Article:
Kanatas, AN orcid.org/0000-0003-2025-748X and Doumas, S (2019) Neoadjuvant immunotherapy: is this the "new" induction chemotherapy? British Journal of Oral and Maxillofacial Surgery, 57 (4). pp. 299-300. ISSN 0266-4356

https://doi.org/10.1016/j.bjoms.2019.02.003

Neo-adjuvant immunotherapy-Is this the 'new' induction chemotherapy?

AN Kanatas and S Doumas

A Kanatas FRCS, MD. Consultant Head and neck surgeon/ Professor, Leeds Teaching Hospitals

S Doumas. Head and Neck fellow, Leeds Teaching Hospitals

Address for correspondence: Anastasios Kanatas, BSc (Hons), BDS, MBChB (Hons), MFDSRCS, MRCSRCS, FRCS (OMFS), MD, PGC. Consultant Surgeon / Honorary Professor, Leeds Teaching Hospitals and St James Institute of Oncology, Leeds Dental Institute and Leeds General Infirmary, LS1 3EX.

Tel: 00447956603118 e-mail: a.kanatas@doctors.org.uk

Immunotherapy is now considered the 4th pillar in cancer treatment. Harnessing the immune system with immune checkpoint inhibitors, co-stimulatory agonists, vaccines, TLR inhibitors, chimeric antigen receptor (CAR) T cell has shown clinical benefit in various cancer types. In addition, the combination of immunotherapy agents and radiotherapy (IMRT or proton beam SBRT) or the so- called metronomic chemotherapy is under investigation.

Immunotherapy has an established role in the metastatic/recurrent head & neck cancer (HNSCC) setting. In this context, Burtness presented at ESMO 2018 the KEYNOTE 048 results comparing standard treatment platinum-based chemotherapy (5-FU with platin) and cetuximab (the control group) vs pembrolizumab vs combination of pembrolizumab (anti-PD1) with platinum based chemotherapy in a phase III 1:1:1 randomised trial. The OS was superior in the pembrolizumab arm especially in tumours expressing PDL-1 (combined positive score >20) (14.9 months vs 10.7 months HR=0.61 p=0.0006). Also, toxicity was more acceptable in the pembrolizumab group (1).

Based on both preclinical and other solid tumour studies and the fact that several immunological perturbations are noted in HNSCC, several groups rekindled their interest in neoadjuvant immunotherapy in locally advanced, resectable tumours. To date, surgery followed by chemo-radiotherapy is the mainstay treatment in locally advanced disease in most instances.

At ASCO 2017, Uppaluri et al. presented their preliminary data in a phase II trial involving 21 patients with stage III/IV, HPV-ve, resectable HNSCC with neoadjuvant and post-op pembrolizumab querying safety and reduction 1-y locoregional recurrence/distast metastases. The results showed that 43% of patients had pathological response to a single dose of anti-PD1 and 48% had clinical to pathological downstaging. Equally important, there was no delay in surgery treatment (NCT0229668) (2). More recently, Duhen et al. checked in a phase Ib trial, the safety and activation of immune response of 16 HNSCC patients who had neoadjuvant anti-OX-40 (co-stimulatory agonist) infusion at 2 days, 1 week and 2 weeks before surgery. The treatment was well tolerated and Activation and proliferation of CD4+ and CD8+ memory T-cell populations in both the TME and periphery peaked between 12 and 19 days after OX40 infusion, as demonstrated by increased levels of Ki67, CD38 and ICOS. In the TIL, expression of CD39, ICOS and PD-1 was increased on CD4+ T cells in most patients and the frequency

of tumour-reactive CD39+CD103+ CD8+ T cells was increased in some patients. IHC analysis revealed striking changes in tissue integrity and increased lymphocyte infiltrates in 4/16 patients (NCT02274155) (3). Hitherto, 9 studies involving neoadjuvant immunotherapy are completed or are underway in HNSCC (Clinicaltrials.gov accessed 2/11/2018).

Seemingly, induction chemotherapy is the prototype, as it has a role in organ preserving chemo-radiotherapy, but failed to show any substantial efficacy in oral cancer. Nevertheless, neoadjuvant immunotherapy doesn't have direct cytotoxic effect; instead, it primes T cells in the draining lymph nodes and the primary tumour site in order to recognise tumour noeantigens and kill tumour cells. Theoretically, there is abundance of neoantigens and TIL can recirculate so they can prevent recurrence, fully purge any residual disease, and prevent distant metastasis especially in HPV+ OPC In the case of adjuvant chemo-radiotherapy there may benefit of the abscopal effects (2,4).

Using immunotherapy post biopsy, but prior to definitive surgery, offers a window phase of treatment in which to deliver therapy and assess clinicoradiologic and biologic response. Various analysis methods allow for correlative studies aimed at deciphering the temporo-spatial changes in tumor microenvironment. Whole exome and RNA sequencing platforms can be applied to understand genomic determinants of immune cell function, facilitating neoantigen prediction modeling and protein expression analysis. Additionally, T cell receptor clonotyping can determine unique gene rearrangement sequences that arise in response to antigen presentation in the lymphocytes infiltrating an individual tumor, and extra- or intracellular cytokine levels can be quantified to understand immune cell signalling (2).

Despite the aforementioned advantages, there are potential risks pertained to immunotherapy before surgery. There is a risk of delaying the surgery due to potential immune related sides effects, but in some phase I trials this does not seem to be the case as mentioned above. Also, alteration of the immune profile may alter healing process and delay radiotherapy. The detrimental potential of hyperprogression should also be considered, as it was described by a French group in 27% patients treated with immune check point inhibitors (especially in the irradiated field) (2).

The timing of immunotherapy in order to maximise the T cell activity as well as the role and extend of lymphadenectomy in the final outcome has yet to be concluded (4).

References

1. https://www.esmo.org/Press-Office/Press-Releases/KEYNOTE048-head-neck-cancer-immunotherapy-Burtness.
2. Hanna GJ, Adkins DR, Zolkind P, Uppaluri R. Rationale for neoadjuvant immunotherapy in head and neck squamous cell carcinoma. Oral Oncol. 2017 Oct;73:65-69. doi: 10.1016/j.oraloncology.2017.08.008.
3. Duhen RA, Ballesteros-Merino C, Bell RB, Leidner R, et al. Neoadjuvant OX40 therapy in patients with head and neck cancer induces profound changes in tumor-infiltrating lymphocytes. J Immunol May 1, 2018, 200 (1 Supplement) 57.40.
4. Melero I, Berraondo P, Rodríguez-Ruiz ME, Pérez-Gracia JL.Making the Most of Cancer Surgery with Neoadjuvant Immunotherapy. Cancer Discov. 2016; 6(12):1312-1314.