The efficacy of low-dose immunotherapy in head-and-neck cancer

Immunotherapy has become the standard of care in many difficult to treat cancers over the last decade. However, accessibility and cost limit its use in low- and middle-income countries like India.[1] The mechanism of action of immune checkpoint inhibitors like nivolumab involves targeting programmed cell death protein 1 (anti-PD-1) on the T-cells leading to its enhanced activation against cancer cells.[2] Immunotherapy at a lower dose may be efficacious. Low-dose immunotherapy is an attractive concept in resource limited settings.[3] This concept emphasizes the shift toward using biologically effective doses (BEDs) rather than the maximum tolerable doses (MTDs) derived from phase I studies as BED is generally much lower than MTD in targeted/immunotherapeutic agents.[4] The estimated cost of immunotherapy at standard doses is Rs 400,000 for 2 months (four cycles of nivolumab), and that of low-dose nivolumab at 40 mg dose is Rs 80,000 for the same period. Despite the cost-benefit, there is a paucity of data for LDI efficacy in the current era.

There are retrospective data for Stage III and IV non-small cell lung cancer with similar overall response rates between low and standard doses of nivolumab.[5] However, there are no case reports on the efficacy of low-dose immunotherapy in head-and-neck cancers. We are describing a patient with carcinoma buccal mucosa who has responded well to low-dose nivolumab. The patient was diagnosed with sarcomatoid carcinoma of the right buccal mucosa and was operated upfront with right buccal mucosa wide local excision + upper alveolectomy + submental flap repair on May 29, 2018, at an outside hospital. The pathological stage was pT2N0; the resection margins were negative, and he did not require adjuvant therapy. With a disease-free interval of 5 months, the patient had a recurrence with fungating growth in the right side of the neck and an ulceroproliferative growth of the right side of the cheek.

![Figure 1: The nodal mass before the start of low dose nivolumab](image1)

![Figure 2: The regression of the nodal mass post 6 cycles](image2)

![Figure 3: Contrast-enhanced computed tomography of the head and neck section showing the size of the nodal mass before the start of low-dose immunotherapy with nivolumab](image3)

![Figure 4: Contrast-enhanced computed tomography of the head and neck section showing the reduction in the size of the nodal mass after 6 cycles of low dose nivolumab](image4)
and mandible yrcT4bN3M0 as per the American Joint Committee on Cancer, 8th edition. He received 2 cycles of docetaxel 75 mg/m², cisplatin 75 mg/m² on day 1, and 5-fluorouracil 750 mg/m² day on days 1–5 as neoadjuvant chemotherapy followed by radical concurrent chemoradiation with 70 Gray/35 fractions RT and cisplatin 30 mg/m² and nimotuzumab 200 mg weekly for seven cycles. He had a second recurrence within 2 months and the PET CECT showed heterogeneously enhancing ulceroproliferative partially necrotic lobulated lesion involving the right neck measuring 7.4 cm × 4.3 cm × 3.9 cm with abutment and compression of the right internal jugular vein with no obvious infiltration. The mass extended from the level of angle of mandible to below the hyoid bone. There was a fluorodeoxyglucose avid lung nodule 1.6 cm × 1.3 cm in the right lower lobe. He was started on palliative oral metronomic therapy with methotrexate and celecoxib subsequently (due to the lack of feasibility for immunotherapy) however had clinical progression within 2 months. The options of changing to triple oral metronomic chemotherapy⁶ versus low-dose immunotherapy were discussed with the patient and relatives and they were keen on the latter option on an experimental basis. He was started on low-dose immunotherapy with nivolumab 40 mg given every 2 weeks. He received six cycles of low-dose nivolumab with clinical response. Repeat imaging showed that the right upper deep cervical nodal mass measured 3.5 cm × 1.9 cm × 1.0 cm and the level V node measured 1.9 cm × 1.5 cm. Thus, the patient had a partial response, as per RECIST v 1.1. He tolerated nivolumab without any major toxicity. PD-ligand 1 (PD-L1) testing had not been done for this patient at baseline. Currently, the patient is being continued on low-dose nivolumab with significant clinical benefit. Figures 1 and 2 shows the clinical image prior to the start of immunotherapy and after 6 cycles of low dose nivolumab respectively and Figures 3 and 4 shows the computed tomography scan prior to and post 6 cycles of low dose nivolumab respectively.

Thus, low-dose immunotherapy offers an attractive option, especially in metastatic/recurrent head-and-neck squamous cell carcinoma in resource limited settings. This needs further validation studies for confirmation of benefit, and this benefit needs to be correlated with the PD-L1 status of the patients.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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