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Progress in targeted therapeutic drugs for oral squamous cell carcinoma

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ABSTRACT

With the rapid development of biomedicine, people have a deeper understanding with the biological characteristics of malignant tumors, and begin to notice that in most tumors, there are over-expression of several molecules such as epidermal growth factor receptor(EGFR), vascular endothelial growth factor (VEGF) and its receptors,mammalian target of rapamycin(mTOR),programmed cell death receptor-1(PD-1),cyclin-dependent kinases(CDKs) and so on, whose levels are closely related to the prognosis of tumors. It has been found that the drugs targeting the above molecules can significantly improve the survival rate of cancer patients, and have the advantages of high selectivity, low toxicity and high therapeutic index. Targeted drugs, as new ones in the field of cancer, have achieved good efficacy in most tumor treatments. Oral cancer is an aggressive malignant tumour that is prone to relapse and metastasis. More than 90% of them are squamous cell carcinoma, and the 5-year survival rate remains at about 50%–60%.The proposing of targeted therapy opens up a new way for the treatment of oral cancer and brings dawn to patients with advanced diseases. Currently,a variety of targeted therapeutic drugs are being tested in various clinical trials in patients with oral squamous cell carcinoma (OSCC)·In this paper, we discuss the research progress of targeted therapeutic drugs in the treatment of OSCC in recent years.

1. Introduction

Oral cancer is one of the most common malignancy in the head and neck, and squamous cell carcinoma accounts for more than 90% of oral and oropharyngeal malignant tumors [1,2]. In 2012,369,200 new cases of oral cancer were reported worldwide,two-thirds of which were diagnosed in developing countries [3]. Oral squamous cell carcinoma (OSCC) has a high recurrence rate and is prone to metastasis. The 5-year survival rate of patients in the earlier stage is about 55%–60%, while that of patients in advanced stage drops to 30%–40% [4]. Unfortunately, 60%–80% of cases are diagnosed at advanced stage, and it is estimated that approximately 145,328 patients die of OSCC worldwide every year [3]. With continuous improvement in diagnosis and treatment technologies, the survival rate of OSCC has been increased, but it remains great challenges of non-specificity,non-selectivity and toxicity in cancer treatment. After undergoing surgery, radiotherapy and/or chemotherapy, most patients are subject to local defects, malformations,dysfunction, drug resistance, and other toxic and side effects that can not bear. Worst of all, the tumors are prone to recurrence and metastasis later, which leads to poor quality of life of sufferers [5,6].

Since the 21st century, genomics,proteomics, metabolomics and other biomedical sciences have developed rapidly. Accordingly, targeted therapies targeting cancer specific genetic targets, such as growth factor receptors, key molecules involved in signal transduction or transcription activation, and genes related to proliferation, division, invasion and metastasis of cancer cells, have gradually become the research hot spot [7]. Distinct from traditional therapeutic methods, targeted therapies select the corresponding therapeutic drugs according to the specific carcinogenic sites, which has the advantages of high selectivity, low toxicity and high therapeutic indexes. Studies have proved that this kind of treatment can improve 5-year survival rate of tumor patients by inducing differentiation of tumor cells or combining with surgery, radiotherapy,chemotherapy and other treatment measures [5]. In recent years, various targeted therapeutic drugs have achieved good results in the treatment of cancer, and new therapeutic target agents have also become a hot spot of concern.

Abbreviations: OSCC, oral squamous cell carcinoma; EGFR, epidermal growth factor receptor; TKIs, tyrosine kinase inhibitors; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; mTOR, mammalian target of rapamycin; PD-1, programmed cell death receptor-1; HNSCC, head and neck squamous cell carcinoma; FDA, Food and Drug Administration; PFS, progression-free survival; OS, overall survival; p-mTOR, phosphorylated mTOR; PD-L1, programmed cell death ligand 1; CDKs, cyclin-dependent kinases; COX-2, cyclooxygenase-2; NSCLC, non-small cell lung cancer

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2. Drugs targeting epidermal growth factor receptor (EGFR)

EGFR is a cytoplasmic transmembrane protein belonging to human epidermal growth factor (HER/ErBb) receptor tyrosine kinase family, which is usually composed of extracellular ligand-binding domain, transmembrane domain and intracellular domain with tyrosine kinase activity. When endogenous ligands such as epidermal growth factor (EGF),transforming growth factor-α(TGF-α),neuregulin, betacellulin (BTC),heparin-binding epidermal growth factor(HB-EGF) and epiregulin (EPR), bind to the extracellular domain of EGFR to form homologous or heterogenous dimers. These dimers activate their intracellular protein tyrosine kinases, lead to the auto phosphorylation of key tyrosine residues in the cytoplasmic domain, and then initiate downstream signaling pathways, such as the Ras-Raf-mitogen-activated protein(MAP) kinase pathway and the phosphatidylinositol 3-kinase/protein kinase B(PI3K/Akt) pathway, eventually give rise to the proliferation, metastasis,anti-apoptosis and angiogenesis of tumor cells [8–10]. Studies have shown that more than 80% of invasive squamous cell carcinomas of the head and neck are over-expressed with EGFR, which is often associated with tumor invasion and metastasis, increased resistance to radiotherapy and chemotherapy, reduced survival rate and poor prognosis [11,12]. Agra et al. reported that patients with tumors that did not express EGFR had better therapeutic outcomes after a rescue surgery, with a 3-year disease-specific survival(DSS) rate of 64.3% compared with 27.2% for those with tumors expressing EGFR [13].

