

## SYSTEMIC THERAPY OF HEAD AND NECK CARCINOMA

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### Summary

Systemic therapy of head and neck carcinoma is reserved for locally advanced and metastatic disease. Concomitant use of cisplatin and irradiation is still standard protocol for treatment of locally advanced disease although immunoradiotherapy with cetuximab seems to be a good alternative with similar results. The best option for first-line treatment of advanced or metastatic disease is polychemotherapy with addition of cetuximab in patients in good clinical condition. Limited options are available for second-line therapy mostly due to poor performance status of the patients. HPV-positive tumors make a special subgroup of HNSCC in which targeted therapy plays the most important role.

KEY WORDS: *squamous cell carcinoma, head and neck, cisplatin, cetuximab, radiotherapy, human papillomavirus*

### SUSTAVNO LIJEČENJE KARCINOMA GLAVE I VRATA

#### Sažetak

Sustavno liječenje karcinoma glave i vrata je rezervirano za lokalno uznapredovalu i metastatsku bolest. Konkomitantna primjena cisplatine uz zračenje još uvijek predstavlja standard liječenja za lokalno uznapredovalu bolest, iako imunoradioterapija s cetuximabom predstavlja dobru alternativu sa sličnim rezultatima. Najbolja opcija za liječenje uznapredovale ili metastatske bolesti je polikemoterapija uz dodatak cetuximaba za sve bolesnike u dobrom kliničkom stanju. Mogućnosti druge linije liječenja su vrlo ograničene, najviše zbog lošeg općeg stanja bolesnika. HPV-pozitivni tumori predstavljaju posebnu podgrupu karcinoma pločastih stanica glave i vrata u kojima najvažniju ulogu igra liječenje ciljanom terapijom.

KLJUČNE RIJEČI: *karcinom pločastih stanica, glava i vrat, cisplatin, cetuximab, radioterapija, humani papilomavirus*

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Carcinoma of the head and neck represents a heterogeneous group of tumours which include tumours originating from lip, oral cavity, hypopharynx, oropharynx, nasopharynx and larynx. Majority of these tumours (around 90%) belong to squamous cell carcinoma group.

Throughout the history, tobacco and alcohol were considered as the main cause of this disease. In the past decade, new break-through was made in understanding head and neck squamous cell carcinoma (HNSCC) pathogenesis when infection with high-risk HPV (Human papillomavirus) and especially with HPV type 16 (HPV16) has been

implicated as a cause of a growing subset of HNSCCs, mainly those arising from the oropharynx (1). Distinction of this subgroup of tumours is of great importance whereas these tumours express different biology and clinical behaviour with more favourable prognosis which might require less intensive therapy.

Early disease (stages I and II) are treated by conservative surgery or radiotherapy with the similar outcome.

Locally advanced HNSCC includes stage III or IV A and B carcinomas that invade proximate structures or spread to cervical lymph nodes,

whereas recurrent/metastatic (R/M) HNSCC involves tumours that present with locoregional recurrence or distant metastases.

Patients with locally advanced disease (stage III and IV) are treated by surgery including reconstruction followed by postoperative radiotherapy. High-risk patients (nodal extracapsular extension and/or R1 resection) are candidates for postoperative chemoradiotherapy with cisplatin as single agent chemotherapy. This is based on Bernier et al. study results published in 2004. Study compared two groups of patients treated for locally advanced head and neck cancer, one with postoperative irradiation plus concomitant chemotherapy (100 mg/m<sup>2</sup> of body-surface area on days 1, 22, and 43 of the radiotherapy regimen) and one with postoperative irradiation alone. The study results showed that addition of chemotherapy to radiotherapy prolongs progression free survival (47% vs. 36%), overall survival (53% vs 40%) and reduces the rate of disease recurrences (18% vs 31%)(2).

Patients who are not candidates for surgery because of nonresectability or the expected outcome of surgery would be mutilation, can be treated by primary chemoradiotherapy.

Historical standard of primary chemoradiotherapy for the locally advanced disease is high dose cisplatin applied concomitantly with radiotherapy. Several studies have shown that concomitant use of cetuximab with radiotherapy in comparison with radiotherapy alone, demonstrated higher response rate, longer disease-free progression and longer overall survival and therefore was included in treatment guidelines. 5-year overall survival reported in Bonner et al. study published in Lancet in 2010. Was 45.6 % in the cetuximab-plus-radiotherapy group and 36.4% in the radiotherapy-alone group (3). There was no head-to-head study comparing cisplatin based chemoradiotherapy and cetuximab based immunoradiotherapy so decision between these two options should be made by the oncologist. Cetuximab is less toxic and as there is no clear evidence of efficacy of cisplatin based chemoradiotherapy in elderly, it could probably be used in elderly and patients with poor performance status.

Several ongoing randomized phase III trials are investigating use of sequential chemoradiotherapy (chemotherapy protocols based on cisplatin and 5-FU with or without the addition of a tax-

ane). According to the published results, application of induction chemotherapy showed no significant survival improvement with significant toxicity (neutropenia, febrile neutropenia, mucositis, nausea and vomiting) when radiation plus high dose three-week cisplatin was used in further course of treatment (4,5). Recommended treatment after induction includes radiotherapy alone or chemoradiotherapy with weekly cisplatin, carboplatin or cetuximab with no significant difference in treatment effectiveness (6,7,8). A French investigative group made an individual-patient meta-analysis of chemotherapy in non-metastatic nasopharyngeal carcinoma (MAC-NPC) that included 19 trials and 4,806 patients which suggested that adding induction chemotherapy or adjuvant chemotherapy to chemoradiotherapy improved the outcome in terms of tumor control probability and survival compared with chemoradiotherapy alone (9).

