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ORIGINAL PAPER

nab-Paclitaxel-based induction chemotherapy followed by cisplatin and radiation therapy for human papillomavirus-unrelated head and neck squamous-cell carcinoma

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Abstract

In patients with locally advanced human papillomavirus (HPV)-unrelated head and neck squamous-cell carcinoma (HNSCC), cisplatin and radiation therapy (CisRT) resulted in a local–regional recurrence (LRR) rate of 35%, progression-free survival (PFS) of 49%, and overall survival (OS) of 60%. We, and others, showed that *nab*-paclitaxel is an active agent in metastatic and locally advanced HNSCC. The aim of this report was to assess the efficacy of *nab*-paclitaxel-based induction chemotherapy and CisRT in HPV-unrelated HNSCC. We performed a retrospective single-institution analysis of patients treated with *nab*-paclitaxel-based chemotherapy and CisRT. Key inclusion criteria included stage III–IV HPV-unrelated HNSCC. Induction chemotherapy included *nab*-paclitaxel and cisplatin (AP), AP + 5-fluorouracil (APF), or APF + Cetuximab (APF-C). Endpoints included LRR, overall relapse, PFS, and OS. Thirty-eight patients were the subject of this analysis. Patient characteristics included median age 59 years (IQR: 54–64) and smoking history in 36 patients (95%). Primary tumor sites included larynx/hypopharynx (27), p16 negative oropharynx (10), and oral cavity (1). Most patients had bulky disease: 82% T_{3-4} ($n = 31$) and 74% N_{2b-3} ($n = 28$). Median follow-up was 44 months (IQR: 23–59). The three-year LRR rate was 16% (95% confidence interval [CI] 7–34) and the overall relapse rate was 22% (95% CI 11–41). The three-year PFS was 64% (95% CI 46–77) and OS was 72% (95% CI 54–84). Among patients with HPV-unrelated HNSCC, *nab*-paclitaxel-based induction chemotherapy and CisRT resulted in a lower-than-expected rate of LRR and more favorable PFS and OS compared to historical results with CisRT.

Keywords *nab*-Paclitaxel · Cisplatin · Radiation · Head and neck cancer · HPV-unrelated

Introduction

Head and neck squamous-cell carcinoma (HNSCC) is the sixth most common cancer. Over 800,000 new cases occurred worldwide in 2016 [1]. Most patients present with locally advanced disease caused by smoking and unrelated to the human papillomavirus (HPV). The risk of cancer recurrence is higher and the progression-free survival (PFS) and overall survival (OS) are lower in HPV-unrelated HNSCC compared to HPV-related disease [2, 3].

Studies conducted over two decades ago showed that concurrent chemotherapy and radiation therapy (CRT) resulted in a lower rate of local–regional recurrence (LRR) and higher OS compared to radiation therapy alone [4–7]. Cisplatin and radiation therapy (CisRT) is the preferred CRT regimen for patients with good performance status and limited co-morbidities. In

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HPV-unrelated HNSCC, CisRT resulted in three-year LRR rate of 35%, PFS of 49%, and OS of 60% [3–5, 8, 9]. Attempts to improve these outcomes by intensification of CisRT or administration of additional therapy before or after CisRT were not successful [7–12].

Nab-paclitaxel is a nanoparticle formulation of albumin-bound paclitaxel that improved drug delivery into tumor cells in comparison to cremophor-based paclitaxel [13–15]. The mechanism of improved drug delivery may involve macropinocytosis, which promotes internalization of extracellular albumin into cells to serve as a nutrient supply. Macropinocytosis can be driven by epidermal growth factor receptor (EGFR) and phosphatidylinositol-3 (PI3) kinase signaling, pathways frequently hyperactivated in HPV-unrelated HNSCC [16, 17]. Interestingly, as seen in lung cancer trials, SCC histology may be more sensitive to *nab*-paclitaxel compared to cremophor-based paclitaxel [18].

