

World Journal of *Clinical Cases*

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REVIEW

- 3932** Liver replacement therapy with extracorporeal blood purification techniques current knowledge and future directions

Papamichalis P, Oikonomou KG, Valsamaki A, Xanthoudaki M, Katsiafylloudis P, Papapostolou E, Skoura AL, Papamichalis M, Karvouniaris M, Koutras A, Vaitis E, Sarchosi S, Papadogoulas A, Papadopoulos D

MINIREVIEWS

- 3949** Prediction models for recurrence in patients with small bowel bleeding
Kim JH, Nam SJ
- 3958** Investigation of possible relationship between atopic dermatitis and salivary biomarkers, stress, and sleep disorders
Estefan J, Ferreira DC, Cavalcante FS, dos Santos KRN, Ribeiro M
- 3967** Value of clinical applications of differential pressure and relative pressure imaging in the left ventricle
Zheng AS, Yu HX
- 3976** Low-dose immunotherapy as a potentiator to increase the response with neo-adjuvant chemotherapy in oral cancers
Rathinasamy N, Muthu S, Krishnan A
- 3980** Kidney disease in patients with chronic liver disease: Does sex matter?
Cooper KM, Colletta A, Moulton K, Ralto KM, Devuni D

ORIGINAL ARTICLE**Case Control Study**

- 3993** Elabela is a reliable biomarker for predicting early onset preeclampsia: A comparative study
Amer Ali E, Nori W, Salman AF, Al-Rawi TSS, Hameed BH, Al-Ani RM

Retrospective Cohort Study

- 4003** Acute-on-chronic liver failure is independently associated with higher mortality for cirrhotic patients with acute esophageal variceal hemorrhage: Retrospective cohort study
Terres AZ, Balbinot RS, Muscope ALF, Longen ML, Schena B, Cini BT, Rost Jr GL, Balensiefer JIL, Eberhardt LZ, Balbinot RA, Balbinot SS, Soldara J

Retrospective Study

- 4019** Elastic fiber degradation in the development of pediatric granuloma annulare: Report of 39 cases
Zhang DY, Zhang L, Yang QY, Xie YC, Jiang HC, Li JZ, Shu H

- 4026** Anti-bacterial mechanism of baicalin-tobramycin combination on carbapenem-resistant *Pseudomonas aeruginosa*

Jin LM, Shen H, Che XY, Jin Y, Yuan CM, Zhang NH

SYSTEMATIC REVIEWS

- 4035** Acknowledging the use of botanicals to treat diabetic foot ulcer during the 21st century: A systematic review

Narzary I, Swarnakar A, Kalita M, Middha SK, Usha T, Babu D, Mochahary B, Brahma S, Basumatary J, Goyal AK

CASE REPORT

- 4060** Pregabalin induced balance disorder, asthenia, edema, and constipation in an elderly adult: A case report

Ma LP, Wen C, Zhao TX, Jiang XM, Gu J

- 4065** Emergency internal iliac artery temporary occlusion after massive hemorrhage during surgery of cesarean scar pregnancy: A case report

Xie JP, Chen LL, Lv W, Li W, Fang H, Zhu G

- 4072** Hemophagocytic lymphohistiocytosis after autologous stem cell transplantation in angioimmunoblastic T-cell lymphoma: A case report

Zhang ZR, Dou AX, Liu Y, Zhu HB, Jia HP, Kong QH, Sun LK, Qin AQ

- 4079** Successful reconstruction of an ankle defect with free tissue transfer in a hemophilia A patient with repetitive hemoarthrosis: A case report

Lee DY, Lim S, Eo S, Yoon JS

- 4084** Primary pelvic *Echinococcus granulosus* infection: A case report

Abulaiti Y, Kadi A, Tayier B, Tuerkan T, Shalayiadang P, Abulizi A, Ahan A

- 4090** Epstein-Barr virus-induced infection-associated hemophagocytic lymphohistiocytosis with acute liver injury: A case report

Sun FY, Ouyang BQ, Li XX, Zhang T, Feng WT, Han YG

- 4098** Cardiac arrest secondary to pulmonary embolism treated with extracorporeal cardiopulmonary resuscitation: Six case reports

Qiu MS, Deng YJ, Yang X, Shao HQ

- 4105** Flared inflammatory episode transforms advanced myelodysplastic syndrome into aplastic pancytopenia: A case report and literature review

Ju B, Xiu NN, Xu J, Yang XD, Sun XY, Zhao XC

- 4117** Frontal penetrating arrow injury: A case report

Rodríguez-Ramos A, Zapata-Castilleja CA, Treviño-González JL, Palacios-Saucedo GC, Sánchez-Cortés RG, Hinojosa-Amaya LG, Nieto-Sanjuanero A, de la O-Cavazos M

- 4123** Chest wall osteochondroma resection with biologic acellular bovine dermal mesh reconstruction in pediatric hereditary multiple exostoses: A case report and review of literature

