in each arm were further randomized to receive 6 or 12 months of chemotherapy. There was no significant difference in disease-free or overall survival between the three arms and between 6 or 12-month chemotherapy, but a significant survival advantage for 5-FU+LV over 5-FU+levamisole ($p<0.05$) was observed.

The Intergroup 0089 study randomized 3,759 patients between 4 treatment arms: standard 5-FU+levamisole for 1 year; the NCCTG regimen of 5-FU and low dose LV for 7 to 8 months; weekly 5-FU (500 mg/m^2) for 6 of 8 weeks for 4 cycles; and the NCCTG regimen of 5-FU and low dose leucovorin with the addition of levamisole for 7 to 8 months. An analysis performed with a median follow-up of 5 years showed that the only planned treatment comparison to reveal a significant difference in overall survival was that between 5-FU+levamisole and 5-FU+low-dose LV+ levamisole, in which the former was inferior ($p=0.0074$). The three-drug combination was not superior to either schedule of 5-FU+leucovorin, suggesting that levamisole is not an essential component of 5-FU based adjuvant chemotherapy (2).

5-FU/ leucovorin and interferon alpha

A further study conducted by the NSABP investigated the role of alpha interferon (IFN) in combination with 5-FU and leucovorin. Two thousand one hundred and twenty-nine patients were randomized to receive six-month treatment with 5-FU (370 mg/m^2) and LV (500 mg/m^2) daily for 5 days every 4 weeks plus or minus IFN (5 x 106 u/m^2) for 7 days of each cycle. Four-year disease-free and overall survivals were identical in the two arms, and toxicity was greater in the IFN arm. On the basis of these results, it seems that this agent has no significant role in adjuvant therapy (11).

Adjuvant portal vein chemotherapy

Adjuvant portal vein chemotherapy may reduce metastatic spread to the liver, which is the major site of disease recurrence in colon cancer. Several confirmatory prospective trials have failed to demonstrate a significant benefit in the reduction of liver recurrences. However, a meta-analysis has shown a modest improvement in OS when patients were treated with portal vein 5-FU infusions as compared to no postoperative therapy (12). Data on more than 3000 individual patients were analyzed and revealed a statistically significant reduction in risk of death of 13±6% and improvement in DFS of 14±5% in favor of portal vein infusion therapy. However, analyzed trials used untreated patients as the control arm, which is not considered to be a standard approach in stage III patients. It remains uncertain whether these beneficial effects result from the unique route of drug administration employed or from the systemic effects of treatment. A randomized trial by the Swiss Group for Clinical Research revealed no survival difference between systemic 5-FU versus portal vein 5-FU infusion versus surgery alone in 769 patients with resected colon or rectal cancer (2). However, the Intergroup currently carries out a large study comparing portal vein infusion and systemic chemotherapy. Until we get the results from the studies comparing systemic versus portal adjuvant chemotherapy, the portal route should be used only in the frame of clinical trial.

Monoclonal antibodies in adjuvant therapy

A murine monoclonal antibody (MoAb) directed against CO 17-1 A (an antigen associated with colorectal cancer cells) has been tested in a small randomized study in stage III colorectal patients (13). The updated seven-year follow-up results of this small study demonstrate that the anti-C017A MoAb can reduce the rates of tumor recurrence and mortality to a similar extent to those observed with 5-FU-based adjuvant chemotherapy (32% reduction in mortality and 23% reduction in recurrence relative to surgery alone). Recently, two randomized trials are comparing the anti-C017-IA MoAb with FU+LV (Europe) or levamisole+5-FU (USA) based regimens.

UFT in adjuvant chemotherapy

UFT is effective as adjuvant chemotherapy in the patients treated with curative resection for colorectal cancer, which was proved in a randomized controlled study on adjuvant chemotherapy with UFT in curatively resected colorectal cancer. The patients were randomized over a 2-year period to receive mitomycin C (6 mg/m^2) 1 day prior to and 1 day following surgery and either oral UFT (400 mg/day) for 1 year or supportive care. A statistically significant increase of the disease-free survival rate over the 3-year median follow-up period has been shown for those patients receiving UFT following mitomycin C (14).

ONGOING AND FUTURE ADJUVANT STUDIES

Development in the near future is likely to arise from drugs and schedules that have demonstrated activity in the advanced disease setting. A number of trials are currently underway in Europe with this in mind. The SAFFA trial, being coordinated by the Royal Marsden Hospital, randomizes patients between 3-month treatment with protracted venous infusion 5-FU and 6-month treatment with the NCCTG regimen of bolus 5-FU and leucovorin. An interim analysis on toxicity has shown highly significant reduction in the incidence of stomatitis, diarrhea, leucopenia, neutropenia and alopecia in the infusional arm. The two Pan-European Trials

