Onkoloji Hastasında Tedavi İlişkili Mukozit Yönetimi

Dr Cem MİRİLİ

Özel Adana Ortadoğu Hastanesi

Kanserde Destek Tedaviler ve Palyatif Bakım Sempozyumu
26 Mayıs 2024

Plan

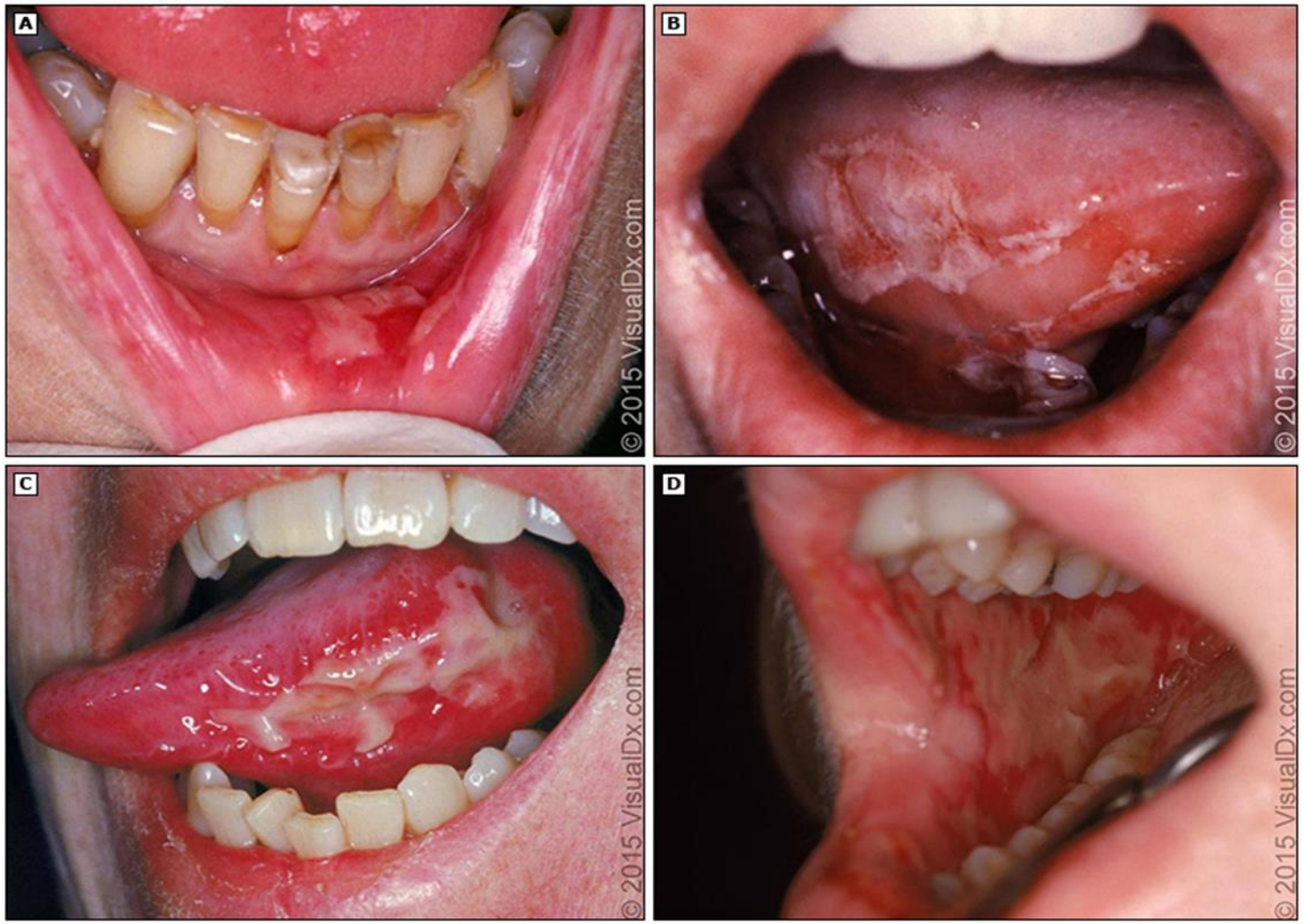
- Mukozit tanımı-prevalans
- Patofizyoloji
- Tanı ve evrelemesi
- Profilaktik tedavi önerileri
- Mukozit tedavi önerileri

Mukoz ıza çıkar?

