TOSSICITA' GASTROINTESTINALE

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IMPORTANZA DELLA CONOSCENZA DEGLI EFFETTI COLLATERALI

- Effetti collaterali inaccettabili per il paziente possono portare all'interruzione della terapia

- La necessità di ulteriori trattamenti per controllare gli effetti collaterali può diminuire la compliance al trattamento oncologico

- Le alterazioni iatrogene alla fisiologia gastrointestinale ed epatica possono alterare la farmacocinetica e biodisponibilità dei farmaci stessi

Include:

- Diarrhoea
- ***Gastrointestinal bleeding, gastrointestinal perforation and wound-healing problems.***
- Hepatic toxicity.
- Elevation of pancreatic enzymes

Common terminology criteria for adverse events (NCI-CTCAE)

Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhoea	None	Increase <4 stools/d over pre-treatment	Increase 4–6 stools/day over pre-treatment	Increase >7 stools/day or incontinence; or need for parenteral support for dehydration	Physiologic consequences requiring intensive care; or haemodynamic collapse
AST and ALT	None	<2.5 ULN	>2.5–5 ULN	5–20 ULN	>20 ULN
Bilirubin	None	<1.5 ULN	>1.5–3 ULN	>3–10 ULN	>10 ULN
Lipase	None	>1–1.5 ULN	>1.5–2 ULN	>2–5 ULN	>5 ULN
Pancreatitis	None	–	–	abdominal pain with pancreatic enzyme elevation	Complicated by shock (acute circulatory failure)
Haemorrhage/bleeding without grade 3 or 4 thrombocytopenia	None	Mild without transfusion	–	Requiring transfusion	Catastrophic bleeding requiring major non-elective intervention

TOSSICITA' GASTROINTESTINALE

DIARREA | **SANGUINAMENTO E PERFORAZIONE GASTROINTESTINALE**

TOSSICITA' EPATICA | **TOSSICITA' PANCREATICA**

INCIDENZA :

Incidence of drug-induced diarrhea in phase I–III studies of molecular targeted cancer drugs.

Drug	Incidence of diarrhea (%)	Reference
Erlotinib	55 (6% grade 3–5) 68 (12% grade 3–4)[a]	Shepherd *et al.* (2005)[2] Herbst *et al.* (2005)[65]
Gefitinib	40–60 (8% grade 2) 58 (3% grade 3–4)[a]	Fukuoka *et al.* (2003)[3] Herbst *et al.* (2004)[66]
Lapatinib	40 (10% grade 3) 60 (13% grade 3–4)	Burrhis *et al.* (2005)[24] Geyer *et al.* (2006)[67]
HKI-272	84	Wong *et al.* (2006)[19]
Sorafenib	33 (24% grade 2–3)	Escudier *et al.* (2005)[10]
Sunitinib	20 (grade 2–3)	Motzer *et al.* (2006)[11]
Imatinib	45	Demetri *et al.* (2002)[14]
Flavopiridol	50	Liu *et al.* (2004)[15]
Bortezomib	32 (8% grade 3–4) 29 (9% grade 3–4)	Fanucchi *et al.* (2003)[34]

[a]Drug used in combination with cytotoxic chemotherapy.

Diarrhoea occurs in about 20–28% of patients undergoing anti-EGFR monoclonal antibody therapy but is rarely severe: 1–2% of grade 3–4.

The incidence and severity of diarrhoea is higher with EGFR-TKIs than with anti-EGFR monoclonal antibodies, which have an incidence of 50–60% including 5% grade 3–4; diarrhoea is a dose limiting toxicity for TKIs.

- **Diarrhoea related to drug toxicity** was also correlated in some studies with a clinical benefit and/or was a predictive factor of tumour response to TKI

•PATOGENESI :

• inibizione dell'EGF, responsabile dell'integrità mucosa, riparazione dell'epitelio, produzione mucina e sintesi PG. Se inibito lesioni ulcerative.

• diarrea associata ad un effetto localizzato degli agenti orali sul tratto intestinale poichè la severità e proporzionale alla dose piuttosto che ai livelli ematici

• EGF riduce la secrezione di cloro e assorbimento Na+, con diarrea secretoria quando i meccanismi di regolazione sono alterati dall'inibizione dell'EGF

• inibizione del VEGFR danno diretto della mucosa su base microvascolare

TOSSICITA' GASTROINTESTINALE

DIARRHEA | SANGUINAMENTO E PERFORAZIONE GASTROINTESTINALE

TOSSICITA' EPATICA | TOSSICITA' PANCREATICA

CLINICA :

- Compare entro 2 settimane dall'inizio del trattamento.
- Dipende dalla dose e non dalla concentrazione plasmatica del farmaco.