for Adjuvant Treatment of Colon Cancer compare the NCCTG regimen with raltitrexed (PETACC-1) and three infusional 5-FU regimens (PETACC-2). Other cytotoxic agents that may have a potential role in adjuvant therapy include the oral fluoropyrimidines (capecitabine, UFT) irinotecan and oxaliplatin. Apart from showing the efficacy in the advanced disease setting, these drugs are easy to administer, compared with either bolus or infusional 5-FU. Randomized trials will be required to establish their comparative efficacy with existing regimens. Many clinical trials on either single-agent or combination regimens comparing new approaches with the standard FU+LV have been activated, including raltitrexed, capecitabine, oxaliplatin, irinotecan, UFT. As in the advanced/metastatic colorectal cancer some new regimens are more effective than FU+LV or protracted 5-FU infusion, a longer survival benefit in the adjuvant setting can also be contemplated. However, until these studies are mature, none of the above mentioned drugs should be used for adjuvant treatment outside clinical trials. Importantly, some ongoing trials are designed to test prospectively also the value of biological markers of chemo sensitivity including thymidylate synthase (TS) and DPD expression. Results of these studies might allow for the first time to tailor adjuvant treatment individually.

CHEMOTHERAPY OF METASTATIC COLORECTAL CANCER

A meta-analysis of 1,381 patients with advanced colorectal cancer showed a significant increase in response rate with bolus 5-FU and LV versus 5-FU alone (23% and 11%, respectively) ($p<0.001$), but no significant difference in median survival (11.5 and 11 months, respectively) (15). Nevertheless, in one large randomized study evaluating several new approaches to enhance the activity of 5-FU in the management of advanced colorectal cancer, the high-dose and low-dose LV plus 5-FU regimens were associated with not only improved response rates and time to progression (TTP) ($p=0.015$ and $p=0.007$) when compared with 5-FU alone, but also with a significantly superior quality of life, including improvement in performance status, weight gain and symptomatic relief ($p<0.05$) (16).

A recent meta-analysis of 1,219 patients treated with infusional 5-FU compared to bolus 5-FU showed that continuous infusion is superior in terms of tumor response (22% vs. 14%) and achieves a slight increase of overall survival (overall hazards ratio 0.88; $p=0.04$). With the continuous infusion schedule, a more acceptable toxicity profile is observed, with hematological toxicity being dose-limiting for bolus regimen and hand-foot syndrome for continuous infusion (17). Continuous infusion allows higher doses of 5-FU than rapid bolus infusion. In the De Gramont et al. study (18), an every two week infusional 5-FU/LV regimen resulted in a 33% response rate versus 14% in the monthly 5-FU/LV bolus daily for 5 days ($p=0.0004$) and a significant advantage in time to progression (TTP) 27.6 weeks versus 22 weeks ($p=0.0012$). In the Kohne et al. study (19), a significantly higher response rate was also observed in the 24-hour 5-FU/LV weekly schedule, 44% compared with 18% on 24 hour 5-FU infusional modulated by interferon; in addition, a significant difference in TTP (7.1 months vs. 3.9 months, $p<0.009$) and survival (16.6 months vs. 12.7 months, $p<0.04$) were also observed. In the Aranda et al. study (20), a significantly higher response rate was observed in the 48-hour 5-FU infusional weekly, 30 % vs. 19% on the 5-FU bolus ($p<0.05$). However, the differences in TTP or survival were not statistically significant. Finally, more recently, the same 24-hour 5-FU/FA weekly regimen used in (21) was compared in a phase III randomized trial to the monthly 5-FU/LV bolus daily for 5 days. The infusional regimen resulted again in a statistically significant difference in response rate (23% vs.18%, $p<0.01$), TTP and survival.

Oxaliplatin

Oxaliplatin is a novel platinum derivative and the first platinum compound to demonstrate significant efficacy in the treatment of advanced colorectal cancer. Preclinical studies have shown that oxaliplatin is active against colorectal cell lines and acts synergistically when coadministered with 5FU. Furthermore, phase II trials of oxaliplatin monotherapy in previously treated or untreated patients with colorectal cancer have shown response rates of between 10% and 24%, with acceptable toxicity (22).

The efficacy of various doses of oxaliplatin in combination with 48-hour bimonthly regimens of LV/5FU has also been evaluated as second-line therapy among patients whose tumors were resistant to LV/5FU alone (the FOLFOX regimens; FOLinic acid, 5FU, OXaliplatin). Various doses and schedules of administration have been evaluated with the aim of defining the regimen that provides optimal efficacy with minimal toxicity (26-31).

The benefit of adding oxaliplatin to LV/5FU in the first-line therapy for patients with metastatic colorectal cancer has been demonstrated in two large international, multicentre, randomized phase III trials (24). The first study involved 200 patients who received a chronomodulated LV/5FU regimen, with or without oxaliplatin, 125 mg/m2, as a 6-hour infusion. Objective tumor responses were observed in 53% of patients in the combination arm compared with only 16% of patients receiving LV/5FU alone ($p<0.0001$). After a median follow-up period of 47 months, median progression-free survival was significantly greater in the in the oxaliplatin group compared with the controls (8.7 months vs. 6.1 months, respectively, $p=0.048$). However, overall survival rates were similar in both groups (19.9 months and 19.4 months).

