The development of clinical research in CRC


Department of Medical Oncology, Ospedali Riuniti, Bergamo, Italy

Introduction

Carcinoma of the colon and the rectum (colorectal cancer) is one of the most common tumor types in the Western world (worldwide it is the fourth most frequently diagnosed malignant disease). Colorectal cancer represents a heterogeneous group of disease that are different for aetiology, incidence, anatomopathological characteristics, clinical history, treatment and prognosis.

Until 15–20 years ago the treatment of this kind of cancer was very difficult due to the lack of available therapies and the poor efficacy of the same.

5-Fluorouracil (5-FU) administered in several schedules since its introduction in 1957 continues to be an integral part of standard first-line therapy for colorectal cancer. Continuous intravenous (i.v.) infusion appears to yield improved response rate and overall survival, with fewer adverse effects compared with i.v. bolus dosing.

The detection of new cytotoxic drugs and treatment regimens, the development of new combination schedules and, above all, of integrate therapy strategies allowed a significant improvement in the treatment of colorectal cancer.

The recent improvement in molecular biology and the consequently development of drugs oriented to biological target seems to be able to reach further goals in gastrointestinal cancer therapy.

The goal of this article is to review newer cytotoxic treatments and biological agents employed for the systemic treatment of colorectal cancer.

Primary surgical therapy/staging and other prognostic indicators

Surgery still remains the cornerstone of treatment for patients with localized colorectal cancer.

The role of laparoscopic techniques in the treatment of colon cancer has been examined recently in different studies showing that, in presence of surgeons with extensive experience, the LAC (laparoscopic-assisted colectomy) gives, at least, non-inferior results in comparison with standard surgery [1–3].

Pathological stage at the time of the detection of the malignancy represents the most important prognostic indicator. The Tumor Node Metastasis (TNM) system of the American Joint Committee on Cancer is now accepted worldwide for staging colorectal cancer and to allow prediction of the expected survival of patients.

The role of sentinel lymph node mapping is also under clinical evaluation, but definitive data are not available [4, 5].

Many studies have demonstrated the utility of chemotherapy in metastating setting in order to prolong survival and improve quality of life compared with palliative care alone [6–8].

Fluorouracil

The cornerstone of medical treatment of colorectal cancer is still represented by fluorouracil, a fluorinated pyrimidine, which acts to inhibit the key enzyme in pyrimidine nucleotide synthesis, thymidylate synthase [9].

The addition of leucovorin, a folate, which stabilize the binding of fluorouracil to the enzyme, enhances the inhibition of DNA synthesis [10].

For a long time the standard treatment for advanced colorectal cancer in the USA was based on intravenous (IV) fluorouracil (5-FU) modulated by calcium leucovorin (LV) using the Mayo Clinic regimen (a 5-day schedule of 5-FU, 370 to 425 mg/mq/day, and LV 20 mg/mq/day repeated every 4–5 weeks). Some studies suggest that this association improves the response rate as compared with single-agent 5-FU, but such an improvement has not been clearly translated into a survival advantage [11].

The side effects of fluorouracil depend on the method of administration of the drug. When the bolus schedule is employed neutropenia, diarrhea and stomatitis are the most common side effects because, when fluorouracil is administered by continuous intravenous infusion, palmar-plantar erythrodysesthesia is more common with less hematologic and gastrointestinal toxicity [12–14].

Although the protracted infusion require portable infusion pumps and central venous lines, which are associated with

*Correspondence to: R. Labianca, Gastrointestinal Oncology Unit, Department of Medical Oncology, Ospedali Riuniti, Bergamo, Italy; Tel: +39 035 269724; Fax: +39 035 266849; E-mail: segroncologia@ospedalirinuniti.bergamo.it

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Oral fluoropyrimidines

New orally-administered fluoropyrimidines provide protracted 5-FU delivery, which offers advantages including schedule flexibility and reductions in professional health care resource requirements, administration costs, and toxicity-related hospitalization [19]. These advantages may reduce the overall cost of treatment [20].

