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EXPERT OPINION

Nanoparticle albumin-bound paclitaxel (nab-paclitaxel): extending its indications

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1. Introduction

The Leone *et al*. Drug Safety Evaluation published in the April issue of *Expert Opinion on Drug Safety* is a comprehensive summary of the literature regarding this novel formulation of paclitaxel. The first taxane introduced into the clinic was taxol – later renamed as paclitaxel. Formulated in Cremophor, its initial checkered history reflects its poor solubility and clinical consequences linked to the solvent itself. Nevertheless, two decades after its approval, paclitaxel and its analog docetaxel are part of therapeutic regimens for cancers of the breast, genitourinary, gynecologic organs and aerodigestive passages, among others [1]. Ten years after its approval, nab-paclitaxel has gained approval for new indications: NSCLC and pancreatic adenocarcinoma. Nab-paclitaxel induces lesser grade 4 neutropenia, but other toxicities such as gastrointestinal symptoms and sensory neuropathy, perhaps related to higher taxane dose rates used, may be adversely impacted. Neuropathy, a key dose-limiting toxicity of taxanes, deserves separate comments. Recent successes, however, suggest that nab-paclitaxel may ultimately demonstrate additional advantages in specific circumstances over its solvent-based older counterpart. Accordingly, this editorial will expand on why and how the indications for nab-paclitaxel may be further extended.

2. Nab-paclitaxel: less or more neurotoxicity?

Sensory neuropathy is a dose-limiting toxicity that is encountered with all taxanes and is a feature of mitotic inhibitors in general. As alluded earlier, this difficult-to-quantify toxicity is not clearly less severe for nab-paclitaxel than its solvent-formulated counterpart. Partly to answer this question, we have extensively reviewed issues concerning neuropathy from solvent-based paclitaxel, docetaxel and nab-paclitaxel derived from randomized trials (**Table 1**) [2]. From such a review, no clear answer emerges because differences in dose and schedule are obvious confounders in what is reported in these studies. Nevertheless, a theoretical consideration is that Cremophor has neurotoxic potential [3]. Moreover, in NSCLC, nab-paclitaxel has a clear advantage and is also better tolerated in patients perhaps at highest risk – those older than 70 years. These differences emerge when both paclitaxel groups are combined with carboplatin: solvent-based paclitaxel had significantly more severe sensory neuropathy (11%) than nab-paclitaxel (3%) [4].

The results in metastatic breast cancer (MBC) (utilizing both every 3-week and weekly schedules and in the latter including combinations with bevacizumab and no platinums) are rather equivocal. Gradishar *et al*.'s 2005 comparison of nab-paclitaxel with paclitaxel (each every 3 weeks) in MBC had more grade 3 neurotoxicity in the nab-paclitaxel group (10 vs 2%, $p < 0.001$) [5]. On the other hand, the incidence of severe neuropathy at 28 days showed that many of the

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Table 1. Nab-paclitaxel and neuropathy in MBC, NSCLC and Panc cancer.

Nab-paclitaxel regimen	Comparator regimen	No. of patients	Grade 3+ neuropathy	Comments	Study
260 mg/m^2 q3 weeks	Paclitaxel 175 mg/m^2 q3 weeks	229, 225	10 vs 2%	MBC: registration trial	Gradishar *et al*. 2005 [5]
300 mg/m^2 q3 weeks	Docetaxel 100 mg/m^2 q3 weeks	76, 74	17 vs 12%	MBC: randomized Phase II	Gradishar *et al*. 2009 – 2012 [11]
100 mg/m^2 q1 week	Docetaxel 100 mg/m^2 q3 weeks	76, 74	8 vs 12%	Same	Gradishar *et al*. 2009 – 2012 [11]
150 mg/m^2 q1 week	Docetaxel 100 mg/m^2 q3 weeks	74, 74	14 vs 12%	Same	Gradishar *et al*. 2009 – 2012 [11]
150 mg/m^2 q1 week + bevacizumab	Paclitaxel 90 mg/m^2 q week + bevacizumab 10 mg q2 weeks	271, 283	25 vs 16%	MBC: noninferiority Phase III	Rugo *et al*. 2012 [8]
100 mg/m^2 q1 week + carboplatin	Paclitaxel 200 mg/m^2 q3 weeks + carboplatin q3 weeks	521, 531	3 vs 11%	NSCLC: registration trial	Socinski *et al*. 2012 [4]
125 mg/m^2 + gemcitabine 1000 mg/m^2 q week	Gemcitabine 1000 mg/m^2 q week	431, 430	17 vs 1%	Panc: registration trial	Von Hoff *et al*. 2013 [12]

