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Phase I study of weekly *nab*-paclitaxel + weekly cetuximab + intensity-modulated radiation therapy (IMRT) in patients with stage III–IVB head and neck squamous cell carcinoma (HNSCC)

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Background: There is a clinical need to improve the efficacy of standard cetuximab + concurrent intensity-modulated radiation therapy (IMRT) for patients with locally and/or regionally advanced HNSCC. Taxanes have radiosensitizing activity against HNSCC, and *nab*-paclitaxel may offer therapeutic advantage in comparison with other taxanes.

Patients and methods: This was a single-institution phase I study with a modified 3 + 3 design. Four dose levels (DLs) of weekly *nab*-paclitaxel were explored (30, 45, 60, and 80 mg/m^2), given with standard weekly cetuximab (450 mg/m^2 loading dose followed by 250 mg/m^2 weekly) and concurrent IMRT (total dose, 70 Gy).

Results: Twenty-five eligible patients (20 M, 5 F) enrolled, with median age 58 years (range, 46–84 years). Primary tumor sites were oropharynx, 19 (10 human papillomavirus [HPV] pos, 8 HPV neg, 1 not done); neck node with unknown primary, 2; larynx 2; and oral cavity and maxillary sinus, 1 each. Seven patients had received prior induction chemotherapy. Maximum tolerated dose (MTD) was exceeded at DL4 (*nab*-paclitaxel, 80 mg/m^2) with three dose-limiting toxicities (DLTs) (grade 3 neuropathy, grade 3 dehydration, with grade 3 mucositis grade 3 anemia) among five assessable patients. There was only one DLT (grade 3 supraventricular tachycardia) among six patients at DL3 (*nab*-paclitaxel, 60 mg/m^2), and this was deemed the MTD. Among 23 assessable patients, the most common ≥ g3 AEs were lymphopenia 100%, functional mucositis 65%, and pain in throat/oral cavity 52%. At a median follow-up of 33 months, 2-year failure-free survival (FFS) is 65% [95% confidence interval (CI) 42% to 81%] and 2-year overall survival (OS) is 91% (95% CI 69–97).

Conclusion: The recommended phase II dose for *nab*-paclitaxel is 60 mg/m^2 weekly when given standard weekly cetuximab and concurrent IMRT. This regimen merits further study as a nonplatinum alternative to IMRT + cetuximab alone.

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Key words: *nab*-paclitaxel, cetuximab, head and neck, squamous, radiation

introduction

For patients with stage III/IVB HNSCC undergoing combined modality therapy, the addition of cetuximab to definitive radiation therapy improved overall survival (OS) in a randomized, phase III clinical trial [1, 2]. There has been a longstanding question regarding the comparative efficacy of cisplatin versus cetuximab when given concurrently with radiation therapy [3]. In a retrospective analysis of patients treated at this hospital, we observed inferior efficacy with cetuximab + concurrent intensity-modulated radiation therapy (IMRT), compared with cisplatin + concurrent IMRT [4]. The general approach has been to preferentially offer cisplatin + concurrent IMRT to fit patients with stage III/IVB HNSCC [5], rather than cetuximab + concurrent IMRT.

However, there are many stage III/IVB HNSCC patients for whom cisplatin therapy given concurrently with definitive radiation therapy may not be appropriate. Some patients may have medical co-morbidities (e.g. renal insufficiency, hearing loss or tinnitus, or cardiac disease) that render them suboptimal candidates for cisplatin, and some patients may be unwilling to accept the potential toxicities of cisplatin. For HNSCC patients who

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receive induction chemotherapy, subsequent radiation therapy given concurrently with cisplatin may be associated with excessive toxicities [6]. As such, there is a clear need for nonplatinum regimens for patients with stage III/IVB HNSCC.

Lipid solvent-based paclitaxel has clinically useful activity when given as a single agent for patients with recurrent or metastatic HNSCC [7], or when given as part of induction chemotherapy for patients with locoregional disease [8]. Lipid solvent-based paclitaxel and cetuximab have been combined in a chemoradiation regimen with encouraging efficacy and acceptable toxicity among head and neck cancer patients [9].

Nanoparticle albumin-bound paclitaxel (*nab*-paclitaxel, Abraxane®) demonstrated superior efficacy over conventional lipid solvent-based paclitaxel in patients with advanced breast cancer [10]. In a phase I study of intra-arterial *nab*-paclitaxel, objective responses were seen in 76% (22 of 29) of HNSCC patients, noting that most of these subjects were previously untreated [11].

