New strategies in colon cancer adjuvant therapy

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Adjuvant therapy in colorectal cancer has always been a controversy during years. Despite the fact that benefit of adjuvant therapy in stage III is clear, a more controversial question concerns efficacy in stage II. The introduction of new drugs in addition to standard regimens has some benefit, but also adds toxicity. Ongoing studies with novel targeted therapies will show their results in the next years. Other open questions include duration of therapy and whether there is a real possibility of selecting patients for treatment on the basis of prognostic factors.

Key words: colon cancer, adjuvant therapy

introduction

Colorectal cancer (CRC) is one of the most frequent cancers in the developed countries and has still high mortality and morbidity. The incidence in Europe is about 58/100 000 cases/year and the mortality is still 30/100 000. This means that about half of patients with a diagnosis of colon cancer die from this disease. A total of 80% of patients at diagnosis have operable disease, but 35% of them present a distant recurrence.

Great advances in early diagnosis have been obtained, however colorectal cancer has a significant burden of mortality when the tumour is inoperable or when there is a high risk of systemic relapse.

5-fluorouracil (5-FU) has been the basis of chemotherapy in colorectal cancer since 1970. When administered alone 5-FU produces only limited responses (5%–20%). In 1980 it appeared clear that it is possible to improve the action of 5-FU with a number of strategies such as the continuous infusion or the biochemical modulation. Therefore during the 1980s several studies designed to enhance the activity of 5-FU were performed and proved, for instance, that the use of folinic acid could improve survival and response rate. Infusional regimens and biochemical modulations opened a period of research of several schedules, first in metastatic disease and then in the adjuvant setting. Europe studied more frequently the infusional administration whereas North America classically preferred bolus schedules.

The first studies in the adjuvant setting were performed by Moertel [1] with the combination of 5-FU and levamisole and demonstrated a decreased recurrence in patients with stage III colon cancer. The mechanism of action of levamisole was not very clear and a biochemical modulation of 5-FU or a role as immune modulator was postulated [2, 3].

In France, De Gramont designed a bolus/infusional schedule known as LV5-FU2, with a high response rate in advanced disease. This regimen was compared with the Mayo Clinic combination in the adjuvant setting and showed similar efficacy but a lower toxicity [4].

After the studies regarding all the possibilities of modulation of 5-FU, the era of new drugs began, with particular emphasis on oxaliplatin and irinotecan. These two drugs have considerable activity in colorectal cancer but different toxicities. Important studies demonstrated the feasibility, the safety and the high level of response in advanced disease of these agents in combination with fluoropyrimidines. The safety profile of these regimens and the high activity were the rational basis for studies in the adjuvant setting.

In the last few years oral fluoropyrimidines were also developed. Capecitabine is an orally administered prodrug of 5-FU: it has been shown to have similar efficacy to bolus regimens for advanced disease with less toxicity. Therefore studies with this drug in the adjuvant setting were initiated and also for uracil-tegafur (UFT).

chemotherapy

There are several open questions at the moment: which is the best therapy, which is the best duration of therapy, the controversial role in stage II and the effect of novel targeted therapies? We will briefly describe the most important studies in this area.

The MOSAIC trial [5] included 2246 patients with stage II or III colon cancer. The patients were randomly assigned to receive LV5-FU2 with or without oxaliplatin (85 mg/m²). In both arms, therapy was given for 12 cycles. Forty per cent of patients had stage II colon cancer and 60% stage III. The primary end point was 3-year disease-free survival (DFS). At the last analysis the study had a median follow-up of 4 years and demonstrated a significantly reduced recurrence rate (21.1% versus 26.1%). However, the subgroup analysis did not reveal...
a statistically significant improvement in DFS for stage II patients treated with oxaliplatin (HR 0.80; 95% CI 0.56–1.15) with DFS rates at 3 years follow-up of 87% and 84.3%, respectively. The 4-year analysis showed a small DFS advantage (85% versus 81.3%) in these patients. Peripheral neuropathy occurred in 92% of patients who received oxaliplatin. In total, 12.4% developed grade 3 neuropathy; however, this persisted in only 1.2% at 12 months and in 0.5% at 24 months. We conclude that FOLFOX improves DFS in colon cancer stage III, but the data remain uncertain about its definitive role in stage II.

