Locally advanced Squamous Cell Carcinoma of the Head and Neck

In the PET-NECK trial, patients with locally advanced (N2/N3) nodal metastases of oropharynx, hypopharynx, larynx, oral cavity, or occult squamous cell carcinoma of the head and neck (HNSCC) receiving chemoradiation and fit for neck dissection, were randomized to planned neck dissection before or after chemoradiation, or chemoradiation followed by FDG-PET 10-12 weeks after chemoradiation, with neck dissection only if PET-CAT showed incomplete or equivocal response. Patients completed the EORTC QLQ general (C30) and head neck specific (HN34 v3) questionnaires and MD Anderson Dysphagia Inventory (MDADI) at baseline, end of treatment, 3 months after treatment, and 12 and 24 months from baseline. Eighty-four percent of the 654 patients had oropharyngeal cancer and 446 patients were tested for p16. Seventy-five percent of the tested patients were p16-positive. P16-positive patients were more likely to have oropharyngeal cancer than p16-negative patients, and were more likely to have lower T and N stage than p16-negative patients. As expected, the prognosis was much better in the p16-positive patients. Baseline global health status was higher in the p16-positive patients. The p16-positive patients experienced a greater drop in global health status during the acute phase of treatment than p16-negative patients. However, they recovered better by 2 years. Swallowing was the main residual deficit in p16-positive patients. Bonner et al. conducted a retrospective analysis of the IMCL-9815 trial, which demonstrated increased treatment efficacy when cetuximab was added to radiotherapy versus radiotherapy alone, evaluating the association of p16 status and feeding tube use. Addition of cetuximab to radiotherapy did not increase feeding tube use in the intent to treatment population, p16-positive oropharyngeal cancer population, nor p16-negative oropharyngeal cancer population. Oosting et al. retrospectively compared cumulative cisplatin dose and toxicity between patients who received 3-weekly and weekly cisplatin during adjuvant radiotherapy for high risk HNSCC (involved resection margins and/or extracapsular extension of lymph node metastases) treated at the Princess Margaret Cancer Center (PM) and the University Medical Center Groningen (UMCG). A total of 270 patients with high risk features were identified, 60 received 3-weekly 100mg/m² cisplatin (PM) and 48 received weekly cisplatin 50mg/m² (UMCG) during adjuvant radiotherapy 60-70 Gy in 33-35 fractions. Fourteen patients received other treatment schedules and no chemotherapy was given to 148 patients (54.8%) with age >70 years (56 patients), poor performance status (24 patients) and cardiovascular morbidity (24 patients) as most common reasons. Adjuvant 3-weekly and weekly cisplatin groups were different with regard to tumor characteristics and surgery. The mean cumulative cisplatin dose was 199.4mg/m² (standard error 5.4) in 3-weekly versus 239.8mg/m² (SE 11.0, p=0.001) in weekly treated patients. Cumulative cisplatin ≥200mg/m² was given to 67.7% of patients in the 3-weekly cohort and 85.2% (p=0.039) in the weekly cohort. The rate of feeding tube dependence 6 months after treatment, osteoradionecrosis, neutropenic fever, and persistent renal function decline were not statistically
different. The retrospective design and limited population sizes precludes comparison of efficacy. Efficacy and applicability to the frequently used weekly 40mg/m² schedule remain to be evaluated. An analysis of the Taiwan National Health Insurance Claims Database and Taiwan Cancer Registry Database demonstrated that patients treated with surgery for stage III or IVA oropharyngeal or hypopharyngeal cancer between 2004 and 2009 have a better OS than patients who did not receive surgery. Dewaele et al. updated a single-center comparison of sequential treatment (induction chemotherapy followed by concurrent chemoradia
tion) and concurrent chemoradiation. After a median follow up of 11.6 years, sequential treatment was associated with a significantly longer time to distant metastasis and time to relapse. The 5-year OS was 29.6 % with concurrent chemoradiation whereas 51.6 % of the patients in the sequential treatment cohort survived beyond 5 years. Second HNSCC primaries and other malignancies accounted for 47% of all deaths beyond 5 years. The most important late local toxicities in surviving patients are dysphagia and xerostomia.

