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Editorial

Neoadjuvant immunotherapy: is this the "new" induction chemotherapy?

Immunotherapy is rapidly becoming another option for the treatment of cancer of the head and neck. Harnessing the immune system with immune checkpoint inhibitors, co-stimulatory agonists, vaccines, toll-like receptor (TLR) inhibitors, and chimeric antigen receptor (CAR) T cells, has shown clinical benefit in various types of cancer.[1,2]

Immunotherapy has an established role in patients with metastatic or recurrent cancer of the head and neck. At the 2018 meeting of the European Society for Medical Oncology (ESMO), Burtness presented the results of the Keynote-048 phase III 1:1:1 randomised trial that compared standard treatment with platinum-based chemotherapy (5-fluorouracil plus cisplatin or carboplatin) and cetuximab (the control group), pembrolizumab alone, and a new combination of pembrolizumab (anti-PD1) plus platinum-based chemotherapy. Overall survival was significantly better in the pembrolizumab arm, particularly in patients with tumours that expressed PDL-1 (combined positive score of more than 20) (14.9 months compared with 10.7 months HR = 0.61, p = 0.0006).[1]

Based on both preclinical and other solid tumour studies, and the fact that several immunological perturbations are present in cancer of the head and neck, several groups have rekindled their interest in neoadjuvant immunotherapy for locally advanced, resectable tumours.

At the American Society of Clinical Oncology (ASCO) in 2017, Hanna et al[2] presented their preliminary data from a phase II trial of 21 patients who were treated with neoadjuvant and postoperative pembrolizumab for stage III/IV, human papilloma virus (HPV)-negative, resectable cancer of the head and neck. The results showed that 43% of patients had a pathological response to a single dose of anti-PD1, and 48% were down-staged clinically or pathologically.[2] More recently, in a phase Ib trial, Duhen et al studied the safety and activation of the immune response in 16 patients with cancer of the head and neck who had neoadjuvant infusion of anti-OX-40 (co-stimulatory agonist) two days, one week, and two weeks, before operation. The treatment was tolerated well and the activation and proliferation of CD4+ and CD8+ memory T-cell populations in both the microenvironment of the tumour and its periphery peaked between 12 and 19 days after infusion, as shown by increased expression of Ki67, CD38, and ICOS.[3]

Induction chemotherapy has a role in organ-preserving chemoradiotherapy, but has not shown any substantial efficacy in oral cancer. Neoadjuvant immunotherapy does not have a direct cytotoxic effect, but it primes T cells in the draining lymph nodes and primary tumour site to recognise tumour neoantigens and to kill tumour cells. The pathological response to immunotherapy also seems different from that seen in classic neoadjuvant chemotherapy. In the first phase II trial of neoadjuvant PD-1 (nivolumab) in 20 patients who had definitive operations for non-small cell lung cancer, Cottrell et al[4] found significant differences in the histopathological features among those who responded to neoadjuvant immunotherapy and chemotherapy. The specific immunological features of the tertiary lymphoid structure and dense plasma cells, together with the proliferative fibrosis and neovascularisation of wound healing or tissue repair, have not, to our knowledge, been recorded in patients treated with chemotherapy, and may account for the different mechanism of action of immunotherapeutic agents. These reactions, together with several others, constitute the so-called "regression bed" that seems to be specific to immunotherapy.[4] Also, it seems that infiltration of the tumour by immune cells could explain the radiological "pseudoprogression" that is seen in some.

As yet, there has been no correlation with prognosis. The use of immunotherapy after biopsy examination, but before definitive surgery, gives the opportunity to deliver treatment and assess response. Whole exome and RNA sequencing platforms can be used to understand genomic determinants of immune cell function, and this facilitates the prediction modelling of neoantigens and analysis of the proteins expressed.[2] Also, clonotyping of T-cell receptors can indicate the rearrangement of unique sequences of genes that arise in response

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to the antigens that are present in the lymphocytes infiltrating an individual tumour, and cytokine levels can be quantified to understand the signalling of immune cells.[2]

Despite the optimism of clinical groups worldwide, the recommendation of preoperative immunotherapy has potential risks. Its timing to maximise the activity of T cells, the exact histopathological features that are seen in patients who respond, as well as the role and extent of lymphadenectomy in the outcome, have yet to be defined.[2,4] There is a risk that operations could be delayed because of potential immunity-related side effects, which could affect the overall outcome, and that changes in the immune profile could alter healing, delay radiotherapy, or produce long-term conditions such as a refractory colitis. The detrimental potential of hyperprogression should also be considered, as it has been described by a French group in 27% patients who were treated with immune check-point inhibitors (particularly in the irradiated field).[2]

At present there remains a lack of longitudinal data on health-related quality of life (HRQoL) after neoadjuvant immunotherapy.[5]

Conflict of interest

We have no conflicts of interest.

References

1. Immunotherapy improves survival in metastatic or recurrent head and neck cancer (ESMO 2018 press release) https://www.esmo.org/Press-Office/Press-Releases/KEYNOTE048-head-neck-cancer-immunotherapy-Burtness (last accessed 1 February 2019).
2. Hanna GJ, Adkins DR, Zolkind P, et al. Rationale for neoadjuvant immunotherapy in head and neck squamous cell carcinoma. *Oral Oncol* 2017;**73**:65–9.
3. Duhen RA, Ballesteros-Merino C, Bell RB, et al. Neoadjuvant OX40 therapy in patients with head and neck cancer induces profound changes in tumour-infiltrating lymphocytes. *J Immunol* 2018;**200**:40.
4. Cottrell TR, Thompson ED, Forde PM, et al. Pathologic features of response to neoadjuvant anti-PD-1 in resected non-small-cell lung carcinoma: a proposal for quantitative immune-related pathologic response criteria (irPRC). *Ann Oncol* 2018;**29**:1853–60.
5. Rogers SN, Lowe D, Lowies C, et al. Improving quality of life through the routine use of the patient concerns inventory for head and neck cancer patients: a cluster preference randomized controlled trial. *BMC Cancer* 2018;**18**:444.

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