Nonetheless, the combination therapy allowed more patients to undergo potentially curative surgery of metastases than in those

receiving LV/5FU alone (32% vs. 21% respectively). In the second randomized study, the role of oxaliplatin in combination with LV5FU2 in the first-line therapy for advanced colorectal cancer was evaluated in 420 patients (25). Subjects received LV5FU2 with or without oxaliplatin (85 mg/m2, administered as a 2- hour infusion) and were followed up for a median period of 28 months. Objective tumor responses were achieved in 51% of patients receiving both regimens, compared with 22% of those allocated to LV5FU2 alone (p=0.0001). Progression-free survival was significantly improved in the oxaliplatin group compared with the control group (9.0 months vs. 6.2 months respectively, p=0.0001). One-year survival rates were 69% in the oxaliplatin group and 59% for the controls, although this difference was not significant. However, metastectomy was possible in twice as many subjects receiving oxaliplatin as among those receiving LV5FU2 alone (6.7% vs. 3.3%). In both of these large studies, the addition of oxaliplatin to LV/5FU regimens was associated with significant differences in tumor response rates and progression-free survival. Although a survival benefit was not demonstrated in these studies, this cannot be ruled out on the basis of these results alone. It is possible that a survival benefit was obscured due to crossover from the control group to the oxaliplatin arm that occurred in both trials. In the first of these studies, 57% of patients allocated to the LV/5FU control arm received oxaliplatin as second-line therapy and; therefore, comparison of the overall survival rates in the two treatment arms may be misleading. Importantly, multivariate analysis of the second randomized study showed that oxaliplatin was a strong independent predictor of overall survival (25).

Irinotecan

Irinotecan is a semisynthetic camptothecin analogue that has activity against advanced colorectal cancer cells. Phase II trials have demonstrated that this agent is effective in patients whose disease has progressed on 5FU-based therapy (30). Responses were demonstrated in the patients who had recurred or progressed following 5-FU based therapy. CPT-11 was granted an accelerated approval by the FDA on the basis of 304 patients included in three phase II trials and other supportive data. Two CR and 27 PR out of 193 patients (overall response rate of 15%), relapsing or progressing after 5-FU therapy were treated at the approved starting dose of 125 mg/m^2. The first large randomized phase III trial V-301 compared best supportive care alone or in combination with CPT-11 in 279 patients. A significant survival advantage was demonstrated in the CPT-11 group compared with the patients receiving supportive care only (1-year overall survival: 36.2 vs. 13.8%, p=0.001**)** (31). The second large randomized phase III trials V 302 (32) compared CPT-11 single drug versus the best estimated 5-FU based regimen (de Gramont regimen). Response rate, survival, and time to progression were significantly higher in CPT-11 group than 5-FU group (RR 4.2 vs. 2.9 months; survival 6.4 vs. .5.1 months; TTP 10.3 vs. 8.5).

In randomized phase II setting study (V-239) (33), the activity of CPT-11 single agent and that of 5-FU/LV (standard Mayo clinic regimen) was studied. One hundred and fifty-nine patients were randomized overall and 156 patients were treated. The overall response rate was 15.4% in CPT-11 treatment group and 9.9% in 5-FU/LV group. Duration of response and stabilization was 7.0 months in CPT-11 treatment group and 5.6 months in 5-FU/LV group (log rank test p=0.015); time to progression was 6.4 months in CPT-11 treatment group and 3.9 months in 5-FU/LV group (log rank test, p=0.028). The safety profile for each drug was as expected. The most frequent adverse events (gr. 3-4 by patient) in the CPT-11 group were neutropenia 41%, diarrhea 25%, nausea 5%, vomiting 9% and asthenia 1%. The most frequent adverse events in the 5-FU/LV group were neutropenia 42%, mucositis 13% vomiting 7% and diarrhea 9%.

A large phase III randomized trial in the patients with metastatic colorectal cancer previously untreated with chemotherapy for advanced disease (total of 387 randomized) demonstrates a significant superiority of combining CPT-11 with 5-FU/LV infusional regimen over the same infusional 5-FU/FA alone. Two different 5-FU/LV infusional regimens were used according to the center: AIO 24-hour infusion weekly x 6 weeks every 7 weeks or de Gramont bolus + 22 hour infusion daily x 2 every 2 weeks. Patient and tumor characteristics were representative of metastatic colorectal cancer population. Significantly higher response rate (41% vs. 23% in per protocol population, p<0.001), longer median duration of response and stabilization (8.6 vs. 6.2 months, p<0.001), longer median TTP (6.7 vs. 4.4 months, p<0.001), longer median time to treatment failure (5.3 vs. 3.8 months, p<0.001) were observed on CPT-11 combination group. In the multivariate analysis on response rate and time to progression, and after adjusting for the most significant covariates, the odds for response was significantly in favor of CPT-11 combination treatment (odds-ratio=2.56, p<0.001) and the risk of progression was significantly higher on 5-FU/LV alone (risk-ratio=1.62, p<0.001). The significantly higher response rate (per protocol population) was also true according to the regimen used: 51% vs. 29% (p=0.045) in the weekly schedule and 38% vs. 22% (p=0.005) in the every 2 weeks schedule. For time to progression and survival, given the uneven distribution in both regimens, statistical significance could only be drawn in patients in the 48-hour infusional regimen group. Both combination regimens, (weekly and every 2 weeks), were feasible at the dose and schedule planned in the study. Although a lower median relative dose intensity was achieved with the weekly combination regimen due to more frequent dose delays and dose reductions, the cumulative dose of 5-