We, and others, showed that *nab*-paclitaxel is an active agent in metastatic and locally advanced HNSCC [19–27]. *Nab*-paclitaxel monotherapy resulted in a tumor response rate of 17% in taxane-refractory HNSCC [19]. As first-line therapy for metastatic disease, *nab*-paclitaxel, platinum, and cetuximab prolonged OS compared to historical results with the EXTREME regimen [20]. We reported favorable outcomes of 30 patients with locally advanced HNSCC treated with *nab*-paclitaxel, cisplatin, 5-fluorouracil and cetuximab (APF-C) followed by CisRT [21]. Efficacy with APF-C and CisRT was better than a historical group treated with docetaxel, cisplatin, 5-fluorouracil and cetuximab (TPF-C) and CisRT [22]. Subsequently, we reported similar outcomes of 30 patients treated with APF (no cetuximab) and CisRT [23]. A retrospective comparative analysis demonstrated no significant difference in efficacy between APF-C and APF [24]. The overall relapse risk was low: 17% with APF-C and 7% with APF. Given the absence of data establishing the benefit of 5-FU in induction regimens, we treated 40 patients with AP (no 5-FU) and CisRT. Preliminary data from this study showed that deletion of 5-FU from the APF regimen did not adversely affect efficacy endpoints [25].

The aim of this retrospective analysis was to assess the efficacy of *nab*-paclitaxel-based induction chemotherapy and CisRT in locally advanced HPV-unrelated HNSCC. We pooled our experience of all patients on our institutional clinical trials and tumor registry with HPV-unrelated HNSCC treated with *nab*-paclitaxel-based induction chemotherapy and CisRT. Herein we report the results of this analysis.

Materials and methods

Patient selection criteria

Patients were identified from a list of enrollments onto institutional clinical trials and the head and neck tumor registry in the interval of 2009–2017, when *nab*-paclitaxel-based induction therapy was applied to patients. Inclusion criteria included locally advanced (Stages III–IV; AJCC 7th Edition) HPV-unrelated HNSCC (defined as larynx, hypopharynx, oral cavity, and p16 negative oropharynx SCC), Eastern Cooperative Oncology Group (ECOG) performance score of 0–1, adequate organ function (serum creatinine and blood counts within normal limits), and no distant metastases. Required treatment included *nab*-paclitaxel-based induction chemotherapy for three cycles followed by CisRT (planned Cisplatin 100 mg/m^2 × 3 doses or 40 mg/m^2 weekly × 7 doses and intensity modulated radiation therapy [IMRT] for 35 fractions [7000 cGy] over 7 weeks). Exclusion criteria included nasopharynx and para-nasal/sinus SCC and treatment with concurrent cetuximab and radiation therapy (CetRT). The Washington University Human Research Protection Office (internal review board) approved the institutional clinical trials and tumor registry and all study participants signed informed consent. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Treatment and assessments

Treatment and assessments were previously described [21, 23, 25]. Briefly, induction chemotherapy consisted of three cycles of either APF-C, APF, or AP followed by CisRT. Assessments of tumor status using RECIST 1.1 included a history taking and physical examination, and computer tomography (CT) scans of the neck and chest that were performed at baseline, after two cycles of induction chemotherapy, and 2, 6, 12, 20, and 36 months after CisRT. Patient co-morbidities were quantified using the Adult Co-morbidity Evaluation (ACE)-27 index [28].

Objectives and statistical analysis

The primary objective of the retrospective analysis was to determine the cumulative incidence of LRR in patients with HPV-unrelated HNSCC treated with *nab*-paclitaxel-based induction chemotherapy followed by CisRT. The definition of LRR was disease recurrence at the primary tumor site and/or regional neck nodes. Time to LRR was defined as the months from the date of diagnosis to local and/or regional relapse. Patients without LLR

were censored at the last follow-up. Secondary objectives were to determine the cumulative incidence of overall relapse (LRR and/or distant), PFS, and OS. Time to overall relapse was defined as the months from the date of diagnosis to relapse. Patients without relapse were censored at the last follow-up. Probabilities of LRR and overall relapse were calculated using cumulative incidence curves. PFS was defined as months from diagnosis to disease progression or death due to disease progression, whichever occurred first. Living patients without progression were censored at the last follow-up. OS was defined as months from diagnosis to death. Living patients were censored at the last follow-up. PFS and OS were evaluated by the Kaplan–Meier (KM) method. SAS Version 9.4 (Cary, NC) was used to perform all statistical analyses.

Results

Patient and tumor characteristics

Patients were identified from a list of enrollments onto institutional clinical trials and the head and neck tumor registry in the interval of 2009–2017, when *nab*-paclitaxel-based induction therapy was applied. One hundred-three patients received *nab*-paclitaxel-based induction chemotherapy (Fig. 1). Thirty-eight patients met selection criteria and were the subjects of this analysis (Table 1).

