

Colorectal Cancer: Expanding Treatment Options

Understanding Fundamental Concepts in CRC Disease Prevention, Diagnosis, and Treatment

ABBREVIATIONS (excluding chemotherapy regimens)

ACS = American Cancer Society	FOBT = fecal occult blood test
ADL = activities of daily living	FSIG = flexible sigmoidoscopy
AE = adverse event	GI = gastrointestinal
AGA = American Gastroenterological Association	HAI = hepatic arterial infusion
AGC = absolute granulocyte count	HFS = hand-foot syndrome
AJCC = American Joint Committee on Cancer	HNPCC = hereditary nonpolyposis colorectal cancer
ANC = absolute neutrophil count	HSR = hypersensitivity reaction
APC = adenomatous polyposis coli	IV = intravenous
ASCO = American Society of Clinical Oncology	LLN = lower limit of normal
BMI = body mass index	LN = lymph nodes
BSC = best supportive care	LV = leucovorin
BV = bevacizumab	MAb = monoclonal antibody
CALGB = Cancer and Leukemia Group B	MOSAIC = Multicenter International Study of Oxaliplatin/ 5-FU/LV in the Adjuvant Treatment of Colon Cancer
CBC = complete blood count	MRI = magnetic resonance imaging
CDC = Centers for Disease Control and Prevention	NCCN = National Comprehensive Cancer Network
CEA = carcinoembryonic antigen	NCI CTC = National Cancer Institute Common Toxicity Criteria
CHF = congestive heart failure	NSABP = National Surgical Adjuvant Breast and Bowel Project
CID = chemotherapy-induced diarrhea	NSCLC = non-small cell lung cancer
CNS = central nervous system	NSS = normal saline solution
CRC = colorectal cancer	OS = overall survival
CT = computed tomographic	PET = positron emission tomography
DCBE = double-contrast barium enema	PETACC-3 = Pan-European Trial in Adjuvant Colon Cancer 3
DCC = deleted in colorectal cancer	PLD = pharyngolaryngeal dysesthesia
DFS = disease-free survival	PPE = palmar-plantar erythrodysesthesia
DLT = dose-limiting toxicity	RFS = relapse-free survival
DMSO = dimethylsulfoxide	RT = radiotherapy
ECOG = Eastern Cooperative Oncology Group	SC = subcutaneous
EGFR = epidermal growth factor receptor	SWOG = Southwestern Oncology Group
FAP = familial adenomatous polyposis	Tis = carcinoma in situ: intraepithelial or invasion of lamina propria
FDA = US Food and Drug Administration	USPSTF = US Preventive Services Task Force
FIT = fecal immunohistochemical test	VEGF = vascular endothelial growth factor
5-FU = 5-fluorouracil	X-ACT = Xeloda in Adjuvant Colon Cancer Therapy

LIST OF CHEMOTHERAPEUTIC REGIMENS

Disclosure

- This table describes the regimens discussed in the accompanying slides and is for informational purposes only.
- Primary references and full prescribing information should be consulted when making patient care decisions.
- Clinicians have the professional responsibility to ensure that drugs are prescribed and used appropriately, based on their own clinical judgment and accepted standards of care.

