

Oral mucosal changes induced by anticancer targeted therapies and immune checkpoint inhibitors

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Abstract Development of biological targeted therapies and immune checkpoint inhibitors has redefined the treatment for many cancers; however, the increasing use of new protocols has led to physicians observing a new spectrum of toxicities. To date, oral adverse events induced by these new anticancer therapies have been mainly reported using nonspecific terminology (“stomatitis,” “mucosal inflammation,” “mucositis”) and remain poorly characterized, with the exception of mammalian target of rapamycin (mTOR) inhibitor-associated stomatitis. Oral toxicities of targeted therapies often display very characteristic features which clearly differ from classic oral injuries observed with cytotoxic chemotherapy and/or radiotherapy. In addition, they frequently affect more than 20% of treated patients and can lead to a significant morbidity or permanent treatment discontinuation. Oral mucosal toxicities described in this review include mTOR inhibitor-associated stomatitis (mIAS); stomatitis, benign migratory glossitis, and osteonecrosis of the jaw associated with multi-targeted kinase

inhibitors of the VEGF and PDGF receptors; mucositis induced by EGFR inhibitors (in monotherapy or in combination with head and neck radiotherapy and/or chemotherapy); hyperkeratotic lesions with BRAF inhibitors; pigmentary changes and lichenoid reactions secondary to imatinib; and more recent data on the “Osler-Weber-Rendu-like syndrome” described with the antibody-drug conjugate, TDM-1. Finally, we provide, to our knowledge, the first available structured data on oral toxicities induced by the new recently FDA- and EMA-approved monoclonal antibodies targeting PD-1. Clinical management of these targeted therapy-related oral changes is also discussed.

Keywords Mucosal changes · Oral cavity · Mucositis · Stomatitis · Mucosal sensitivity · Dysgeusia · Xerostomia · Lichenoid reaction · Hyperkeratotic lesion · Oral squamous cell carcinoma · Benign migratory glossitis · Hyperpigmentation · Angiogenesis inhibitors · EGFR inhibitors · BRAF inhibitors · mTOR inhibitors · BCR-ABL inhibitor · Cancer · Targeted therapies · Immune checkpoint inhibitors · Immunotherapy · Oral adverse events · Osteonecrosis of jaw · mIAS · Telangiectasias · Anti-PD-1

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Introduction

Substantial progress in our understanding of the mechanism of oncogenesis has led to the emergence of numerous targeted anticancer therapies in the last decade [1–4]. Their therapeutic effects result mostly from the inhibition of specific molecular receptors and intracellular signaling pathways involved in tumor progression. Immune checkpoint inhibitors are also emerging as promising anticancer agents for a wide range of cancers (e.g., metastatic melanoma, advanced or refractory nonsmall cell lung cancer, renal cell cancer, Hodgkin lymphoma) by enhancing immune responses against malignant cells

[5–9]. Their use is expected to increase exponentially in the future as their approval is extended to different tumor types [10, 11]. Both targeted agents and immunotherapies now represent a major part of the oncologists' therapeutic arsenal and have redefined the treatment principles for many cancers.

Cutaneous toxicities are among the most frequently observed adverse events associated with the majority of targeted therapies. These toxicities are now well characterized, both in terms of their prevalence and in their multiple clinical manifestations [12–18]. Cutaneous toxicities also represent the most prevalent immune-related adverse events (IRae) associated with anticancer immunotherapies. The mechanism of action of immune checkpoint inhibitors involves triggering cytotoxic T-cell activation and induces a specific toxicity profile that is primarily of immunologic origin [5, 19, 20].

Oral changes induced by targeted therapies are less well described and have been only sporadically characterized mainly reported using nonspecific terminology ("stomatitis," "mucositis"), except for mammalian target of rapamycin (mTOR) inhibitor-associated stomatitis (mIAS). However, oral toxicities of targeted therapies (Table 1) are not uncommon in clinical practice and frequently display very characteristic features [21–32] which differ significantly from those observed with chemotherapeutic agents [21, 23, 25, 26, 33].

Similarly, oral changes induced by immune checkpoint inhibitors have received limited attention to date in clinical trials [6–9, 20, 34–37], even though a spectrum of associated oral adverse events has recently emerged [20, 37, 38].

The purpose of our review is to describe the main oral mucosal changes observed with targeted therapies and immune checkpoint inhibitors. These oral toxicities clearly differ from classic oral injuries observed with chemotherapy and/or radiation therapy but might similarly impair patients' quality of life and might require dose modification or discontinuation of the treatment.

Mammalian target of rapamycin (mTOR) inhibitors (Table 1)

mTOR inhibitor-associated stomatitis (mIAS)

Incidence mIAS or aphthous-like stomatitis is a frequent and well-characterized oral toxicity in cancer patients treated with mTOR inhibitor therapy (everolimus, temsirolimus, deferolimus) [22, 27, 28, 32, 39]. The lesions are very similar to those initially described in transplant patients treated with sirolimus [32, 40]. mIAS is considered as a class effect [22], for which meta-analyses indicate the overall incidence of *any grade* and *high grade* (≥ 3) (following NCI-CTCae) ranges from 33.5 to 52.9% and from 4.1 to 5.4%, respectively, regardless of the type of mTOR inhibitor therapy [22, 39].

Overall, mIAS represents the most prevalent adverse event associated with this therapy and is the most frequent dose-

limiting toxicity [22, 39]. It is also the third most frequent severe adverse event associated with mTOR inhibitors (everolimus, temsirolimus) [12, 22, 27, 29, 39] that can lead to dose modifications [22, 32, 39, 41] in about 5% of treated patients [22]. In addition, mIAS accounts for more than 10% of reasons for treatment discontinuation, reported to affect 2% of treated patients [22, 42].

Finally, it is important to note that the incidence of mIAS reported in pivotal studies has shown a tendency to decrease over time, potentially due to prevention and earlier management, as well as patient education.

Comparison between everolimus and temsirolimus

Everolimus-induced mIAS represents the most common adverse event reported with this drug [43–48]. The incidence of mIAS of *any grade* associated with *everolimus* ranges from 24 to 64%, according to the main pivotal studies [7, 43, 45–48] (Table 2). This incidence appears higher than that of all-grade mIAS induced by temsirolimus, which ranges from 14 to 40% of treated patients [49–52] (Table 2). Moreover, indirect comparisons between temsirolimus and everolimus reveal that the incidence of high-grade (≥ 3) mIAS with temsirolimus is less than 7% [49–52] and slightly lower than with everolimus [7, 43, 45–48] (Table 2).

mTOR inhibitors in combination with endocrine agents In patients treated for breast cancer with the combination of everolimus and exemestane, mIAS represents the most common severe adverse event leading to dose reduction or interruption [42] and is the second most frequent cause of treatment discontinuation [101, 102]. In the BOLERO-2 trial, the incidence of all-grade stomatitis was 67% (with 33% grade ≥ 2 and 8% with grade 3 toxicity) in patients treated with everolimus (10 mg per day) plus exemestane (25 mg per day) for metastatic breast cancer [102]. In summary, this therapeutic combination significantly increases the incidence of all-grade mIAS [44, 101, 102] compared to everolimus monotherapy.

Clinical presentation mIAS is now a well-described clinical toxicity which mostly occurs within the first cycle of treatment [22, 29, 41], with a median time to onset of 10 days following the initiation of the treatment [27, 32, 39]. In the BOLERO-2 trial, the median time to grade ≥ 2 onset was 2 weeks [102]. In addition, a recent meta-analysis conducted on phase 3 trials of everolimus (alone or in combination) as a treatment for different forms of solid cancers and tuberous sclerosis complex showed that a second flare occurred in about 40% of treated patients [42]. Nonetheless, both the rate of occurrence and degree of severity of mIAS generally decrease during the subsequent cycles of treatment [22].

mIAS is characterized by single or multiple, painful, and well-circumscribed round/ovoid superficial ulcers. The lesions generally measure a few millimeters in diameter and

Table 1 Main oral changes induced by targeted anticancer therapies and immune checkpoint inhibitors: summary table

Class of targeted therapies	Drugs	Mechanism of action/targets	Indications	Main oral toxicities	International nonproprietary name
mTOR inhibitors	Everolimus Temozolimus	STKI targeting mTOR	Renal cell carcinoma Mantle cell lymphoma	<ul style="list-style-type: none"> • mIAS:mTOR inhibitor-associated stomatitis (aphthoid lesions) • Dysgeusia • Xerostomia 	Afinitor® Torisel®
EGFR (or HER1) inhibitors	Cetuximab	Monoclonal antibody targeting EGFR	Colorectal cancer Head and neck carcinoma	<ul style="list-style-type: none"> • Limited mucositis^a and aphthoid lesions (nonkeratinized mucosa) • Dysgeusia 	Erbuitux® Vectibix® Tarceva®
HER inhibitors	Panitumumab Erlotinib Gefitinib Lapatinib Trastuzumab emtansine Afatinib	TKI targeting EGFR TKI targeting EGF (ErbB1) and HER2 (ErbB2) receptors Monoclonal antibody targeting HER2; antibody-drug conjugate with chemotherapy (emtansine) TKI targeting EGF (ErbB1), HER2 (ErbB2), ErbB3 and ErbB4 receptors	Nonsmall cell lung cancer Nonsmall cell lung cancer Nonsmall cell lung cancer HER2+ breast cancer HER2+ breast cancer Nonsmall cell lung cancer	<ul style="list-style-type: none"> • Limited mucositis and aphthoid lesions (nonkeratinized mucosa) • Mucosal bleeding and telangiectasia 	Iressa® Tyverb® Kadcyla®
Pan-HER inhibitors	Dacomitinib	Irreversible TKI targeting EGFR, HER2, and HER4 tyrosine kinases	Nonsmall cell lung cancer	<ul style="list-style-type: none"> • Limited mucositis and aphthoid lesions (nonkeratinized mucosa) • Dysgeusia 	Giotrif®
Angiogenesis inhibitors	Bevacizumab	Monoclonal antibody targeting VEGF	Breast cancer Nonsmall cell lung cancer Ovarian cancer Glioblastoma Cervical cancer	<ul style="list-style-type: none"> • Benign migratory glossitis • Osteonecrosis of jaw • Mucosal bleeding • Delayed wound healing 	Avastin®
	Sunitinib	TKI targeting VEGFR 1–3, PDGFR α β , c-KIT, RET, FLT3, CSF-1R	Metastatic renal cell carcinoma Advanced GIST Metastatic neuroendocrine tumor	<ul style="list-style-type: none"> • Oral dysesthesia • Aphthoid lesions • Benign migratory glossitis 	Sutent®
	Sorafenib	TKI targeting VEGFR 2–3, PDGFR β , c-KIT, RET, RAF, FLT3	Hepatocellular carcinoma Renal cell carcinoma Thyroid carcinoma	<ul style="list-style-type: none"> • Osteonecrosis of jaw • Dysgeusia (sunitinib, cabozantinib) • Xerostomia 	Nexavar®
	Pazopanib	TKI targeting VEGFR 1–3, PDGFR α β , c-KIT	Renal cell carcinoma	• Dyschromia (sunitinib)	Votrient®
	Axitinib	TKI targeting VEGFR 1–3	Sarcoma		Inlyta®
	Cabozantinib	TKI targeting VEGFR, AXL, MET	Renal cell carcinoma Hepatocellular carcinoma Metastatic renal cell carcinoma Medullary thyroid cancer		Cometriq®
BCR-ABL inhibitor	Imatinib	TKI targeting BCR-ABL (Philadelphia chromosome), PDGFR α β , c-Kit, CSF-1R, SCF receptors	Chronic myeloid leukemia Acute lymphoid leukemia GIST Myelodysplasia	<ul style="list-style-type: none"> • Lichenoid reactions • Hard palate pigmentation • Dysgeusia 	Glivec®

