ANTICANCER THERAPY-INDUCED MUCOSITIS AND DIARRHOEA:
Prevalence and Management Strategies

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DISCLOSURES

• Consultant / Advisory Boards / Speaker: Tesaro, Sanofi, Roche, MSD, TEVA, Norgine, Prostrakan, Leo pharma, Janssen, Hospira, Boehringer, AMGEN, Pierre Fabre Oncologie, Vifor Pharma

• Associations: ESMO, ASCO, MASCC, AFSOS, AESCO
MUCOSITIS

Thanks to Vincent Sibaud for the pictures and teaching
DEFINITION

A disorder characterized by inflammation of the oral mucosal

<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse Event</strong></td>
<td>1</td>
</tr>
<tr>
<td>Mucositis oral</td>
<td>Asymptomatic or mild symptoms; intervention not indicated</td>
</tr>
</tbody>
</table>
PREVALENCE AND PRESENTATION
**Chemotherapy Induced Mucositis**

*Non-keratinized mucosa* (buccal mucosa, floor of the mouth, ventral side of the tongue, soft palate...)

Diffuse, large, poorly circumscribed, erythematous or *ulcerated lesions* – covered with a *pseudomembrane* (epithelial debris, altered leucocytes, fibrin)

*Drugs: 5FU, cisplatin, cyclophosphamide, methotrexate, taxanes, cytarabine......combination*

Radiotherapy Induced Mucositis

**keratinized** (hard palate, dorsal aspect of the tongue, attached gingiva) and **non-keratinized** mucosa; **within** the irradiated field

Depends dose and radiotherapy protocol

Aphthous-like lesions – m TOR inhibitors (everolimus, temsirolimus)

mIAS (mTOR inhibitor associated stomatitis), 30-50% all grade, 5% high grade - Mostly occurs within the first cycle (<8 weeks) – median time to onset: 10 days

Class-effect (everolimus, temsirolimus, sirolimus) - the most frequent dose-limiting toxicity

Single or multiple, painful, well-circumscribed round superficial ulcers on the nonkeratinized mucosa

Aphthous-like lesions – everolimus and exemestane

Incidence of all-grade stomatitis: 67% (grade 2: 33%, grade 3: 8%)

Most common severe adverse event leading to dose reduction/interruption

Second most frequent cause of discontinuation

Targeted therapy-related mucositis / stomatitis

angiogenesis inhibitors (7-29%) - sorafenib (Nexavar®), sunitinib (Sutent®), axitinib (Alymta®), pazopanib (Votrient®), cabozantinib (Cometriq®); anti EGFR (5-60%) - cetuximab (Erbitux®), erlotinib (Tarceva®), panitumumab (Vectibix®), afatinib (Giotrif®), dacomitinib (+++)......

• Self-limiting lesions, aphtous-like lesions, dysgueusia, dysesthesia, nonspecific « stomatitis»

(diffuse mucosal hypersensitivity/dysesthesia, in some cases associated with erythema or painful inflammation of the oral mucosa +/- well-demarcated ulcerations)

Geographic tongue and angiogenesis inhibitors (sorafenib, sunitinib, pazopanib, axitinib, bevacizumab)

* VEGF (vascular endothelial growth factor) or VEGFR inhibition

Geographic tongue and angiogenesis inhibitors (sorafenib, sunitinib, pazopanib, axitinib, bevacizumab)

bevacizumab discontinuation W+8

BRAF inhibitors (vemurafenib, dabrafenib in monotherapy)

hyperkeratotic lesions (verrucous, papillomatous) – Squamous cell carcinomas

Paradoxical activation of the MAP kinase pathway in BRAF wild-type keratinocytes

Asymptomatic hyperkeratotic multifocal mucosal lesions on both keratinized and non keratinized mucosa

Associated with cutaneous hyperkeratotic lesions (SCC, papillomas, keratoacanthoma, keratosis pilaris-like lesions...)

