ADJUVANTS THERAPY IN ORAL CANCER

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ABSTRACT Oral cancer management is multimodality and multidisciplinary. Surgery is still the primary procedure for oral cancer treatment. Primary radiation therapy also recommended as a primary treatment, particularly intolerant or unwilling operation patients. Postoperative radiation therapy improved survival and regional control. Intensity modulation radiation therapy enhanced radiation toxicity and quality of life. Neo-adjuvant chemotherapy had minimum benefits related to Disease-free survival (DFS) and Overall survival (OS), despite tumor shrinkage. However, platinum-based chemotherapy adjuvants along with radiation in patients with advanced stage increases locoregional control improved DFS and OS.

Over-expression of Epidermal Growth Factor Receptor (EGFR) showed poor prognosis in oral cancer. Targeting EGFR therapy emerged potential procedure combined with chemoradiotherapy in improving eradication of cancer. Therefore, novel molecular targeting therapy had been explored for oral cancer therapy. Photodynamic therapy has been a treatment procedure involving administration of photosensitizers, followed by light radiation, used as palliative treatment for relapsed or resistant to treatment of head and neck cancer. Deficiency of specific immune systems contributed to outcomes treatment of oral cancer. Immunotherapy intended to stimulate a robust immune system against the cancer cell. The selection of treatment determined probability of cancer eradication, preventing cancer relapse, oral function and cosmetic outcomes, performance status and availability of resources and expertise. Adjuvant therapy played a role in oral cancer treatment as most patients came in an advanced stage.

KEYWORDS adjuvant therapy, oral cancer, Radiotherapy, Chemotherapy, Immunotherapy, Photodynamic

1. Introduction

Oral cancer is a kind of cancer on the surface of lips mucosa, mouth, tongue, buccal mucosa, upper and lower gingiva, retro-molar trigone, soft and hard palate [1]. Oral cavity has complex anatomy and its function such as speaking, swallowing, and face projection [1]. Globally, oral cavity cancer was about 300,400 new cases and 145,300 cancer death in 2012 [2]. Most of the oral cancers suffered by Asian and estimated 168,850 new cases and approximately 11% were from Southeast Asian people [3]. It was about 18,071 oral cancer cases in Southeast Asia and 8,508 cancer death in 2012 [3]. While, oral cancer in Indonesia was about 5,329, and 2,250 cancer death [3]. About 60% of oral cancer patients were in an advanced stage, and average five years survival was under 60%, and recurrence range was from 30% to 47% [2,4]. Quality of life of postoperative oral cancer patients through surgery and radiotherapy had functional disabilities and psychosocial morbidities such as mucositis, xerostomia, and fibrosis [5,6].

The purpose of the oral cancer management is cancer-free, preventing relapse, preventing the emergence of new cancer, and recovering oral cavity function and cosmetics [7]. Early-stage oral cancer could be treated by surgery or radiation [7,8]. However, most patients were in an advanced stage, the results of the treatment were less satisfied [7,8].

The primary treatment for oral cancer is surgery, and surgical resection is the fastest method of eradicated cancer [9,10]. Although solely radiotherapy was recommended by the National Comprehensive Cancer Network (NCCN) guidelines for early-stage cancer, however, a combination of chemo-primary
Radiotherapy often conducted if the operation method was impossible because of the extent of cancer, the physical condition of patients and deficit resection results [8-9]. Thus, primary radiotherapy combined with chemotherapy was for intolerant or unwillingly operation procedures patients [8-9].

Epidermal growth factor receptor (EGFR) targeted biological agents combined with chemoradiotherapy was a potential therapy and currently being evaluated in clinical trials [10,11]. While photodynamic therapy was a treatment procedure that involved photosensitizer and radiation. Nowadays, photodynamic palliative treatment therapy was used for head and neck cancer [12,13].

In early stage cancer, the single therapy of surgery is a prior treatment of choice. Unfortunately, most patients were in advanced stages for which treatment results were unsatisfied. In that case, adjuvant therapy played a role. Apart from a wide range of surgical, adjuvants and molecular pathogenesis mechanisms therapies, oral cavity cancer prognosis remained poor, particularly in advanced stage cancer [14]. This paper discussed the role of adjuvants in oral cancer management, molecular targets and future therapeutic strategies.