Patient characteristics included median age of 59 (IQR: 54–64) years, smoking history in 36 patients (95%), and moderate-to-severe ACE co-morbidity index in 17 patients (45%). Most patients had SCC of the larynx, hypopharynx, or p16 negative oropharynx. TN classification included $T_{3–4}$ in 31 patients (82%) and $N_{2b–3}$ in 28 patients (74%).

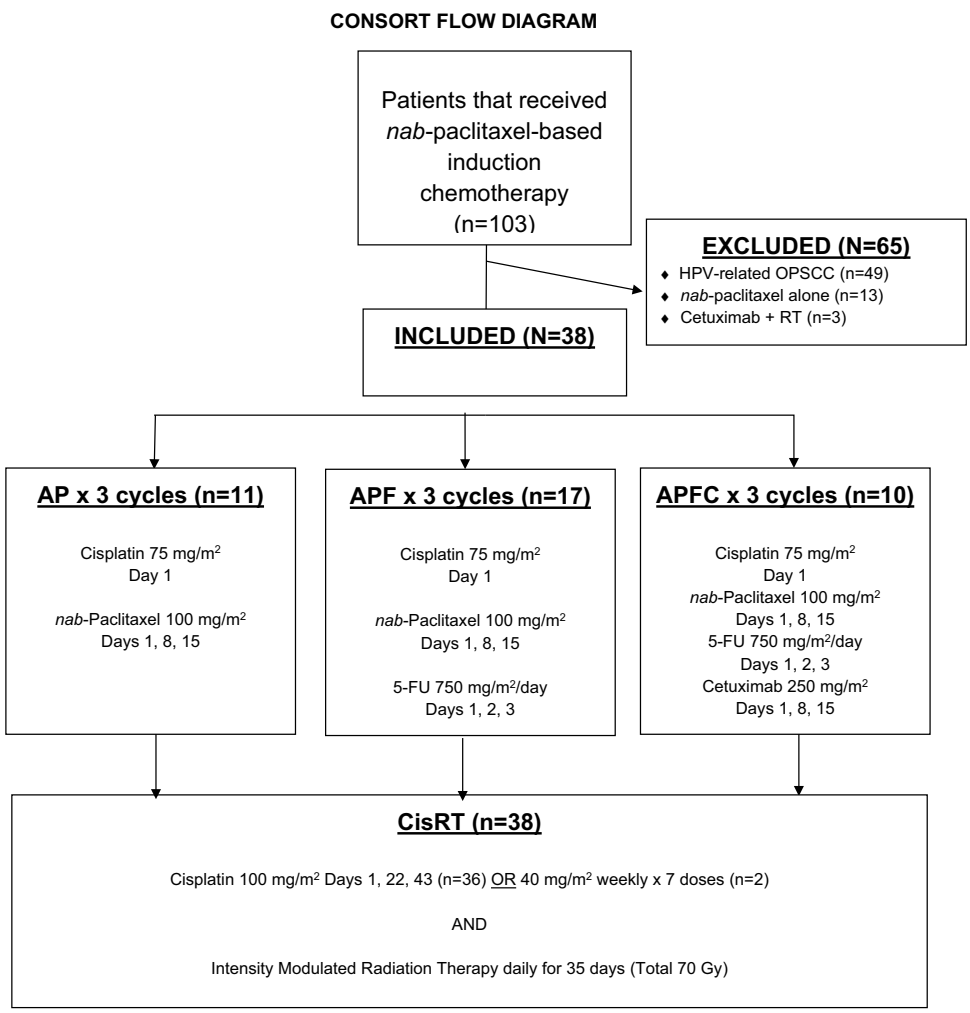

Fig. 1 Consort flow diagram of patient selection and treatment

Table 1 Baseline characteristics

Sex	
Female	9 (24%)
Male	29 (76%)
Age (years)	
Median	59
Range	43–70
Co-morbidity score (ACE)	
None to mild	21 (55%)
Moderate to severe	17 (45%)
Smoking history	
Current or prior use	36 (95%)
Never smoker	2 (5%)
Primary site	
Larynx	22 (58%)
Oropharynx	10 (26%)
Hypopharynx	5 (13%)
Oral cavity	1 (3%)
T Classification	
1–2	7 (18%)
3–4	31 (82%)
N classification	
0–1	10 (26%)
2b	6 (16%)
2c–3	22 (58%)

Treatment

Figure 1 summarizes the treatment that patients received. The distribution of *nab*-paclitaxel-based induction regimens used to treat the 38 patients included APF-C 26% ($n=10$), APF 45% ($n=17$), and AP 29% ($n=11$). CisRT included high-dose bolus cisplatin in 36 patients (95%) and weekly cisplatin in 2 patients (5%).

