Editorial Commentary

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

Javier Martinez-Trufero^, Ana Comin Orce, Pablo Gomez Mugarza, Susana Barriendos Sanz, Eugenia Ortega Izquierdo

Medical Oncology Department, University Hospital Miguel Servet, Zaragoza, Spain

Correspondence to: Javier Martinez-Trufero. Medical Oncology Department, University Hospital Miguel Servet, Zaragoza, Spain.
Email: jmtrufero@seom.org.

Comment on: Rosenberg AJ, Agrawal N, Pearson AT, *et al.* 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. Br J Cancer 2022;127:1497-506.

Keywords: Nab-paclitaxel; sequential therapy (ST); recurrent head and neck squamous cell carcinoma; re-irradiation

Submitted Jan 31, 2023. Accepted for publication Mar 21, 2023. Published online Apr 06, 2023.
doi: 10.21037/tcr-23-131
View this article at: https://dx.doi.org/10.21037/tcr-23-131

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-bind paclitaxel is an antineoplastic drug synthetized 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 derivated 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

^ ORCID: 0000-0002-0997-2573.

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

Study	Treatment	Setting	Primary endpoint	Secondary endpoint	Others
Oppelt *et al.* (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 *et al.* (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 *et al.* (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 *et al.* (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 *et al.* (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 *et al.* (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 *el 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) ≥20 and CPS ≥1 populations and pembrolizumab-chemotherapy (platinum and 5-FU) improves OS in the PD-L1 CPS ≥20, CPS ≥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 ≥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^2 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^2.

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 ≥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.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Translational Cancer Research*. The article did not undergo external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-131/coif). JMT received payment or honoraria for lectures from Astra-Zeneca, Pharmamar, Merck, Clovis, MSD, GSK, and meeting travel expenses from Pharmamar, MSD, Merck, and served on advisory board of Pharmamar, Boehringer-Ingelheim, Deciphera, Eisai. EOI received Payment or honoraria for lectures from Ipsen, Pharmamar, Merck, Eisai, MSD, GSK, and meeting travel expenses form MSD, Merck, and served on advisory board of Eisai. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Budach W, Bölke E, Kammers K, et al. Induction chemotherapy followed by concurrent radio-chemotherapy versus concurrent radio-chemotherapy alone as treatment of locally advanced squamous cell carcinoma of the head and neck (HNSCC): A meta-analysis of randomized trials. Radiother Oncol 2016;118:238-43.
2. Kim R, Hahn S, Shin J, et al. The Effect of Induction Chemotherapy Using Docetaxel, Cisplatin, and Fluorouracil on Survival in Locally Advanced Head and Neck Squamous Cell Carcinoma: A Meta-Analysis. Cancer Res Treat 2016;48:907-16.
3. Iocca O, Farcomeni A, Di Rocco A, et al. Locally advanced squamous cell carcinoma of the head and neck: A systematic review and Bayesian network meta-analysis of the currently available treatment options. Oral Oncol 2018;80:40-51.
4. Hitt R, López-Pousa A, Martínez-Trufero J, et al. Phase III study comparing cisplatin plus fluorouracil to paclitaxel, cisplatin, and fluorouracil induction chemotherapy followed by chemoradiotherapy in locally advanced head and neck cancer. J Clin Oncol 2005;23:8636-45.
5. Vermorken JB, Remenar E, van Herpen C, et al. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. N Engl J Med 2007;357:1695-704.
6. Rosenberg AJ, Agrawal N, Pearson AT, et al. 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. Br J Cancer 2022;127:1497-506.
7. Ibrahim NK, Desai N, Legha S, et al. Phase I and pharmacokinetic study of ABI-007, a Cremophor-free, protein-stabilized, nanoparticle formulation of paclitaxel. Clin Cancer Res 2002;8:1038-44.
8. Yardley DA. nab-Paclitaxel mechanisms of action and delivery. J Control Release 2013;170:365-72.
9. Oppelt P, Ley J, Daly M, et al. nab-Paclitaxel and cisplatin followed by cisplatin and radiation (Arm 1) and nab-paclitaxel followed by cetuximab and radiation (Arm 2) for locally advanced head and neck squamous-cell carcinoma: a multicenter, non-randomized phase 2 trial. Med Oncol 2021;38:35.
10. Johnson KCC, Ley J, Oppelt P, et al. nab-Paclitaxel-based induction chemotherapy followed by cisplatin and radiation therapy for human papillomavirus-unrelated head and neck squamous-cell carcinoma. Med Oncol 2019;36:93.
11. Weiss J, Gilbert J, Deal AM, et al. Induction chemotherapy with carboplatin, nab-paclitaxel and cetuximab for at least N2b nodal status or surgically unresectable squamous cell carcinoma of the head and neck. Oral Oncol 2018;84:46-51.
12. Adkins D, Ley J, Oppelt P, et al. nab-Paclitaxel-based induction chemotherapy with or without cetuximab for locally advanced head and neck squamous cell carcinoma. Oral Oncol 2017;72:26-31.
13. Sheth S, Gilbert J, Deal AM, et al. Mature follow up of induction chemotherapy with carboplatin, nab-paclitaxel, cetuximab in head and neck squamous cell carcinoma. Oral Oncol 2022;127:105807.
14. Adkins D, Ley J, Atiq O, et al. Nanoparticle albumin-bound paclitaxel with cetuximab and carboplatin as first-line therapy for recurrent or metastatic head and neck cancer: A single-arm, multicenter, phase 2 trial. Oral Oncol 2021;115:105173.
15. Tahara M, Greil R, Rischin D, et al. Pembrolizumab with or without chemotherapy for first-line treatment of recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC): 5-year results from KEYNOTE-048. Ann Oncol 2022;33:S295-S322.
16. Dzienis MR, Cundom JE, Fuentes CS, et al. Pembrolizumab (pembro) + carboplatin (carbo) + paclitaxel (pacli) as first-line (1L) therapy in recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC): Phase VI KEYNOTE-B10 study. Ann Oncol 2022;33:S295-S322.
17. Spencer SA, Harris J, Wheeler RH, et al. Final report of RTOG 9610, a multi-institutional trial of reirradiation and chemotherapy for unresectable recurrent squamous cell carcinoma of the head and neck. Head Neck 2008;30:281-8.
18. Dionisi F, Fiorica F, D'Angelo E, et al. Organs at risk's tolerance and dose limits for head and neck cancer re-irradiation: A literature review. Oral Oncol 2019;98:35-47.
19. Martínez-Trufero J, Lozano Borbalas A, Pajares Bernad I, et al. Sequential chemotherapy regimen of induction with panitumumab and paclitaxel followed by radiotherapy and panitumumab in patients with locally advanced head and neck cancer unfit for platinum derivatives. The phase II, PANTERA/TTCC-2010-06 study. Clin Transl Oncol 2021;23:1666-77.

Cite this article as: Martinez-Trufero J, Comin Orce A, Gomez Mugarza P, Barriendos Sanz S, Ortega Izquierdo E. 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. Transl Cancer Res 2023;12(4):692-696. doi: 10.21037/tcr-23-131