2. Radiotherapy

Radiotherapy used two methods, i.e., external beam radiation therapy (EBRT) or brachytherapy, with or without systemic therapy (chemotherapy agent and therapeutic targeting). EBRT was generally used as a) adjuvant operation to increase regional controls for unfavourable pathological characteristics, b) primary cases for intolerant surgery and c) treatment in recurrent or persistent cancer [8,9,15]. Brachytherapy was radiotherapy method with positioning radioactive source to target area [15,16]. The advantage of brachytherapy was right dose distribution in a small target area. Radioactive brachytherapy source used was I-125 and Ir-192 [15,16]. Low-dose Brachytherapy (LDR), high-dose Brachytherapy (HDR) and pulsed-dose rate (PDR) brachytherapy techniques offered optimisation of dose distribution with changing half-life radioactive with computerised planning and delivery. Brachytherapy could be used as a) the initial stage of apparent primary tumour (superficial, unbound firmly and located more than 5 mm from mandible), b) as an adjuvant to surgery in close or positive resection margin, c) As external combined radiotherapy to increase dose in high-risk areas [15,16,17].

An indication of radiation therapy post surgery (PORT) was for advanced stage cancer, pN2 pN3, perineural invasion until extracapsular invasion and a positive margin [15,16,17]. Although the prognosis was poorly associated with these variables, the addition of a PORT increased survival and locoregional control (LRC) [17].

A Retrospective Study compared surgery solely, and PORT combined surgery showed that a significant increase in the LRC, Disease-free survival (DFS) and Overall survival (OS) on the PORT group. Although patients might experience longer survival with the PORT, the potential toxicity of radiation both acute or chronic either significantly affected patient’s quality of life (QoL) [17,18].

Intensity Modulated Radiation Therapy (IMRT) replaced conventional radiotherapy. IMRT had less radiation side effects and quality of life improvement, although comparison of survival showed no difference between conventional and radiotherapy IMRT. Therefore, IMRT would be a standard PORT treatment for oral cavity cancer [15,16].

After surgery, left cancer cells would result in recurrence. The remained a tumour was more resistant in the presence of a post-operative scar, mutant, and hypoxia. Therefore, the interval time of radiotherapy post operating remained controversial. Previous literature showed that there were an increased odds ratio rate of local recurrence head and neck cancer patients who started adjuvant radiotherapy more than six weeks after surgery [15-17]. Other retrospective study showed there was a poor influence due to delay in PORT initiation [15-17]. Therefore it was recommended that radiation conducted within six weeks after surgery [16]. Delay in beginning radiotherapy had severe consequences, such as regional recurrence that might prevent [15-17].

Radiotherapy had toxic side effects. Acute toxicity included oral mucositis and dysphagia. It showed the increase of incidence of irradiation bilateral, though it was self-limiting [17-18]. Further toxicity effects were Osteoradionecrosis (ORN), xerostomia and dysphagia [17-18]. Toxicity also increased with chemoradiation combined with PORT. Acute and severe toxicities in trials of RTOG 9501 reported by Cooper et al. showed each of PORT was 46%, and Postoperative chemoradiotherapy (POCRT) was 78%. While the trial of EORTC 22931 showed the level of muscular fibrosis higher on POCRT (10% vs 5%) and lowered xerostomia [14% vs 22%] [17-18]. Spontaneous ORN depended on dose and volume related to mandible which received radiotherapy exceed than 50-60 Gy [17-18].

3. Chemotherapy

In oral cavity Carcinoma, chemotherapy was used as; (a) adjuvant postoperative on high risk, (b) for advanced stage post-surgery patients (c) Primary treatment for unwillingly operation cases, (d) recurrence cases, and (d) palliative chemotherapy [19].