Currently, two types of drugs against this target have been applied in clinical practice:One is monoclonal antibodies that recognize extracellular ligand binding domain and interfere with receptor activation, such as cetuximab and nimotuzumab, and the other is tyrosine kinase inhibitors (TKIs), which bind to cytoplasmic region and affect downstream signal transduction, such as gefitinib, erlotinib and afatinib,etc. [14].

Cetuximab is a chimeric human-mouse IgG1 monoclonal antibody, which was approved by the Food and Drug Administration (FDA) in 2006 in conjunction with radiotherapy for first-line treatment of locally advanced head and neck squamous cell carcinoma (HNSCC) [15]. By binding to the extracellular ligand binding domain of EGFR, cetuximab can competently inhibit endogenous ligand-activated receptors, thereby increasing cell apoptosis, reducing cell proliferation, invasion and metastasis, and angiogenesis. The binding of cetuximab to the receptor also leads to the internalization and degradation of the antibody-receptor complex, which down-regulates EGFR expression [16]. Phase I trials showed that cetuximab was well tolerated and characterized by acne-like rash, the occurrence and severity of which was a predictor of clinical reactions to drugs. Other adverse reactions included infusion reaction, discomfort,fever, nausea, diarrhea and constipation,etc. [15]. A retrospective study in Japan from 2012 to 2015 assessed the efficacy of cetuximab in locally advanced and recurrent/metastatic OSCC. The results showed that the total effective rate in locally advanced patients was 57.1%, the median progression-free survival (PFS) and overall survival (OS) were 5.5 months and 8.0 months, respectively.Meanwhile, the total effective rate in distantly metastatic patients was 60.0%, the median PFS and OS were 3.8 months and 5.8 months, respectively.The grade 3-4 adverse reactions included infusion reaction (4 cases),neutropenia, hypophosphatemia, upper gastrointestinal bleeding, hepatotoxicity and mucositis (1 case each). There was one death associated with cetuximab due to interstitial pneumonia. Acne-like rash was observed in all cases, but no grade 3 or 4 rash was reported. Hypomagnesemia was observed in 10 cases. Compared with the non-cetuximab treatment group in the historical control study, the one-year OS of cetuximab treatment was improved, indicating that cetuximab had a significant effect on patients with unresectable locally advanced and recurrent/metastatic oral cancer, although there was no significant difference between the two groups after one year($P = 0.246$) [6]. Cetuximab monotherapy as second-line therapy for platinum resistant recurrent/metastatic HNSCC had a response rate of 10%–13% and a median PFS of 2.2–2.8 months [8]. In phase III clinical trials, cetuximab combined with radiotherapy for locally advanced HNSCC and with platinum-based chemotherapy as first-line treatment for recurrent/metastatic HNSCC(including OSCC) have achieved higher response rates and significantly increased overall survival rate [6]. In 2008, Vermorken et al. conducted a multicenter randomized phase III clinical trial in 81 centers in 17 European countries. They were surprised to find that, compared with chemotherapy alone, cetuximab added to cisplatin/5-fluorouracil (PF) prolonged OS from 7.4 months to 10.1 months ($P = 0.04$), PFS from 3.3 months to 5.6 months ($P < 0.001$), and tumor response rate increased from 20% to 36% ($P < 0.001$) [17]. In addition, preclinical studies have found that cetuximab can enhance the role of paclitaxel in OSCC by down-regulating the expression of paclitaxel-induced p65 [18]. Park used xenograft OSCC model in nude mice without thymus, and randomly assigned nude mice with subcutaneous tumors to receive cetuximab alone, paclitaxel alone, cetuximab plus paclitaxel or placebo(control). The results showed that cetuximab alone, paclitaxel alone and the combined treatment of them resulted in 50%,52% and 67% inhibition of tumor proliferation in vivo, respectively [19]. Furthermore, Ritter et al. used high-dose-rate brachytherapy combined with cetuximab and paclitaxel to treat 94 patients with recurrent HNSCC (including OSCC). They found that the disease-free survival(DFS) and OS of the study group were 8.7 and 14.8 months, respectively, whereas the control group(only by function preserving tumor debulking and brachytherapy) were 3.9 and 6.1 months, and the toxicity above grade 3 did not increase [20]. Disappointingly, cetuximab failed to improve disease-free or overall survival in patients with stage III-IV OSCC who received cisplatin concurrent with radiotherapy [21]. Although the benefits of cetuximab in clinical trials are encouraging, drug resistance is inevitable. It has been reported that cetuximab is only effective against wild-type EGFR, and some common mutated forms, such as EGFRvIII, are resistant to treatment [22].