Alshehri A

- 4133** Massive pulmonary embolism in Klippel-Trenaunay syndrome after leg raising: A case report
Lo CY, Chen KB, Chen LK, Chiou CS
- 4142** Improved super-elastic Ti-Ni alloy wire intrusion arch for skeletal class II malocclusion combined with deep overbite: A case report
Yang CY, Lin CC, Wang LJ, Chen YH, Yu JH
- 4152** Glucocorticoid pulse therapy in an elderly patient with post-COVID-19 organizing pneumonia: A case report
Park S, Jang Y, Koo SM, Nam BD, Yoon HY
- 4159** Endoscopic and surgical treatment of jejunal gallstone ileus caused by cholecystoduodenal fistula: A case report
Fan WJ, Liu M, Feng XX
- 4168** Application of advanced platelet-rich fibrin for through-and-through bony defect during endodontic surgery: Three case reports and review of the literature
Algahtani FN, Almohareb R, Aljamie M, Alkhunaini N, ALHarthi SS, Barakat R
- 4179** Facial Merkel cell carcinoma in a patient with diabetes and hepatitis B: A case report
Ren MY, Shi YJ, Lu W, Fan SS, Tao XH, Ding Y
- 4187** Pregnancy and lactation-associated osteoporosis with pyogenic spondylitis: A case report
Zhai K, Wang L, Wu AF, Qian Y, Huang WM
- 4194** Hourglass-like constriction of the anterior interosseous nerve in the left forearm: A case report
He R, Yu JL, Jin HL, Ng L, Wang JC, Li X, Gai TT, Zhou Y, Li DP
- 4202** Crohn's disease in human immunodeficiency virus-infected patient: A case report
Vinikaite A, Kurlinkus B, Jasinskaite D, Strainiene S, Buineviciute A, Sadauskaite G, Kiudelis V, Kazenaite E

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Low-dose immunotherapy as a potentiator to increase the response with neo-adjuvant chemotherapy in oral cancers

Narmadha Rathinasamy, Sathish Muthu, Anand Krishnan

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Abstract

Neo-adjuvant chemotherapy (NACT) is utilized in locally advanced oral cancers to reduce the tumor burden and downstage the tumor to be amenable for definitive surgical management. Its long-term results compared to upfront surgical resection was not encouraging. Immunotherapy has now been used not only in recurrence and metastatic setting but also in the locally advanced tumor management regimens. The purpose of this concept paper is to bring forward the rationale to use a fixed low-dose immunotherapy agent as a potentiator to the standard NACT regimen and recommend their future investigation in oral cancer management.

Key Words: Immunotherapy; Neo-adjuvant chemotherapy; Oral cancer

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Core Tip: There is a need to potentiate the effect of neo-adjuvant chemotherapy (NACT) in oral cancers. The utilization of immunotherapy to enhance NACT has been shown to reduce metastasis and recurrence. Hence, the concept of low-dose immunotherapy as a potentiator of NACT could be implemented in routine practice. Moreover, low-dose immunotherapy-enhanced NACT helps us understand the predictors of treatment response.

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INTRODUCTION

Neo-adjuvant chemotherapy (NACT) has been tried in locally advanced oral cancers to obtain a favorable pathological response (< 10% viable tumor cells) along with downstaging the tumor to be amenable for definitive surgical management[1]. However, the long-term results of such management did not result in a significant long-term survival compared to upfront surgical resection without chemotherapy[1]. Hence, there is a need for a synergistic combination with the chemotherapy regimen to potentiate their action and mark a significant effect upon implementation. The increasing evidence demonstrating the effectiveness of immunotherapy in the recurrent and metastatic setting has widened its horizons of utility into the locally advanced tumor management regimens for a host of reasons[2,3]. First, the incorporation of immunotherapy into the curative management protocol would reduce their progression to metastasis and local recurrence. Second, their potential to downsize the tumor thereby reducing the morbidity and the extent of surgical resection are intriguing. Moreover, the addition of immunotherapy in the neo-adjuvant setting would help us understand the predictors of response to such therapy combinations[4]. However, the heightened cost of such a combination limits their investigation. The purpose of this concept paper is to bring forward the rationale to use a fixed low-dose immunotherapy agent as a potentiator to the standard NACT regimen and recommend their future investigation in oral cancer management.

RATIONALE OF LOW DOSE IMMUNOTHERAPY

The receptor occupancy assays of the programmed cell death ligand 1 (PD-L1) molecules expressed on the peripheral blood lymphocytes with the use of a varying dose of anti-PD-1 immunotherapy agents demonstrated saturation kinetics at doses as low as 0.1-0.3 mg/kg demonstrating their avidity to the host receptors[5]. Such affinity at low dose concentrations also lasted for nearly 3 mo post-administration similar to the higher dose regimens. Hence an anti-PD-1 immunotherapy agent such as nivolumab at a concentration as low as 0.1 mg/kg would be sufficient to produce a therapeutic receptor blockade compared to the standard dosing regimens[6]. Moreover, phase-1 studies validated the concept with their finding that the response of the immunotherapy agent does not decrease with the decreased dose thereby demonstrating a non-linear dose-response curve for immunotherapy agents[5-7].

