Immunotherapy for head and neck squamous cell carcinoma

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Summary Over the past years immuno-oncology has evolved and become a novel promising strategy for cancer therapy. Immune checkpoint inhibitors such as pembrolizumab or nivolumab, which target the interaction between programmed death receptor 1/programmed death ligand 1 (PD-1/PDL-1) and PDL-2, have been recently approved for the treatment of various malignancies and are currently being investigated in clinical phase III trials for head and neck squamous cell carcinoma (HNSCC). Data available from these trials indicate substantial activity accompanied by a favorable safety and toxicity profile in this patient population. This review article focuses on the molecular background, gives an overview of current clinical data of checkpoint inhibitors in HNSCC, and points out future challenges such as the need for appropriate biomarkers for these novel compounds.

Keywords head and neck squamous cell carcinoma · immunotherapy · checkpoint inhibitor · PDL-1 · PD-1

Relevance of immune cell infiltration in head and neck cancer

Head and neck squamous cell carcinoma (HNSCC) induces an immune suppressive state via various mechanisms. Patients with HNSCC have altered lymphocyte homeostasis (mainly reduced levels of CD3+, CD4+, and CD8+ T cells) compared to healthy controls [6]. This imbalance even remains 2 years after treatment with curative intent [6]. Consistently, a higher number of tumor infiltrating CD4+ and CD8+ lymphocytes is associated with better overall survival in HNSCC patients [7]. Additionally, natural killer cell (NK) function is impaired in HNSCC patients, which is accompanied by elevated levels of TGF beta and soluble major histocompatibility complex Class I chain-related peptide A [8, 9]. In human papilloma virus (HPV)-positive oropharyngeal carcinoma patients, an increased number of CD56+ cytotoxic NK cells was reported, which might contribute to the fa-
vorable prognosis of this subpopulation \[10\]. The role of regulatory FoxP3+ T-cells (T regs) is still a matter of debate in HNSCC. A recent meta-analysis suggested that T regs are even favorable with respect to prognosis in HNSCC \[11\]. While the anti-inflammatory effect of T regs might contribute to this finding, only a subpopulation of T regs such as CD4+, CD25 high+, and FoxP3+, which were described to be elevated in HNSCC, are activated and act as potent immunosuppressors \[12\]. Finally, myeloid depressor cells (MDSC) and macrophages of the M2 phenotype are found in HNSCC tissues and peripheral blood facilitating an immunosuppressive state \[5\].

Immune escape mechanisms in head and neck cancer

HNSCC cells apply certain strategies to escape immunosurveillance and subsequent elimination. On the one hand they interact indirectly with the immune system in order to maintain an immunosuppressive microenvironment. Secretion of cytokines such as TGF beta, interleukin 10, or VEGF establishes a tumor-promoting immunosuppressive environment \[2\]. Additional factors such as the secretion of interleukin 6, which prevents the activation of T cells, NK cells or dendritic cells maturation via STAT3, further modulates the cellular immune system resulting in conditions, which facilitate immune escape \[2\].

On the other hand a key component for immune escape of HNSCC cells is the reduction of their inherent immunogenicity by downregulating (but not complete loss) human leukocyte antigen (HLA) class I molecules and disrupting of the antigen-processing machinery (APM) \[13\]. Apart from that HNSCC exploit the fact that the immune system is tightly regulated through immune checkpoints in order to avoid autointeraction or immune system over-activation under physiological circumstances.

Immune checkpoints

In recent years the introduction of immune checkpoint inhibitors for therapeutic purposes has revolutionized cancer treatment. T cell regulation, i.e., activation or inhibition is mediated via co-stimulatory or co-inhibitory signals. This interaction is exerted via ligand/receptor interaction. T cells harbor a myriad of both activating receptors such as OX-40, GITR, or CD 28 and inhibitory receptors (the so-called immune checkpoints) such as programmed death receptor 1 (PD-1) or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) \[14\]. Activation of this immune checkpoints results in T cell deactivation (Fig. 2; \[15\]). Hijacking these pathways by tumor cells contributes to their successful immune escape. For HNSCC tumors it has been reported that 45–80% express programmed death ligand 1 (PDL-1) \[16\]. In addition, exposure of HNSCC cells to therapy can result in tumor PDL-1 upregulation: It has been observed that HNSCC patients have elevated PDL-1 expression compared to healthy controls and that chemotherapy and radiation causes an PDL-1 upregulation in HNSCC patients, which lasts up to one year \[17\]. PDL-1 overexpression in tumor cells is induced via extrinsic interferon gamma secretion by NK or CD8+ cells or by intrinsic oncogenic drivers \[18\]. Very recently, the EGFR/JAK2/STAT-1 axis was identified for HNSCC to act as such a driver pathway \[18\]. Apart from that, HNSCC cells can respond to cetuximab treatment with recruitment of CD4+, FOXP3+ intra-tumoral T regs expressing CTLA-4, CD39, and TGF\(\beta\), which results in suppression of cetuximab-mediated antibody-dependent cellular cytotoxicity (ADCC) and poor prognosis \[19\]. Preclinical data indicate that CTLA-4 blockade with the monoclonal antibody ipilimumab might restore cetuximab sensitivity \[20\].

