

SYSTEMIC THERAPY FOR COLORECTAL CANCER

Introduction

Until 1994, fluorouracil (5-FU) was the only effective chemotherapeutic drug for colorectal cancer (CRC). Recent advances include newer cytotoxic chemotherapies, and biologic agents effective against CRC (Table 1)

- Pathological stage at the time of presentation remains the most important prognostic indicator in CRC (Table 2).
- Prospective studies have demonstrated that the use of chemotherapy in patients with metastatic disease prolongs survival and enhances quality of life in comparison to palliative care alone.
- In patient with stage III disease the routine use of adjuvant 5-FU-based systemic therapy is associated with an approximately 30 % reduction in the risk of disease recurrence, and a 22 to 32 % reduction in mortality.
- For patients with stage II disease, the American Society of Clinical Oncology does not support routine adjuvant chemotherapy.
- However, adjuvant therapy may be indicated for patients with:
 - inadequately sampled lymph nodes
 - T4 lesions, perforation
 - poorly differentiated histology.

Fluoropyrimidines

5-FU is an inhibitor of the **thymidylate synthase**, the rate-limiting enzyme in pyrimidine nucleotide synthesis. 5-FU is usually administered with **leucovorin (LV)**, a reduced folate that stabilizes the binding of 5-FU to thymidylate synthase, thereby enhancing the inhibition of DNA synthesis.

Efficacy: Randomized trials in patients with Stage III disease demonstrated that 5-FU/LV increased the probability of remaining free of tumor recurrence after 5 years from 42 to 58% and the likelihood of 5-year overall survival from 51 to 64%.

In patients with advanced CRC, 5-FU/LV reduces tumor size by 50% or more in approximately 20% of patients and prolongs median survival from approx. 6 to 11 months.

Side Effects: Depend on the method of administration

- Bolus treatment of 5 consecutive days every 4-5 weeks: neutropenia, stomatitis.
- Weekly bolus doses: diarrhea.
- Continuous IV infusion: less hematologic and GI toxicity, more hand-foot syndrome.

Oral fluoropyrimidines

Oral 5-FU was designed to overcome the problems seen with I.V. 5-FU therapy, and inconvenience associated with central venous access. However, 5-FU is unsuitable for oral

administration due to variable mucosal concentrations of dihydropyrimidine dehydrogenase, a major catabolic enzyme of the drug. Strategies to overcome this problem included:

- (1) the co- administration of oral 5-FU with drug that inhibit the action of the enzyme
- (2) the administration of 5-FU prodrugs that are absorbed intact and metabolically activated after intestinal absorption.

Example of 1 is a combination of **uracil** (enzyme inhibitor) plus **tegafur** (prodrug) with oral LV. In two randomized trials, this therapy resulted in a response rate and median survival similar to those obtained with parenteral 5-FU/LV.

Example of 2 is **Capecitabine (Xeloda®)**, a prodrug that undergoes a 3-step enzymatic conversion to 5-FU. Two randomized trials comparing capecitabine to the monthly schedule of 5-FU/LV reported that the rate of objective response in patients treated with capecitabine was moderately improved (19 to 25%, as compared with 15%); median overall survival however, was similar between the two regimens (12 and 13 months).

Side effects: Xeloda®- Hand-foot syndrome (+), diarrhea, N/V and BM suppression.

As monotherapy, the oral fluoropyrimidines appear to be safer, more convenient and cost effective when compared with bolus IV 5-FU given on 5 consecutive days every 4-5 weeks.

Regional therapy with fluoropyrimidines

Infusions of 5-FU or an analogue compound, **floxuridine** into the hepatic artery results in a doubling of the response rate achieved with IV 5-FU. However, most of the randomized studies have failed to demonstrate improvement in cure rate with this type of adjuvant therapy after resection of hepatic metastasis as compared to surgery alone or systemic chemotherapy; only one trial reported a significant difference in 2 year survival with hepatic infusion therapy.

Side effects: chemical hepatitis, cholangitis, catheter-related complications and high cost.

Irinotecan and oxaliplatin- containing regimens

Irinotecan and oxaliplatin are newer drugs approved for use in patients with metastatic CRC, most often in combination with 5-FU/LV.

