Fluorouracil (5-FU) Toxicities and Strategies for Management

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Objectives

- Identify and describe the hematological, dermatological, and gastrointestinal toxicities of 5-fluorouracil.
- Describe methods to manage patients with 5-fluorouracil-related toxicities
- Describe the use of uridine triacetate in patients with 5-fluorouracil overdose or in patients who exhibit severe adverse reactions.

5-Flourouracil (5-FU)

- History
  - 5-FU is a cytotoxic drug that has been used for more than 40 years to treat various cancers such as breast and colorectal
  - 1950's
    - Heidelberger and colleagues found that hepatoma cells in rats had a greater uptake of uracil compared to normal cells
    - Heidelberger attached a fluorine atom to the 5 position of uracil pyrimidine base
      - First example of targeted therapy

Heidelberger C, Chaudhuari NK, Danenberg P, et al. Fluorinated pyrimidines. A new class of tumor inhibitory compounds. *Nature* 1957; **179**: 663–6

5-Flourouracil (5-FU)

- History
  - 1970's
    - Administration of 5-FU by continuous infusion was found to greatly improve response rates in the treatment of anal and colon cancers
  - 1980's
    - Infusional administration of 5-FU could be used more widely with the availability of central venous access and pumps for outpatient administration

DeVita VT et al. A history of cancer chemotherapy. Cancer Research 2008;68:8643-53

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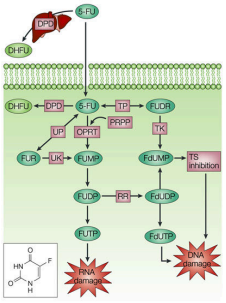
5-FU Mechanism of Action

- 5-FU is a synthetic analogue of pyrimidine
- In the body it is converted to several active metabolites
- The active metabolites can incorporate into DNA and RNA which disrupts the structures and protein synthesis
- The active metabolites prevents DNA synthesis by inhibiting thymidilate synthetase (TS)
- 5-FU has a stronger cytotoxic affect on proliferating cells than resting ones.



Nature Reviews | Cancer

Langley, DB et al. 5FU: Mechanisms of action and clinical strategies. Nature Reviews Cancer 2003;3:330-8

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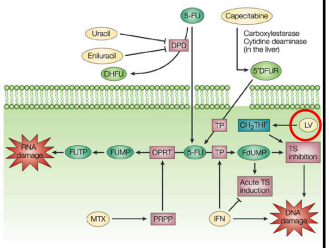
Leucovorin

- Administered prior to 5-FU
- Is folinic acid, an active metabolite of folic acid
- Stabalizes the bond between the 5-FU active metabolite and TS
- Causes a decrease in the production of thymidylate
- Enhances the activity of 5-FU



Nature Reviews | Cancer

Langley, DB et al. 5FU: Mechanisms of action and clinical strategies. Nature Reviews Cancer 2003;3:330-8

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Administration

- 5-Flourouracil
  - Is administered as multiple dosage forms
    - Intravenous
    - Orally as pro-dug, capecitabine (Xeloda)
    - Topical
  - Intravenous 5-FU given in many regimens and in a variety of schedules

Examples of 5-FU Regimens

Name	Chemotherapy Regimen
Roswell Park	Leucovorin 500 mg/m2 IV over 2 hours; followed by 5-Fluorouracil 500 mg/m2 IV bolus Administered on days 1, 8, 15, 22, 29, 35 Repeat every 8 weeks
Mayo Clinic	Leucovorin 20 mg/m2 IV bolus daily on days 1-5; followed by 5-Fluorouracil 425 mg/m2 IV bolus daily on days 1-5 Repeat every 4 weeks
mFOLFOX6	Oxaliplatin 85 mg/m2 IV over 2 hours day 1 Leucovorin 400 mg/m2 IV over 2 hours on day 1; followed by: 5-Fluorouracil 400 mg/m2 IV bolus on day 1, then 5-Fluorouracil 1200 mg/m2 /day CIV x 2 days (total 2400 mg/m2 CIV over 46 hours) Repeat every 14 days
CMF	Cyclophosphamide 100 mg/m2 PO days 1-14 Methotrexate 40 mg/m2 IV bolus days 1 and 8 Fluorouracil 600 mg/m2 IV bolus days 1 and 8 Repeat every 28 days

5-FU Toxicities

- Toxicities of 5-FU include:
  - Hematological
  - Dermatological
  - Gastrointestinal
  - Cardiovascular
  - Ophthalmic
  - Toxicities vary depending on the regimen and administration of 5-FU