FU was higher with this regimen compared with the every 2 week regimen resulting in a high efficacy profile. Indeed, the weekly schedule per se offers a higher flexibility both in the safe management of severe toxicities and in the adaptation to practical convenience. As expected, a higher incidence of toxicities occurred in the CPT-11 combination group than in the 5-FU/Lvgroup without CPT-11. Diarrhea and neutropenia were the most frequent toxicities with the CPT-11 combination. However, diarrhea grade 3-4 (21.6%) was in the range of what is usually reported with CPT-11 single agent although the highest incidence was observed in the weekly schedule (44.4% of patients and 18.8% of cycles). Conversely, neutropenia was more frequent on the every two-week combination regimen. Alopecia was experienced by 48% of patients in the CPT-11 combination group and by 15% in 5- FU/LV group without CPT-11. According to the regimen used, grade 1 and 2 alopecia was experienced by 26% and 11 % of patients, respectively in the combination with the AIO regimen. In the combination with the de Gramont regimen, grade 1 and 2 alopecia was experienced by 32% and 25% of patients, respectively. In the 5-FU/LV group without CPT-11, grade 1 and 2 alopecia was experienced by around 12% and 5% of patients, respectively, irrespective of the regimen used. The safety profile of the CPT-11 combination group compares favorably with that usually reported with CPT-11 as a single agent. The evolution of Global health status (QL) was slightly better in the CPT-11 combination group. The median time to deterioration of QL by 5% or 20% significant over baseline was significantly longer with the CPT-11 combination and was close to statistical significance for the 10% and 30% levels of deterioration. The benefits resulting from the higher efficacy and better quality of life on CPT-11 combination counterbalance the safety profile which is comparable to that of other combination chemotherapies e.g. in breast and lung cancers. CPT-11 in combination with 5-FU/FA infusional should be considered as the treatment of choice in first-line treatment of advanced colorectal cancer (2).

Irinotecan combinations compared to oxaliplatin combinations

In the Intergroup study N9741 695 patients with previously untreated metastatic colorectal cancer who received a combination of 5FU/LV with irinotecan (IFL), 5FU/LV with oxaliplatin (FOLFOX 4 regimen) or oxaliplatin and irinotecan were randomized (34). The results showed that the Folfox 4 regimen was superior to the other two arms: the survival, TTP and response rate were significantly higher, but time to treatment failure was identical. Median survival, median TTP and response rate were IFL 14.1months, 6.9 months and 29%, Folfox 4 18.6 months, 8.8 months and 38% and oxaliplatin+irinotecan 16.5 months, 6,7 months and 29%, respectively. In the Folfox regimen, however, infusional 5FU/LV is used, while in the IFL regimen a weekly bolus 5FU/LV is used. Infusional regimens are known to produce a higher response rate and longer TTP compared with bolus regimens of 5FU/LV.

Tomudex (Raltitrexed)

Tomudex is a selective folate-based thymidylate synthase inhibitor without other effects on DNA or RNA. It requires transport by the cell membrane reduced folate carrier for cellular uptake, and polyglutamation by the enzyme folylpolyglutamate synthetase for optimal TS inhibition. A large phase II study in untreated patients with colorectal cancer demonstrated a 26% overall response rate in 176 patients with a median time to progression of 4.2 months and a median survival of 9.6 months. WHO grade 3-4 leucopenia and diarrhea were seen in 6% and 9.8% of patients respectively (35). In a European phase 3 trial, this drug was compared with the most commonly used 5FU/leucovorin regimen. Recorded response rates were low in both arms of the study, although a little higher in the raltitrexed arm (16.5% and 20%). There was not difference in survival.

Oral fluoropyrimidines

Oral fluoropyrimidines are as active as intravenous fluoropyrimidines. Compared to intravenous 5FU, oral fluoropyrimidines have safety advantages, clinical benefits and are more convenient for patients. Three oral drugs have been developed: eniluracil, capecitabine and uracil / tegafur (UFT). Two randomized phase III studies comparing oral eniluracil (5-ethynyluracil) dihydropyrimidine dehydrogenase inactivator plus 5FU with intravenous bolus 5FU/LV for advanced colorectal cancer found decreased survival in the eniluracil arms. Both studies suggested that eniluracil / 5FU was inferior to a standard intravenous 5FU / LV regimen so eniluracil was withdrawn from further study (36,37).