Imatinib* and palatine pigmentary changes

* Gleevec ®: PDGF-receptor, c-Kit and BCR-ABL inhibition

“Blue-grey” asymptomatic hyperpigmentation of the hard palate

Similar to that of hyperpigmentation due to antimalarials

Immune checkpoint inhibitors (PD-1, PD-L1)

< 5% of treated patients. Lichenoid reactions, xerostomia

Oral mucosal toxicities – Key points

- **Chemotherapy**: more diffuse mucositis, poorly limited lesions, non-keratinized mucosa

- **Radiation therapy**: severe mucositis localized into the irradiated field, non-keratinized and/or keratinized mucosa

- **Targeted therapies**: self-limiting lesions; well-demarcated; non-keratinized mucosa; sometimes very characteristic.

- **Immune checkpoint inhibitors**: lichenoid reactions, xerostomia.

MANAGEMENT
Mucositis management –Be aggressive !!!

**Oral supportive care:** strict preventive and curative oral basic cares; soft toothbrush, non medicated oral rinses (normal saline), topical steroids, low level laser therapy, pain management, morphine mouthwash, dose modification......

**Aphthous-like lesions – SWISH trial**

- A US-based, non-randomised, phase 2, single-arm trial
- 85 postmenopausal women receiving everolimus and exemestane for hormone receptor-positive metastatic breast cancer
- Prophylactic use of a dexamethasone-based mouthwash, beginning on Day 1 of cycle 1 (10ml, swish for 2mn, and spit; 4 times daily for 8 weeks)

By 8 weeks, the incidence of grade ≥2 stomatitis was 2%, without any grade 3 - Indirect comparison with historical controls from BOLERO-2 study: 33% of grade ≥2 stomatitis (p<0.0001)

- All-grade mIAS incidence: 21% (SWISH) versus 61% (BOLERO-2)

Management of oral and gastrointestinal mucosal injury: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up

D. E. Peterson¹, C. B. Boers-Doets², R. J. Bensadoun³ & J. Herrstedt⁴, on behalf of the ESMO Guidelines Committee*

¹Department of Oral Health and Diagnostic Sciences, School of Dental Medicine, Program in Head and Neck Cancer and Oral Oncology Program, Norel Comprehensive Cancer Center, UConn Health, Farmington, USA; ²Department of Clinical Oncology, Leiden University Medical Center, Leiden and IMPAQTT, Wormer, The Netherlands; ³Centre de Haute Energie (CH.E), Nice, France; ⁴Department of Oncology, Odense University Hospital, University of Southern Denmark, Odense, Denmark
EVALUATION - Oral mucositis

WHO Scale :
• Grade 0 = no oral mucositis
• Grade 1 = erythema and soreness
• Grade 2 = ulcers, able to eat solids
• Grade 3 = ulcers, requires liquid diet (due to mucositis)
• Grade 4 = ulcers, alimentation not possible (due to mucositis)

NCI-CTCAE V4.03 :

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucositis oral</td>
<td>Asymptomatic or mild symptoms; intervention not indicated</td>
<td>Moderate pain; not interfering with oral intake; modified diet indicated</td>
<td>Severe pain; interfering with oral intake</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Death</td>
</tr>
</tbody>
</table>

Definition: A disorder characterized by inflammation of the oral mucosal.

National Cancer Institute CTCAE; http://evs.nci.nih.gov/ftp1/CTCAE/About.html
PREVENTIVE MEASURES

BASIC ORAL CARE

• Maintenance of optimal nutritional support throughout the entire period of cancer therapy

• Daily oral hygiene routine, including brushing teeth and the gums four times a day with a soft brush and using mouth rinses.

NO RECOMMENDATION

• normal saline, sodium bicarbonate, mixed medication, mouthwash, chlorhexidine

SPECIFIC / TARGETED THERAPY

• saline-containing mouthwashes (higher risk of infection)
### Table 1. Example of a Basic Oral Care Protocol (expert opinion)

Two key strategies for mitigation of oral mucosal injury before and during treatment are:
- Maintenance of optimal nutritional support throughout the entire period of cancer therapy.
- Developing a daily oral hygiene routine, including brushing teeth and the gums four times a day with a soft brush and using mouth rinses. This approach can contribute to the reduction and, ideally, prevention of oral tissue injury and associated pain, nutritional compromise, and related adverse outcomes.

