Review

Evolving Evidence of the Efficacy and Safety of *nab*-Paclitaxel in the Treatment of Cancers with Squamous Histologies

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Abstract

Taxanes, such as paclitaxel and docetaxel, are well-established cytotoxic chemotherapeutics used in the treatment of a variety of cancers, including those of squamous histology. In their formulation, both agents require solvents, which have been associated with hypersensitivity reactions, peripheral neuropathy, hepatic toxicities, and impaired drug delivery. *nab*-Paclitaxel is a novel, albumin-bound form of paclitaxel with improved tolerability, bioavailability, and efficacy compared with solvent-based paclitaxel. Currently, *nab*-paclitaxel is approved for the treatment of metastatic breast cancer, locally advanced/metastatic non-small cell lung cancer (NSCLC), and metastatic pancreatic cancer. Clinical studies suggest that *nab*-paclitaxel may be particularly effective in cancers with squamous histology, including NSCLC. This article reviews the emerging evidence supporting *nab*-paclitaxel as an effective agent in the treatment of malignancies of squamous histology.

Key words: *nab*-paclitaxel, squamous cell carcinoma, non-small cell lung cancer (NSCLC), head/neck cancer, nasopharyngeal carcinoma, esophageal cancer

Introduction

Cytotoxic chemotherapy is an essential component of cancer treatment, and taxanes are recommended agents for numerous cancers with squamous cell carcinoma (SCC) [1-4]. Paclitaxel and its semi-synthetic analogue docetaxel are taxanes that act as microtubule stabilizers to inhibit cell division and, ultimately, lead to cell death [5-7]. Despite their considerable efficacy, paclitaxel and docetaxel are limited by their formulation requirements. Both agents are extremely hydrophobic and require the use of solvents to enhance solubility and create an injectable solution [8, 9]. Paclitaxel is formulated in the castor oil derivative Kolliphor EL (originally Cremophor EL), and docetaxel is formulated using polysorbate 80. These solvents are associated with impaired drug delivery and toxicities such as peripheral neuropathy and hypersensitivity reactions requiring the use of steroid pretreatment [8-12].

nab-Paclitaxel is an albumin-bound form of paclitaxel that was designed to overcome the limitations associated with solvent-based taxanes [13]. The use of 130-nm albumin particles as carriers in *nab*-paclitaxel's formulation improves tolerability by eliminating the need for chemical solvents. The albumin formulation also improves drug bioavailability, as *nab*-paclitaxel has demonstrated increased paclitaxel tumor delivery in preclinical models compared with solvent-based paclitaxel [14]. In a population pharmacokinetic/pharmacodynamic study, *nab*-paclitaxel also demonstrated faster and deeper

tissue penetration and slower elimination than its solvent-based counterpart in patients with advanced solid tumors [15]. It is hypothesized that *nab*-paclitaxel utilizes receptor-mediated albumin transcytosis to internalize paclitaxel in the tumor interstitium [16, 14, 17]. Other evidence suggests that passive diffusion due to enhanced vascular permeability may play a role [18].

Squamous cell carcinomas can be difficult to treat, and patients with this particular histology comprise a large unmet need, as outcomes may be worse for those with SCC compared with other histologies [19, 20]. In addition, some agents may not be indicated for treating SCC due to efficacy or safety issues [21, 22]. Recently, *nab*-paclitaxel has demonstrated activity in several SCC tumor types, such as non-small cell lung cancer (NSCLC), cervical cancer, and head and neck cancers, including cancer of the oropharynx, esophageal cancer, and nasopharyngeal cancer (NPC). Here we provide an overview of recent studies of *nab*-paclitaxel in SCC.

Potential mechanism of tumor delivery of *nab*-paclitaxel in cancers

nab-Paclitaxel has been postulated to enter tumors through interaction with secreted protein acidic and rich in cysteine (SPARC), also known as osteonectin or BM-40 [23, 24]. SPARC is an albumin-binding protein with similar affinity to that of the albumin receptor (gp60) itself, and high SPARC expression may possibly be associated with tumor progression in several cancers [17, 24]. SPARC expression has been associated with poor outcomes in NSCLC, head and neck cancer, breast cancer, and early stage pancreatic cancer [25-29].

