Editorial

Taxane Analogues: Distinguishing Royal Robes from the "Emperor's New Clothes"

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Whenever anticancer agents of therapeutic impact are identified, analogue development reflexively surges forward. In these situations, the quest to build a better mousetrap is typically massive and resource-intensive as exemplified by the search for superior DNA intercalating agents, which spanned several decades with little to show in terms of catching a larger number of mice (1). Such evaluations have rarely led to the discovery of the holy grail, agents that portend significantly greater antitumor activity and/or vastly different antitumor spectra compared with the prototypical agents in their classes. This is not to say such analogues have not become well entrenched in our clinical arsenal, but one wonders where we might have been had such resources had been applied to other pursuits. Furthermore, the strategies leading to the regulatory approval of analogues have generally relied on knowledge about the prototypical agent's positive performance in clinical situations in which the prototype had not undergone registration, largely due to patent expiration and the lack of commercial viability (2, 3). In fewer circumstances, registration strategies have entailed demonstrating noninferiority of the analogue compared with the reference compound (4). The more common and somewhat opportunistic approach to analogue development and registration is becoming increasingly more difficult as progressively greater numbers of agents are registered, filling a gradually diminishing number of unmet and/or "niche" indications. The diminishing returns inherent in analogue development must be considered in light of the limited resources available for clinical evaluations, as well as the recent elucidation of novel targets unique to the malignant phenotype from which therapeutics of greater incremental value than analogues of nonspecific cytotoxic agents will likely be developed.

Taxane analogues with greater therapeutic indices than the prototypical taxanes (*e.g.*, paclitaxel and docetaxel) are being sought due to the substantial utility of the taxanes in a wide variety of clinical settings, not to mention their enormous commercial success (5–7). Ideal candidates for clinical development are those analogues that truly possess greater antitumor activity and broader antitumor spectra than their prototypes. Still other potentially deserving taxane analogues may possess superior toxicological, pharmacological, and pharmaceutical properties that may portend less tangible, albeit real, clinical benefits in terms of reduced toxicity, greater ease of administration, and greater patient convenience. In such cases, concerns related to resource allocation are counterbalanced by the sizeable impact of the taxanes in treating patients with various early- and advanced-stage malignancies, which may amplify even seemingly negligible advantages. Nevertheless, lessons learned from developing analogues of other classes of anticancer agents have taught us that imposters often lurk in the midst, generally masquerading as true treasures, when in reality they are nothing more than developmental black holes consuming precious resources.

Due to a substantial increase in the availability of unique rationally developed, target-based therapeutics, which will likely require large screening trials to permit "go/no go" decision making, weeding out such imposters — preferably in preclinical development and before the onset of resource-intensive Phase III evaluations — is more important than ever. However, anticancer drug development, as we know it, is a rather chaotic process carried out in largely noninterdigitating tracks in the private sector. Although the chaotic and privatized elements of this process drive innovation in part, the fragmentation of the process may also stymie the development of universal benchmarks that are required to weed out imposters and prioritize resource allocation. Until universal benchmarks are developed, validated, and broadly adopted, the weeding out process will require the guts and fortitude displayed by the boy who boldly exclaimed that his emperor was indeed not wearing any clothes in the Hans Christian Andersen tale *The Emperor's New Clothes.*

So then, what might be some clear indications that a taxane analogue may actually be wearing clothes, and perhaps even stylish clothes at that? Although most taxane analogues are being developed under the guise of possessing greater cytotoxic potency and broader antitumor spectra than paclitaxel and/or docetaxel in select preclinical models, such results do not necessarily imply that the candidates will demonstrate greater therapeutic indexes *in vivo* unless they are inherently less toxic to normal tissues. Furthermore, the term greater potency is being used quite loosely these days, most commonly to describe a rightward shift in dose-response curves *in vitro*, a leftward shift in the growth of poorly established xenografts, or a leftward shift in the survival curve of animal treated with the drug soon after xenograft implantation. However, there are few situations, if any, when analogues claimed to be of greater potency based solely on dose-response curve shifting have subsequently demonstrated superior antitumor activity over prototypical agents in the clinic. This infers that the go/no go bar and the preclinical criteria from which decisions are made to move analogues forward are set too low. In general, the cytotoxic agents that