Nimotuzumab is a humanized IgG1 monoclonal antibody drug that is clinically used to treat HNSCC, glioblastoma and nasopharyngeal cancer [23]. Compared with cetuximab, it has the biological activity characteristics of high degree of humanization (up to 95%), relatively moderate affinity and long half-life,which can significantly reduce the side effects such as immunogenicity and skin toxicity. Nimotuzumab has been demonstrated to be involved in mediating anti-tumor effects by suppressing the proliferation, survival and angiogenesis of cancer cells. It has been reported that docetaxel-cisplatin and fluorouracil combined with nimotuzumab were used for the treatment of patients with advanced oral cancer. The efficacy of the combined treatment group was 95%(19/20), and that of the conventional chemotherapy group was just 65%(13/20) ($P < 0.05$), and no serious adverse reactions occurred in the two groups [24]. Moreover,a randomized clinical trial conducted at three cancer specialist centers in India assessed the safety and efficacy of nimotuzumab in combination with radiotherapy and chemotherapy or radiotherapy alone. A total of 92 patients with stage III-IVa squamous cell carcinoma whose primary site was in the oral cavity, oropharynx and larynx were recruited in the study. The results showed that after 24 weeks treatment, the overall effective rates of nimotuzumab combined with chemoradiotherapy, nimotuzumab combined with radiotherapy, chemoradiotherapy alone and radiotherapy alone were 100%,76%,70%,40%,respectively.30 months later, the survival rate of nimotuzumab combined with chemoradiotherapy group was the highest(69.57%), followed by nimotuzumab combined with radiotherapy group(39.13%) ($P < 0.02$), and PFS was significantly prolonged after the addition of nimotuzumab [25]. These results indicate that nimotuzumab in combination of chemoradiotherapy has extensive clinical application value in treating OSCC.

Gefitinib, the first oral EGFR-TKIs, can rapidly alleviate the symptoms of about 40% of patients with non-small cell lung cancer(NSCLC) and show good tolerance, and has been granted the approval for the

treatment of advanced NSCLC in the United States, Japan, Australia and other countries [26]. In vivo and in vitro studies have demonstrated that gefitinib could inhibit the proliferation of oral squamous cell lines in a dose-dependent and time-dependent manner, leading to cell cycle arrest, cell accumulation in G1 phase and cell decrease in S phase [27,28]. In situ nude mice model, 6(46.2%) of 13 gefitinib treated animals and 12 control animals (100%) were observed to have metastasis after a in situ injection of OSCC cell lines with high level green fluorescent protein(GFP)-SAS-L1 into the tongue. This may be that after exposure to gefitinib,down-regulation of integrin expression and FAK phosphorylation results in decreased cell adhesion to fibronectin in OSCC, thus contributing to the reduction of spontaneous metastasis of these highly metastatic tumors [28]. Phase II/III studies reported the recommended dose of gefitinib monotherapy was 250 or 500 mg/day, with response rates ranging from 1.4% to 10.6% [8]. Regrettably, phase III studies indicated that neither gefitinib at 250 mg/day nor gefitinib at 500 mg/day could improve the overall survival rate compared with methotrexate [29]. Surprisingly, recurrent/metastatic OSCC has a better efficacy in the combination of gefitinib with paclitaxel and platinum-based chemotherapy, with a median PFS of 4.8 months and OS of 9.5 months [30]. However, in a phase II clinical trial, the combination of gefitinib with cisplatin/5-Fu concurrent radiotherapy did not improve outcomes but increased toxicity. A total of 60 previously untreated patients with stage III/IV squamous cell carcinoma in the oral cavity, oropharynx, larynx or hypopharynx were recruited in the study.42% of the patients were gefitinib intolerant and 5(8%) died of treatment-related diseases. The overall survival rate for 2,3 and 4 years were 80%,71%,69%,respectively.With a median follow-up of 54 months, the distant metastasis control rate at 2,3 and 4 years was 88%.Compared with the historical cohort study, the acute toxicity including renal dysfunction and unplanned rehospitalization were worse [31].