The following information is presented as a portfolio of patient-based instructions for which health professional guidance is recommended.

#### General measures
- Inspect your oral mucosa daily.
- Have your dental team eliminate sources of trauma (e.g. ill-fitting prostheses; fractured teeth).
- Lubricate lips with (sterile) vaseline/white paraffin (petrolatum), lip balm, or lip cream. Be aware that vaseline/white paraffin (petrolatum) should not be used chronically on the lips, as this promotes mucosal cell dehydration and is occlusive leading to risk of secondary infection.
- Drink ample amount of fluids to keep the mouth moist.

#### Brushing teeth and gums
- Use a soft toothbrush or swab (as tolerated) after meals and before sleep. Brushing with a soft toothbrush reduces risk of bleeding. Each month you should utilise a new soft toothbrush.
- Clean the dentition and gingiva with a mild fluoride-containing, non-foaming toothpaste.
- Brush teeth twice a day (after meals and at bedtime) according to the Bass or modified Bass method. If using an electric toothbrush, utilise the technique cited in the product description instead.
- Rinse the brush thoroughly after use with water and store the toothbrush in a cup with the brush head facing upward.
- If you are used to do so, clean the area between the teeth once a day. Consult a dental hygienist/dentist about the most appropriate interdental cleaner (floss, toothpick, brushes). In case you are not used to use interdental cleaners on a regular base, do not start with it while on cancer therapy, since it can break the epithelial barrier, visible through gingival bleeding.

#### Rinse mouth
- Rinse mouth with an alcohol-free mouthwash upon awakening and at least four times a day after brushing, for ~1 min with 15 ml mouthwash; gargle; and then spitt out. During the first half hour after rinsing, avoid eating and drinking.

#### Denture care
- Remove dentures before performing oral care. Brush dentures with toothpaste and rinse with water; clean the gums.
- Defer wearing dental prostheses as much as possible until the lining tissues of your mouth are healed. If in the hospital, soak the denture for 10 min in an antimicrobial solution (e.g. chlorhexidine 0.2% if available) before inserting in your mouth.

#### Avoid painful stimuli
- Smoking
- Alcohol
- Certain foods such as tomatoes, citrus fruits, hot drinks and spicy, hot, raw, or crusty foods.
ORAL MUCOSITIS - GUIDELINES

RECOMMENDATIONS IN FAVOR OF AN INTERVENTION

PREVENTION

• Bolus 5-fluorouracil chemotherapy: 30 min of oral cryotherapy (II).
• high-dose chemotherapy and total body irradiation, followed by autologous stem cell transplantation, for a hematological malignancy:
  • Recombinant human keratinocyte growth factor-1 (KGF-1/palifermin) (60 µg/kg per day for 3 days before conditioning treatment and for 3 days after transplant) (II).
• Head and neck cancer with moderate dose radiation therapy (up to 50 Gy), without concomitant chemotherapy:
  • benzydamine mouthwash (I).
ORAL MUCOSITIS - GUIDELINES

RECOMMENDATIONS IN FAVOR OF AN INTERVENTION

TREATMENT

• HSCT conditioned with high-dose chemotherapy, with or without total body irradiation:
  • Low-level laser therapy (wavelength at 650 nm, power of 40 mW, and each square centimeter treated with the required time to a tissue energy dose of 2 J/cm²), (II).

• HSCT:
  • controlled analgesia with morphine (II).
LOW LEVEL LASER THERAPY

• Once a day, every day (min 3/week)
• t.(s)=D (J) x Surface (cm2) / Power (W)

Intra-oral laser application

Transcutaneous laser application

• 58 years old – locally advanced head and neck carcinoma. Treated with chemo/radiation therapy/ targeted therapy (cetuximab). Managed for grade 2 mucositis.

Which is the most likely offending agent? (choose the single best response):

1. Chemotherapy
2. Anti EGFR (cetuximab)
3. Radiation therapy
4. candida albicans superinfection
• 58 years old – locally advanced head and neck carcinoma. Treated with chemo/radiation therapy/ targeted therapy (cetuximab). Managed for grade 2 mucositis.