Table 1 (continued)

Class of targeted therapies	Drugs	Mechanism of action/targets	Indications	Main oral toxicities	International nonproprietary name
Immune checkpoint inhibitors	Nivolumab	Monoclonal antibody targeting PD-1	Darier-Ferrand dermatofibrosarcoma		
	Pembrolizumab		Melanoma	• Xerostomia	Opdivo®
	Atezolizumab	Monoclonal antibody targeting PD-L1	nonsmall cell lung cancer Metastatic nonsmall cell lung cancer urothelial carcinoma	• Dysgeusia • Lichenoid reactions	Keytruda® Tecentriq®
BRAF inhibitors	Dabrafenib Vemurafenib	STKI targeting BRAF	Melanoma	• Mucosal hyperkeratotic lesions ^b (linea alba, hard palate, gingiva...) • Gingival hyperplasia • Secondary squamous cell carcinoma	Tafinlar® Zelboraf®
ALK inhibitor	Crizotinib	TKI targeting ALK, MET, ROS1	Nonsmall cell lung cancer	• Dysgeusia	Xalkori®
Hedgehog pathway inhibitor	Vismodegib	Targeting SMO protein	Basal cell carcinoma	• Dysgeusia • Ageusia	Erivedge®

STKI serine threonine kinase inhibitor, TKI tyrosine kinase inhibitor

^a Grade ≥ 3 mucositis is frequent when cetuximab is associated with head and neck radiotherapy for locally advanced squamous cell carcinoma

^b These induced lesions do not develop when BRAF inhibitors are associated with MEK inhibitors

display a central gray area that is surrounded by an erythematous halo, mimicking recurrent aphthous stomatitis or herpetic lesions [22, 27, 32, 39, 42] (Fig. 1a, b). Major lesions can nonetheless sometimes be observed (Fig. 1c). mIAS mainly develops on the nonkeratinized mucosa (buccal mucosa, soft palate, ventral side and lateral borders of the tongue, or floor of the mouth) [22, 27, 32, 39].

These clinical features clearly differ from cytotoxic chemotherapy-induced mucositis, in which lesions are often more diffuse, larger, poorly circumscribed, and covered with a pseudomembrane consisting of fibrin, altered leucocytes, and epithelial debris (Fig. 2) [21, 103–105]. Gastrointestinal involvement is also frequently observed in mucositis associated with chemotherapy, whereas mIAS typically spares other mucosae [27, 28, 32, 39, 42].

Management mIAS is a significant complication that can negatively impair adherence to the cancer treatment and affect the patient's quality of life. Therefore, prophylactic treatment and early recognition of this toxicity are fundamental.

Prevention

Early management consists of the promotion of good oral hygiene. Firstly, pretherapeutic oral screening is recommended in order to identify dental or periodontal disease outbreaks and ensure proper treatment. Oral examination is also necessary to eliminate potential sources of trauma (ill-fitting dentures, defective restorations, broken teeth, dental calculus, etc.) and detect preexisting mucosal disease [106]. Good oral health also relies on basic oral care interventions [33, 106–110] (Table 3).

In a recent phase 2 prevention trial (SWISH trial), Rugo et al. [111] reported on the prophylactic use of 10 mL of alcohol-free dexamethasone (0.5 mg/5 mL, four times daily for 8 weeks) mouthwash to prevent mIAS in patients receiving everolimus 10 mg/exemestane 25 mg for HR+, HER2– advanced or metastatic breast cancer. The incidence of all-grade mIAS in this group was 21.2%, with 2.4% developing grade ≥ 2 mIAS, and no patients developing grade 3. Indirect comparison with the BOLERO-2 trial clearly indicates that prophylaxis with dexamethasone mouthwash significantly reduces the incidence or prevents the occurrence of all grades of mIAS, especially grade ≥ 2 mIAS.

Treatment

In general, no intervention is required for grade 1 mIAS, except for maintaining a good standard of oral hygiene. Topical steroids should be considered as the first line of treatment for grade 2 mIAS [22, 32, 33, 39, 112]. Topical steroid mouthrinse (e.g.,

Table 2 Incidence of oral mucosal changes in selected phase I–III trials conducted with targeted anticancer therapies and immune check point inhibitors

Agent class	Drug	Authors	Study design	Clinical settings and interventions	Stomatitis		Dysgeusia		Xerostomia	
					All grade (%)	Grade ≥ 3 (%)	All grade (%)	Grade ≥ 3 (%)	All grade (%)	Grade ≥ 3 (%)
mTOR inhibitors	Everolimus	Motzer et al. [7]	II	Advanced or metastatic, clear-cell, RCC; lenvatinib (24 mg/day), everolimus (10 mg/day) or lenvatinib + everolimus (18 and 5 mg/day, respectively) administered orally in continuous 28-day cycles.	42	1			6	0
		Yao et al. [43]	II	Advanced, low-grade or intermediate grade pancreatic neuroendocrine tumors; everolimus 10 mg/day or placebo.	64	7	17	0		
		Baselga et al. [44]	III	HER+ advanced BC; everolimus 10 mg + exemestane 25 mg or exemestane + placebo.	56	8	21	<1		
		Armstrong et al. [45]	II	Nonclear-cell RCC; everolimus 10 mg/day or sunitinib 50 mg/day; 6-week cycles of 4 weeks with treatment followed by 2 weeks without treatment.	48	9	32	0		
		André et al. [46]	III	HER2+ trastuzumab-resistant advanced BC; everolimus (5 mg/day) + weekly trastuzumab (2 mg/kg) + vinorelbine (25 mg/m ²) or placebo + trastuzumab + vinorelbine, in 3-week cycles (BOLERO-3).	62	13				
		Motzer et al. [47]	III	Advanced clear-cell RCC, nivolumab 3 mg/kg IV every 2 weeks or 10 mg everolimus tablet orally once daily.	29	4				
		Choueiri et al. [48]	III	Advanced RCC, cabozantinib 60 mg/day or everolimus 10 mg/day.	24	2	9	0		
		Hudes et al. [49]	III	Metastatic RCC; temsirolimus 25 mg IV weekly, 3 million U of interferon α (with an increase to 18 million U) subcutaneously three times weekly or temsirolimus 15 mg IV weekly + 6 million U of interferon α three times weekly.	20	1				
		Hudes et al. [49]	III	Metastatic RCC; temsirolimus 25 mg IV weekly, 3 million U of interferon α (with an increase to 18 million U) subcutaneously three times weekly or temsirolimus 15 mg IV weekly + 6 million U of interferon α three times weekly.	20	1				
		Wolff et al. [50]	III	HER+ metastatic BC; letrozole 2.5 mg/day + temsirolimus 30 mg/day (5 days every 2 weeks) versus letrozole + placebo.	14	1				
Tensirolimus		Hutson et al. [51]	III	Metastatic RCC; temsirolimus 25 mg once weekly or oral sorafenib 400 mg twice/day.	22	2				
		Rini et al. [52]	III	Metastatic RCC; temsirolimus (25 mg intravenously, weekly) or IFN (9 MIU subcutaneously thrice weekly) + bevacizumab (10 mg/kg intravenously, every 2 weeks).	26	7				
		Ansell et al. [53]	II	Mantle cell lymphoma; temsirolimus 25 mg/week + rituximab 375 mg/m ² /week for 4 weeks during the first cycle and thereafter a single dose of rituximab every other 28-day cycle.	40	0				

Table 2 (continued)

