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**CHEMIOTERAPIA PRECAUZIONALE**  
**NEL CANCRO DEL COLON**

RICERCA SVOLTA PER DR. DIEGO RATTI

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# CHEMIOTERAPIA PRECAUZIONALE NEL CANCRO DEL COLON

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## ABSTRACT

Improving adjuvant therapy for rectal cancer by combining protracted-infusion fluorouracil with radiation therapy after curative surgery.

**N Engl J Med 1994 Aug 25;331(8):502-7** (ISSN: 0028-4793)

O'Connell MJ; Martenson JA; Wieand HS; Krook JE; Macdonald JS; Haller DG; Mayer RJ; Gunderson LL; Rich TA

Mayo Clinic, Rochester, Minn.

**BACKGROUND.** The combination of radiation therapy and chemotherapy with fluorouracil plus semustine after surgery has been established as an effective approach to decreasing the risk of tumor relapse and improving survival in patients with rectal cancer who are at high risk for relapse or death. We sought to determine whether the efficacy of chemotherapy could be improved by administering fluorouracil by protracted infusion throughout the duration of radiation therapy and whether the omission of semustine would reduce the toxicity and delayed complications of chemotherapy without decreasing its antitumor efficacy. **METHODS.** Six hundred sixty patients with TNM stage II or III rectal cancer received intermittent bolus injections or protracted venous infusions of fluorouracil during postoperative radiation to the pelvis. They also received systemic chemotherapy with semustine plus fluorouracil or with fluorouracil alone in a higher dose, administered before and after the pelvic irradiation. **RESULTS.** With a median follow-up of 46 months among surviving patients, patients who received a protracted infusion of fluorouracil had a significantly increased time to relapse ( $P = 0.01$ ) and improved survival ( $P = 0.005$ ). There was no evidence of a beneficial effect in the patients who received semustine plus fluorouracil. **CONCLUSIONS.** A protracted infusion of fluorouracil during pelvic irradiation improved the effect of combined-treatment postoperative adjuvant therapy in patients with high-risk rectal cancer. Semustine plus fluorouracil was not more effective than a higher dose of systemic fluorouracil given alone.

Adjuvant therapy in rectal cancer: analysis of stage, sex, and local control--final report of intergroup 0114.

**J Clin Oncol 2002 Apr 1;20(7):1744-50** (ISSN: 0732-183X)

Tepper JE; O'Connell M; Niedzwiecki D; Hollis DR; Benson AB; Cummings B; Gunderson LL; Macdonald JS; Martenson JA; Mayer RJ

Department of Radiation Oncology, University of North Carolina, Chapel Hill 27599-7512, USA.

[tepper@radonc.unc.edu](mailto:tepper@radonc.unc.edu).

**PURPOSE:** The gastrointestinal Intergroup studied postoperative adjuvant chemotherapy and radiation therapy in patients with T3/4 and N+ rectal cancer after potentially curative surgery to try to improve chemotherapy and to determine the risk of systemic and local failure. **PATIENTS AND METHODS:** All patients had a potentially curative surgical resection and were treated with two cycles of chemotherapy followed by chemoradiation therapy and two additional cycles of chemotherapy. Chemotherapy regimens were bolus fluorouracil (5-FU), 5-FU and leucovorin, 5-FU and levamisole, and 5-FU, leucovorin, and levamisole. Pelvic irradiation was given to a dose of 45 Gy to the whole pelvis and a boost to 50.4 to 54 Gy. **RESULTS:** One thousand six hundred ninety-five patients were entered and fully assessable, with a median follow-up of 7.4 years. There was no difference in overall survival (OS) or disease-free survival (DFS) by drug regimen. DFS and OS decreased between years 5 and 7 (from 54% to 50% and 64% to 56%, respectively), although recurrence-free rates had only a small decrease. The local recurrence rate was 14% (9% in low-risk [T1 to N2+] and 18% in high-risk patients [T3N+, T4N]). Overall, 7-year survival rates were 70% and 45% for the low-risk and high-risk groups, respectively. Males had a poorer overall survival rate than females. **CONCLUSION:** There is no advantage to leucovorin- or levamisole-containing regimens over bolus 5-FU alone in the adjuvant treatment of rectal cancer when combined with irradiation. Local and distant recurrence rates are still high, especially in T3N+ and T4 patients, even with full adjuvant chemoradiation therapy.

## Progress in the Treatment of CRC: Changing Practice Standards?

Ramesh K. Ramanathan, MD

The 39th Annual Meeting of the American Society of Clinical Oncology (ASCO) proved to be a pivotal meeting for colorectal cancer (CRC). A number of trials were presented with the potential to change clinical practice, which in turn will affect the lives of the many thousands of patients with CRC. Most importantly, for the first time in large clinical trials involving CRC, the newer targeted agents were shown to be of benefit in the treatment. Presentations at the colorectal Oral Session spanned the range of advancements in staging, prognostication, adjuvant therapy, and metastatic disease and are highlighted in this review.

