A Concise Review on Targeted Therapy for Oral Cancer

Thariny E¹, Ezhilarasan D², Brundha M.P.³

¹Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai-77, Tamilnadu, India
²Department of Pharmacology, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai-77, Tamil Nadu, India
³Department of General Pathology, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai-77, Tamilnadu, India

ABSTRACT

Oral Cancer has become a center of attraction in the world, causing health problems. Carcinoma that involves the lip, tongue, mouth surface, palate, and throat is also serious if not diagnosed and treated. Current treatment strategies involve surgical removal, using chemotherapeutic drugs and radiation therapy. The event of targeted therapy aid in medicine together with oral cancers is that the basic dependence of neoplasm cells on biological pathways which might be coupled to medicine that inhibit those pathways. The resistance of tumor cells to anticancer drugs is a known method which is investigated experimentally at the molecular level. Immunotherapeutic agent resistance is thought to affect the efficacy of anticancer remedies. The induced or intrinsic drug resistance has a strong effect on the survival and cancer growth prognosis by suppression of cancer-associated cell signaling pathways of cancer patients. Targeted therapy also has a significant inhibitory ability, thus demonstrating the high quality of treatment. Hence this concise review discusses the implementation of molecular targeted therapy in the treatment of oral cancer.

INTRODUCTION

Oral cancer is a life-threatening disease which forms tumours in the head and neck area. According to the International Agency Research Cancer-World Health Organisation evaluates that the oral cancer rate has been increased from 10 million to 15 million cases in 2020. The etiological factors which cause oral cancer include tobacco use, change of lifestyle and diet, alcohol intake, viral infections, occupational risk, and genetic factors. Educational and financial services concentrate on high-cost, high-morbidity, and unnecessary high-mortality procedures in the global population. Oral cancer can strike mental and physical health, social and personal life. This disease can severely affect the normal functioning of the body, which decreases the quality of life of an individual. The traditional method of treatment, which includes surgical procedures and chemotherapy rely on the tumor location, and on the feasibility of organ preservation. However, their function in treating oral cancer is non-selective and can harm normal tissue. Chemoradiotherapy, in particular, is associated with systemic toxicity that also decreases patient commitment and prevents treatment from being completed on time. Developing targeted therapies to target...
chosen pathways. The targeted cancer therapies are medications which inhibit cancer development by obstructing the specific molecules that intricates the progression of tumors (Williams, 2010).

The targeted therapy drugs mainly aim at selective inhibition of the molecules and the cells which cause the changes in oral cancer. Target therapy can be successful than the conventional treatments and fewer noxious to normal cells in the body. These targeted molecules are normally present in the cell but in case of cancer, they get mutated or overexpressed. Newer studies are going for better understanding of the mechanism in inhibiting the tumor proliferation by particularly targeting the proteins or signalling pathway that aids in the progression of cancer without affecting the normal cells (Du et al., 2014).

Targeted therapy with small and monoclonal antibodies can serve as an alternative for chemotherapy, radiotherapy, etc., in treating oral cancer. This therapy also has a few side effects on normal body cells. While these targeted therapies are selective, they can have significant unwanted changes which includes skin rashes, abnormal organ function. The drug delivery system also plays a major role in exhibiting the result of targeted therapy.

This therapy specifically induces cell death by induction of apoptosis or by evoking the immune system indirectly for the deduction and elimination of abnormal cells and their harmful products. Targeted therapy through small molecule drugs by oral administration can spread into cells and function on targets within the cell. Another type of targeted cancer therapy is mAbs.

Such medications are given in a parenteral fashion, however, because they are protein in nature and vulnerable to degradation by the intestinal mucosa. Some monoclonal antibodies are guided to target the outside surface of the cell since they are not able to perforate the membrane of the cell. There are multiple modalities of treatment used to treat cancer, including chemotherapy, immunotherapy, radiation therapy, cryosurgery, and hormone therapy. Owing to its limited side effects, targeted therapy has gained popularity over all other cancer therapies (Nagao, 2020).

Chemotherapy is a method of anti-cancer treatment in which cancer proliferating cells are destroyed by using powerful chemicals. But this treatment can cause adverse effects like hair loss, dry skin, anaemia, weight loss, sores and neurological disorders in which it causes dysfunction of the brain leading to mood swing, impair attention and concentration (Oun et al., 2018).