We designed and conducted this phase I study to determine the maximum tolerated dose (MTD) of weekly *nab*-paclitaxel that can be added to conventional dosing of cetuximab and IMRT [1, 2] for patients with stage III/IVB HNSCC.

patients and methods

patients

This single-institution study was approved by the Institutional Review Board of this hospital, and all patients provided written informed consent. Eligible patients were ≥18 years of age with histologically or cytologically confirmed stage IIII/IVB HNSCC, Karnofsky performance status (KPS) of at least 70%, and adequate organ function. Additional eligibility criteria are provided in supplementary Material, available at *Annals of Oncology* online. After a protocol amendment in May 2010, prior induction chemotherapy was allowed if patients had adequately recovered from toxicities of induction chemotherapy such that all inclusion criteria for the study were met.

primary objective

The primary objective was to establish the MTD of weekly intravenous (i.v.) *nab*-paclitaxel given with weekly cetuximab and concurrent IMRT in this patient population.

treatment plan

Patients received the standard cetuximab loading dose (400 mg/m^2 i.v.) >4 but <10 days before the start of radiation therapy. Daily IMRT (6996 cGy) was administered concurrently with standard cetuximab (250 mg/m^2 i.v. weekly) and *nab*-paclitaxel (i.v. weekly, per dose escalation scheme; Table 1) for the duration of radiation therapy. Supplementary Material, available at *Annals of Oncology* online provides additional information about the treatment plan and scheduled assessments.

Table 1. Dose escalation scheme

Planned dose level	*nab*-Paclitaxel, mg/m^2 i.v. weekly
1	30
2	45
3 (MTD)	60
4	80

MTD, maximum tolerated dose.

dose escalation plan

A modified 3 + 3 phase I dose escalation design was used, with modifications similar to those used in other phase I studies in head and neck cancer [12–15]. If one or two of the initial three patients in a dose level (DL) experienced dose-limiting toxicty (DLT) (other than grade 4 mucositis and/or death), then three additional patients were enrolled on the study and treated at that DL. If three or more patients in a six-patient cohort experience DLT, then the MTD would be deemed to have been exceeded. Three additional patients would be enrolled at the next lower DL as needed to achieve a total of six assessable patients at that lower DL. If ≤2 of 6 patients experienced DLT at this DL, this would be the phase II recommended dose. (For grade 4 mucositis and/or death, the MTD would be exceeded if there were two such events at a given DL.)

dose-limiting toxicity definition and statistical considerations

DLT was defined as any of the following: grade 4 neutropenia (absolute neutrophil count [ANC] < 500/mm^3) for more than 7 days, grade 4 neutropenia accompanied by fever, grade 4 thrombocytopenia, any other grade 3 toxicity requiring radiotherapy treatment delay of ≥7 calendar days, grade 4 toxicity (with the exception of anaphylactic reaction to cetuximab), or any grade 3 toxicity, other than those specified as typical of standard treatment with radiation and concurrent cetuximab. Additional information regarding DLT definition is provided in supplementary Methods, available at *Annals of Oncology* online. Failure-free survival (FFS) and OS were measured from the date of the cetuximab loading dose until the event date or most recent clinical assessment. Survival times were estimated according to the method of Kaplan and Meier.

results

Between October 2008 and October 2011, 25 patients were enrolled. Median age was 58 years (range, 46–84 years) and median KPS was 90 years (range 80–100 years). Baseline characteristics are summarized in Table 2. The reasons for not pursuing cisplatin with concurrent radiation therapy for these patients were prior induction chemotherapy ($N = 7$, 4 of whom were treated on a protocol) [16], baseline hearing loss or tinnitus ($N = 7$), cardiac co-morbidities ($N = 4$; history of coronary artery disease, 2; mild congestive heart failure, 1; atrial fibrillation, 1), and renal insufficiency ($N = 2$). Five patients on the study had no apparent contraindications to cisplatin, but opted for the study because of their concerns about the potential side-effects of cisplatin.

Two patients were not assessable for toxicity or efficacy. One patient developed an infection at the percutaneous gastrostomy tube site before any study treatment, and received only cetuximab with IMRT off protocol. The other inassessable patient experienced a hypersensitivity reaction during the cetuximab loading dose and was removed from study at that time. Neither patient received any *nab*-paclitaxel on this study. Treatment delivery is summarized in supplementary Table S1, available at *Annals of Oncology* online.

dose escalation and adverse events

At DL1 (*nab*-paclitaxel, 30 mg/m^2), there was one DLT (grade 4 pneumonia) among six patients. At DL2 (*nab*-paclitaxel, 45 mg/m^2), there were two DLTs. A 75-year-old woman with supraglottic laryngeal squamous cell cancer and history of prior carotid endarterectomy experienced a grade 4 cerebrovascular accident, which was probably related to her baseline atherosclerosis. A 71-year-old man with base of tongue squamous cell cancer experienced a grade 3 exacerbation of his known baseline mild congestive heart failure. Because a contributory role for study drug could not be excluded for either of these events, both were deemed DLT. Because there were no more than two DLTs among six patients at DL2, escalation to the next DL was allowed per protocol.

