Targeted cancer therapies
Oral health care implications

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ABSTRACT

Background. Targeted treatments have been incorporated into oncology protocols, often with
more traditional therapies, and are not totally free of adverse reactions, some of which affect the
orofacial region.

Methods. The authors searched PubMed, the Cochrane Library, and the US Food and Drug
Administration Approved Drug Products database to identify reported adverse effects of targeted
agents in the orofacial region as well as other implications in oral health care. Their principal focus
was the relatively newer category of molecularly targeted drugs which are called small molecules
(SMs).

Results. The authors identified several categories of SMs and biological agents (for example,
monoclonal antibodies) with adverse effects in the orofacial region. The oral and perioral regions
are also fields for which there are therapeutic applications for targeted therapies, particularly to treat
malignant neoplasms such as head and neck cancers.

Conclusions. SMs are the most rapidly growing group of targeted cancer treatments. Patients
receiving SMs and other targeted antineoplastic agents may require oral medicine advice and
special-care dentistry.

Practical Implications. In this narrative review, the authors focus mainly on the orofacial adverse
effects of targeted cancer therapies and outline many of the agents that are in use so the dentally
focused reader can familiarize themselves with these adverse effects and agents.

Key Words. Small molecules; biologics; adverse effects mouth.

Cancers (malignant neoplasms) are a group of diseases characterized by the uncontrollable
division of abnormal cells, which also have the potential to infiltrate normal tissues and
metastasize throughout the body.1 Traditional therapies have included surgery and radio-
therapy, but both can produce adverse effects. Chemotherapy is designed to destroy malignant cells
but also harms normal proliferating tissues mainly in bone marrow and mucocutaneous sites, again
with significant adverse effects.2 The discoveries of researchers in molecular biology and molecular
carcinogenesis studies have helped perceive and organize a long search for new drugs with specific
molecular actions to affect specific targets in the cells.3 Some of these drugs—biological
agents—target specific extracellular targets and are used mainly in the management of immune-
mediated diseases, and certain of them have applications in cancer therapy. Chemicals termed
small molecules (SMs) block intracellular molecular pathways and target various molecular hall-
marks.4 An increasing number of SMs is available (Table 1) in a growing field, in which some 90%
of the articles on targeted cancer therapeutics have been published since 2010.

TARGETED CANCER THERAPIES

- Targeted drugs are developed to attack certain targets on cancer cells, currently being achieved
mainly by altering specific cell signaling using monoclonal antibody (mAb) biological agents
and SMs.
mAbs are manufactured antibodies—large molecules designed to attack a cellular target. There are many examples, and their generic names (as opposed to the trade or brand names) all end in -mab. They must be administered by injection.

SM drugs are chemicals like most other medications, and their generic names usually end in -ib, which stands for the word inhibitor (Table 1 and Box). Unlike antibodies, SMs can penetrate into the interstices of a tumor and target intracellular signaling proteins. Their main advantages over conventional cancer therapeutic agents and mAbs include ease of production and the potential for oral administration. SMs are expensive, although the costs for monthly treatments are comparable with those for mAbs.

Various SM pathways and interplays are depicted in Figure 1. Our main focus in this article is on SMs.

SMs are divided into categories signified by the suffix of their name (Box 1). Some SMs that may interfere in more than 1 signal transduction pathway are shown in Table 2.

CLINICAL IMPLICATIONS OF MOLECULAR CARCINOGENESIS: CHOOSING TARGETED THERAPIES FOR VARIOUS COMMON CANCERS

Breast cancer
Human epidermal growth factor receptor 2 (HER2) (also known as ERBB2) is a protein found on the surface of some breast cancer tumor cells and acts as a receptor for growth factors. The treatment response to both chemotherapy and a targeted anti-HER2 therapy is affected by HER2 expression. Women whose tumors “overexpress” HER2 particularly benefit from a number of targeted drugs. A significant advancement in treatment of HER2-positive breast cancer is trastuzumab, an mAb.

The drug acts by binding to the HER2 extracellular component and neutralizes the effect of HER2 signaling, thereby stopping the proliferation and survival of HER2-expressing cancer cells.

Now many other drugs with similar targeting are available, for example, lapatinib, pertuzumab, and trastuzumab emtansine.

Colon cancer
The KRAS oncogene is mutated in 40% of colon cancers and 15% to 30% of non—small-cell lung cancers (NSCLC). It encodes a small GTPase protein and becomes active secondary to extracellular stimuli or signals (growth factors, cytokines, and hormones) in a procedure mediated by cell surface receptors.

The epidermal growth factor receptor (EGFR) is a major molecular component in colorectal cancer pathophysiology, and KRAS is a well-described effector molecule of signal transduction from ligand-bound EGFR to the nucleus.

When mutated, KRAS remains continuously active and no longer requires the activation of the EGFR. This means that cancer cells continue to proliferate, grow, and move, despite the use of drugs that inhibit EGFR.

Patients with metastatic cancer of the colon who are candidates for treatment with anti-EGFR antibodies (for example, panitumumab and cetuximab) should be tested for KRAS mutations.

Patients with a normal KRAS gene respond better to treatment with mAbs that prevent the growth and survival of cells expressing EGFR and have a better prognosis compared with patients with mutant KRAS. The newest guidelines of the National Comprehensive Cancer Network (a not-for-profit alliance of 27 of the world’s leading cancer centers) state that a normal (nonmutated) KRAS also requires analysis for the B-Raf protein (BRAF) gene (another downstream effector of EGFR), because resistance to anti-EGFR antibodies has been reported in patients with nonmutated KRAS and was possibly linked to BRAF mutations.

Lung cancer
An interesting phenomenon that occurs in lung cancer is the fusion phenomenon of EML4-ALK genes into a unique gene structure. Actually, it is an abnormality in the DNA structure of some patients with lung cancer, in which 2 genes are moved (through various mechanisms) and welded to create a “new” gene formation. This new DNA fragment produces a functional protein, EML4-ALK, which in turn affects the homeostasis of the cell population forming cells with malignant behavior and thus lung cancer. This phenomenon is observed in a small percentage of patients who

ABBREVIATION KEY

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>BP</td>
<td>Bisphosphonates.</td>
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<td>EGFR</td>
<td>Epidermal growth factor receptor.</td>
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<td>FDA</td>
<td>Food and Drug Administration.</td>
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<td>HER2</td>
<td>Human epidermal growth factor receptor 2.</td>
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<td>HNSCC</td>
<td>Head and neck squamous cell carcinoma.</td>
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<td>mAbs</td>
<td>Monoclonal antibodies.</td>
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<td>MRONJ</td>
<td>Medication-related osteonecrosis of the jaws.</td>
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<tr>
<td>NSCLC</td>
<td>Non—small-cell lung cancer.</td>
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<td>PD-1</td>
<td>Programmed cell death 1.</td>
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<td>SM</td>
<td>Small molecule.</td>
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<td>TKI</td>
<td>Tyrosine kinase inhibitor.</td>
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<td>VEGF</td>
<td>Vascular endothelial growth factor.</td>
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