Recommended first-line treatment in R/M HNSCC is combination platinum/fluorouracil with or without cetuximab for fit patients (10). The epidermal growth factor receptor (EGFR) is overexpressed in up to 90% of cases of HNSCC and its overexpression correlates with poor clinical outcomes (11,12). Cetuximab is a monoclonal antibody against the extracellular domain of EGFR and it is the only targeted agent currently approved for HNSCC. Addition of cetuximab to polychemotherapy (cisplatin at a dose of 100 mg/m<sup>2</sup> of body-surface area on day 1 or carboplatin AUC5 as a 1-hour intravenous infusion on day 1 plus fluorouracil at a dose of 1000 mg/m<sup>2</sup>/day for 4 days every 3 weeks) in the first-line treatment of recurrent or metastatic head and neck cancer, was shown to improve OS (10,1 vs. 7,4 months), PFS (5,6 vs. 3,3 months), and response rates (36% vrs 20%) in EXTREME study. Based on results of this trial, the drug was included in ESMO and NCCN guidelines for treatment of R/M HNSCC (13). In patients, whose polychemotherapy tolerability is anticipated to be poor, monochemotherapy should be treatment of choice. Drugs that should be considered in single-agent protocols include methotrexate, docetaxel, 5-FU, cetuximab and platinum-based drug, all with similar results (response rates 15-35%) (14). Limited options are available for second-line therapy mostly because small proportion of patients are fit enough to be suitable candidates for second-line therapy. Standard treatment

of patients with incurable metastatic or locally advanced disease should be directed by patient's performance status. Phase II trial was conducted with afatinib (oral irreversible ErbB family blocker) which showed similar clinical activity to cetuximab (15). Based on these results, the phase III LUX Head and Neck 1 clinical trial presented at the 2014 ESMO meeting assessed the efficacy of afatinib as monotherapy compared with single-agent methotrexate as second-line treatment in HNSCC (16). The study showed increase in PFS of 0.9 months, improvement in tumour shrinkage and response rate in afatinib group, whereas no improvement in OS was noted. Given results are unlikely to lead to drug approval but studies evaluating adjuvant afatinib in locally advanced HNSCC after chemoradiotherapy are ongoing (LUX Head and Neck 2) and they will hopefully clarify the role of afatinib in HNSCC.

It is especially important to emphasize the role of immunotherapy in the context of treatment of HPV-positive HNSCC. Lyford-Pike et al. demonstrated that the PD-1/PD-L1 (programmed cell death ligand) pathway is involved in immune resistance of HPV-associated HNSCC (17). PD-L1 binds to the PD-1 receptor and activates the PD-1 checkpoint pathway, which blocks the immune response by downregulating T-cell effector functions and subsequently facilitates HPV infection and development of HPV associated lesions (18). PD-1 antibodies which inhibit the interaction between PD-1 and PD-L1 are being evaluated in clinical trials in a variety of cancers. Pembrolizumab and nivolumab have been already approved for the treatment of metastatic malignant melanoma (19,20). The clinical response to anti-PD-1 antibodies has correlated with PD-L1 expression and with the presence of tumour-infiltrating lymphocytes in several tumours, including HNSCC (21). Some novel anti-PD-L1 antibodies are also being evaluated in clinical trials in HNSCC (for example anti PD-1 antibodies nivolumab, pidilizumab and lambrolizumab and PD-L1 targeted agents atezolizumab and durvalumab mostly in phase I and II clinical trials). Efforts are made to develop therapeutic vaccines that will induce a cellular T-cell immune response to recognize and eliminate HPV-infected cells (22). Combining the vaccine with chemotherapy and immunotherapy will hopefully increase the activity of vaccine and help with better disease control. Preclinical data sug-

gest that HPV vaccination could act as an immune-stimulating agent, resulting in the improvement of response rates to an anti-PD-1 checkpoint inhibitor (23). These strategies are expected to be studied in further clinical trials.

It is also important to mention the efforts that are made in field of personalized cancer therapy. In four recent studies, based on whole-exome sequencing of altogether 190 HNSCC specimens, investigators identified key mutations of several tumour suppression genes, such as TP53 (60%), CDKN2A (9% to 74%), PI3KCA (8% to 20%), Notch (9% to 19%) and PTEN (13.6%)(24,27). These studies revealed, for the first time, the presence of novel inactivating mutations in tumour suppressor genes that regulate cellular squamous differentiation within the normal stratified squamous epithelium, such as NOTCH1, TP63, and FBXW7, as driver genetic events of neoplastic transformation in the head and neck area. MOSCATO 01 trial included 78 heavily pretreated patients with HNSCC whose biopsy specimens, obtained from the primary or metastatic tumour sites, were subjected to comparative genomic hybridization and next-generation sequencing for up to 74 target genes (28). Results were reviewed to identify actionable molecular aberrations for which targeted therapy may be available through clinical trials or approved drugs. Following pathways were observed: fibroblast growth factors (FGFs) and their receptors (FGFRs; 35%), phosphoinositide 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) (26%), MYC (24%), CDKs/Cyclins (13%), EGFR (9%), HER2 (7%), Notch (4%), and KIT (2%). Altogether 10 patients were treated with a targeted therapy on the basis of the genomic profile. Three of them attained partial response, three had stable disease, one developed disease progression, and two were not evaluable. This study shows early results of a personalized medicine strategy in R/M HNSCC, and further results will be awaited with great interest.

Despite all the innovations in therapy and better understanding of pathogenesis, there is still no significant improvement in survival rates and prognosis of patients with advanced head and neck cancer. First positive results were observed with the use of biological treatment and we have high expectations from future research with this type of therapy. It is also important to emphasize the need

for prevention strategies which would identify high-risk population and work on early detection of the disease.

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