

Colorectal Cancer

Current Treatments and Future Directions 2004

A live continuing education program for nurses and pharmacists



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1

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Program Overview

- Review current disease profile
 - Risk factors
 - Screening guidelines
 - Pathophysiology
 - Tumor staging
- Differentiate chemotherapeutic treatment options
 - Adjuvant CRC
 - Metastatic CRC
- Identify pre- and posttreatment assessment parameters
- Outline treatment-related issues and interventions
- Summarize promising future therapeutics

2

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US Estimated 2004 New Cancer Cases and Deaths

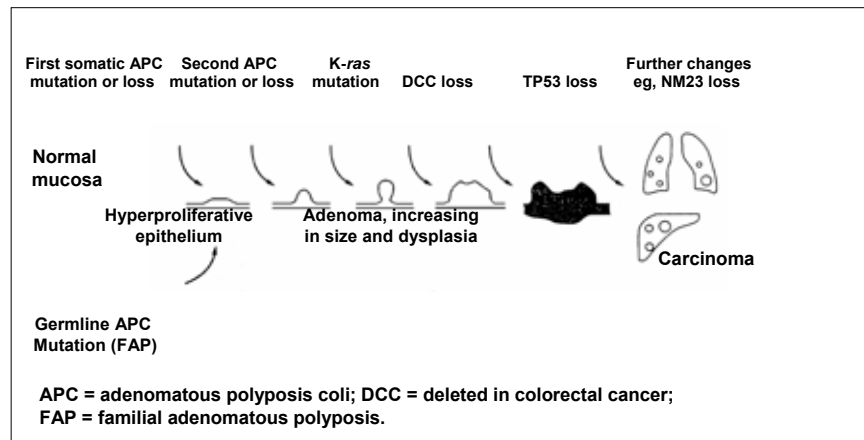
	Cases	Deaths		Cases	Deaths
Prostate	230,110	29,900		Breast	215,990 40,110
Lung and bronchus	93,110	91,930		Lung and bronchus	80,660 68,510
Colon and rectum	73,620	28,320		Colon and rectum	73,320 28,410
Urinary bladder	44,640	8,780		Uterine corpus	40,320 7,090
Melanoma	29,900	5,050		Ovary	25,580 16,090
Non-Hodgkin's lymphoma	28,850	10,390		Non-Hodgkin's lymphoma	25,520 9,020
Kidney and renal pelvis	22,080	7,870		Melanoma	25,200 2,860
Leukemia	19,020	12,990		Pancreas	16,120 15,830
Pancreas	15,740	15,440		Urinary bladder	15,600 3,930
All sites	699,560	290,890		All sites	688,470 272,810

Data from ACS. Cancer Facts & Figures 2004 (www.cancer.org).

3

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Colorectal Cancer Development *Adenoma to Carcinoma Sequence*



Adapted from Bishop and Hall 1994, with permission.

4

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Etiology

Modifiable Risk Factors for Colon Cancer

Factors	Relative Risk	Strength of Evidence
Alcohol (> 1 drink/d vs none)	1.4	Probable
Obesity (> 27 BMI vs < 21)	1.5	Definite
Eating red meat*	1.5	Probable
Smoking (≥ 25 cigarettes/d vs none)	1.5	Possible
High vegetable consumption (≥ 5 servings/d)	0.7	Possible

*Consumption by top 25% compared with lower 25%.
 BMI = body mass index.
 Colditz et al. 2000.

5

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Risk Factors for CRC

Family History

Risk Factor	Relative Risk Increase
1 first-degree relative	1.72
2 or more relatives	2.75
1 or more first-degree relatives and age < 45	5.37
1 or more first-degree relatives and age > 60	Not statistically significant

Fuchs et al. 1994.

6

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National Guidelines for CRC Screening Average Risk \geq 50 Years

Test/Procedure	Frequency
Fecal occult blood test (FOBT) and flexible sigmoidoscopy	FOBT annually and flexible sigmoidoscopy every 5 y
Flexible sigmoidoscopy	Every 5 y
FOBT	Annually
Colonoscopy	Every 5–10 y depending on findings
Double-contrast barium enema (DCBE)	Every 5–10 y

American Cancer Society; American Gastroenterological Association; National Cancer Institute; National Comprehensive Cancer Network; Colon Cancer Alliance.

7

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TNM Staging of CRC



Stage I
T1 limited to mucosa/
submucosa
T2 invades muscle



Stage II
T3 through muscle, wall,
T4 into nearby tissue



Stage III
N1 (1–3 LN)
N2 (> 3 LN)
N3 (blood vessel)



Stage IV
distant metastasis

LN = lymph nodes.
From MUSChealth.com, with permission.

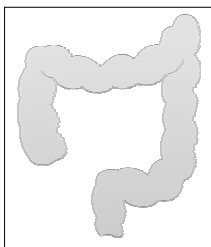
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Colorectal Cancer Clinical Features

Right-Sided Tumors

- Dull abdominal pain
- Palpable mass in right lower quadrant of abdomen
- Melena
- Anemia, malaise, indigestion, weight loss



Left-Sided Tumors

- Change in bowel habits
- Cramps, flatulence
- ↓ stool caliber
- Bright red blood in stool
- Incomplete stool evacuation

Rectal Tumors

- Bleeding
- Tenesmus

9

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FDA Approvals for Chemotherapy of Metastatic CRC

1960s	5-FU used for CRC
1980s	5-FU/LV used to prolong survival
1996	Irinotecan receives accelerated approval for second-line chemotherapy (full approval received in 1998)
2000	Irinotecan (in combination with bolus or infusional 5-FU/LV) approved for first-line treatment
2001	Capecitabine approved for first-line treatment
2002	Oxaliplatin (in combination with infusional 5-FU/LV) approved for second-line treatment
2004	Oxaliplatin (in combination with infusional 5-FU/LV) approved for first-line treatment
2004	Cetuximab (in combination with irinotecan, or alone if irinotecan not tolerated) approved for second-line treatment
2004	Bevacizumab (in combination with infusional 5-FU-based chemotherapy) approved for first-line treatment

5-FU = fluorouracil; LV = leucovorin.
Approved oncology drugs. www.fda.gov/cder/cancer.