Irinotecan (Campostar, CPT-11)

Irinotecan is a semisynthetic derivative of the natural alkaloid camptothecin, which exerts a cytotoxic effect through the interaction with the enzyme **topoisomerase I**, leading to DNA fragmentation and cell death.

Side effects: Diarrhea, bone marrow suppression, nausea, vomiting and alopecia.

Efficacy:

- Second line: 2 randomized trials of single-agent irinotecan as a second-line therapy in patients with advanced CRC who had previously received bolus 5-FU showed a 2-3

month improvement in median overall survival as compared with either best supportive care alone or 5-FU given by continuous infusion, accompanied by similar or improved quality of life.

- First-line: Irinotecan was examined in combination with 5 FU/LV as initial therapy for metastatic colorectal cancer (IFL); the three drug combination was twice as likely as 5FU/LV alone to result in a 50% or greater shrinkage of tumor dimensions, resulting in a two-month extension in median survival.

Side effects: Adding Irinotecan to bolus 5FU/LV increases the likelihood of clinically significant myelosuppression and diarrhea.

Oxalipatin (Eloxatin)

Oxalipatin is a platinum derivative that **induces cellular apoptosis**. Oxalipatin and 5FU have been shown to be highly synergistic, possibly due to the down-regulation of thymidylate synthase by oxalipatin, which thereby potentiates the efficacy of 5-FU.

Side effects: Neuropathy. Renal dysfunction, alopecia, ototoxicity are uncommon.

Efficacy:

Combination of oxalipatin with 5-FU/LV followed by a 46 hour infusion of 5-FU (**FOLFOX**) results in response rates and time to disease progression that are superior to those achieved with FU/LV when given as first- line or second-line treatment for metastatic colorectal cancer. There is a trend for improved overall survival.

Is there an optimal first-line therapy for metastatic disease?

Comparisons of irinotecan + 5-FU/LV regimens with oxalipatin + 5-FU/LV combinations for the initial treatment of metastatic colorectal cancer have recently been reported (Table 3). Data suggest **equivalence between irinotecan-based regimens and oxalipatin-based regimens** when combined with comparable 5-FU therapies.

The optimal sequence of these chemotherapy agents is currently unclear. The choice of initial therapy could depend on a given patient's coexisting conditions at baseline: patients who have an underlying neuropathy, irinotecan-based regimens may be more appropriate and patients with underlying bowel dysfunction, oxalipatin-based therapy may be more appropriate. Despite the choice of initial therapy, exposure to each of these cytotoxic agents at some time over the course of a patient's disease has been associated with prolonged survival.

Targeted therapies

Laboratory studies have identified molecular sites in tumor tissue that may serve as specific targets for treatment. The goal of such a therapeutic strategy is the interruption of cellular pathways essential for tumor growth, survival and metastasis and potentially less toxic effects.

Cetuximab (Erbix – C-225)

Erbix is a **monoclonal antibody against the epidermal growth factor receptor**.

Side effects: Acne-like rash, drying and fissuring of the skin.

Efficacy:

Preclinical studies have shown that not only that therapeutic synergy exists between cetuximab and chemotherapeutic agents, but also that such synergy can occur in tumor cells already resistant to Irinotecan.

Saltz and colleagues (Table 4) gave a combination of cetuximab and irinotecan to 121 patients with advanced CRC whose tumor had been found to be unresponsive to irinotecan; 19 % of the patients had radiographically objective tumor shrinkage. To determine whether this antitumor effect was due to synergy between the two drugs or due to the independent activity of cetuximab, 60 similar patients were treated with the antibody alone; 10% of them had radiographically significant tumor regression. These experiences were confirmed and extended by Cunningham and colleagues, who randomly assigned 329 patients with advanced colorectal cancer that was refractory to irinotecan to receive either cetuximab with irinotecan or cetuximab alone. This larger clinical trial resulted in an almost identical, 23 % rate of disease regression in patients given the combination and 11 % in those who received single-agent cetuximab.

Obs: These trials included only patients with immunohistochemical evidence of epidermal growth factor expression.