### **Staging of Colorectal Cancer**

The TNM (tumor, node, metastases) system is the widely accepted standard for staging of cancer. It has been long recognized that stage III CRC patients form a heterogeneous group, with 5-year survival ranging from 20% to 60%. This wide variation in survival for stage III patients is due to the lack of stratification for depth of invasion (T1-T4) and degree of lymph node involvement (N1-N2). Greene and colleagues<sup>[1]</sup> evaluated 5988 stage III rectal cancer patients, entered into the National Cancer Database between 1991 and 1993.<sup>[2]</sup> Survival rates were calculated by dividing stage III patients into 3 new subgroups (Table 1).

**Table 1. Stratification of Stage III Rectal Cancer**

Stage	5-Year Survival	
	Surgery	Surgery + AT
Stage IIIA (T1-2, N1)	39%	NR
Stage IIIB (T3-4, N1)	21.7%	40.9%
Stage IIIC (Any T, N2)	12.2%	28.9%

AT, adjuvant therapy; NR, not reported.

These 3 different subgroups differed in 5-year survival, with stage IIIC (any T, N2) patients having a 5-year survival of only about 12% with surgery alone and 29% with adjuvant therapy. Adjuvant therapy proved to be of benefit in all 3 subtypes. These results support the stratification of stage III patients into 3 subsets (A, B, and C), and are now part of the new staging system.<sup>[3]</sup> Future adjuvant therapy trials in rectal cancer should incorporate the new staging system and, particularly, stage IIIC patients should be selected for aggressive therapy as they have an extremely poor prognosis.

## Early Disease

### Adjuvant Therapy for Colorectal Cancer

Oxaliplatin in combination with infusional 5-fluorouracil (5-FU) (FOLFOX4) is now a new standard regimen for first-line therapy of advanced CRC and is being evaluated in the adjuvant setting.<sup>[4,5]</sup> DeGramont and colleagues<sup>[6]</sup> presented results of this trial, in which 2248 patients with stage II or stage III CRC following surgery were randomized to FOLFOX4 every 2 weeks for 6 months (12 cycles) or to the control arm with infusional 5-FU (LV5FU2) for a similar period of time. The main objective of the study was to determine the 3-year disease-free survival (DFS) for the 2 arms, and the study was powered to demonstrate a 25% decrease in the risk of recurrence at 3 years.

Toxicity analysis of this study was presented at the 2002 ASCO meeting and showed that FOLFOX4 was well tolerated in the adjuvant setting.<sup>[7]</sup> Results of this study revealed a significantly better 3-year DFS of 77.8% for patients receiving FOLFOX4 vs 72.9% for patients receiving LV5FU2. The relative risk reduction was 23% in favor of patients receiving FOLFOX4, and the benefit of adjuvant therapy was approximately similar for both stage II and stage III patients (Table 2).

**Table 2. Results of the MOSAIC Trial**

Regimen	3-Year DFS	Comments
FOLFOX4	77.8%	Grade 3 neuropathy: 12%
LV5FU2	72.9% ( $P < .001$ )	

DFS, disease free survival. LV5FU2 employs leucovorin (LV) 200mg/m<sup>2</sup> as a 2-hour infusion, 5-FU 400mg/m<sup>2</sup> bolus, and 600mg/m<sup>2</sup> over 22 hours via continuous infusion, days 1 and 2 every 2 weeks. FOLFOX employs the LV5FU2 regimen, plus oxaliplatin 85mg/m<sup>2</sup> day 1 every 2 weeks

Therapy with oxaliplatin can result in peripheral neuropathy, which generally is reversible. It was reassuring that patients receiving FOLFOX4 had a decrease in grade 3 peripheral neuropathy from

12.4% to 1% on follow up at 12 months after therapy. The results of the study indicate that the FOLFOX4 regimen improves the 3-year DFS. Overall survival was not the main objective of this study, but based on historical data, it is likely that a 3-year DFS improvement will lead to an overall survival advantage.<sup>[8,9]</sup>

At this point, it is perhaps premature to integrate oxaliplatin into the adjuvant therapy of all patients with stage II and stage III CRC, although patients with a high risk of recurrence such as stage IIIC or resected M1 disease may be candidates. Data from the NSABP C07 trial, which randomized patients to a bolus regimen of 5-FU and leucovorin (LV) with or without oxaliplatin, should be available in the next 1-2 years, and should help clarify the role of oxaliplatin in adjuvant therapy.

**Postoperative Adjuvant Therapy for Rectal Cancer**

Postoperative adjuvant chemotherapy with a 5-FU-based regimen and pelvic radiation therapy (RT) is the standard of care for patients with stage II and III rectal cancer.<sup>[10,11]</sup> The relative benefits of bolus 5-FU/LV or protracted venous infusion (PVI)-5-FU during the period of RT have been explored, but not compared clinically in randomized trials. A previous randomized study showed a benefit for DFS and overall survival in patients receiving PVI-5-FU and concurrent RT vs bolus 5-FU and RT.<sup>[11]</sup> However, administration of PVI-5-FU requires surgical placement of an indwelling venous catheter with the potential risk of thrombosis, infection, or device failure, and hence a bolus regimen of 5-FU/LV is widely used with RT in clinical practice.