10

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Newer Agents in CRC Management

Agent/Action	Indication	Approved Regimens	DLTs
<u>Irinotecan</u> Topoisomerase I inhibitor	1st and 2nd line for metastatic CRC	<ul style="list-style-type: none"> ▪ Single agent ▪ IFL ▪ FOLFIRI 	<ul style="list-style-type: none"> ▪ Diarrhea ▪ Neutropenia
<u>Capecitabine</u> 5-FU prodrug	1st line for metastatic CRC	<ul style="list-style-type: none"> ▪ Single agent 	<ul style="list-style-type: none"> ▪ PPE
<u>Oxaliplatin</u> Platinum analog	1st and 2nd line for metastatic CRC	<ul style="list-style-type: none"> ▪ In combination with 5-FU/LV (FOLFOX4) 	<ul style="list-style-type: none"> ▪ Peripheral neuropathy ▪ Neutropenia
<u>Bevacizumab</u> Anti-VEGF MAb	1st line for metastatic CRC	<ul style="list-style-type: none"> ▪ In combination with 5-FU-based regimens 	<ul style="list-style-type: none"> ▪ Hypertension ▪ Bleeding ▪ GI perforation ▪ Thrombus
<u>Cetuximab</u> Anti-EGFR MAb	2nd line for metastatic CRC	<ul style="list-style-type: none"> ▪ Single agent ▪ In combination with irinotecan (IFL or FOLFIRI) 	<ul style="list-style-type: none"> ▪ Acneiform rash ▪ Infusion reactions ▪ Interstitial lung disease

11

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Bolus vs Infusional 5-FU/LV *Efficacy and Safety*

- Bolus regimens (United States)
 - Mayo Clinic (monthly)
 - Roswell Park (weekly)
- Infusional regimens (Europe)
 - de Gramont (biweekly)
 - AIO (weekly)
- Phase III randomized trial comparing bolus (Mayo Clinic) with infusional (de Gramont) methods in first-line therapy
- Results: Infusional regimen
 - ↑ overall response rate (32.6% vs 14.5%)
 - ↑ median progression-free survival (27.6 vs 22 weeks)
 - Comparable overall survival
 - ↓ toxicity

de Gramont et al. 1997; Meta-analysis Group in Cancer. 1998.

12

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Irinotecan (Camptosar®)

- Topoisomerase I inhibitor
- First- and second-line treatment of metastatic CRC
- FDA-approved chemotherapy regimens:
 - Single-agent irinotecan (weekly or every 3 wk schema)
 - Irinotecan + bolus 5-FU/LV (IFL)
 - Irinotecan + infusional 5-FU/LV (FOLFIRI)
- DLTs: late-onset diarrhea and neutropenia
 - Risk minimized with patient monitoring, education, adherence to intensive loperamide regimen

NCCN Guidelines-Colon Cancer v.2.2004; Saltz et al. 2000; Douillard et al. 2000.

13

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Capecitabine (Xeloda®)

- 5-FU prodrug
- First-line treatment for metastatic CRC when single-agent fluoropyrimidine is preferred
- FDA-approved chemotherapy regimen:
 - Capecitabine 1,250 mg/m² twice daily (total daily dose 2,500 mg/m²) X 2 wks followed by 1 wk rest
 - Doses 12 h apart orally with water within 30 minutes of eating (breakfast or dinner).
- Efficacy equivalent to that of IV bolus 5-FU/LV with lower toxicity profile
- DLT: palmar-plantar erythrodysesthesia (PPE)

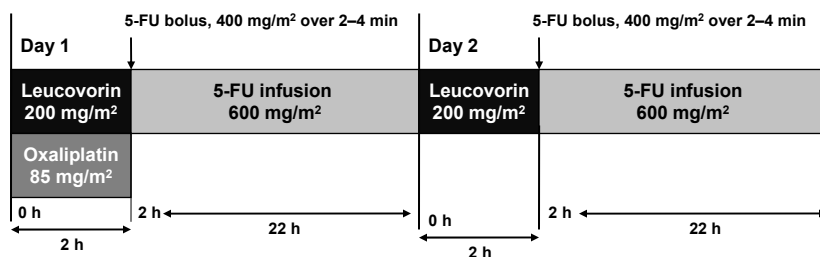
NCCN Guidelines-Colon Cancer v.2.2004; Hoff et al. 2001; Twelves et al., 2001.

14

Notes: _____

Oxaliplatin (Eloxatin™)

- Third-generation platinum analog
- First- and second-line treatment of metastatic CRC
- FDA-approved chemotherapy regimen
 - Oxaliplatin + infusional 5-FU/LV (FOLFOX4)
- DLT: neurotoxicity (reversible)



de Gramont et al. 2000; NCCN Guidelines-Colon Cancer v.2.2004.