Agent class	Drug	Authors	Study design		Clinical settings and interventions	Stomatitis		Dysgeusia		Xerostomia	
			Trial phase	N		All grade (%)	Grade ≥ 3 (%)	All grade (%)	Grade ≥ 3 (%)	All grade (%)	Grade ≥ 3 (%)
HER inhibitors	Afatinib	Park et al. [54]	IIb	N = 319p	Stage IIIB/IV NSCLC; afatinib (40 mg/day) or gefitinib (250 mg/day).	64	4				
		Miller et al. [55]	IIb/III	N = 585p	Stage IIIB/IV lung adenocarcinoma; afatinib (50 mg/day) or placebo	61	3	6	0		
		Wu et al. [56]	III	N = 364p	Stage IIIB/IV NSCLC; afatinib (40 mg/day) or gemcitabine IV 1000 mg/m ² on day 1 and day 8 + cisplatin 75 mg/m ² on day 1 of a 3-week schedule for up to six cycles.	51.9	5.4				
		Machiels et al. [57]	III	N = 483p	Recurrent, metastatic or progressing HNSCC; afatinib (40 mg/day) or IV methotrexate (40 mg/m ² /week).	39	7				
		Soria et al. [58]	III	N = 795p	Stage IIIB or IV squamous cell carcinoma of the lung; afatinib (40 mg/day) or erlotinib (150 mg/day).	29	4				
		Sequist et al. [59]	III	N = 345p	Stage IIIB/IV lung adenocarcinoma; 40 mg afatinib/day or up to six cycles of cisplatin plus pemetrexed chemotherapy at standard doses every 21 days.	72.1	8.7				
		Harbeck et al. [60]	III	N = 508p	HER2+ BC; afatinib (40 mg/day) + IV vinorelbine (25 mg/m ² /week) or IV trastuzumab (2 mg/kg/week after 4 mg/kg loading dose) + vinorelbine.	25	4				
		Geyer et al. [61]	III	N = 324p	HER2+ locally advanced or metastatic BC; lapatinib 1250 mg/day continuously + capecitabine (2000 mg/m ² of body surface area on days 1 through 14 of a 21-day cycle) or monotherapy (capecitabine alone 2500 mg/m ² on days 1 through 14 of a 21-day cycle).	15	0				
		Goss et al. [62]	III	N = 3147p	Early-stage HER2+ BC; lapatinib (1500 mg) or daily placebo for 12 months.	6	<1				
		Park et al. [54]	IIb	N = 319p	Stage IIIB/IV NSCLC; afatinib (40 mg/day) or gefitinib (250 mg/day).	24	0				
Gefitinib	Gefitinib	Mok et al. [63]	III	N = 1217p	Pulmonary adenocarcinoma; gefitinib (250 mg/day) or carboplatin (at a dose calculated to produce an area under the curve of 5 or 6 mg/ml/min) + paxitaxel (200 mg/m ² of body surface area).	17	0.2				
		Mitsudomi et al. [64]	III	N = 118p	Stage IIIB/IV NSCLC or postoperative recurrence harboring EGFR mutations; gefitinib (250 mg/day orally) or cisplatin (80 mg/m ² , IV) + docetaxel (60 mg/m ² , IV), administered every 21 days for three to six cycles.	19	0				
		Soria et al. [58]	III	N = 795p	Stage IIIB or IV squamous cell carcinoma of the lung; afatinib (40 mg/day) or erlotinib (150 mg/day).	8	0				
		Ramalingam et al. [65]	III	N = 878p	Locally advanced or metastatic NSCLC; daconitib (45 mg/day) or erlotinib (150 mg/day) with matching placebo.	20	0				
		Ciuleanu et al. [66]	III	N = 424p	Locally advanced, recurrent, or metastatic NSCLC; erlotinib 150 mg/day or chemotherapy (standard docetaxel or pemetrexed regimens).	<1	0				
Erlotinib	Erlotinib	Soria et al. [58]	III	N = 795p	Stage IIIB or IV squamous cell carcinoma of the lung; afatinib (40 mg/day) or erlotinib (150 mg/day).	8	0				

Table 2 (continued)

Agent class	Drug	Authors	Study design		Clinical settings and interventions	Stomatitis		Dysgeusia		Xerostomia	
			Trial phase	N		All grade (%)	Grade ≥ 3 (%)	All grade (%)	Grade ≥ 3 (%)	All grade (%)	Grade ≥ 3 (%)
Dacomitinib		Zhou et al. [67]	III	N = 165p	Stage IIIB or IV NSCLC and a confirmed activating mutation of EGFR; oral erlotinib (150 mg/day) or up to four cycles of gemcitabine plus carboplatin	13	1				
		Shepherd et al. [68]	III	N = 731p	Stage IIIB or IV NSCLC; oral erlotinib, at a dose of 150 mg/day or placebo.	19	<1				
		Ramalingam et al. [65]	III	N = 878p	Locally advanced or metastatic NSCLC; dacomitinib (45 mg/day) or erlotinib (150 mg/day) with matching placebo.	37	4				
		Ellis et al. [69]	III	N = 720p	Advanced or metastatic NSCLC; oral dacomitinib 45 mg once-daily or matched placebo.	41	3	6	0	8	<1
		Jänne et al. [70]	II	N = 89p	Advanced nonsmall cell lung cancer; dacomitinib orally once daily (45 or 30 mg).	40	4	15	0	14	0
Cetuximab		Cunningham et al. [71]	III	N = 329p	Refractory metastatic colorectal cancer; cetuximab and irinotecan (at the same dose and schedule as in a prestudy regimen) or cetuximab monotherapy.		0.9				
		Price et al. [72]	III	N = 1010p	Chemotherapy-refractory wild-type KRAS exon 2 metastatic colorectal cancer; panitumumab (6 mg/kg once every 2 weeks) or cetuximab (initial dose 400 mg/m ² ; 250 mg/m ² once a week thereafter).	7	0				
		Bonner et al. [73]	III	N = 424p	Locally advanced HNSCC; head and neck radiotherapy alone for 6–7 weeks or radiotherapy + weekly doses of cetuximab: 400 mg/m ² initial dose, followed by seven weekly doses at 250 mg/m ² .		62				
		Magrini et al. [74]	II	N = 70p	Locally advanced HNSCC; CD1DP 40 mg/m ² once/week or CTX 400 mg/m ² as a loading dose followed by CTX 250 mg/m ² once/week concomitant to radical RT.		59				
		Bonner et al. [75]	III	N = 424p	Locally advanced HNSCC; high-dose radiotherapy alone or high-dose radiotherapy + weekly cetuximab at an initial dose of 400 mg/m ² of body surface area, followed by 250 mg/m ² weekly for the duration of radiotherapy.		56				
		Ang et al. [76]	III	N = 891p	Stage III to IV HNSCC; radiation and cisplatin without or with cetuximab.		43				
		Lordick et al. [77]	III	N = 904p	Advanced gastric cancer; 3-week cycles of twice-daily capecitabine 1000 mg/m ² (on days 1–14) and IV cisplatin 80 mg/m ² (on day 1), with or without weekly cetuximab (400 mg/m ² initial infusion on day 1 followed by 250 mg/m ² per week thereafter).	37	4				
		Kim et al. [78]	III	N = 938p	Recurrent or progressive NSCLC; initially, patients were randomly assigned to receive either pemetrexed (500 mg/m ²) or docetaxel (75 mg/m ²) and then randomly assigned within each group to receive their chemotherapy with or	19	0				

Table 2 (continued)

Agent class	Drug	Authors	Study design	Clinical settings and interventions	Stomatitis		Dysgeusia		Xerostomia		
					All grade (%)	Grade ≥ 3 (%)	All grade (%)	Grade ≥ 3 (%)	All grade (%)	Grade ≥ 3 (%)	
Angiogenesis inhibitors	Panitumumab	Primrose et al. [79]	III	N = 271p	without cetuximab (400 mg/m ² at first dose and 250 mg/m ² weekly thereafter). Resectable colorectal liver metastases; chemotherapy with or without cetuximab before and after liver resection: oxaliplatin 85 mg/m ² intravenously over 2 h and fluorouracil bolus 400 mg/m ² intravenously over 5 min, followed by a 46 h infusion of fluorouracil 2400 mg/m ² repeated every 2 weeks (regimen one) or oxaliplatin 130 mg/m ² intravenously over 2 h and oral capecitabine 1000 mg/m ² twice daily on days 1–14 repeated every 3 weeks (regimen two). Patients who had received adjuvant oxaliplatin could receive irinotecan 180 mg/m ² intravenously over 30 min with fluorouracil instead of oxaliplatin (regimen three). Cetuximab was given as an intravenous dose of 500 mg/m ² every 2 weeks with regimen one and three or a loading dose of 400 mg/m ² followed by a weekly infusion of 250 mg/m ² with regimen two.	3					
		Price et al. [72]	III	N = 1010p	Chemotherapy-refractory wild-type KRAS exon 2 metastatic colorectal cancer; panitumumab (6 mg/kg once every 2 weeks) or cetuximab (initial dose 400 mg/m ² ; 250 mg/m ² once a week thereafter).	5	<1				
		Vermorken et al. [80]	II	N = 657p	Recurrent or metastatic HNSCC; six 3-week cycles of IV cisplatin (100 mg/m ² on day 1 of each cycle) and fluorouracil (1000 mg/m ² on days 1–4 of each cycle); the experimental group also received intravenous panitumumab (9 mg/kg on day 1 of each cycle).		10				
		Leone et al. [81]	II	N = 89p	Wild-type KRAS advanced biliary tract cancer; gemcitabine (1000 mg/m ²) + oxaliplatin (100 mg/m ²) with or without panitumumab (6 mg/kg) for up to 12 cycles.	22.2	0				
	Sorafenib	Wadell et al. [82]	III	N = 553p	Advanced esophagogastric adenocarcinoma; eight 21-day cycles of open-label EOC (epirubicin 50 mg/m ² and oxaliplatin 130 mg/m ² on day 1 and capecitabine 1250 mg/m ² /day on days 1–21) or modified-dose EOC plus panitumumab (mEOC + P; epirubicin 50 mg/m ² and oxaliplatin 100 mg/m ² on day 1, capecitabine 1000 mg/m ² /day on days 1–21, and panitumumab 9 mg/kg on day 1).	64	4				
		Hutson et al. [51]	III	N = 512p	Metastatic RCC; temsirolimus 25 mg once weekly or oral sorafenib 400 mg twice/day.	7	0				
		Motzer et al. [83]	III	N = 570p	Clear-cell metastatic RCC; dovitinib (500 mg orally according to a 5-days-on and 2-days-off schedule) or sorafenib (400 mg orally twice daily).	19	<3	3	0	4	0

Table 2 (continued)