Capecitabine, a fluoropyrimidine carbamate, is not intrinsically cytotoxic, but is converted to 5FU in tumor tissue through three enzymatic steps. Two large, randomized, multicentre phase III studies compared intermittent capecitabine (1250 mg/m^2 b.i.d. for 14 days followed by a 7 day rest) with intravenous bolus 5FU/LV (Mayo Clinic regimen) as first-line treatment of metastatic colorectal cancer. The trials had identical protocols, conduct and monitoring. In both trials, capecitabine had a superior response rate, equivalent overall survival and time to disease progression and more favorable safety profile than 5FU/LV (38,39). Integrated analysis of the data from these two studies (1207 participants) found a higher response rate in the capecitabine arm than with the Mayo regimen (26% vs. 17%). Median time to disease progression was equivalent (4.6 months with capecitabine and 4.7 months with 5FU/ LV). Median overall survival was 12.9 months with capecitabine and 12.8 months with 5FU / LV. Grade

3-4 neutropenia was more frequent with 5FU / LV than with capecitabine (21.1% vs. 2.2%). Grade 3 hand-foot syndrome occurred more frequently in the capecitabine group (17.1% vs. 0.5%). Diarrhea, stomatitis, nausea, alopecia and hospitalization for adverse events were less frequent with capecitabine (40).

UFT is an oral combination of uracil and 5FU prodrug tegafur (1-2(tetrahydrofuranyl)-5-fluorouracil) in a fixed molar ratio of 4:1. Uracil prevents 5FU degradation by inhibiting dihydropyrimidine dehydrogenase, which is the primary catabolic enzyme for 5FU. Tegafur converted by cytochrome P450 izozymes in the liver to 5FU has the same anti-tumor activity and metabolism as IV 5FU. Both uracil and tegafur are well absorbed after oral administration (41,42). UFT increases in efficacy when combined with LV due to dual modulation of 5FU at the level of dihydropyrimidine dehydrogenase and at the level of the thymidylate synthase-ternary complex (42).

Several studies phase I and II have assessed varying regimens of UFT with or without LV for advanced colorectal cancer (43-47). The optimal dosage is 300-400 mg/m^2/day UFT in three divided doses for 28 days every 35 days with 60-150 mg/day LV. The overall response rate ranges from 19% to 43% and median time to progression ranges from 4.4 months to 6.8 months. Most participants in these trials had not received previous adjuvant 5FU based chemotherapy. The major dose-limiting toxicities were diarrhea, nausea and vomiting, mucositis and abdominal cramps. Due to the high response rate and a favorable toxicity profile reported in phase II studies, randomized phase III studies were initiated to compare UFT and oral leucovorin to a standard Mayo Clinic regimen of bolus 5FU/LV. In the study by Douillard and colleagues (48) the primary efficacy analysis was based on survival. The secondary efficacy parameters included response rates and quality of life. There were no differences between groups in performance status, age, previous adjuvant therapy, and tumor burden or secondary chemotherapy. The study found that UFT/LV was as effective as intravenous 5FU/LV and better tolerated in the palliation of patients with metastatic colorectal cancer. Survival and overall response rate were equivalent, however, the response rate for UFT/LV was much lower than in several phase II studies. The reasons for this are unclear, but it is possible that patient selection factors played a part.

Patients treated with UFT/LV experienced less severe hematologic and nonhematologic toxicity compared to 5FU / LV. The incidence of severe diarrhea, the most common side effect associated with UFT/LV, was not statistically significant (21% v 16%). There was a significant difference in median time to progression between the UFT/LV and 5FU/LV arms in favor of 5FU/LV, but tumor assessment schedules differed between arms.

Carmichael and colleagues conducted a randomized phase III trial with an identical protocol where the primary efficacy analysis was time to progression. There was no significant difference in time to progression between the UFT/LV and 5FU/LV arms (3.4 months v 3.3 months respectively). In Carmichael's study, 380 people received either UFT (300 mg/m^2/day) plus LV (90 mg/day), administered for 28 days every 35 days, or an intravenous Mayo Clinic regimen of bolus 5FU/LV every 35 days. The Mayo Clinic regimen was used every 35 days to avoid an assessment bias on the primary study endpoint by allowing patients to be assessed every 5 weeks before each course. The median survival time was 12.2 months for UFT/LV and 10.3 months for 5FU / LV with response rates of 11% and 9% respectively (49).

These two randomized trials, and others with oral fluoropyrimidines, suggest that UFT/LV and capecitabine provide an equally effective, but safer, oral alternative to the standard intravenous bolus 5FU/LV regimen for metastatic colorectal cancer (38,39). In general, patients express a preference for oral chemotherapy as long as the treatments are equally effective in terms of convenience and access to medication outside the clinic (50). For example, in a randomized trial comparing patients' preferences for first-line oral or intravenous treatment, each participant received at least one cycle of oral UFT (300 mg/m^2/day) and LV (90 mg/day), administered in three divided doses for 28 days every 35 days, or one cycle of intravenous bolus 5FU/LV (Mayo Clinic regimen). Most participants preferred oral UFT/LV and continued oral treatment because it interfered less with their daily activities and was associated with fewer adverse effects (51). Another study suggests that quality of life is significantly reduced in people who receive hospital-administered chemotherapy compared to those having home-based treatment (52).