15

Notes: _____

Cetuximab (Erbix™)

- Anti-EGFR MAb
- Second-line treatment for metastatic CRC
- FDA-approved chemotherapy regimen
 - in combination with irinotecan for patients refractory to single-agent irinotecan
 - as single agent for patients unable to tolerate irinotecan
- Adverse effects:
 - Hypersensitivity
 - Acneiform rash
 - Interstitial lung disease
 - Fever, sepsis, dehydration
 - Kidney failure
 - Pulmonary embolism
 - Diarrhea

Lenz et al. 2004; Cunningham et al. 2003; VanCutsem et al. 2001; NCCN Guidelines-Colon Cancer v.2.2004.

16

Notes: _____

Bevacizumab (Avastin™)

- Anti-VEGF MAb
- First-line treatment for metastatic CRC
- FDA approved chemotherapy regimen:
 - In combination with any 5-FU-based chemotherapy
- Adverse Effects
 - GI perforation
 - Minor (epistaxis) or major hemorrhage
 - Hypertension
 - Nephrotic syndrome
 - Proteinuria
 - Congestive heart failure (CHF)
 - Wound dehiscence

Fyfe et al. 2004; Hurwitz et al. 2004; NCCN Guidelines-Colon Cancer v.2.2004.

17

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First-Line Chemotherapy for Metastatic CRC

FDA Approved	Investigational
▪ 5-FU/LV	▪ Irinotecan + 5-FU/LV + cetuximab
▪ Irinotecan + bolus or infusional 5-FU/LV	▪ Oxaliplatin + 5-FU/LV + cetuximab
▪ Single-agent capecitabine	▪ Capecitabine + oxaliplatin (CapOx or XELOX)
▪ Oxaliplatin + infusional 5-FU/LV (FOLFOX4)	▪ Oxaliplatin + 5-FU/LV + bevacizumab
▪ Bevacizumab + 5-FU-based regimen	▪ Oxaliplatin + capecitabine + bevacizumab

18

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Irinotecan for First-Line Metastatic CRC

- **Pivotal Trials** (phase II) demonstrate efficacy of adding irinotecan to either bolus or infusional 5-FU/LV:
 - ↑ median overall survival by 2.2 to 3.3 months
 - ↑ incidence of severe (grade 3/4) diarrhea
- **Adverse Effects:** High 60-day mortality rate due to GI toxicity (ie, diarrhea)
- **Safety Precautions**
 - Close clinical monitoring
 - Aggressive and early therapeutic intervention
 - Withhold therapy if unresolved drug-related toxicities

Saltz et al. 2000; Douillard et al. 2000; Rothenberg et al. 2001.

19

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Capecitabine for First-Line Metastatic CRC

- **Pivotal trial** (phase III) comparing capecitabine with bolus 5-FU/LV revealed:
 - ↑ response rate (9.3% higher)
 - Comparable overall median survival times
12.5 months (capecitabine) vs 13.3 months (5-FU/LV)
- **Adverse effects**
 - ↓ rates of selected side effects (diarrhea, nausea, alopecia, neutropenia)
 - ↑ rates of hand-foot syndrome and hyperbilirubinemia

Hoff et al. 2001; Twelves et al. 2001.

20

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Oxaliplatin for First-Line Metastatic CRC N9741: Efficacy Results

Efficacy Results	IFL (n = 264)	FOLFOX4 (n = 267)	IROX (n = 264)
Overall response rate, %	31	45	35
Time to disease progression, mo	6.9	8.7	6.5
Overall survival, mo	15.0	19.5	17.4

- Overall response rate was significantly higher with FOLFOX4 vs IFL or IROX
- Both time to disease progression and median survival were significantly longer with FOLFOX4 vs IFL or IROX
- This improved efficacy, and favorable toxicity profile led to the approval of oxaliplatin + infusional 5-FU/LV for first-line treatment of CRC

Goldberg et al. 2004.

21

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Oxaliplatin for First-Line Metastatic CRC N9741: Safety Results

- Registration trial for first-line approval

Adverse Event	Toxicity Grade 3/4, %			
	IFL (n = 264)	FOLFOX4 (n = 267)	P Value	IROX (n = 264)
Nausea	16	6	.001	19
Vomiting	14	3	.001	22
Diarrhea	28	12	.001	24
Febrile neutropenia	15	4	.001	11
Dehydration	9	4	.03	6
Paresthesia	3	18	.001	7
Neutropenia	40	50	.04	36

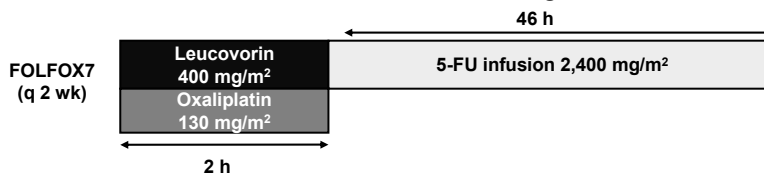
Goldberg et al. 2004.

22

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Improving Oxaliplatin-Based Therapy for First-Line Metastatic CRC

- DLT is cumulative sensory neuropathy
- Regimens are being developed to reduce this DLT and allow the reintroduction of oxaliplatin
- A Phase II trial compared FOLFOX4 with FOLFOX7
 - Comparable efficacy and toxicity
 - Reintroduction of FOLFOX was possible
 - FOLFOX7 is a more convenient regimen



deGramont et al. 2004. Abstract 3525.