HEMATOLOGICAL TOXICITIES
NEUTROPENIA

Hematological Toxicities

- Bone marrow suppression is primarily neutropenia as well as some thrombocytopenia, and anemia
- Neutropenia can be severe or fatal
- Neutrophil nadir occurs between days 9 – 14 after administration

Grem JL et al. Pharmacokinetics and pharmacodynamic effects of 5-fluorouracil given as a one-hour IV infusion Cancer Chemother Pharmacol 2001;47:117-25

Neutropenia

- Grading
  - Common Terminology Criteria for Adverse Events (CTCAE) by the National Cancer Institute (NCI)

NCI CTCAE	Adverse Effect
Grade 1	<LLN to 1500/microL
Grade 2	1000 to 1500/microL
Grade 3	500 to 1000/microL
Grade 4	<500/microL

Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0, June 2010, National Institutes of Health, National Cancer Institute.

Hematological Toxicities

- Hematological toxicities
  - Neutropenia occurs more often with bolus infusion compared to continuous infusion 5-FU
  - Meta-analysis
    - Included 6 randomized trials with 1219 patients
    - Patients received various regimens for advanced colorectal cancer
    - Neutropenia was the primary hematologic toxicity
    - Severe anemia and thrombocytopenia occurred in < 5% of patients

Meta-analysis group in cancer. Toxicity of 5-FU in patients with advanced colorectal cancer. JCO 1998;16:3537-41.

Hematological Toxicities

- Hematological toxicities
  - Meta-analysis results
    - 4% of patients who received a regimen with continuous infusion 5-FU had grade 3 or 4 neutropenia
    - 31% of patients who received a regimen with bolus 5-FU had grade 3 or 4 neutropenia ($p<0.0001$)
    - Patients with poor performance status were at a higher risk for hematologic toxicity

Meta-analysis group in cancer. Toxicity of 5-FU in patients with advanced colorectal cancer. JCO 1998;16:3537-41.

Hematological Toxicities

- Management
  - Monitor CBC/diff prior to each cycle or weekly, depending on the treatment schedule
  - Withhold treatment for grade 4 hematologic toxicity
    - May resume therapy after resolution or improvement to grade 1 at a reduced dose
    - For patients who are receiving regimens with bolus and continuous infusion and develop hematologic toxicity (e.g. FOLFOX or FOLFIRI)
      - Consider discontinuing the bolus and resume the continuous infusion at full dose

Adrucil (fluorouracil injection) [prescribing information]. North Wales, PA: Teva Pharmaceuticals Inc; October 2017

GASTROINTESTINAL TOXICITIES
ORAL MUCOSITIS

Oral Mucositis

- Inflammatory and/or ulcerative lesions that can occur in the pharyngeal, laryngeal and esophageal regions
  - Incidence in patients receiving 5-FU varies
    - Can occur in up to 22% receiving 5-FU alone with or without leucovorin
    - 5-FU combination regimens have a reported incidence of up to 74%
    - Incidence is higher with bolus versus continuous infusion 5-FU
    - Women are more likely to develop mucositis than men (63% vs 52%)

Sloan, JA et al. Sex differences in fluorouracil-induced stomatitis. JCO 2000;18(2):412-20.

Oral Mucositis

- Clinical Presentation
  - Can occur 4-7 days after 5-FU administration
  - Initially can present as erythema with or without burning
  - Develop to elevated white, painful patches
  - Can progress to epithelial sloughing
  - Ulcerations can heal within 14 days

Perry's The Chemotherapy Source Book. Management of ToxicityPhiladelphia :Wolters Kluwer Health/Lippincott Williams & Wilkins, 2012

Oral Mucositis

- Oral Mucositis
  - Pathophysiology is complex and described as a 5 stage process ultimately leading to painful ulceration and inflammation
  - Can affect daily function, nutrition, and Quality of Life
  - Can result in increased infection risk, dose delays, or dose disruptions

Perry's The Chemotherapy Source Book. Management of ToxicityPhiladelphia :Wolters Kluwer Health/Lippincott Williams & Wilkins, 2012

Oral Mucositis

- Grading

NCI CTCAE	Adverse Effect
Grade 1	Asymptomatic or mild symptoms; intervention not indicated
Grade 2	Moderate pain, not interfering with oral intake; modified diet indicated
Grade 3	Severe pain, interfering with oral intake
Grade 4	Life-threatening consequences; urgent intervention indicated

Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0, June 2010, National Institutes of Health, National Cancer Institute.