US NATIONAL CANCER INSTITUTE CRITERIA FOR GRADING THE SEVERITY OF DIARRHOEA (version 3.0)	
CTCAE GRADE	**CRITERI / IMPATTO**
1	Fino a 4 scariche/die rispetto al basale
2	Aumento da 4 a 6 scariche/die. Liquidi E.V. < 24 h nessuna modifica all'attività quotidiana
3	> 7 scariche/die incontinenza; liquidi E.V. > 24 h Ospedalizzare il paziente Modifica delle attività quotidiane
4	Conseguenze gravi (collasso cardiocircolatorio)
5	Morte

Porta C, et al.Clin Exp Med 2007:7:127

Evaluation and Diagnostic Testing Recommendations for Diarrhea (any Grade) (Table II)

History and Physical Examination

- Family history of autoimmune diseases
- Physical examination including assessment of patient for fever, dizziness, abdominal pain/cramping, and weakness
  - i.e., rule out risk for sepsis, bowel obstruction, dehydration
- History of onset and duration of diarrhea
- Travel history
- Description of number of stools and stool composition (e.g., watery, bloody, nocturnal)
- Medication profile to identify diarrheogenic agents
- Dietary profile to identify diarrheogenic foods

Laboratory Testing

- Stool work-up
  - Occult blood determination
  - Culture for enteric pathogens (Salmonella, *Escherichia coli*, *Campylobacter*, infectious colitis)
  - *Clostridium difficile*
- WBC, CRP, ESR, electrolytes, and BUN/Cr
- **Calprotectin**
- Consider colonoscopy in selected cases

BUN=blood urea nitrogen; CBC=complete blood count; Cr=creatinine

Coutre, Leukemia & Lymphoma, 2015

90% risoluzione spontanea
Loperamide ?
Diosmectite

Diet Modification Recommendations for Patients with Diarrhea

Diet Modifications

- Drink plenty of fluids, 8–12 glasses a day of oral-rehydration drinks (e.g., Gatorade®, Powerade®, Pedialyte®), other clear liquids, or clear broth to replace lost fluids and minerals
- Eat 5–6 small meals each day
- Eat low-fat, high-protein foods such as lean meat and eggs
- Try BRAT (bananas, rice, applesauce, toast) diet to help lessen the number of bowel movements
- Try crackers, gelatin, noodles, or oatmeal
- Eat cooked instead of raw vegetables, and remove skins from fruits before eating
- Avoid fried, fatty, greasy, or spicy foods
- Avoid milk (if it makes the diarrhea worse), milk products (including ice cream), and acidic drinks (e.g., tomato juice, citrus juices, fizzy soft drinks)
- Avoid foods that cause gas (e.g., broccoli and cabbage) and high-fiber foods
- Avoid caffeine, alcohol, and herbal supplements (some may cause diarrhea)

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MISURE PREVENTIVE E TRATTAMENTO:

5-10% riduzione dose

Assenza di risposta: Octreotide acetato 0,5mg sc/8ore, per 24-48 ore. Interrompere < 24 ore dalla risoluzione.

Gestione evento

Diarrea Grado 1 o 2

-Idratare il paziente e correggere eventuali squilibri elettrolitici

-Somministrare farmaci antidiarroici (per es. loperamide 2 mg). Se necessario, incrementarne la dose fino alla massima raccomandata approvata 4 mg , max 20 mg /die). Proseguire la somministrazione di loperamide per 12 ore dalla cessazione dei movimenti intestinali.

