



# Sequential therapy with induction chemotherapy and chemoradiotherapy in pre-irradiated recurrent head and neck squamous cell carcinoma incorporating nab-paclitaxel— a commentary of the phase I trial of AFHX followed by concomitant FHX scheme

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Sequential therapy (ST) with induction chemotherapy (ICT) followed by concomitant chemoradiotherapy (CCT) has been widely investigated as a radical curative approach in locally advanced head and neck squamous-cell carcinoma (LA-HNSCC), specially in case of bulky disease and/or when larynx preservation is needed (1,2). The exact role of this strategy in the treatment is still an object of controversy (3). However, there is much less experience using this strategy in recurrent or metastatic disease.

Among all drugs that have been tested in this setting, addition of taxanes to ICT have been shown as one of the most active agents that have clearly improved the results of this ST (4,5).

We are going to analyze the article of Rosenberg *et al.* (6), who have reported a phase I study of ST with AFHX [nab-paclitaxel, 5-fluorouracil (5-FU), hydroxyurea], followed by concomitant FHX plus radiotherapy scheme in a selected group of patients with some remarkable peculiarities : recurrent disease and previously radiated patients.

## Nab paclitaxel in head and neck squamous-cell carcinoma (HNSCC)

Albumin-bound paclitaxel is an antineoplastic drug synthesized in 2002 (7). It contains a non-crystalline Paclitaxel molecule bound to a human serum albumin, conforming a nanoparticle. Its antitumoral effect does not differ from paclitaxel stabilizing microtubular assembly. Nab-paclitaxel avoids toxicity derived from solvent-based paclitaxel-dilutors, increasing the drug access to tumor tissues (8). Although it is not a standard of care in HNSCC, several studies have analysed its efficacy in locally advanced disease.

In 2021, Oppelt *et al.* studied nab-paclitaxel with or without cisplatin (9). Seventy percent of patients treated with the drug combination achieved a clinical complete response (CR), and 98% showed tumor shrinkage above 50%. Also Johnson *et al.* analyzed patients treated with different combinations in non-human papillomavirus

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**Table 1** Evidence of nab-paclitaxel in HNSCC in different settings

Study	Treatment	Setting	Primary endpoint	Secondary endpoint	Others
Oppelt <i>et al.</i> (9)	Arm 1: nab-P + Cisplatin + CRT with Cisplatin; Arm 2: nab-P + CRT with Cetuximab	Phase II; stage III/IV; candidate for CRT; induction therapy	Arm 1: cCR 70%; Arm 2: cCR 20%	Arm 1: ORR 60%; relapse 12.5%; G3–4 toxicity 58%. Arm 2: ORR 53%; relapse 32.5%; G3–4 toxicity 43%	Better response and survival if HPV-related
Johnson <i>et al.</i> (10)	Arm 1: nab-P + Cisplatin; Arm 2: nab-P + Cisplatin + 5-FU; Arm 3: nab-P + Cisplatin + 5-FU + Cetuximab	Retrospective; locally-advanced stage; HPV negative; CRT with Cisplatin; induction therapy	44-mo-LRR 16%	3-y overall relapse rate 22%; 3-y PFS 64%; 3-y OS 72%	–
Weiss <i>et al.</i> (11)	Carboplatin + nab-P + Cetuximab + CRT	Phase II; N2b or greater/unresectability; induction therapy	ORR 76.3%; no cPD	cCR 28.9%; 2-y PFS 72%; 2-y OS 80%	HPV status unrelated Better survival if response
Adkins <i>et al.</i> (12)	Arm 1: Carboplatin + nab-P + 5FU + CRT; Arm 2: nab-P + Cisplatin + 5-FU + Cetuximab + CRT	Phase II; stage III/IV; induction therapy	cCR in HPV-unrelated 77% vs. 33% (P=0.024)	Relapse 7% vs. 17% (P=0.37); CIDD 2.9 vs. 3.7% (P=0.82); 2-y OS 93% vs. 90% (P=0.64)	HPV status unrelated
Sheth <i>et al.</i> (13)	Nab-P + Carboplatin + Cetuximab	Phase II; unresectable/N2b or greater; induction therapy	ORR 76.3%	5-y PFS 69.2%; 5-y OS 71.6%	cCR 28.9%
Adkins <i>et al.</i> (14)	Nab-P + Platin + Cetuximab	Phase II; incurable disease	mPFS 6.1 mo	ORR 60%; cCR 17%; mDoR 5.4 mo; mOS 17.8 mo	HPV status unrelated