Which is the most likely offending agent? (choose the single best response):

1. Chemotherapy

2. Anti EGFR (cetuximab)

3. **Radiation therapy**

4. *candida albicans* superinfection
Diarrhoea in adult cancer patients: ESMO Clinical Practice Guidelines†

P. Bossi¹, A. Antonuzzo², N. I. Cherny³, O. Rosengarten³, S. Pernot⁴, F. Trippa⁵, U. Schuler⁶, A. Snegovoy⁷, K. Jordan⁸ & C. I. Ripamonti⁹, on behalf of the ESMO Guidelines Committee*
**DEFINITION**

A disorder characterized by frequent and watery bowel movements

<table>
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<th>Grade</th>
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<tbody>
<tr>
<td>Adverse Event</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Increase of &lt;4 stools per day over baseline; mild increase in ostomy output compared to baseline</td>
</tr>
</tbody>
</table>

CTCAE 4.02 - October 15, 2009 : Gastrointestinal disorders
GI INJURIES

Panel 1: Categories of chemotherapy-induced gastrointestinal tract injuries

- Panenteritis, enterocolitis, or mucositis
- Antimetabolites
  - Cytosine arabinoside, methotrexate, fluoropyrimidines (fluorouracil, capecitabine, tegafur-uracil), multtargeted folinic acid antagonists (pemetrexed, raltitrexed, gemcitabine)
- Plant alkaloids
  - Vinca alkaloids (vincristine, vinorelbine), epipodophyllotoxins (etoposide), taxanes (paclitaxel, docetaxel), topoisomerase I inhibitors (irinotecan)
- Cytotoxic antibiotics
  - Anthracyclines (doxorubicin, daunorubicin, idarubicin, aclacinomycin with prednisone)
- Alkylating agents
  - Cyclophosphamide, platinum (cisplatin, carboplatin, oxaliplatin, nedaplatin)

Abdominal pain
- Antimetabolites
  - Gemcitabine
- Autoimmune colitis
  - Monoclonal antibodies
  - Ipilimumab
- Ischaemic colitis
  - Monoclonal antibodies
  - Antibodies against VEGF (bevacizumab)
- Plant alkaloids
- Taxanes (docetaxel, paclitaxel)
- Gastrointestinal leucocytoclastic vasculitis
- Miscellaneous
  - Sirolimus

UNDER-REPORTING

PREVALENCE

• Chemotherapy induced = 5 – 47% (grade 3-4)
  • Warning dihydropyrimidine dehydrogenase (DPD) mutation (5FU)
• TKI induced = 28% (grade ≥ 3) but 50% (all grades)
• VEGF inhibitors = 66% (pazopanib, sunitinib, sorafenib)
• Check Point Inhibitors = 10-25% (Grade ≥3) but > 50% (all grades)

### Table 4. Frequency and severity of diarrhoea with frequently used combinations of ChT agents

<table>
<thead>
<tr>
<th>ChT</th>
<th>Incidence of grade 3 and 4 diarrhoea (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CapelRI</td>
<td>47</td>
</tr>
<tr>
<td>FOLFOX/IRI</td>
<td>20</td>
</tr>
<tr>
<td>miFL</td>
<td>19</td>
</tr>
<tr>
<td>Bolus fluorouracil with folinic acid</td>
<td>16</td>
</tr>
<tr>
<td>Irinotecan with fluorouracil and folinic acid</td>
<td>15</td>
</tr>
<tr>
<td>Docetaxel with capcitabine</td>
<td>14</td>
</tr>
<tr>
<td>FOLFIRI</td>
<td>14</td>
</tr>
<tr>
<td>FLOX</td>
<td>10</td>
</tr>
</tbody>
</table>

TKI induced diarrhoea

- Could be related to excess chloride secretion caused by dysregulated EGFR signalling.
- Gut motility altered
- Colonic crypt damage
- Changes to intestinal microflora
- Altered nutrient metabolism
- Altered transport in the colon.