Diarrea Grado ≥3

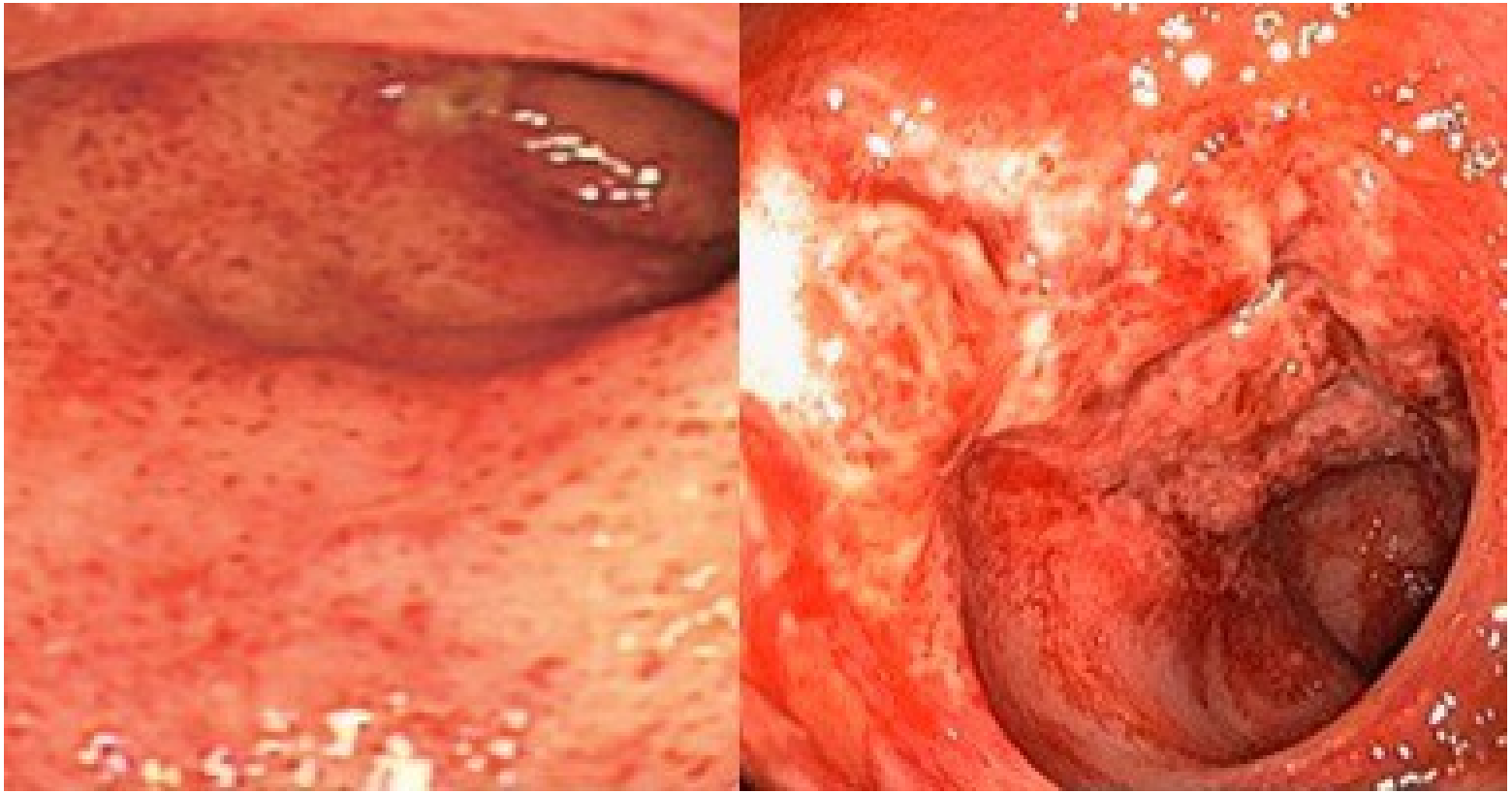
-Idratare il paziente per via endovenosa per ≥ 24 ore

-Ospedalizzare il paziente per monitorare le sue condizioni;

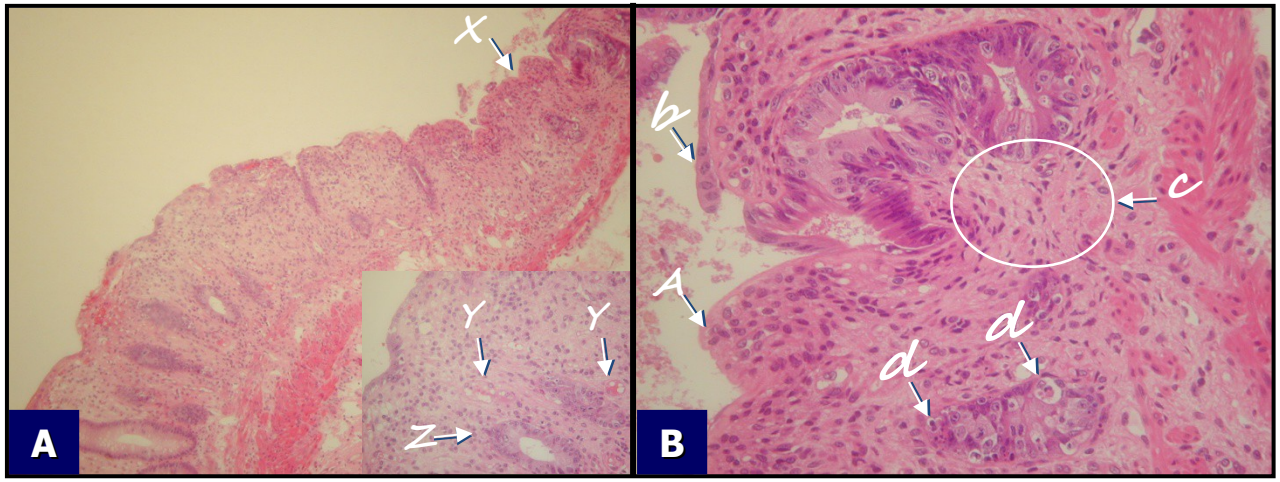
-Effettuare un esame microbiologico delle feci;