Oral Mucositis

- Prevention
  - Basic good oral hygiene
    - Use of salt and/or baking soda mouth rinses
    - Avoidance of alcohol-based mouth rinses
    - Use of a soft toothbrush, replaced on a regular basis
    - Prophylactic oral care including oral examination prior to chemotherapy initiation

Lalla RV et al. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. Cancer 2014;120:1453. Peterson DE et al. Management of oral and GI mucositis: ESMO Clinical Practice Guidelines. Ann Oncol 2011;22(Suppl 6):v261.

Oral Mucositis

- Prevention
  - Oral cryotherapy for bolus 5-FU
    - MASCC/ISOO recommend to swish ice chips for 30 minutes while and after administration of bolus 5-FU
    - Found to reduce the incidence of the development of mucositis
      - One study had 40 patients hold ice in their mouths from the beginning of bolus injection of 5-FU until 10 minutes after the infusion
      - Cryotherapy was at performed at random cycles
      - Mucositis developed in 6.7% of cycles with cryotherapy and 38.9% of cycles without cryotherapy

Lalla RV et al. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. Cancer 2014;120:1453. Baydar M, et a. Prevention of oral mucositis due to 5-FU treatment with oral cyrotherapy. J Nat Med Assoc 2005 9(8):1161-4

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Oral Mucositis

- Treatment
  - Oral care
    - Salt/baking soda mouth rinses
    - Gentle teeth cleaning
  - Dietary modifications
    - Avoid acidic, salty or dry foods
  - Analgesics
    - Topical
      - Use of mouthwashes that contain viscous lidocaine
        - » Many combinations available
        - » No one mouthwash is superior
        - » Effective but short duration of action

Lalla RV et al. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. Cancer 2014;120:1453. Peterson DE et al. Management of oral and GI mucositis: ESMO Clinical Practice Guidelines. Ann Oncol 2011;22(Suppl 6):v261.

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Oral Mucositis

- Treatment
  - Analgesics
    - Systemic
      - If pain is not adequately controlled with topical therapies, oral or parenteral opiates may be required
  - Therapy should be held for Grade 3 or 4 mucositis
  - Resume therapy at a reduced dose once mucositis has improved

Lalla RV et al. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. Cancer 2014;120:1453. Peterson DE et al. Management of oral and GI mucositis: ESMO Clinical Practice Guidelines. Ann Oncol 2011;22(Suppl 6):v261.

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GASTROINTESTINAL TOXICITIES
DIARRHEA

Diarrhea

- Pathophysiology
  - 5-FU damages intestinal crypt cells by inducing mitotic arrest
  - Leads to increased fluid secretions into the intestinal lumen and diarrhea

Perry's The Chemotherapy Source Book. Management of ToxicityPhiladelphia :Wolters Kluwer Health/Lippincott Williams & Wilkins, 2012

Diarrhea

- Grading

NCI CTCAE	Adverse Effect
Grade 1	Increase of less than four stools per day over baseline; mild increase in ostomy output compared with baseline
Grade 2	Increase of four to six stools per day over baseline; moderate increase in ostomy output compared with baseline
Grade 3	Increase of seven or more stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared with baseline; limiting self-care activities of daily living
Grade 4	Life-threatening consequences; urgent intervention indicated

Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0, June 2010, National Institutes of Health, National Cancer Institute.

Diarrhea

- Incidence
  - All grades of diarrhea reported in patients up to 72% and grade 3/4 reported up to 30% depending on the regimen
  - Higher incidence with bolus versus infusional 5-FU
  - Higher incidence when 5-FU is combined with leucovorin

Diarrhea Incidence By Regimen

Regimen	Grade 3/4 Diarrhea Incidence
5-FU (CIV)	6 – 13%
FOLFIRI (Bolus & CIV)	11 – 14%
Mayo Clinic (Bolus)	21 – 24%
IFL (Bolus)	25 – 28%
Roswell Park (Bolus)	13 – 30%

Diarrhea

- Management
  - Patient assessment
    - Obtain history
      - Diarrhea onset, duration, number of stools, composition
      - Medications profile to identify all diarrheogenic agents
      - Diet to identify diarrhea-induced foods
    - Assess for signs of dehydration, sepsis or bowel obstruction
    - Rule out infectious causes such as *C.diff*

