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MINIREVIEWS

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

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 chemo-induction[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].

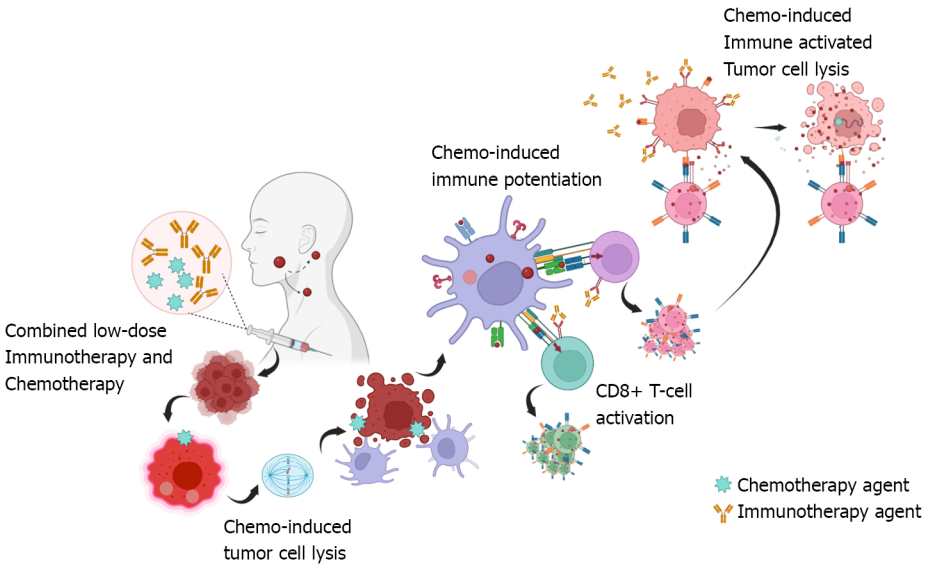

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Figure 1 The potentiation role of low-dose immunotherapy with the standard potentiation neo-adjuvant chemotherapy in oral cancers.

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 lose-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

Author contributions: Rathinasamy N performed the conceptualization; Muthu S did the data curation; Rathinasamy N and Muthu S did the data analysis; the manuscript writing and revision by all authors.

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