HNSCC, head and neck squamous-cell carcinoma; nab-P, nab-paclitaxel; CRT, chemoradiotherapy; 5-FU, 5-fluorouracil; HPV, human-papillomavirus; cCR, clinical complete response; LRR, local-regional recurrence; ORR, objective response rate; cPD, clinical progressive disease; mPFS, median progression-free survival; mo, month; OS, overall survival; y, year; CIDD, cumulative incidence of death of disease; mDoR, median duration of response.

(HPV) related tumors, showing a 3-year local-regional recurrences of 16% and an overall relapse rate of 22%. Three-year progression-free survival (PFS) was 64% and overall survival (OS) was 72% (10). In another study, the combination of nab-paclitaxel, Carboplatin and Cetuximab showed a response rate (RR) of 76% (11).

Adkins *et al.* showed no differences in OS, cumulative incidence of death of disease or of relapse between two groups treated with nab-paclitaxel, cisplatin, 5-FU with or without Cetuximab respectively (12). Recently, Sheth *et al.* published long-term follow-up data from a phase II study of induction carboplatin, nab-paclitaxel and cetuximab for high-risk patients > cN2a or unresectable tumors, showing ORR of 76.3% and 28.9% CRs. Five-year PFS was 69.2% and 5-year OS 71.6% (13).

In the metastatic setting, Adkins *et al.* used this drug in combination with a Platine component and weekly

Cetuximab in a phase 2 trial in the irresectable or metastatic disease. Patients reached a median PFS of 6.1 months, with a 60% of objective response rate (ORR) and a 17% of CRs. Median OS was 17.8 months (14).

Around 50% of patients with locally advanced HNSCC will recur after primary treatment, mainly with regional disease. Re-irradiation in this setting remains a potentially curative treatment option but with high toxicity.

In *Table 1* we show the most relevant clinical studies incorporating nab-paclitaxel in HNSCC. All of them are performed mostly in LA-HNSCC. As far as we know, no previous studies have been reported with ST with nab-paclitaxel in previously irradiated HNSCC.

### Outcome analysis

In this context, Rosenberg *et al.*'s (6) study induction

carboplatin and nab-paclitaxel followed by re-irradiation concomitant with nab-paclitaxel and 5-FU as ST has demonstrated a PFS rate at 60 months of 23%, and an OS rate at 60 months of 25%, similar to previous reports in this setting. In responders following ICT (28 patients) these outcomes are higher with PFS rate of 38% and OS rate of 44%. These results are somehow remarkable, since pre-irradiated patients have worse prognosis. But drop-off rate during ICT of 41% (20 patients of 48) seems too high considering the radical intention of treatment. We miss a detailed report of RR to ICT in their text.

Historically, systemic regimens for recurrent HNSCC were known to lead to high-grade toxicity and result in median survivals under a year, until the irruption of immunotherapy. Nowadays, results of immunotherapy (IT) trials in recurrent HNSCC (that were not available when Rosenberg's trial was designed) have to be considered when we evaluate new potential treatment strategies.

KEYNOTE-048 trial with a long term follow up, confirms that pembrolizumab alone improves OS in the programmed death-ligand 1 (PD-L1) Combined Positive Score (CPS)  $\geq 20$  and CPS  $\geq 1$  populations and pembrolizumab-chemotherapy (platinum and 5-FU) improves OS in the PD-L1 CPS  $\geq 20$ , CPS  $\geq 1$ , and total populations, compared with cetuximab-chemotherapy. For patients receiving pembrolizumab-chemotherapy, the OS rate at 60 months is 16% in total population and 23.9% in CPS  $\geq 20$  populations (15). These results raise the question of the role of re-irradiation, over all in patients with PDL-1 expression.