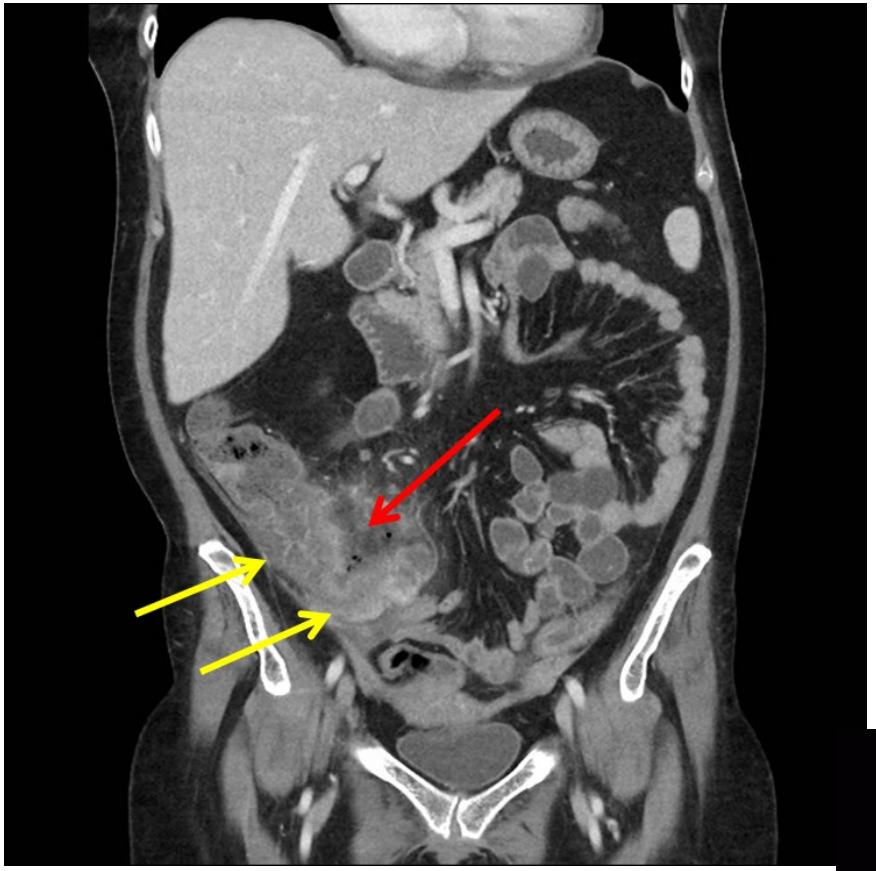
-Continuare loperamide;

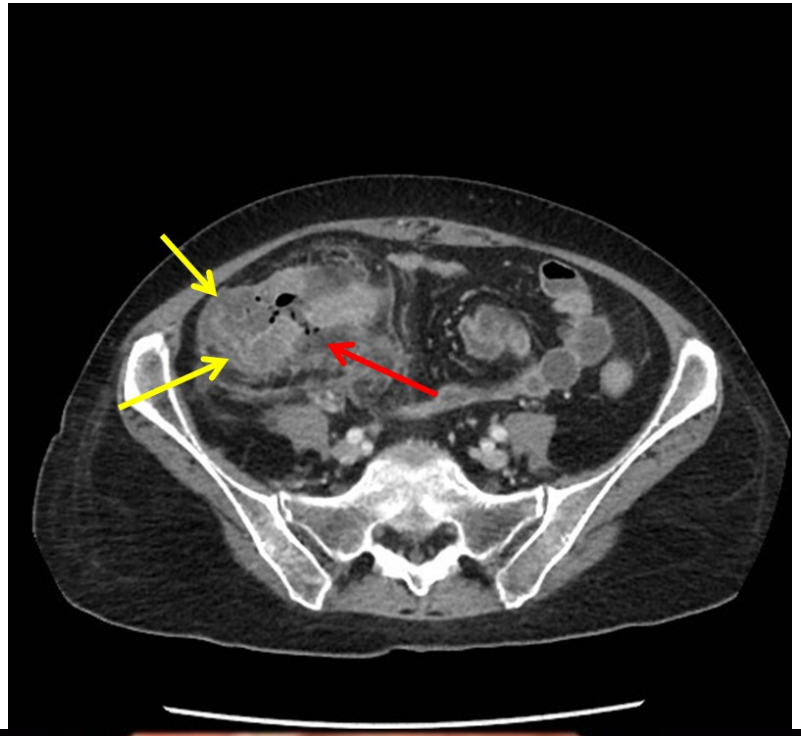
-Considerare l'uso profilattico di un antibiotico per il paziente neutropenico