MBC: Metastatic breast cancer; NSCLC: Non-small-cell lung cancer; Panc: Pancreatic.

nab-paclitaxel patients had recovered from their sensory neuropathy and yielded a similar incidence to the solvent-formulated paclitaxel. This experience introduces yet another variable to the incidence of sensory neuropathy beyond dose and schedule: what is the time to reversibility. Patient self-reporting in randomized blinded trials may be a way out of this unanswered conundrum.

3. Why nab-paclitaxel?

The introduction of a special formulation for paclitaxel was a logical outgrowth of the difficulties in rendering soluble a drug that required the potent lipid solvent dimethyl sulfoxide for any laboratory study. The clinical formulation relied on Cremophor and enabled taxol to undergo Phase I testing in the 1980s, but the drug was nearly discarded by the National Cancer Institute because of the challenges in its intravenous delivery. Subsequently, issues of this clinical formulation begging for resolution included the need to administer therapy in volumes exceeding 500 ml with the requirement for special tubing, the use of slow infusions to diminish occasionally fatal acute hypersensitivity reactions and the more chronic problems raised by the concomitant use of glucocorticoids and antihistamines. In addition to these essential requirements for its safe drug delivery, the use of Cremophor posed challenges of its own: toxicities such as flushing from the solvent itself, a profound effect on taxane pharmacology most clearly demonstrated by the prolonged terminal phase resulting in nonlinearity and a prolonged terminal half-life. This altered pharmacology and theoretical effects of a prolonged exposure to low doses of paclitaxel could play a role in recovery from neurotoxicity. Further, micelle formation and drug aggregates could interfere with optimal drug uptake by tumors relative to various normal tissues. Drug uptake by tumors is further complicated by an independent effect of Cremophor on P-glycoprotein and other exporters [3].

In addition to solvent-related challenges resulting from solvent-based paclitaxel, there are some additional inherent conveniences and advantages in using the albumin-bound nab-paclitaxel. A short infusion is a convenience not to be underestimated – it allows this drug to be more easily incorporated in complex regimens and may also tip the balance in foregoing the routine needed for insertion of a central line. Even more importantly, circumventing the need for steroid premedication is most advantageous in the presence of preexisting diabetes, a history of hepatitis, and a myriad of other conditions (e.g., autoimmune disease, asthma, osteopenia) where pulse glucocorticoids are relatively contraindicated. Finally, there are instances (such as with superior vena caval syndrome) when the volume of the infusate may be a factor in tolerance of solvent-based paclitaxel.

Theoretical advantages could be implicated in possibly decreasing the incidence of allergic reactions to platinums (this was suggested by the significantly increased reactions on retreatment of patients with ovarian cancer sensitizing to carboplatin with carboplatin + solvent-based paclitaxel as opposed to carboplatin + PEGylated liposomal doxorubicin in the Calypso trial [6]). Intraperitoneal (IP) administration of a taxane may be more predictably delivered to

Table 2. Areas where nab-paclitaxel may offer advantages over current taxane use.

Disease	Regimen(s)	Comments and suggested trial(s)
Breast	N vs P [5,8]	See comment **Table 1**: N superior to P in PFS on every 3-week schedule; noninferior in weekly + bevacizumab. Could scalp cooling with N decrease alopecia? [13]
NSCLC	CarboN vs CarboP	See comment **Table 1**: N and P used weekly in combination with every 3-week Carbo. With better tolerance in older adults, is there a role for maintenance N?
Endometrial	CarboP [14]	Regimen has emerged as key chemotherapy backbone: N substituting for P may allow a triplet and/or weekly scheduling better
Gastric and gastroesophageal junction	DCF vs CF [15]	D increases efficacy but also substantial toxicity; triplets with N needs to be tested
Head and neck	D-> CR [16]	D increases efficacy; area for N induction?
Prostate	D; Cabazitaxel [17]	Both are approved but toxicities inhibit trials in combination with other drugs (and radiation)
Kaposi's sarcoma	P + HAART [18]	As in breast cancer, if N is effective in low weekly doses, could scalp cooling diminish alopecia? [13]
Germ cell cancer	P-containing multidrug [19]	Long-term CR: could N add to these?
Small-cell lung cancer	P triplet [20]	Timely to explore taxanes in area of few recent advances
Melanoma	P +/- Carbo or temozolomide (dacarbazine) [21,22]	Activity of P or N as single agents or in combination; could N increase effects of immunotherapy, Braf inhibitors?