UFT/LV and capecitabine are effective and well-tolerated drugs. In the future, they may replace intravenous 5FU/LV as a first-line therapy for people with metastatic colorectal cancer, especially in cases when combination chemotherapy with irinotecan or oxaliplatin is not suitable. Ongoing studies of UFT/LV combinations with oxaliplatin, irinotecan, or both may further improve palliative treatment of people with advanced colorectal cancer.

CONCLUSION

Adjuvant chemotherapy with 5FU/LV combination is now accepted as an effective, standard treatment following surgery for stage III colorectal cancer. Current clinical trials are investigating new agents, such as oral fluoropyrimidines, irinotecan and oxaliplatin, in the adjuvant setting. However, despite improvements in survival with adjuvant chemotherapy there is still a high risk of recurrence following surgery and the prognosis for patients with advanced disease remains poor. In patients with advanced disease several newer agents, in particular, irinotecan and oxaliplatin have recently become accepted treatment strategies, offering the chance of prolonged survival. Furthermore oral fluoropyrimidines

provide an equally effective, but safer, oral alternative to the standard intravenous bolus 5FU/LV regimen for metastatic colorectal cancer and they are more convenient for patients.

Many newer agents are being studied such as doxifluridine, new inhibitors of thymidylate synthase (ZD9331), oral camptothecins (Rubitecan), multitarget antifolate antimetabolite (Premetrexet), inhibitors of epidermal growth factor receptor (Cetuximab), COX-2 inhibitors (celecoxib) and farnesyltransferaze inhibitors (Zarnestra). Molecular biology and studies of cancer vaccines are providing a growing number of tools for targeting a colorectal cancer. The ability to target these new approaches to tumors based on molecular profiling, raises the possibility for future biotherapeutic targeting of colorectal cancer.