In a study by Smalley and colleagues,<sup>[12]</sup> 1917 patients with resected rectal cancer were randomized to 3 arms of 5-FU-based chemotherapy and concurrent radiation (Table 3).

**Table 3. Schema of Intergroup Trial 0144**

	<b>Chemotherapy Before and After RT</b>	<b>Chemotherapy During RT (50.4-54.0 Gy)</b>
Arm 1	5-FU, 450-500 mg/m <sup>2</sup> daily for 5 days repeated every 28 days; 2 cycles before and after RT	5-FU by PVI, 225 mg/m <sup>2</sup> /d
Arm 2	5-FU by PVI 300 mg/m <sup>2</sup> /d for 42 days before and 56 days after RT	5-FU by PVI, 225 mg/m <sup>2</sup> /d
Arm 3	5-FU, 380-425 mg/m <sup>2</sup> + LV 20 mg/m <sup>2</sup> daily for 5 days; LEV 150 mg days 2-3, 14-16 of each cycle, repeated every 28 days; 2 cycles before and after RT	5-FU 400 mg/m <sup>2</sup> + LV 20 mg/m <sup>2</sup> days 1-4 of weeks 1 and 5 of RT

5-FU, 5- fluorouracil; LEV, levamisole; LV, leucovorin; PVI, protracted venous infusion; RT, radiation therapy.

The arms were well balanced, toxicity was acceptable, and treatment-related mortality was less than 1% for all 3 arms. None of the arms had an advantage in terms of toxicity, recurrent free survival (3 year survival, 68% to 69%), or overall survival (3-year survival, 81% to 83%). It appears, based on this study, that a bolus regimen of 5-FU or 5-FU/LV could be used in place of PVI 5-FU. However, we should keep in mind that these results are preliminary. Local recurrence from rectal cancer may occur a number of years later, and long-term follow up is needed to evaluate fully the effectiveness of these regimens.<sup>[10]</sup>

**Advanced Disease**

**Quality-of-Life Data for N9741**

Interim analysis of N9741 was presented at last year's ASCO meeting, which showed significant improvement in terms of survival and response rate for patients receiving FOLFOX 4 vs IFL.<sup>[4]</sup> At this year's meeting, Goldberg and colleagues<sup>[13]</sup> presented updated efficacy and quality-of-life (QOL) data. Final analysis of this trial revealed that FOLFOX4 resulted in improved response rate, time to progression, and overall survival vs IFL. Therapy with FOLFOX4 also resulted in the lowest incidence of grade 3/4 toxicities. The results with IROX were intermediate (Table 4).

**Table 4. N9741: IFL Vs FOLFOX4 Vs IROX in Advanced Colorectal Cancer**

Regimen	Response Rate	TTP (months)	Median Survival (months)
IFL	30%	6.9	14.8
FOLFOX4	40% ( <i>P</i> = .02)	8.8 ( <i>P</i> = .004)	19.1 ( <i>P</i> = .006)
IROX	30%	6.7	17.0

All *P* values are comparison between FOLFOX4 and IFL. TTP, time to progression.  
 IFL: Irinotecan 125 mg/m<sup>2</sup> + leucovorin 20 mg/m<sup>2</sup> + 5-FU 500 mg/m<sup>2</sup>, weekly x 4, 2 weeks off  
 FOLFOX4: Oxaliplatin 85 mg/m<sup>2</sup> day 1 + leucovorin 200 mg/m<sup>2</sup>/5-FU 400 mg/m<sup>2</sup> bolus + 600 mg/m<sup>2</sup> as a 22 hour infusion days 1 and 2 every 2 weeks  
 IROX: Oxaliplatin 85 mg/m<sup>2</sup> + irinotecan 200 mg/m<sup>2</sup> day 1, every 3weeks

QOL data were collected at baseline and every 3 months with a patient completion rate of 85%. Although there were differences in single-item symptoms and specific elements, overall QOL was similar for all 3 arms. Dr. Goldberg commented that future studies should assess QOL at more frequent intervals, as differences in adverse events and symptoms experienced by patients during therapy may be evident at shorter time intervals.

For clinical practice, this study shows clear superiority of the FOLFOX4 regimen, which should be considered a standard first-line regimen for patients with advanced, untreated CRC. There is limited experience with the IROX regimen and the role of this regimen in first-line therapy needs to be determined.