Among six patients at DL3 (*nab*-paclitaxel, 60 mg/m^2), there was one DLT. This was an episode of grade 3 supraventricular tachycardia in a 73-year-old man with base of tongue squamous cell cancer. This event was thought to be due to dehydration in the context of mucositis in the radiation field.

At DL4 (*nab*-paclitaxel, 80 mg/m^2), there were three DLTs among five assessable patients. A 55-year-old man with base of tongue squamous cell cancer experienced grade 3 neuropathy after his sixth treatment with *nab*-paclitaxel. Although he had received prior induction chemotherapy, he had no neuropathy at the start of the current study. A 65-year-old man with base of tongue squamous cell cancer experienced grade 3 dehydration and grade 3 mucositis after his second *nab*-paclitaxel treatment, which was deemed DLT because it occurred early in the treatment course. A 52-year-old woman with squamous cell cancer of the oral tongue developed grade 3 anemia (hemoglobin 7.7 mg/dl) after her fourth treatment with *nab*-paclitaxel. There was no clinical evidence of bleeding. Although she had received prior induction chemotherapy, her hemoglobin level on the day that she received the cetuximab loading dose on the current study was 10.3 mg/dl.

Table 3 summarizes the DLTs that were observed in this study. The DLTs at DL4 (*nab*-paclitaxel, 80 mg/m^2) were felt to be directly related to the study drug (neuropathy, anemia) or at least indirectly related to the study drug due to intensification of toxicities in the radiation field (mucositis with dehydration). As such, MTD was deemed to have been exceeded at DL4 (*nab*-paclitaxel, 80 mg/m^2). There had been only one DLT among six assessable patients previously treated at DL3 (*nab*-paclitaxel 60 mg/m^2 weekly). DL3 was deemed the MTD for the study, and enrollment to the study was stopped.

Among 23 patients assessable for toxicity, the most common treatment-related adverse events of grade 3 or greater were lymphopenia (grade 3, 70%; grade 4, 30%), functional mucositis (grade 3, 65%; grade 4, 0%), and pain in the radiation field (grade 3, 39%; grade 4, 13%). There were no treatment-related deaths. Table 4 summarizes all adverse events (regardless of attribution) occurring in at least 33% of patients at any grade, or occurring in more than one subject at grade 3 or 4.

Table 2. Baseline characteristics

Parameters	Summary ($N = 25$)
Age in years, median (range)	58 (46–84)
Gender	20 M, 5 F
KPS, median (range)	90 (80–100)
Primary tumor site	
Oropharynx	19 (10 HPV pos, 8 HPV neg, 1 not done)
Neck node, occult primary	2 (1 HPV pos, 1 not done)
Larynx	2
Oral cavity	1
Maxillary sinus	1
Prior induction chemotherapy	7[a]
Stage	
III	3
IVA	21
IVB	1

[a]TPF (docetaxel + cisplatin + 5-fluorouracil), $N = 2$; TP + everolimus, $N = 4$ [16]; carboplatin + paclitaxel + cetuximab, $N = 1$.
KPS, Karnofsky performance status; HPV, human papillomavirus.

efficacy and long-term functional outcomes

Among 23 assessable patients at a median follow-up of 33 months, 2-year FFS rate is 65% [95% confidence interval (CI) 42% to 81%] and 2-year OS rate is 91% (95% CI 69–97). Among nine patients who experienced recurrent disease, patterns of

Table 3. Summary of DLTs

Dose level	Age (years)	Gender	KPS, baseline	Primary site	Prior induction chemotherapy	DLT
1	65	M	90	BOT	No	Pneumonia, g.4
2	75	F	90	SG larynx	No	CVA, g.4
2	71	M	80	BOT	No	CHF, grade 3
3	73	M	90	BOT	No	SVT, grade 3
4	55	M	80	BOT	Yes[a]	Neuropathy, grade 3
4	65	M	100	BOT	No	Dehydration, grade 3 and mucositis, grade 3
4	52	F	80	Oral tongue	Yes[b]	Anemia, grade 3

[a]TP (docetaxel + cisplatin) + everolimus [16].
[b]TPF (docetaxel + cisplatin + 5-fluorouracil).
Abbreviations for primary site: BOT, base of tongue (oropharynx); SG, supraglottic.
Abbreviations for DLTs: CVA, cerebrovascular accident; CHF, congestive heart failure exacerbation; SVT, supraventricular tachycardia.