REFERENCES

1. Boyle P. Some recent developments in the epidemiology of colorectal cancer In: Bleiberg H, Rougier P, Wilke HJ, editors. Management of colorectal cancer London: Martin Dunitz; 1998. p. 19-34.
2. Midgley RS, Kerr DJ. Systemic adjuvant chemotherapy for colorectal cancer. In: Bleiberg H, Rougier P, Wilke HJ, editors. Management of colorectal cancer London: Martin Dunitz; 1998. p. 126-37.
3. (the) Nordic gastrointestinal Tumour Adjuvant Therapy Group. Expectancy or primary chemotherapy in patients with advanced asymptomatic colorectal cancer: A randomised trial. J Clin Oncol 1992;10:904-11.
4. Scheithauer W, Rosen J, Kornek CV, Sebesta C, Depisch D. Randomised comparison of combination chemotherapy plus supportive care with supportive care alone in patients with metastatic colorectal cancer. Br Med J 1993;306:752-5.
5. Peters GJ, van der Wilt CL, van Groeningen CJ, Laurensse EJ, Pinedo HJ. Thymidylate synthase inhibition after administration of fluorouracil with or without Leucovorin in colon cancer patients: implications for treatment with fluorouracil. J Clin Oncol 1994;12:2035-42.
6. Benz C, Cadman E. Modulation of 5-fluorouracil metabolism and cytotoxicity by antimetabolite pre-treatment in human colorectal adenocarcinoma HCT-8. Cancer Res 1981;41:994-9.
7. IMPACT: Efficacy of adjuvant fluorouracil and folinic acid in B2 colon cancer. J. Clin. Oncol 1999;17:1356-63.
8. Moertel CG, Fleming TR, Macdonald JS, Haller DG, Laurie JA, Tangen CM et al. Fluorouracil plus levamisole as effective adjuvant therapy after resection of stage III colon carcinoma: a final report. Ann. Internal Med 1995;122:321-6.
9. IMPACT: Efficacy of adjuvant fluorouracil and folinic acid in colon cancer. Lancet 1995;345:934-44.
10. O'Connell MJ, Laurie JA, Kahn M, Fitzgibbons RJ, Erlichman C, Shephard L et al. Prospectively randomised trial of postoperative adjuvant chemotherapy in patients with high-risk colon cancer. J Clin Oncol 1999;16(1):295-300.
11. Wolmark N, Bryant J, Smith, Grem J, Allegra C, Hyams D et al. Adjuvant 5-FU and leucovorin with or without interferon alpha-2a in colon carcinoma: NSABP C-05 protocol J Natl Canc Inst 1998;90:1810-91.
12. Piedbois P, Buyse M, Gray R et al. Portal vein infusion is an effective adjuvant treatment for patients with colorectal cancer. Proc Am Soc Clin Oncol 1995;14:444.
13. Reithmuller G, Schneider-Gradicke E, Schlimok G, Schmiegel V, Raab R, Hoffken K et al. Randomised trial of monoclonal antibody for adjuvant therapy of resected Dukes' C colorectal carcinoma. Lancet 1994:343;1177-81.
14. Haller DG. Fluorouracil, leucovorin and levamisole adjuvant therapy for colon cancer; preliminary results of INT-0089. Proc Am Soc Clin Oncol 1996;15:486.
15. International multicentre pooled analysis of colon cancer trials (IMPACT) investigators. Efficacy of adjuvant fluorouracil and folinic acid in colon cancer. Lancet 1995;345:939-44.
16. The Advanced colorectal cancer meta-analysis project. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: evidence in terms of response rate. J Clin Oncol 1992;10:896-903.
17. (the) Meta-analysis Group in cancer: Efficacy of intravenous continuous infusion of fluorouracil compared with bolus administration in advanced colorectal cancer. J Clin Oncol 1998;16:301-8.
18. de Gramont A, Bosset JF, Milan C, Rougier P, Bouche O, Etienne PL et al. Randomised trial comparing monthly low-dose leucovorin and fluorouracil bolus with bimonthly high-dose leucovorin and fluorouracil bolus plus continuous infusion for advanced colorectal cancer; a french intergroup study. J Clin Oncol 1997;15:808-15.
19. Kohne CH, Schoffski P, Wilke H, Kaufer C, Andreesen R, Ohl U et al. Effective biomodulation by leucovorin of high-dose infusion fluorouracil given as a weekly 24-hour infusion: Results of a randomised trial in patients with advanced colorectal cancer. J Clin Oncol 1998;16:418-26.
20. Aranda E, Diaz-Rubio E, Cervantes A, Anton-Torres A, Carrato A, Massuti T et al. Randomised trial comparing monthly low-dose leucovorin and fluorouracil bolus with weekly high-dose 48-hour continuous-infusion fluorouracil for advanced colorectal cancer: Spanish Cooperative Group for gastrointestinal Tumour Therapy (TTD) study. Ann Oncol 1998;9:727-31.
21. Weh HJ, Zschaber R, Cunningham D et al. A randomised phase III study comparing weekly folinic acid (FA) and high-dose 5- fluorouracil (5-FU) with monthly 5-FU/FA (day 1-5) in untreated patients with metastatic colorectal carcinoma. Onkologie 1988;21:403-7.
22. Diaz-Rubio E, Sastre J, Zariboni A, Labianca R, Cortes-Funes H, de Braud F et al. Oxaliplatin as single agent in previously untreated colorectal carcinoma patients: a phase II multicentric study. Ann Oncol 1998;9:105-8.
23. Levi F, Misset JL, Brienza S, Adam R, Metzger G, Itzakhi M et al. A shronopharmacologic phase II clinical trial with 5-fluorouracil, folinic acid and oxaliplatin using an ambulatory multichanel programmable pump: high antitumor effectiveness against metastatic colorectal cancer. Cancer 1992;69:9893-900.
24. S, Perpoint B, Zidani R, Lebail N, Fagginalo R, Focan C et al. Phase III multicenter randomized trial of oxaliplatin added to chronomodulated fluorouracil-leucovorin as first line treatment of metastatic colorectal cancer. J Clin Oncol 2000;18:136-47.
25. deGramont A, Figer A, Seymour M, Homerin M, Hmissi A, Cassidy J et al. Leucovorin and 5-fluorouracil with or without oxaliplatin in advanced colorectal cancer. J Clin Oncol 2000;23:136-47.
26. deGramont A, Gastiaburu J, Tournigand C et al. Oxaliplatin with high-dose folinic acid and 5-fluorouracil 48 hour infusion in preatreated metastatic colorectal cancer. Proc AM Soc Clin Oncol 1994;13:220.
27. Andre T, Bensmaine MA, Louvet C, Srancois E, Lucas V, Desseigne F et al. Multicenter phase II study of bimonthly high-dose leucovorin, fluorouracil infusion and oxaliplatin for metastatic colorectal cancer resistant to the same leucovorin and fluorouracil regimen. J Clin Oncol 1999;17:3560-8.

28. Maindrault-Goebel F, Louvet C, Andre T, Carola E, Lotz JP, Molitor JL et al. Oxaliplatin added to the simplified bimonthly leucovorin and 5-fluorouracil regimen as second line therapy for metastatic colorectal cancer (FOLFOX 6). Eur J Cancer 1999;35:1338-42.

29. Maindrault-Goebel F, deGramont A, Louvet C et al. High-dose intensity oxaliplatin added to the simplified bimonthly leucovorin and 5-fluorouracil regimen as second line therapy for metastatic colorectal cancer (FOLFOX 7). Proc Am Soc Clin Oncol 1999;18:265.

30. Pitot HC, Wender D, O'Connell M et al. A phase II trial of CPT-11 (irinotecan) in patients with metastatic colorectal carcinoma. A North Central Cancer Treatment Group (NCCTG) study. Proc Am Soc Clin Oncol 1994;13:573.

31. Cunningham D, Pyrhonen D, James RD, Punt CJ, Hickish TF, Heikkila R et al. Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. Lancet 1998;352:1413-8.