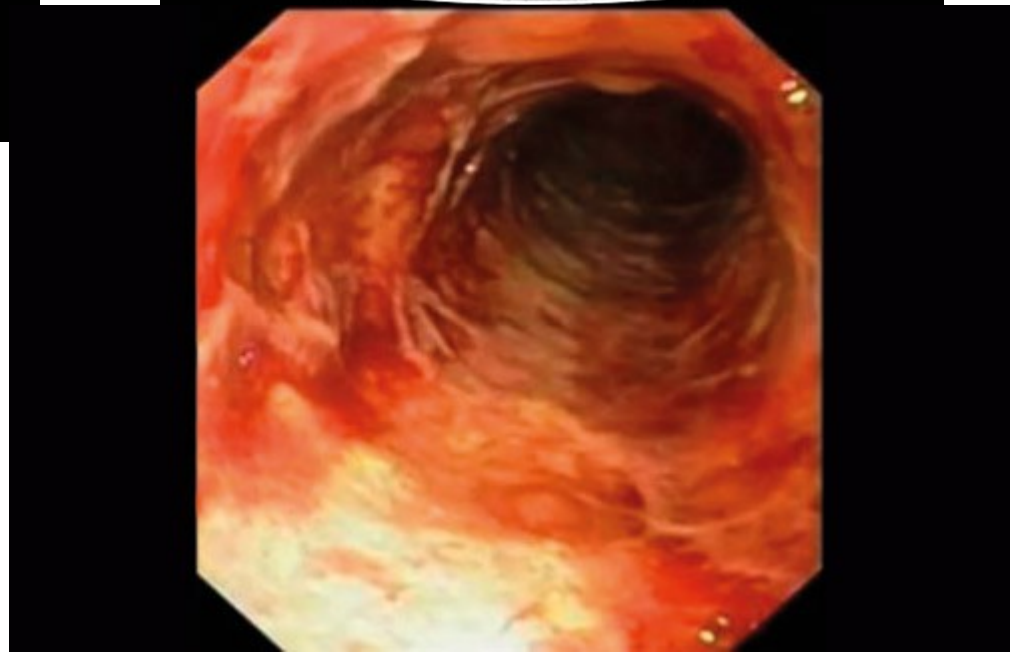


GVHD
(trapianto di midollo)