Benson AB et al. Recommended guidelines for the treatment of cancer treatment-induced diarrhea. JCO 2004;22:2918-26

Diarrhea

- Diarrhea Management
  - Non-pharmacological management
    - Avoidance of foods that aggravate diarrhea
      - Dairy, caffeine, alcohol, high fiber/fat foods, spicy foods
    - Drink clear fluids
    - Eat frequent, small meals
      - Recommend BRAT diet
        - » Bananas, rice, applesauce and toast
    - Ensure patients stop laxatives and stool softeners

Benson AB et al. Recommended guidelines for the treatment of cancer treatment-induced diarrhea. JCO 2004;22:2918-26

Diarrhea

- Diarrhea Management
  - Pharmacological treatment – first line
    - Loperamide
      - Acts directly on smooth muscle of intestinal wall to decrease motility
      - Has little to no systemic absorption
      - Rapid onset of action
      - Reduces fecal incontinence and bowel movement frequency
      - Standard dose
        - » 4 mg after initial episode then 2 mg after each loose stool or every 4 hr
      - Aggressive dose
        - » 4 mg then 2 mg every 2 hours (or 4 mg every 4 hr)

Benson AB et al. Recommended guidelines for the treatment of cancer treatment-induced diarrhea. JCO 2004;22:2918-26

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Diarrhea

- Diarrhea Management
  - Pharmacological management – second line
    - Diphenoxylate/atropine (Lomotil)
      - 5 mg (of diphenoxylate) q 6 hours
    - Tincture of opium
      - 10 mg/mL solution – 6 mg every 4 – 6 hours
    - Octreotide
      - Initiate 100 to 150 mcg SC TID and titrate to response
  - For grade 3 or 4 diarrhea, withhold therapy until resolves to grade 1 or less and then initiate at a reduced dose

Benson AB et al. Recommended guidelines for the treatment of cancer treatment-induced diarrhea. JCO 2004;22:2918-26

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DERMATOLOGICAL TOXICITIES
HAND-FOOT SYNDROME

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Hand-Foot Syndrome (HFS)

- Also known as Palmar-Plantar Erythrodysesthesia (PPE)
- Clinical Presentation
  - May initially present with tingling sensation on palms or soles of the feet
  - Followed by symmetric, erythematous rash and edema
  - Can develop to scaling, blisters and desquamation
  - Can impair daily activities including grasping and walking
  - Onset can range from 3 days to 10 months

Perry's The Chemotherapy Source Book. Management of Toxicity. Philadelphia :Wolters Kluwer Health/Lippincott Williams & Wilkins, 2012

Hand-Foot Syndrome (HFS)

- Grading

NCI CTCAE	Adverse Effect
Grade 1	Minimal skin changes or dermatitis (eg, erythema, edema, or hyperkeratosis) without pain
Grade 2	Skin changes (eg, peeling, blisters, bleeding, edema, or hyperkeratosis) with pain, limiting instrumental ADL
Grade 3	Severe skin changes (eg, peeling, blisters, bleeding, edema, or hyperkeratosis) with pain, limiting self-care ADL
Grade 4	

Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0, June 2010, National Institutes of Health, National Cancer Institute.

Hand-Foot Syndrome (HFS)

- Pathophysiology
  - Not well understood, some proposed mechanisms:
    - Direct toxic effect on eccrine glands which may have higher drug concentrations in the palms and soles
    - Epidermal basal cells in the palms have a high proliferative rate making them more sensitive to this adverse effect

Perry's The Chemotherapy Source Book. Philadelphia :Wolters Kluwer Health/Lippincott Williams & Wilkins, 2012

Hand-Foot Syndrome (HFS)

- Incidence
  - Higher incidence with continuous infusion 5-FU compared to bolus injection
  - Meta-analysis
    - Included 6 randomized trials with 1219 patients who received various regimens for advanced colorectal cancer
    - 34% of patients who received a regimen with continuous infusion 5-FU had HFS
    - 13% of patients who received a regimen with bolus 5-FU had HFS
    - Older patients and women were at higher risk for HFS

Efficacy of IV continuous infusion of fluororuacil compared with bolus adminstration in advanced colorectal cancer JCO 1998; 16(1):301-8

Hand-Foot Syndrome (HFS)

- Prevention
  - Urea 10% cream
    - Apply to hands and feet three times daily
    - Has been shown to reduce incidence of HFS in patients taking capecitabine
  - Reduce friction
- Treatment
  - Symptoms usually improve over 5 - 7 days once 5-FU is discontinued
  - Therapy should be held for grade 2 or 3 HFS and initiate at a lower dose once symptoms resolve to grade 1

