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Dynamic Concept of Management of Stomatitis Induced by Targeted Therapies

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Abstract

The development of targeted therapies represents a major advance in the cancer treatment. Although they are better tolerated than chemotherapies because they are more specific to the cancer cell, they are not necessarily devoid of undesirable effects, particularly dermatological ones. In fact, the dermatological manifestations of targeted therapies are very common. Cutaneous effects are now well known but the discovery of side effects at the level of the oral cavity is more recent because it has a lower incidence than the effects skin, and represent a real burden for patients. Hence the need for a good understanding on the part of the dentist and close monitoring thereof.

Keywords: public health; cancer; epidemiological reports

Introduction

Cancer is a major public health concern, with the latest global epidemiological reports from 2018 indicating that more than 18,078,957 cancers were diagnosed per day [1]. To deal with this pathology responsible for more than 9555027 deaths per day in 2018 worldwide, the search for anti-cancer therapies has become a paramount issue. Treatments such as chemotherapy, radiotherapy or surgery are nowadays not very specific to the cancer cell and are the cause of serious adverse effects, sometimes responsible for therapeutic failure. Thanks to advances in molecular biology, the concept of targeted therapy was born in 1990. These treatments target one or more of the characteristics acquired by the cancer cell and thus make it possible to act more specifically against each cancer. Adverse effects are generally fewer in number and of lower intensity, and as regards the oral cavity, they have not yet been well studied [2]. The development of targeted therapies represents a major advance in cancer management. Although they are better tolerated than conventional chemotherapies because they are more specific to the cancer cell, they are not, however, devoid of undesirable effects, in particular dermatological effects. Indeed, the dermatological manifestations of targeted therapies are very frequent. These skin effects are now well known, but the discovery of side effects at the level of the oral cavity is more recent because it has a lower incidence than the skin effects, and represents a real burden for the patients. Hence the need for a good understanding on the part of the dentist and for close follow-up. Targeted therapy treatment is becoming more and more frequent, since its administration does not require long-term hospitalization; the city dentist may therefore have to meet patients during treatment, forcing him to broaden his skills in a new field of action. This work was carried out with the aim of improving the daily support and care of patients on targeted therapies [3].

Indications and Mechanisms of Action of Targeted Therapies

Targeted therapies are a group of treatments that are part of a "precision" therapeutic strategy. By specifically targeting certain proteins, they block mechanisms that are indispensable to the proliferation of cancer cells and/or, more generally, to the development of the tumour. As research advances, scientists are increasingly discovering molecular mechanisms within cancer cells or cells in the tumour environment that contribute to the tumour's progression and/or spread to the body. These findings make it possible to develop treatments specifically to block a tumour process or, on the contrary, to activate a mechanism participating in the control of the tumour [4]. The first targeted therapies came in the 2000s in the treatment of some blood and then breast cancers. There are now about 50 of them,

indicated for the treatment of nearly 20 cancers. Many target proteins that are mutated in cancer cells and whose dysfunction is partly responsible for the tumour's development (Table 1).

Table 1: Summary Table of The Different Molecules.

Target	Class	Molecules (Name Commercial)	Indications
EGF/EGFR	Ca Monoclonal	Cetuximab	Metastatic colorectal cancer with wild-type RAS gene Head and neck squamous cell carcinoma
	You's	Panitunumab	Metastatic colorectal cancer without RAS mutation
		Pertuzumab	Breast cancer metastatic or recurrent
		Gefitinib	NSCLC with EGFR mutations
		Erlotinib	Metastatic NSCLC therapy
		Lapatinib	Breast cancer with HER2 overexpression
VEGF	Ca Monoclonal	Bevacizumab	NSCLC mCRC Breast cancer metastatic CRm
	TKi's	Sorafenib	Advanced hepato-cellular carcinoma or metastatic
		Sunitinib	Kidney cancer clear cell Cancer metastatic renal
		Axitinib	Advanced kidney cancer
		Pazopanib	Advanced kidney cancer
mTOR		Temsirolimus	Mantle cell lymphoma
		Everolimus	Receptor breast cancer hormone positive
B-RAF	You's	Sorafenib	Progressive thyroid carcinoma
		Vemurafenib	Unresectable melanoma or BRAF V600 mutated metastatic
		Dabrafenib	Same indications as Vemurafenib
MEK	You's	Trametinib	Unresectable melanoma or BRAF V600 carrier metastatic
		Cobimetinib	Unresectable melanoma or BRAF V600 carrier metastatic
RANK-L	Ca Monoclonal	Denosumab	Osteoporosis, bone metastases

Oral Manifestations of Targeted Therapies

Mucositis is inflammation of the oropharyngeal mucosa involving the epithelium and underlying connective tissue; causing ulcers. When the disease is transmitted to the oral mucosa (most commonly), it is also called stomatitis. Oral mucositis can range from simple enanthema to necrosis of ulcers, and symptoms and signs range from simple discomfort to life threatening. When the patient can no longer eat properly due to severe pain. It is an undesirable effect common to several anticancer treatments such as chemotherapy, radiotherapy but also targeted therapies [5].