23

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Oxaliplatin With Capecitabine for First-Line Metastatic CRC

- Randomized Phase II trial compared capecitabine and irinotecan (CapIri) with capecitabine and oxaliplatin (CapOx)
 - Comparable response rates: 37.5% vs 49.3%
 - Comparable survival: 15.8+ months
 - Toxicity profiles similar after irinotecan dose reduction
- Phase II trial (XELOX): evaluated oxaliplatin and capecitabine
 - Overall response rate 45%
 - Median survival 19.5 months
 - Severe (grade 3/4) toxicities
 - Sensory neuropathy 16%
 - Diarrhea 16%
 - Nausea/vomiting 13%
 - Neuropathic pain 6%
 - Neutropenia 7%
 - Thrombocytopenia 4%
 - Hand-foot syndrome (grade 3) 2%

Grothey et al. 2003. Abstract 1022; Van Cutsem et al. 2003. Abstract 1023; Cassidy et al. 2004.

24

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IFL + Bevacizumab (BV) vs IFL for First-Line Metastatic CRC

- Approval based on Phase III trial comparing IFL + BV 5 mg/kg every 2 weeks vs IFL + placebo (N = 815)
- IFL + BV safety results
 - Grade 3 hypertension, easily managed with oral medications
 - GI perforations (6 vs 0 events)
- Efficacy:

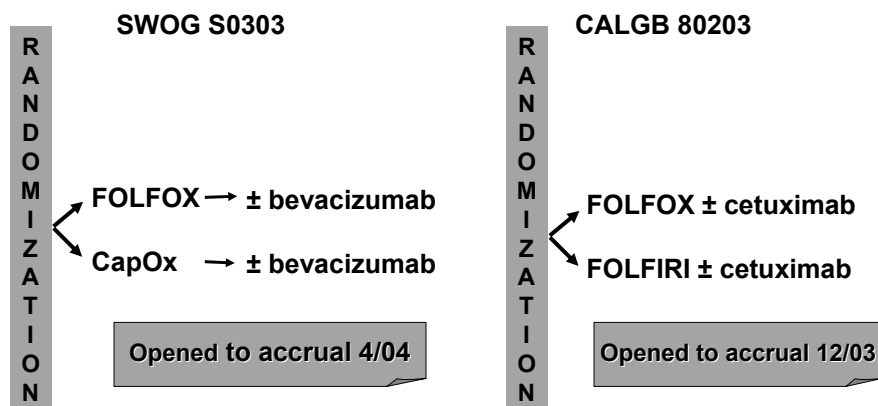
	IFL + BV (n = 403)	IFL (n = 412)	P
Objective response rate, %	45	35	.0029
Median survival, mo	20.3	15.6	.000003
Progression-free survival, mo	10.6	6.2	< .000001
Duration of response, mo	10.4	7.1	

Hurwitz, et al. 2004. Abstract 3646; Fyfe et al. 2004. Abstract 3617.

25

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Biologic Agents in First-Line CRC



26

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Second-Line Chemotherapy for Metastatic CRC

FDA Approved	Investigational
Single-agent irinotecan	Multiple regimens including but not limited to anti-angiogenics, monoclonal antibodies, and anti-idiotypic vaccines
Oxaliplatin + infusional 5-FU/LV	
Irinotecan + cetuximab	

27

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Cetuximab in Second-Line CRC EMR 62202-007 “BOND” Trial

- Patients with EGFR + tumors refractory to irinotecan + 5-FU/LV
- Patients in the cetuximab alone arm were allowed to cross over to the combination arm

	Irinotecan + Cetuximab (n = 218)	Cetuximab (n = 111)
Efficacy		
Overall response rate, %	22.9	10.8
Time to tumor progression, mo	4.1	1.5
Overall survival, mo	8.6	6.9
Most common grade 3/4 toxicities		
Diarrhea, %	21.2	1.7
Asthenia, %	13.7	10.4
Acne-like rash, %	9.4	5.2

Cunningham et al. 2004.

28

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Chronology of Adjuvant Therapy for Colon Cancer

- 1990** 5-FU/levamisole better than surgery alone
- 1994** 5-FU/LV better than surgery alone
- 1998** 5-FU/LV better than 5-FU/levamisole
Treatment duration ↓ to 6 months
Monthly treatments equivalent to weekly
- 2002** Semimonthly 5-FU/LV = monthly bolus 5-FU/LV
- 2003** 5-FU/LV + oxaliplatin = survival advantage in stage III
- 2004** Bolus 5-FU/LV + irinotecan = no survival advantage in stage III
Capecitabine equivalent to 5-FU/LV
- 20??** Tailored therapies based on molecular and pathologic characteristics

29

Notes: _____

TNM Staging of CRC



Stage I
T1 limited to mucosa/
submucosa
T2 invades muscle



Stage II
T3 through muscle, wall,
T4 into nearby tissue



Stage III
N1 (1-3 LN)
N2 (> 3 LN)
N3 (blood vessel)



Stage IV
distant metastasis

LN = lymph nodes.
From MUSChealth.com, with permission.