Capcitabine is a fluorouracil prodrug with a side-effect profile similar to that of protracted infusion of fluorouracil [21–23]. In comparison to the monthly schedule of fluorouracil and leucovorin [22, 23], the rate of objective response was moderately better in the arm of capcitabine treatment with similar overall survival.

UFT is an orally administered dihydropyrimidine dehydrogenase (DPD) inhibitory fluoropyrimidine composed of a fixed combination of tegafur and uracil in a 1:4 molar ratio. Tegafur is an orally bioavailable prodrug of 5-FU and it is metabolized into 5-FU following intestinal absorption; uracil reversibly inhibits the primary catabolic enzyme for 5-FU, which is represented by DPD, maintaining active drug levels for a prolonged period and thus simulates a continuous infusion of 5-FU. This inhibition predominates in tumour cells over normal tissues so that the combination increases the tumour concentration and antineoplastic activity of 5-FU.

The principal dose-limiting toxicities associated with oral UFT are myelosuppression [24] or gastrointestinal toxicities [25], depending on the administration schedule. The toxicities are always lower than toxicities associated with infused-FU/LV.

UFT is commonly used in Japan. Japanese investigators studied UFT about 20 years ago but interpretation of the data was difficult because dissimilar methodologies, criteria, and standards were used [26]. Results of these studies have demonstrated that UFT administered at dose of 300–600 mg/day is extremely well-tolerated and shows evidence of antitumour activity in a wide variety of solid tumours [27].

Since the initial studies using UFT alone have produced encouraging results, researchers have proposed using an additional modulator, such as LV, to act on the anabolism of 5-FU by increasing available reduced folates and thereby stabilizing the binding of 5-FdUMP to TS. Orzel™ is the tradename for the combination UFT/LV.

UFT achieves a response rate of 25–42% when modulated with LV in the treatment of advanced colorectal cancer [28–30], a rate similar to that achieved with 5-FU/LV.

In monotherapy, oral fluoropyrimidines appear to have a good safety and cost-effectiveness profile when compared with monthly bolus schedule, but is still unclear if these benefits would remain when compared with weekly bolus or when oral fluoropyrimidines are administered in combination with other parenteral chemotherapies.

Adjuvant therapy

Many early trials of adjuvant chemotherapy failed to show a significant improvement in either overall or disease-free survival for patients receiving treatment compared to concurrently randomized control patients receiving no adjuvant therapy. Perhaps this is because previous studies included a limited number of patients with a suboptimal adherence to treatment [31–34].

More recent randomized trials have shown that intravenous fluorouracil with or without leucovorin did improve results in patients with stage III disease [35–38].

At this time, there are not sufficient data to determine if there is any advantage to the 3-drug combination of 5-FU, leucovorin and levamisole over any of the previously noted 2-drug regimens. There are also insufficient data to distinguish whether high-dose, intermediate-dose, or low-dose leucovorin is most advantageous as a modulator of 5-FU.

Oral fluoropyrimidines therapies (capcitabine or UFT) appear to guarantee equivalent efficacy to parenteral fluorouracil [39, 40]. Randomized trials indicate that elderly patients (>70 years) derived equal benefit from adjuvant treatment as younger individuals and should not be excluded from these treatments based solely on age [41].

The potential value of adjuvant therapy for patients with stage II colon cancer remains controversial. The results of the studies are contradictory. Investigators from the NSABP have indicated that the reduction in risk of recurrence by adjuvant therapy in patients with stage II disease is of similar magnitude to the benefit seen in patients with stage III disease treated with adjuvant therapy, although an overall survival advantage has not been established [42].

A randomized trial of postoperative 5-FU plus levamisole compared to surgery alone, showed no survival advantage to postoperative adjuvant chemotherapy [43].

Patients with stage II colon cancer remain candidates for clinical trials in which either surgery alone or 5-FU-leucovorin represents standard therapy [44–46].
Metastatic disease

At this time, there is a role for combination chemotherapy as first line treatment in fit patients.

Recently, many authors demonstrated the superiority of the combination treatments (Oxaliplatin or Irinotecan plus fluorouracil/leucovorin) which are to be considered, to date, the standard as first-line therapy for patients with metastatic colorectal cancer.