Agent class	Drug	Authors	Study design		Clinical settings and interventions	Stomatitis		Dysgeusia		Xerostomia	
			Trial phase	N		All grade (%)	Grade ≥ 3 (%)	All grade (%)	Grade ≥ 3 (%)	All grade (%)	Grade ≥ 3 (%)
	Axitinib	Motzer et al. [84]	III	N = 723p	Clear-cell metastatic RCC; axitinib (5 mg twice daily) or sorafenib (400 mg twice daily).	12	<0.5	8	0		
		Cheng et al. [85]	III	N = 1074p	Advanced hepatocellular cancer; sunitinib 37.5 mg once/day or sorafenib 400 mg/day.	9.8	0.5				
		Motzer et al. [84]	III	N = 723p	Advanced RCC; axitinib (5 mg twice daily) or sorafenib (400 mg twice daily).	15	1	11	0		
		Motzer et al. [83]	III	N = 570p	Clear-cell metastatic RCC; dovitinib (500 mg orally according to a 5-days-on and 2-days-off schedule) or sorafenib (400 mg orally twice daily).	11	<1	11	0	8	0
	Pazopanib	Motzer et al. [86]	III	N = 1110p	Metastatic RCC; continuous dose of pazopanib (800 mg once daily) or sunitinib in 6-week cycles (50 mg once daily for 4 weeks, followed by 2 weeks without treatment).	14	1	26	<1		
	Sunitinib	Armstrong et al. [45]	II	N = 108p	Nonclear cell RCC; everolimus 10 mg/day or sunitinib 50 mg/day; 6-week cycles of 4 weeks with treatment followed by 2 weeks without treatment.	27	0	49	0	10	0
		Cheng et al. [85]	III	N = 1074p	Advanced hepatocellular cancer; sunitinib 37.5 mg once/day or sorafenib 400 mg twice/day.	16.5	1.5				
		Motzer et al. [86]	III	N = 1110p	Metastatic RCC; continuous dose of pazopanib (800 mg once daily) or sunitinib in 6-week cycles (50 mg once daily for 4 weeks, followed by 2 weeks without treatment).	27	1	36	0		
		Motzer et al. [87]	II	N = 750p	Metastatic RCC; either repeated 6-week cycles of sunitinib (at a dose of 50 mg given orally once daily for 4 weeks, followed by 2 weeks without treatment) or interferon alfa (at a dose of 9 MU given subcutaneously three times weekly).	25	1			11	0
	Lenvatinib	Raymond et al. [88]	III	N = 171p	Advanced, well-differentiated pancreatic neuroendocrine tumors; sunitinib 37.5 mg/day or placebo.	22	4	20	0		
		Gore et al. [89]	III	N = 4371p	Metastatic RCC; sunitinib 50 mg orally once daily on a 4–2 schedule (4 weeks on treatment, 2 weeks off).	27	3	24	1		
		Motzer et al. [7]	II	N = 153p	Advanced or metastatic, clear cell RCC; lenvatinib (24 mg/day), everolimus (10 mg/day) or lenvatinib + everolimus (18 mg/day and 5 mg/day, respectively) administered orally in continuous 28-day cycles.	25	2			12	0
		Choueiri et al. [48]	III	N = 658p	Advanced RCC; cabozantinib 60 mg daily or everolimus 10 mg daily.	22	2	24	0		
BCR-ABL inhibitors	Cabozantinib	Elisei et al. [90]	III	N = 330p	Medullary thyroid cancer; cabozantinib (140 mg/day) or placebo.	29	1.9	34.1	0.5		
	Bevacizumab	Tournigand et al. [91]	III	N = 700p	Metastatic colorectal cancer; bevacizumab (7.5 mg/kg every 3 weeks) or bevacizumab + erlotinib (150 mg once daily).	4	0				
	Imatinib	O'Brien et al. [92]	III	N = 1106p	Chronic-phase CML; imatinib 400 mg/day or interferon alfa + cytarabine with escalating doses of interferon alfa (target dose, 5 million U/m ² of	2.9	0			2.2	0

Table 2 (continued)

Agent class	Drug	Authors	Study design		Clinical settings and interventions	Stomatitis		Dysgeusia		Xerostomia	
			Trial phase	N		All grade (%)	Grade ≥ 3 (%)	All grade (%)	Grade ≥ 3 (%)	All grade (%)	Grade ≥ 3 (%)
PD-1/PDL-1 inhibitors	nivolumab	Demetri et al. [93]	III	N = 147p	body surface area/day). Once maximal tolerated dose of interferon α was achieved, subcutaneous low-dose cytarabine was added at a dose of 20 mg/m ² /day (maximal daily dose, 40 mg) for 10 days every month. Advanced GIST; 400 mg or 600 mg of imatinib/day.			8.2	0		
		Raymond et al. [94]	II	N = 112p	Recurrent glioma; imatinib started at a dose of 600 mg/d with dose escalation to 800 mg in case of no toxicity; during the trial this dose was increased to 800 mg/d with escalation to 1000 mg/d.	4.5 ^a	0				
		Rizvi et al. [6]	II	N = 117p	Refractory squamous NSCLC; IV nivolumab 3 mg/kg every 2 weeks.					6	0
		Robert et al. [9]	III	N = 418p	Metastatic melanoma without a BRAF mutation; nivolumab 3 mg/kg of body weight every 2 weeks + dacarbazine-matched placebo every 3 weeks or dacarbazine 1000 mg/m ² of body surface area every 3 weeks + nivolumab-matched placebo every 2 weeks.			2.9	0		
		Topalian et al. [34]	I	N = 107p	Advanced melanoma; IV nivolumab every 2 weeks for up to 96 weeks.	2	<1	2	0	6.5	0.9
		Borghaei et al. [35]	III	N = 582p	Nonsquamous NSCLC; nivolumab 3 mg/kg of body weight every 2 weeks or docetaxel 75 mg/m ² of body surface area every 3 weeks.	2	0				
CTLA-4 inhibitor	Ipilimumab	Motzer et al. [47]	III	N = 821p	Advanced clear-cell RCC; nivolumab 3 mg/kg IV every 2 weeks or 10 mg everolimus tablet orally once daily.						
		Robert et al. [8]	III	N = 834p	Advanced melanoma; pembrolizumab 10 mg/kg of body weight every 2 weeks (a) or every 3 weeks (b) or four doses of ipilimumab 3 mg/kg every 3 weeks.			(a) 3.6 (b) 1.8	0 0	(a) 7.2 (b) 4	0 0
		McDermott et al. [36]	Ia	N = 70p	Metastatic RCC; atezolizumab intravenously every 3 weeks.	4	0			3	0
		Robert et al. [8]	III	N = 834p	Advanced melanoma; pembrolizumab 10 mg/kg of body weight every 2 weeks (a) or every 3 weeks (b) or four doses of ipilimumab 3 mg/kg every 3 weeks.			1.2	0	0.4	0
ALK inhibitors	Crizotinib	Shaw et al. [95]	III	N = 347p	Advanced or metastatic ALK-positive lung cancer; crizotinib 250 mg twice/day or IV chemotherapy with either pemetrexed (500 mg/m ² of body surface area) or docetaxel (75 mg/m ²), every 3 weeks.			26	0		
		Shaw et al. [96]	I	N = 50p	Advanced NSCLC; crizotinib at the standard oral dose of 250 mg twice daily.			18	0		
		Camidge et al. [97]	I	N = 143p	ALK-positive stage III or IV NSCLC; oral crizotinib 250 mg twice daily in 28-day cycles.			11	0		
		Solomon et al. [98]	III	N = 343p	Advanced ALK-positive nonsquamous NSCLC; oral crizotinib 250 mg twice daily or IV chemotherapy (pemetrexed, 500 mg/m ² of body	14	1	26	0		

Table 2 (continued)

Agent class	Drug	Authors	Study design		Clinical settings and interventions	Stomatitis		Dysgeusia		Xerostomia	
			Trial phase	N		All grade (%)	Grade ≥ 3 (%)	All grade (%)	Grade ≥ 3 (%)	All grade (%)	Grade ≥ 3 (%)
Hedgehog pathway inhibitor	Vismodegib	Sekulic et al. [99] Basset-Seguin et al. [100]	II II	N = 96p N = 499p	surface area + either cisplatin (75 mg/m ²) or carboplatin, target area under the curve of 5 to 6 mg per milliliter per minute) every 3 weeks for up to six cycles. Metastatic BCC; oral vismodegib 150 mg/day. Locally advanced or metastatic BCC; 150 mg oral vismodegib capsules once a day on a continuous basis in 28-day cycles.	51 53 22 ^b	0 2 2 ^b				

p patients, RCC renal cell carcinoma, BC breast cancer, NSCLC non-small cell lung cancer, HNSCC head and neck squamous cell carcinoma, CML chronic myeloid leukemia, GIST gastrointestinal stromal tumor, BCC basal cell carcinoma

^a For the group with dose of imatinib = 800 mg

^b Ageusia

dexamethasone mouth rinse (0.1 mg/mL)) is the preferred treatment in case of multiple lesions or lesions that are difficult to reach for local application [33]. For limited lesions that can be reached for topical application, high potency corticosteroids (clobetasol 0.05% gel or cream) is an alternative. In cases where the lesion does not resolve, a combination of intralesional steroid injections (e.g., triamcinolone) and clobetasol 0.05% gel or cream should be used for treatment. The association of low-level laser therapy (wavelength of 633–685 or 780–830 nm, power output of between 10 and 150 mW, energy density 2–3 J/cm², and no more than 6 J/cm² on the tissue surface treated) [113] with topical corticosteroids provides some immediate pain relief and may promote healing of the ulcerations. These data need to be confirmed by prospective studies.

For highly painful (grade ≥ 3), intolerable grade 2 or recurrent mIAS, dose reduction or treatment interruption (see below) and systemic corticosteroids should be considered (high-dose pulse therapy with 30–60 mg or 1 mg/kg oral prednisone/prednisolone for 1 week, followed by dose tapering over the second week) [33], while continuing topical interventions. Antifungal therapy may be administered on a case by case basis [112].

For moderate pain management, anesthetic mouthwash (lidocaine viscous, 2%), topical analgesic (e.g., doxepin rinse), coating agents or systemic analgesics can be helpful. Topical nonsteroidal anti-inflammatory drugs (amlexanox 5% oral paste) or paracetamol, in combination with an immediate release oral opioid or fast acting fentanyl preparation, have been proposed as management options. In case of severe pain, other types of analgesic administration routes should be considered [33].

Dose reduction, interruption, or discontinuation (see Table 4)

mIAS may also be managed by dose adjustments. The severity and/or the recurrence of the lesions as well as the time needed to recover will determine whether full dosing can be resumed or whether dose reduction or discontinuation is required [101, 102, 110, 114, 115].