The most frequent chemotherapy drugs used for oral cavity cancer was the taxanes (paclitaxel and docetaxel), adriamycin (anthracyclines and epirubicin), platinum (cisplatin and carboplatin), and antimetabolites (methotrexate and 5-fluorouracil) [19,20].

The role of neoadjuvant chemotherapy was still controversial [19]. In a previous random study of neoadjuvant chemotherapy with cisplatin and fluorouracil (PF) post-surgery compared with sole surgery, the five-year survival rate was the same, i.e., 55% [19]. However, the primary chemotherapy appeared to play a role in decrease size of tumours, reduce the number of patients who needed mandibulectomy, radiation therapy, or both. However, more extensive studies suggest neoadjuvant chemotherapy should not recommend for clinical use of [19].

Regarding concomitant postoperative platinum-based chemotherapy and radiation (CRT) in advanced stage patients, Head and neck squamous cell carcinoma (HNSCC) showed good results in the LRC, DFS, and OS. While European Organisation for Research and Treatment of Cancer (EORTC) 22931 research, LRC rate (RT 69% vs. 82% CRT, p= 0.007) and RTOG-9501 research (RT 72% vs. 82% CRT, p= 0.011), showed patient with CRT repaired LRC significantly in 5 years, EORTC 22931 research showed rate for DFS (RT 36% vs. 47% CRT, P = 0.04). Radiation Therapy Oncology Group (RTOG)-9501 research showed a rate of RT 30% vs. CRT 40%, p = 0.04 [19-21]. Others, RTOG-0234 research showed adding adjuvant cetuximab with adjuvant chemoradiotherapy had better OS. For cisplatin groups had HR 0.72 (P = .04), and docetaxel Group of HR 0.69(P = .001). There was a reduction of metastatic far on docetaxel and cetuximab up to 45% [19-21].

Despite aggressive surgery with adjuvant therapy, it was
about 50% of patients experienced recurrent or metastasis. Palliative chemotherapy was one of the treatment options[19-21]. Purpose of palliative chemotherapy was to lengthen survival without disrupting the quality of life[19-21]. The most frequent regimen was a combination of cisplatin plus 5-FU, with response rates was approximately 30%. Platinum combined with paclitaxel with 32-48% response rate, and docetaxel combined with cisplatin had 33-50% response rate for acceptable toxicity. The trial of Eastern Cooperative Oncology Group (ECOG) and Southwest Oncology Group (SWOG) were to compare cisplatin 5-FU without disrupting the quality of life[19-21]. The most frequent patients [22-23].

platinum-based chemotherapy was significantly prolonged OS in platinum-fluorouracil regimens had not affected the quality of life of recurrent or metastasis HNSCC patients. Platinum chemotherapy combined with cetuximab currently became the first-line standard therapy for HNSCC recurrent or metastatic patients [22-23].

5. Photodynamic Therapy

Photodynamic Therapy (PDT) was a treatment procedure with sensitive light drugs, known as a photosensitizer, followed by light wavelengths as responding with a sensitiser. In rich oxygen tissues, free radical cytotoxic resulted in direct death tumour cells, microvascular damage, and induction of inflammatory reaction on target location [24-25].

Photodynamic Therapy used for cancer treatment because of specificity and sensitivity in tumour cells. Antitumor effect of PDT resulted in the death of tumour cells directly or blood vessels damage of tumours and activation of non-specific immunity system and specific tumour cells indirectly [24-25]. Because of the location and visibility of direct oral cavity cancer was an ideal model for photodynamic therapy [24-25].

Previous research studies reviewed benefits PDT for treatment of head and neck cancer, included oral cavity [24-25]. Retrospective study results and clinical trials reported that PDT was an appropriate alternative procedure for early-stage oral cancer as morbidity was much lower compared with conventional therapy. Superficial cancer in the range of permeability of light sources (i.e., 0.5-1 cm) showed the best response. Advantages of PDT compared with conventional treatment, such as surgery, radiotherapy, and chemotherapy was having a potential saving of tissues, maintaining oral cavity and cosmetic function long-term good, improving quality of life, repeated therapy in the same recurrent lesion, minimal scar, cost-effectiveness, and simplicity of the technique of [24-25].