#### Final Results of EFC4584

Rothenberg and colleagues<sup>[14]</sup> presented the results of EFC4584, which randomized patients with CRC refractory to IFL therapy to 1 of 3 different regimens: LV5FU2 vs oxaliplatin vs FOLFOX4. Based on interim analysis<sup>[15]</sup> showing a superior time to progression (TTP) and higher response rate for patients receiving FOLFOX4 vs the other 2 arms, the FOLFOX4 regimen was approved by the US Food and Drug Administration (FDA) as second-line therapy in advanced CRC. At this meeting, Dr. Rothenberg presented the final analysis with median survival and QOL data (Table 5).

**Table 5. Final Results of EFC4584: 5-FU/Leucovorin Vs Oxaliplatin Vs the Combination Following Irinotecan, 5-FU, and Leucovorin**

Regimen	Response Rate	TTP (months)	Median Survival (months)	Improvement of Tumor Symptoms
Oxaliplatin	1.1%	1.9	8.1	10%
LV5FU2	0.7%	2.6	8.7	15%
FOLFOX4	9.6%	5.6	9.8	28%

TTP, time to progression.

Oxaliplatin: 130 mg/m<sup>2</sup> every 3 weeks

LV5FU2: Leucovorin 200mg/m<sup>2</sup> as a 2-hour infusion, 5-FU 400 mg/m<sup>2</sup> bolus and 600 mg/m<sup>2</sup> 22-hours continuous infusion, days 1-2, every 2 weeks

FOLFOX4: LV5FU2 + oxaliplatin 85 mg/m<sup>2</sup> day 1, every 2 weeks

TTP for patients receiving FOLFOX4 was significantly improved (5.6 months) compared with the other 2 arms (1.9 months for single-agent oxaliplatin and 2.6 months for LV5FU2). Relief of tumor-related symptoms were also significantly higher for patients receiving FOLFOX4. The overall survival for patients receiving FOLFOX4 was 9.8 months vs 8.1 and 8.7 months for the other 2 arms, respectively, which was not of statistical significance. It was noted that 42% of the patients who received LV5FU2 subsequently received oxaliplatin on an expanded access program. FOLFOX4 resulted in a higher rate of nausea/vomiting, diarrhea, neutropenic fever, and peripheral neuropathy than did LV5-FU2.

It was surprising that improvements in response rate and TTP for patients receiving FOLFOX4 did not translate into a survival advantage. Dr. Rothenberg commented that a number of factors may have resulted in this outcome: patients receiving LV5FU2 might have had a better than expected survival, salvage treatment with oxaliplatin could have influenced survival in patients receiving LV5FU2, and the effect of FOLFOX4 on survival is brief when used in a salvage setting. Despite the lack of survival advantage, there is benefit in terms of response rate and relief of tumor symptoms, and FOLFOX4 can be considered a salvage regimen for CRC patients who have progressive disease after IFL therapy.<sup>[5]</sup>

## Targeted Therapies in Advanced Disease

### Cetuximab

Cetuximab (C225) is a chimeric monoclonal antibody that binds to the external domain of the epidermal growth factor receptor (EGFR). Overexpression of EGFR is seen in most tumors, including CRC, and preclinical studies have shown C225, as a single agent and in combination therapy, to have marked activity.<sup>[16]</sup> C225 as a single agent and in combination with chemotherapeutic agents, particularly irinotecan, showed activity in refractory CRC. In particular, a great deal of interest was evoked by phase 2 findings that C225 may have activity in irinotecan-refractory CRC when added to the same agent.<sup>[17,18]</sup>

Cunningham and colleagues<sup>[19]</sup> presented the results of a trial in which CRC patients were randomized to C225 alone or to the combination of C225 and irinotecan. Patients eligible for this study had refractory disease, which was defined as having progressive disease within 3 months of irinotecan therapy; 536 patients were screened, 470 were EGFR-positive (82%), and 329 patients were randomized in a 2:1 ratio. Patients who received C225 alone were allowed to cross to the combination of C225 and irinotecan on progression.

**Table 6. C225 Alone or in Combination With Irinotecan in Irinotecan-Refractory Patients**

Regimen	Grade 3/4 Toxicity		Response Rate	TTP (months)	Median Survival (months)
	Diarrhea	Rash			
C225 (n = 111)	2%	5.2%	10%	1.5	6.9
C225 + Irinotecan (n = 218)	45%	9.4%	22%	4.1	8.6

TTP, time to progression.

C225: 400 mg/m<sup>2</sup> first infusion, then 250 mg/m<sup>2</sup> weekly

C225+ irinotecan: C225 400 mg/m<sup>2</sup> first infusion, then 250 mg/m<sup>2</sup> weekly + irinotecan at the prior dose and schedule received

The study showed that patients who received combination therapy had a statistically significant improvement in TTP (4.1 months vs 1.5 months). The response rate (22% vs 10%) and the median survival (8.6 and 6.9 months), however, were not significantly different. The degree of EGFR staining did not have any correlation to response, but patients who had grade 2 or higher skin toxicity had a higher chance of responding to therapy. This study confirms the activity of single-agent C225. It is not clear whether the results of this study, with supporting phase 2 data, will be adequate for regulatory approval of C225, and confirmatory large randomized trials may be needed. Future trials should incorporate C225 into active first-line regimens for CRC, such as FOLFOX or FOLFIRI.

