Editorial Commentary

Induction therapy in recurrent head and neck squamous cell carcinoma: is it time to consider response as a determinant of treatment selection?

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In locoregionally advanced head and neck squamous cell carcinoma (HNSCC), disease recurrence occurs in 50–60% of patients usually within 1–2 years after curative-intent, multi-modal treatment (1,2). Despite high rates of recurrent HNSCC (R-HNSCC), the optimal treatment for this population remains unknown (3-6). Salvage surgery or re-irradiation may be offered for curative intent, however palliative systemic therapy is often utilized due evidence of surgically unresectable disease (7). Irrespective of treatment received for R-HNSCC, survival rates are dismal (4,6-11) and are associated with significant toxicities (9). Induction therapy is an alternative option yet currently has a category 3 recommendation (major disagreement) within the National Comprehensive Cancer Network guidelines (4).

Rosenberg *et al.* conducted a "*Phase I study of nab-paclitaxel-based induction followed by nab-paclitaxel-based concurrent chemotherapy and re-irradiation in previously treated head and neck squamous cell carcinoma*" (12). Forty-eight adult patients were enrolled; all had an Eastern Cooperative Oncology Group (ECOG) performance status <2 without clinically measurable metastatic disease. Patients received induction chemotherapy with two cycles of carboplatin and nab-paclitaxel every 21 days. Response to induction therapy determined definitive treatment. Seventeen patients discontinued after induction including 7 patients due to progressive disease. Responders (n=31) received surgery and/or chemoradiotherapy consisting of either AFHX (n=28; nab-paclitaxel, 5-fluorouracil, hydroxyurea and a cumulative radiation dose of 60–75 Gy) or AXX (n=3; nab-paclitaxel and a cumulative radiation dose of 50 Gy). Using a dose escalation strategy (10 to 100 mg/m^2), the recommended phase II dose of nab-paclitaxel was 100 mg/m^2. Adverse events (AEs) ≥ grade 3 were reported in 16/28 (57.1%) patients receiving AFHX, including oral mucositis (46%), anemia (25%), and radiation dermatitis (21%). With an average study follow up of 5.6 years, 12 patients remained alive, but the majority had significant radiotherapy-related late toxicities. Only one-third of patients were feeding tube and tracheostomy-independent (33%). In terms of late-onset toxicities, 42% developed osteoradionecrosis and 25% developed trismus. Median progression-free survival (PFS) and overall survival (OS) were 10.3 and 12.3 months respectively.

In patients with first line recurrent or metastatic HNSCC (1L R/M HNSCC), the current benchmark for treatment selection is KEYNOTE-048, which was a phase

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3 trial comparing standard of care (SOC; cetuximab plus platinum and fluorouracil) *vs.* pembrolizumab monotherapy and pembrolizumab plus platinum and fluorouracil. In all comers, the OS was 10.7 months (SOC arm), 11.5 months (pembrolizumab monotherapy), and 13.0 months (pembrolizumab plus chemotherapy) (7). Compared to the regimens used in KN-048 (2.3–5.3 months), AFHX had a numerically improved PFS (10.3 months) as well as more "classic" approach of concurrent cisplatin plus radiotherapy (7 months), which also evaluated patients with R-HNSCC (8). Nevertheless, an OS difference between these regimens was not observed. While cross-trial comparisons should be made cautiously, it is unclear that treatment escalation with induction chemotherapy plus AFHX is beneficial enough to support its use compared to either pembrolizumab or pembrolizumab plus chemotherapy.

Notable limitations are worth mentoning in the Rosenberg trial. First, the authors did not report the percentage of responders to induction chemotherapy based on human papillomavirus (HPV) status, which is associated with distinct pathogenesis, response to treatment, and prognosis compared to HPV negative HNSCC (3,13). Notably, 14 patients in the trial had HPV associated disease. Therefore, one may question if subjects with HPV^+ disease drove the survival benefit. A stratified or adjusted analysis by HPV status would be helpful in addressing these concerns. Second, adjuvant re-irradiation following surgery in R-HNSCC is controversial and is associated with significant early and late toxicities. Therefore, its utilization has to balance the potential survival benefits and impact on quality of life (14-16). In the current study, all patients who responded to induction were re-irradiated irrespective of their pathologic response or previous radiotherapy status. Interestingly, while the AXX arm was closed prematurely due to limited enrollment, patients received a total dose of 30 Gy rather than the standard 60–68 Gy (14-16). Third, while nab-paclitaxel 100 mg/m^2 was the recommended Phase II dose, the authors do not provide a breakdown of AEs or efficacy based on lower nab-paclitaxel dose levels. It is possible that lower doses may achieve similar efficacy to higher doses, thus resulting in lower overall toxicity. Finally, previous systemic therapy details were also not reported, which is generally selected based on patient and tumor characteristics (10,11,14). The ASCO guidelines on the management of 1L R/M HNSCC endorse the use of combined positive score (CPS) and platinum resistance to determine the optimal systemic therapy (17).

Induction chemotherapy has been associated with reduced local failure rates and longer metastasis-free survival in previously untreated, locally advanced HNSCC (18,19). A growing body of literature in HNSCC and other malignancies have shown that response to induction therapy may predict response to definitive treatment (20,21). Rosenberg *et al.* reported that patients who responded to carboplatin plus nab-paclitaxel induction had a median OS of 36.8 months, whereas the total cohort (including non-responders) had a median OS of 12.3 months (12). Recently, immunotherapy has also been evaluated in the neoadjuvant setting both as monotherapy and in combination (22,23). Induction chemoimmunotherapy was superior to induction chemotherapy in terms of objective response rate (85% *vs.* 68%), 2-year PFS (27% *vs.* 44%) and 2-year OS (61% *vs.* 70%) (24). In patients with advanced HPV negative HNSCC, neoadjuvant durvalumab [anti-programmed death-ligand 1 (anti-PD-L1) antibody] combined with hypofractionated stereotactic body radiation therapy (SBRT) followed by surgery achieved impressive major pathologic response (75%) and complete response (44%) rates (25). These aforementioned trials were evaluated in patients with previously untreated HNSCC and raise the question of whether immunotherapy with or without radiation therapy should also be considered in R-HNSCC.

Treatment escalation is usually reserved for patients with high-risk disease who are fit enough to tolerate an intensified regimen. This is particularly relevant in the R-HNSCC population, who have previously received multi-modality therapy and are likely to have chronic treatment-associated side effects. The Rosenberg study evaluated a treatment strategy with significant intensification that did not have have significantly improved long term survival/cure rates, when compared to KN-048 regimens that are Food and Drug Administration (FDA) approved. This highlights the need for the field to develop local-control modalities that are specific to R-HNSCC.

In conclusion, the optimal regimen for R-HNSCC or second primary tumor remains unanswered however should remain an area of active investigation. We applaud the Rosenberg study team for conducting an excellent study and providing more data using an induction approach. We advocate for the incorporation of immunotherapy in the induction setting for this patient population. Furthermore, the presence (or absence) of response to induction therapy could be a viable strategy to determine whether a patient should be offered definitve therapy in general, as well as specific selection of treatment (i.e., surgical *vs.* non surgical based therapy). Whether this alone is an acceptable

biomarker warrants further investigation.

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