Dysgeusia

Incidence Everolimus also frequently causes dysgeusia, which has been reported in 9 to 32% of treated patients [43–45, 48] (Table 2). However, no dose adjustment is generally necessary (Table 2).

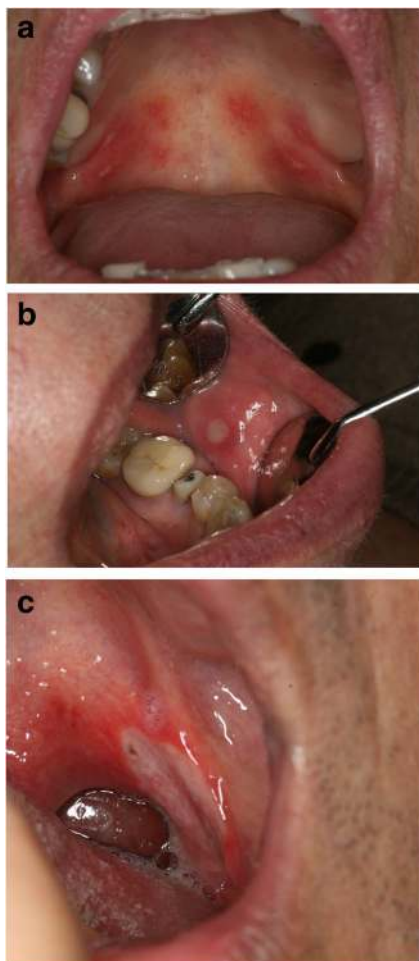


Fig. 1 **a** Multiple mIAS of the soft palate with mTOR inhibitor (everolimus). **b** Typical mIAS with an erythematous halo on nonkeratinized mucosa (everolimus). **c** A major aphthous-like ulceration with everolimus (mIAS)

Although less frequently described, dysgeusia can also be induced by temsirolimus [116].

Management As dysgeusia is benign, it is frequently overlooked. Nevertheless, the impact on patients' quality of life can be significant, with a high risk of malnutrition and weight



Fig. 2 Widespread mucositis of the lateral ventral side of the tongue induced by chemotherapy (nonkeratinized mucosa)

Table 3 General supportive care measures to prevent mucositis

Basic oral care and oral hygiene recommendations:

- Tooth brushing two or three times a day with an ultra-soft or soft toothbrush with fluoride toothpaste (in case of burning, use minimally flavored toothpaste, e.g., children's toothpaste/gel, dry mouth children's toothpaste/gel)
- Flossing/interdental cleaning after each meal
- Mouth washing with bland solutions four to six times a day (sterile water, normal saline, or sodium bicarbonate)
- Cleaning removable dental prostheses
- Consider oral moisturizers
- To avoid:
 - Alcohol-containing rinses and toothpaste with sodium lauryl sulfate
 - Alcohol or peroxidase containing mouthwash products
 - Antifungal or antimicrobial products without specific indications
 - Spicy, acidic, hard, crunchy and/or high temperature food
 - Alcoholic drinks
 - Tobacco

Oral examination by specialist practitioner:

- Before oncologic treatment: preoperative dental and periodontal screening with treatment as appropriate
- Elimination of traumatic factors (dental or prosthetic origin)
- During and after treatment: regular dental and periodontal examination

loss [117–121]. To date, there is no standardized preventive or curative treatment for dysgeusia [122] and symptomatic dietary measures should be considered (Table 5). Weight monitoring is recommended. The management of contributing factors is also crucial (e.g., smoking, alcoholism, poor oral hygiene, oropharyngeal infections) [121].

Other toxicities

Xerostomia has been reported in only one comparative study, in which it occurred in 6% of everolimus-treated patients [7] (Table 2). It is generally mild in this context. No cases of temsirolimus-associated xerostomia have been reported. Basic oral care and dietary recommendations associated with artificial saliva substitutes (moisturizing spray, glycerol-based oral spray) should be recommended if the symptoms severely impact health-related quality of life (Table 5).

Rare cases of osteonecrosis of the jaw have been very sporadically reported with everolimus [123] mostly when it has been used in association with antiresorptive agents [124].

EGFR and pan-HER inhibitors (Table 1)

Agents targeting the epidermal growth factor receptor (EGFR or HER1) also represent an important strategy in the management of many cancers (colorectal, lung, head and neck, and

Table 4 Modified management algorithm for mIAS

Grade* 1 Erythema of mucosa with asymptomatic or mild symptoms	Supportive cares: basic oral care ^a and symptomatic management in case of mild symptom (steroid mouthwash) No dietary modifications Continue mTOR inhibitor Monitor for change in severity
Grade* 2 Patchy ulceration with moderate pain but no interference with oral intake	Symptomatic management and supportive cares: basic oral care ^a , topical steroids, low-level laser therapy (LLLT), modified diet Dose adjustment: <ul style="list-style-type: none"> • If toxicity is tolerable → No dose adjustment required • If toxicity becomes intolerable → Temporary dose interruption until recovery to grade ≤ 1 → Reinitiate mTOR at same dose • If toxicity recurs at grade 2 → Manage as first grade 3 episode: interrupt mTOR until recovery to grade ≤ 1 → Reinitiate at a lower dose (i.e., 5 mg/day for everolimus) Monitor for change in severity
Grade* 3 Confluent ulcerations or pseudomembranes with severe pain interfering with oral intake	Symptomatic management and supportive cares: basic oral care, a systemic corticosteroids, LLLT, morphine mouthwash, modified diet, systemic analgesics Dose adjustment: <ul style="list-style-type: none"> • Temporary dose interruption until recovery to grade ≤ 1; reinitiate mTOR at a lower dose • If toxicity recurs at grade 3 → Manage as grade 4: consider discontinuation Monitor for change in severity
Grade* 4 Tissue necrosis, significant spontaneous bleeding with symptoms associated with life-threatening circumstances	Permanent discontinuation–supportive measures

Grade* refers to NCI CTCAE v4.0

^a Basic oral care: see Table 3

breast cancers). They include monoclonal antibodies (cetuximab, panitumumab) and specific tyrosine kinase inhibitors (erlotinib, gefitinib). This group also includes also multitargeted kinase inhibitors, targeting both the EGF receptor and other receptors of the HER (or ErbB) family, such as afatinib, lapatinib, and dacomitinib.

Given the fundamental role of EGFR in homeostasis of the epidermal and epithelial cells, the therapeutic inhibition of this receptor is associated with cutaneous or mucosal toxicities in the majority of anti-EGFR-treated patients [12, 14, 23, 125, 126].

Mucositis

Incidence

EGFR/HER1 tyrosine kinase inhibitors (Table 1)

Oral adverse events induced by tyrosine kinase inhibitors targeting EGFR are less frequently reported than skin toxicities [125, 127].

The incidence of mucositis induced by erlotinib in monotherapy varies between 8 and 20% [58, 65, 67, 68] (Table 2). Similar, although slightly higher, incidence values of 17 to 24% have been reported for gefitinib [54, 63, 64, 128] (Table 2). Moreover, the *incidence rate of high-grade* (≥ 3) mucositis has never been reported to exceed 1%, neither with erlotinib nor gefitinib. As a consequence, few treated patients require dose modifications as a result of oral mucositis [68, 128].

Pan-HER tyrosine kinase inhibitors (Table 1)

Conversely, with the new generation of pan-HER tyrosine kinase inhibitors, mucositis appears to be one of the main toxicities, after paronychia, diarrhea, and papulopustular rash [55, 59, 128, 129]. The incidence of *all-grade mucositis* induced by afatinib appears to be significantly higher than that of erlotinib- or gefitinib-induced mucositis [128] and ranges from 25 to 72.1% [54–60] (Table 2).

Dacomitinib, another irreversible pan-HER tyrosine kinase inhibitor [69], also induces mucositis more frequently

Table 5 Main interventions for management of oral toxicities

Toxicities	Interventions
Mucositis/Stomatitis/aphthoid lesions	Basic oral care ^a , steroids (topical, intralesional, oral), morphine mouthwash, systemic analgesics, low level laser therapy (LLLT) Dose reduction, interruption, or discontinuation to be discussed with the oncologist Offset of radiotherapy sessions to be discussed with the radiotherapist
Hyperkeratotic lesions	No specific local interventions; monthly examination and biopsy in case of irregular lesions
Pigmentation/mucosal dyschromia	No specific local interventions; monthly examination and biopsy in case of irregular lesions
Geographic tongue	No specific local interventions; avoidance of irritating foods; steroid mouth rinse three times per day for a few days or tacrolimus cream (0.1%) for painful lesions
Dysgeusia	Dietary recommendations ^b Dose reduction or changes to medication to be discussed with the oncologist
Lichenoid lesions	Topical steroids (clobetasol propionate) for painful lesions; regular oral examinations with long-term surveillance Dose reduction, interruption, or discontinuation to be discussed with the oncologist
Telangiectasia/mucosal hemorrhage	Basic oral care ^a Dose reduction, interruption, or discontinuation to be discussed with the oncologist
Xerostomia	Basic oral care ^a ; dietary recommendations ^b Hydration, sugar-free gum or candy stimulants; sialogogues: pilocarpine, sulfarlem, civemiline, bethanechol; artificial saliva substitutes (palliation); thermal water.
Dysesthesia	Basic oral care ^a ; avoidance of irritating foods and symptomatic relief through topical analgesics. Medications for neuropathy (clonazepam, gabapentin, antidepressants).
Osteonecrosis of the jaw	Basic oral care ^a Depending on the stage: antibacterial mouthwash, pain medication, antibiotics, pentoxifylline, vitamin E, LLLT. Conservative measures or surgical debridement can be successful at early stages. Extensive resection is solely indicated in cases of extended necrosis.

^a Basic oral care: see Table 3

^b Dietary recommendations: frequent drinks between meals, maintaining good oral hygiene, chewing slowly, diversifying and favoring foods for which flavor is not too distorted, and further enhancing the flavor of food using seasonings and flavorings, consuming cold foods, and avoiding overly fragrant foods

than erlotinib or gefitinib [65] and is associated with an all-grade incidence of about 40%, similar to that of afatinib [69, 70] (Table 2). In addition, high-grade (≥ 3) mucositis induced by afatinib and dacomitinib may occur in 3 to 8.7% of treated patients [54–59, 65, 69, 70] (Table 2), which may lead to more frequent dose reductions or discontinuation of the treatment.