- Kanser te ere tüm gasrointe ülseratif lezyonlar
- Konvansi
- Yüksek d

- Genelde

Chemotherapy-related mucositis



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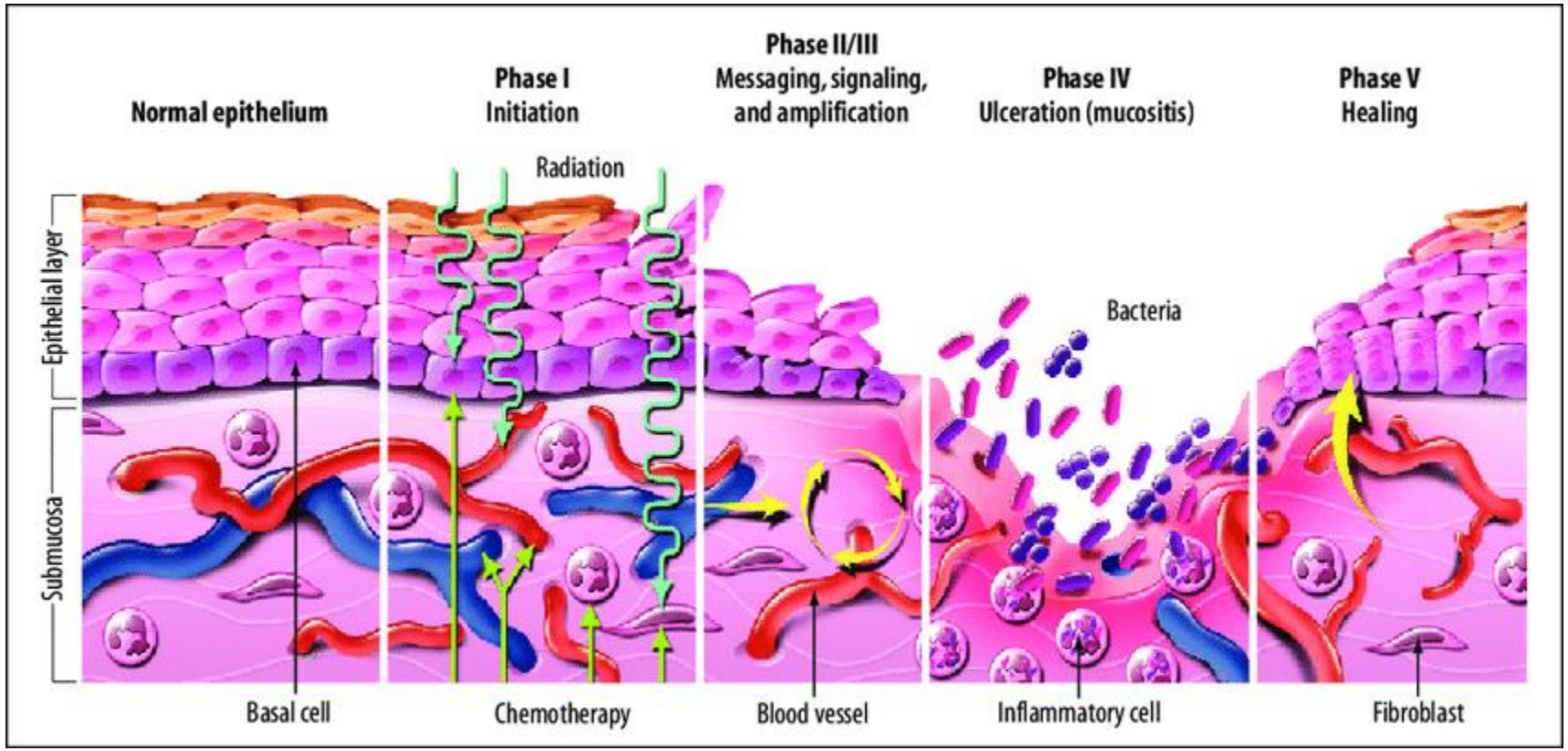
Patofizyoloji



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 :

	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Mucositis oral	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain; not interfering with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the oral mucosal.					