Data regarding SPARC expression and *nab*-paclitaxel activity remain limited, particularly in the SCC setting. SPARC expression was associated with a higher response rate in a study of 60 patients with head and neck cancer treated with *nab*-paclitaxel

[23]. Patients with SPARC positivity (n = 12) demonstrated an overall response rate (ORR) of 83% compared with 25% in patients who were SPARC negative (n = 4). A phase I/II study assessed SPARC expression in patients with advanced NPC treated with *nab*-paclitaxel plus cisplatin [30]. SPARC was assessed in 62 cases, and patients with both high stromal and tumoral SPARC expression demonstrated an ORR of 82% compared with 20% in patients with low stromal and high tumoral SPARC expression. In addition, patients with both low stromal and tumoral SPARC expression demonstrated an ORR of 80%, and patients with high stromal and low tumoral SPARC expression had an ORR of 60%. As head and neck cancers are predominantly of SCC histology, these studies provide additional clues regarding outcomes in patients with SCC histology treated with *nab*-paclitaxel. SPARC expression and *nab*-paclitaxel activity were also evaluated in a single-arm phase II trial of patients with advanced NSCLC who were ineligible for bevacizumab treatment (due to bleeding risk, bevacizumab is contraindicated in patients with SCC or hemoptysis) [31]. The study enrolled 63 patients, the majority of whom (76%) had SCC. No association was observed between tumoral or stromal SPARC expression and response to treatment with *nab*-paclitaxel plus carboplatin. Although the results are intriguing, these studies were performed in a limited patient population. In one of the largest studies assessing SPARC, a phase III trial of patients with pancreatic cancer, SPARC expression was neither predictive nor prognostic of overall survival (OS) [32].

Current clinical data for *nab*-paclitaxel in malignancies of SCC histology

Emerging data from recent clinical trials suggest that *nab*-paclitaxel may be particularly effective and well tolerated in patients with cancers of SCC histology (Tables 1 and 2).

Table 1. Select efficacy outcomes of trials of *nab*-paclitaxel regimens in squamous cell carcinoma.

No. of SCC Patients	Regimen	OS, Median mo	PFS, Median mo	Reference
NSCLC				
63	*nab*-P 260 mg/m^{2,a} + Carbo AUC 6 q3w	9.7	5.0	Bertino et al [31]
40	*nab*-P 125 mg/m^2 qw 2/3 + cisplatin 75 mg/m^2 or Carbo AUC 5 q3w	NR	5^b	Fang et al [33]
43	*nab*-P 260 mg/m^2 q3w	11	NR	Green et al [34]
229	*nab*-P 100 mg/m^2 qw + Carbo AUC 6 q3w	10.7	5.6	Socinski et al [36]
221	sb-P 200 mg/m^2 q3w + Carbo AUC 6 q3w	9.5	5.7	
60	*nab*-P 135 mg/m^2 qw 2/3 + Carbo AUC 5 q3w	11.9^c	5.7	Yang et al [38]
64	Gem 1250 mg/m^2 qw 2/3 + Carbo AUC 5 q3w	14.4	4.8	
Head and Neck				
17	*nab*-P 75-100 mg/m^2 qw 2/3 + Cis 75-100 mg/m^2 q3w + 5-FU 1000 mg/m^2/d × 96 h q3w, followed by CRT	Not reached	Not reached	Loong et al [40]
30	*nab*-P 100 mg/m^2 qw + Cetux 250 mg/m^{2,d} qw + Cis 75 mg/m^2 q3w + 5-FU 750 mg/m^2/d × days 1-3 q3w, followed by CRT	NR	NR	Adkins et al [41]
11	Cetux 400 mg/m^2 week 1 followed by Cetux 250 mg/m^2 qw +	NR	NR	Nedzi et al [42]

	Cis 20 mg/m² qw + *nab*-P 25 mg/m²,e qw with IMRT			
Esophageal				
33	*nab*-P 250 mg/m² q4w + Cis 75 mg/m² q3w	15.5	6.2	Shi et al [44]
35	*nab*-P 100 mg/m² days 1, 8, 22, 29 + Cis 75 mg/m² days 1, 22	NR	NR	Fan et al [43]
Nasopharyngeal				
23	*nab*-P 260 mg/m² q3w + Cis 75 mg/m² q3w	NR	7	Zhang et al [28]
22	*nab*-P 140 mg/m² days 1, 8 q3w + Cis 75 mg/m² q3w		6	
24	*nab*-P 100 mg/m² qw + Cis 75 mg/m² q3w		9	
Cervical				
37	*nab*-P 125 mg/m² qw 3/4	9.4	5.0	Alberts et al [47]