C: Cisplatin; Carbo: Carboplatin; CR: Complete responses; D: Docetaxel; F: 5-Fluorouracil; N: Nab-paclitaxel; NSCLC: Non-small-cell lung cancer; P: Solvent-based paclitaxel; PFS: Progression-free survival.

surface tumor in IP administration (unpublished, City of Hope, M Cristea and R Morgan). Currently not explained are the differing effects on myelosuppression and neuropathy; however, not fully exploited is the potential for lesser or more predictable toxicity when used in combination, particularly with platinums. Even for alopecia, there has been a recent rekindling of interest on ice caps to prevent taxane-induced hair loss. Could the more predictable time of exposure with nab-paclitaxel result in better protection by cooling following nab-paclitaxel as opposed to the solvent-based taxanes?

4. How to extend the indications of nab-paclitaxel?

It is ironic that the new indications of nab-paclitaxel in lung cancer and in pancreatic cancer have become established as its advantages vis-à-vis paclitaxel in breast cancer is being questioned [7]. In the recent intergroup Phase III trial, the advantage in therapeutic indices of nab-paclitaxel over solvent-based paclitaxel was no longer apparent in the weekly schedules as opposed to the original every 3-week schedules [8]. However, from our comments in the preceding section, nab-paclitaxel has clear advantages in several scenarios and is often recommended for selected patient subsets with MBC. Venous access issues arise not uncommonly when the existence or the threat of postmastectomy lymphedema further impairs drug administration. Although solvent-base paclitaxel is not a vesicant, it may lead to local inflammation on infiltration, and its delivery in large volumes is an additional challenge for weekly administration in the presence of limited venous access. Such issues not infrequently lead to the need for placement of a central venous line potentially adding problems and expense.

In ovarian cancer, the adoption of the weekly paclitaxel schedule has been swift after the striking results of the 'dose-dense', weekly paclitaxel 'first-line' combination with carboplatin [9]. But this advantage also raises some practical issues: i) the need for better venous access; ii) economic and acute plus chronic clinical impact of more colony-stimulating factor use; and iii) additive problems from more frequent precautions against hypersensitivity. These problems that potentially impact quality of life beyond sensory neuropathy may be largely obviated through the use of nab-paclitaxel. In fact, Phase III studies including weekly taxanes for in all gynecologic cancers both as part of first line or regimens for recurrence would have great appeal among women (as noted earlier) and facilitate accrual if one arm included nab-paclitaxel. Taken globally, however, these issues may be applicable to taxane treatment of breast cancer and transcend treatment interests in other areas where taxanes are useful (e.g., prostate cancer, Kaposi's sarcoma, neuroendocrine and germ-cell tumors, among others).

Finally, solvent-based paclitaxel has been part of IP trials in ovarian cancer and is currently part of a standard regimen adopted from the Gynecologic Oncology Group (GOG172) when optimal debulking is achieved. This regimen, however, has been associated not only with prominent neuropathy (partly from the high dose of IP cisplatin) but also with catheter complications [10]. Nab-paclitaxel may prove to have an

advantage by the IP route and studies beyond Phase I are needed.

5. Conclusion

The desirable features of nab-paclitaxel described earlier must be leveraged further in seeking additional clinical indications (**Table 2**). Pragmatically, there are compelling reasons for exploring some advantages of nab-paclitaxel that are related to patient-related preferences. Driving future drug development, however, knowledge of tumor biology and actual intracellular delivery may ultimately strengthen its use in specific indications – such as has recently occurred in pancreatic cancer.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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