Bevacizumab (Avastin)

Tumor growth and metastasis are dependent on angiogenesis. **Bevacizumab is an antibody directed against the vascular endothelial growth factor.**

Efficacy

A small, randomized, phase 2 trial in patients who had received no prior treatment for their metastatic disease showed that bevacizumab, as compared with 5FU/LV alone, improved the likelihood of a tumor response. This effort led to two concurrent randomized, phase 3 trials. Hurwitz and colleagues assigned 815 patients to receive either IFL with bevacizumab or IFL with placebo. **The addition of bevacizumab led to an impressive, statistically significant increase in the rate of response and a 4.7 month prolongation in median overall survival.** In a study involving patients considered unable to tolerate irinotecan, Kabbinavar et al. found that bevacizumab added to 5-FU/LV improved response rates and extended the time to tumor progression but did not significantly prolong median survival.

Side effects: Reversible hypertension and proteinuria

Reference:

1. Meyerhardt JA, Mayer, R. Systemic therapy for colorectal cancer. N Engl J Med 2005;352:476-97

Table 1. Glossary of Treatments for Colorectal Cancer.*

<p>FDA-approved drugs Fluorouracil Capecitabine (Xeloda) Irinotecan (Camptosar) Oxaliplatin (Eloxatin) Cetuximab (Erbix) Bevacizumab (Avastin)</p> <p>FDA-approved combination regimens IFL: Irinotecan, bolus fluorouracil, and leucovorin — first-line therapy FOLFIRI: Irinotecan, infusional fluorouracil, and leucovorin — first-line therapy† FOLFOX: Oxaliplatin, infusional fluorouracil, and leucovorin — first- and second-line therapy Intravenous fluorouracil and bevacizumab — first-line therapy Cetuximab and irinotecan — therapy for EGFR-positive,‡ irinotecan-refractory disease</p>

- * FDA denotes Food and Drug Administration, and EGFR epidermal growth factor receptor.
- † FOLFIRI, as described by Douillard et al.,⁴ is the more commonly used variation of another combination of infusional fluorouracil, leucovorin, and irinotecan approved by the FDA.
- ‡ Immunohistochemistry testing is used to determine EGFR status.

Table 2. TNM Staging System for Colorectal Cancer.*

Stage	TNM Classification	Five-Year Survival %
I	T1–2, N0, M0	>90
IIA	T3, N0, M0	} 60–85
IIB	T4, N0, M0	
IIIA	T1–2, N1, M0	} 25–65
IIIB	T3–4, N1, M0	
IIIC	T (any), N2, M0	
IV	T (any), N (any), M1	5–7

Primary tumor (T)
 TX: Primary tumor cannot be assessed
 Tis: Carcinoma in situ
 T1: Tumor invades submucosa
 T2: Tumor invades muscularis propria
 T3: Tumor penetrates muscularis propria and invades subserosa
 T4: Tumor directly invades other organs or structures or perforates visceral peritoneum

Nodal status (N)
 NX: Regional lymph nodes cannot be assessed
 N0: No metastases in regional lymph nodes
 N1: Metastases in one to three regional lymph nodes
 N2: Metastases in four or more regional lymph nodes

Distant metastases (M)
 MX: Presence or absence of distant metastases cannot be determined
 M0: No distant metastases detected
 M1: Distant metastases detected

Table 3. Comparative Trials of Irinotecan and Oxaliplatin as First-Line Therapy for Metastatic Colorectal Cancer.*

Trial and Regimens	No. of Patients	Rate of Response %	P Value†	Median Time to Progression mo	P Value	Median Overall Survival mo	P Value‡
Goldberg et al. ⁷⁷							
IFL	264	31		7.0		15.0	
FOLFOX	267	45	<0.001	9.3	0.002	19.5	<0.001
IROX	264	35	0.3	6.5	0.5	17.4	0.04
Tournigand et al. ⁷⁸ ‡							
FOLFIRI	109	56		8.5		21.5	
FOLFOX	111	54	NS	8.0	0.3	20.6	0.99
Grothey et al. ⁷⁹ ‡							
Irinotecan plus capecitabine	79	43		7.9		>16	
Oxaliplatin plus capecitabine	82	51	0.3	7.9	0.3	>16	NS