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

Mukozit derecesini etkileyen faktörler

- tedavi ajanına, hangi dozda hangi yöntemle hangi sıklıkla uygulandığına
- Hastanın ilacı tolerasyonuna
- İlacın metobolizmasını etkileyen genetik yolaklara
- İmmun sinyallere ve hücre iyileşme kapasitesine
- Sigara içmeye

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 (bolusss) , cisplatin****, cyclophosphamide, methotrexate,* ***taxanes,*** *cytarabine……****combination***

Vigarios E, Sibaud V. Mucosal reactions to anticancer treatments. *In: Atlas of Dermatologic Conditions in Oncology: Skin Reactions to Chemotherapy. Fabbrocini G, Lacouture ME, Tosti A (eds), 2018.*

Radiotherapy Induced Mucositis

keratinized (hard palate, dorsal aspect of the tongue, attached gingiva) and **non-keratinized** mucosa;
whithin the irradiated field
Depends dose and radiotherapy protocol

Moslemi D et al. Management of chemo/radiation-induced oral mucositis in patients with head and neck cancer: a review of the current literature. Radiother Oncol 2016; 120: 13-20.

Aphtho

mIAS (mT

grade - M

median t

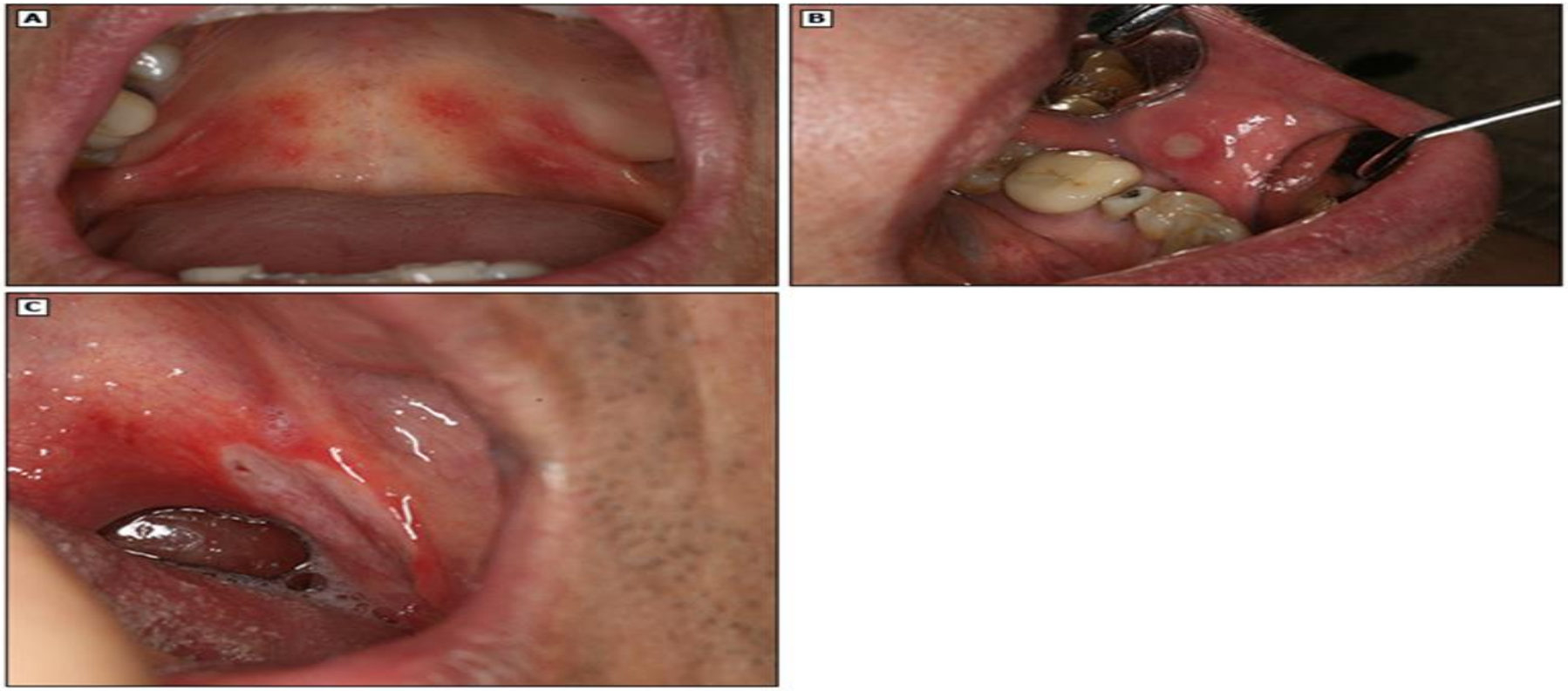
Class-effe

dose-limi

Single or

nonkerat

Stomatitis with aphthous-type ulcers in a patient treated with a mechanistic (previously called mammalian) target of rapamycin (mTOR) inhibitor