Erlotinib is another small molecule tyrosine kinase inhibitor. The recommended second-stage evaluation dose is 150 mg/day. In clinical trials, the combination therapy is more effective than the single agents treatment [22]. In vitro studies, erlotinib showed the capability of inhibiting the growth of tongue squamous cell carcinoma(SCC-15) in a dose-dependent manner. It appeared to be that erlotinib had effects on SCC-15 cells by the inhibition of intra-S phase and G2/M transition of the cell cycle. Besides, Erlotinib can synergistically inhibit the growth of SCC-15 cells with cisplatin and radiation [32]. Phase II studies indicated that the response rate of erlotinib monotherapy was 4.3%, with a median duration of 16.1 weeks [33]. However, the response rate increased to 21% after a combination with cisplatin, and the median PFS and OS were 3.3 and 7.9 months, respectively.What's more, the incidence of toxicity above grade 3 was the lowest [34]. To be astonished, the response rate grew to 62% after a combined treatment with cisplatin, docetaxel and erlotinib [35]. Erlotinib is currently in the third stage of oral cancer prevention. It is well known that the Erlotinib Prevention of Oral Cancer(EPOC) study is the largest EGFR-targeted chemoprevention clinical trial in HNSCC activated to date. When patients with high-risk oral precancerous lesions were given erlotinib for one year, the incidence of oral cancer at 3 years was estimated at 65% in patients with a prior history of oral cancer and 35% in those without it. Statistics indicated that EPOC had 85% power to detect a 40% reduction in the risk of oral cancer, and bilateral type I error rate was 5% [8]. However, the results of a randomized,placebo-controlled trial conducted from 2006 to 2012 revealed that although erlotinib could block the progress of oral cancer in patients with high-risk oral precancerous lesions, it could not improve the cancer-free survival rate of high-risk patients [36].

Afatinib is an oral irreversible ErBb family blocker with strong activity against wild-type and mutant EGFR (including EGFRvIII) and HER-2. An open randomized phase II trial conducted in 43 centers in Belgium, France, Spain and the United States showed that the antitumor activity of afatinib was comparable to cetuximab [37].

3. Vascular endothelial growth factor (VEGF) and its receptor inhibitors

Tumor angiogenesis plays a significant role in local growth, invasion and metastasis of tumors. Therefore, inhibiting angiogenesis is considered to be effective in the treatment of OSCC [38]. VEGF is a diffusible endothelial cell-specific mitogen and angiogenic factor, which involved in increasing vascular permeability. It has been regarded as one of the major molecules of tumor angiogenesis and is highly expressed in OSCC [39]. VEGF transmits signals by binding to two classes of endothelial cell receptors, such as Flt-1 (Fms-like tyrosine kinase) and KDR(kinase domain region)/Flk-1 (fetal liver kinase-1), which are believed to be the major signal receptors governing endothelial cell permeability, proliferation and differentiation [40]. Additionally, VEGF may be responsible for promoting angiogenesis and matrix formation directly through its role as endothelial growth factor, or indirectly encouraging tumor growth by increasing vascular permeability, leading to plasma protein extravasation, fibrin deposition, and eventually replacing the generated matrix with blood vessels [41]. The agents against VEGF and its receptors include monoclonal antibodies, such as bevacizumab, or multi-kinases inhibitors, such as sorafenib and vandetanib.

Bevacizumab is a humanized monoclonal antibody against vascular endothelial growth factor-A(VEGF-A), and it has been approved by FDA for standardized treatment of colorectal cancer, NSCLC and renal cell carcinoma [42]. By competitively binding to the VEGF receptors, it inhibits the biological activity mediated by VEGF, reduces tumor angiogenesis, and consequently, suppresses the growth of tumors. A phase II study found that the combination therapy of bevacizumab, cetuximab plus cisplatin concurrent with radiation was well tolerated in phase III/IVB HNSCC(including OSCC), with 2-year PFS and OS rates of 88.5% and 92.8%,respectively.The most common grade 3 toxic reactions were lymphopenia, mucositis and dysphagia [43]. However, frequent bleeding after bevacizumab treatment has been reported in some small phase II trials in recent years. In a phase II trial that recruited 30 patients with advanced squamous cell carcinoma originating in the oropharynx, hypopharynx, larynx and oral cavity, two patients developed hemorrhage without grade 5 toxicity after treatment with bevacizumab concurrent with docetaxel and radiotherapy. The most common local toxicities were mucositis and dermatitis [44]. While in another phase II trial, the efficacy of bevacizumab(15 mg/kg) combined with pemetrex (500 mg/m^2) was reported to be good, with a total response rate of 30% and a disease control rate of 86%.The median PFS was 5 months and the median OS was 11.3 months. Simultaneously, six patients(15%) developed grade 3 to 5 bleeding events:four were grade 3 and two were fatal [45]. Therefore, it is an urgent problem for bevacizumab to find the best dose and biomarker to reduce the risk of bleeding as much as possible without affecting the efficacy.

Sorafenib is a multi-target and multi-kinase inhibitor, which is able to inhibit the growth and proliferation of tumor cells and suppressing tumor angiogenesis by an inhibition of various targets, such as Raf serine/threonine kinase, VEGFR(vascular endothelial growth factor receptor)1–3, platelet derived growth factor receptor β (PDGFR-β),c-Kit, and Flt-3,etc..Moreover, sorafenib can induce apoptosis of tumor cells by down-regulating Mcl-1 [46]. In vitro studies have observed a potent radio- and chemical sensitizing effect on sorafenib [47]. Combination of sorafenib with radiation showed a synergistic effect on OSCC cells by suppression of radiation-induced NF-κB activity and its regulated downstream effector proteins [48]. Furthermore, sorafenib could significantly suppress the proliferation of cisplatin resistant tongue cancer cells and induce apoptosis. This may be accountable for the concentration-dependent inhibition of tongue cancer resistance associated protein 1(TCRP1) expression by the drug [49]. Sorafenib has been approved in the European Union for the treatment of hepatocellular carcinoma [50], but further clinical trials are required to verify the efficacy in OSCC.