30

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Adjuvant Chemotherapy for Colon Cancer NCCN Treatment Guidelines

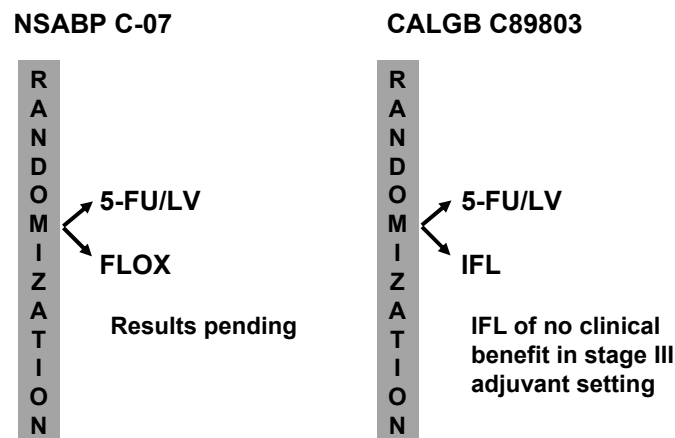
- **For patients with T3-4, N0, M0 disease**
 - 5-FU/leucovorin
 - Add radiation therapy if T4
 - Clinical trial
- **For patients with T1-4, N1-2, M0 disease**
 - 5-FU/leucovorin
 - Add radiation therapy if T4
 - Oxaliplatin + infusional 5-FU/LV (FOLFOX)
- **For patients with resectable liver or lung metastases**
 - 5-FU/LV
 - Irinotecan + infusional 5-FU/LV (FOLFIRI)
 - Oxaliplatin + infusional 5-FU/LV(FOLFOX)
 - Single-agent capecitabine
 - Hepatic artery infusion therapy ± 5-FU/LV or infusional 5-FU*

*For liver metastasis only.
NCCN Guidelines-Colon Cancer v.2.2004.

31

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Recently Closed Trials in Adjuvant Colon Cancer



Smith et al. 2003. Abstract 1181; Saltz, et al. 2004. Abstract 3500.

32

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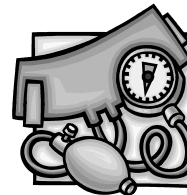
Oxaliplatin in Adjuvant Colon Cancer *MOSAIC Trial*

- **Efficacy**
 - 3-year DFS was significantly better for FOLFOX4: 77.8% vs 72.9% for 5-FU/LV ($P < .01$)
 - FOLFOX4 reduced risk of recurrence by 23%
 - No data yet on overall survival
- **Adverse Events**
 - Incidence of neutropenia, diarrhea and parasthesia significantly higher than 5-FU/LV
- **Conclusion:** Adding oxaliplatin (FOLFOX4) improves the adjuvant treatment of colon cancer

DFS = disease-free survival.
Andre et al. 2004.

33

Notes: _____



Patient Care Considerations



34

Notes: _____

Managing Patients Undergoing Chemotherapy for CRC

- Drug administration issues and techniques
- Pre- and posttreatment assessment parameters
- Side effect prevention and management
 - General guidelines
 - Specific guidelines
- Patient/family teaching points

35

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Drug Administration Considerations

Agent	Reconstitution & Compatibility	Administration
Irinotecan	<ul style="list-style-type: none"> ▪ Stable 24 h in D5W ▪ Particulates seen in NSS admixtures under refrigeration 	<ul style="list-style-type: none"> ▪ Use within 6 h of reconstitution
Capecitabine	<ul style="list-style-type: none"> ▪ Oral agent supplied in 150- and 500-mg tablets 	<ul style="list-style-type: none"> ▪ Instruct pt to take at end of meal with water ▪ Total daily dose not to exceed 2,500 mg/m²
Oxaliplatin	<ul style="list-style-type: none"> ▪ Incompatible with NaCl ▪ Reconstitute 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 ▪ Consider extending infusion time to 6 h
Bevacizumab	<ul style="list-style-type: none"> ▪ Incompatible with dextrose solutions ▪ Reconstitute with NSS 	<ul style="list-style-type: none"> ▪ Beginning at 90 min decrease infusion time in 30-min increments with each of three tolerated doses to 30-min infusions
Cetuximab	<ul style="list-style-type: none"> ▪ 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

36

Notes: _____

General Considerations: Drug Administration *Patient Teaching Points Continuous Infusion*

- **Assessment Parameters**
 - Special learning needs (eg, language barriers, illiteracy, risk for noncompliance, transportation)
 - Ability/motivation to self-manage central line, infusion pump and symptoms
 - Support systems (eg, in-home care partner, access to assistance)
- **Instructional Points**
 - Demonstrate pump set-up and maintenance
 - Review troubleshooting steps
 - Provide reinforcement materials and contact numbers
 - Review “red flags” (ie, when to call for help)

37

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Managing Patients Undergoing Chemotherapy for CRC *Side Effects*

Cutaneous

- Acneiform rash
- PPE
- Extravasation

Genitourinary

- Proteinuria/
nephrotic syndrome

Gastrointestinal

- Stomatitis
- Nausea/vomiting
- Diarrhea



Myelosuppression

- Infection
- Bleeding
- Fatigue

Pulmonary

- Interstitial pneumonitis

Neurotoxicity

- Dysesthesia
- PPE

Acute Drug Reactions

- Hypersensitivity
- Hypertension

38

Notes: _____

General Chemotherapy Side Effect Management *Neutropenia, Thrombocytopenia, Anemia*

Patient Education

- Discuss likelihood
- Teach hygiene measures
- Instruct to
 - Avoid visitors who may have infection
 - Avoid aspirin or aspirin-containing OTC medications
 - Contact physician or nurse for
 - Fever of 100.5°F or greater
 - Easy bruising or bleeding