Abbreviations: 5-FU, 5-fluorouracil; AUC, area under the curve; Carbo, carboplatin; Cetux, cetuximab; Cis, cisplatin; CRT, chemoradiation; Gem, gemcitabine; IMRT, intensity-modulated radiation therapy; *nab*-P, *nab*-paclitaxel; NR, not reported; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; q3w, every 3 weeks; q4w, every 4 weeks; qw, weekly; qw 2/3, the first 2 of 3 weeks; qw 3/4, the first 3 of 4 weeks; sb-P, solvent-based paclitaxel; SCC, squamous cell carcinoma.

ᵃ Reduced from 300 mg/m² due to excess neuropathy.

ᵇ 67% of patients had SCC.

ᶜ Results not final. At the time of report, 62% of survival events had been recorded.

ᵈ Loading dose of Cetux 400 mg/m² given on day 1.

ᵉ *nab*-P dose reduced to 20 mg/m² after treatment of first 6 patients.

Table 2. Select safety outcomes of trials of *nab*-paclitaxel regimens in squamous cell carcinoma.

No. of SCC Patients	Regimen	Key Grade ≥ 3 Adverse Events (%)	Reference
NSCLC			
63ᵃ	*nab*-P 260 mg/m²,b + Carbo AUC 6 q3w	Neutropenia (19), anemia (11), thrombocytopenia (11), neuropathy (30)	Bertino et al [31]
40	*nab*-P 125 mg/m² qw 2/3 + cisplatin 75 mg/m² or Carbo AUC 5 q3w	Thrombocytopenia (10), neuropathy (7.5ᶜ)	Fang et al [33]
43ᵈ	*nab*-P 260 mg/m² q3w	Neutropenia (9), neuropathy (5)	Green et al [34]
222ᵉ	*nab*-P 100 mg/m² qw + Carbo AUC 6 q3w	For *nab*-P regimen: neutropenia (43), anemia (26), thrombocytopenia (22), neuropathy (3)	Socinski et al [36]
214ᵉ	sb-P 200 mg/m² q3w + Carbo AUC 6 q3w	For sb-P regimen: neutropenia (51), anemia (4), thrombocytopenia (7), neuropathy (12)	
59	*nab*-P 135 mg/m² qw 2/3 + Carbo AUC 5 q3w	For *nab*-P regimen: neutropenia (70), anemia (22), thrombocytopenia (35)	Yang et al [38]
65	Gem 1250 mg/m² qw 2/3 + Carbo AUC 5 q3w	For Gem regimen: neutropenia (42.2), anemia (27), thrombocytopenia (44)	
Head and Neck			
17	*nab*-P 75-100 mg/m² qw 2/3 + Cis 75-100 mg/m² q3w + 5-FU 1000 mg/m²/d × 96 h q3w, followed by CRT	Neutropenia (23), thrombocytopenia (6)	Loong et al [40]
30	*nab*-P 100 mg/m² qw + Cetux 250 mg/m² qw + Cis 75 mg/m² q3w + 5-FU 750 mg/m²/d × 72 h q3w, followed by CRT	Neutropenia (20), anemia (3), thrombocytopenia (3)	Adkins et al [41]
10ᶠ	Cetux 400 mg/m² followed by Cetux 250 mg/m² qw + Cis 20 mg/m² qw + *nab*-P 25 mg/m² qw with IMRT	Lymphopenia (11)	Nedzi et al [42]
Esophageal			
33	*nab*-P 250 mg/m² q4w + Cis 75 mg/m² q2w	Neutropenia (3), neuropathy (3)	Shi et al [44]
35	*nab*-P 100 mg/m² q3w + Cis 75 mg/m² q3w	Neutropenia (11), anemia (9), thrombocytopenia (6)	Fan et al[43]
Nasopharyngeal			
23	*nab*-P 260 mg/m² q3w + Cis 75 mg/m² q3w	For *nab*-P 260 regimen: neutropenia (65), anemia (13)	Zhang et al [28]
22	*nab*-P 140 mg/m² qw 2/3 + Cis 75 mg/m² q3w	For *nab*-P 140 regimen: neutropenia (67), anemia (5)	
24	*nab*-P 100 mg/m² qw + Cis 75 mg/m² q3w	For *nab*-P 100 regimen: neutropenia (61), anemia (9)	
Cervical			
35	*nab*-P 125 mg/m² qw 3/4	Neutropenia (9), anemia (11), thrombocytopenia (3)	Alberts et al [47]