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have distinguished themselves are those capable of inducing major regressions or curative activity in well-established xenografts, particularly those that are clearly refractory to the reference agents, which might more closely reflect the clinical situations in which they will be evaluated. It is very unlikely that dose-response curve shifting alone will provide adequate coverage for an emperor.

A similar argument can be made in response to claims that worthy analogues are those that are less susceptible to relevant drug resistance mechanisms than the prototypical agents in their class. The comparative term less could signify practically anything, and the phrase "less susceptible" is somewhat nebulous because any particular analogue is either more or less susceptible to a resistance mechanism than any other compound. However, the real issue is how much less susceptible is significant? In other words, how much less susceptibility to any particular resistance mechanism will confer clinical relevance or connote tangible superiority in the clinic? Or does any degree of susceptibility to a resistance mechanism infer that the analogue will likely be no more effective than the emperor's new clothes? With regard to multidrug resistance conferred by Pgp[2] overexpression, which is responsible for extruding taxanes and other bulky natural products across both plasma membranes and the blood-brain barrier, and/or associated coexpressed resistance mechanisms, the degree of taxane resistance displayed by tumor cells is usually several orders of magnitude greater than that of sensitive parental tumor cells (8). Despite the development of analogues that are substantially weaker substrates for Pgp and/or associated drug reflux mechanisms, there are few circumstances, if any, in which such analogues have demonstrated broader antitumor spectra in the clinic relative to the prototypical agents in their class. This has even been the case with analogues that are very weak substrates for efflux proteins, possibly because achieving the requisite higher concentrations and exposure levels necessary to overcome even low-level drug resistance is not feasible in clinical practice. This reasoning indicates that projections that taxane analogues will possess broader antitumor spectra and/or retain a relevant degree of clinical activity in paclitaxel-resistant malignancies may relate only to analogues that are completely, and not just relatively, non-cross-resistant. It is unlikely that any taxane, by definition, will ever fulfill this requirement. Nevertheless, although raising the bar regarding preclinical criteria required to move analogues forward may be construed as somewhat nihilistic and result in missed opportunities, the adoption of more stringent criteria would raise the stakes and redirect precious resources toward therapeutics of potentially greater clinical impact.

In this issue of *Clinical Cancer Research*, Plummer *et al.* (9) describe the results of a well-conducted Phase I study of BMS-184476, a 7-methylthiomethyl ether of paclitaxel, which is being developed in part because, according to the authors, "it has shown equal or superior efficacy to paclitaxel" in preclinical studies (9). From a cytotoxic potency standpoint, however, the cumulative results of preclinical studies indicate that BMS-184476 possesses greater potency than paclitaxel in tubulin polymerization assays and against both paclitaxel-sensitive and -resistant tumors (10–13). Upon closer examination of these claims, the conclusion that BMS-184476 has greater potency than prototypical taxanes is largely based on the phenomenon of dose-response curve shifting instead of an innate capacity to consistently induce regression of human tumor xenografts that are resistant to equitoxic doses of paclitaxel (10, 11). Despite being a weaker Pgp substrate, BMS-184476 appears to be no better clothed than the emperor because the agent is still unavoidably an avid Pgp substrate. Dose-response curve shifting is also evident in studies demonstrating that HCT-116 human colon cancer cells with multidrug resistance conferred by Pgp overexpression are at least 62-fold more resistant to paclitaxel than sensitive wild-type cells, whereas the resistance factor for BMS-184476, albeit substantially less (15-fold), is still quite profound (10, 11). Similarly, an examination of the relative activities of BMS-184476 and paclitaxel against tumors with acquired resistance mediated by tubulin mutations reveals a similar curve shifting paradigm. The resistance factors of BMS-184476 and paclitaxel against human ovarian cancer A2780 with taxane resistance conferred by a tubulin mutation were 9-fold and 32-fold, respectively (10, 11). Although synthesizing taxane analogues with these properties may certainly represent a move in the right direction, it does not necessarily mean that the emperor is any better clothed or any less naked because resistance factors of this magnitude, albeit lower than the prototypical taxanes, are not likely to be overcome in clinical practice. Furthermore, although the prominent clinical activity reported by Plummer *et al.* (9) in taxane-sensitive malignancies is undoubtedly reassuring about the inherent validity of BMS-184476 as a relevant antitumor agent, the very nature of this activity should not imply that BMS-184476 is any more effective than available taxanes. The emperor's clothes would have been more admired had BMS-184476 demonstrated relevant activity in malignancies outside the traditional realm of the taxanes or in taxane-refractory cancers.