Electronic data capturing of quality of life instruments using touch screen technology is time saving for patients and hospital staff (Van Oevelen, P331). Touch screen questionnaires are completed very efficiently and completely. Only a minority of patients preferred the paper version. Results are available in real time and can be used by physicians as part of the history taking at the outpatient clinic.

Recurrent/metastatic Squamous Cell Carcinoma of the Head and Neck

In the TTCC-2009-03 phase II trial, 40 patients with recurrent/metastatic (R/M) HNSCC were treated with weekly paclitaxel 80/mg/m² and panitumumab 6 mg/kg every 2 weeks until disease progression or unacceptable toxicity. The overall response rate (primary endpoint) was 47.5 % (95 % confidence interval: 32-63) with 15 % complete and 32.5 % partial responses. Stable disease was observed in 27.5 % of the patients. Median progression-free (PFS) and OS was 7.5 months (95 % CI: 4.9-8.3) and 9.9 months (95 % CI: 7.9-16.3), respectively. There were 6 (15 %) fatal adverse events, from which one was related to both paclitaxel and panitumumab.

In UNICANCER ORL03, 29 eligible patients with R/M HNSCC with tumor progression after platinum, anti-
EGFR and taxanes, were treated with cabazitaxel 25 mg/m² every 3 weeks with G-CSF support. All patients had received at least 2 previous lines of chemotherapy and cetuximab. The primary endpoint was non-progression at 6 weeks. At least 6 non-progressions were required to consider the drug worthy of further study. The primary endpoint was met, as 8 patients (27.6 %; 95 % CI: 12.7-47.2) had stable disease. The main grade 3-4 toxicity was neutropenia with 8 patients (26 %) having at least one event despite G-CSF use. Chow et al. presented the post hoc analyses of the KEY-
NOTE 012 trial conducted with the aim to identify sub-
populations of R/M HNSCC patients who may derive the greatest clinical benefit from pembrolizumab treatment. Overall response rate appeared higher for patients who received ≥ 2 prior therapies, and for patients whose tumors were ≥ the median tumor size. Overall response rate was comparable between those patients who were HPV-positive or HPV-negative.

Nasopharyngeal carcinoma

KEYNOTE-028 is a non-randomized, multicohort phase 1b trial of pembrolizumab inpatients with PD-L1 positive advanced solid tumors. Pembrolizumab was administered at a dose of 10 mg/kg every 2 weeks. Twenty-seven patients were enrolled in the nasopharyngeal carcinoma (NPC) cohort. Twenty-five patients had received prior therapy for R/M disease. Nine patients had received >5 therapies. The overall confirmed response rate was 25.9 % (95 % CI: 11.1-46.3). Stable disease was observed in 51.9 % of the patients. Preliminary findings suggest that plasma EBV DNA may correlate with response to pembrolizumab treatment. Elevation of plasma EBV DNA may be an early sign of progressive disease.

Chan et al. analyzed diagnostic tumor biopsies taken before radical (chemo)radiation from 161 NPC patients for PD-L1 expression on tumor cells and tumor-infiltrating immune cells, and for CD8 immune cell-infiltration. Additionally, matching pre/post treatment paired tumor samples from 153 patients were analyzed for changes of PD-L1 and CD8 expression. The majority (75%) of biopsies expressed PD-L1 on ≥ 1% of tumor-infiltrating immune cells, whereas the expression on tumor cells was lower (24% on ≥ 1% of TC). No prognostic value of PD-L1 expression could be demonstrated.

Elevated EBV DNA copies and a high neutrophil-lymphocyte rate are associated with an unfavourable prognosis in patients with locally advanced endemic NPC. Ma et al. evaluated a novel dual-endpoint of plasma EBV DNA clearance and PET response in assessing early re-
sponse to chemotherapy in patients receiving neoadjuvant chemotherapy for T3-4 NPC or palliative...
chemotherapy for metastatic NPC. The dual-endpoint of EBV DNA clearance of <10 days and PET response at 4-6 weeks after starting chemotherapy is a better predictor of PFS than achieving a RECIST response at 10-12 weeks. Patients with EBV DNA clearance of <10 days had better PFS, but PET response alone and RECIST response alone did not predict PFS or OS.14