### Bevacizumab

Vascular endothelial growth factor (VEGF) is necessary for tumor angiogenesis, with increased expression seen in CRC and most other tumors.<sup>[19]</sup> Anti-VEGF antibodies in animal studies as a single agent and in combination therapy have shown significant activity.<sup>[20]</sup> Bevacizumab (BV) is a recombinant humanized monoclonal antibody currently being investigated in a number of tumor types. A phase 2 randomized study in untreated advanced CRC patients identified a BV dose of 5 mg/kg every 2 weeks in combination with chemotherapy for future studies.<sup>[20]</sup> Coagulation abnormalities such as thrombosis and bleeding in addition to hypertension and proteinuria were identified as potential safety concerns with this agent.<sup>[21]</sup>

There was a great deal of interest regarding this study, results of which were made available a few weeks prior to the ASCO meeting. Due to the significance of the results, Hurwitz and colleagues<sup>[22]</sup> presented a late-breaking abstract at the CRC Oral Session. In this study, 800 patients with untreated CRC were randomized to the IFL regimen plus placebo, or to IFL with the addition of BV. A third group of patients received 5-FU/LV with the addition of BV, but this arm was discontinued after 100 patients were randomized. The addition of BV to bolus IFL therapy resulted in an increased survival, progression-free survival, and response rate compared with the control arm of IFL alone (Table 7).

**Table 7. Bevacizumab in Combination With Bolus IFL as First-line Therapy**

Regimen	Response Rate	PFS (months)	Median Survival (months)
IFL+ Placebo (n = 412)	35%	6.2	15.6
IFL+BV (n = 405)	45% ( <i>P</i> = .0029)	10.6 ( <i>P</i> < .00001)	20.3 ( <i>P</i> = .00003)

PFS, progression free survival.

BV: Bevacizumab 5 mg/kg every 2 weeks

IFL: Irinotecan 125 mg/m<sup>2</sup> + leucovorin 20 mg/m<sup>2</sup> +5-FU 500 mg/m<sup>2</sup> day weekly for 4 weeks, 2 weeks off

Thromboembolic events were similar in both groups. Although grade 3 hypertension was significantly increased compared with the control arm, Dr. Hurwitz commented that hypertension was easily controlled with medication. The survival difference of approximately 4 months is remarkable, and BV may gain FDA approval. However, this study combined BV with IFL, which was shown to be inferior to the FOLFOX4 regimen.<sup>[4]</sup> Future studies need to evaluate BV in combination with FOLFOX or FOLFIRI, and a number of studies are in the planning stage and should be open to accrual in the near future.

## ARTICOLI

Il trattamento chemioterapico consiste nella somministrazione di farmaci in grado di distruggere le cellule cancerose. La chemioterapia è talvolta impiegata dopo l'intervento chirurgico al colon ed al retto per evitare che il male si propaghi (viene denominata terapia "adiuvante" o "precauzionale"). La chemioterapia può anche essere impiegata per tenere sotto controllo un tumore che non può essere totalmente asportato con l'operazione o per controllare la crescita delle metastasi. Può essere impiegato un solo farmaco o una combinazione di più farmaci.

La chemioterapia viene solitamente somministrata a cicli: dopo un periodo di trattamento segue un periodo di "riposo"; i farmaci possono essere somministrati per bocca oppure per via venosa o all'interno di una cavità corporea. Per favorire la somministrazione dei farmaci si può inserire, con un piccolo intervento in day hospital, in anestesia locale, un dispositivo sottocutaneo connesso direttamente con una grossa vena (port). La chemioterapia è un trattamento in genere sistemico nel senso che i farmaci attraverso le vie venose si propagano in tutto il corpo.

Nell'ambito di studi clinici, i ricercatori stanno studiando per tumori metastatici del fegato nuovi metodi per somministrare i farmaci direttamente nel vaso arterioso che entra nel fegato (chemioterapia locoregionale intraepatica).

In genere la chemioterapia viene somministrata ambulatoriamente. Tuttavia a seconda dei farmaci impiegati e delle condizioni generali del paziente, può essere richiesto un breve ricovero.

## CHEMIOTERAPIA

Nel carcinoma del colon-retto la chemioterapia può essere utilizzato in fase adiuvante a scopo precauzionale dopo un intervento chirurgico o in una fase metastatica della malattia stessa. Il farmaco base utilizzato nei diversi schemi di terapia è il 5-Fluorouracile che può essere somministrato secondo diverse modalità o in associazione ad altri farmaci a seconda della estensione della neoplasia. I chemioterapici maggiormente impiegati sono: Irinotecan, Oxaliplatino, Raltitrexed, capecitabina e mitomicina C. La maggior parte di essi può presentare degli effetti collaterali tra cui stanchezza, nausea, vomito, diarrea, formicolii, alle estremità delle mani e dei piedi, mucosite e riduzione del valore dei globuli bianchi. La tossicità è in genere lieve e comunque facilmente controllabile. Le opzioni terapeutiche e la durata dei trattamenti sono adattate alle singole situazioni cliniche mantenendo comunque una buona qualità di vita.