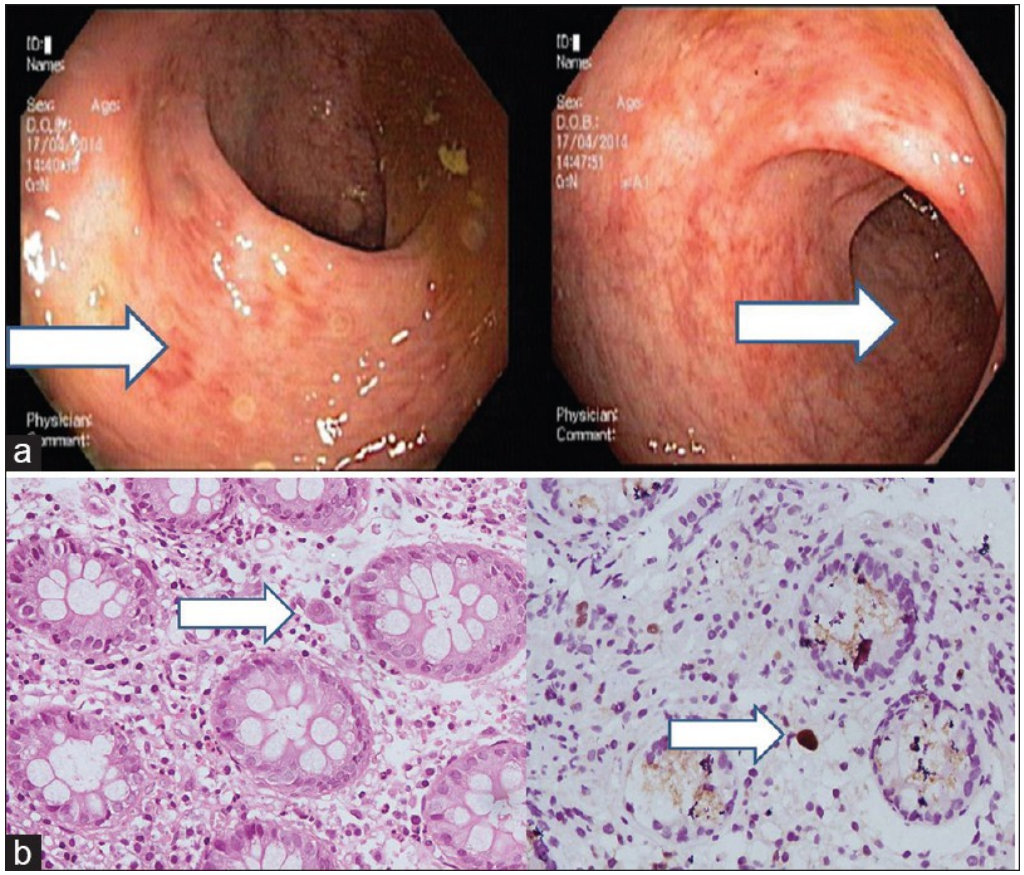




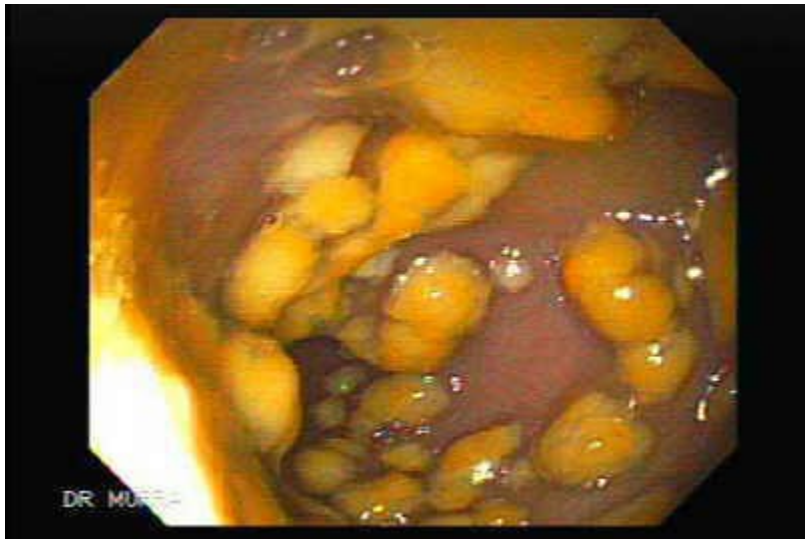




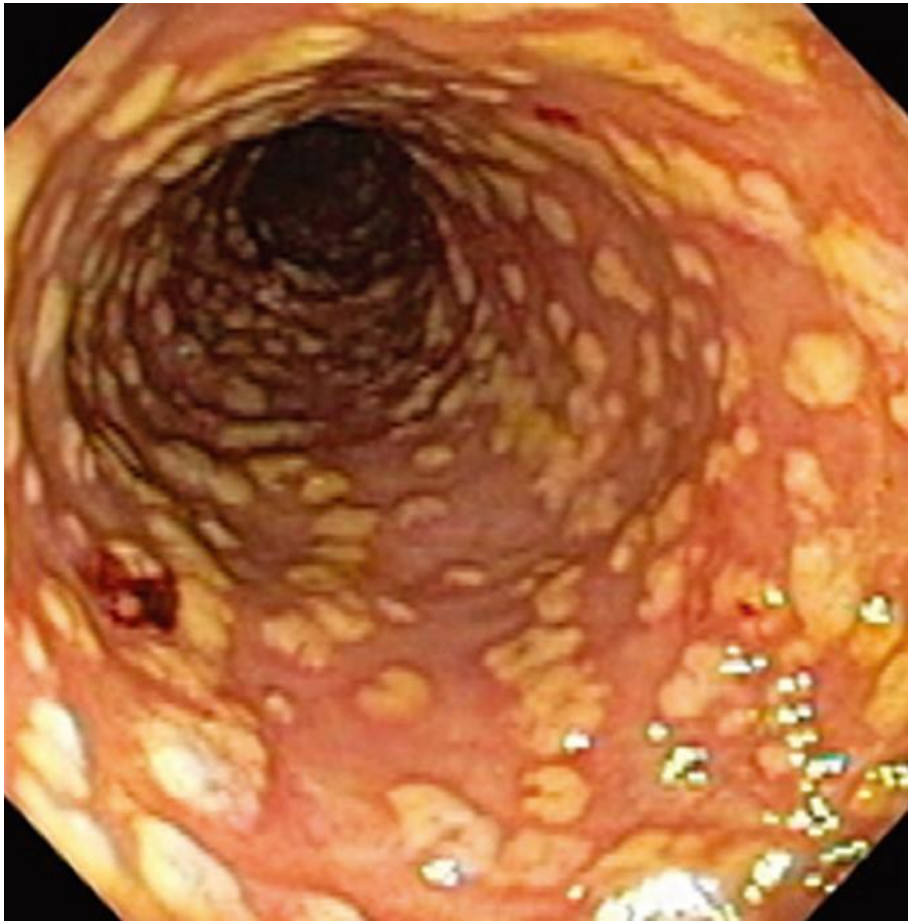
Neutropenic colitis
(chemioterapia)