The NSABP protocol C-07 trial [6] treated 2492 patients from 2000 to 2002 with stage II and III colon cancer. Patients were randomly assigned to FULV (Roswell Park regimen) or to FLOX (identical FULV plus oxaliplatin 85 mg/m² on days 1, 15 and 29 of each cycle). Twenty-nine per cent of patients were stage II and 71% were stage III. The primary end point was 3-years DFS. Median follow-up at analysis was 34 months. The hazard ratio (HR) was 0.79 in favour of FLOX with a relative reduction of risk of 21% and an absolute risk of 4%. No pooled analysis for stage is presented. Eighty-five per cent of patients suffered from neuropathy during the treatment and 29% at 12 months after stopping the treatment. Survival data are not yet available. This trial is important because it confirms the increased activity of oxaliplatin when added to FULV in the adjuvant setting.

PETACC-3 [7] is an international trial that reported 3278 patients from 2000 until 2002 with stage II and III colon cancer randomized between FOLFIRI and LV5-FU2. The median follow-up was 32 months. The primary end point was 3-year DFS in stage III. Secondary end points were DFS in pooled population in stage II/III, RFS (equal to DFS with the exclusion of second non-colorectal cancer) in stage III, overall survival and safety. HR was 0.89 in favour of FOLFIRI, but no statistical significance was demonstrated (3-year DFS was 62.9% for FOLFIRI and 59.9 for De Gramont regimen). An acceptable toxicity was shown in the experimental arm.

The CALGB 89803 trial randomized patients with stage III colon cancer to bolus 5-FU/FA (Roswell Park regimen) or FULV + irinotecan 125 mg/m² weekly (IFL) for 4 weeks on and 2 weeks off for a total of 30 weeks. The trial was prematurely closed due to the findings of a higher death rate related to treatment in the IFL arm.

The ACCORD 2 study compared LV5-FU2 regimen ± irinotecan 180 mg/m² in patients with ‘high risk’ stage III colon cancer. High risk was defined as N2 or N1/N2 with obstruction or perforation. Once again, irinotecan did not improve DFS (HR was 1.19), with a higher toxicity.

All these data show that the addition of irinotecan to FULV regimens does not improve DFS and may increase toxicity. However, the long-term results of PETACC-3 are awaited with interest.

More recently, adjuvant chemotherapy trials in colorectal cancer concerned the use of the 5-FU prodrugs. The X-ACT study [8] randomly assigned approximately 2000 patients with stage III only disease to receive single-agent capcitabine at a dose of 2500 mg/m² on days 1–14 in eight 3-weeks cycles or to receive 6 months of FULV (Mayo). The primary end point was to show the equivalence in terms of DFS between the two schedules. Capcitabine was shown to be at least equivalent to 5-FU/LV with a trend towards superiority in terms of 3-year DFS. The NSABP C-06 trial [9] compared adjuvant intravenous 5-FU/FA (Roswell Park Regimen: 500 mg/m² and FA 500 mg/m² for 6 of each 8 weeks for three cycles) with UFT/FA (300 mg/m²/day and FA 90 mg/day on days 1–28, ever 35 days for five cycles) in 1608 patients with stage II or III colon cancer. The trial demonstrated equivalent efficacy between UFT/FA and FULV with a 5-year figure of 78% in both arms. Both regimens are similar in toxicity profiles.

These studies clearly support the hypothesis that oral fluoropyrimidines are at least as effective as intravenous 5-FU and FA in the adjuvant treatment of colon cancer. Combination studies of oral fluoropyrimidines with oxaliplatin and CPT-11 are ongoing and results are eagerly awaited.

**targeted therapies**

Although these chemotherapy regimens have improved survival in the adjuvant setting, there is still more work to be done. Research into advanced CRC suggests a potential approach: the use of targeted agents with chemotherapy. Recent phase III studies have shown that targeted agents improve survival in patients with advanced CRC, and two anti-angiogenic drugs, bevacizumab and cetuximab, are currently approved for use in advanced CRC. Bevacizumab, a monoclonal antibody targeting the vascular endothelial growth factor (VEGF), was the first anti-angiogenic drug to show improved efficacy when used in combination with irinotecan and oxaliplatin for first- and second-line treatment of CRC. Cetuximab, another monoclonal antibody, targets the epidermal growth factor receptor (EGFR). It has shown efficacy in third-line therapy, with studies underway in the first-line setting. On the basis of these positive results, there is great interest in whether these biological agents can improve survival in the adjuvant-therapy setting. Although no results have been published yet, researchers have developed a rationale for the use of targeted therapy and several studies are underway.