Monoclonal antibodies targeting EGFR (Table 1)

Mucositis appears to occur less frequently with cetuximab or panitumumab monotherapy than with tyrosine kinase inhibitors [30]. These monoclonal antibodies, however, are seldom used as a monotherapy and are usually combined with chemotherapeutic regimens and/or radiation therapy. In one comparative phase III study, the incidence of all-grade mucositis was 7% in patients treated with cetuximab and 5% in

those treated with panitumumab (<1% of grade 3 in both groups) [72] (Table 2). High-grade (≥ 3) mucositis was also noted in less than 1% of patients in an earlier study of patients treated with cetuximab monotherapy [71] (Table 2).

Cetuximab or panitumumab in combination with chemotherapy

Cetuximab and panitumumab are most often used in association with chemotherapy (fluorouracil, cisplatin, folfox, or folfiri chemotherapeutic regimens), particularly when being used for the treatment of advanced colorectal and head and neck cancers. Cetuximab and panitumumab when combined with chemotherapy both significantly increase the risk of developing *mucositis of any grade* compared to chemotherapy alone [77–79, 81, 82, 130, 131] (Table 2), with a relative risk of high-grade (≥ 3)

mucositis ranging from 2.69 [131] to 3.44 [130].

Cetuximab in association with head and neck radiation therapy

The incidence of high-grade (≥ 3) mucositis is high when cetuximab is combined with radiotherapy (about 60%) [73, 75, 132]. The main pivotal studies [73, 75, 132] (Table 2), however, indicate that the addition of cetuximab to radiotherapy does not have a significant impact on the incidence of high-grade (≥ 3) mucositis *in comparison to radiotherapy alone* [73–75] (Table 2). More recently, Bonner et al. reported that, regardless of p16 status, the addition of cetuximab to cervical radiotherapy did not impact the incidence, time to onset, severity, or duration of mucositis [132] (Table 2).

However, our experience and that of other authors [133] indicates that a higher incidence of severe mucositis is commonly observed with this therapeutic combination. The same tendency is observed when combining cetuximab with head and neck radio-chemotherapy, versus head and neck radio-chemotherapy alone [76] (Table 2). Finally, the incidence of high-grade (≥ 3) mucositis also seems to be higher when cetuximab is used in combination with radiotherapy than when chemotherapy is used in combination with radiotherapy in head and neck cancer [74] (Table 2).

Clinical presentation In most cases, HER inhibitor-induced mucositis in monotherapy corresponds to a moderate erythema with limited and superficial ulcers (Fig. 3a–c), occurring

shortly after treatment introduction [21, 125, 133]. This form of mucositis sometimes takes on the appearance of aphthous-like lesions, although these lesions are less typical than those described above with mTOR inhibitors. All areas of the nonkeratinized oral mucosa may be involved. Lip lesions are quite common, including erythema, erosions, cracks [129], and angular cheilitis [134]. Deeper mucosal ulcerations are occasionally noted and more common when used in combination with cytotoxic therapies. Associated symptoms may range from mild tenderness to pain and difficulties with food intake [125, 134].

Head and neck radiotherapy alone is associated with mucosal lesions strictly confined onto the irradiation fields. These lesions involve both keratinized (Fig. 3d) and nonkeratinized mucosa. The addition of cetuximab to cervical radiotherapy for locally advanced squamous cell carcinoma is also associated with severe lesions involving both nonkeratinized and keratinized areas. Paradoxically, anterior and labial mucosal involvement (Fig. 3e) is more common, even though these locations generally receive a lower total dose of irradiation [135]. These lesions are frequently multiple and polycyclic and often associated with significant functional impairment. Interestingly, mucosal pain may present with limited mucosal change. Similarly, the association of monoclonal antibodies targeting EGFR with chemotherapy is associated with more severe mucosal involvement (Fig. 3f).

Management As for mIAS, prevention of EGFR inhibitor-associated mucositis relies on maintaining good oral hygiene resulting from basic oral care interventions (Table 3) and prior elimination of outbreaks and sources of local trauma [106, 125]. Treatment guidelines were initially based on the



Fig. 3 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 (anti EGFR). 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

MASCC guidelines for the management of cytotoxic chemotherapy- and radiotherapy-induced mucositis [107, 125]. The latest ESMO clinical practice guidelines [33] suggest, as for mIAS, using steroids (topical, intralesional or systemic) as the first-line treatment for mucositis induced by anti-EGFR therapy. Like mIAS, the use of low-level laser therapy [113] and 0.2% morphine mouthwash or doxepin rinse may improve control of symptoms and pain particularly patients with grade ≥ 3 mucositis, treated with cetuximab combined with chemotherapy and/or head and neck radiotherapy [33].

Dose adjustment—offset of radiotherapy session

In general, no dose adjustment is needed for EGFR tyrosine kinase inhibitor-associated grade 1 or 2 mucositis. For patients with grade 3 mucositis, temporary discontinuation of treatment may be necessary. The EGFR tyrosine kinase inhibitor treatment can resume at half the initial dose once mucositis has improved to grade 2, and then be increased as long as there is no worsening of symptoms [129]. Cessation of cetuximab therapy is recommended for patients with grade ≥ 3 mucositis associated with the combined use of cetuximab and head and neck radiotherapy [136]. Generally, the radiation dose or schedule is not compromised by such events [136].

Other oral toxicities

Dysgeusia and xerostomia are mainly reported with new generation HER tyrosine kinase inhibitors. Dysgeusia has been described in 6 to 15% of patients treated with dacomitinib and afatinib [55, 69, 70] (Table 2). In addition, 8 to 14% of patients treated with dacomitinib have been reported to develop xerostomia [69, 70] (Table 2).

Angiogenesis inhibitors (Table 1)

This class of targeted therapies is characterized by its inhibitory effect on tumor neoangiogenesis. It includes *monoclonal antibodies* that directly inhibit vascular endothelial growth factor (VEGF) (bevacizumab, ramucirumab) and *tyrosine kinase inhibitors* that target angiogenic receptors (vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR)), and other signaling pathways (sunitinib, sorafenib, pazopanib, axitinib, cabozantinib).

The main oral toxicities reported in pivotal studies include nonspecific stomatitis, dysgeusia, and xerostomia, which may occur alone or in association. Approximately one quarter of patients treated with multitargeted antiangiogenic kinase inhibitors develop an oral adverse event within the first 2 months of starting therapy [25]. Sunitinib and sorafenib are the two drugs that are most frequently associated with oral adverse events

[25], but oral toxicities have also been frequently reported with cabozantinib, a new multitargeted kinase inhibitor.

Dose adjustment (<10% of treated patients) [25, 137] and treatment discontinuation (about 1% of treated patients) [25, 137] due to oral toxicities are rarely needed.

In contrast, bevacizumab and ramucirumab-induced stomatitis is uncommon.

Stomatitis

Incidence In the main pivotal studies [7, 45, 48, 51, 83–90, 138] (Table 2), the incidence of all-grade stomatitis induced by angiogenesis inhibitors ranges from 7 to 29%, depending on the drug used. Comparative studies underlines that the incidence of all-grade angiogenesis inhibitor-associated stomatitis is lower than that of all-grade mIAS [7, 28, 45, 48, 51] (Table 2).

With sunitinib, stomatitis appears to be one of the most frequent adverse events after diarrhea, fatigue, and nausea [89, 139]. Main pivotal studies have reported that the incidence of any grade stomatitis ranges from 16.5 to 27% with sunitinib [45, 85–89] (Table 2). The incidence of any grade stomatitis associated with sunitinib appears to be higher than that of stomatitis associated with other multitargeted antiangiogenic kinase inhibitors, in particular sorafenib—for which the incidence of all-grade stomatitis is reported to range from 7 to 19% [51, 83–85] (Table 2).

On the other hand, the incidence of all-grade stomatitis with cabozantinib is similar to that reported with sunitinib, having been reported in 22 to 29% of treated patients [48, 90] (Table 2).

The incidence of high-grade (≥ 3) stomatitis has never been reported to exceed 4% with any multitargeted angiogenesis inhibitor [7, 45, 48, 83, 84, 86–89, 139] (Table 2).

Clinical presentation The broad term “stomatitis” has been used to describe mucosal injuries or toxicities, such as mucosal sensitivity, taste alterations, dry mouth, and necrosis of jaw associated with angiogenesis inhibitors [26]. However, the stomatitis induced by this therapeutic family is more of a diffuse mucosal hypersensitivity/dysesthesia [25], in some cases associated with moderate erythema [28] or painful inflammation of the oral mucosa (including burning mouth, discomfort induced by hot or spicy foods) [25]. Such symptoms appear quite rapidly in the first weeks of treatment [28, 140] and gradually disappear [21, 25]. In some cases, well-limited ulcerations of the nonkeratinized mucosa were also noted (Fig. 4). Unusually, the stomatitis may manifest as linear lingual ulcers of the nonkeratinized mucosa, particularly with sunitinib or sorafenib [21, 137].

Management Management of angiogenesis inhibitor-induced stomatitis currently relies on the same prophylactic and



Fig. 4 Well-limited ulceration of the nonkeratinized mucosa with sunitinib (multikinase angiogenesis inhibitor)

curative interventions as described for mIAS or stomatitis induced by EGFR inhibitors (Table 5). Mucosal sensitivity may require dietary modifications, such as avoiding irritating foods and tobacco [25].

Dysgeusia

Dysgeusia appears to be the second most frequent oral adverse event [25] induced by multitargeted antiangiogenic kinase inhibitors. Taste changes are most often reported with sunitinib and cabozantinib, for which the incidence of all-grade dysgeusia ranges from 20 to 49% [45, 86–89] and 24 to 34% of treated patients [48, 90], respectively (Table 2). High-grade dysgeusia is clearly uncommon, occurring in below 1% of treated patients [7, 45, 48, 83, 84, 86–89, 138] (Table 2).

Comparative studies indicate that dysgeusia is more common in patients treated with angiogenesis inhibitors than in those treated with mTOR inhibitors [45, 48] (Table 2).