Abbreviations: 5-FU, 5-fluorouracil; AUC, area under the curve; Carbo, carboplatin; Cetux, cetuximab; Cis, cisplatin; CRT, chemoradiation; Gem, gemcitabine; IMRT, intensity-modulated radiation therapy; *nab*-P, *nab*-paclitaxel; NR, not reported; NSCLC, non-small cell lung cancer; q2w, every 2 weeks; q3w, every 3 weeks; q4w, every 4 weeks; qw, weekly; qw 2/3, the first 2 of 3 weeks; sb-P, solvent-based paclitaxel; SCC, squamous cell carcinoma.

ᵃ Included patients ineligible for bevacizumab; 76% had SCC.

ᵇ Reduced from 300 mg/m² due to excess neuropathy.

ᶜ Reported as neurotoxicity.

ᵈ 67% of patients had SCC.

ᵉ For sensory neuropathy, n = 226 in the *nab*-P + Carbo arm and n = 218 in the sb-P + Carbo arm.

ᶠ Adverse events reported here were acute toxicities related to the protocol.

nab-Paclitaxel in NSCLC of SCC histology

Patients with NSCLC of SCC histology may be at risk for worse outcomes than patients with other histologies [19]. Generally, platinum doublets are the preferred first-line treatment for this patient population, and treatment choice is further restricted because some agents recommended for the treatment of advanced NSCLC are not indicated for SCC histology [22, 21, 20]. For example, pemetrexed and bevacizumab are not indicated in SCC due to a lack of efficacy and an increased risk of bleeding events, respec-

tively [21, 22]. *nab*-Paclitaxel plus carboplatin is approved for treatment of NSCLC of any histology, and evidence suggests that the regimen may be particularly effective in patients with SCC histology [13].

Several early studies of *nab*-paclitaxel provided some evidence of its activity in patients with SCC NSCLC [31, 33, 34]. One of these studies, mentioned previously, enrolled 63 patients with advanced NSCLC who were ineligible for bevacizumab therapy (48 patients had SCC) [31]. Patients in this study received *nab*-paclitaxel plus carboplatin. This treatment regimen resulted in a 38% ORR, with 32% of patients experiencing stable disease and 16% experiencing progressive disease. The median progression-free survival (PFS) and OS were 5.0 and 9.7 months, respectively. The most common grade ≥ 3 toxicities included hematologic toxicities, sensory neuropathy, and fatigue. Another study evaluated the safety and efficacy of *nab*-paclitaxel in combination with a platinum agent in stage III/IV SCC NSCLC [33]. Chemotherapy-naive patients (N = 40) received *nab*-paclitaxel and either cisplatin or carboplatin. The ORR was 63%, the disease control rate was 93%, and 30% of patients experienced stable disease. Patients receiving *nab*-paclitaxel combined with cisplatin vs carboplatin achieved an ORR of 74% vs 52%. Adverse events were not reported separately for the cisplatin and carboplatin arms, but grade ≥ 3 toxicities included leukocytopenia, thrombocytopenia, baldness, and nausea/vomiting. Finally, a phase II study enrolled 43 patients with advanced NSCLC, and most (67%) had SCC; all patients were treated with single-agent *nab*-paclitaxel [34]. Overall, 7 patients had a confirmed overall response, 5 of whom had SCC; grade ≥ 3 toxicities occurred in 21% of patients.