### Chemioterapia della malattia metastatica

La percentuale di risposta ad un trattamento convenzionale della malattia metastatica non supera il 20-30% con una sopravvivenza mediana attesa di circa 12 mesi; purtuttavia la maggioranza degli esperti ritiene giustificato ricorrere ad un trattamento chemioterapico nei pazienti con malattia recidivata e/o con metastasi a distanza, magari utilizzando anche la radioterapia su localizzazioni ben identificabili, uniche e/o in posizione strategica. Il farmaco maggiormente utilizzato è sempre il 5FU generalmente associato ad Ac. Folinico secondo gli schemi più abitualmente applicati. Esistono, oggi, nuovi farmaci o nuove combinazioni di farmaci che però sono ancora da considerarsi sperimentali in fase II; è quindi buona norma avere parametri di valutazione sicuri da poter controllare in modo tale da sospendere un trattamento convenzionale che si stia dimostrando

inefficace per poter inserire tali pazienti in studi di fase II con l'utilizzo di nuove terapie. In particolari situazioni ( metastasi epatiche o pelviche come unica sede di malattia documentabile) può essere indicato un trattamento locoregionale cui si rimanda nell'apposito capitolo.

### Progetti speciali di ricerca

Sono attualmente in corso alcuni trials clinici in cui strutture oncologiche aziendali sono coinvolte; qui di seguito vengono riportate le sinossi di tali studi i cui protocolli, per esteso, sono disponibili presso l'Ufficio Trials e Data Management della Oncologia Medica di Ravenna.

#### 4.1.7.1 Chemioterapia adiuvante del carcinoma del colon

- Studio Clinico Intergruppo di Terapia Adiuvante del Carcinoma del Colon Stadi Dukes B2,B3,C: randomizzato fra MTX + 5FU + Levamisolo vs 5FU + LV + Levamisolo (INTACC 02 / R1608).
- A prospective randomized multicenter phase III clinical trial comparing the effects of PANOREX injection plus 5FU/Leucovorin versus 5FU/Leucovorin versus PANOREX injection alone, in patients with surgically resected stage III (Dukes C) carcinoma of the colon. (Wellcome / R1609)

### Chemioterapia della malattia metastatica

Studio clinico multicentrico randomizzato di fase III in pazienti con carcinoma del colon retto avanzato: confronto tra (A) MTX @ 5FU bolo e (B) MTX @ 5FU bolo, alternato a 5FU infusione continua + L-LV (IST Genova / R1607).

### Follow-up programmato

Come già si è avuto modo di dire, il follow-up rappresenta un momento fondamentale dell'iter terapeutico di tutte le neoplasie, in particolare di quelle in cui una precoce diagnosi di recidiva o metastasi può far mettere in campo strategie terapeutiche atte a modificare la storia naturale della malattia.

Ciò è particolarmente vero per le neoplasie del colon e del retto, che, avendo storie naturali differenziate, hanno anche approcci diagnostici differenti: i due algoritmi sono qui di seguito riportati:

### **ALGORITMO DIAGNOSTICO PER IL FOLLOW-UP NELLE NEOPLASIE DEL COLON OPERATO RADICALMENTE (con o senza chemioterapia precauzionale)**

MESI DOPO IL TRATTAMENTO							
3	6	12	18	24	36	48	60

VISITA CLINICA	+	+	+	+	+	+	+	+
MARCATORI	+	+	+	+	+	+	+	+
COLONSCOPIA (CLISMA d.m.c.)		+		(+)		+		(+)
RX TORACE		+	+		+	+	+	+
ECOGRAFIA EP.		+	+	+	+	+	+	+

**ALGORITMO DIAGNOSTICO PER IL FOLLOW-UP  
NELLE NEOPLASIE DEL RETTO OPERATO RADICALMENTE  
(con o senza chemioterapia precauzionale)**

MESI DOPO IL TRATTAMENTO							
3	6	12	18	24	36	48	60

VISITA CLINICA	+	+	+	+	+	+	+	+
MARCATORI	+	+	+	+	+	+	+	+
RETTOSCOPIA	+	+		+			+	
COLONSCOPIA				+				+
RX TORACE		+	+		+	+	+	+
ECO GRAFIA EP.		+	+	+	+	+	+	+
TAC PELVI		+		+		+		+

# ADVANCES IN COLORECTAL CANCER TREATMENT

from Medscape General Medicine [™]  
Posted 04/10/2002

**Manuel Hidalgo, MD**

## Introduction

Although incidence and mortality continue to be high, progress has been made in the diagnosis, treatment, and prevention of colorectal cancer. This column will provide a summary of the most relevant issues and recent publications, with a critical perspective on management of patients with advanced disease, adjuvant treatments, and prediction of outcome following treatment.