Benign migratory glossitis

Patients treated with angiogenesis inhibitors may also develop benign migratory glossitis or geographic tongue. This adverse event was initially described with bevacizumab [141], and we have reported the occurrence of similar lesions with sorafenib and sunitinib [142]. These lesions gradually regress after treatment discontinuation (Fig. 5a, b). We have also observed geographic tongue with pazopanib (Fig. 6) and axitinib. The impact of these events remains unclear [143]. Induced benign migratory glossitis can be moderately painful but usually does not require any treatment modification or specific local treatment [21] (Table 5).

Other oral toxicities

Xerostomia Depending on the series, 4 to 12% of patients treated with multitargeted antiangiogenic tyrosine kinase inhibitors develop grade 1 to 2 xerostomia [7, 45, 83, 87] (Table 2).

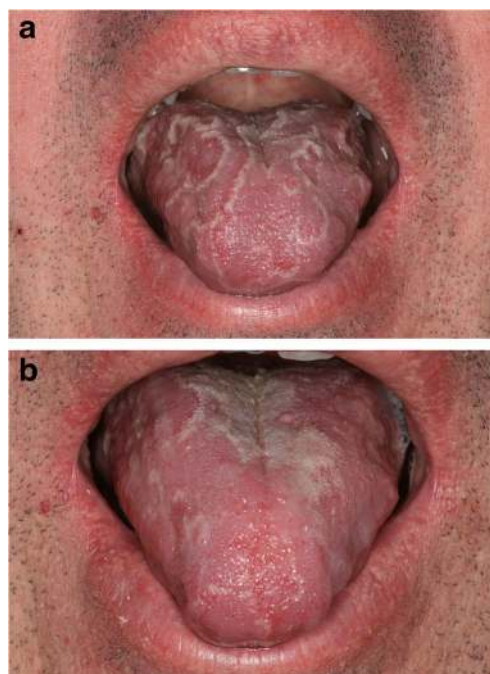


Fig. 5 **a** Geographic tongue induced by bevacizumab (12 months after treatment introduction). **b** Significant improvement after bevacizumab discontinuation

Bleeding and delayed healing The inhibition of VEGF or its receptors by angiogenesis inhibitors (sorafenib, sunitinib, vandetanib, axitinib, bevacizumab, etc.) induces significant changes in vascular permeability and can promote mucocutaneous bleeding [144]. Between 20 and 40% of patients treated with bevacizumab reported moderate bleeding, mostly of the nasal mucosa [12, 138]. Delayed wound healing can also occur with antiangiogenic agents (sunitinib, bevacizumab); these adverse events should be considered before oral surgery.

Medication related osteonecrosis of the jaw (MRONJ) In oncology, MRONJ is known to occur with antiresorptive agents (bisphosphonates—zoledronic acid, pamidronate, and inhibitor of receptor activator of nuclear factor κ B ligand (RANKL), denosumab) and occurs in 3 to 10% of treated patients depending on the indication (osseous metastases or myeloma) [145]. The association of these drugs with



Fig. 6 Geographic tongue with pazopanib

antiangiogenic targeted therapies (sunitinib, bevacizumab) increases the risk to develop MRONJ (Fig. 7) [145, 146] more often after oral surgery [147–149]. Few data of MRONJ are also reported with sorafenib, cabozantinib, alfibcept, and mTOR inhibitor monotherapy [124, 147]. MRONJ remains an underdiagnosed adverse event because of inadequate or restrictive diagnostic criteria [147] and because early lesions may have few symptoms. Strategies for management rely on expert opinion [150]. Depending on the stage, antibacterial mouthwashes, pain medication, and antibiotics may be recommended. Conservative measures or surgical debridement can be successful during the early stages. Extensive resection of necrotic bone is indicated solely in cases of extended necrosis [148] (Table 5).

Recommendations for oral surgery

Before introduction of antiangiogenic treatment, patients should undergo oral screening (including a comprehensive oral exam with radiographs), be informed about maintaining oral hygiene and should receive all necessary dental treatments [151]. The dentist should contact the oncologist before any oral surgery is carried out on patients treated with angiogenesis inhibitors. Dental/periodontal management should be limited to unavoidable surgical interventions during the course of antiangiogenic treatment. The therapeutic window should always be evaluated during antiangiogenic targeted therapy. Monoclonal antibodies and tyrosine kinase inhibitors might be stopped at least 2 and 1 week, respectively, before oral surgery. The treatment can be reinitiated after mucosal healing. Dental screening and preoperative dental treatments remain key management approaches for prevention of MRONJ and delayed healing [149–151].

Mucosal yellow discoloration Although quite exceptional, yellow diffuse staining of the oral mucosa (Fig. 8) can be observed with sunitinib. This induced coloration occurs



Fig. 7 Osteonecrosis of the jaw induced by the association of bevacizumab and denosumab



Fig. 8 Yellow pigmentation of the soft palate with sunitinib

frequently in the skin and appears to be directly related to the color of the drug itself. It is associated with characteristic colored urine [152]. No specific management is required.

Hyperkeratotic lesions Finally, we have observed sporadic cases of *oral hyperkeratotic lesions* in patients treated with the pan-RAF inhibitor, *sorafenib*. In addition, this multitargeted antiangiogenic tyrosine kinase inhibitor has recently been reported to induce development of oral squamous cell carcinoma [144].

BCR-ABL inhibitor: imatinib (Table 1)

Imatinib is a first-generation BCR-ABL inhibitor targeting c-KIT and the PDGFR. It is frequently associated with oral toxicities which are now well-characterized.

Lichenoid reactions

Development of oral lichenoid reactions [153–155] (Fig. 9) is the most frequent oral adverse event of imatinib. It can occur in isolation or in association with lichenoid nail or skin lesions [155–158]. This toxicity has only rarely been reported in the literature [155]. Our clinical experience indicates that these mucosal lesions are relatively frequent but probably underestimated due to their typically asymptomatic nature. The lesions are polymorphic, combining more or less characteristic reticular/striated lesions with symptomatic ulcerative,



Fig. 9 Lichenoid lesion of the border of the tongue induced by imatinib

erosive, or atrophic lesions. They are preferentially localized on the buccal or lingual mucosa [153, 157–159].

These lesions gradually develop after a few months of treatment [154, 155, 159]. Their discovery is often fortuitous, and thus, systematic oral examination of the oral cavity is required in patients treated with imatinib.

Given the potential risk of malignant transformation of lichenoid reactions, regular monitoring of these lesions is recommended [160]; however, it is not known if the lichenoid changes seen with imatinib may have malignant risk. Symptomatic forms are generally treated with high potency topical corticosteroid therapy, and imatinib treatment can be continued in almost all cases.

To our knowledge, there have been no reports of similar lesions with new generation BCR-ABL inhibitors, such as dasatinib, nilotinib, ponatinib, or bosutinib.

Pigmentary changes

More unusually, a fairly typical “blue-gray” asymptomatic hyperpigmentation of the hard palate may be noted in patients treated with imatinib (Fig. 10) [161–166]. Pigmentation in other locations has been described in anecdotal reports [167]. Discovery of the oral hyperpigmentation is usually fortuitous, and the time of onset is unknown. The pathophysiological mechanism seems similar to that of hyperpigmentation due to antimalarials (drug metabolite deposition in the mucosa and complex formation with hemosiderin or melanin) [18]. Direct inhibition of c-kit (which is physiologically expressed in the oral mucosa) by imatinib has been also implicated in this mechanism by some authors [161, 162].

To your knowledge, this reaction has not been described with new generation BCR-ABL inhibitors.

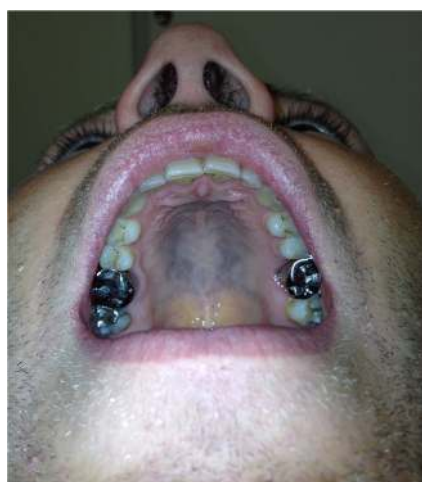


Fig. 10 Typical blue/gray hyperpigmentation of the hard palate with imatinib

Immune checkpoint inhibitors (Table 1)

Use of cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death-1 (PD1) and its ligand (PDL-1) inhibitors, either as single agents or in combination, results in a distinct spectrum of toxicities, mostly related to activation of the immune system [168]. Among the multiple IRae reported with these drugs, dermatologic toxicities represent the most frequent adverse events [19, 20, 168].

Use of both PD-L1 and PD-1 (nivolumab, pembrolizumab) inhibitors has been found to be associated with nonspecific stomatitis or oral mucosal inflammation in sporadic cases [35, 36, 47, 169, 170], but no grade ≥ 3 adverse events have been reported. Recently, more characteristic oral lesions with PD-1 or PD-L1 inhibitors have been described [20, 38, 171, 172].

Xerostomia

Xerostomia (generally grade 1–2) has been reported in about 6% of patients treated with nivolumab [6, 34] (Table 2) for melanoma (Fig. 11a) and in between about 4 and 7.2% of pembrolizumab-treated patients [8] (Table 2). In addition, we have observed severe grade 3 xerostomia in exceptional cases (Fig. 11b). The xerostomia shows clinical features of a



Fig. 11 **a** Xerostomia with associated black hairy tongue induced by anti-PD-1 (nivolumab). **b** Severe Sjögren-like syndrome (nivolumab). **c** Lymphohistiocytic infiltrate surrounding salivary glands with positive PD-1 immunostaining (Sjögren-like syndrome, nivolumab) (original magnification $\times 10$)

Gougerot-Sjögren-like syndrome, with cytotoxic T-lymphocyte infiltration of accessory salivary glands (Fig. 11c). However, anti SSA and anti SSB antibodies screening is generally negative.

Dysgeusia

Moderate dysgeusia (grade 1 or 2) has been noted in less than 3% of PD-1 and PD-L1-treated patients [8, 9, 35, 47] (Table 2). Xerostomia and dysgeusia appear less commonly with the anti-CTLA-4 agent, *ipilimumab* [8] (Table 2).