Assessment and Action

- **Assess**
 - CBC with platelet count prior to each cycle
 - Spontaneous bleeding
- **Action**
 - Take neutropenic precautions and antibiotics
 - Transfuse blood products or inject erythropoietin as prescribed
 - Discuss with physician dose reduction or delay if indicated, based on grade of toxicity
 - Institute hematopoietic growth factors at physician's discretion

39

Notes: _____

General Chemotherapy Side Effect Management *Nausea, Vomiting, Stomatitis*

Patient Education

- Discuss likelihood
- Review medications
- Discuss bowel movements
- Instruct
 - Antiemetic self-management
 - When to call physician or nurse
 - Proper oral hygiene
 - Comfort measures

Assessment and Action

- **Assess**
 - Frequency and timing
 - Number of episodes
 - Character of emesis
 - Mucous membranes
 - Nutritional and hydration status
 - Ability to take oral liquids or solids
- **Action**
 - Administer antiemetic therapy
 - Give patient home medication schedule

40

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General Chemotherapy Side Effect Management *Diarrhea*

Patient Education

- Discuss likelihood
- Evaluate patient's definition of diarrhea
- Emphasize importance of hydration and diet
- Give instructions on taking antidiarrheal agents
- Instruct to contact physician or nurse if experiencing increase in stool count over baseline

Assessment and Action

- **Assess**
 - Assess change over baseline, number, frequency, color, consistency
 - Inquire about medications taken and fever
 - Closely monitor weight, skin turgor, and blood pressure
- **Action**
 - Administer antidiarrheal agents as ordered
 - Administer IV hydration if ordered
 - Recommend dietary modifications

41

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NCI Common Toxicity Criteria for Diarrhea

Severity Grade	1	2	3	4
Diarrhea without colostomy	Increase of < 4 stools/day over pretreatment	Increase of 4-6 stools/day, or nocturnal stools	Increase of ≥ 7 stools/day or incontinence; or need for parenteral support for dehydration	Physiologic consequences requiring intensive care; hemodynamic collapse
Diarrhea with colostomy	Mild increase in loose, watery colostomy output compared with pretreatment	Moderate increase in loose, watery colostomy output compared with pretreatment, but not interfering with normal activity	Severe increase in loose, watery colostomy output compared with pretreatment, interfering with normal activity	Physiologic consequences, requiring intensive care; hemodynamic collapse

National Cancer Institute Common Toxicity Criteria, Version 2.0 (NCI CTC).

42

Notes: _____

Special Considerations: Irinotecan *Diarrhea*

Early diarrhea

- Cholinergic mechanism
- Symptoms: rhinitis, salivation, miosis, lacrimation, abdominal cramping
- Treatment: atropine 0.25–1 mg IV or SC (for symptom control)

Late diarrhea

- Result of changes to the intestinal mucosa
- Reabsorption of water and electrolytes is altered
- Treatment: loperamide 4 mg followed by 2 mg q2h or after every unformed stool until patient is diarrhea-free for 12 hours

Camptosar [package insert]. Available at:
http://www.pfizer.com/download/uspi_camptosar.pdf.

43

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NCI Recommendations for Management of Chemotherapy-Induced Diarrhea in Patients Receiving IFL Regimen

CLINICAL PRESENTATION INTERVENTION

- | | |
|--|---|
| • Diarrhea (any grade) | • Oral loperamide (2 mg q2h) until diarrhea-free for 12 h |
| • Diarrhea persists on loperamide for > 24 h | • Oral fluoroquinolone x 7 days |
| • Diarrhea persists on loperamide for > 48 h | • Stop loperamide; hospitalize patient; administer IV fluids |
| • ANC < 500 cell/mm ³ (regardless of fever or diarrhea) | • Oral fluoroquinolone (continue until resolution of neutropenia) |

Rothenberg et al. 2001.

44

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Special Considerations: Capecitabine *Palmar-Plantar Erythrodysesthesia* (PPE)

Grade I



Grade II



Grade III



Slide courtesy of Cheryl Moore, RN, Cancer Center of Boston.

45

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Special Considerations: Capecitabine *PPE*

PREVENTION

- Baseline skin assessment and pre-treatment assessment
- Assess patient self-care ability and need for home support
- Teach patient self-management techniques

INTERVENTION

- Decrease dose and/or administration frequency (eg, 21-28-day cycle)
- Offer drug holiday
- Pyridoxine (Vitamin B₆)
- Topical medications (eg, DMSO, Bag Balm)
- Teach patient what to report, when, and to whom
- Teach patient how to minimize PPE development and morbidity

DMSO = dimethyl sulfoxide.

46

Notes: _____

Special Considerations: Capecitabine
PPE

Patient Education Points

PREVENTION

- Reduce friction and heat exposure
- Take short showers with tepid water
- Avoid tight gloves (eg, in dishwashing)
- Avoid pressure on soles and palms
- Avoid jogging, aerobics, jumping
- Avoid squeezing hand (eg, using trowel or knife to cut vegetables, meats)

INTERVENTION

- Use cool temperatures to relieve tenderness
- Gently apply emollients (eg, Bag Balm)
- Take vitamin B₆ as prescribed
- Take analgesics, (eg, acetaminophen)
- Call nurse or physician if palms or soles become red or tender
- Take drug holiday as needed with MD approval

47

Notes: _____

Special Considerations: Oxaliplatin
Physiology of Neurotoxicity

Peripheral Nerve	Function Affected
Sensory nerves	
Large fibers	Vibration and proprioception (position sense)
Small fibers	Touch, pain, temperature
Motor nerves (voluntary movement)	Reflexes, strength, muscle tone, coordination
Autonomic nerves (involuntary movement)	Blood pressure, bowel/bladder, motility, sexual function