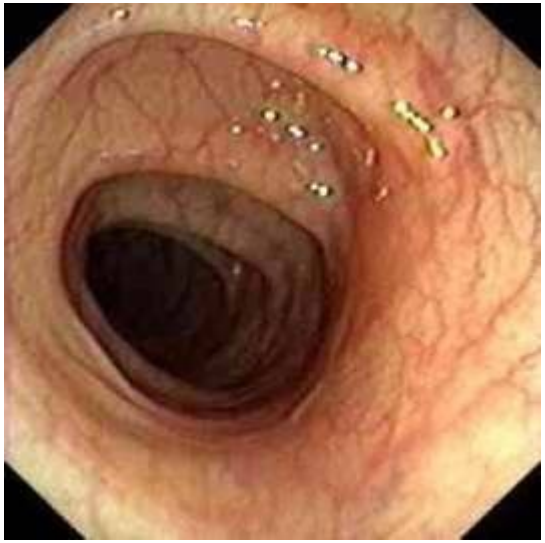


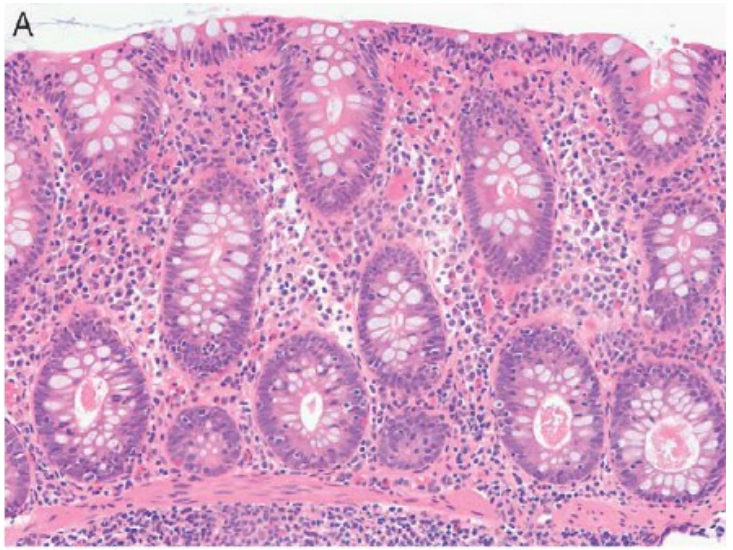
CMV Colitis

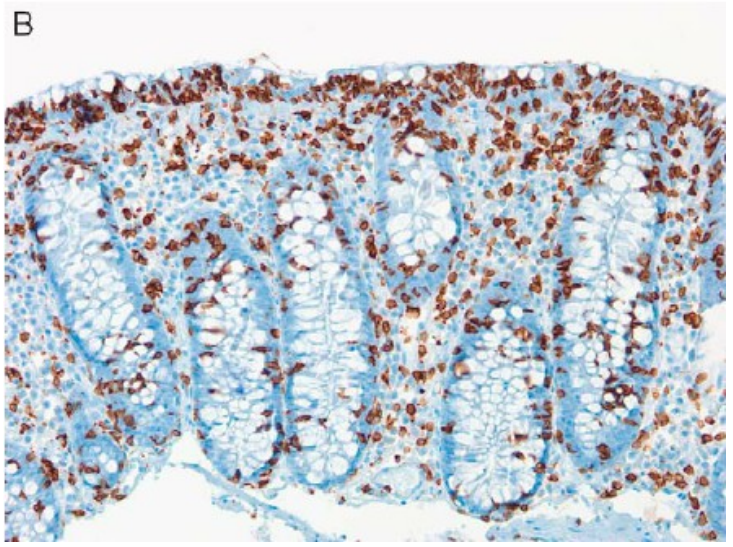


Pseudomembranous colitis
(Clostridium Difficile)