More robust evidence of the activity of *nab*-paclitaxel in SCC NSCLC came from a recent multicenter phase III registrational trial, in which more than 1000 chemotherapy-naive patients with advanced NSCLC received either weekly *nab*-paclitaxel plus carboplatin or solvent-based paclitaxel plus carboplatin [35]. In the intent-to-treat population, treatment with *nab*-paclitaxel plus carboplatin significantly improved the primary endpoint (ORR) compared with the solvent-based regimen (33 vs. 25%; 95% CI, 1.082-1.593; *P* = 0.005), with a trend toward increased OS and PFS. In a subanalysis of patients with SCC (n = 450), *nab*-paclitaxel plus carboplatin resulted in a significantly better ORR compared with solvent-based paclitaxel plus carboplatin (41% vs. 24%; response rate ratio 1.680; 95% CI, 1.27-2.22; *P* < 0.001) [36]. Similar to the intent-to-treat population, an approximately 1-month longer median OS was noted for patients with SCC in the *nab*-paclitaxel and carboplatin arm compared with those treated with solvent-based paclitaxel and carboplatin, but this difference was not significant (10.7 vs. 9.5 months; hazard ratio [HR] 0.89; 95% CI, 0.72-1.10; *P* = 0.28). Safety was similar regardless of histology. In a retrospective analysis of the same phase III trial, patients with SCC treated with *nab*-paclitaxel plus carboplatin beyond 4 cycles had a median PFS and OS from time of randomization of 6.8 and 13.8 months, respectively, with no new safety signals compared with the intent-to-treat population [37]. The ABOUND.sqm study has been initiated to further examine *nab*-paclitaxel for the treatment of SCC NSCLC in the maintenance setting (NCT02027428).

A randomized phase II trial recently compared the efficacy and safety of first-line *nab*-paclitaxel plus carboplatin versus gemcitabine plus carboplatin in more than 120 patients with advanced SCC of the lung [38]. ORR, the study's primary endpoint, was 46% and 30% for *nab*-paclitaxel plus carboplatin versus gemcitabine plus carboplatin, respectively (*P* = 0.085). There was no significant difference between the treatment arms with respect to median PFS and OS. However, median PFS improved approximately 19% with *nab*-paclitaxel plus carboplatin treatment (5.7 vs. 4.8 months, respectively; HR, 0.907; 95% CI, 0.588-1.399; *P* = 0.657). Treatment with *nab*-paclitaxel plus carboplatin was associated with a higher incidence of neutropenia and leukocytopenia compared with gemcitabine plus carboplatin, but no other significant differences in grade ≥ 3 toxicities were noted. These safety results are consistent with the previous report from the phase III trial in this patient subset [36]. Although the results of this study support the efficacy of *nab*-paclitaxel plus carboplatin in patients with SCC, these data should be interpreted with caution, as only 62% of events had been reported at the time of publication [38].

nab-Paclitaxel in SCC of the head and neck (SCCHN)

SCCs account for most head and neck cancers [39]. Treatment of SCCHN is complicated and relies on several approaches, including chemotherapy [4]. With this strategy, the preferred treatment regimen for locally advanced (LA) disease is high-dose cisplatin plus concurrent radiotherapy. However, taxane-based regimens are also recommended as induction or sequential chemotherapeutic approaches. Taxanes have also demonstrated activity in the metastatic setting, and paclitaxel and docetaxel (each combined with cisplatin or carboplatin, or as monotherapy) are recommended agents for the treatment of recurrent, unresectable, or metastatic head and neck cancers. Additional treatment options could benefit

patients with this disease.

nab-Paclitaxel has been investigated in SCCHN, and early clinical evidence supports the feasibility of induction chemotherapy (IC) with *nab*-paclitaxel. A dose-determining phase I trial recently evaluated the safety and efficacy of combining *nab*-paclitaxel with cisplatin and fluorouracil as IC followed by chemoradiation (CRT) with carboplatin in previously untreated patients with LA-SCC of the oropharynx [40]. Although median PFS and OS had not been reached at the time of publication, the estimated 1-year PFS rate was 79% (95% CI, 0.49-0.93), and the estimated 1-year OS rate was 86% (95% CI, 0.49-0.96). Grade ≥ 3 toxicities included neutropenia, lymphopenia, and hyponatremia. This combination regimen was determined to be feasible for patients with LA-SCCHN and good baseline performance status.

A recent phase II trial further demonstrated promising results with combination *nab*-paclitaxel IC in LA-SCCHN [41]. Patients (N = 30) received IC with *nab*-paclitaxel, cetuximab, cisplatin, and 5-fluorouracil followed by concurrent CRT with cisplatin. After 2 cycles of IC, patients who demonstrated a complete response (CR) or partial response (PR) were given an additional cycle of treatment while patients who had stable disease or progressive disease at the primary site received definitive CRT. This combination *nab*-paclitaxel induction regimen resulted in a CR and PR rate at the primary tumor of 53% and 47%, respectively. The estimated 2-year OS was 84% and the estimated 2-year PFS rate was 65%. Grade ≥ 3 toxicities included fatigue, neutropenia, acneiform rash, and hypokalemia.