Many taxane analogues, in which paclitaxel is linked to complex carrier moieties and delivery systems, including polyamino acids (*e.g.*, L-glutamic acid), omega-3-fatty acids (*e.g.*, docosahexaenoic acid), liposomes, polymers (*e.g.*, dextrans), and solvents, are undergoing clinical development. The original rationale for developing many of these analogues arose from the unacceptably high incidence of HSRs associated with paclitaxel formulated in relatively large quantities of polyoxyethylated castor oil, which has been reduced substantially by using premedication and slower infusion rates (14). Nevertheless, several of these analogues have been redressed as taxanes with greater potency than paclitaxel by virtue of increased tumor penetration and/or more protracted plasma concentrations, potentially resulting in more prolonged tumor exposure. Other analogues have been repackaged as relatively inert prodrugs that permit the administration of much higher paclitaxel doses. However, the significance of many of these claims is not supported by preclinical data, and these claims may be considered somewhat immaterial from a pharmacological perspective. For example, although the duration of taxane exposure is perhaps the most important pharmacological determinant of taxane effect, predic-

[2] The abbreviations used are: Pgp, p-glycoprotein; C_{ss}, concentration at steady state, ECOG, Eastern Cooperative Oncology Group; HSR, hypersensitivity reaction.

tions about the potential success of various analogues should not be based solely on the duration of exposure achieved by biologically active drug concentrations in human plasma (15). Such extrapolations from plasma to tumor have many potential pitfalls, particularly in situations in which the drug concentrations achieved in plasma and peripheral tissues are widely disparate, which is the case for the taxanes. Tissue/plasma taxane concentration ratios of several orders of magnitude are achieved in tumors and virtually all peripheral tissues, except brain and testes that possess active physiological barriers to structurally bulky natural products conferred by the Pgp multidrug transporter and other resistance mechanisms (16–19). Therefore, the use of plasma as a window to gauge whether pharmacological conditions that are optimal *in vitro* can be achieved *in vivo* may substantially underestimate drug concentrations and taxane exposure achieved in peripheral tissues and tumors. More importantly, given the wide tissue distribution, avid tissue binding, and protracted tissue sequestration of the taxanes, even when administered as brief infusions, it is difficult to fathom that various carrier moieties will substantially increase intratumoral drug concentrations and/or prolong intratumoral exposure by increments that are pharmacologically and clinically relevant.

Perhaps the most innovative means to achieve protracted taxane exposure in the peripheral compartment is by administering taxanes on more frequent dosing schedules (20–22). Although the development of the weekly administration schedule was initially based on clinical empiricism, its pharmacological soundness has been realized retrospectively and supported by the results of preclinical pharmacological and mass balance studies in both animals and humans, which demonstrate extraordinarily high taxane concentrations in tumors and peripheral tissues followed by nearly complete excretion of drug within 1 week following treatment (17, 20–22). Indeed, the weekly administration schedule has resulted in higher therapeutic indices in many clinical situations by virtue of reduced toxicity, but this emperor also remains somewhat poorly clothed with regard to the lack of robust data substantiating claims of relevant activity in malignancies that are clearly taxane refractory (15, 16).

