

5-FLUOROURACIL:

Class: Antineoplastic Agent, Antimetabolite (Pyrimidine Analog)

Indications: -Breast cancer - Colon cancer -Gastric cancer -Pancreatic cancer
-Anal carcinoma -Bladder cancer -Cervical cancer -Esophageal cancer
-Head and neck (squamous cell) -Hepatobiliary cancer

Available dosage form in the hospital: 1G VIAL|| 250MG VIAL||500MG/10ML AMP

Trade Names: Aduracil , 5-FU (DE); Curacil (ID); Fivoflu (IN, PH, VE); Florida (IN); Fluonco (PH); Flurablastin (DK, FI, NO, SE); Fluracetyl (BE, MY, NL, PH); Fluroblastin (VE); Fluroblastine (BE); Fu Ke (CL); La-Fu (CZ); Phauracil (PK); Ribofluor (DE); Sinofuan Implant (CL); Triosules (AR); Utoral (PH)

Dosage:

-Breast cancer (unlabeled dosing): I.V.:

- CEF regimen:* 500 mg/m² on days 1 and 8 every 28 days (in combination with cyclophosphamide and epirubicin) for 6 cycles (Levine, 1998)
- CMF regimen:* 600 mg/m² on days 1 and 8 every 28 days (in combination with cyclophosphamide and methotrexate) for 6 cycles (Goldhirsch, 1998; Levine, 1998)
- FAC regimen:* 500 mg/m² on days 1 and 8 every 21-28 days (in combination with cyclophosphamide and doxorubicin) for 6 cycles (Assikis, 2003)

-Colorectal cancer (unlabeled dosing): I.V.:

- FLOX regimen:* 500 mg/m² bolus on days 1, 8, 15, 22, 29, and 36 (1 hour after leucovorin) every 8 weeks (in combination with leucovorin and oxaliplatin) for 3 cycles (Kuebler, 2007)
- FOLFOX6 and mFOLFOX6 regimen:* 400 mg/m² bolus on day 1, followed by 1200 mg/m²/day continuous infusion for 2 days (over 46 hours) every 2 weeks (in combination with leucovorin and oxaliplatin) until disease progression or unacceptable toxicity (Cheeseman, 2002)
- FOLFIRI regimen:* 400 mg/m² bolus on day 1, followed by 1200 mg/m²/day continuous infusion for 2 days (over 46 hours) every 2 weeks (in combination with leucovorin and irinotecan) until disease progression or unacceptable toxicity; after 2 cycles, may increase continuous infusion fluorouracil dose to 1500 mg/m²/day (over 46 hours) (Andre, 1999)
- Roswell Park regimen:* 500 mg/m² (bolus) on days 1, 8, 15, 22, 29, and 36 (1 hour after leucovorin) every 8 weeks (in combination with leucovorin) for 4 cycles (Haller, 2005)

-Gastric cancer (unlabeled dosing): I.V.:

- CF regimen:* 750-1000 mg/m²/day continuous infusion days 1-4 and 29-32 of a 35-day treatment cycle (preoperative chemoradiation; in combination with cisplatin) (Tepper, 2008; NCCN Gastric Cancer Guidelines v2.2012)
- ECF regimen (resectable disease):* 200 mg/m²/day continuous infusion days 1-21 every 3 weeks (in combination with epirubicin and cisplatin) for 6 cycles (3 cycles preoperatively and 3 cycles postoperatively) (Cunningham, 2006)
- ECF or EOF regimen (advanced disease):* 200 mg/m²/day continuous infusion days 1-21 every 3 weeks (in combination with epirubicin and either cisplatin or oxaliplatin) for a planned duration of 24 weeks (Sumpter, 2005)

-*TCF or DCF regimen*: 750 mg/m²/day continuous infusion days 1-5 every 3 weeks or 1000 mg/m²/day continuous infusion days 1-5 every 4 weeks (in combination with docetaxel and cisplatin) until disease progression or unacceptable toxicity (Ajani, 2007; Van Cutsem, 2006; NCCN Gastric Cancer Guidelines v2.2012)

-*ToGA regimen (HER2-positive)*: 800 mg/m²/day continuous infusion days 1-5 every 3 weeks (in combination with cisplatin and trastuzumab) until disease progression or unacceptable toxicity (Bang, 2010)

-Pancreatic cancer (unlabeled dosing): I.V.:

-*Chemoradiation therapy*: 250 mg/m²/day continuous infusion for 3 weeks prior to and then throughout radiation therapy (Regine, 2008)

-*Fluorouracil-Leucovorin*: 425 mg/m²/day (bolus) days 1-5 every 28 days (in combination with leucovorin) for 6 cycles (Neoptolemos, 2010)

-*FOLFIRINOX regimen*: 400 mg/m² bolus on day 1, followed by 1200 mg/m²/day continuous infusion for 2 days (over 46 hours) every 14 days (in combination with leucovorin, irinotecan, and oxaliplatin) until disease progression or unacceptable toxicity for a recommended 12 cycles (Conroy, 2011)

-Anal carcinoma (unlabeled use): I.V.: 1000 mg/m²/day continuous infusion days 1-4 and days 29-32 (in combination with mitomycin and radiation therapy) (Ajani, 2008)

-Bladder cancer (unlabeled use): I.V.: 500 mg/m²/day continuous infusion days 1-5 and days 16-20 (in combination with mitomycin and radiation therapy) (James, 2012)

-Cervical cancer (unlabeled use): I.V.: 1000 mg/m²/day continuous infusion days 1-4 (in combination with cisplatin and radiation therapy) every 3 weeks for 3 cycles (Eifel, 2004)

