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Mouth Cancer for Clinicians Part 12: Cancer Treatment (Chemotherapy and Targeted Therapy)

Abstract: A MEDLINE search early in 2015 revealed more than 250,000 papers on head and neck cancer; over 100,000 on oral cancer; and over 60,000 on mouth cancer. Not all publications contain robust evidence. We endeavour to encapsulate the most important of the latest information and advances now employed in practice, in a form comprehensible to healthcare workers, patients and their carers. This series offers the primary care dental team in particular, an overview of the aetiopathogenesis, prevention, diagnosis and multidisciplinary care of mouth cancer, the functional and psychosocial implications, and minimization of the impact on the quality of life of patient and family.
Clinical Relevance: This article offers the dental team a brief overview of chemotherapy and targeted therapy.
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Chemotherapy alone cannot cure mouth cancer and thus traditionally has rarely been used in mouth cancer therapy except for palliation or in combination with radiotherapy, or occasionally to treat lip cancer. Some regard chemotherapy as the optimal treatment for recurrent/metastatic head and neck cancer. Chemotherapy given concurrently with radiotherapy may improve local control and has now become the standard of care in advanced disease and appears to have a survival benefit compared to radiotherapy alone but also gives greater adverse effects (toxicities) which limit its application. Systemic chemotherapy, as part of primary treatment, can be administered with radiotherapy (chemo-radiotherapy, CRT) either:

- Before (induction or neo-adjuvant chemotherapy) or
- During (concomitant chemotherapy) or
- After (adjuvant chemotherapy).

There is increasing evidence proving the benefits of chemotherapy in all these settings, but at the cost of higher treatment-related toxicity. Therefore, if the cancer is advanced (advanced stage III or stage IV), radiation treatment schedules sometimes include a chemotherapy (or a biological regimen), most commonly using cisplatin and cetuximab, respectively. Occasionally, other drugs used in chemotherapy may include fluorouracil (5-FU), carboplatin and paclitaxel.

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What is the role of chemotherapy treatment (CTX)?

Chemotherapy is the use of anti-cancer (cytotoxic) drugs to destroy cancer cells. However, these agents also damage other rapidly-dividing cells, especially in epithelia and haematopoietic tissue, and so few lack adverse effects. Drugs used include mainly intravenous cisplatin, fluorouracil (5-FU), carboplatin, gemcitabine, taxanes and methotrexate. TPF (Taxanes such as docetaxel or paclitaxel); Platinum;

Fluorouracil) is a common regimen. These agents can be given:

- Before radiotherapy or (rarely) before surgery;
- Simultaneously with radiotherapy (chemo-radiation);
- After surgery or radiotherapy (adjuvant chemotherapy);
- If the cancer has metastasized, or recurred after earlier treatment.

Induction chemotherapy

The rationale for induction chemotherapy is that drug delivery is likely to be better in untreated, well-vascularized cancers; disease may be down-staged before definitive treatment and micro-metastases may be targeted. Induction chemotherapy may reduce distant metastases, increase organ preservation and improve survival rates. Combinations (PF) of cisplatin and 5-fluorouracil every 3 weeks is the most common regimen and yields a 5% improvement in 5-year survival. Single agent cisplatin, which in the past has been shown to be as effective as multiple drug regimens, is now being challenged by the introduction of the use of taxanes.

Disadvantages might include added toxicity without improved survival and a delay of definitive radiotherapy leading to greater resistance of surviving cancer cells.

Induction chemotherapy used in the post-operative setting shows comparable toxicity but improved outcomes compared to patients receiving post-operative CRT alone.

What are the adverse effects of chemotherapy treatment (CTX)

Chemotherapy is usually given slowly intravenously over perhaps an hour or more and can lead to a range of adverse effects including the following.

Anaemia

Chemotherapy can reduce erythropoiesis and cause anaemia.

Bleeding

Chemotherapy can impede platelet production leading to bruising or bleeding, such as bleeding gingivae, epistaxis or purpura.

Fatigue

Fatigue is very common after chemotherapy, especially towards the end of treatment.