nab-Paclitaxel has also been evaluated as part of a CRT regimen following IC with cetuximab and cisplatin for patients with LA-SCCHN [42]. In this phase I dose-determining study (standard 3+3 design), patients (N = 11) received cetuximab followed by CRT with cetuximab, cisplatin, and *nab*-paclitaxel 25 mg/m² weekly. Two dose-limiting toxicities occurred in the first 6 patients receiving the regimen with *nab*-paclitaxel 25 mg/m², thus the weekly *nab*-paclitaxel dose was reduced to 20 mg/m². Of 10 patients, 7 achieved a CR at the primary tumor site after treatment with this regimen. Acute toxicity was manageable, and grade ≥ 3 lymphopenia was the only reported adverse event to occur in ≥ 10% of patients. This study demonstrated that weekly *nab*-paclitaxel 20 mg/m² is the maximum tolerated dose in this CRT regimen for patients with LA-SCCHN, and a phase II trial is planned.

nab-Paclitaxel in NPC

Both isolated local recurrences and distant metastases are common in patients with NPC, presenting substantial treatment challenges [4]. The recommended treatment for early-stage disease is radiotherapy with or without platinum-based chemotherapy, as well as IC with a cisplatin-taxane combination regimen. Suggested treatment regimens for metastatic NPC are the same as those for head and neck cancers discussed previously. Identifying new agents for the treatment of this disease could improve outcomes for this patient population.

nab-Paclitaxel has been investigated in the treatment of NPC, yielding encouraging results [28]. In a phase I/II dose-finding study in patients with metastatic NPC, chemonaive patients or patients in whom previous standard treatment had failed were treated with cisplatin 75 mg/m² every 3 weeks plus 1 of 3 *nab*-paclitaxel regimens: *nab*-paclitaxel 260 mg/m² every 3 weeks (n = 23), 140 mg/m² days 1 and 8 every 3 weeks (n = 22), or 100 mg/m² weekly (n = 24). The ORR was similar between all treatment arms (68%, 63%, and 65% for *nab*-paclitaxel 260 mg/m², 140 mg/m², and 100 mg/m², respectively; *P* = 0.94) but significantly higher in chemonaive patients versus those previously treated (100% vs. 53%; *P* < 0.01). Grade ≥ 3 toxicities included neutropenia, leukocytopenia, and anemia.

nab-Paclitaxel in esophageal SCC (ESCC)

Treatment of esophageal cancer relies on a combined modality approach due to the aggressive nature of the disease [3]. For patients with ESCC, recommended treatment of locoregional disease includes surgery, chemotherapy, and CRT. The National Comprehensive Cancer Network guidelines list treatment with carboplatin plus paclitaxel as both a preferred preoperative and definitive CRT regimen [3]. Recommended treatment options for patients with LA unresectable, locally recurrent, or metastatic ESCC include chemotherapy doublets or triplets, including taxane-platinum combinations. In these settings, taxane-based regimens are also listed as preferred options (categories 1, 2A, and 2B) for both first- and second-line treatment. Given the complicated nature of this disease and the resulting treatment challenges, additional effective therapeutic strategies are necessary.

A recent phase II trial evaluating *nab*-paclitaxel in combination with cisplatin for resectable LA-ESCC yielded positive results [43]. Patients received *nab*-paclitaxel plus cisplatin followed by esophagectomy. At 4 to 6 weeks after resection, patients received adjuvant treatment with 2 cycles of the combination chemotherapy regimen described. A total of 35 patients were enrolled in the study, with 30 proceeding to surgery. The pathologic complete response rate was 13%, with downstaging observed in more than 60% of

patients. All of the patients who proceeded with surgery after neoadjuvant chemotherapy had an R0 resection. Grade ≥ 3 toxicities included neutropenia, anemia, and thrombocytopenia.

nab-Paclitaxel plus cisplatin could also be a feasible first-line treatment option for metastatic ESCC [44]. In one study, patients who received no prior treatment for metastatic disease (N = 33) were treated with *nab*-paclitaxel followed by cisplatin. While no CR was observed, 20 patients achieved a PR. The ORR was 61%, and median PFS and OS were 6.2 and 15.5 months, respectively. Treatment was well tolerated, with only 4 patients experiencing grade 3 toxicities. Incidence of grade ≥ 3 toxicities was low and included leukocytopenia and neutropenia.