Name	Regimen	Reference
Single agents		
Capecitabine	1,250 mg/m ² po bid, days 1 through 14, followed by 7 days rest <i>Repeat every 3 weeks</i>	Hoff et al. <i>J Clin Oncol.</i> 2001;19:2282-2292.
Irinotecan	125 mg/m ² IV over 90 minutes, days 1, 8, 15, 22 <i>Repeat every 6 weeks</i> or 300-350 mg/m ² IV over 30 to 90 minutes <i>Repeat every 3 weeks</i>	Saltz et al. <i>N Engl J Med.</i> 2000;343:905-914. Fuchs et al. <i>J Clin Oncol.</i> 2003; 21:807-814.
Cetuximab	400 mg/m ² IV over 2 hours week 1 followed by 250 mg/m ² IV over 1 hour weekly	Cunningham et al. <i>N Engl J Med.</i> 2004;351:337-345.
Protracted 5-FU infusion	300 mg/m ² daily protracted IV infusion	Lokich et al. <i>J Clin Oncol.</i> 1989;7:925-932.
Combination regimens		
5-FU/LV Roswell Park regimen	LV 500 mg/m ² IV over 2 hours, days 1, 8, 15, 22, 29, 36 5-FU 600* mg/m ² IV bolus 1 hour after start of LV, days 1, 8, 15, 22, 29, 36 <i>Repeat every 8 weeks</i> *NCCN guidelines recommend a dose of 5-FU 500 mg/m ² IV bolus 1 hour after start of LV, days 1, 8, 15, 22, 29, 36	Petrelli et al. <i>J Clin Oncol.</i> 1989;7:1419-1426.
5-FU/LV Mayo regimen	LV 20 mg/m ² IV bolus, days 1 through 5 5-FU 425 mg/m ² IV bolus 1 hour after start of LV, days 1 through 5 <i>Repeat cycle at 4 and 8 weeks and every 5 weeks thereafter</i>	Poon et al. <i>J Clin Oncol.</i> 1991;9:1967-1972. O'Connell et al. <i>J Clin Oncol.</i> 1997;15:246-250.
5-FU/LV de Gramont regimen (LV5FU2)	LV 400 mg/m ² IV over 2 hours, days 1 and 2 [†] 5-FU 400 mg/m ² IV bolus, then 600 mg/m ² IV over 22 hours, days 1 and 2 <i>Repeat every 2 weeks</i>	de Gramont et al. <i>J Clin Oncol.</i> 2000;18:2938-2947.
5-FU/LV + bevacizumab	LV 500 mg/m ² IV days 1, 8, 15, 22, 29, 36 [†] 5-FU 500 mg/m ² days 1, 8, 15, 22, 28, 36 Bevacizumab 5 mg/kg IV every 2 weeks	Hurwitz et al. <i>J Clin Oncol.</i> 2005; 23:3502-3508.
FOLFOX4	Oxaliplatin 85 mg/m ² IV over 2 hours, day 1 LV 200 mg/m ² IV over 2 hours, days 1 and 2 5-FU 400 mg/m ² IV bolus, then 600 mg/m ² IV over 22 hours, days 1 and 2 <i>Repeat every 2 weeks</i>	Rothenberg et al. <i>J Clin Oncol.</i> 2003;21:2059-2069. André et al. <i>N Engl J Med.</i> 2004;350:2343-2351. Goldberg et al. <i>J Clin Oncol.</i> 2004;22:23-30.
FOLFOX6	Oxaliplatin 100 mg/m ² IV over 2 hours, day 1 LV 400 mg/m ² IV over 2 hours, day 1 [†] 5-FU 400 mg/m ² IV bolus, then 2,400 to 3,000 mg/m ² IV over 46 hours	Tournigand et al. <i>J Clin Oncol.</i> 2004;22:229-237.
mFOLFOX6	Oxaliplatin 85 mg/m ² IV over 2 hours, day 1 LV 400 mg/m ² IV over 2 hours, day 1 [†] 5-FU 400 mg/m ² IV bolus, then 1,200 mg/m ² daily IV on days 1 and 2 infusion	
FOLFOX7	Oxaliplatin 130 mg/m ² IV over 2 hours, day 1 LV 400 mg/m ² IV over 2 hours, day 1 [†] 5-FU 2,400 mg/m ² IV over 46 hours, continuous infusion <i>Repeat every 2 weeks for 6 cycles</i>	de Gramont et al. <i>J Clin Oncol.</i> 2004;22(suppl 14). Abstract 3525.
OPTIMOX1	FOLFOX7 for 6 cycles, then LV 400 mg/m ² IV over 2 hours [†] followed by 5-FU 400 mg/m ² bolus and 3,000 mg/m ² IV infusion over 46 hours <i>repeated every 2 weeks for 12 cycles, then</i> FOLFOX7 for 6 cycles	Tournigand et al. <i>J Clin Oncol.</i> 2006;24:394-400.

LIST OF CHEMOTHERAPEUTIC REGIMENS (CONT)