Hair

Chemotherapy drugs used to treat mouth cancer, except taxotere, rarely cause significant hair loss, although some people may notice hair thinning or temporary hair loss. Hair almost always grows back within 3–6 months after chemotherapy has finished. In the meantime, a hat, scarf or wig may be needed.

Hearing

Cisplatin may induce tinnitus, and loss of ability to hear some high-pitched sounds. Any tinnitus usually improves when treatment ends. Hearing loss tends to be more severe with higher doses and longer courses of chemotherapy, and may be permanent. Occasionally, the sense of balance may be affected.

Infections

Chemotherapy often depletes white blood cells, especially granulocytes (granulocytopenia or neutropenia), causing a liability to infections beginning about 7 days after chemotherapy and reaching a maximum 10–14 days after treatment begins. Granulocyte Colony-Stimulating Factor (G-CSF: *Filgrastim*) may be used to stimulate the proliferation and differentiation of granulocytes to minimize these effects.

Mucositis

Unlike the case with radiotherapy, chemotherapy is usually administered over a short time, so the mucosal injury tends to be acute, but affects the whole gastrointestinal tract. CTX appears to injure the mucosal barrier, with activation of the NF-kB pathway and release of cytokines, such as TNF alpha, IL-1 and IL-6. Since CTX-induced damage affects the entire alimentary tract mucosae, terms such as alimentary mucositis and mucosal barrier injury are also then appropriately used. Chemotherapy may induce mouth ulcers or mucositis (Figure 1), which usually appears within 4–7 days after initiation of treatment and peaks within 2 weeks. Mucositis typically presents as widespread erythema, ulceration, swelling and atrophy. Mucositis presents with:

- Pain;
- Erythema;
- Ulceration;
- Sometimes bleeding.

Mucositis is seen especially with CTX using:

- Cisplatin;
- Etoposide;
- Melphalan.

Mucositis is also seen with:

- Anthracyclines (bleomycin, dactinomycin, daunorubicin, doxorubicin, epirubicin, idarubicin, mitomycin, mitoxantrone);
- Antimetabolites (cytarabine, fluorouracil, floxuridine, methotrexate, thioguanine);
- Antimitotics (taxanes, eg docetaxel, paclitaxel; vinca alkaloids, eg vinblastine, vindesine).

However, it is seen less with:

- Asparaginase;
- Carmustine.

Risk factors for CTX mucositis include:

- Age;
- Body mass index;
- Co-morbidities (eg diabetes mellitus, impaired renal function);
- Female gender;
- Genetic determinants;
- Mucosal trauma;
- Poor oral health;
- Salivary function.

Many patients report oral mucositis as the most debilitating and troublesome adverse effect of chemotherapy, and that opioid analgesics do not always adequately relieve pain, but instead lead to other issues such as dry mouth and constipation. Mucositis

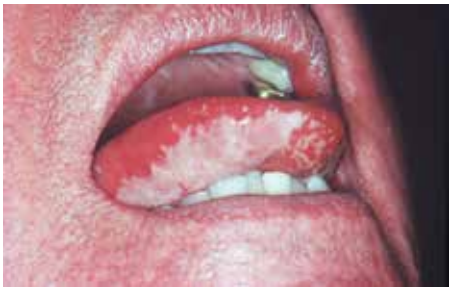

Figure 1. Mucositis.

is also associated with poorer treatment outcomes and increased financial burdens, longer hospital stays, and increased use of narcotics and nutritional support. Drinking plenty of fluids, and cleaning teeth regularly and gently with a soft toothbrush, can help.

Interventions which have some proven success with some evidence base include:

- Excellent oral care, including pre-treatment dental evaluation;
- Oral cryotherapy using ice popsicles;
- Exposure to soft laser.

Interventions which show some statistically significant evidence of a benefit also include aloe vera, amifostine, granulocyte-colony stimulating factor (G-CSF), intravenous glutamine, honey, sucralfate and Polymixin/Tobramycin/Amphotericin (PTA) antibiotic pastille/paste.