(A) Multiple mIAS of the soft palate with mTOR inhibitor (everolimus).
(B) Typical mIAS with an erythematous halo onnonkeratinized mucosa (everolimus).
(C) A major aphthous-like ulceration with everolimus (mIAS).

mTOR: mechanistic (previously called mammalian) target of rapamycin; mIAS: mTOR inhibitor-associated stomatitis.

Rugo HS, et al. Meta-a

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

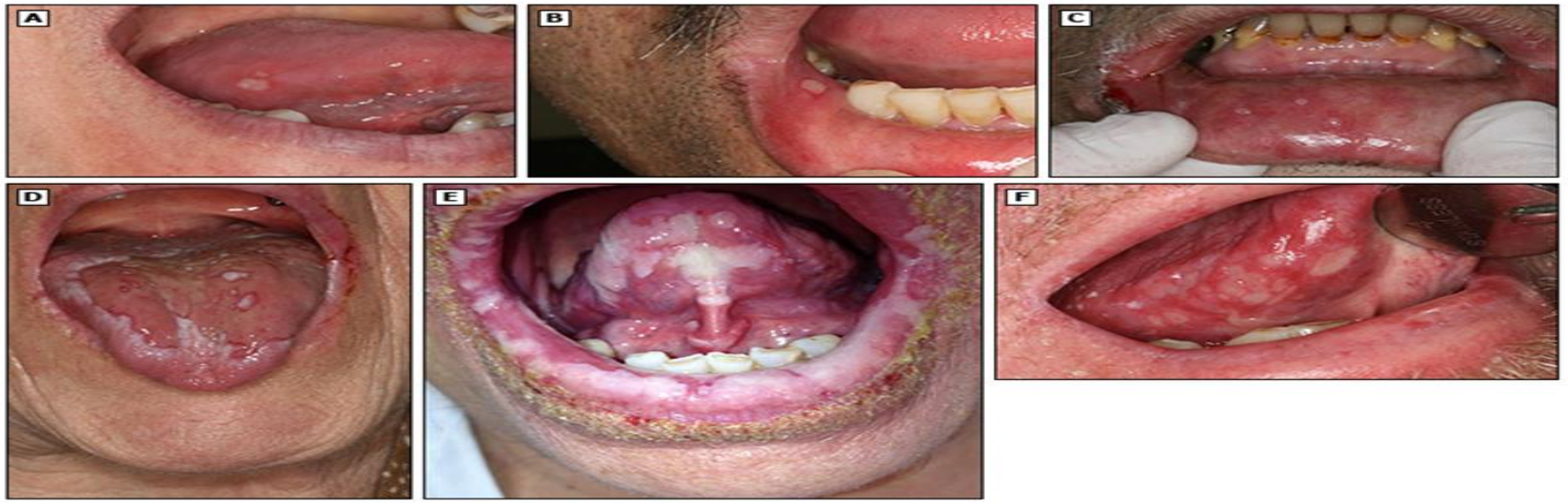
Second most frequent cause of

discontinuation

Rugo HS, et al. Meta-analysis of stomatitis in clinical studies of everolimus: incidence and relationship with efficacy. Ann Oncol 2016; 27: 519-25.

Targeted therapy-related mucositis / stomatitis

Oral mucositis in patients treated with chemotherapy agents that target the epidermal growth factor receptor (EGFR) or human EGFR2 (HER2)



A) Grade 1 mucositis with panitumumab (monoclonal antibody targeting EGFR).

B) Mucositis induced by afatinib (pan-HER tyrosine kinase inhibitor).

C) Mucositis involving the labial mucosa induced by erlotinib in monotherapy (antiEGFR).

D) Diffuse radio-induced mucositis affecting the keratinized mucosa (dorsum of the tongue).