**anti-VEGF agents**

A number of findings point to the potential for anti-VEGF therapy for CRC. VEGF is expressed in approximately 50% of CRC and increased VEGF expression is significantly correlated with advanced lymph node status and distant metastasis. Among patients with the highest levels of VEGF expression, survival was significantly worse than in patients with negative or lower levels of VEGF expression. Preoperative serum VEGF levels have also been shown to correlate with advanced tumour stage or nodal status at the time of surgery. In one study, serum VEGF levels were measured prospectively in 81 patients undergoing curative resection for CRC. It was found that the serum VEGF levels were significantly higher in patients who went on to develop metastases than in those who did not. Moreover, VEGF levels were predictive of future metastases independent of nodal status and adjuvant chemotherapy, with a positive predictive value of 73% and a negative predictive value of 85%.

Bevacizumab has been demonstrated to neutralize the biological properties of human VEGF, including endothelial cell...
mitogenic activity, vascular-permeability-enhancing activity and angiogenic properties. It would appear then that the use of an anti-VEGF therapy such as bevacizumab in the early stages of the disease, when tumours are small and potentially reliant on VEGF, or after tumour resection would inhibit further growth and metastasis, thus improving disease control.

The clinical benefit of oxaliplatin-containing regimens as adjuvant therapy for CRC, and the data showing significant survival benefit when bevacizumab is used as first-line therapy in patients with metastatic CRC, together create a rationale for combining bevacizumab with oxaliplatin-containing regimens as adjuvant therapy in patients with CRC. This combination is, in fact, currently being examined in three large phase III trials: NSABP C08 (USA), AVANT (multinational) and ECOG 5202 (USA).

National Surgical Adjuvant Breast and Bowel Project (NSABP) C08. This study is seeking to compare DFS in 2700 patients with resected stage II or III CRC treated with modified FOLFOX6 (mFOLFOX6) either with or without bevacizumab. Patients in both groups will receive oxaliplatin 85 mg/m² with concurrent leucovorin 400 mg/m² on day 1 every 2 weeks followed by intravenous bolus 5-FU 400 mg/m² followed by a single continuous infusion of 5-FU 2400 mg/m² over 46 h. This treatment regimen will be repeated every 2 weeks for a total of 12 cycles (6 months). Patients on the bevacizumab arm will receive bevacizumab 5 mg/kg intravenously before oxaliplatin on day 1 of each chemotherapy cycle and will continue every 2 weeks during and after the completion of all chemotherapy cycles for a total duration of 1 year.

The trial has 90% power to reveal a 25% reduction in risk of progression after 5 years and 82% power to reveal a 25% reduction in risk of death after 7 years. Its primary goal is to compare DFS between the two regimens and its secondary goal is to compare survival. Bevacizumab is associated with certain adverse events; this trial will also, therefore, seek to assess the incidence and duration of proteinuria, delayed vascular events including myocardial infarction and central nervous system ischaemia, and thrombosis in patients receiving chemotherapy plus bevacizumab.

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Data are expected in late 2008. The treatment phase consists of two parts of 24 weeks each, for a total of 48 weeks. The cycle duration during weeks 1–24 in arms A and B is 2 weeks with a total of 12 planned cycles, and in arm C, 3 weeks for a total of eight cycles. The cycle duration during weeks 25–48 of bevacizumab as a single agent will be 3 weeks for a total of eight cycles for patients on arms B and C. In arm A, the visit schedule for patients on observation only will be 3 weeks as well.

Patients are eligible if they are chemotherapy-naïve and have undergone surgery with curative intent. The primary objective is to demonstrate whether FOLFOX4 plus bevacizumab and/or XELOX plus bevacizumab will yield superior DFS to FOLFOX. The trial is powered to show a 23% reduction in the hazard ratio in the bevacizumab arms. The investigators also hope to evaluate and compare the perceived convenience and satisfaction with chemotherapy among patients and medical care utilization in the three treatment groups.

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Allergic loss of chromosome 18q and microsatellite instability (MSI) in colon tumours are prognostic markers. However, the role of these abnormalities as predictive markers of response to adjuvant therapy has yet to be determined. This study will prospectively evaluate the role of these markers as prognostic variables and as potential predictors of chemotherapy response. The markers will be used to stratify risk among stage II patients and determine who will receive adjuvant chemotherapy.

Patients with retention of 18q alleles will be considered low risk and will be observed. Patients with 18q loss of heterozygosity will be designated as high risk and will be randomized to receive adjuvant therapy with FOLFOX, with or without bevacizumab for 12 cycles plus an additional 12 cycles of bevacizumab after chemotherapy.