Clinical immunotherapy data

Currently there are dozens of clinical trials evaluating the efficacy and safety of immune checkpoint inhibitors as monotherapy or in combination regimens in HNSCC. Table 1 lists selected clinical trials with PD-1, PD-L1, and CTLA-4 inhibitors, which are tested in HNSCC at the moment. Data that the PD-1 antibody pembrolizumab might be effective in metastatic/recurrent (R/M) HNSCC patients were
generated in the Keynote 12 phase I/II trial. This study had a head and neck cohort (inclusive expansion) and included 132 patients with R/M HNSCC, who were partially heavily pretreated (37% had 3 or more lines of therapy). Patients received pembrolizumab 200 mg every 3 weeks. Primary objective was overall survival benefit was more prominent in the p16+ group and especially patients with a PDL-1 expression $>1\%$ benefited from the treatment. Of note the study was not designed to find OS differences with respect to platinum-refractory R/M HNSCC patients compared to investigator’s choice (cetuximab, methotrexate, or docetaxel). Primary objective was overall survival (OS). The study was stopped early due to superiority of the nivolumab arm. Patients receiving nivolumab had a median OS of 7.5 months and a 1-year OS rate of 36% compared to 5.1 months and 16.6% in the standard arm (HR 0.70; CI: 0.51–0.96; $p = 0.0101$) [22].

In the subgroup analysis it was shown that the survival benefit was more prominent in the p16+ group and especially patients with a PDL-1 expression $>1\%$ benefited from the treatment. Of note the study was not designed to find OS differences with respect to p16 or PDL-1 status and was positive for the overall study population [22]. In terms of toxicity no new safety issues arose compared to the Keynote 012 trial. Apart from checkpoint inhibitors several other immunotherapy strategies, which are not focus of this review article, such as adoptive cell transfer or cancer vaccines are in clinical development. Oncolytic viruses selectively target cancer cells, deliver antigens, and cause a host immune response. The attenuated herpes simplex virus talimogene laherparepvec (T-VEC) has been recently approved for melanoma treatment and studies in HNSCC (in combination with checkpoint inhibitors) are underway [23].

### Biomarkers for checkpoint inhibitor therapy

Identification of predictive biomarkers in order to select patients, who benefit from checkpoint inhibitor treatment will be crucial. The first and obvious potential biomarker is the evaluation of PDL-1 expression in tumor tissue. However, several shortcomings are linked to this approach. First, there a technical issues, as there are several, partially not validated, PDL-1 antibodies available for immunohistochemistry and no cut-off level has been defined for positivity so far. Second, PDL-1 is a dynamic biomarker, which expression might vary even within the tumor tissue or depending on the time point. Finally, the observation that also patients, who do not show PDL-1 expression, might respond to checkpoint blockade is well documented [24]. In non-small cell lung cancer it has been shown that patients, who are heavy smokers, respond better to nivolumab compared to never smokers [25]. This phenomenon can be explained with a higher mutational burden in this patient population, which results in neo-antigen release and a subsequent boost in immunogenicity of the tumor. Since HNSCC cells were found to harbor one of the highest somatic mutation frequency among all solid tumors and similar molecular smoking patterns were identified in HNSCC patients, this concept might apply to HNSCC as well [26]. In addition, the role of PDL-2, another ligand of the PD-1 receptor is still poorly understood. Data from the keynote 12 trial showed that there is
a discordance between PDL-1 and PDL-2 expression in a subpopulation of patients and suggest that PDL-2 expression is associated with higher ORR after adjusting for PDL-1 expression [27]. However, further research is necessary to incorporate these findings into the daily clinical practice.

Conclusion and perspectives

No new drugs have been approved for HNSCC since the introduction of cetuximab more than 10 years ago. Phase III trial results of the checkpoint inhibitor trials are eagerly awaited and the approval of nivolumab based on the checkmate 141 data can be expected in 2016/2017. Trials evaluating combinations of checkpoint inhibitors with other costimulatory or inhibitory molecules or oncolytic viruses are ongoing. Finally, there is sound scientific rationale to incorporate immunotherapy in curative treatment protocols for non R/M HNSCC and to go for an immunotherapy combination with radio(chemo)therapy. All in all, immunotherapy offers exciting new perspectives for patients suffering from HNSCC after years of negative clinical trials.