E) High-grade ≥3 mucositis induced by the association of head and neck radiotherapy and cetuximab.

F) Mucositis induced by cetuximab and chemotherapy (carboplatin and 5FU) in combination.

EGFR: epidermal growth factor receptor; HER: human epidermal growth factor receptor; 5FU: 5-fluorouracil.

Vigari

Geographic tongue and angiogenesis inhibitors (sorafenib, sunitinib, pazopa

(Sorafenib): Erythematous erosions, with loss of filiform papillae, surrounded by white circinate rims.

* *VEGI*

Hubiche T, Valenza B, Chevreau C, Fricain JC, Del Giudice P, Sibaud V. Geographic tongue induced by angiogenesis inhibitors. Oncologist 2013; 18: e16-7.

BRAF inhibitors (vemurafenib, dabrafenib in monotherapy)

hyperkeratotic lesions (verrucous, papillomatous) – Squamous cell carcinomas

Fig 1. (a, b) Oral hyperkeratotic lesions of the jugal mucosa and the marginal gingiva. (c) Microinvasive squamous cell carcinoma of the lip.

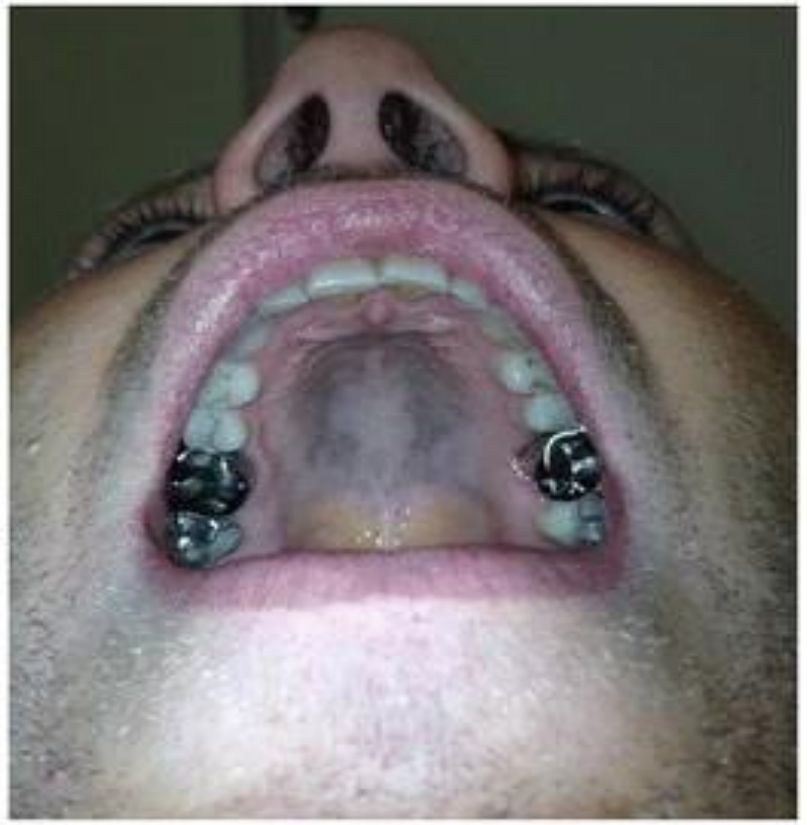
Vigarios E, Lamant L, delord JP, Sibaud V. Oral squamous cell carcinoma and hyperkeratotic lesions with BRAF inhibitors. Br J Dermatol 2015; 172: 1680-2.

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 hyperpimentation due to ***antimalarials***