Vandetanib is another receptor tyrosine kinase(RTK) inhibitor that effectively inhibits the activity of VEGFR-2 and EGFR tyrosine kinase. Preclinical studies have shown that vandetanib was able to inhibit the proliferation of multiple xenograft tumor cells, including OSCC. Zhou et al. reported that, after a treatment with vandetanib(25 mg/kg/day) on 4-nitroquinoline-1-oxide(4-NQO) induced oral carcinogenesis model in mice for 24 weeks, the incidence of dysplasia and OSCC in vandetanib treated mice was significantly lower(treatment group vs control group, 12% vs 71%,$P \leq 0.001$) than that in the control group (only with water containing vehicle), which demonstrated that vandetanib might be an effective chemopreventive agent for OSCC [51]. Moreover, in situ nude mice model, vandetanib, cisplatin and radiotherapy were used alone or in combination. The results implicated the combination regimen of vandetanib, cisplatin and radiation was superior to other treatments(including double combinations) in anti-tumor effects, prolonging survival and reducing cervical lymph node metastases in vivo. It also increased apoptosis of endothelial cells associated with tumors and decreased microvessel density [52]. Furthermore, vandetanib adding to the combination therapy of cisplatin and radion was shown to effectively overcome the resistance of HNSCC patients, and had the potential as a novel therapeutic strategy for advanced HNSCC patients. Further study of this regimen in clinical trails may be warranted [53].

4. Mammalian target of rapamycin (mTOR) inhibitors

PI3K/Akt signal transduction pathway has a great impact on regulating cell growth and proliferation, and it is found to be abnormally expressed in various tumor tissues. mTOR is an atypical serine/threonine protein kinase. As a downstream molecule of P13K/AKT signal transduction pathway, it plays a key role in tumor development, invasion, metastasis and angiogenesis [54,56]. Over-expression of phosphorylated mTOR(p-mTOR) has been proved to be associated with poor prognosis of oral cancer. Li et al. reported that 85(53%) of 160 patients with tongue squamous cell carcinoma were found to have over-expression of p-mTOR.The 5-year OS and PFS rates were 41% and 39% respectively, while those with low expression of p-mTOR were 64% and 57%,respectively [55]. mTOR inhibitors restrain the growth of tumors and make them sensitive to radiation, cytotoxic drugs and EGFR inhibitors [56]. At present, some small molecule agents, including rapamyecin and its derivatives, such as temsirolimus and everolimus, are being tested in various cancerous clinical trials [57].

Rapamycin is limited in its application due to its poor water solubility, poor absorption capacity and low bioavailability. **Temsirolimus** is a prodrug converted to rapamycin after intravenous infusion. Studies have demonstrated that temsirolimus can inhibit the proliferation and migration of HSC-2 OSCC cells in vitro, and suppress the growth of xenografts of OSCC in vivo. In the study of Okui et al., it was found that temsirolimus blocked the mTOR signaling to inhibit bone destruction related to the invasion of OSCC not only by suppressing osteoclastogenesis and osteoclast function, but also by inhibiting the proliferation and migration of tumors, indicating that mTOR was the critical mediator of osteolytic destruction in the microenvironment of bone tumors [58]. In a multicenter phase II trial that recruited 40 patients with recurrent and metastatic HNSCC (including OSCC) who received platinum-based chemotherapy or cetuximab before, the PFS rate was 40% after 12 weeks of treatment with temsirolimus, 57.6% of patients were stable, and 39% of patients with shrinkage tumors, but the median PFS and OS were shorter at 56 and 152 days, respectively [59].

Everolimus, an oral active derivative of rapamycin, has been approved for the treatment of advanced renal cancer, progressive or metastatic pancreatic neuroendocrine tumors that cannot be resected, and advanced estrogen receptor(ER) positive and HER-2 negative breast cancer [60]. It is currently in phase II/III clinical trials as an anticancer drug, either alone or in combination. And it has been proved to be able to enhance DNA damage induced apoptosis of tumor cells and increase the radiosensitivity to cancer cells [61]. In vitro studies, everolimus has also been shown to have anti-angiogenesis and anti-tumor cell proliferation effects. However, studies have confirmed that the anti-angiogenesis mechanism of everolimus was different from that of the inhibitors of EGFR, and the efficacy could be enhanced when combined with these drugs [62]. But the results of clinical trials conducted in everolimus were discouraging due to the highly toxicity. In a small phase II trial, the median PFS and OS were just 1.5 and 4.5 months, respectively.What's worse, three patients withdrew due to toxicity [63]. Fortunately, the combination of erlotinib and everolimus was well tolerated, with median PFS and OS at 11.9 weeks and 10.25 months, respectively [64]. However, the therapeutic effect of temsirolimus combined with erlotinib was poor. Among the 12 patients recruited, 50% of them withdrew from treatment on account of severe toxicity mainly including fatigue, diarrhea, pneumonia and head and neck edema, with the PFS of 1.9 months and the median OS of 4.0 months [65]. Owing to the lack of clear and predictable biomarkers and the limited sample size, mTOR inhibitor combinations failed to achieve significant clinical benefits in the treatment of OSCC [66].