Claims that taxane analogues are superior to the prototypical taxanes based on the ability to administer higher doses of paclitaxel are even more easily refuted. Many questions regarding optimal dosing in the clinic were addressed even before paclitaxel received regulatory approval. The cumulative results of these efforts indicate that no single administration dose or schedule clearly portends superior efficacy. Instead, there appear to be threshold doses or concentrations, the precise magnitude of which depends on the specific tumor type, below which only negligible antitumor activity is observed. In addition, there appear to be plateau doses or concentrations, above which no further antitumor activity of clinical importance is observed (19). The paclitaxel concentrations at which most relevant effects plateau are well within the range of plasma concentrations and are certainly less than intracellular concentrations achieved in the clinic at commonly used doses that require neither cytokine nor hematopoietic stem cell support ($\leq$1–10 μM; Ref. 19). The most plausible explanation for this behavior is the saturation of paclitaxel binding sites on β-tubulin at dose schedules associated with these plateau concentrations ($\geq$175 mg/m^2 over 3 h; Ref. 19).

Furthermore, the collective results of now seemingly ancient randomized clinical trials in various malignancies indicate that plateauing of antitumor efficacy ensues at paclitaxel doses that can be readily administered without cytokine or hematopoietic stem cell support (14, 23–28). Although randomized clinical trials in women with advanced ovarian cancer (National Cancer Institute of Canada CTG OV.9 and Gynecologic Oncology Group 134) and metastatic breast cancer (BMS 048 and Cancer and Leukemia Group B 9342) have demonstrated that higher doses may result in some increased benefit, the magnitude of this effect is negligible (14, 23–25). In Cancer and Leukemia Group B 9342, for example, women with metastatic breast cancer were randomized to treatment with paclitaxel doses of either 175, 210, or 250 mg/m^2 on a 3-h schedule without initial hematopoietic growth factor support (25). As expected, both severe sensory neurotoxicity and myelosuppression were more common in the high- and moderate-dose arms than in the lower-dose arm. Although there was a borderline correlation between paclitaxel dose and time to treatment failure (3.8, 4.1, and 4.8 months), no statistically significant relationships between paclitaxel dose and either disease response (21%, 28%, and 22%) or survival (3.8, 4.1, and 4.8 months) were evident.

Diminishing returns have also been noted in randomized trials involving widely disparate doses of paclitaxel in patients with advanced non-small cell lung cancer (ECOG 5592) and head and neck cancer (ECOG 1193; Refs. 26–28). In ECOG 5592, chemotherapy-naive stage IIIb−IV non-small cell lung cancer patients were randomized to treatment with cisplatin (75 mg/m^2, i.v.) on day 1 and etoposide (100 mg/m^2, i.v.) on days 1–3 or cisplatin (75 mg/m^2, i.v.) combined with either a low dose of paclitaxel (135 mg/m^2; 24-h schedule) or a higher dose of paclitaxel (250 mg/m^2; 24-h schedule) with granulocyte colony-stimulating factor (26). Although response rates and survival were superior in the paclitaxel-containing arms (median, 9.9 *versus* 7.6 months; 1-year survival, 39.9% *versus* 31.8%, $P = 0.048$), there were no differences in response or survival between the two paclitaxel arms. In addition, although there was a statistically significant ($P < 0.001$) difference in paclitaxel C_{ss} between the low- and high-dose paclitaxel arms, no relationships between paclitaxel C_{ss} and either response, time to disease progression, or survival were apparent (27). The results of both ECOG 5592 and ECOG 1193, which demonstrated identical antitumor and pharmacodynamic results in patients with advanced head and neck cancers, indicate that neither response nor time to disease progression is influenced by either paclitaxel dose or C_{ss} in patients treated with paclitaxel doses in a widely disparate range pushing on the inner and outer edges of the dosing envelope (28). With regard to taxane analogues, whose rationale for development rests solely on claims related to the delivery of higher taxane doses and achieving higher plasma concentrations, the collective results of randomized trials in breast, ovarian, lung, and head and neck cancers should quell any doubts about the state of undress of this emperor.