-Esophageal cancer (unlabeled use): I.V.:

-*CF regimen*: 750-1000 mg/m²/day continuous infusion days 1-4 and 29-32 of a 35-day treatment cycle (preoperative chemoradiation; in combination with cisplatin) (Tepper, 2008; NCCN Esophageal and Esophagogastric Junction Cancers Guidelines v2.2012)

-*ECF regimen (resectable disease)*: 200 mg/m²/day continuous infusion days 1-21 every 3 weeks (in combination with epirubicin and cisplatin) for 6 cycles (3 cycles preoperatively and 3 cycles postoperatively) (Cunningham, 2006)

-*ECF or EOF regimen (advanced disease)*: 200 mg/m²/day continuous infusion days 1-21 every 3 weeks (in combination with epirubicin and either cisplatin or oxaliplatin) for a planned duration of 24 weeks (Sumpter, 2005)

-*TCF or DCF regimen*: 750 mg/m²/day continuous infusion days 1-5 every 3 weeks or 1000 mg/m²/day continuous infusion days 1-5 every 4 weeks (in combination with docetaxel and cisplatin) until disease progression or unacceptable toxicity (Ajani, 2007; Van Cutsem, 2006; NCCN Esophageal and Esophagogastric Junction Cancers Guidelines v2.2012)

-Head and neck cancer, squamous cell (unlabeled use): I.V.:

-*Platinum-Fluorouracil regimen*: 1000 mg/m²/day continuous infusion days 1-4 every 3 weeks (in combination with cisplatin) for at least 6 cycles (Gibson, 2005) or 600 mg/m²/day continuous infusion days 1-4, 22-25, and 43-46 (in combination with carboplatin and radiation) (Denis, 2004; Bourhis, 2012)

-*TPF regimen*: 1000 mg/m²/day continuous infusion days 1-4 every 3 weeks (in combination with docetaxel and cisplatin) for 3 cycles, and followed by chemoradiotherapy

(Posner, 2007) or 750 mg/m²/day continuous infusion days 1-5 every 3 weeks (in combination with docetaxel and cisplatin) for up to 4 cycles (Vermorken, 2007)

-*Platinum, 5-FU, and cetuximab regimen*: 1000 mg/m²/day continuous infusion days 1-4 every 3 weeks (in combination with either cisplatin or carboplatin and cetuximab) for a total of up to 6 cycles (Vermorken, 2008)

-**Hepatobiliary cancer (unlabeled use)**: I.V.: 600 mg/m² (bolus) on days 1, 8, and 15 every 4 weeks (in combination with gemcitabine and leucovorin) (Alberts, 2005).

Geriatric

Refer to adult dosing

Renal impairment:

No dosage adjustment provided in the manufacturer's labeling; however, extreme caution should be used in patients with renal impairment. The following adjustments have been recommended: $Cl_{cr} < 50$ mL/minute and continuous renal replacement therapy (CRRT): No dosage adjustment necessary (Aronoff, 2007).

Hemodialysis:

Administer standard dose following hemodialysis on dialysis days (Janus, 2010).

Administer 50% of standard dose following hemodialysis (Aronoff, 2007).

Hepatic impairment:

No dosage adjustment provided in the manufacturer's labeling; however, extreme caution should be used in patients with hepatic impairment. The following adjustments have been recommended: Floyd, 2006: Bilirubin > 5 mg/dL: Avoid use.

Koren, 1992: Hepatic impairment (degree not specified): Administer $< 50\%$ of dose, then increase if toxicity does not occur.

Dosing: Obesity

ASCO Guidelines for appropriate chemotherapy dosing in obese adults with cancer: Utilize patient's actual body weight (full weight) for calculation of body surface area- or weight-based dosing, particularly when the intent of therapy is curative; manage regimen-related toxicities in the same manner as for nonobese patients; if a dose reduction is utilized due to toxicity, consider resumption of full weight-based dosing with subsequent cycles, especially if cause of toxicity (eg, hepatic or renal impairment) is resolved (Griggs, 2012).

Dosing: Adjustment for Toxicity

According to the manufacturer, treatment should be discontinued for the following: Stomatitis or esophagopharyngitis, leukopenia (WBC $< 3500/mm^3$), rapidly falling white blood cell count, intractable vomiting, diarrhea, frequent bowel movements, watery stools, gastrointestinal ulcer or bleeding, thrombocytopenia (platelets $< 100,000/mm^3$), hemorrhage

Common side effect:

Cardiovascular: Angina, arrhythmia, heart failure, MI, myocardial ischemia, vasospasm, ventricular ectopy

Central nervous system: Acute cerebellar syndrome, confusion, disorientation, euphoria, headache, nystagmus, stroke

Dermatologic: Alopecia, dermatitis, dry skin, fissuring, nail changes (nail loss), palmar-plantar erythrodysesthesia syndrome, pruritic maculopapular rash, photosensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis, vein pigmentation

Gastrointestinal: Anorexia, bleeding, diarrhea, esophagopharyngitis, mesenteric ischemia (acute), nausea, sloughing, stomatitis, ulceration, vomiting

Hematologic: Agranulocytosis, anemia, leukopenia (nadir: days 9-14; recovery by day 30), pancytopenia, thrombocytopenia

Local: Thrombophlebitis

Ocular: Lacrimation, lacrimal duct stenosis, photophobia, visual changes

Respiratory: Epistaxis

Miscellaneous: Anaphylaxis, generalized allergic reactions

Pregnancy Risk Factor: D