5. Agents targeting the programmed cell death receptor 1 (PD-1)

Immunotherapy has become an increasingly attractive strategy in cancer treatment, which improves the body's defense against tumors by activating the patient's normal immune system. Programmed cell death receptor-1 (PD-1) belongs to the CD28 family and is expressed on T cells, DC cells, natural killer cells, macrophages and B cells [67]. And programmed cell death ligand 1(PD-L1), also known as B7-H1 or CD274, is a co-stimulatory molecule with important regulatory functions in cellular immunity. PD-1 binding with PD-L1 will lead to the non-responsiveness and/or apoptosis of effector T cells, thus resulting in immune escape of tumor [68]. Researchers reported that 50–90% of oral cancer patients showed over-expression of PD-L1 [69]. The increased expression of PD-L1 and PD-1 also showed to be positively correlated with cervical lymph node metastasis, and their co-expression was related to the prognosis of various malignant tumors such as OSCC, melanoma and NSCLC [70,71]. Immune checkpoint inhibitors targeting the interaction of PD-1 on T cells with the PD-L1 on cancer cells have been shown to extend the survival of patients with advanced OSCC. Through the study of oral carcinogenic model in mice, it was found that anti-PD-1 treatment could significantly reduce the oral lesions in mice and prevent their malignant progression, thus proving that blocking PD-1 could control oral precancerous lesions [72].

At present, there are two drugs that target PD-1,**pembrolizumab** and **nivolumab**, which have been approved by FDA for the treatment of advanced melanoma and have been shown to significantly improve PFS and OS in patients with melanoma [73]. Pembrolizumab,a humanized monoclonal antibody, was approved by FDA for recurrent or metastatic HNSCC patients in August 2016, with an objective response rate(ORR) of 18.2% and a severe adverse reaction rate of 7.6%, and the tolerance was good [73,74]. In 2016, the American Cancer Society published the results of a phase III clinical trial of nivolumab for platinum-refractory HNSCC(including OSCC) patients. It came out that nivolumab reduced the risk of death by 30% compared with those assigned to receive one of three single-agent chemotherapies-docetaxel or methotrexate or cetuximab, with a median OS of 7.5 months and 5.1 months, respectively.Moreover, 1-year survival rate was double that of patients given single-agent chemotherapy, reaching 36% [75]. Trials are currently underway to evaluate the efficacy of nivolumab in combination with chemotherapy and/or radiotherapy for locally advanced OSCC and other HNSCCs.

6. Cyclin-dependent kinase (CDK) inhibitors

Cancer is a pathological manifestation characterized by hyper-

proliferation of cells. Actually, the excessive proliferation of malignant cells is always associated with altered expression of cyclin-dependent kinases(CDKs) and their regulators [76]. After all, cell cycle is normally controlled by cyclin and its regulatory partner, CDKs.CDKs, protein kinases belonging to the serine/threonine subfamily, are heterodimer complex composed of a catalytic kinase subunit and a regulatory cyclin subunit. Based on their functions, CDKs can be divided into two subgroups:cell cycle CDKs (e.g. CDK1,CDK2, CDK4 and CDK6) and transcriptional CDKs (e.g. CDK7, CDK8 and CDK9) [77]. The activity of CDKs is considered to be regulated by phosphorylation and dephosphorylation of the catalytic subunit. CDK-activation kinase (CAK) regulates the normal function of CDKs through positive phosphorylation, while endogenous inhibitors,CIP/KIP (including p21/CIP/WAF1,p27/KIP1 and p57/KIP2) or INK4 (including p16/INK4A,p15/INK4B,p18/INK4C and p19/INK4D), direct negative phosphorylation events through protein-protein interactions with individual cyclins or CDK-cyclin complexes [77–79].