Oral-pharyngeal and gastrointestinal mucositis are among the common undesirable effects limiting the various anti-cancer treatments such as chemotherapy, radiotherapy but also targeted therapies. These lesions vary depending on the type of cancer treatment. The inflammatory process that causes mucositis is thought to be initiated by the production of free radicals. They have two actions: direct by direct damage to the mucosa and vessels, indirect by activation of transcription factors [1,3,5]. Some patients may be at higher risk of developing mucositis, particularly if they have some of the following risk factors: age, -oral problems or personal history of mucositis, -poor oral hygiene, -smoking, -alcoholism, -diabetes [2]. Mucositis may have a negative impact on the implementation of the anticancer treatment (reduction and/or spacing of doses, poor compliance) and therefore on the prognosis of the patient. They can cause feeding difficulties and degrade the patient's nutritional status [6]. The term mucositis should be reserved only for chemotherapy or radiotherapy treatments since mucositis induced by the targeted therapies remains confined to the oral mucosa: it will be more readily referred to as stomatitis [7]. This toxicity related to targeted therapies is recognized as one of the most common. The most commonly used classifications by health care practitioners regarding the assessment method is the WHO score that ranks the intensity of mucositis. The latter takes into account the degree of pain; erythema and the ability to feed (Table 2).

Table 2: Classification of mucositis according to the WHO.

Grade	WHO Classification
0	No Mucin
1	Erythema, Unpleasant Sensation
2	Erythema; Ulcer; Solid Feeding Possible
3	Ulcers; Liquid Feeding Only Possible
4	Unable to Feed per os, Feeding Enteral or Parenteral

Oral mucositis induced by targeted therapies is very different from chemo- or radio-induced mucositis which manifests as an ill-defined enanthema and multiple ulcerations, both of which can extend to the gastrointestinal mucosa. The targeted therapies also vary in terms of their "mucitogenic" power, very variable according to whether one considers anti-EGFR, anti-VEGF, mTOR inhibitors or tyrosine kinase inhibitors.

Stomatitis Induced by mTOR Inhibitors

(EVEROLIMUS AND TEMSIROLIMUS): Adverse effects of mTOR inhibitors have been studied, including skin rash, asthenia, anorexia, anaemia, nausea, and vomiting. And stomatitis. Stomatitis is among the most common and limiting toxicities of mTOR inhibitors. The lesions described are well-demarcated, painful aphtoid ulcers, sometimes surrounded by an erythematous halo. Suggesting aphthous or herpetic stomatitis, and causing functional discomfort that is often very significant with respect to the macroscopic appearance and the size of the lesion, generally less than 0.5 cm in diameter [8]. appear soon after the start of treatment, with a peak frequency around the fifth day, but some studies report instead a median time of 10 to 15 days between the start of treatment and the appearance of lesions [9]. Often during the first cycle. Stomatitis with an mTOR inhibitor tends to regress and then disappear gradually, often over 2 to 3 weeks without leaving scars, but it recurs in about 25% of cases, and remains localized to the non-keratinized mucosa: the lips, cheeks, soft palate, ventral and lateral surfaces of the tongue. These lesions are severe in less than 10% of cases, however the pain felt and the inability to eat are very important. Although dose-dependent, sometimes requiring temporary interruption or dose reduction in at least 10% of patients. A review of 44 studies involving more than 2,800 patients (including 345 with breast cancer) showed that stomatitis was the most common adverse event of any grade (73.4%), and the third most common of Grade 3 or 4 adverse events (20.7% of patients and 10% of all mucositis), responsible for 27% of dose reductions and 13% of patient's discontinuation due to toxicity. A meta-analysis by Rugo H.S et al. of 1455 patients treated with Everolimus for malignancy found 67% stomatitis; most stomatitis was Grade 1 or 2, and only 9% were Grade 3 or 4 [10].

Stomatitis Induced by Targeted Anti-Angiogenic Therapies

Because VEGF is an important regulator of oral mucosal hemostasis, targeted anti-angiogenic therapies will produce oral side effects. They can cause lesions similar to stomatitis induced by mTOR inhibitors, but their severity is less severe and rarely warrants discontinuation of treatment. These include both multi-target tyrosine kinase inhibitors (pazopanibe, sorafenib and sunitinib) and monoclonal antibodies (bevacizumab and aflibercept), which have been reported in different studies to be between 20% and 46% of all grade stomatitis (3% to 5% grade 3-4) for sunitinib, stomatitis is the 3rd most common adverse reaction behind hypertension and neutropenia. Although no re-adjustment of therapy is required, stomatitis of all grades was noted with an incidence of 5-38% for sorafenib and 9-10% for pazopanib [2,11].