Follow-up and efficacy outcomes

The median follow-up was 44 months (IQR: 23–59). LRR events occurred in five patients (13%). The three-year cumulative LRR rate was 16% (95% CI 7–34) (Fig. 2a). Overall (LRR and/or distant) relapse events occurred in eight patients (21%). The three-year cumulative overall relapse rate was 22% (95% CI 11–41) (Fig. 2b). The three-year PFS was 64% (95% CI 46–77) and OS was 72% (95% CI 54–84) (Fig. 3).

Causes of death

Sixteen patients (42%) expired. Causes of death included co-morbidities in five patients (13%), relapse of disease in five (13%), second cancers in four (11%), and unknown in two (5%).

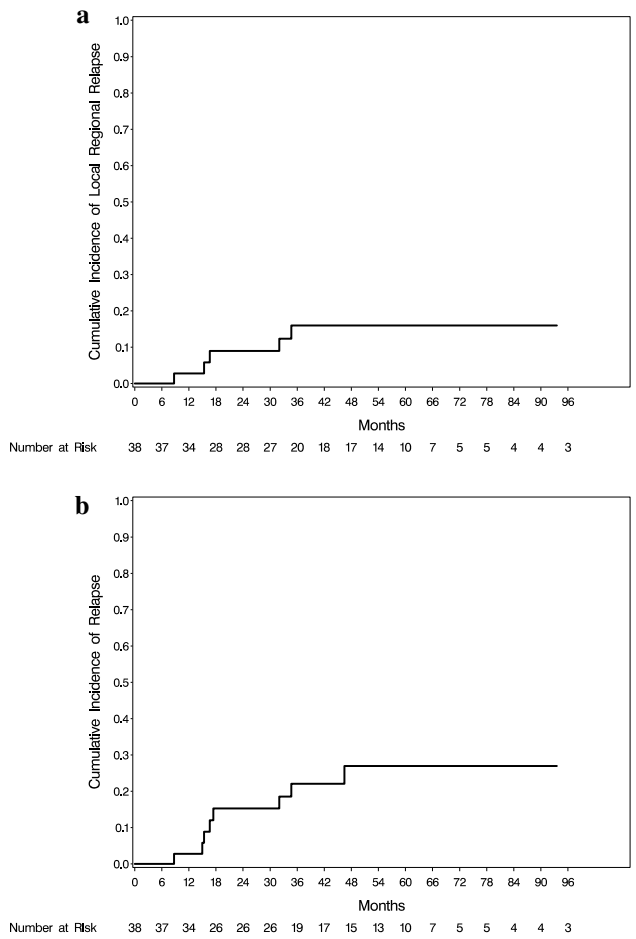

Fig. 2 Cumulative incidence of relapse **a** local–regional recurrence (LRR). **b** Overall relapse

Discussion

Among patients with locally advanced HPV-unrelated HNSCC, relapse of disease is the dominant cause of treatment failure after CisRT. The majority of relapse events occur at local or regional sites. The LRR rate after CisRT is 35% [3–5, 8, 9]. Attempts to improve these outcomes by intensification of CisRT or administration of additional therapy before or after CisRT were not successful [7–12]. In this report, *nab*-paclitaxel-based induction chemotherapy followed by CisRT resulted in an estimated three-year LRR rate of 16% (95% CI 7–34) and a three-year cumulative overall relapse rate of 22% (95% CI 11–41). As a result, the three-year PFS of 64% (95% CI 46–77) and OS of 72% (95% CI 55–84) were better-than-expected compared to historical reports with CisRT [3–5, 8, 9].