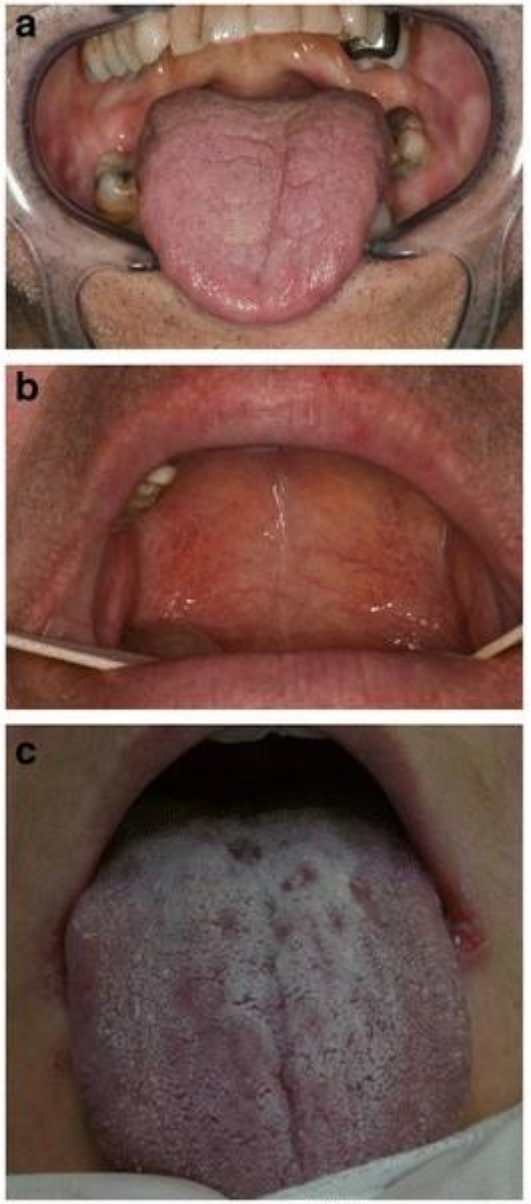
Vigarios E, Epstein J, Sibaud V. Oral mucosal changes and mucositis induced by targeted anticancer therapies. Support Care Cancer 2017; 25: 1713-39.

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

< 5% of treated patients. Lichenoid reactions, xerostomia

No grade 3 lesion

a Xerostomia with associated black hairy tongue induced by anti-PD-1 (nivolumab).



Sibaud V, Eid C, Belum VR, Combemale P, Lamant L, Motzer R, Vigarios E, Lacouture ME. Oral lichenoid reactions associated with anti-PD-1/PD-L1 therapies: clinicopathological findings. J Eur Acad Dermatol Venereol, 2017.

Oral mucosal toxicities – Key points

- **chemotherapy**: more diffuse mucositis, poorly limited lesions, non keratinized mucosa
- **Radiation therapy**: severe mucositis localized into the irradiated field, nonkeratinized and/or keratinized mucosa
- **Targeted therapies**: self-limiting lesions;well-demarcated; nonkeratinized mucosa; sometimes very caracteristic.
- **Immune checkpoint inhibitors**: lichenoid reactions, xerostomia.

Vigarios E, Epstein J, Sibaud V. Oral changes and mucositis induced by targeted anticancer therapies. Support Care Cancer. 2017 May;25(5):1713-1739.

Mukozit yönetimi

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 techniques 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 spit 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).

ORAL MUCOSITIS - GUIDELINES

SUGGESTION IN FAVOR OF AN INTERVENTION

PREVENTION

- All age groups and across all cancer treatment modalities :
  - Oral care protocols (III).
- High-dose melphalan, with or without total body irradiation, as conditioning for HSCT :
  - Oral cryotherapy (III).
- Radiotherapy, without concomitant chemotherapy, for head and neck cancer :
  - Low-level laser therapy (wavelength ~632.8 nm) (III).
- **Oral cancer patients receiving radiation therapy or chemoradiation :**
  - **Systemic zinc supplements administered orally (III).**

ORAL MUCOSITIS - GUIDELINES

RECOMMENDATIONS AGAINST AN INTERVENTION

PREVENTION not be used

- Radiation therapy for head and neck cancer :
  - PTA (polymyxin, tobramycin, amphotericin B) and BCoG (bacitracin, clotrimazole, gentamicin) antimicrobial lozenges and PTA paste (II).
- High-dose chemotherapy, with or without total body irradiation, for HSCT or in patients receiving radiation therapy or concomitant chemoradiation for head and neck cancer :
  - Iseganan antimicrobial mouthwash (II),
- Chemotherapy for cancer (I), or in patients receiving radiation therapy (I) or concomitant chemoradiation (II) for head and neck cancer :
  - Sucralfate mouthwash

ORAL MUCOSITIS - GUIDELINES

RECOMMENDATIONS AGAINST AN INTERVENTION

TREATMENT not be used

- **Chemotherapy for cancer (I), or radiation therapy (II) for head and neck cancer :**
  - **sucralfate mouthwash.**