The use of regimen with only 5-FU modulated by leucovorin has to be reserved for those patients not able to stand a combination treatment.

Oxaliplatin (Eloxatin), a new platinum derivative, combined with 5-FU and leucovorin, has shown promising activity in previously treated and untreated patients with metastatic colorectal cancer and in patients with 5-FU refractory disease [47–51].

Differently from cisplatin and carboplatin, the major side effect of oxaliplatin is the neuropathy (dysestesias and paresthesias) usually dose-dependent, transient and diminishing after the cessation of treatment.

The use of oxaliplatin in combination has been studied in a randomised trial in which it was compared with 5-FU and leucovorin alone in the treatment of chemotherapy-naive patients [52]. Response rates and progression-free survival of the oxaliplatin-based regimen were essentially double that of the fluorouracil and leucovorin regimen, while overall survival was not significantly different between the two groups. At the ASCO 2002 meeting, data were reported on the weekly combination of oxaliplatin/5-FU/LV (FUFOX) and FOLFOX4 regimen [53].

In both cases the oxaliplatin combination showed advantages in response rate, time to progression and overall survival compared with the control arm.

Irinotecan (Camptosar, CPT-11) a topoisomerase-I inhibitor, showed a 10–20% partial response rate in patients with metastatic colon cancer. It is active both in chemotherapy-naive patients and in patients progressing on 5-FU therapy. [54, 55] The most frequent toxic effects include diarrhea, nausea and vomiting, bone marrow suppression and alopecia.

Two randomized European trials compared CPT-11 with either retreatment with infusional 5-FU or best supportive care in patients with colorectal cancer refractory to 5-FU. In both trials, survival and quality-of-life was better for patients treated with CPT-11 over 5-FU or supportive care [55, 56]. Two phase III prospective randomized, controlled trials were designed to evaluate the combination of 5-FU, leucovorin, and CPT-11 to 5-FU and leucovorin alone in first line therapy. The first of these trials compared the bolus 5-FU, leucovorin, and CPT-11 to bolus 5-FU and leucovorin alone and to CPT-11 demonstrating significant benefit in terms of confirmed response rates, time-to-tumour progression, and overall survival for the combination schedule [57].

In the second trial of combination chemotherapy with CPT-11 compared two different regimens of infusional 5-FU and folinic acid (either the AIO [Arbeitsgemeinschaft Internische Onkologie] or the de Gramont regimen) [58].

CPT-11 was administered weekly or biweekly according to the schedule of the infusional 5-FU. In this trial there was also improvement in response rate, time-to-tumour progression, and median survival. For the most important endpoint, median survival, the combination arm was associated with better median survival (17.4 months, compared with 14.1 months for the 5-FU and folinic acid arm (P = 0.032)). Combined analysis of pooled data confirmed the activity of this combination [59].

It is necessary to be prudent in order to control the potential synergetic toxic effects of adding irinotecan to bolus fluorouracil and leucovorin (increased probability of the likelihood of severe myelosuppression and diarrhea): adjustment in dosing and scheduling of the regimen are frequently necessary [57, 60–62].

In a multicenter American trial the treatments with IFL, FOLFOX and IROX (a combination of irinotecan and oxaliplatin) were compared. Best response rate, time to progression disease, and overall survival were observed in patients treated with FOLFOX regimen. However, this apparent superiority could be related to the use of different ways of 5-FU administration (continuous and bolus) and differences in second-line treatment, rather than different efficacy between CPT-11 and oxaliplatin [63, 64]. Two randomized European trials compared treatment with FOLFIRI followed by FOLFOX regimen versus FOLFIRI followed by FOLFOX as first line therapy for metastatic colorectal cancer [65], and capecitabine combined with irinotecan or oxaliplatin [66] failing to demonstrate the superiority for either of these.

After the development and approval of irinotecan and oxaliplatin for the treatment of patients with advanced colorectal cancer, these drugs are now being tested in patients with local or recurrent disease. In a phase III trial, Saltz and colleagues compared the treatment of stage III patients with IFL or bolus fluorouracil and leucovorin. The results after a median follow-up of 2.6 years showed that IFL regimen did not improve overall survival and the risk of recurrence, but significantly reduced the risk of severe toxic effects like diarrhea and myelosuppression [67].