## Advanced Disease: Standard Treatment

In 2000, two large, prospective, randomized clinical trials demonstrated that the addition of CPT-11 to a regimen of either bolus 5-fluorouracil (5-FU) or infusional 5-FU with leucovorin increased the survival of patients with advanced colorectal carcinoma.<sup>[1,2]</sup> Consequently, this triple-drug regimen has become the standard of care for this disease. The weekly regimen of bolus 5-FU/leucovorin/CPT-11 pioneered by investigators at Memorial Sloan Kettering Cancer Center in New York has been the most widely used regimen in the United States.<sup>[1]</sup>

Almost simultaneously, results of other large randomized clinical studies investigating the role of capecitabine, an oral fluoropyrimidine, and oxaliplatin became available. Randomized comparison of intravenous 5-FU vs capecitabine showed similar efficacy and a different spectrum of toxicities.<sup>[3,4]</sup> Although treatment with oxaliplatin-based regimens resulted in higher response rates and longer time to treatment failure, overall survival did not improve in oxaliplatin-treated patients.<sup>[5,6]</sup> Subsequent studies have incorporated these novel agents in the treatment of patients with resected colorectal cancer and the efficacy of new combinations are being tested in advanced disease. Some of these studies have been recently completed and their results are eagerly awaited.

Soon after the trial results established the superior efficacy of triple-therapy regimens, worrisome data regarding the toxicity of the Saltz regimen became available. Analysis of the results obtained by the North Central Cancer Treatment Group (NCCTG)/Intergroup 9741 and the Cancer and Leukemia Group B (CALGB) 89803 trial, using a new toxicity parameter (60-day all-cause mortality) and real-time monitoring, found a higher mortality in the group receiving the triple-therapy regimen compared with the group receiving control treatment.

Lethal events in the triple therapy-treated patients increased from 0.8% and 1.1 % in the CALGB 89803 and N9741, respectively, in the control arms, to 2.5% and 3.5 %, respectively, in the experimental arms. Accrual to both studies was suspended in April 2001, and an expert panel was convened to review the toxicity data. The recommendations from this panel have been recently published in the *Journal of Clinical Oncology*.<sup>[7]</sup>

Two toxic syndromes were identified: a gastrointestinal syndrome consisting of nausea, vomiting, diarrhea, abdominal pain, dehydration, fever, and neutropenia, and a vascular syndrome consisting of pulmonary embolism, myocardial infarction, and cerebrovascular accidents. The panel recommended that healthcare providers using this regimen be aware of these toxicities. Patients should be monitored by experienced physicians on a weekly basis during the first cycle of treatment. Toxicity should be managed aggressively with the use of loperamide, hydration, and a more liberal use of oral fluoroquinolone antibiotics in patients with diarrhea and neutropenia in the absence of fever, or diarrhea and fever in the absence of neutropenia. Weekly treatment should be discontinued in the presence of grade 2 toxicities until patients have recovered for at least 24 hours.

These data have implications for both practicing physicians and clinical investigators. It is clear that the use of triple-therapy regimens either following the Saltz schedule or the infusional schedule are associated with increased survival, and these should be the treatments of choice for patients who meet the eligibility criteria used in the 2 studies. The infusional regimens widely used in Europe have been demonstrated to be active and are associated with less toxicity.

Modifications of the Saltz regimen using a 2 weeks every 3 weeks regimen or lower doses of the agents are also being used. It should be noted, however, that these modifications are deviations from the original regimen that resulted in improved survival, and thus, in the absence of specific data from randomized trials, there are no grounds to assume that they will be equally effective. Modifications of the Saltz regimen as well as of other regimens including alternating schedules, sequential schedules, and integration of other active drugs such as oxaliplatin and capecitabine should be investigated in properly planned clinical trials.

## Advanced Disease: Novel Agents

Over the last few years, advances in molecular and cancer biology have led to the identification of a number of abnormal pathways in cancer cells that represent potential targets for anticancer drug development. A variety of novel agents targeting these specific anomalies have been developed in early clinical trials, and some of them have been tested in patients with colon cancer. Two of these strategies include inhibitors of the epidermal growth factor receptor (EGFR) and angiogenesis inhibitors. However, for different reasons, the results obtained, thus far, have been of limited value.

The EGFR is a transmembrane receptor that is overexpressed in patients with colon cancer. A substantial number of preclinical studies have demonstrated the role of EGFR overexpression and activation in colon cancer cells and have shown that pharmacologic inhibition of the EGFR results in tumor growth inhibition. Different strategies have been explored in preclinical studies and in the clinic to inhibit the EGFR, including monoclonal antibodies against the extracellular domain of the receptor and small-molecule inhibitors of the receptor tyrosine kinase.<sup>[8]</sup>

Monoclonal antibody C-225, a humanized anti-EGFR, has been developed for patients with colon cancer. Planning of the study investigating the effects of C-225 in patients with colorectal cancer was based on preclinical and clinical observations that treatment with C-225 in combination with CPT-11 inhibited growth of CPT-11-resistant tumors.