Lichenoid reactions

Schaberg et al. [172] reported one case of lichenoid lesion with PDL-1 inhibitor therapy and Hofmann et al. [171] reported one case of oral lichen planus with pembrolizumab. We have also observed several cases of mucosal lesions, which were clinically and histologically consistent with oral lichenoid lesions, developing as a result of treatment with PD-1 and PD-L1 [20]. These lesions generally occurred several months after treatment induction. Histopathology and immunophenotypic analysis of the lichenoid lesions associated with anti-PD1 and anti-PDL-1 therapy seem to reveal greater histiocytic infiltrate than that observed in similar nondrug-related lichenoid reactions (i.e., lichen planus, lichen planus-like keratoses) [172].

Lesions may appear as whitish papules (confluent in places), in reticular or linear streaks, and are sometimes associated with erythema. The dorsal and lateral sides of the tongue, lips, gingiva, hard palate, or buccal mucosae (Fig. 12a–c) can be involved. Patients may report pain or soreness but the lesions can also be asymptomatic. The perianal area or vulva can also be affected [172]. Topical corticosteroids should be considered if lesions are painful (Table 5).

BRAF inhibitors (Table 1)

Vemurafenib and dabrafenib are two FDA-approved selective BRAF inhibitors for the treatment of mutated BRAF^{V600} metastatic melanoma. When used in monotherapy, dermatologic adverse events, particularly hyperkeratotic lesions, represent the most common toxicities of these targeted therapies. A broad spectrum of induced hyperkeratotic lesions has been reported, including verrucous papillomas, keratosis pilaris-like rashes, and malignant epithelial tumors, such as keratoacanthoma or squamous cell carcinoma [173–175]. Hyperkeratotic lesions are probably induced by proliferation of wild-type BRAF keratinocytes, secondary to the paradoxical

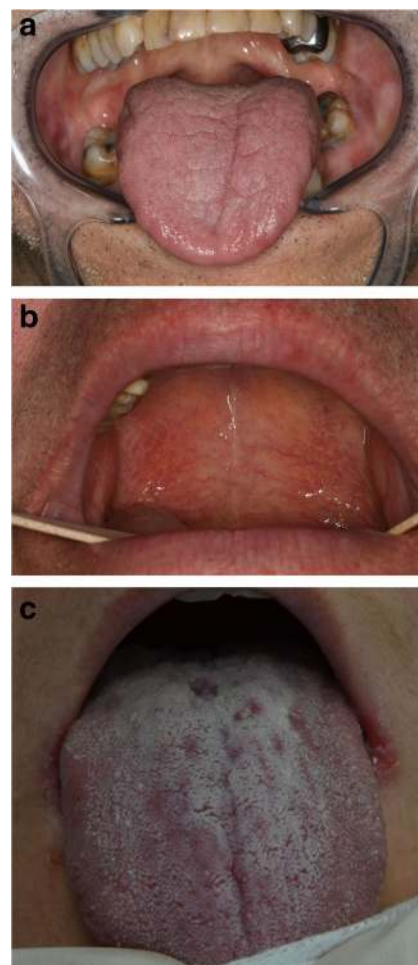


Fig. 12 a Lichenoid lesion of the dorsum of the tongue with nivolumab (anti-PDL-1). b Lichenoid lesion of the soft palate induced by nivolumab. c Lichenoid reaction of the dorsum of the tongue

activation of the intracellular mitogen-activated protein (MAP) kinase pathway [174, 176, 177].

The oral toxicity of BRAF inhibitors has only been described recently [31, 178, 179]. This toxicity is characterized by the sometimes rapid development of asymptomatic hyperkeratotic multifocal mucosal lesions on both the keratinized and nonkeratinized mucosa, predominantly located on the linea alba (Fig. 13a), the marginal gingiva, the hard palate (Fig. 13b), the lateral borders of the tongue (Fig. 13c), or the labial mucosa. All lesions exhibit similar features and sometimes have a verrucous or papillomatous appearance [31]. We have recently reported the first case of squamous cell carcinoma (SCC) on vemurafenib-induced hyperkeratotic lesions of the labial mucosa [31]. Due to the usually asymptomatic nature of these lesions and the lack of systematic oral examinations in treated patients, the incidence of induced hyperkeratotic lesions is not known.

As the incidence of BRAF inhibitor-induced cutaneous SCC is clearly higher than that of oral SCC, oral examinations



Fig. 13 **a** Hyperkeratotic lesions of the linea alba induced by a BRAF inhibitor (anti-BRAF vemurafenib). **b** Hyperkeratotic lesions of the marginal gingiva and hard palate (anti-BRAF dabrafenib). **c** Hyperkeratotic lesion involving the dorsum of the tongue (anti-BRAF vemurafenib)

should be carried out on a regular basis at all follow up visits and oral hyperkeratotic lesions should be treated with caution and biopsy is recommended in case of doubt. Furthermore, anecdotal observations of vemurafenib-induced *inflammatory gingival hyperplasia* have been recently reported [178, 179].

BRAF inhibitors are now mostly used in combination with MEK inhibitors (vemurafenib with cobimetinib, and dabrafenib with trametinib). By blocking the downstream MAP kinase pathway, MEK inhibitors significantly restrict the development of secondary hyperkeratotic lesions [13, 180]. Therefore, it is anticipated that these mucosal lesions will be less reported in the near future.

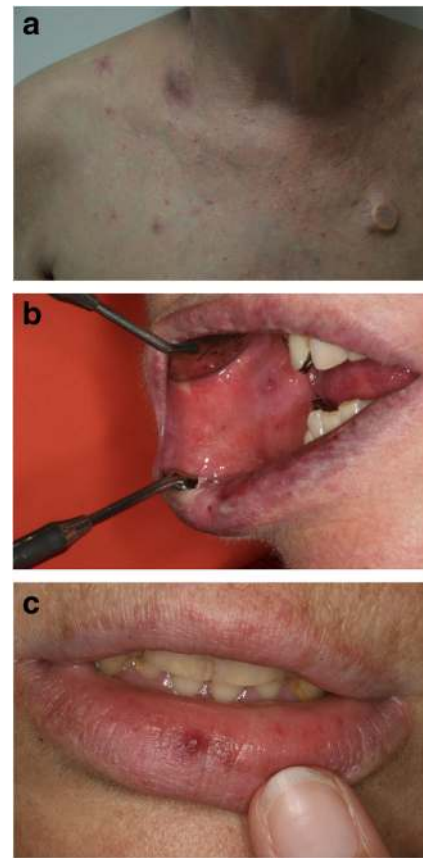


Fig. 14 **a** Cutaneous telangiectasias induced by the glycoconjugate monoclonal antibody TDM1. **b, c** Mucosal telangiectasias of the buccal and labial mucosa with TDM1

Other targeted therapies with oral toxicities

ALK inhibitors (Table 1)

Crizotinib is an oral small-molecule tyrosine kinase inhibitor targeting the anaplastic lymphoma kinase (ALK), MET, and ROS1 tyrosine kinases. The main reported oral toxicity induced by this therapy is moderate dysgeusia (grade 1 or 2) (Table 2), which affects 11 to 26% of treated patients [95–98] (Table 2). Moreover, all-grade stomatitis occurs in less than 15% of treated patients, with no reports of any high-grade ≥ 3 cases [98] (Table 2).

Hedgehog pathway inhibitors (Table 1)

Vismodegib is a first-in-class, oral, selective Hedgehog pathway inhibitor, FDA-approved for the treatment of locally-advanced or metastatic basal cell carcinomas. One of the most frequent reported toxicities is grade 1/2 dysgeusia, for which the incidence ranges from 51 to 84% depending on the series [13, 99, 100, 181] (Table 2). High-grade ≥ 3 dysgeusia has been reported in about 2% of treated patients (Basset-Seguín et al. 100). Furthermore, vismodegib also induces *ageusia*

[100] (Table 2) in 22% of treated patients, with an incidence of 2% for high-grade ≥ 3 toxicity. Dysgeusia is the second most common vismodegib-induced adverse event after muscle spasms [100, 181]. It can lead to treatment interruption (6% of patients) and generally occurs within the first 6 months of therapy [181].

Management (Table 5) Due to the high incidence of vismodegib-induced taste changes, informing and educating patients about this adverse event is required at initiation of vismodegib therapy. Early nutritional screening and routine nutritional counseling from a dietician should be considered in order to prevent significant weight loss. Investigation of the nature and severity of taste changes require study in order that approaches to management can be developed [182].

Trastuzumab-emtansine (T-DM-1) (Table 1)

We have recently described the development of cutaneous (Fig. 14a) and mucosal telangiectasias (Fig. 14b, c), mimicking Osler-Weber-Rendu syndrome [183, 184], with the antibody-drug conjugate ado-trastuzumab emtansine (T-DM-1, FDA-approved for the treatment of HER2+ metastatic breast cancer).

These oral mucosal lesions can be observed on the whole mucosa (palate, tongue, lips, and jugal mucosa). They blanch during diascopy and appear dome-shaped with surrounding small radiating dilated vessels. On the skin, they appear as spider telangiectasias.

Epistaxis, digestive, or gynecological bleeding occurs in about 30% of T-DM-1-treated patients, without the systematic presence of associated thrombocytopenia. These bleeding events may, at least in part, be linked to the mucosal vascular malformations [184]. Given the potential risk of hemorrhage, screening for mucosal telangiectasia is recommended (Table 5).

Conclusion

Oral toxicities of targeted therapies and immune checkpoint inhibitors develop less frequently than the more common and prominent cutaneous toxicities. However, the oral changes may be underreported using general toxicity scales and relying upon patient report. These oral adverse events also appear to be less symptomatic than chemotherapy-induced mucositis but may require dose adjustments. Oral lesions can be clinically quite specific, and systematic examination of the oral mucosa is recommended as part of the monitoring regimen of patients treated with these drugs. Physicians should be aware of these induced mucosal changes. Early recognition and

appropriate management are necessary in order to limit dose modifications and preserve patients' quality of life. Study of approach to management of oral toxicities is required to improve guidance for improved patient care.

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