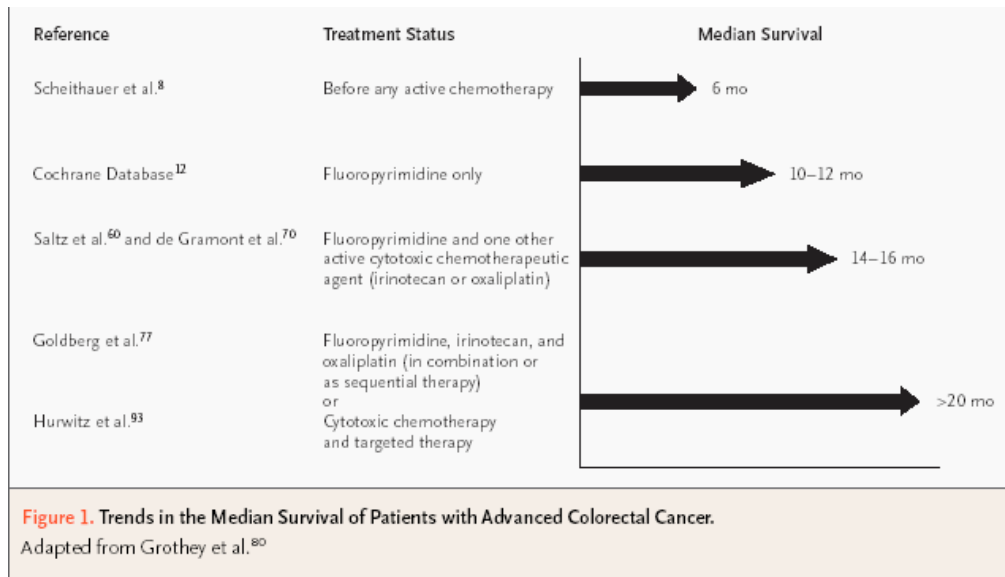
- * This table includes the results of trials of first-line therapy only. IFL denotes irinotecan and bolus fluorouracil; FOLFOX oxaliplatin, infusional fluorouracil, and leucovorin; FOLFIRI irinotecan, infusional fluorouracil, and leucovorin; and NS not significant.
- † P values are for the comparison with the IFL regimen (the control) in the trial reported by Goldberg et al.,⁷⁷ with the FOLFIRI regimen in the trial reported by Tournigand et al.,⁷⁸ and with the irinotecan and capecitabine regimen in the trial reported by Grothey et al.⁷⁹
- ‡ In these studies, patients crossed over to the other group at the time of progression of disease or intolerance of first-line therapy.

Table 4. Trials of Targeted Therapies in Metastatic Colorectal Cancer.*						
Trial and Regimen	Type of Study	No. of Patients	Rate of Response	Median Time to Progression	Median Overall Survival	
			%	mo	mo	
Cetuximab						
Saltz et al. ⁸⁸ : cetuximab and irinotecan	Phase 2	121	19	NR	NR	
Saltz et al. ⁸⁹ : cetuximab only	Phase 2	57	11	1.4	6.4	
Cunningham et al. ⁹⁰	Randomized, phase 2					
Cetuximab only†		111	11	1.5	6.9	
Cetuximab and irinotecan		218	23	4.1	8.6	
Bevacizumab						
Kabbinavar et al. ⁹¹	Randomized, phase 2					
Fluorouracil and leucovorin		36	17	5.2	13.8	
Fluorouracil, leucovorin, and bevacizumab		68	32	7.4	16.1 and 21.5‡	
Kabbinavar et al. ⁹²	Phase 3					
Fluorouracil and leucovorin		105	15	5.5	12.9	
Fluorouracil, leucovorin, and bevacizumab		104	26 (P=0.06)	9.2 (P<0.001)	16.6 (P=0.16)	
Hurwitz et al. ⁹³	Phase 3					
IFL		412	35	6.2	15.6	
IFL and bevacizumab		403	45 (P=0.004)	10.6 (P<0.001)	20.3 (P<0.001)	

* NR denotes not reported, and IFL irinotecan, fluorouracil, and leucovorin.

† Patients in the cetuximab-only group were allowed to cross over to the cetuximab-and-irinotecan group on progression of disease. Fifty-four of the patients who initially were randomly assigned to single-agent cetuximab crossed over, with 3.6 percent having a partial response and 35.7 percent having stable disease.

‡ In this trial, two groups received bevacizumab: one group received 10 mg per kilogram of body weight and had a median overall survival of 16.1 months, and the other group received 5 mg per kilogram and had a median overall survival of 21.5 months.



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February 14, 2005