**Thyroid cancer**

The phase 3 SELECT trial was a randomized, double-blind, placebo-controlled trial of lenvatinib in radioactive iodine refractory differentiated thyroid cancer.13 Overall survival analysis was confounded by the fact that 82.2 % of the placebo-treated patients switched to open-label lenvatinib after confirmed disease progression. To adjust for crossover, a rank preserving structural failure time model was used. Adjusting for crossover, the hazard ratio was 0.53 (95% CI: 0.34-0.82; p= 0.0051). Median OS had not been reached after 34 months of follow-up for the lenvatinib arm and was 19.1 months (95%: 14.3-not reached) in the placebo crossover arm.15 Among patients who had an objective response to lenvatinib in the SELECT trial, comparable PFS was seen regardless of the time at which response was achieved.16

Patients included in the SELECT trial were stratified based on the following three 131I-refractory criteria (RR-DTC): 1) No 131I uptake; 2) disease progression within 12 months of 131I therapy despite13I avidity at the time of treatment; or 3) extensive (>600 mCi) cumulative 131I exposure. In this analysis, comparable efficacy and safety profiles were observed in lenvatinib-treated patients regardless of RR-DTC criteria, which may be attributed to a large overlap between patients fulfilling several or all criteria. Differing definitions for RR-DTC may be equally valid as both the lenvatinib and placebo arms exhibited similar PFS outcomes across all groups.17

**Parotid gland tumors**

Most parotid gland tumors are not radiosensitive. Carbon ions have a higher relative biological effectiveness and allow an improved dose distribution. Koto et al. treated 46 patients with parotid gland tumors with carbon ion radiotherapy between May 1997 and April 2012. The total dose was 57.6 Gy in 16 fractions in 26 patients and 64 Gy in 16 fractions in 20 patients. After a median follow-up of 65 months, the 5-year local control rate was 74.5%. Grade3 skin reaction occurred in 1 patient, one patient developed grade 3 mandible osteoradionecrosis, 1 ipsilateral blindness, and 5 ipsilateral hearing loss.18

**Basic science and translational research**

The prospective DDFMISO trial confirmed the significant negative prognostic value of tumor hypoxia determined by PET/CT imaging during the initial phase of radiochemotherapy in locally advanced HNSCC. Comparison of tumor hypoxia in week 2 versus hypoxia before treatment in the same patient, i.e. a measure of reoxygenation capacity in which the patient serves as his own control, was superior to applying absolute threshold values between cohorts.19 Li et al. (P189) identified a radiosensitizing effect of the dual PI3K/mTOR inhibitor NVP-BEZ235, in oral cancer cells, including radioresistant oral cancer cells.20 EGFR copy number gain FISH may identify HNSCC patients who will benefit from panitumumab administration and may be a useful marker to predict efficacy of panitumumab in platinum-pretreated HNSCC.21 Cytoplasmic S100A2 overexpression is associated with poor prognosis in OSCC patients. Depletion of S100A2 induces sensitivity of oral cancer cells to chemotherapeutic agents.22

Current evidence identifies the circulating tumor cells (CTC) detection assay as an extremely specific, but low sensitivity test in HNSCC. Presence of CTCs indicates a worse disease-free survival. Expression of CD70 in neoplastic cells contributes to the development of an immunosuppressive tumor microenvironment, thereby promoting tumor immune escape and cancer progression.23 Finally, CD70 expression was found in 69% of HNSCC, displaying a statistical significant association with poor tumor differentiation.24

**References**

1. Mehanna H, Wong W, McConkey C et al. Differences in the quality of life (QoL) and functional outcomes of treatment between HPV associated (HPV+) and HPV- patients receiving primary chemoradiotherapy in PET-NECK - a multi-centre randomised phase III controlled trial (RCT) comparing PETCT guided active surveillance with planned neck dissection (ND) for locally advanced (N2/N3) nodal metastases (LAMM) in patients with head and neck squamous cell cancer (HNC) treated with primary radical chemoradiotherapy (CRT). Presented at ECC 2015; Abstract 11LBA.


Congress Highlights