Immunotherapy is another treatment in which it boosts the immune system to fight against the cancerous cells. This may also cause side effects like edema of a leg due to fluid retention, dyspnea, congestion of sinuses, etc. Hormone therapy is a type of hormonal therapy that aims to add, block or remove hormones from the body to terminate the cancer growth. Side effects include gaining of weight, memory problems, thinning of hair and abnormal changes in bones and muscles (Patil, 2020).

Cryosurgery is a kind of surgery requiring the use of intense cold to kill abnormal tissues, such as tumors. Side effects Swelling, Scarring, Lack of feeling for 12 to 18 months in the treatment area, lack of pigmentation, loss of hair in the treatment area. Cancer radiation therapy involves skin problems because of powerful radiation beams to kill the side effects of cancer cells. At the same time, it causes a high cytotoxic effect on the cells. It may also cause burning dry skin with peeling experience. Fatigue describes a feeling almost invariably tired or drained. Targeted therapy also plays a pivotal role in dentistry, as it reduces oral cancer proliferation and metastasis, thereby reducing mortality and morbidity rates. To date, nearly 30 drugs in targeted therapy have been accepted for treating a wide range of forms of human cancer in clinical use, separately or in combination with any other treatment like chemotherapy. Targeted therapy can be more effective when combined with chemotherapy or immunotherapy that has a supra-additive effect (Dinardo, 2018).

The purpose of this review is to give a clear explanation of its method of targeted therapy and its impact on oral cancer in order to provide advanced cancer cure care.

**MATERIALS AND METHODS**

Oral cancer develops in the head and neck area, which includes the mucous membrane of the mouth and throat. There are many types of cancer among which oral cancer stands at 6 th position worldwide. Alcohol consumption and smoking have a vital role in the cause of oral cancer. However, there is growing evidence in some patients, human papillomavirus is also considered as one of the etiological factors in causing oral cancer which is associated about 20% with oral cancer (Stefani, 2002).

Currently, the treatment for oral carcinoma includes postoperative radiotherapy surgery, surgical removal of tumor, radiation therapy along with surgery, radiation therapy alone and chemotherapy together with additional treatments. Such traditional treatment approaches are nevertheless correlated with serious side effects of this type of
Mucositis caused by radiation, and loss of organ function as systemic toxicity. Thus, the oncology branch focuses on understanding OSCC’s molecular basis for targeting selective pathways involved in carcinogenesis. Oral cancer occurs as a change in 2 factors, in alteration of DNA or RNA (Marcuzzan et al., 2018).

**Molecular Alterations in Oral Cancer**

In OSCC molecular alterations were divided into changes to DNA profiling and changes in RNA profiling. Changes to DNA profiling includes Oncogenic changes and Tumor Suppressor Gene Alterations(TSG). Oncogenes are genes associated with tumors present in all types of those cancers. For carcinogenesis to occur, it is necessary to alter or mutate either one or more of the oncogenes in a cell to activate the pathways. These proto-oncogenes include primarily cell proliferation and growth. Epidermal growth factor (EGFR) is a glycoprotein present in the transmembrane with tyrosine kinase activity which contributes a major role in controlling the growth and survival of cancerous cells. Cyclin D1 Which is encoded by gene CCND1 controls the growth of the tumor. RAS mutations are significant in which they show resistance to inhibitor therapy of EGFR. Melanomas, some gliomas, thyroid carcinoma expresses BRAF gene (Pracht and Berthold, 2014). Tumor suppressor gene gets altered or mutated to make the carcinogenesis pathway get activated. The p53 gene located on chromosome 17p13 was one of the familiar tumor proteins related to head and neck cancer. Some of the genetic changes in oral cancer includes deletion, amplification and point mutation; Tumor suppressor gene CDKN2A most commonly gets inactivated by deletion or methylation. Alterations in RNA profiling include tumor cells that are advanced with capability in analysing the messenger RNA which are abnormally expressed (over or under-expressed), are identified by microarray RNA profiling (Suda and Mitsudomi, 2014).

**About targeted therapy**

Drugs used in targeted therapy tend to obstruct the proliferation of cancer cells and the spread of cancer via particular molecules. It was first performed to illustrate the capacity of the drug that specifically aims at microorganism. However, now it serves as a treatment for oral cancer. The success of targeted therapy treatment lies in identifying the correct goal for the eradication of cancer.

The genetic modification leading to mutation and receptors facilitating cell survival and proliferation is one of the bases of cancer incidence. Genome sequencing can be used to identify the cancer markers which aids the researchers to differentiate between normal and neoplastic cells to recognize improvements in the sequencing of signals technology can sequence a wide range of cancerous genomes to expose genetic heterogeneity between a normal and abnormal cell in a person. This is important in determining the effective drug production against the aim targets. Targeted therapy has targets to control the disease which includes growth factors like VEGF, EGFR etc., molecules in signalling, protein in the cell cycle, apoptosis controller and molecule that promotes angiogenesis (Gotwals et al., 2017).