Specifically, the CDKs, which have been identified to regulate the transition of different phases of the cell-cycle, are the key components of cell-cycle initiation, progression and control. Increased expression of cyclin and CDKs or decreased levels of endogenous CDK regulators/inhibitors such as INK4 or CIP/KIP have been observed in a variety of malignancies [76]. For instance, increased expression of CDK1, especially cyclin B1, is frequently observed in many advanced cancers such as colon, lung,breast, oral cavity, prostate and esophageal cancers [77]. Chang et al. claimed that the expression of CDK1 gene in OSCC was 17.2 times of that in normal tissues, and its over-expression was associated with malignant behaviors [80]. Chen et al. also found that CDK1 protein was over-expressed in patients with recurrent OSCC or lymph node metastasis, and the 5-year cumulative survival rate of CDK1 positive cases was significantly lower than that of the CDK1 negative ones ($P < 0.05$). It seems that the expression of CDK1 is a prognostic indicator of OSCC survival [81]. Nagata et al. studied the correlation between the expression of 11 cell-cycle related genes in OSCC tissues and clinical events. The results showed that CDK gene expression rates such as CDK1/CDKN1B and CDK2/CDKN1A could be used as reliable parameters for evaluating lymph node metastasis (LNM), primary site recurrence (PSR), distant metastasis and disease-specific death (DSD) risk. Among them, CDKN1B (p27) and CDKN1A (p21) are CDK inhibitors belonging to the CIP/KIP family [82]. Notably,down-regulation of p27 protein, an endogenous CDK inhibitor, was also observed in 87% of OSCC cases, which was well correlated with metastasis and poor prognosis. Interestingly, proteasome inhibitors can induce OSCC cell apoptosis through the accumulation of p27 [83]. Likewise, the expression of p16 was down-regulated in oral cancer, whose inactivation was considered as an early event of oral cancer [84].

Because of the significant role of CDKs in cell-cycle regulation and cellular transcription, they have become natural targets for anti-cancer therapy. Moreover, studies have elucidated that CDK inhibitors have therapeutic potential for a variety of diseases, including cancer, diabetes, kidney disease, neurodegenerative diseases and infectious diseases [85]. At present, numerous CDK antagonists are promoted in clinical trials to treat a variety of malignant tumors. CDK inhibitors such as flavopiridol, palbociclib and ribociclib are being tested in phase I/II clinical trials.

Flavopiridol,a semi-synthetic flavonoid-based pan-CDKs inhibitor, is the first CDK inhibitor used in human clinical trials. Flavopiridol has been reported to inhibit cell proliferation by blocking G1/S and G2/M phases and induce cytotoxicity by inhibiting transcriptional CDKs such as CDK7 and CDK9. Moreover, it was found to inhibit the growth of OSCC cells in a time-and dose-dependent manner. Mihara et al. were amazed to find that the expression of cyclin A, cyclin B and cyclin D1, CDK1 and CDK4 decreased after exposure to flavopiridol, respectively.Furthermore, although the expression of Bcl-2 and Bax remained unchanged,Bcl-xL was down-regulated and Bcl-xs was up-regulated after exposure to flavopiridol, suggesting that flavopiridol not only inhibited CDKs directly, but inhibited the activation pathway of CDKs and activated Bcl-x apoptotic pathway to induce OSCC cell apoptosis [86]. Regrettably, flavopiridol failed to yield desirable clinical results in phase II studies of tumors like metastatic melanoma, endometrial carcinoma and multiple myeloma, and its development as a single cancer treatment agent was also forced to terminate due to unwanted pharmacological effects, such as bone marrow suppression and diarrhea [77]. Fortunately, flavopiridol may enhance the antitumor effect of chemotherapeutic drugs. Some researchers also found that flavopiridol could suppress DNA repair and led to cell-cycle redistribution by the inhibition of CDKs to enhance the radiosensitivity of tumor cells [87]. In this sense, flavopiridol combined with radiotherapy and/or chemotherapy may be a feasible option.

Palbociclib and **ribociclib** are two selective small molecule inhibitors of CDK4/CDK6, which have been approved by FDA for the treatment of advanced breast cancer [77]. In addition to inhibiting CDK4/6, palbociclib has been reported to induce G1 arrest by blocking the phosphorylation of retinoblastoma protein (RB) and its related proteins such as p107 and p130 [77,88]. Recent studies have clarified that up-regulation of EGFR can also induce the elevation of cyclin D1 and CDK4 [89]. Therefore, the combination of CDK inhibitors and EGFR inhibitors may be a good scheme. In phase I trials, palbocilib in combination with cetuximab was designed to treat cetuximab-resistant and platinum-resistant patients with recurrent/metastatic HNSCC(including OSCC), and 88% disease control rate was achieved. The optimal tumor response in the patients with cetuximab resistance was partial response (PR) in 1, disease control (DC) in 5, and the median time-to-progression (TTP) was 112 days (range: 28–168). While in platinum-resistant cases, the best tumor response was PR in 1, DC in 3 and median TTP for 112 days (range:28–112 days). The combination of the two drugs was considered safe [90]. However, the efficacy of ribociclib combined with cetuximab did not meet the expectations. One patient out of six developed dose-limiting toxicity (DLT) (grade 4 thrombocytopenia lasting more than 7 days). The most common 3/4 grade treatment-related adverse events were neutropenia (n = 2), anemia (n = 2),thrombocytopenia (n = 1),hypocalcemia (n = 2), hypokalemia (n = 2),hypomagnesemia (n = 1) and hypoglycemia (n = 1) [89].