Though there is little evidence base for prevention or treatment, calcium folinate may inhibit ulcers related to 5-fluorouracil (5-FU), and some patients find that sucking ice can inhibit mucositis and is soothing. Various mouthwashes and agents may help relieve pain (Article 11). There are many other preparations empirically used, often variants on the 'magic mouthwash' (viscous lidocaine, diphenhydramine, bismuth salicylate and a corticosteroid). Emergent agents being trialled include buprenorphine transdermal patches for analgesia, agents designed to enhance resolution-supplements (eg glutamine, zinc sulphate), enzymes involved in the detoxification of reactive oxygen species (eg glutathione-S-transferase) and antimicrobial peptides. The traditional Chinese medicine Rhodiola algida has been reportedly beneficial. In addition, approaches aimed at modifying overexpression of pro-inflammatory cytokines offer promise.

Nausea or vomiting

Chemotherapy commonly causes nausea or vomiting. Some agents can cause diarrhoea. Anti-emetics may help reduce or prevent nausea or vomiting but can cause constipation.

Other oral effects

Other oral adverse effects of chemotherapy (CTX) can include:

- Bleeding – thrombocytopenia increases the liability to gingival and oral bleeding;
- Hyposalivation and infections – especially candidal, herpesviruses and human papillomaviruses;
- Pain–related to mucositis or infections, or to drugs such as vinca alkaloids and doxorubicin;
- Taste disturbances: some cytotoxic agents can be responsible, such as histone acetylase inhibitors (vorinostat; romidepsin);
- Tooth maldevelopment in young people.

Sensory

Chemotherapy involving cisplatin, 5-FU or docetaxel may induce peripheral neuropathy with hypoaesthesia or paraesthesia in the hands and feet. These sensation changes can persist or even worsen for 2–3 months after stopping chemotherapy before slowly improving, and it can take up to two years if such symptoms are to improve. Sometimes changes are permanent. Pyridoxine may be of some benefit.

What is the role of chemo-radiotherapy?

Radiotherapy may be combined with chemotherapy for use instead of surgery, especially for some oropharyngeal cancers that have spread locally or into regional lymph nodes (locally advanced cancer). Chemo-radiotherapy (CRT) improves the rates of organ conservation and loco-regional control rates and is associated with a 6% increase in survival. Cisplatin chemotherapy schedules are the most effective. Chemo-radiotherapy (CRT) is mainly used to treat cancers:

- That cannot be removed with surgery;
- In harder-to-reach areas such as the nasopharynx or throat;
- When surgery could cause unacceptable changes to speech or swallowing or facial characteristics;
- Which are advanced involving multiple sites of the head and neck.

Concomitant chemotherapy is more effective than induction or adjuvant therapy, improving loco-regional control rates, organ conservation and survival, when single agent cisplatin is the cytotoxic agent of choice. Patients treated surgically who prove to have extra-capsular spread in the involved cervical lymph nodes and/or positive surgical margins obtain the maximum benefit from post-operative CRT.

Unfortunately, CRT causes increased acute toxicity: the immediate adverse effects are often similar to, but worse than, for chemotherapy and radiotherapy alone. Drugs may act as radiosensitizers and increase the mucositis produced by RT, and this is seen especially with regimens involving:

- Cisplatin and fluorouracil;
- Cisplatin, epirubicin and bleomycin;
- Carboplatin.

Only 70–80% of patients tolerate three chemotherapy cycles, so most centres use either two cisplatin cycles, weekly low dose cisplatin or single agent carboplatin. Combinations of paclitaxel and carboplatin weekly, 5-FU and carboplatin and 5-FU and mitomycin-C are other choices.

High-dose, intra-arterial cisplatin and CRT (RADPLAT) may minimize drug toxicity by using simultaneous intravenous infusion of the neutralizing agent sodium thiosulphate, with a two-year overall survival of stage IV cancer of ~65%.

CRT has thus emerged as the 'standard of care' for organ preservation in advanced oropharyngeal cancers.