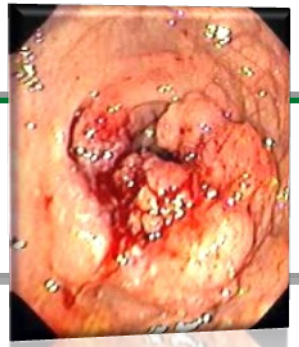








Lymphocitic colitis
(idelalisib)



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INCIDENZA :

Frequenza 5 volte maggiore nei pt trattati con Bevacizumab + CHT rispetto alla sola CHT

Deiescenza della sutura nel 2- 4.5% dei pts se intervento chirurgico durante terapia.

CAVEAT : Bevacizumab emivita circa 21 giorni

- Iniziare somministrazione non < 28 gg da chirurgia maggiore
- Interrompere somministrazione 28-42 gg prima intervento chirurgico.

Porta C, et al.Clin Exp Med 2007:7:127

Gastrointestinal perforations

- GI perforation (i.e., GI perforation, fistula formation, and/or intra-abdominal abscess), occurred in 2.4% of patients receiving bevacizumab alone or in combination with chemotherapy in 3 clinical trials for metastatic colorectal cancer.
- life-threatening condition,fatal in 30% of cases.
- Manifestations of these adverse GI effects included abdominal pain with constipation and vomiting (emesis).
- The mechanism unknown. may be due to the shrinkage of tumour masses embedded in the intestinal wall, or may occur at the site of previous surgery. Other risk, factors include abscesses, diverticula or an inflammatory process involving the GI tract

Gastrointestinal bleeding

- **Bevacizumab:** Severe or fatal hemorrhages, including hemoptysis, GI bleeding, hematemesis, CNS hemorrhage, epistaxis, and vaginal bleeding, occurred up to fivefold more frequently in patients receiving bevacizumab and chemotherapy than in those receiving chemotherapy alone.
- **sorafenib** : was not associated with digestive haemorrhage or variceal bleeding in cirrhotic patients treated for hepatocellular carcinoma.
- **Imatinib,** at a high dose of 800 mg/d was responsible for digestive haemorrhage-related death in four patients

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INCIDENZA :

Table 4 Incidence and clinical pattern of drug-induced hepatotoxicity.

Drug	Incidence of hepatotoxicity (%)	Clinical pattern of hepatotoxicity	Histological features	Physiopathology
Erlotinib or gefitinib	11 (2% grade 2–3)	Cytolytic hepatitis Isolated hyperbilirubinemia	Chronic hepatitis with active necrosis	Direct action (targeting of hepatocytes that overexpress EGFR) UGT1A1 (UD11) inhibition
Imatinib	10 (4% grade 3)	Cytolytic hepatitis	Hepatic necrosis; sometimes mild cholestasis; no granuloma or fatty infiltration	Hypersensitivity Metabolic reaction
Gemtuzumab	2	Portal hypertension	Sinusoidal obstruction syndrome	Exposure to unconjugated calicheamicin in the circulation
	16 (grade 3–4)	Cytolitic hepatitis		Non-specific uptake of the antibody–calicheamicin complex by Kuppfer cells
	25 (grade 3–4)	Hyperbilirubinemia		Receptor-mediated uptake of the antibody–calicheamicin complex through CD33 expression

Porta C, et al.Clin Exp Med 2007:7:127

AST/ALT

	Any grade (%)	Grade 3-5 (%)
Gefitinib	55-75	14-26
Erlotinib	6-37	2-4*
Afatinib	0-20	1
Crizotinib	38%	16%

Monitoraggio indici di funzionalità epatica ogni 2 settimane per i primi due mesi

Se aumenti ≤ 5 volte il LSN (al massimo grado 2) continuare terapia

Se aumenti > 5 volte il LSN, ma ≤ 20 volte il LSN alla prima occorrenza interrompere il trattamento fino a miglioramento e eventuale riduzione di dose.

Se nuova occorrenza e/o aumento > 20 volte il LSN interrompere definitivamente

TOSSICITA' GASTROINTESTINALE

Elevation of pancreatic enzymes

Elevation of lipase can be observed with the small oral multi-targeted therapies sorafenib, sunitinib and nilotinib.

Recommendations of tests according to treatment

	Liver tests			Lipase if abdominal pain
	W0	W1 to W4	Every M	
Imatinib	+	+	+	
Sunitinib	+		+	+
Lapatinib	+		+	
Sorafenib				+
Nilotinib				+

W: week; M: Month