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Letter to the editor

Immunotherapy is a preferred option for oral cancer patients during COVID-19 pandemic?



Dear Editor,

Currently, the outbreak of coronavirus disease 2019 (COVID-2019) has become the chief public challenge for many countries across the world. COVID-2019 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with high infectivity [1]. By 2th of June 2020, more than six million individuals were confirmed, with 376,320 deaths [2]. To control and defeat the pandemic of COVID-2019, some strategies are advisable, which include isolation, social distancing and hand hygiene [3,4]. In addition, treatment modalities for oral cancer have to be prudentially modified during this special period (Table 1). In the article published in your journal, experts have recommended temporarily postponed surgery for oral cancer patients, when nonsurgical treatments are equivalent to surgery [4,5].

In this scenario, radiotherapy with or without concomitant chemotherapy ((C)RT) plays an important role in treating oral cancer. Chemotherapeutic medicines often include platinum, paclitaxel, fluorouracil and others in clinic, which have been demonstrated the curative intent in preserving organs [6,7]. However, these cytotoxic medicines could kill both cancer cells and normal human cells, leading to adverse events such as diarrhea, myelosuppression and immune suppression etc [8,9]. And patients experienced (C)RT become more susceptible to infection of virus such as SARS-CoV-2, though N95-respirators and other personal protective equipment may protect them from COVID-2019 infection [10].

Immune checkpoint inhibitors (ICIs), especially programmed death 1(PD-1)/ programmed death ligand 1(PD-L1) inhibitors, has achieved great progression in treating head and neck cancers during recent decades. As one of PD-1 inhibitors, pembrolizumab has shown the superior effectivity and safety in treating head and neck squamous cell carcinoma (HNSCC) than standard chemotherapies, with median overall survival 8.4 months versus 6.9 months ($P < 0.01$) [11]. Nivolumab also has been demonstrated to improve survival of refractory HNSCC patients compared with standard single-agent therapy [12]. Based on above randomized controlled clinical trials, pembrolizumab and nivolumab have been approved by Food and Drug Administration (FDA) to treat patients with recurrent or metastatic HNSCC [11,13].

Considering clinical benefits of immunotherapy, we hypothesized that ICIs might be a better option than conventional chemotherapies, when oral cancer patients require to make a delicate balance between cancer treatment and COVID-2019 prevention [14]. It is well-known that acquired immunity plays a decisive role in defending against carcinoma and virus infection, which involves subgroups of T lymphocytes. Regulatory T cells (Treg cells) are $CD4^+$ T cells, and function as the effectors of immunosuppression by producing IL-10 or express PD-1/PD-L1 [15–17]. Thus, PD-1 blockade could inhibit the suppressive function of Tregs and improve immunocompetence of oral cancer patients against COVID-2019 infection [18]. In addition, PD-1/PD-L1 in-

hibitors may be effective in patients initially infected by COVID-2019. It reported that progression of COVID-2019 involves different subsets of 'exhausted T cells'(Tex) [15]. Compared with Tex at advanced stage, Tex at early stage are obviously responsive to PD-1 blockade. Besides, the expression of PD-1 was significantly increased, when COVID-2019 patients deteriorated to severe symptoms requiring intensive care. Apparently, PD-1 has close contact with the pathogenesis of COVID-2019, which indicating the possible efficacy of PD-1/PD-L1 inhibitors in treating COVID-2019 patients at early-stage. However, receiving PD-1/PD-L1 inhibitors may cause lung toxicity, which further exacerbate pneumonia caused by COVID-2019. The incidence of lung toxicity associated with PD-1/PD-L1 inhibitors ranges from 2% to 4% in HNSCC patients [9,19]. Though the incidence low, lung toxicity remains the most fatal adverse event associated with PD-1/PD-L1 inhibitors. Therefore, the possible overlap between immuno-related lung toxicity and COVID-2019 related pneumonia should be considered, especially when oral cancer patients receiving PD-1/PD-L1 inhibitors. Taken together, immunotherapy such as PD-1 inhibitors might be preferred in oral cancer patients with or without COVID-2019 infection, and treatment-related lung toxicity ought to be cautiously considered. This hypothesis remained to be validated or refuted by informative data in future, and the appropriate intervention for oral cancer patients should be judged after evaluating personal condition.

In conclusion, the COVID-2019 outbreak has involved over 200 countries across the world, and posed tremendous challenge to the treatment of oral cancer patients. On one hand, oral cancer patients are vulnerable to COVID-2019 infection, owing to the immunosuppress caused by disease progression or received treatment. On the other hand, temporary deferred treatment for oral cancer patients may result in more intensive surgery and worse outcomes. In this scenario, whether to postpone treatment for oral cancer patients should be decided by evaluating the risk of infection and risk of death after treatment. Considering the close relationship between PD-1 and COVID-2019 infection, immunotherapy such as PD-1 inhibitors might provide an alternative for oral cancer patients, which requires to be validated in future.