EGFR Inhibitor-Induced Stomatitis

The main toxicity of this treatment is skin rash. In fact, the EGFR receptor plays a fundamental role in the regulation of basal keratocytes of the skin, however, this receptor is also present in the epithelial cells of the mucosa and in particular of the oropharyngeal sphere. (Gegitinib-afatinib-erlotinib...etc.) are molecules used which may be responsible for inflammatory lesions of the oral mucosa. The most common oral adverse effect is stomatitis; it affects nonkeratinized mucosa, and the rate of stomatitis involvement varies from 2 to 36% depending on the EGFR inhibitor (erlotinib; cetuximab, and gefitinib) and does not appear to be dose-dependent. The lesions encountered preferentially affect the non-keratinized mucosa (ventral and lateral face of the tongue, floor of the mouth, soft palate, jugal mucosa) [8]. These ulcers may take the form of a diffuse erythema or

symptomatic ulcers that are more or less limited. These are shallower and less severe than those seen with conventional chemotherapy. In general, lesions develop rapidly after treatment is initiated and then gradually subside. Severe disease is uncommon (1 to 3% Grade 3 with sunitinib). Therefore, dose adjustment or discontinuation of treatment is rarely necessary because the functional gene is mostly moderate. The combination of cetuximab with radiation therapy is common for the treatment of locally advanced ENT cancers [3,11].

Management of Odontology Patients Treated with Targeted Therapies and Their Side Effects

Oral rehabilitation: The elimination of infectious foci of dental origin is recommended according to the French society of oral surgery before the implementation of a targeted therapy, to prevent the subsequent occurrence of oral complications during the treatment. According to the French Agency for the Safety of Medicines and Health Products, the former French Agency for the Safety of Health Products, the extraction of infected non-restorable teeth where the prognosis is reserved is patronized in the context of targeted therapies associated with an ONJ risk. Surgical care should be done before the start of the treatment and a delay of 15 days should be respected for the healing of the mucosa ideally, it should wait for the bone healing, corresponding to 120j It is formally contraindicated to implement a treatment with denosumab if an oral lesion is not healed [12]. Management of bleeding risk This applies to patients treated with an mTOR inhibitor (everolimus, tensirolimus) or with anti-angiogenic agents (sorafenib, suntinib, pazopanib, bevacizumab) which may induce thrombocytopenia and hence dl-haemostasis disorder. Not having recommendations regarding the management of the bleeding risk induced by targeted therapies, so we will base ourselves on the recommendations concerning the patients on antithrombotic [13].

Management of the risk of infections of dental origin in case of an infection such as acute cellulitis; osteitis or aggressive periodontitis: a curative anti-biotherapy associated with a local treatment is often necessary. In contrast to the general population in the context of a treatment of chronic cellulitis, peri-implantitis, periodontal abscess and a complementary curative anti-biotherapy [5,8,10].

Topical therapy is recommended for immunocompromised patients. Choice of antibiotic depends on infection and patient.

- Mild to moderate immunosuppression: No contraindication to non- invasive care and no special precautions.
- Mild to moderate immunosuppression: For invasive procedures, either surgical or non-surgical, special precautions to be taken (antibiotic prophylaxis 1 h before the procedure and until healing for invasive care).
- Severe immunocompromise: Hospital or community care and not invasive procedures [14].

Management of Scarring Delay Targeted therapies cause delayed scarring which favors the occurrence of complications in general any surgery during treatment should be avoided as long as there are no studies explaining surgical care in patients treated with targeted therapies. According to various studies: There is a 6-8 week waiting period between surgery and the last bevacizumab injection [15].

- Implementation of the targeted therapy until complete healing of the mucosa.
- Flaps should be avoided (except partially thick flaps to provide vascularization of the underlying bone).
- Making the most hermetic sutures.
- Regular Control.

Management of the risk of osteonecrosis of the jaws: Patients taking denosumab, sunitinib, bevacizumab is most at risk of osteonecrosis of the jaws [16].

Patient Management After Targeted Therapy

Unlike bisphosphonates, denosumab does not remain incorporated into the bone matrix and has a short half-life of 28 days, a return to the physiological state of the osteoclasts and osteoblasts is observed approximately 6 months after the last injection so until this time it is recommended to apply the same precautions regarding the risk of ONJ [17,18]. The time to recovery of hematological values after discontinuation of targeted therapies is not known, but will be faster after discontinuation of toxin kinase since they have a short half-life (hours to days) than after discontinuation of monoclonal antibodies with a longer half-life (days to weeks) It is recommended in the weeks and months following discontinuation of targeted therapy to perform a blood test prior to any invasive procedure in order to verify hematological values [19,20].

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