48

Notes: _____

Special Considerations: Oxaliplatin *Neurotoxicity*

Acute	Cumulative
<ul style="list-style-type: none"> • Early: 1st 2 h–2 d • 90% of patients • Precipitated by cold exposure <ul style="list-style-type: none"> – Dysesthesia and paresthesia – Affects buccal and pharyngolaryngeal areas – Tightness in back of throat – Distal extremities – Muscle cramping – Jaw spasm • Resolves within 14 d; may occur with subsequent cycles 	<ul style="list-style-type: none"> • Later: > 750–800 mg/m² • 10%–15% of patients • Similar to cisplatin neurotoxicity • Hand/foot numbness, tingling <ul style="list-style-type: none"> – Interferes with ADL—using buttons and zippers – Difficulty walking due to impaired proprioception – Tandem gait and Romberg's positive • Increasing infusion time from 2-6 h may reduce symptoms experienced • Usually resolves in 4–6 mo; may be up to 12 mo

49

Notes: _____

Special Considerations: Oxaliplatin *Neurosensory Toxicity Scale*

Grade	Symptoms
0	None
1	Paresthesia or dysesthesia* that resolves after a short duration and does not interfere with function
2	Paresthesia or dysesthesia* that interferes with function but not ADLs
3	Paresthesia or dysesthesia* with pain or with functional impairment that also interferes with ADLs
4	Persistent paresthesia or dysesthesia* that is disabling or life threatening

*May be cold induced.

Note: Neuropathy grading scale above is a study-specific neurotoxicity scale, which is different from the National Cancer Institute Common Toxicity Criteria, Version 2.0 (NCI CTC).

50

Notes: _____

Special Considerations: Oxaliplatin *Acute Sensory Neuropathy*

Prevention

- Consider calcium gluconate 1 g and magnesium sulfate 1 g infusion 15 minutes pre- and postchemotherapy

Patient Education

- Discuss likelihood
- Explain possible symptoms
- Discuss management approaches with patient and family
- Caution to avoid cold exposure

Assessment and Action

- **Assess**
 - Check vital signs to distinguish pharyngolaryngeal dysesthesia from hypersensitivity reactions
- **Action**
 - Keep patient calm
 - Offer warm liquids
 - Manage with appropriate supportive care

51

Notes: _____

Special Considerations: Oxaliplatin *Acute Sensory Neuropathy Prevention*

- Acquired channelopathy with increased neuronal excitability
- Retrospective study examining the influence of treatment with calcium gluconate 1 g and magnesium sulfate 1 g infusions 15 minutes before and 15 minutes after oxaliplatin

Results

Toxicity, %	Treated Group (n = 96)	Control Group (n = 65)	P
Neuropathy,* any grade	20	45	0.003
Neurotoxicity, grade 3	7	26	0.001
Pharyngolaryngeal dysesthesia	0	9	10 ⁻⁸

* at the end of treatment.

Gamelin et al. 2004

52

Notes: _____

Special Considerations: Oxaliplatin *Preventing Cold Dysesthesia* *Patient Education*

- Avoid cold weather, when possible
- Wear mittens, socks, footwear, hat, scarf
- Avoid breathing deeply in cold air or when opening freezer or refrigerator
- Wear gloves when reaching into freezer or refrigerator
- Avoid cold beverages, ice chips, and frozen foods
- Enter preheated car
- Avoid excessive air conditioning
- Sip fluids through a straw



Wilkes 2002.

53

Notes: _____

Special Considerations: Oxaliplatin *Cumulative Sensory Neuropathy*

Patient Education

- Discuss likelihood (common: associated with oxaliplatin)
- Functional impairment
- Explain that symptoms
 - Usually regress between cycles but tend to last longer with subsequent doses
 - Usually resolve within 4 to 6 months
- Describe possible symptoms
- Discuss safety measures and interventions

Assessment and Action

- **Assess**
 - Baseline neuroassessment
 - Neuroassessment after each cycle
- **Action**
 - Teach measures to prevent injury and manage symptoms
 - Prolong infusion
 - Reduce or delay dose, or discontinue treatment, if indicated, based on grade of toxicity

Wilkes 2002.

54

Notes: _____

Special Considerations: Oxaliplatin Cumulative Sensory Neuropathy Interventions

PREVENTION

- Assess home water temperature; use tepid water
- Use protective gloves when washing dishes
- Use pot holders when cooking
- **Clothing:** Wear cotton socks, gloves in cold temperatures
- **Lighting:** Ensure well-lit rooms without glare
- **Environment:** Clear walkways; use nonskid showers and tub mats

INTERVENTION

Nonpharmacologic Interventions

- Exercise
- Hydrotherapy
- Massage, magnets, acupuncture
- Electrotherapy: transeletrical nerve stimulation
- Dietary supplements and diet
- Home remedies

Pharmacologic Interventions

- Topical analgesics
- Adjuvant analgesics
- Opioid analgesics

55

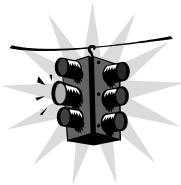
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Special Considerations: Oxaliplatin Cumulative Sensory Neuropathy Management