Name	Regimen	Reference
FOLFOX4 + bevacizumab	Bevacizumab 10 mg/kg IV, day 1 Oxaliplatin 85 mg/m ² IV over 2 hours, day 1 LV 200 mg/m ² IV over 2 hours, days 1 and 2 5-FU 400 mg/m ² IV bolus, then 600 mg/m ² IV over 22 hours, days 1 and 2 <i>Repeat every 2 weeks</i>	Giantonio et al. 2005 ASCO GI Cancers Symposium. Abstract 169a.
FLOX	Oxaliplatin 85 mg/m ² IV over 2 hours, days 1, 15, 29 LV 500 mg/m ² IV, days 1, 8, 15, 22, 29, 36 [†] 5-FU 500 mg/m ² IV bolus, days 1, 8, 15, 22, 29, 36 <i>Repeat every 8 weeks for 3 cycles</i>	Wolmark et al. <i>J Clin Oncol.</i> 2005;23(suppl 16). Abstract 3500.
IFL Saltz regimen	Irinotecan 125 mg/m ² IV over 90 minutes, days 1, 8, 15, 22 LV 20 mg/m ² IV bolus, days 1, 8, 15, 22 5-FU 500 mg/m ² IV bolus, days 1, 8, 15, 22 <i>Repeat every 6 weeks</i>	Saltz et al. <i>N Engl J Med.</i> 2000;343:905-914. Saltz et al. <i>J Clin Oncol.</i> 2004;22(suppl 14). Abstract 3500.
FOLFIRI	Irinotecan 180 mg/m ² IV over 2 hours, day 1 LV 400 mg/m ² IV over 2 hours prior to 5-FU, days 1 and 2 [†] 5-FU 400 mg/m ² IV bolus followed by 5-FU 600 mg/m ² IV over 22 hours, days 1 and 2, or Irinotecan 180 mg/m ² over 90 minutes, day 1 LV 400 mg/m ² IV over 2-hour infusion, day 1 [†] 5-FU 400 mg/m ² IV bolus, then 1,200 mg/m ² , days 1 and 2 (total 2,400 mg/m ² over 46–48 hours continuous infusion) <i>Repeat every 2 weeks</i> [NCCN guidelines recommend addition of bevacizumab 5 mg/kg IV every 2 weeks]	Douillard et al. <i>Lancet.</i> 2000;355:1041-1047. André et al. <i>Eur J Cancer.</i> 1999; 35:1343-1347.
IFL + bevacizumab	Irinotecan 125 mg/m ² IV over 90 minutes, days 1, 8, 15, 22 LV 20 mg/m ² IV, days 1, 8, 15, 22 5-FU 500 mg/m ² IV, days 1, 8, 15, 22 <i>Repeat every 6 weeks</i> Bevacizumab 5 mg/kg IV over 90 minutes,* day 1 <i>Repeat every 2 weeks</i> *If first infusion is well tolerated, subsequent infusions may be administered over 60 minutes and then 30 minutes.	Hurwitz et al. <i>N Engl J Med.</i> 2004; 350:2335-2342.
Cetuximab + irinotecan	Cetuximab 400 mg/m ² IV over 2 hours <i>week 1</i> followed by 250 mg/m ² IV over 1 hour <i>weekly</i> Irinotecan 125 mg/m ² IV weekly for 4 consecutive weeks, followed by 2 weeks rest, or 180 mg/m ² every 2 weeks, or 350 mg/m ² IV every 3 weeks	Cunningham et al. <i>N Engl J Med.</i> 2004;351:337-345.
XELOX	Oxaliplatin 130 mg/m ² IV over 2 hours, day 1 Capecitabine 1,000 mg/m ² bid, days 1 through 14	Cassidy et al. <i>J Clin Oncol.</i> 2004;22:2084-2091.
CAPOX or CAPOX + bevacizumab	Oxaliplatin 130 mg/m ² IV, day 1 Capecitabine 850 mg/m ² po bid, days 1 through 14 <i>Repeat every 22 days</i> [NCCN guidelines recommend addition of bevacizumab 7.5 mg/kg every 3 weeks or 5 mg/kg every 2 weeks]	Hochster et al. 2006 ASCO GI Cancers Symposium. Abstract 244.

5-FU = 5-fluorouracil; LV = leucovorin.

[†]Leucovorin dose is 400 mg/m² in the United States and 200 mg/m² in Europe based on the isomer used.

For additional colorectal cancer regimens, please visit www.managecrc.com

GENERALIST SUPPLEMENTAL SLIDES

Supplemental Slides

Generalist Deck

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Drug Administration Considerations

Agent	Reconstitution and Compatibility	Administration
Irinotecan	Stable 24 h in D5W Particulates seen in NSS admixtures under refrigeration	<ul style="list-style-type: none"> • Use within 6 h of reconstitution if kept at room temperature
Capecitabine	Oral agent supplied in 150- and 500-mg tablets	<ul style="list-style-type: none"> • Instruct patient to take at end of meal with water • Total daily dose not to exceed 2,500 mg/m²
Oxaliplatin	Incompatible with NaCl Dilute in D5W and flush line with D5W after oxaliplatin Avoid contact with aluminum products	<ul style="list-style-type: none"> • Consider pretreatment to prevent hypersensitivity reactions • Classified as irritant, but extravasation injuries reported; monitor closely during administration
Bevacizumab	Incompatible with dextrose solutions Reconstitute with NSS	<ul style="list-style-type: none"> • First dose is given over 90 min; if well tolerated, second dose over 60 min; third and subsequent doses may be given over 30 min if tolerated
Cetuximab	Do not shake or dilute contents of 50-mL vial	<ul style="list-style-type: none"> • DO NOT administer as IV push or bolus • Infuse through low-protein-binding 0.22-micron in-line filter • Pretreat to minimize hypersensitivity reactions

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Patient Access

Table. Estimated Drug Costs for Eight Weeks of Treatment for Metastatic Colorectal Cancer.