<table>
<thead>
<tr>
<th>Warning signs</th>
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<tbody>
<tr>
<td>Massive dehydration</td>
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<tr>
<td>Fever</td>
</tr>
<tr>
<td>Peritonitis</td>
</tr>
<tr>
<td>Blood loss</td>
</tr>
<tr>
<td>Delirium</td>
</tr>
<tr>
<td>Renal impairment</td>
</tr>
<tr>
<td>Febrile neutropaenia, neutropaenic sepsis</td>
</tr>
<tr>
<td>Sepsis</td>
</tr>
<tr>
<td>Shock</td>
</tr>
<tr>
<td>Electrolyte disturbances</td>
</tr>
<tr>
<td>Abdominal cramps not relieved by loperamide</td>
</tr>
<tr>
<td>Inability to eat</td>
</tr>
<tr>
<td>Persistent nausea, vomiting and dehydration accompanied by urine reduced output</td>
</tr>
<tr>
<td>Previous admission for diarrhoea</td>
</tr>
</tbody>
</table>
Figure 2. Algorithm for therapeutic approach.

- Treatment setting: ambulatory and/or outpatient supportive care outpatient unit.
- In-hospital treatment.
- Consider *Clostridium difficile, Salmonella, Campylobacter* and other causes of infectious colitis.
- CBC, complete blood count; i.v., intravenous; s.c., subcutaneous; tid, three times a day.

Uncomplicated diarrhoea
- Oral hydration
- Dietary modification
- Loperamide (4 mg initially, 2 mg after every loose stool to maximum of 16 mg/day)
- Avoid skin irritation
- Notify treating physician

Complicated diarrhoea (e.g. fluid depletion, vomiting, fever)
- Administer: Loperamide (4 mg initially, 2 mg after every loose stool to maximum of 16 mg/day)
  - i.v. fluids and electrolytes
- Daily evaluation:
  - CBC
  - Electrolytes
  - Urinary output
- Consider octreotide: s.c. 100–150 µg tid or i.v. 25–50 µg tid
  - Escalation up to 500 µg tid
- Consider antibiotics:
  - Fluoroquinolones
  - Metronidazole
  - Broad spectrum
- Stool evaluation:
  - Blood and stool microbiology testing

Figure 1. Algorithm for diagnostic exams of ChT-related diarrhoea.

*In case of neutropenic fever, management according to ESMO guidelines on management of febrile neutropenia [11].

CBC, complete blood count; ChT, chemotherapy; CRP, C-reactive protein; CT, computed tomography; ESMO, European Society for Medical Oncology; PPI, proton pump inhibitor; STEC, Shiga toxin-producing Escherichia coli; US, ultrasound.
Role of diet

• Spices and beverages such as coffee and alcohol should be avoided and reduction of insoluble fibre intake may also be useful [V, C].

• In patients presenting with diarrhea during ChT, avoidance of milk and dairy products (apart from yogurt and firm cheeses) may be a reasonable strategy to reduce the intensity and duration of symptoms [V, C].
Management of neutropenic enterocolitis

- **Broad-spectrum antibiotics, G-CSFs, nasogastric decompression, i.v. fluids,** bowel rest and serial abdominal examinations [V, A]
- Antibiotics should cover enteric gram-negative organisms, gram-positive organisms and anaerobes [V, A]
  - 1\textsuperscript{st}: monotherapy with **piperacillin-tazobactam** or imipenem-cilastatin
  - 2\textsuperscript{d}: Combination therapy with **cefepime** or ceftazidime along with **metronidazole** [V, A].
  - In cases which do not respond to antibacterial agents, **amphotericin** should be considered [V, A]
- **Anticholinergic, antidiarrhoeal and opioid agents** should be **avoided** since they may aggravate ileus [V, A]
- **Indications for surgery:**
  - Persistent gastrointestinal bleeding after correction of thrombocytopenia and coagulopathy;
  - Evidence of free intraperitoneal perforation;
  - Abscess formation;
  - Clinical deterioration despite aggressive supportive measures
- Failure to remove the necrotic focus in these severely immunocompromised patients is often fatal [V, A].
- Primary anastomosis is not generally recommended in such severely immunocompromised patients because of the increased incidence of anastomotic leak [V, A]