Conflict of interest

T. Fuereder declares that there are no competing interests.

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References

1. Mapara MY, Sykes M. Tolerance and cancer: mechanisms of tumor evasion and strategies for breaking tolerance. J Clin Oncol. 2004;22:1136–51. doi:10.1200/jco.2004.10.041.
2. Muenst S, et al. The immune system and cancer evasion strategies: therapeutic concepts. J Intern Med. 2016; doi:10.1111/joim.12470.
3. Gillison ML. Oropharyngeal cancer: a potential consequence of concomitant HPV and HIV infection. Curr Opin Oncol. 2009;21:439–44. doi:10.1097/CCO.0b013e32832f3e1b.
4. http://image.slidesharecdn.com/tumourclasss-110703094237-phpapp02/95/tumourclasss-26-728.jpg?cb=1309686256. Accessed: 13.6.2016.
5. Ferris RL. Immunology and immunotherapy of head and neck cancer. J Clin Oncol. 2015;33:3293–304. doi:10.1200/jco.2015.61.1509.
6. Kuss I, Hathaway B, Ferris RL, Gooding W, Whiteside TL. Decreased absolute counts of T lymphocyte subsets and their relation to disease in squamous cell carcinoma of the head and neck. Clin Cancer Res. 2004;10:3755–62. doi:10.1158/1078-0432.ccr-04-0054.
7. Nguyen N, et al. Tumor infiltrating lymphocytes and survival in patients with head and neck squamous cell carcinoma. Head Neck. 2016; doi:10.1002/hed.24406.
8. Dasgupta S, Bhattacharya-Chatterjee M, O’Malley BW. Inhibition of NK cell activity through TGF-beta 1 by down-regulation of NKGD2 in a murine model of head and neck cancer. J Immunol. 2005;175:5541–50.
9. Kloss S, et al. Increased sMICA and TGFbeta levels in HNSCC patients impair NKGD2-dependent functionality of activated NK cells. Oncoimmunology. 2015;4:e1055993 doi:10.1080/2162402x.2015.1055993.
10. Wagner S, et al. CD56-positive lymphocyte infiltration in relation to human papillomavirus association and prognostic significance in oropharyngeal squamous cell carcinoma. Int J Cancer. 2016;138:2263–73. doi:10.1002/ijc.29962.
11. Shang B, Liu Y, Jiang SJ, Liu Y. Prognostic value of tumor-infiltrating FoxP3+ regulatory T cells in cancers: a systematic review and meta-analysis. Sci Rep. 2015;5:15179 doi:10.1038/srep15179.
12. Badoual C, et al. Prognostic value of tumor-infiltrating CD4+ T-cell subpopulations in head and neck cancers. Clin Cancer Res. 2006;12:465–72. doi:10.1158/1078-0432.ccr-05-1886.
13. Lalami Y, Awada A. Innovative perspectives of immunotherapy in head and neck cancer. From relevant scientific rationale to effective clinical practice. Cancer Treat Rev. 2016;43: 113–23. doi:10.1016/j.ctrv.2016.01.001.
14. Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. Nature. 2011;480:480–9. doi:10.1038/nature10673.
15. http://labiotech.eu/pfizer-merck-ovarian-cancer-trial-avelumab-pdl1-immunooncology/. Accessed: 13.6.2016.
16. Zandberg DP, Strome SE. The role of the PD-L1/PD-1 pathway in squamous cell carcinoma of the head and neck. Oral Oncol. 2014;50:627–32. doi:10.1016/j.oraloncology.2014.04.003.
17. Parikh F, et al. Chemoradiotherapy-induced upregulation of PD-1 antagonizes immunity to HPV-related oropharyngeal cancer. Cancer Res. 2014; doi:10.1158/0008-5472.can-14-1913.
18. Concha-Benavente F, et al. Identification of the cell-intrinsic and -extrinsic pathways downstream of EGFR and IFN-gamma that induce PD-L1 expression in head and neck cancer. J Immunol. 2015;195:2874–84. doi:10.1001/jimmunol.2015.05-1886.
19. Agrawal N, et al. Exome sequencing of head and neck squamous cell carcinoma reveals inactivating mutations in NOTCH1. Science. 2011;333:1154–7. doi:10.1126/science.1206923.
20. Jie HB, et al. CTLA-4(+) regulatory T cells increased in cetuximab-treated head and neck cancer patients suppress NK cell cytotoxicity and correlate with poor prognosis. Cancer Res. 2015;75:2200–10. doi:10.1158/0008-5472.can-14-2788.
21. Cheng. ASCO 2015, oral presentation.
22. Gillison. AACR 2016, oral presentation.
23. Kohlhapp FJ, Kaufman HL. Molecular pathways: mechanism of action for talimogene laherparepvec, a new oncolytic virus immunotherapy. Clin Cancer Res. 2016;22:1048–54. doi:10.1158/1078-0432.ccr-15-2667.
24. Brahmer J, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med. 2015;373:123–35. doi:10.1056/NEJMoa1504627.
25. Borghaei H, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med. 2015;373:1627–39. doi:10.1056/NEJMoa1507643.
26. Alexandrov LB, et al. Prognostic value of tumor-infiltrating FoxP3+ regulatory T cells in cancers: a systematic review and meta-analysis. Sci Rep. 2015;5:15179 doi:10.1038/srep15179.
27. Yealy, ECCO 2015, oral presentation.

Immunotherapy for head and neck squamous cell carcinoma 69