More recently a single-arm study with carboplatin-paclitaxel and pembrolizumab (5FU-free regimen) has showed an ORR of 42.7% and a 12-month OS rate of 58%, with a favorable safety profile (16). 5-FU alternatives are needed because of associated cardiovascular and dihydropyrimidine dehydrogenase deficiency-related toxicities, along with costs, and complications associated with continuous 4-day infusion.

Interesting is the role of ICT as a tool to select patients for re-irradiation. Among the 48 patients who started induction, 28 patients showed at least non-progression. For these patients the 5-year OS was 44%, suggesting the role of ICT as a biomarker for subsequent response to chemo-re-irradiation, and avoiding toxicities in patients unlike to benefit.

### Toxicity analysis

The aim of this study was to demonstrate the maximum

tolerable dose of nab-paclitaxel in this ST. In the ICT phase with carboplatin, the most frequent grade 3 adverse effects were anemia in 10% and hypophosphatemia in 6% of patients. During the concomitant chemoradiotherapy (CCRT) phase [AFHX + radiotherapy (RT)], at seven dose levels, the most frequent grade 3 events were anemia (25%), mucositis (46%), and radiodermatitis (21%), although the study does not specify whether these toxicities were greater with increasing doses of chemotherapy. Grade 3 or higher toxicity was observed in 58% of patients overall and 57% during AFHX. Two patients at the 20 mg/m<sup>2</sup> dose level developed dose-limiting toxicity with grade 4 mucositis, however the optimal dose for a phase II study is estimated to be 100 mg/m<sup>2</sup>.

In the RTOG 9610 trial, which analyzed the toxicities of reirradiation together FHX chemotherapy, 38% of grade 3, 17% grade 4 and 7.6% grade 5 toxicities were detected, mainly hematological and mucositis, not different from those detected in this phase I when nab-paclitaxel was added (17).

Regarding late toxicities, 12 patients were still alive at 60 months of follow-up, 67% of them required enteral tube feeding, 25% tracheostomy, 42% presented osteoradionecrosis and 25% trismus. Only 33% did not require enteral feeding by tube or tracheostomy.

In a pooled analysis of 39 studies involving approximately 3,800 patients undergoing reirradiation of the head and neck, the rate of any grade  $\geq 3$  late toxicity was 29%; the most common toxicities included radionecrosis, dysphagia requiring enteral feeding tube placement, and trismus. Additionally, the estimated rate of fatal carotid bleeding was 4%. Not very different from the results of the study analyzed (18).

Therefore, a priori, based on these data, it does not appear that adding nab-paclitaxel adds greater short- and long-term toxicities.

### Conclusions

In summary, this study explores prospectively a sequential approach of ICT plus CCRT in relapsed metastatic head and neck squamous cell cancer (RM-HNSCC) patients, including nab-paclitaxel for first time in this setting. The study gives us a very useful information about the feasibility of this strategy, even in a complicated scenario as it is recurrent disease, treated with a not always friendly approach as is reirradiation. Besides that, the study is also a good example of the viability of sequential treatment

without platin compounds.

The primary end-point was to establish the maximum tolerated dose, recommended phase II dose, safety of nab-paclitaxel when given in this combination, and to explore the role of response to ICT as a predictive factor. These objectives have been widely achieved, and results are available for future research. Adding nab-paclitaxel to the CCRT with FHX does not seem to increase significantly the toxicity

However the study presents some issues that may question its usefulness. The first one is the long duration of recruitment (7 years), clearly excessive. In such period of time from 2013 to 2020, treatment landscape of RM-HNSCC has drastically changed with the onset of IT. Outcome results of this approach do not differ significantly from those achieved with combined approaches of CT and IT, even without re-irradiation.

In the other hand, it is also questionable to keep exploring concomitant regimens as FHX, that are so far from being standard, and that probably add more toxicity that would be permissible in a non-curative context.

The main utility of this study probably is that it is a good basis of work, where new less toxic schemes can be built, adding new agents as IT. In our experience, regimens of ST without platin compounds are feasible in LA-HNSCC (19), and should be considered specially for unfit patients. Modified schemes of this regimen, maybe incorporating immuno-checkpoints inhibitors could be a potential research pathway.

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