Regimen	Drugs and Schedule of Administration	Drug Costs ^a
Regimens containing fluorouracil		
Mayo Clinic	Monthly bolus of fluorouracil plus leucovorin	63
Roswell Park	Weekly bolus of fluorouracil plus leucovorin	304
LV5FU2	Biweekly fluorouracil plus leucovorin in a 48-hr infusion	263
Regimens containing irinotecan or oxaliplatin		
Irinotecan alone	Weekly bolus	9,497
IFL	Weekly bolus of fluorouracil plus irinotecan	9,539
FOLFIRI	LV5FU2 with biweekly irinotecan	9,381
FOLFOX	LV5FU2 with biweekly oxaliplatin	11,889
Regimens containing bevacizumab or cetuximab		
FOLFIRI with bevacizumab	FOLFIRI with fortnightly bevacizumab	21,399
FOLFOX with bevacizumab	FOLFOX with biweekly bevacizumab	21,033
Irinotecan with cetuximab	Weekly irinotecan plus cetuximab	30,790
FOLFIRI with cetuximab	FOLFIRI and weekly cetuximab	30,675

^a Costs represent 95 percent of the average wholesale price in May 2004.

From Schrag. *N Engl J Med.* 2004;351:317-319, with permission.

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GENERALIST SUPPLEMENTAL SLIDES (CONT)

Patient Access (cont)

- ONCOLINE for capecitabine
 - http://www.xeloda.com/considering_xeloda/reimbursement.asp
- First resource for irinotecan
 - http://www.camptosar.com/hcp/pdf/First_Resource.pdf
- Care for oxaliplatin
 - <http://www.eloxatin.com/docs/pdf/CareBrochure.pdf>
- Access to Care Foundation for bevacizumab
 - <http://www.avastin.com/avastin/reSummaryPro.m>
- Access for cetuximab
 - http://www.erbitux.com/erbitux/channels/content.jsp?BV_useBVcookie=Yes&channelid=-1073760180

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Molecular Profiling: Current Predictive Markers for 5-FU, Oxaliplatin, and Irinotecan in CRC

- 5-FU
 - TS (overexpression leads to resistance to 5-FU)
 - TP (low expression associated with response and survival)
 - DPD (associated with response to 5-FU)
 - p53 (conflicting data)
- Oxaliplatin
 - ERCC1 (high level shown to be predictive of poor response in patients receiving oxaliplatin and 5-FU)
 - XPD (may be important in prediction of outcome to oxaliplatin)
- Irinotecan
 - Topoisomerase-1 (studies have shown a positive relationship between topoisomerase-1 activity and sensitivity to irinotecan, but it has not been proven)

Allen and Johnston. *J Clin Oncol*. 2005;23:4545-4552.

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Clinical Application of Genomics to the Treatment of CRC


- Irinotecan metabolized by enzymes exhibiting polymorphic activity
- Active metabolite SN38 is glucuronidated to inactive UGT1A1
- Retrospective and case-controlled study
 - Genotypes either heterozygous or homozygous for *UGT1A1**28 would be a significant risk factor for severe irinotecan toxicity
- UGT1A1 genotyping may help identify patients at risk
- In 2005, the FDA approved an in vitro assay diagnostic test that can detect 2 genetic polymorphisms in the *UGT1A1* gene

Ando et al. *Clin Cancer Res*. 2000;60:6921-6926.
Genzyme Genetics. UGT1A1 molecular assay. Available at: <http://www.genzymegenetics.com>.

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GENERALIST SUPPLEMENTAL SLIDES (CONT)

Symptom Management in Patients Undergoing Chemotherapy for CRC



Integumentary <ul style="list-style-type: none">• Acneiform rash• PPE• Extravasation• Alopecia		Myelosuppression <ul style="list-style-type: none">• Infection• Bleeding• Fatigue
Vascular <ul style="list-style-type: none">• TEs		Pulmonary <ul style="list-style-type: none">• Interstitial pneumonitis
Genitourinary <ul style="list-style-type: none">• Proteinuria/nephrotic syndrome		Neurotoxicity <ul style="list-style-type: none">• Dysesthesias• PPE
Gastrointestinal <ul style="list-style-type: none">• Stomatitis• Nausea/vomiting• Diarrhea		Acute Drug Reactions <ul style="list-style-type: none">• Hypersensitivity• Hypertension

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