**Mechanism of action**

The therapeutic drugs used in targeted therapy can show various biological properties. These drugs operate upon the targets that are selected to control the progression of new cell formation leading to abnormal proliferation of cells. Drugs in targeted therapy can congest the signals which promote the growth of neoplastic cells, interfere with the regulation of cell cycle, instigate apoptosis to destroy neoplastic cells. The immune mechanism is stimulated by attacking the cancerous cell, along with the constitutions of the microenvironment of the tumor (Sawyers, 2004).

**Different types of targeted therapy**

**Small molecules**

The small molecules characterized by comparatively low molecular weight capable of penetrating through cells; Targeting specific protein inside the cell. Most of the small molecule inhibitors inhibit the kinase and interrupt the signals that enable carcinogenesis. Enzymes like cyclin-dependent kinase, poly ADP ribose polymerase (PARP) inhibitor are targeted by the small molecules in order to activate apoptosis, checkpoints in the cycle (Ke and Shen, 2017).

**Monoclonal antibodies**

Monoclonal antibodies (mAbs) are usually targeted toward the cell surface from outside because they cannot go into the cell as they are large in size. mAbs directly target the protein outside the cell and terminate the human proliferation by communicating with the receptor and ligand. After binding to the cancer cell, the small molecule acts either by direct or indirect mechanism. The direct mechanism usually involves the binding of small molecules through receptors of cells, proteins on the membrane and antigens leading to cell death.

**Cancer vaccines**

Cancer vaccines react by immune responses that are mediated to produce anti tumor effects that
Table 1: Representation of molecules that underwent clinical trials for oral cancer by Targeted therapy.

| Trial Number  | Trial  | Drug                        | Target                  | Subtype                                      |
|---------------|--------|-----------------------------|-------------------------|----------------------------------------------|
| NCT01195922   | Phase 1, 2 | Rapamycin, Sirolimus        | Specific inhibitor mTOR | Mouth, head and neck, tongue neoplasm, carcinoma of Squamous cells. |
| NCT03174275   | Phase 2 | Carboplatin, Durpalumab, Nab-Paclitaxel, Cisplatin | EGFR inhibitor         | Oral Squamous cell carcinoma, oropharynx, and lip. |
| NCT01434394   | Phase 2, 3 | Erbitux                  | EGFR inhibitor         | Locally advanced malignant, oropharyngeal carcinoma. |
| NCT00462735   | Phase 2 | Cetuximab, Hydroxyurea, Fluorouracil | EGFR inhibitor         | Head and neck, Nose neoplasm, paranasal sinus. |
| NCT01254617   | Phase 1 | Cetuximab, Lenalidomide   | EGFR inhibitor immune system focusing | Recurrent lip and oral cavity Squamous cell carcinoma |
| NCT00272181   | Nil     | Proxinium                  | EGFR inhibitor         | Squamous cell carcinoma of Head and neck |
| NCT00570232   | Phase 2 | Erlotinib                  | EGFR inhibitor         | Head and Neck cancer 1. Squamous Cell, Recurrent Lip and oral Cavity 2. Squamous Cell Carcinoma |
| NCT0125635    | Phase 2 | Temsirolimus               | a specific inhibitor of mTOR | 1. Recurrent oral Cavity Veruccous Carcinoma 2. Recurrent 3. Oropharyngeal Squamous Cell Carcinoma |
| NCT00588770   | Phase 3 | 1. Docetaxel, 2.Fluorouracil, 3. Carboplatin | VEGF inhibitor         | 1. Recurrent Salivary Gland cancer, 2. Salivary Gland Acinic Cell tumor |
| NCT00095563   | Phase 2 | 1. Lapatinib, Ditosylate  | EGFR inhibitor         | 1. Head and Neck carcinoma |
| NCT01345682   | Phase 3 | Afatinib                   | EGFR inhibitor         | 1. Head and Neck carcinoma |

Source: Home - clinicalTrials.gov; last accessed date: May 14 2020.

are differentiated into the patient-specific type and non-patient specific type. In patient-specific type, the vaccines are obtained from the tumor cells of the patient itself, while nonspecific are generated by generalizing and immunological effects which exhibit an anti-tumor activity in a small group of patients (Ezhilarasan et al., 2018).