Based on ECOG’s previous experience with an analysis of MSI/18q markers, it is expected that the high-risk control group will have a 3-year DFS rate of 80% and that the low-risk group undergoing observation may exhibit a 3-year DFS rate of about 90%, but that rate is not exactly known. With 3 years of follow-up, there will be at least an 88% power to detect a 37% difference in median DFS for the high-risk group (absolute difference of 5%, from 80% to 85%). There is approximately an 84% power to detect a 37% difference in median overall survival (absolute difference of 5% at 5 years, from 80% to 85%) with the analysis.

anti-EGFR agents

The EGFR is commonly expressed in CRC but not in most normal tissues, raising the possibility that this receptor could serve as a target for highly selective therapy. Based on preclinical studies demonstrating that antagonists of EGFR resulted in the inhibition of tumour growth, the development of clinical reagents has been aggressively pursued. Cetuximab is a chimeric immunoglobulin G1 monoclonal antibody that targets the extracellular domain of the EGFR, competitively inhibiting ligand binding and, hence, EGFR activation. In addition, cetuximab has been shown to have both single-agent activity and the potential ability to partially reverse resistance to...
a chemotherapy drug. Its potential for use in the adjuvant setting appears promising, therefore, particularly for its ability to directly target tumour cells and thereby target micrometastases in which angiogenesis has not yet occurred.

As with bevacizumab, the rationale for anti-EGFR therapy and the success of cetuximab in advanced CRC has led to research into its use in the adjuvant setting. At this time, there is one ongoing phase II study.

North Central Cancer Treatment Group (NCCTG) N0147. N0147 began as a randomized phase III trial comparing three different chemotherapy regimens with or without cetuximab, but after the research showed oxaliplatin-containing regimens to be more effective than those containing irinotecan, it was modified so that patients accrued after June 2005 have not received irinotecan. The two current enrolling arms are modified FOLFOX6 or modified FOLFOX6 plus cetuximab. Of note, patients do not have to have tumours that express EGFR to be eligible. The study, expected to enrol 2300 patients, is designed to assess DFS as the primary end point. The trial will enrol 1150 patients in each arm, yielding a 90% power to detect a hazard ratio of 1.3. Secondary end points include overall survival, toxicity, quality of life and translational markers.

Translational markers in the study include many molecular tumour characteristics, pharmacogenetic markers, gene expression profiling and others (including, for example, chromosomal abnormality [3, 7, 18] loss of heterozygosity, centromere amplification, VEGF expression, microvessel density, MSI, thymidylate synthase, dihydropyrimidine dehydrogenase, carboxylesterase-2, EGFR, topoisomerase I, uridine diphosphate glucuronosyltransferase 1A1 and others).

conclusions

The optimal regimen in adjuvant therapy is still to be defined. Oxaliplatin adds a significant benefit in absolute risk of recurrence with an important, but reversible, neurological toxicity. Irinotecan improved the outcome in one study with an acceptable toxicity, whereas other schedules with this did not improve the outcome, but only increased toxicity.

Oral fluoropyrimidines showed similar activities to intravenous therapy and it must now be clarified if a benefit will be obtained with the addition of oxaliplatin or irinotecan.

The role of adjuvant therapy in stage II remains controversial and also the duration of therapy is still to be defined. It should be possible that 3–4 months will be equivalent to 6, with a lower burden of treatment; a large-scale clinical trial on this topic is ongoing in Italy under the leadership of GISCAD (Italian Group for the Study of Gastrointestinal Cancer).

Targeted agents, especially bevacizumab and cetuximab, are expected to offer potentially well-tolerated and effective options for the adjuvant treatment of CRC in the near future. At the same time, further evaluation of certain toxicities—in particular, complications of bevacizumab with wound healing and gastrointestinal perforation—will define the safety of these agents in the adjuvant setting of CRC. We look forward to the results of the aforementioned studies in the next few years. The introduction of novel targeted therapies must be investigated and could change the scenario again.

From a methodological point of view [10, 11], 3-year DFS seems to be a good surrogate end point for 5-year overall survival (OS) after Sargent’s analysis of 13 international trials.

Every new drug is expected to add a small benefit against high costs and toxicity. In the future it will be worthwhile to stratify patients according to the level of risk. It is clear that there are phenotypes that are more aggressive and are related to a high risk of systemic relapse. Node-positive status, obstruction, perforation of the tumour and lymphovascular invasion are already used as criteria of choice in clinical practice. Other biological parameters (such as thymidilate synthase expression, K-ras, the loss of part of 18q, including the region containing DCC, the overexpression of marker X, the polisomy and mutations of EGFR) must be investigated in order to establish the best therapy for each patient.

references