In case of recurrent or development of new primary tumour area was previously conducted PDT, PDT therapy could be repeated in the same area several times without cumulative toxicity, in spite of extensive morbidity of ionising radiation or surgery. Also, conventional therapy would not interfere with the PDT procedure and vice versa [24-25].

6. Immunotherapy

There are many types of Immunotherapy to treat cancer: a) Monoclonal Antibodies, Targeting EGFR (cetuximab and nimotuzumab), Targeting PD-1 & PD-L1 (nivolumab and pembrolizumab), b) Cancer Vaccines: Protein-based (p53, MAGE, or HPV), Cell-based (dendritic cell-based). c) Nonspecific Immunotherapies; IL-2, IFN-α, IFN-γ, IRX-2 [26,27].

The decline of the specific immune system due to conventional therapy influenced the outcome of long-term treatment. Purpose of Immunotherapy was stimulating the immune system against the lasting cancer cell. Immunotherapy was a new option for HNSCC patients treatment. HNSCC would not be affected by the immune system by means of 1) escaped from the immune system recognition through down-regulation of human regulation of antigen (HLA), immunosuppressive factor secretion 2)-prostaglandin E2, vascular endothelial growth factor (VEGF), Interleukin (IL-10), or transforming growth factor-β, 3) inhibited T cell function known as regulatory T cell (Treg) [26,27].

Systemic cell-mediated Immunotherapy in HNSCC such as Cytokine-based immunotherapy functioned by delivering cytokines proinflammation both in regional and systemic antitumor responses. Some cytokines were more explored for HNSCC treatment, including GM-CSF, IL-2, IFN-γ, IL-12, and IRX-2 [26,27].

Immunotherapy Antibody Monoclonal Antibody (MAb) such as EGFR inhibitors had been developed its function by binding
domain extracellular, a binding ligand of EGF receptor (e.g., cetuximab), or inhibiting receptor activity of intracellular tyrosine kinase. Another treatment strategy was immunotherapy: via MAb plus radiotherapy which targeting CEA, an antigen founded on the surface of the majority of HNSCC patients. Phase 1 trial was high doses of 90Y such as labelled anti-CEA humanised MAb, combined with doxorubicin. It had been proved the results with excellent tolerate and antitumor activity [26,27].

Recent updates to the NCCN 2018 Guidelines for Head and neck cancer: Addition of nivolumab and pembrolizumab for the treatment of recurrent or metastatic Head and neck cancer [28]. Nivolumab prolonged survival, as compared with standard therapy, among patients with platinum-refractory squamous-cell carcinoma of the head and neck. Nivolumab was associated with fewer toxic effects of grade 3 or 4 than standard therapy (13.1% vs 35.1%) and with the maintenance of quality of life among patients with treatment-refractory cancer that otherwise has serious adverse effects on quality of life as it leads to death [29]. Nivolumab improved OS and objective response rate (ORR) in CheckMate 141 trial, with a manageable safety profile [30].

Cancer Vaccines had been researching used protein base and base cell dendritic nanotechnologies methods such as: 1) protein base, combined with 1 or more peptide/protein were expressed by HNSCC like p53, MAGE, or HPV. It was expected that the immune system in response to adjuvant therapy, reacted to tumour cells by expressing specific antigens. 2) dendritic cell base was dendritic cells removed from cancer patients through leukapheresis and stimulated with appropriate tumour antigens, then injected back into the patient then body activated specific T cells against a tumour [27,29].

Summary
In conclusion, with advanced surgery and adjuvant therapy, early-stage oral cancer has a good quality of life, an increase in disease-free survival and overall survival rate. However, advanced stage oral cancer was still in poor prognosis and survival. Currently, surgical Management followed by adjuvant therapy remained to become a therapeutic procedure for oral cancer. Chemoradiotherapy with new chemotherapeutic agents, target- ing therapy, immunotherapy and photodynamic therapy were optional treatments for oral cancer, which those were continu- ously researched and expected improved treatment outcomes for oral cancer patients.

Competing interests
The authors declare that they have no competing interests.

References


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