Aphthous-like lesions – SWISH trial

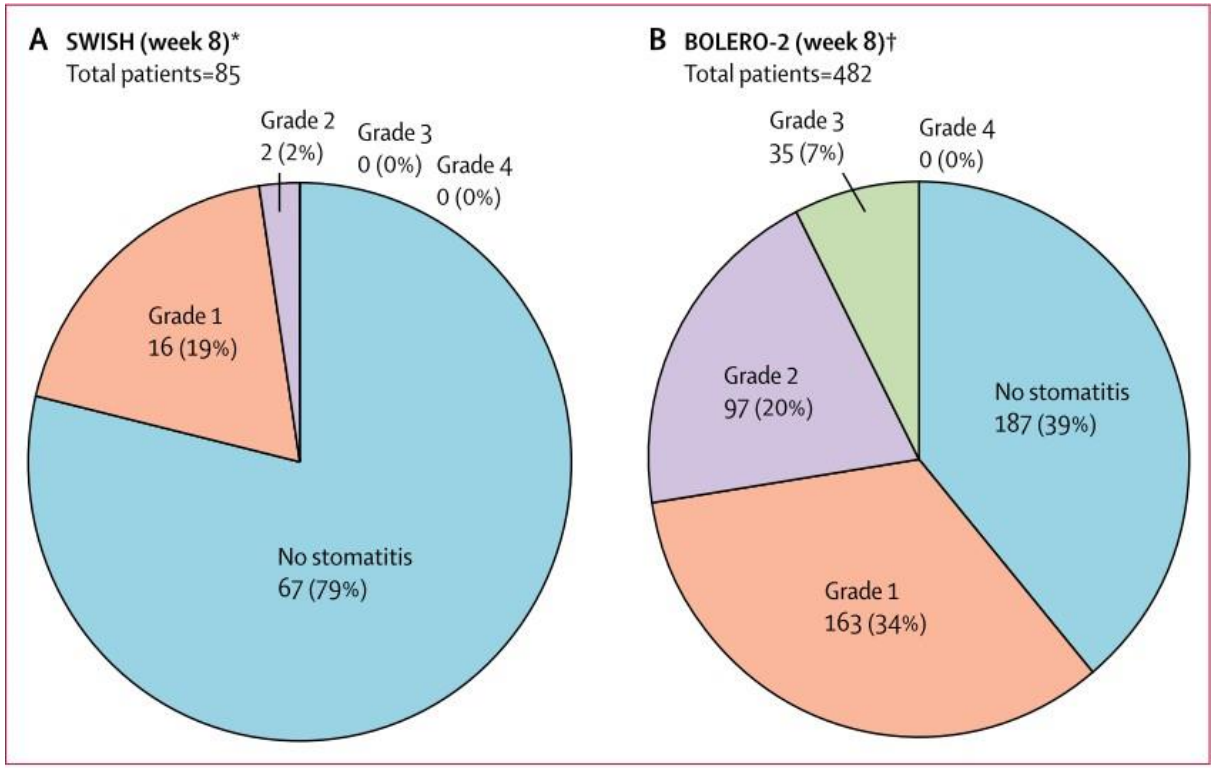


Figure 2: **Proportion of patients with stomatitis at week 8 in (A) SWISH and (B) BOLERO-2**

- 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*)

Rugo HS, et al. Prevention of everolimus-related stomatitis in women with hormone receptor-positive, HER2 negative metastatic breast cancer using dexamethasone moutwash (SWISH): a single-arm, phase 2 trial. *Lancet Oncol 2017, march 14.*

MASCC/ISOO Clinical Practice Guidelines for the Management of Mucositis Secondary to Cancer Therapy

Sharon Elad, DMD, MSc[1]; Karis Kin Fong Cheng, RN, PhD[2]; Rajesh V. Lalla, DDS, PhD[3]; Noam Yarom, DMD[4]; Catherine Hong, BDS, MS[5]; Richard M. Logan, BDS, MDS, PhD[6]; Joanne Bowen, PhD[7]; Rachel Gibson, PhD[8]; Deborah P. Saunders, DDS[9]; Yehuda Zadik, DMD, MHA [10]; Anura Ariyawardana, BDS, MS[11]; Maria Elvira Correa, DDS, PhD[12]; Vinisha Ranna, DDS[13]; and Paolo Bossi, MD[14]; for the Mucositis Guidelines Leadership Group of the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO)

MASCElad, Sharon, et al. "MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy." *Cancer* 126.19 (2020): 4423-4431.