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Treatments approaches

- **Oral Rehydration Therapy** is generally appropriate for **mild diarrhea** [I, A]. Oral Rehydration Solution are more appropriate in severe diarrhea [II, A]

- Rapid fluid resuscitation is not necessary in patients with mild to moderate hypovolaemia [I, A]. The rate of fluid administration must be greater than the rate of continued fluid losses, (urine plus gastrointestinal losses [I, A]

- If the patient has tachycardia and is **potentially septic**, an **initial fluid bolus** of 20 mL/kg should be given [I, A]

- Fluid replacement is continued at a rapid rate until the clinical signs of hypovolaemia improve [I, A]

- Fluid balance should aim for an **adequate central venous pressure** and urine output >0.5 mL/kg/h [I, A].

- Patients who develop oliguric **acute kidney injury** (<0.5 mL/kg/h) despite adequate volume resuscitation, as judged by central venous pressure, are at risk of developing pulmonary oedema and the advice of **intensive-care experts or nephrologists** must be urgently sought [V, B]
Treatment approaches

- **Loperamide** can be started at an initial dose of 4 mg followed by 2 mg every 2–4 h or after every unformed stool [II, B]. The maximum daily dose of loperamide is 16 mg.

- Other opioids, such as tincture of opium, morphine or codeine can be used [V, C].

- The usual starting dose for octreotide is 100–150 μg s.c./i.v. tid [IV, B]. The dose can be titrated up to 500 mg s.c./i.v. tid or 25–50 mg/h by continual i.v. infusion [V, B].

- **Uridine triacetate (Vistogard)** (dose of 10 g orally every 6 h for 20 doses) is indicated for the management of early-onset, severe or life-threatening toxicity including diarrhoea within 96 h following the end of 5-FU or capecitabine administration [II, B].

- **Oral budesonide** may be suggested for treatment of ChT-induced diarrhoea that was refractory to loperamide [IV, C]. Prophylactic use of budesonide is not recommended [II, B].

- In the case of bile salt malabsorption, **bile acid sequestrants** (e.g. cholestyramine, colestipol, colesevelam) may be an active adjuvant therapy [III, B].
Checkpoint inhibitors SAE induced

- Dysimmune enterocolitis
- Celiac disease
- Dysimmune hyperthyroidism
Treatment approaches

- **Immunotherapy-induced diarrhoea:**
  - **Grade 1:** symptomatic treatment with *oral rehydration and antidiarrheal treatment*, racecadotril or loperamide [III, A]
  - **Grade 2:** *budesonide* 9 mg once a day can be added to the symptomatic treatment, if no bloody diarrhea [V, C]; *oral corticosteroids* (0.5–1 mg/kg/day prednisone equivalent) are recommended in the case of diffuse ulceration or bleeding, or persistent symptoms after 3 days with symptomatic treatments 6 budesonide [III, A]
  - **Grade 3 and 4:** 1–2 mg/kg/day prednisone equivalent, with i.v. injections first [III, A]. Loperamide and opioids should be avoided. If symptoms persist for > 3–5 days, infliximab 5 mg/kg once every 2 weeks until resolution is recommended [III, A]. Vedolizumab could be an efficient and safe alternative to infliximab [V, C].

Checkpoint inhibitors SAE induced

Know the immune-toxicity spectrum
Identify dysimmunity risk factors
Inform patients and their healthcare providers

PREVENT

Resolution kinetic
Relapse, recurrence
Immunosuppression complications

MONITOR

Baseline check-up
On-treatment follow-up
Off-treatment follow-up

ANTICIPATE

Symptomatic treatment
Patient information
Discuss:
- Immunotherapy suspension?
- Refer to organ specialist?
- Corticosteroids?
- Other immunosuppressive drugs?

TREAT

Baseline values = reference values
Eliminate progression
Always consider dysimmune toxicities

DETECT