Drug Class	Indication	Drug (po)	Usual Starting Dose	Usual Effective Dose Range, mg	Schedule
Anticonvulsants	Neuropathic pain	Gabapentin	300 mg/d	330–3,600	q 8 h
		Carbamazepine	200 mg/d	600–1,200	q 6–8 h
Antidepressants	Neuropathic pain	Amitriptyline	10–25 mg/d	50–150	q d
		Clomipramine	10–25 mg/d	50–150	q d
Selective serotonin reuptake inhibitor	Role unclear	Venlafaxine	50 mg prior to	37.5 BID 20–40	× 1 wk q d
		Paroxetine	20 mg/d		
Topical		EMLA Cream Lidocaine patches Capsaicin Crème	25 g		prn prn prn
Miscellaneous		Glutamine	10 mg TID		3 d after treatment

56

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Special Considerations: Oxaliplatin *Cumulative Sensory Neuropathy Prophylaxis*

“Stop and Go” strategy (OPTIMOX study)

- Stop
 - After predefined cumulative oxaliplatin dose *or*
 - When sensory neurotoxicity of certain grade develops
- Go
 - When sensory neuropathy has regressed *or*
 - When oxaliplatin therapy required to stop tumor progression

Andre et al. 2003; de Gramont et al. 2004

57


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Special Considerations: Oxaliplatin *Hypersensitivity Reactions*

Grade 1 (mild), grade 2 (moderate)

- **Symptoms**
 - Hives
 - Rash
 - Fever
 - Itch
 - Anxiety
- **Actions**
 - Medicate: acetaminophen, diphenhydramine
 - Monitor vital signs q 15 min
 - Physician may resume IV

Grade 3/4 (severe)

- **Symptoms**
 -  **Patient complains of feeling cold: red flag!**
 - Anxiety, dizziness, shortness of breath, bronchospasm, nausea and vomiting
- **Actions**
 - Stop infusion
 - Bolus NSS for pressure
 - Medicate: diphenhydramine epinephrine, aminophylline
 - Cardiovascular support
 - Do not rechallenge!

Thomas et al. 2003.

58

Notes: _____

Special Considerations: Oxaliplatin *Extravasation*

- **PREVENTION**

- Use central line or port if available
- Monitor continuously if administering via peripheral line

- **INTERVENTION**

- **At first patient complaint of pain or other findings, STOP THE INFUSION**
- Follow institutional guidelines for extravasation management (eg, application of cold, administration of antidote agents or other drugs, plastic surgeon referral)
- Report and document findings



Brown et al. 2001.

59

Notes: _____

Special Considerations: Bevacizumab *Adverse Effects*

- GI Perforation
- Bleeding
- Hypertensive Crisis
- Nephrotic Syndrome
 - Proteinuria
- Thromboembolic Events
- Wound Healing
- Congestive Heart Failure

Giantonio et al. 2004; Hambleton et al. 2004;
Scappaticci et al. 2004; Novotny et al. 2004.

60

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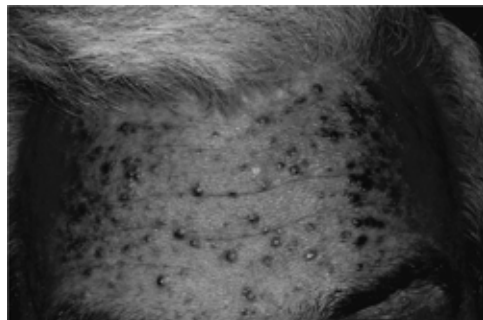
Special Considerations: Cetuximab *Adverse Effects*

- Infusion reactions
- Acneiform rash
- Interstitial lung disease

61

Notes: _____

Special Considerations: Cetuximab *Adverse Effects*



Slide courtesy of Howard Hochster, MD, New York University, New York City.

62

Notes: _____

CRC Treatment Summary

- Major improvements in the management of metastatic CRC provide more options for patients:
 - Infusional 5-FU is superior to IV bolus administration
 - Multiple regimens now available for first-and second line therapy (eg, irinotecan or oxaliplatin in combination with infusional or bolus 5-FU/LV or oral capecitabine)
 - Promising new biologic agents approved (eg, bevacizumab, cetuximab); integration with existing chemotherapeutic regimens could significantly improve patient outcomes
- Clinical trials confirm benefit and define adjuvant therapies as standard of care for selected patients
 - FOLFOX for patients with high-risk stage II and III colon cancer
 - Capecitabine is equivalent to 5-FU/LV

63

Notes: _____

CRC Patient Care Summary

- Comprehensive patient assessment and education are critically important to successful treatment outcomes
- Prevention and effective management of treatment-related side effects will increase patient tolerance and encourage continued therapy
- New and more complex treatment regimens will require increasingly knowledgeable and skilled practitioners

64

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On the Horizon

Screening & Prevention

- Fecal DNA screening
- Virtual colonoscopy with PET scanning to diagnose and stage
- Chemopreventive agents
 - COX-2 inhibitors

Adjuvant Therapy

- Clinical trials evaluating improved combinations
 - MOSAIC trial added oxaliplatin to standard 5-FU/LV after surgery (recurrence rate reduced) for stage III
 - NSABP C-08 added bevacizumab

• Molecular Profiling

• Molecularly Targeted Therapy

- Tyrosine kinase inhibitors
 - ZD1839 (gefitinib, Iressa)
 - OSI-774 (erlotinib, Tarceva)
 - PTK787/ZK 222584

- Antiangiogenesis agents

- Endostatin
- VEGF inhibitors
 - Vaccines
 - CEAvac

• Outcomes Prediction

- Insulin-like growth factors (IGF-1) and IGR binding protein-3 (IGFBP-3)

65

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End of Presentation

Please click on "close window" below to return to the main program

66

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