Perry's The Chemotherapy Source Book. Management of Toxicity. Philadelphia :Wolters Kluwer Health/Lippincott Williams & Wilkins, 2012

URIDINE TRIACETATE
FOR LIFE-THREATENING TOXICITIES

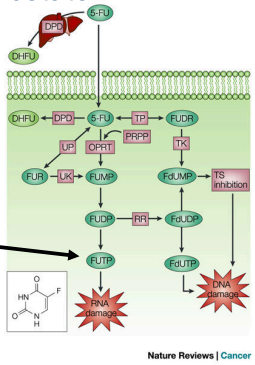
Uridine Triacetate
Vistogard®

- FDA approved September 2015
- Indicated for emergent treatment of adults and pediatric patients:
  - Following a 5-FU or capecitabine overdose
  - Who exhibit early-onset, severe or life-threatening toxicity (cardiac or CNS) and/or early-onset, unusually severe adverse reactions (GI or neutropenia) within 96 hours following the end of 5-FU or capecitabine administration
- Not recommended for treatment of non-emergent adverse effects

Vistogard (uridine triacetate) [prescribing information]. West Conshohocken, PA; BTG International Inc; December 2015

Uridine Triacetate

- Mechanism of Action
  - 5-FU is converted to FdUMP and 5UTP
  - 5UTP is incorporated into RNA resulting in cytotoxicity
  - Uridine triacetate is converted to uridine in the circulation
  - Uridine competes with FUTP incorporation into RNA



Nature Reviews | Cancer

Vistogard (uridine triacetate) [prescribing information]. West Conshohocken, PA; BTG International Inc;December 2015. Langley, DB,et al. 5FU: Mechanisms of action and clinical strategies. Nature Reviews Cancer 2003;3:330-8

Uridine Triacetate

- Adult Dosing
  - 1 packet (10 grams) orally every 6 hours for 20 doses
- Pediatric Dosing
  - 6.2 grams/m2 (not to exceed 10 grams/dose) orally every 6 hours for 20 doses
- Packet is mixed in 3 to 4 ounces of food such as applesauce, pudding or yogurt
- May be administered via nasogastric or gastrostomy tube

Vistogard (uridine triacetate) [prescribing information]. West Conshohocken, PA; BTG International Inc; December 2015.

Uridine Triacetate

- FDA approved based on combination of 2 single arm, open label trials
  - Included patients who had either experienced a 5-FU or capecitabine overdose or presented with severe toxicities
    - Overdose was defined as the administration of 5-FU at a dose or infusion rate greater than than the maximum tolerated dose for that patient's regimen
  - Primary outcome was survival at 30 days or until resumption of chemotherapy if prior to 30 days

Vistogard (uridine triacetate) [prescribing information]. West Conshohocken, PA; BTG International Inc; December 2015.

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Uridine Triacetate

- Combination of 2 single arm, open label trials results
  - N = 135 patients treated with uridine triacetate
    - 112 patients had 5FU overdose
      - 94% overdosed by infusion rate
      - 4% overdosed by 5FU dose
      - 3% overdosed by infusion rate and dose
    - 96% survived or resumed chemotherapy within 30 days
    - 4% died
  - Only 2 patients discontinued uridine triacetate due to intolerance (e.g. nausea/vomiting, diarrhea)
  - Compared to retrospective historical data of 25 patients overdosed by 5-FU
    - 84% of these patients died

Vistogard (uridine triacetate) [prescribing information]. West Conshohocken, PA; BTG International Inc; December 2015.

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Uridine Triacetate

- Limited Distribution
  - Ordering
    - Inpatient use
      - Order from the manufacturer, BTG
      - Distributed by Cardinal Health
    - Outpatient use
      - Order from the manufacturer
      - Distributed by specialty pharmacy Biologics Specialty Pharmacy or through Cardinal Health
      - Patients are enrolled into a case management program

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Summary

- 5-FU is a widely utilized cytotoxic agent, used in many different regimens
- Neutropenia, oral mucositis, and diarrhea are toxicities that are more likely to be caused by bolus injections of 5-FU
- HFS occurs at a higher incidence with a continuous infusion of 5-FU
- These toxicities can be managed with appropriate patient assessment and dose reductions as needed
- Uridine triacetate is available for patients who exhibit severe toxicities following a 5-FU overdose

Questions?