RECOMMENDATIONS IN FAVOR OF AN INTERVENTION (ie, strong evidence supports effectiveness in the treatment setting listed):

- 1. The panel recommends that 30 min of oral cryotherapy be used to prevent oral mucositis in patients receiving bolus 5-fluorouracil chemotherapy (II).
  - The panel recommends using oral *cryotherapy* to prevent OM in patients undergoing autologous HSCT when the conditioning includes high-dose melphalan
- 2. The panel recommends that recombinant human keratinocyte growth factor-1 (KGF-1/palifermin) be used to prevent oral mucositis (at a dose of 60 lg/kg per day for 3 days prior to conditioning treatment and for 3 days after transplant) in patients receiving high-dose chemotherapy and total body irradiation, followed by autologous stem cell transplantation, for a hematological malignancy (II).
- 3. The panel recommends that 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), be used to prevent oral mucositis in patients receiving HSCT conditioned with high-dose chemotherapy, with or without total body irradiation (II).
- 4. The panel recommends that patient-controlled analgesia with morphine be used to treat pain due to oral mucositis in patients undergoing HSCT (II).
- 5. **The panel recommends that benzydamine mouthwash be used to prevent oral mucositis in patients with head and neck cancer receiving moderate dose radiation therapy (up to 50 Gy), without concomitant chemotherapy (I).**

RECOMMENDATIONS IN FAVOR OF AN INTERVENTION

1. No guideline was possible regarding the *use of saline or sodium bicarbonate* rinses in the prevention or treatment of OM in patients undergoing cancer therapy because of limited data.
   An expert opinion complements this guideline: Despite the limited data available for both saline and sodium bicarbonate**, the panel recognizes that these are inert, bland rinses that increase oral clearance, which may be helpful for maintaining oral hygiene and improving patient comfort**.
2. The panel suggests oral *glutamine* for the prevention of OM in patients with H&N cancer who receive receiving RT-CT
3. *Honey* is suggested for the prevention of OM in patients with H&N cancer who receive treatment with either RT or RT-CT

RECOMMENDATIONS AGAINST AN INTERVENTION (ie, strong evidence indicates lack of effectiveness in the treatment setting listed):

- 1. The panel recommends that PTA (polymyxin, tobramycin, amphotericin B) and BCoG (bacitracin, clotrimazole, gentamicin) antimicrobial lozenges and PTA paste not be used to prevent oral mucositis in patients receiving radiation therapy for head and neck cancer (II).
- 2. The panel recommends that iseganan antimicrobial mouthwash not be used to prevent oral mucositis in patients receiving high-dose chemotherapy, with or without total body irradiation, for HSCT (II), or in patients receiving radiation therapy or concomitant chemoradiation for head and neck cancer (II).
- 3. The panel recommends that sucralfate mouthwash not be used to prevent oral mucositis in patients receiving chemotherapy for cancer (I), or in patients receiving radiation therapy (I) or concomitant chemoradiation (II) for head and neck cancer.
- 4. The panel recommends that sucralfate mouthwash not be used to treat oral mucositis in patients receiving chemotherapy for cancer (I), or in patients receiving radiation therapy (II) for head and neck cancer.
- 5. The panel recommends that intravenous glutamine not be used to prevent oral mucositis in patients receiving high-dose chemotherapy, with or without total body irradiation, for HSCT (II).

Sonuç olarak…

- Kanser tedavisi sırasında mukozal şikayetler çok sık görülür
- Mutlaka her vizitte sorgulanmalıdır
- Öncelik önleme üzerine olmalı ve doğru eğitimler verilmelidir
- Sadece kemoterapi/radyoterapi değil hedefe yönelik ilaçlar ve immunoterapi alan hastalarda da dikkat edilmelidir
- Mukozit tespit edildiğinde agresif şekilde tedavi başlanmalıdır
- Ağız hijyeni, çalkalamalar, ağrı kesiciler, benzamidin, glutamin akılda tutulmalıdır

Dikkatiniz için teşekkürler