nab-Paclitaxel in cancers of the cervix

SCC accounts for the majority of cervical cancers [45]. Patients who develop metastatic disease have a poor prognosis [46]. Chemotherapy is recommended for patients with metastatic disease who are not candidates for radiotherapy or surgery, and combination paclitaxel and/or platinum-based regimens as well as treatment with single agents (including cisplatin, carboplatin, and paclitaxel) are recommended first-line options [2]. Although cisplatin is considered to be the most effective agent for patients with metastatic disease, platinum-based monotherapy outcomes can be worse in these patients, given the frequent use of this treatment in primary disease. For women who have progressed after first-line treatment and for those who are not candidates for combination chemotherapy, single-agent second-line therapy with several agents including docetaxel is recommended. However, more effective second-line treatment options are needed.

nab-Paclitaxel has demonstrated antitumor activity in this patient population [47]. The Gynecologic Oncology Group evaluated *nab*-paclitaxel monotherapy in women with metastatic or recurrent SCC or nonsquamous cervical cancer who had progressed or relapsed after prior treatment. In this phase II trial, 35 patients were evaluable for efficacy. The ORR was 29% (95% CI, 14.6%-46.3%) with PRs lasting a median of 6.0 months (range, 1.5-9.2 months). Another 15 patients (43%) had stable disease lasting a median of 5.8 months (range, 3.7-11.4 months). The median PFS and OS were 5 and 9.4 months, respectively. Grade ≥ 3 toxicities were uncommon, but included anemia, fatigue, and neutropenia.

Summary of the outcomes of *nab*-paclitaxel in the treatment of cancers with SCC histology

Efficacy

The studies discussed in this review demonstrate that *nab*-paclitaxel is an important treatment option among various solid tumors of SCC histology. *nab*-Paclitaxel regimens have demonstrated ORRs ranging from 38% to 74% and a median OS ranging from 9.7 to 10.7 months [31, 33, 36, 38]. Although results are limited, in patients with SCCHN, including ESCC as well as NPC, *nab*-paclitaxel regimens have demonstrated encouraging survival results in this population; a median OS of up to 15.5 months has been reported [28, 40-44]. In patients with cervical cancer, which is most often of SCC histology, *nab*-paclitaxel plus cisplatin has also demonstrated favorable results, with a 29% ORR and a median OS of 9.4 months [47]. Further studies are warranted to confirm the findings of these early studies; however, early results in these various tumor types with SCC histology indicate the promising activity of *nab*-paclitaxel.

Safety

Across all studies of *nab*-paclitaxel regimens in SCC histology mentioned in this review, the most common grade ≥ 3 adverse events observed include neutropenia, anemia, thrombocytopenia, and peripheral neuropathy [28, 31, 33, 34-36, 38, 40-44, 47]. These events are consistent with those reported in phase III trials of *nab*-paclitaxel combination regimens in patients with unselected advanced NSCLC and advanced pancreatic cancer and *nab*-paclitaxel monotherapy in metastatic breast cancer [35, 48, 49]. These adverse events are manageable with dose modifications, and in the case of peripheral neuropathy, several of the phase III studies demonstrated improvement from grade ≥ 3 to lower grades within ≈1 month in most patients [35, 48, 49]. Overall, the safety profile of *nab*-paclitaxel–based regimens appears to be consistent across multiple studies.

Conclusions

nab-Paclitaxel has demonstrated improved tolerability, drug bioavailability, and efficacy compared with its solvent-based counterpart. Currently, *nab*-paclitaxel is approved for monotherapy treatment of metastatic breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy (prior therapy should have included an anthracycline unless contraindicated), first-line treatment of LA or metastatic NSCLC in combination with carboplatin in patients

who are not candidates for curative surgery or radiation therapy, and first-line treatment of metastatic pancreatic cancer in combination with gemcitabine [13]. However, several studies provide evidence that supports a potential role for *nab*-paclitaxel in cancers with SCC histology, including NSCLC, ESCC, SCCHN, NPC, and cervical cancer. Although results are encouraging, further clinical research is necessary to elucidate the role of *nab*-paclitaxel–based regimens in these and other SCCs.

Acknowledgements

Competing Interests

The authors have declared that no competing interest exists.

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