**Gene therapy**

Gene therapy works by inculcating the genetic material like DNA or RNA into neoplastic cells to suppress or prevent the development. The benefits of selective molecular therapy are its capacity to deliver drugs effectively—highly specific, but less harmful than traditional chemotherapy. Common adverse effects of this treatment are rashes, low blood pressure, proteinuria, pigmentation defect and hepatotoxicity. The side effects occur in normal cells due to abnormal regulation of inhibited molecules (Curran, 2007).

**Intervention of targeted therapy in oral cancer**

Targeted therapies using small-molecule inhibitors are as follows. Molecules that underwent clinical trials for oral cancer by targeted therapy is mentioned in (Table 1).

**EGFR inhibition (Gefitinib and Erlotinib)**

EGFR upregulation is not only seen in cancerous tissue but also in normal tissue adjacent to it. This concept is called field cancerization, which is defined as a multifocal growth of precancerous or cancerous...
lesion during the carcinogenic epithelial exposure.

**EGFR directed mAbs** (Cetuximab, Panitumub, and Zalutumumab)

Putative mechanisms of anticancer behaviour dependent on the EGFR mAb are divided into groups. In the first group, the extracellular domain of EGFR is prevented from binding with ligands which may sequentially lead to degradation of the respective receptor. The second group attach to the EGFR indirectly by evoking the immune system, which induces cytotoxicity mediated by antibody, complimentary system and complimentary cell-dependent mechanism. mTOR (Rapamycin Everolimus and Temsirolimus), and PARP (Poly (ADP-ribose)- Iniparib and olaparib. Cetuximab is the only targeted molecule that is approved for HNSCC treatment by the Food and Drug Administration (FDA). According to the FDA guidelines, this medicinal product is approved for use under the following conditions locally or regionally advanced HNSCC in combination with radiation therapy, recurrent locoregional disease or metastatic HNSCC in combination with 5-FU platinum-based therapy and recurrent or metastatic progression of HNSCC after Platinum Therapy.

**Tyrosine kinase inhibitors**

Sorafenib, Sunitinib, Lapatinib EGFR tyrosine kinase inhibitors show the conceptual benefits of stopping signal activation of cytoplasm as well when compared with agents that block extracellular activation.

**BCR-ABL inhibitors**

Imatinib was the first discovered target in targeted therapy to treat chronic myeloid leukemia. It prevents the chromosomal translocation of the BCR-ABL protein kinase (Lee et al., 2018).

**Inhibition of growth inhibitory signals**

In the normal state, the cell growth and death are maintained by tumor suppressor gene but incase of cancer the tumor suppressor gene gets mutated, leading to uncontrolled proliferation of cells, ultimately leading to the neoplastic condition.

**Initiators of apoptosis**

Apoptosis may be initiated by triggering an intracellular and extracellular pathway. After the activation of caspase and cascade, destruction of cells occurred by enzymes released from these processes. Alteration in apoptosis good leads to avoidance of programmed cell death and can serve as a possible target for targeted therapy.

**PD-1 inhibitors**

The monoclonal antibody Nivolumab (Opdivo) prevents apoptotic protein 1 and affects the PD-1 interaction with ligands. PD-L1 and PD-L2 are the two types of ligands (Gupta and Others, 2017).

**Angiogenesis inhibitors** (Bevacizumab and Vandetanib)

The growth factor of the endothelial vascular cells has a strong capacity to induce neovascularization and proliferation of neoplastic cells. About 40 percent of cancer exhibited vascular endothelial growth factor. The kinase inhibitors HNSCC, sunitinib, sorafenib, and pazopanib affect several pathways involved in the development of malignant tumours. It blocks the vascular spread of neoplasm, besides blocking tyrosine kinase pathways.

**Inhibitors of tissue invasion and metastasis**

Doxycycline has various inhibitory effects for the production and activity of MMP. Cyclooxygenase-2 is one of the factors which are abnormally expressed in the malignant condition in head and neck cancer. Celecoxib selective COX-2 inhibitors do away with tumor development in experimental models.

**Carcinoembryonic antigen**

CEA definition is not commonly accepted in head and neck cancer. CEA is a potential target for specific HNSCC immunotherapy through vaccines (Hamakawa, 2008).

**Mechanism of targeted therapy drugs on oral cancer**

The occurrence of head and neck cancer is a multi-stage disease that results in carcinogenesis. Clonal cell spread causes genomic instability identified by biomarkers, oral premalignant lesion measurement, and intraepithelial neoplasia.