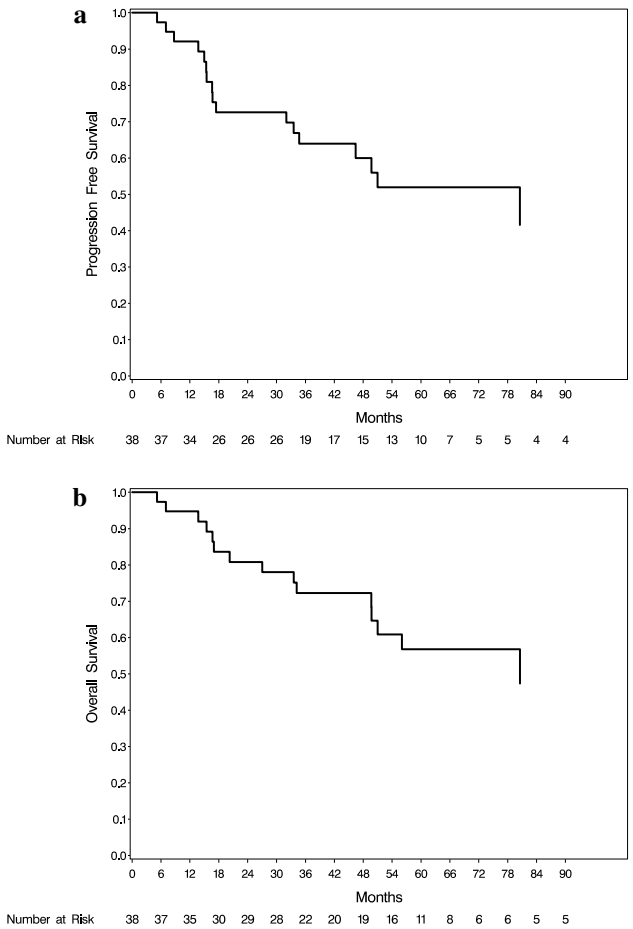

Fig. 3 Survival outcomes. **a** Progression-free survival (PFS). **b** Overall survival (OS)

One reason for the low LRR rate observed in our report may be due to the high rate of major tumor response after *nab*-paclitaxel-based induction chemotherapy, resulting in lower pre-treatment tumor volume before CisRT. In HPV-unrelated HNSCC treated with CisRT alone, higher T or N classification predicts for a higher LRR rate and lower PFS and OS [3, 9]. T and N classification are clinical surrogates of tumor volume. Prior studies demonstrated the dominant influence of pre-treatment tumor volume on relapse risk after radiation therapy [3, 9, 29–34], with larger pre-treatment tumor volume prognostic of higher LRR rate and lower survival. The complete tumor response rate at the primary site was higher with *nab*-paclitaxel-based induction chemotherapy regimens (53–77%) [21, 23] compared to cisplatin and 5-FU (21%) [5] or docetaxel, cisplatin and 5-FU (9–17%) [35, 36]. Thus, *nab*-paclitaxel-based induction chemotherapy significantly reduced tumor volume before CisRT, which may be an explanation for the low rate of LRR observed in our trial.

In this report, co-morbidity and second cancers collectively were more common causes of death than the primary head and neck cancer (24% vs. 13%, respectively). This outcome contrasts with previous reports of patients with HPV-unrelated HNSCC that showed disease recurrence was the most common cause of death following CisRT [3, 9]. The low rate of disease recurrence following *nab*-paclitaxel-based induction chemotherapy and CisRT amplified the proportional significance of co-morbidity and second cancers as causes of death. Most patients with HPV-unrelated HNSCC have a smoking history and other risk factors that place them at substantial risk of death from co-morbidity and second cancers. These data highlight the importance of more effectively addressing smoking cessation and reduction of other risk factors as complementary measures to increase OS in patients with HPV-unrelated HNSCC.

Our analysis has several limitations. This report was a single-institution retrospective analysis, the results of which require validation in a multicenter prospective controlled trial. The sample size was small, and there was heterogeneity of *nab*-paclitaxel-based induction regimens. However, the selection criteria focused on patients with poor-prognosis locally advanced HPV-unrelated HNSCC, good performance status and organ function, and all treated with CisRT, reflecting a common patient subset in clinical practice. The eligibility criteria also represented a broad cross section of patients with HPV-unrelated HNSCC in that 95% were smokers, and 45% had a moderate-to-severe ACE co-morbidity index.

Among patients with locally advanced HPV-unrelated HNSCC, *nab*-paclitaxel-based induction chemotherapy followed by CisRT resulted in a lower-than-expected rate of LRR and a more favorable PFS and OS compared to historical reports with CisRT alone. Further studies of *nab*-paclitaxel-based chemotherapy in HPV-unrelated HNSCC are warranted.

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Compliance with ethical standards

Conflict of interest Douglas R. Adkins has received research grants from Celgene. All remaining authors have declared no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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