According to the current clinical results of CDK inhibitors, little clinical benefits have been achieved. We have to admit that the development of single-selective CDK inhibitors becomes extremely difficult due to the high similarity between ATP binding sites of CDKs, which simultaneously determines current CDK inhibitors have the problems of indiscriminate killing of normal cells in proliferation and the limited efficacy of selective drugs targeting cell-cycle to regulate CDKs [91]. It has been reported that at least 21 kinases share more than 70% structural and sequence homology in regard to CDK2-ATP binding site [77]. More intensive efforts should be made to develop isoform-specific CDK inhibitors. The good news is that, the study of the crystal structure of different CDKs will help to design more effective subtypes of CDK inhibitors.

7. Other potential targets

7.1. Cyclooxygenase-2 (COX-2) inhibitor

Cyclooxygenase(COX), also known as prostaglandin synthase, is a rate-limiting enzyme for conversion of arachidonic acid into prostaglandin, containing two subtypes,COX-1 and COX-2. COX-2 is always over-expressed in many cancers, including OSCC, but rarely expressed in normal mucosa [92]. It plays an important role in tumor growth and proliferation by affecting mitosis, cell adhesion, immune monitoring, apoptosis and angiogenesis [93]. Celecoxib is a non-steroidal anti-inflammatory drug that selectively inhibits COX-2. It has been found that celecoxib could significantly inhibit the adhesion, movement, invasion and metastasis of Tca8113 cells of human tongue squamous cell carcinoma, indicating that COX-2 may be an important gene promoting the

invasion and metastasis of OSCC cells [94]. In addition, the association between COX-2 and EGFR has been suggested. The effects of the combination of celecoxib with cetuximab on the growth of tumor cells in nude mice were studied by utilizing OSCC xenotransplantation model. It was found that low concentration of cetuximab and celecoxib combined application could largely inhibit proliferation, migration and invasion of HSC-3 tumor cells, and reduce the production of PEG2 and the expression of vascular endothelial growth in vitro. The results also showed that this combination regimen could significantly induce apoptosis compared with the two drugs alone [95]. Moreover, the combination of erlotinib and celecoxib also has been shown to synergistically inhibit the growth of OSCC cells [96]. Therefore, combined therapy targeting these two pathways is a potential drug candidate for the treatment of OSCC.

7.2. Endostatin

Endostatin, functioned as a specific endogenous angiogenesis inhibitor, has been shown to promote endothelial cells apoptosis and inhibit the binding of VEGF to endothelial cells by binding to heparin sulfate(HS), integrin and nucleolin receptors on endothelial cells, thus suppressing the proliferation of tumor cells and angiogenesis [97]. Hsu et al. investigated the association between endostatin and tumor growth and lymph node metastasis in animals implanted with oral cancer cells, revealing that endostatin may be responsible for inhibiting lymphangiogenesis and lymph node metastasis by down-regulating the production of VEGF-C in tumor cells. In addition, immunohistochemical analysis also uncovered the expression of endostatin was negatively correlated with lymph node metastasis [98]. It has been reported that endostatin combined with chemotherapy was effective in the treatment of refractory tumors including HNSCC, NSCLC and other solid tumors which are not sensitive to chemotherapy [99]. Therefore, endostatin is considered to be an effective candidate for treating OSCC.

8. Conclusion

Targeted therapy emphasizes the treatment of cancer at the molecular level, which is highly targeted and specific, greatly reducing the host toxicity and improving the quality of life of patients. As a potential new method, it has been widely used in the treatment of OSCC and other malignant tumors, and has good prospects for development. At present, the clinical progress of new targeted therapy drugs has fully demonstrated the correctness and feasibility of the theory of targeted therapy. However, as a multi-factor,multi-step and multi-gene inherited disease, oral cancer is still not fully understood in terms of its molecular pathogenic mechanism. Worst of all, it is prone to mutation during its development process, resulting in many challenges for targeted therapy, such as molecular identification, drug resistance and the exploration of reliable biomarkers. Although it is possible to improve the drug resistance of cancer through combination with radiotherapy and chemotherapy or multi-target combination therapy and multi-target sequential therapy, it is still unable to fundamentally solve this problem according to the theories and technologies we have mastered at present. However, we are firmly convinced that with the development of various disciplines and technologies, targeted technology will continue to improve. It is believed that in the near future, targeted therapy can replace the traditional methods and become the first choice for tumor treatment.

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Authors' contributions

Lian Liu, Jili Chen, Xinjia Cai, Zhigang Yao, Junhui Huang contributed to draft the manuscript text.Lian Liu and Junhui Huang designed the concept and Lian Liu mainly drafted and revised the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors have declared that there are no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.suronc.2019.09.001.

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