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Table 1
Status and strategies for oral cancer patients during COVID-2019 pandemic.

Status	Strategies
1. Be more susceptible to COVID-2019 infection.	1. Social distance, hand hygiene and supplement of nutrition in daily life.
2. Be more vulnerable to adverse complication associated with COVID-2019.	2. Reduce hospital visits and appropriate protective equipment such as medical mask etc.
3. Lack of medical resources to protect patients from COVID-2019 infection.	3. Replace surgery with (C)RT or immunotherapy temporarily to slow disease progression.
4. Postponed treatments promote disease progression and poor prognosis.	4. Screen asymptomatic patients, reduce aerosol-generating procedure and record trajectory, when surgery is urgent.

COVID-2019: coronavirus disease 2019; (C)RT: radiotherapy with or without concomitant chemotherapy.

References

- [1] Del Rio C, Malani PN. COVID-19-New Insights on a Rapidly Changing Epidemic. *JAMA* 2020.
- [2] Coronavirus disease (COVID-19) outbreak situation. Available from: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019>.
- [3] Kennedy DM, Zambrano GJ, Wang Y, Neto OP. Modeling the effects of intervention strategies on COVID-19 transmission dynamics. *J Clin Virol Off Publicat Pan American Soc Clin Virol* 2020;128:104440.
- [4] Meng L, Hua F, Bian Z. Coronavirus Disease 2019 (COVID-19): Emerging and Future Challenges for Dental and Oral Medicine. *J Dent Res* 2020;99:481-7.
- [5] Bhattacharjee A, Patil VM, Dikshit R, Prabhaskar K, Singh A, Chaturvedi P. Should we wait or not? The preferable option for patients with stage IV oral cancer in COVID-19 pandemic. *Head Neck* 2020;42:1173-8.
- [6] Pignon JP, le Maître A, Maillard E, Bourhis J. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. *Radiother Oncol J European Soc Therapeut Radiol Oncol* 2009;92:4-14.
- [7] Tang C, Chan C, Jiang W, Murphy JD, von Eyben R, Colevas AD, et al. Concurrent cetuximab versus platinum-based chemoradiation for the definitive treatment of locoregionally advanced head and neck cancer. *Head Neck* 2015;37:386-92.
- [8] Sato K, Hayashi Y, Watanabe K, Yoshimi R, Hibi H. Concurrent chemoradiotherapy with intravenous cisplatin and docetaxel for advanced oral cancer. *Nagoya J Med Sci* 2019;81:407-14.
- [9] Cohen EEW, Soulières D, Le Tourneau C, Dinis J, Licitra L, Ahn M-J, et al. Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma (KEYNOTE-040): a randomised, open-label, phase 3 study. *Lancet* 2019;393:156-67.
- [10] Balazy A, Toivola M, Adhikari A, Sivasubramani SK, Reponen T, Grinshpun SA. Do N95 respirators provide 95% protection level against airborne viruses, and how adequate are surgical masks? *Am J Infect Control* 2006;34:51-7.
- [11] Larkins E, Blumenthal GM, Yuan WS, He K, Sridhara R, Subramaniam S, et al. FDA Approval Summary: Pembrolizumab for the Treatment of Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma with Disease Progression on or After Platinum-Containing Chemotherapy. *Oncologist*. 2017;22:873-8.
- [12] Ferris RL, Blumenschein Jr. G, Fayette J, Guigay J, Colevas AD, Licitra L, et al. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. *N Engl J Med* 2016;375:1856-67.
- [13] Gavrielatou N, Doumas S, Economopoulou P, Foukas PG, Psyrris A. Biomarkers for immunotherapy response in head and neck cancer. *Cancer Treat Rev* 2020;84:101977.
- [14] Bersanelli M. Controversies about COVID-19 and anticancer treatment with immune checkpoint inhibitors. *Immunotherapy* 2020;12:269-73.
- [15] Chiappelli F, Khakshooy A, Greenberg G. CoVID-19 Immunopathology and Immunotherapy. *Bioinformatics* 2020;16:219-22.
- [16] Schreiber RD, Old LJ, Smyth MJ. Cancer immunoeediting: integrating immunity's roles in cancer suppression and promotion. *Science (New York, NY)* 2011;331:1565-70.
- [17] Xia Y, Jin R, Zhao J, Li W, Shen H. Risk of COVID-19 for patients with cancer. *Lancet Oncol* 2020;21:e180.
- [18] Bersanelli M, Scala S, Affanni P, Veronesi L, Colucci ME, Banna GL, et al. Immunological insights on influenza infection and vaccination during immune checkpoint blockade in cancer patients. *Immunotherapy*. 2020;12:105-10.
- [19] Segal NH, Ou S-HI, Balmanoukian A, Fury MG, Massarelli E, Brahmer JR, et al. Safety and efficacy of durvalumab in patients with head and neck squamous cell carcinoma: results from a phase I/II expansion cohort. *Eur J Cancer* 2019;109:154-61.

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