ABT-263 (Navitoclax) substantially increased rates of expression of the C / EBP-homologous protein and its messenger RNA, leading to programmed cell death in four different cell lines originating from human oral cancer (Yang, 2019).

A small-molecule Geftinib and inhibitor of tyrosine kinase was effective in cancer treatment. A clinical trial (Phase II) documented a good activity and showed an improvement in the health of patients with recurrent cancer in head and neck.

Erlotinib is orally administered small-molecule against EGFR. Erlotinib mainly inhibits the tyrosine-kinase. A clinical phase trial (I / II) revealed the erlotinib with cisplatin and radiotherapy was effective in locally advanced HNSCC.

Treatment with PI-828 and PI-103 exhibited growth inhibition and growth of OSCC cells with associated...
changes in the regulation of cell cycle, apoptosis induction, and reduced invasiveness of the epithelium (Aggarwal, 2019).

Patients suffering from oral cancer caused by human papillomavirus can be treated with pemetrexed/etoposide separately, or in conjugation with cisplatin, a chemotherapeutic drug, can serve as an effective drug in oral cancer and an alternate may be used as novel alternatives in a for concurrent chemoradiotherapy. However, further investigations are still needed.

Recent studies revealed numerous targeted therapy drugs such as bortezomib, vorinostat, resveratrol, and colchicine can be used as a potential chemotherapeutic drug in treating oral cancer.

In vitro and in vivo study showed that the photo thermal therapy, photo dynamic therapy along with chemotherapy produced a synergistic outcome, thereby significantly improving therapeutic effectiveness compared to cancer monotherapy. Previous research also reported an elevated level of SPARC cystine which causes head and neck cancer and CAF (chemotherapeutic combination cyclophosphamide, doxorubicin hydrochloride (adriamycin) and fluorouracil).

Powerful antioxidant astaxanthin (AXT) causes inhibition of PI3K / Akt and downregulation of NF-κB and STAT-3 signaling pathways in an oral neoplastic cell which is demonstrated in the cell line of hamster buccal carcinogenesis model (Kowshik, 2019).

Drugs preventing neovascularization in oral cancer include nimotuzumab and cetuximab, and EGFR inhibitor aids in the prevention of invasion and migration in epithelial cells during carcinogenesis. Chlorine e6-Photo dynamic therapy along with these drugs, can decrease the growth of tumor cells in various endothelial cancers.

Celastrol induced apoptosis of cells by the downregulation of Bcl-2 expression, not Bcl-xL. Celastrol mainly aims at hindering JNK I/II signalling, which is the main pathway for apoptosis (Lin, 2019).

An animal study with nude mice demonstrated knockdown xenografting cancer with reduced cell growth and a high level of apoptosis with AKT dephosphorylation after chemotherapy with S-1.

8αTGH extracted from V. cinerea induces the inhibition of STAT2 and STAT3 phosphorylation, the arrest of M phase of the cycle, thereby reducing the growth of neoplastic cells (Pouyfung et al., 2019).

BRCA2 knockdown using low inhibiting RNA suppression elevated the human oral cells more sensitive (SAS and HSC3) to 5-FU (Nakagawa, 2014).

outcomes of targeted therapy in oral cancer

A monoclonal antibody drug bevacizumab acts against vascular endothelial growth factors which give rise to poor wound healing and stomatitis. Some of the common adverse effects caused by VEGF inhibitors are aphthous-like ulcers. Platelet-Derived Growth Factor can cause dysgeusia. Mucositis and peripheral neuritis is caused by HERS, trastuzumab. Sorafenib can alter the taste sensation, causing dysgeusia.

The targeted therapy provides better treatment with minimal side effects compared to other treatments for cancer. It is noted for 3 main outcomes, namely, locoregional tumor control without affecting other organs, disease-free survival by cancer cell eradication, to its core, and quality of life by providing a cure in such a way that the disease does not occur in an individual (Mehta, 2019).

CONCLUSIONS

Targeted therapy in the medicinal field could serve as an effective platform in treating cancer. By inculcating this method of treatment in oral cancer may produce predictable effects without harming the normal function of the body. Targeted therapy can also be combined with other anticancer therapies which could bring a synergistic effect. The main advantage of this targeted therapy is that it concentrates only on the affected cells by identifying their receptors; thereby, it does not produce any severe side effects as seen in chemotherapy or radiotherapy. Thus, the result greatly suggests that the effectiveness of targeted therapy has been taken into account and extended to improve oral disease care strategies in dentistry in order to provide effective care.

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