32. Rougier P, van Cutsem E, Bajetta E, Niederle N, Possinger K, Labianca R et al. Randomised trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure for patients with metastatic colorectal cancer. Lancet 1998;352:1407-18.

33. Conti JA, Nancy E, Kemeny E, Huang Y, Tong WP, Chou TC et al. Irinotecan is an active agent in untreated patients with metastatic colorectal cancer. J Clin Oncol 1996;14:709-15.

34. Goldberg RM. N9741: a phase III study comparing irinotecan to oxaliplati-containing regimens in advanced colorectal cancer. Clin Colorectal Cancer 2002;2:81.

35. Jackman AL, Farrugia DC, Gibson W, Kimbell R, Harrap KR, Stephens TC et al. ZD 1694 (Tomudex): A new thymidylate synthase inhibitor with activity in colorectal cancer. Eur J Cancer 1995;31:1277-82.

36. Levin J, Schilsky R, Burris H et al. North American phase III study of oral eniluracil (EU) plus oral 5-fuorouracil (5-FU) versus intravenous (IV) 5-FU plus leucovorin (LV) in the treatment of advanced colorectal cancer (ACC). Proc Am Soc Clin Oncol 2001;20 (Abstract 523).

37. van Custen E, Sorensen J, Cassidy J et al. International phase III study of oral eniluracil (EU) plus 5-fuorouracil (5-FU) versus intravenous (IV) 5-FU plus leucovorin (LV) in the treatment of advanced colorectal cancer (ACC). Proc Am Soc Clin Oncol 2001;20:(Abstract 522).

38. Hoff PM, Ansari R, Batis G, Cox J, Kocha W, Kuperminc M et al. Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: results of a randomized phase III study. J Clin Oncol 2001;19:2282-92.

39. Cutsem E, Twelves C, Cassidy J, Allman D, Bajetta E, Boyer M et al. Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large phase III study. J Clin Oncol 2001;19:4097-106.

40. Hoff PM. Capecitabine as first-line treatment for metastatic colorectal cancer (CRC): integrated results of 1207 patients (pts) from 2 randomized, phase III studies. Ann Oncol 2000;11Suppl.4:60(Abstract 263).

41. Rustum YM, Maestrick A, Cao S, Vanhoefer U, Yin MB, Wilke H et al. Thymidylate synthase inhibitors in cancer therapy: direct and indirect inhibitors. J Clin Oncol 1997;15:389-400.

42. Wellington K, Goa KR. Oral tegafur/uracil. Drugs & Aging 2001;18:935-50.

43. Pazdur R, Lassere Y, Rhodes V, Ajani JA, Sugarman SM, Patt YZ et al. Phase II study of uracil and tegafur plus oral leucovorin: An effective oral regimen in the treatment of metastatic colorectal cancer. J Clin Oncol 1994;12:2296-300.

44. Gonzales-Baron M, Feliu J, de la Gandara I, Espinosa E, Colmenarejo A, Martinez B et al. Efficacy of oral tegafur modulation by uracil and leucovorin in advanced colorectal cancer: A phase II study. Eur J Cancer 1995;31:2215-9.

45. Feliu J, Gonzales-Baron M, Espinosa E, Garcia Giron C, de la Gandara I, Espinosa J et al. Uracil and tegafur modulated with leucovorin: An effective regimen with low toxicity for the treatment of colorectal cancer. Cancer 1997;79:1884-9.

46. Saltz LB, Leichman CG, Young CW, Muggia FM, Conti JA, Spiess T et al. A fixed-ratio combination of uracil and ftorafur (UFT) with low dose leucovorin. Cancer 1995;75:782-5.

47. Diaz-Rubio E, Sastre J, Abad A, Navarro M, Aranda E, Carrato A et al. UFT plus or minus calcium folinate for metastatic colorectal cancer in older patients. Oncology 1999;13 Suppl:35-40.

48. Douillard JY, Hoff PM, Skillings JR, Eisenberg P, Davidson N, Harper P et al. Multicenter phase III study of uracil / tegafur and oral leucovorin versus fluorouracil and leucovorin in patients with previously untreated metastatic colorectal cancer. J Clin Oncol 2002;20:3605-16.

49. Carmichael J, Popiela T, Radstone D, Falk S, Borner M, Oza A et al. Randomized comparative study of tegafur / uracil and oral leucovorin versus parenteral fluorouracil and leucovorin in patients with previously untreated metastatic colorectal cancer. J Clin Oncol 2002;20:3617-27.

50. Liu G, Franssen E, Fitch M, Warner E. Patient preferences for oral versus intravenous palliative chemotherapy. J Clin Oncol 1997;15:110-5.

51. Borner M, Schöffski P, de Wit R et al. A randomized crossover trial comparing oral UFT (uracil/tegafur) + leucovorin (LV) and intravenous fluorouracil (FU) + LV for patient preference and pharmacokinetics in advanced colorectal cancer. Proc Am Soc Clin Oncol 2000;19:191a (Abstract 741).

52. Payne SA. A study of quality of life in cancer patients receiving palliative chemotherapy. Soc Sci Med 1992;35:1505-9.