What is the role of newer targeted (biologic) cancer therapies?

Therapies being developed to target specific molecules and pathways in carcinogenesis generally aim to have less frequent and severe adverse effects than does conventional chemotherapy or chemo-radiotherapy. Most squamous cell cancers of the head and neck, including mouth cancer, have Epidermal Growth Factor Receptors (EGFRs) on their surface. EGFR oncogene over-expression produces adverse outcomes in head and neck cancer.

EGFR Inhibitors (EGFRI) affect signal transduction pathways, thereby inhibiting cell proliferation. One monoclonal antibody (mAb) is cetuximab (Erbitux) (Table 1), a targeted or biological therapy that blocks EGFR from attaching to these cancer receptors and may inhibit growth and also make the tumour more sensitive to radiotherapy. Cetuximab combined with RT, versus RT alone, showed comparable toxicities except for higher incidences of acneiform rashes, mucosal toxicity and infusion reactions. Cetuximab is the most

Therapies	Available Agents	Possible Oral Adverse Effects
EGFR inhibitors (FDA approved)	Cetuximab	Mouth ulcers
EGFR inhibitors	Panitumumab, erlotinib in combination with gemcitabine	Mouth ulcers
mTOR (*mammalian target of rapamycin*) inhibitors	Deforolimus, rapamycin (sirolimus), everolimus and temsirolimus	Mouth ulcers
Raf multi-kinase inhibitors	Sorafenib	Dysgeusia
Tyrosine kinase inhibitors (TKIs) of platelet-derived growth factor (PDGF)	Imatinib	Mouth ulcers, dysgeusia
TKIs of PDGF and vascular endothelial growth factor (VEGF)	Sunitinib	Mouth ulcers, dry mouth, dysgeusia

Table 1. Targeted therapies for OSCC and main oral adverse effects.

commonly used targeted therapy for head and neck cancer given as an intravenous infusion. It may be used in combination with radiotherapy for patients who are not fit enough to cope with the adverse effects of chemo-radiation. A recent European randomized trial showed that adding cetuximab to a standard chemotherapy regimen (platinum/5-FU) leads to an important survival benefit and this, with support of an additional smaller study in the US, may change practice.

The National Institute for Health and Care Excellence (NICE), however, has ruled that cetuximab did not represent a cost-effective treatment in most cases and has recommended it only be used in people who:

- Are in a good state of health (likely to make a good recovery if treated);
- Are unable to have chemotherapy for medical reasons (for example, because they have renal disease or are pregnant).

The other main EGFRI is panitumumab. Panitumumab can induce stomatitis.

Erlotinib and gefitinib are small molecule Tyrosine Kinase Inhibitors (TKIs) of EGFR. Lapatinib is a TKI active against EGFR and Her-2. Combining CTX with TKIs makes scientific sense as both agents are active in head and neck cancer and have different mechanisms of action, but gefitinib, in combination with CTX (docetaxel and carboplatin), produced mucositis and myelosuppression in many patients.

Anti-angiogenic approaches with mTORs (mammalian Target Of Rapamycin [sirolimus]) inhibitors such as everolimus, temsirolimus and deforolimus or anti- Vascular Endothelial Growth Factor (VEGF) antibodies which inhibit VEGF also show some promise.

Other emerging mAbs are not necessarily designed to target the tumour directly, but to block or activate specific co-signalling pathways to enhance anti-tumour immunity: an example is the programmed death ligand 1 (PD-L1, B7-H1, CD274).

Complications of targeted therapy

The adverse effects of cetuximab are usually mild, with flu-like symptoms such as a headache, fever, chills or dizziness when the infusion is being given. The most common other adverse effect is a transient rash which usually starts within two weeks of the first treatment but typically resolves spontaneously. Generally speaking, targeted therapies have less severe adverse effects than does conventional CTX but, if combined with conventional CTX, adverse effects (such as oral ulceration) may actually be increased (Table 1). Bevacizumab is a monoclonal antibody against VEGF, which can cause stomatitis and impaired wound healing. Aphthous-like ulcers are the most common adverse effects of VEGF inhibitors. Sunitinib maleate is a TKI of VEGF and Platelet-Derived Growth Factor (PDGF) which may induce stomatitis or dysguesia, or dry mouth. Trastuzumab, a MAb against HER2 can cause mucositis and neuropathy. Imatinib and sorafenib can cause taste changes.