Taxane analogues that offer broader antitumor spectra and increased efficacy are analogous to the emperor putting on the Ritz in top coat and cane, whereas some taxane analogues have occasionally been sighted in attire that might be construed as undignified. Sometimes, emperors may dress in rather informal

attire, which may not seem suitable for royalty at first glance. However, a closer examination may occasionally reveal a bold fashion statement, akin to taxane analogues that are orally bioavailable, are associated with less toxicity or more predictable pharmacokinetics, or show a reduced propensity for drug-drug interactions. For still other taxane analogues, the principal issue relates to whether or not these garments provide even the most basic of sartorial requirements. These analogues might be those that purport increased ease of administration, increased patient convenience, and administration on unencumbered schedules (*e.g.*, rapid i.v. infusion, no premedication). Nevertheless, what constitutes fashion in terms of taxane analogues may truly be in the eyes of the beholder. Although such attributes may seem minimal in the grand scheme of things, the enormity of the clinical utility of the taxanes may greatly amplify the overall clinical impact of analogues that possess even marginal advantages. Therefore, a reasonable magnitude of clinical benefit may be conferred by taxanes that are not formulated in polyoxyethylated castor oil, including those formulated in liposomes, emulsions, or microspheres, or by paclitaxel molecules linked to polymers, fatty acids, amino acids, or solvents. Indeed, many of the aforementioned approaches have preliminarily been successful from a feasibility standpoint, but the jury is still out. The incidence of severe HSRs related to paclitaxel formulated in polyoxyethylated castor oil in patients receiving premedication is very low (<5%), and a vast experience with new taxane analogues is required to gauge their relative advantage from a HSR perspective (5, 14). Furthermore, the etiology of HSRs associated with paclitaxel is not completely understood. HSRs may be caused by either paclitaxel itself or its polyoxyethylated castor oil vehicle, but the latter is most likely responsible because it induces similar manifestations in dogs, and other drugs formulated in it induce nearly identical reactions (5). Although it has been reasoned that the reduced quantity of polyoxethylated castor oil required to formulate BMS-184476 might be advantageous from pharmaceutical and toxicological standpoints, and HSRs were not observed in the study detailed by Plummer *et al.* (9), HSRs have been noted in patients receiving BMS-184476 as a 1-h i.v. infusion without premedication (29). Further experience in a larger number of patients is required to gauge the relative advantages of BMS-184476 in terms of its propensity to cause HSRs. Although the low incidence of HSRs to date supports further development of the agent without obligatory premedication, this strategy may require modification as clinical development proceeds. In other words, this emperor is looking pretty darn naked.

For those "well-dressed" taxane analogues possessing either more prominent antitumor activity than approved taxanes in potentially sensitive neoplasms or compelling activity in malignancies that are clearly taxane refractory, the path to regulatory approval is reasonably clear. Unexceptional analogues, like naked emperors, will likely be recognized and weeded out early by well-designed and rigorous clinical evaluations and forthright investigators. However, the path to registration for potentially worthy taxane analogues dressed in somewhat skimpy, albeit functional, attire is much more tortuous. For those analogues that may confer clinical benefit by virtue of their unique toxicological, pharmacological, and/or pharmaceutical characteristics, the simplest registration strategies, which in reality entail proof of noninferiority, are daunting from both logistical and financial perspectives. Unless both regulators and oncologists work together to streamline evaluation and registration processes for this category of worthy agents, perhaps by formulating creative bridging strategies, many taxane analogues with meritorious pharmaceutical, pharmacological, and toxicological properties will likely be considered naked before their attributes are recognized.

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