Table 4. Summary of all adverse events ($N = 23$, assessable for toxicity)

Adverse event	Any grade, *N* (%)	Grade 3, *N* (%)	Grade 4, *N* (%)
Fatigue	23 (100)	3 (13)	0
Lymphopenia	23 (100)	16 (70)	7 (30)
Mucositis, functional	23 (100)	15 (65)	0
Nausea	23 (100)	3 (13)	0
Pain: oral cavity/throat/pharynx/larynx	23 (100)	9 (39)	3 (13)
Albumin, low	22 (96)	0	0
Glucose, high	22 (96)	0	0
Mucositis: clinical exam, oral cavity	22 (96)	8 (35)	0
Weight loss	21 (91)	2 (9)	0
Constipation	20 (87)	0	0
Hemoglobin, low	20 (87)	3 (13)	0
Dysphagia	17 (74)	5 (22)	0
Leukocytes, low	17 (74)	1 (4)	0
Rash: acne/acneiform	16 (70)	2 (9)	0
AST elevation	15 (65)	0	0
Vomiting	15 (65)	1 (4)	9
ALT elevation	14 (61)	0	0
INR elevation	14 (61)	0	0
Rash, dermatitis associated w/RT	14 (61)	6 (26)	0
Fever (non-neutropenic)	13 (57)	0	0
Infection, other	13 (57)	1 (4)	1 (4)
Pain: headache	13 (57)	0	0
Cough	12 (52)	0	0
Rash/desquamation	11 (48)	1 (4)	0
Neuropathy, sensory	9 (39)	1 (4)	0
Platelets, low	9 (39)	0	0
Sodium, low	9 (39)	2 (9)	0
Dysgeusia	9 (39)	0	0
Diarrhea	8 (35)	0	0
Magnesium, low	8 (35)	1 (4)	0
Pain: neck	8 (35)	0	0
Phosphate, low	8 (35)	2 (9)	0
Potassium, low	7 (30)	2 (9)	0
Dehydration	4 (17)	2 (9)	0
Confusion	2 (9)	1 (4)	1 (4)

failure were distant only ($N = 4$), local/regional only ($N = 3$), and both distant and local/regional ($N = 2$). Among 10 patients with human papillomavirus (HPV)-positive oropharynx squamous cell cancer, 2-year FFS rate was 70% (95% CI 33% to 89%) and 2-year OS rate was 100%. The three HPV-positive oropharynx squamous cell cancer patients who experienced recurrent disease all had tobacco histories of 20 pack-years or greater.

Long-term functional outcome data [17] are provided in supplementary Material results, available at *Annals of Oncology* online and supplementary Table S2, available at *Annals of Oncology* online.

discussion

This phase I study establishes that the MTD of *nab*-paclitaxel is 60 mg/m^2 weekly when given with standard weekly cetuximab and concurrent IMRT for patients with stage III/IVB HNSCC. For the entire study population, the most common ≥ grade 3 AEs were lymphopenia, functional mucositis, and pain in throat/oral cavity.

The MTD of *nab*-paclitaxel obtained in this study (60 mg/m^2 weekly) can be compared with the doses of lipid solvent-based paclitaxel (30–40 mg/m^2 weekly) that are currently applied in head and neck cancer chemoradiation [9, 18–20]. Recognizing the important caveat that features of these HNSCC chemoradiation regimens differ, our findings are consistent with a general observation from studies in other disease types that the MTD of *nab*-paclitaxel typically is 1.5- to 2-fold higher than the MTD of lipid solvent-based paclitaxel [21].

Although it is not possible to draw efficacy conclusions from a phase I trial, it is notable that the efficacy results observed in the study (2-year FFS, 65%; 2-year OS, 91%) are numerically superior to the results among stage III/IVB HNSCC patients treated with cetuximab + IMRT off protocol at this institution (2-year FFS, 45%; 2-year OS, 67%) [4]. The results of this study should also be viewed in the context of the fact that, at the time that this study was open to accrual, fit patients were generally encouraged to receive cisplatin-based chemoradiation, either off protocol or on another study of cisplatin-based chemoradiation that was open at this center. Most of the subjects in the current study had at least a relative contraindication to cisplatin-based chemoradiation. This study population is felt to represent a somewhat

less favorable prognostic group than the populations of our cisplatin-based chemoradiation clinical trials.