Chemotherapy or radiotherapy and targeted agents

The addition of cetuximab to induction CT in head and neck cancer treatment gave a response in the primary site, 17% partial and 83% complete and was well tolerated, with a rash in 50% of patients but no additional toxicity. Cetuximab plus cisplatin showed improved overall survival in metastatic head and neck cancer patients. Cetuximab with paclitaxel and carboplatin for induction treatment followed by cisplatin-based CRT was a tolerable regimen with response rates that were comparable to historical controls and cetuximab plus TPF for induction treatment was safe and tolerable, with 100% response rates. Combining CT with Tyrosine Kinase (TK) inhibitors makes scientific sense as both agents are active in head and neck cancer and have different mechanisms of action. Gefitinib, in combination with CT (docetaxel and carboplatin) as induction, produced mucositis and myelosuppression in many patients.

Cetuximab combined with radiotherapy showed significantly improved disease-free survival, loco-regional control rates and overall survival versus radiotherapy alone, with comparable toxicities except for higher incidences of acneiform rashes, mucosal toxicity and infusion reactions. Several trials have incorporated EGFR inhibitors with CT and

RT. Panitumamab, carboplatin and paclitaxel with IMRT as primary treatment in patients with advanced carcinoma produced grade 3 mucositis and dysphagia in more than 94%. Other agents used include:

- Erlotinib;
- Gefitinib;
- Lapatanib.

Anti-angiogenic approaches with anti-VEGF (vascular endothelial growth factor) antibodies also show some promise when combined with CRT.

How can mouth cancer care be summarized?

Early stage disease

Single-modality surgery or radiation are options for curative-intent treatment in early stage mouth cancers. Tumours of the mobile tongue or floor of mouth are amenable to surgical resection and reconstruction with good cosmetic and functional results. Radiation therapy produces a long-term risk of hyposalivation and osteonecrosis. Chemo-radiotherapy used mainly for base of tongue or tonsillar carcinomas improves locoregional control, overall survival and the risk of distant metastasis and also can allow organ preservation in some subtypes.

The rates of occult lymph node metastases in node-negative T1 and T2 tumours ranges between 6% and 46%: the decision to treat clinically uninvolved cervical lymph nodes with either surgery or radiation is controversial. Promising reports have emerged about the role of sentinel cervical lymph node biopsy.

Loco-regionally advanced disease

Loco-regionally advanced stage III to IV cancers have suboptimal results from surgery and post-operative RT and therefore post-operative chemo-radiotherapy plays an increasing role in the definitive management. Overall and disease-free survival are improved in chemo-radiotherapy with cisplatin but, although this significantly improves survival endpoints, toxicity is significant. Overall survival and loco-regional control favour radiation and cetuximab in specific cases.

Metastatic disease

Palliation of symptoms is the primary goal in metastatic cancer since curative options do not exist. A range of chemotherapeutic agents and targeted treatments have produced beneficial responses but often at the cost of incremental toxicity. Palliative care involves helping to:

- Control any symptoms such as pain, sickness or breathing problems;
- Support with diet and physical care;
- Rehabilitation.

Treatment success is usually measured by the length of survival from cancer, which is the key primary endpoint and of major importance. Patients generally are indeed living longer; current long-term reports show an overall 60% survival rate, but some patients continue to experience disease and treatment-related sequelae, including speech and swallowing issues and facial dysmorphy in extreme cases.

Summary

Advantages of chemotherapy

Advantages of chemotherapy include that:

- Normal anatomy is maintained;
- General anaesthesia is not needed.

Disadvantages of chemotherapy

Disadvantages mainly include the facts that:

- Adverse effects are common;
- Cure is uncommon.

Further reading

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