RATIONALE FOR COMBINING NEO-ADJUVANT IMMUNOTHERAPY WITH CHEMOTHERAPY

Immunotherapy orchestrates their action through cytotoxic lymphocytes which react with cancer cells to get activated resulting in cancer cell lysis. However, the effect of immunotherapy agents is limited by the permeability of the cytotoxic lymphocytes and their contact with the cancer cells expressing their respective antigens. The situation is also compounded by the immune suppression counter-mechanisms acting at the tumor site. On the other hand, chemotherapy results in disruption of the tumor stroma thereby increasing the permeability of the cytotoxic lymphocytes and decreasing the production of immune suppressive cytokines produced by the cancer cells. Moreover, chemotherapy increases the expression of tumor antigens to be detected by the cytotoxic lymphocytes as shown in Figure 1[8].

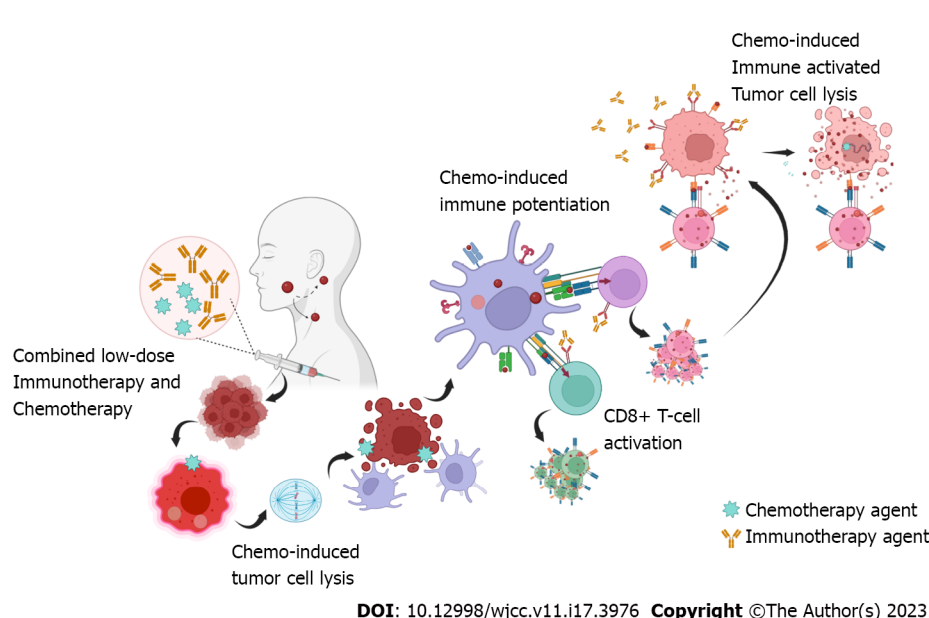


Figure 1 The potentiation role of low-dose immunotherapy with the standard potentiation neo-adjuvant chemotherapy in oral cancers.

LIMITATIONS

The main limitation behind the introduction of the immunotherapy agents into the treatment regimens could be the economic burden to the patient or the payers. With the introduction of the fixed dose-dose strategy in immunotherapy, the major burden is lifted thereby making the advantages of the therapy affordable to the patient[9]. However, even at low-doses addition of immunotherapy agents to the existing potentiation chemotherapy regimens increase the cost of treatment but it could be considered a cost-efficient alternative to reduce the events of recurrence or metastasis[3]. Moreover, alternate strategies are being devised to identify the therapeutic efficiency of the immunotherapy apart from the dosage regimen traditionally utilized[10].

The recent clinical trial results of Patil *et al*[11] comparing the overall survival of patients treated with traditional metronomic chemotherapy combined with a low dose (20 mg) of nivolumab in head and neck squamous cell carcinoma demonstrated superiority in overall survival compared to the traditional metronomic chemotherapy. The encouraging results of this study would recommend the addition of fixed low-dose immunotherapy in the routine NACT regimens in oral cancers to gain additional benefits without any financial constrain from the traditional dosing regimens.

CONCLUSION

Combining the advantages of two classes of induction agents, chemotherapy and immunotherapy, when used in combination in the curative setting of locally advanced oral cancers would benefit the patient to downstage the tumor effectively to make curative surgical resection less morbid and more successful[12]. Taking the pharmacokinetics, receptor occupancy analysis, and synergistic co-stimulation, low-dose anti-PD-1 immunotherapy agents proves to be a valuable addition to the existing neo-adjuvant induction chemotherapy regimens to potentiate their action in locally advanced oral cancers counteracting the economic burden involved with the immunotherapy treatment combinations.

FOOTNOTES

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