The MOSAIC study compared the toxic effects and efficacy of FOLFOX4 with a 5-FU-leucovorin regimen administered for 6 months in over 2000 patients with resected stage II or III colon cancer. Preliminary data demonstrated a significant improvement in disease-free survival in the FOLFOX treated group of patients with stage III disease; the benefit for stage II disease patients is not yet statistically significant [68, 69].

Patients treated with FOLFOX4 experienced more frequent toxic effects consisting mainly of neutropenia (41% > grade 3) and reversible peripheral sensorial neuropathy (12.4% grade 3). These results are still preliminary, however, and information is lacking with regard to overall survival suggesting that FOLFOX4 is a therapeutic option for patients with resected stage III colon cancer [68, 69].
Targeted therapies

The recent improvement in molecular biology and the consequently development of drugs oriented to a biological target could allow, theoretically, further goals to be reached in gastrointestinal cancer therapy.

The main goal of such therapies is the interruption of cellular pathways absolutely necessary for tumor growth, survival and metastasis maybe with less toxic effects.

The epidermal growth factor receptor (EGFR) is commonly implicated in signaling pathways that are frequently deregulated in cancer cells. The receptor, which is located on the surface of normal epithelium, is overexpressed in colorectal cancer and has been associated with a poorer prognosis [70–72].

Cetuximab (C-225, Erbitux) is a monoclonal antibody that specifically blocks the EGFR which has been recently approved in USA for the treatment of advanced colorectal cancer.

Patients enrolled in trials with Cetuximab have previous immunohistochemical evidence of epithelial growth factor receptor expression.

Saltz and colleagues treated 121 patients unresponsive to prior irinotecan treatment with a combination of cetuximab and irinotecan: 19% of the patients showed an objective tumor reduction versus 10% of patients treated with cetuximab alone in a following trial [73, 74]. Perhaps this effect was due to synergy between irinotecan and antibody.

These data were confirmed by a larger trial in which patients with advanced colorectal disease refractory to irinotecan were randomized to receive either cetuximab or cetuximab plus irinotecan (23% of disease regression in the combination arm versus 11% in single-agent arm) [75].

The most evident side effect of cetuximab is an acne-like rash and drying and fissuring of the skin which could condition the quality of life of patients in terms of interpersonal relations.

No relation between the expression of receptor and clinical responses was detected in clinical trials while there was a correlation between the presence and the severity of the acne-like rash and survival: patients with a skin rash of any grade had a superior survival to patients with no skin rash.

There are also on-going phase III studies in patients not previously treated with irinotecan, and a large phase II study in heavy pre-treated patients.

Trials with Iressa and Tarceva, two EGFR-related tyrosine-kinase inhibitors, are actually carrying out in colorectal cancer in association with schedule containing 5-FU plus irinotecan or oxaliplatin. At this moment it is impossible to judge the real efficacy of these treatment options.

A tumor growth is guaranteed by new blood-vessel formation. Blocking this kind of angiogenesis seems to be an interesting way of control the tumor growth and spread of cancer cells.

Bevacizumab (Avastin) is a humanized antibody directed against the vascular endotelial growth factor.

Different clinical trials examined the efficacy of bevacizumab in combination with chemotherapeutic agents for the treatment of patients with advanced colorectal cancer [76–78].

In a phase III trial patients were randomized to receive either IFL with bevacizumab or IFL with placebo: the addition of antibody improved the response rate and the median overall survival [77].

Giantonio and colleagues recently reported a statistically-significant prolongation in median survival with the addition of bevacizumab to FOLFOX regimen (the control arm was FOLFOX alone) in patients with advanced colorectal cancer previously treated with irinotecan-based schedule [79]. The treatment with bevacizumab seems to be well tolerated: the main side effects are reversible hypertension and proteinuria. It is still unclear if the activity of bevacizumab in combination with chemotherapeutic agents is primarily due to an antiangiogenic mechanism or an alteration of the tumor vascular system, thereby enhancing the intracellular access of others drugs [77, 80].

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