In this trial, patients with EGFR overexpressing colorectal tumors and CPT-11 refractory disease, as demonstrated by progression during treatment with a CPT-11-based regimen, were treated with the same CPT-11 regimen in combination with C-225. A total of 120 patients were treated and a 22.5% response rate was obtained. Of note, patients who developed cutaneous toxicity, a typical toxic event in patients treated with C-225, had a higher response rate (29%) as compared with those who did not have a rash (3%).<sup>[9]</sup>

The data from this study were intended to support an application for approval of C-225 for patients with colorectal cancer. However, major criticisms regarding the design of the study and the quality of the data, as well as the lack of a comparative arm assessing the activity of C-225 alone in patients with CPT-11-refractory and EGFR-positive advanced colorectal cancer, led to a refusal by the US Food and Drug Administration to review the application. At the present time, the real value of C-225 and of other EGFR-interacting agents is unknown and additional studies will have to be performed to determine the antitumor effects of these agents alone or in combination with chemotherapy.

The second class of targeted agents that has been evaluated in large-scale clinical trials in patients with colorectal cancer is molecules known as angiogenesis inhibitors. The process of blood vessel formation is a key pathologic event in the development and dissemination of malignant tumor cells. A variety of agents targeting this process within different molecular pathways are currently in clinical development.

One of such agents developed for colorectal cancer patients is SU5416, a specific inhibitor of the vascular endothelial growth factor receptor (VEGFR) tyrosine kinase. In preclinical models, SU5416 was shown to inhibit VEGFR-dependent signaling pathways in endothelial cells and to mediate antiangiogenic and antitumor effects. In a trial reported by Rosen and colleagues,<sup>[10]</sup> patients with untreated metastatic colorectal cancer received increasing doses of SU5416 (85 mg/m<sup>2</sup> and 145 mg/m<sup>2</sup>) administered twice weekly intravenously, in combination with standard doses of 5-FU/leucovorin therapy using either the Mayo Clinic or the Roswell Park regimen. The primary objective of the study was to determine the safety of this combination regimen.

While both regimens with full-dose SU5416 seemed to be tolerable, the Roswell Park arm showed fewer grade 3/4 toxicities (nausea, vomiting, diarrhea, mucositis, neutropenia). No pharmacokinetic interactions were observed. At the time of the preliminary report, 6 of 28 patients had responded to

the treatment. On the basis of these data, a randomized trial was initiated. However, a preliminary analysis failed to prove any advantage in the experimental vs the control group, and the trial was, therefore, closed to accrual.

## Adjuvant Treatment of Colorectal Cancer

A series of randomized clinical trials have established that postoperative treatment with 5-FU and leucovorin for 6 months after curative surgery is the standard of care in patients with resected stage 3 colon cancer. Composite analysis of prior randomized clinical trials of adjuvant treatment in colon cancer, as well as population-based studies, indicated that treatment with 5-FU containing chemotherapy is equally effective in elderly patients and in young individuals, suggesting that older patients should not be excluded from adjuvant treatment just because of older age.<sup>[11,12]</sup> Randomized trials have been completed or are underway to determine whether novel regimens containing CPT-11, oxaliplatin, and capecitabine result in better outcomes in this setting.

Recent retrospective studies have examined the role of molecular and genetic markers as predictors of outcome in patients with colon cancer. These markers include assessment of mutations and chromosome alterations that are relevant in the pathogenesis of colon cancer, as well as the analysis of biomarkers related to the mechanism of action of chemotherapeutic drugs. For example, high expression of the 5-FU intracellular target thymidine synthetase (TS) has been related to resistance to the agent, suggesting that patients with high levels of this enzyme should be good candidates to investigate nonfluoropyrimidine-containing adjuvant regimens.<sup>[13-15]</sup> However, a recent study failed to demonstrate a relationship between expression of TS in the primary tumor and resistance to 5-FU.<sup>[16]</sup> Prospective confirmation of this finding using standardized methods is required before final conclusions can be drawn.

## Conclusions

The standard treatment for patients with advanced colon cancer has changed and should consist of the triple 5-FU/leucovorin/CPT-11 regimen. The incorporation of new active agents such as CPT-11, oxaliplatin, and capecitabine into the treatment of patients with early-stage disease is expected to result in the cure of more patients. Although the results obtained, thus far, with novel targeted compounds have been disappointing, a significant number of new agents are being developed, and it is hoped that this will result in a meaningful improvement in outcomes. Finally, it is anticipated that risk and treatment assessment using molecular markers will eventually lead to tailored treatment for the individual patient.

### Funding Information

Manuel Hidalgo, MD, has disclosed that he receives grants for clinical research from Novartis, Wyeth-Ayerst, and OSI Pharmaceuticals. He serves as an advisor or consultant for Novartis, Astra Zeneca, Genentech, and OSI Pharmaceuticals.