The current phase I study regimen provides a research direction that should be explored in the aftermath of the initial negative results of RTOG 0522, a randomized phase III evaluation of cetuximab + cisplatin + radiation therapy in stage III-IVB HNSCC [22]. With the caveat that the median follow-up of RTOG 0522 is only 2.4 years, there is no evidence that the addition of cetuximab to cisplatin + RT improves efficacy in this disease. In RTOG 0234, a phase II randomized comparison of cetuximab + docetaxel versus cetuximab + cisplatin given concurrently with postoperative RT, 2-year OS (79% versus 69%) and 2-year FFS (66% versus 57%) were numerically superior in the cetuximab + docetaxel arm, although these differences did not reach statistical significance [23]. The results of RTOG 0522 and RTOG 0234 strongly suggest that enhancing the radiosensitization effect of cetuximab with taxanes is an appropriate direction for further study in HNSCC, whereas the addition cisplatin does not appear to be viable strategy to improve the efficacy of cetuximab + RT in this disease.

Three recent reports found that weekly lipid solvent-based paclitaxel + cetuximab achieved objective response rates of 54%–55% in patients with recurrent and/or metastatic HNSCC [24–26]. It is only a small extrapolation to posit that these results support the further development of regimens that include *nab*-paclitaxel + cetuximab. *Nab*-paclitaxel may be the preferred taxane to incorporate in future HNSCC studies, because of superior efficacy of *nab*-paclitaxel versus lipid solvent-based paclitaxel in other disease types [10, 27], and the lack of requirement for steroid premedication.

For patients with large primary tumors or bulky nodal disease, *nab*-paclitaxel-based induction chemotherapy [28] followed by IMRT + *nab*-paclitaxel + cetuximab would seem to be a compelling study option. For patients with more favorable features who are not felt to require induction chemotherapy, the chemoradiation regimen in this study merits further research as an alternative to primary cisplatin + concurrent radiation. Noting the longstanding concerns regarding the efficacy of primary cetuximab + concurrent radiation [3, 5], the addition of *nab*-paclitaxel to the Bonner regimen, as we report here, may present a possible study option that avoids the toxicities of cisplatin.

In summary, this phase I study demonstrates the feasibility of adding weekly *nab*-paclitaxel to the Bonner regimen. The study regimen may be appropriate for further research as a nonplatinum alternative for stage III/IVB HNSCC patients, including those with bulky disease who require induction chemotherapy and those with more favorable features for whom primary chemoradiation is planned.

funding

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disclosure

NL and ES have served as consultants for Bristol Myers Squibb. All remaining authors have declared no conflicts of interest.

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Treatment-related outcome of oropharyngeal cancer patients differentiated by HPV dictated risk profile: a tertiary cancer centre series analysis

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Background: To date, no treatment modality has been identified as more effective for oropharyngeal cancer (OPC), and no predictive factors are known to guide treatment decision for this disease. This retrospective study evaluates the differential effects of diverse treatment options for OPC according to patient risk profiles.

Patients and methods: We considered two series of locally advanced squamous cell OPC patients treated with either surgery followed by radiotherapy (surgical series) or chemoradiation (CRT) with/without induction docetaxel, cisplatin and 5-fluorouracil (TPF) chemotherapy (CRT series). Smoking habits, tumor p16 expression/human papillomavirus (HPV) status and T and N stage were analyzed to stratify the patients according to Ang's risk profile (low, intermediate and high risk). Overall survival (OS) and disease-free survival were calculated with the Kaplan–Meier method.

Results: Globally, 171 patients were considered, 56 in surgical and 115 in CRT series. Patients were stratified in low- (20% of surgical and CRT groups), intermediate- (23% and 41%) and high-risk (57% and 39%) groups. In the surgical series, 5-year OS was 54.5%, 46.9% and 40.0% in low, intermediate and high Ang's risk profiles, respectively, whereas in the CRT series those were 100%, 78.9% and 46.7%, respectively. In the multivariable analyses, adjusting for inhomogeneity between the treatment group, the CRT effect was significantly higher in the low- and intermediate-risk groups (*P*-value for the interaction treatment risk group = 0.034 in the OS analysis).

Conclusions: In this retrospective analysis, low- and intermediate-risk OPC patients had a better survival when treated with CRT compared with open surgery followed by radiation therapy. These data suggest that different treatment approaches might be essential in determining outcome results.

Key words: oropharyngeal cancer, human papilloma virus, chemoradiation, risk profile, survival

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