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Classical taxane versus the new generation, nab-paclitaxel chemotherapy in the treatment of breast cancer

Abstract

Breast cancer (BC) remains the most invasive diagnosed cancers among female, affecting 25% of total number of cancers worldwide. Systematic chemotherapies still remain one of the effective treatments for BC. One of the common and powerful chemotherapies that have been used in the past decade is taxane. Taxane are a class of anticancer compounds that are known to cause cell cycle arrest and apoptosis induction (cell death). They are used for the treatment of malignant tumors specifically BC along with other chemotherapies such as anthracycline. However, the neurotoxic effects that are associated with the use of taxane are still challenging. Recently, nanoparticle albumin bound taxane (nab-paclitaxel) was developed, resulting in lowering of the side effects that are associated with the use of taxane and enhancing its delivery to the targeted cancer cells. Nab-paclitaxel has been subjected to several clinical trials to evaluate its efficacy in the treatment of various types of cancers including BC. The results indicated that nab-paclitaxel showed an improved efficacy and promising outcomes in the treatment of various forms of BC. This review focuses on the comparison of classical taxane to the new generation, nab-paclitaxel chemotherapy, with emphasis on their comparative efficacy in metastatic BC (MBC) and triple negative metastatic BC (TNMBC) treatment, concluding that nab-paclitaxel has improved efficacy, safety data and with a more convenient administration confirming an optimal treatment option for patients in both cases. Future work is needed to optimize dosing schedules and combination regimens of nab-paclitaxel, which could broaden the clinical utility of this agent.

Keywords: taxane, nab-paclitaxel, breast cancer, metastatic breast cancer, triple negative metastatic breast cancer

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Abbreviations: BC, breast cancer; MBC, metastatic breast cancer; TNMBC, triple negative metastatic breast cancer

Introduction

BC is considered the most frequently diagnosed invasive malignancy-affecting females in both the developed and developingcountries.[1–3] The prevalence of BC worldwide accounted for about 25% of total cancer cases diagnosed (1.68million), and is responsible for 15% of cancer deaths (520,000) throughout the globe.[4,5] In the United States, recent epidemiological study estimated that 23,000 new cases of invasive BC are diagnosed annually resulting in almost 40,000 deaths.[6] Unfortunately, it is believed that metastatic BC actual prevalence is likely to be higher than the estimates, since many women live with the tumor for many years before being diagnosed.[7] Localized BC tumors have high potential of being cured with various established systemic therapies.[8] In the past 30years, BC systemic therapies have evolved from using anthracycline as chemotherapeutic agents during the 1980s to the use of taxane chemotherapy in the 1990s, and more recently the biological therapies such as perception in 2000s.[9,10] Taxane were used in combination with anthracycline and other alkylating agents in order to improve the overall survival (OS) rate, and disease free survival (DFS) among metastatic BC (MBC) patients.[10,11] Therefore, taxane chemotherapy still remains an effective treatment for BC and is considered as the first line of therapy used for the treatment of MBC with success rate ranging from 25% to 69%.[12,13]

There are two main types of taxane: paclitaxel and docetaxel- second generation.[14] The US Food and Drug Administration (FDA) was the first to approve paclitaxel for treating ovarian cancer in 1992 and subsequently for the treatment of MBC in 1994.[15] In addition, taxane chemotherapy has been included in the management of early stage BC and issued routinely in combination with trastuzumab (Herceptin®) and anthracycline.[11,13,14] However, paclitaxel resulted in the induction of a high cytotoxicity in BC patients and especially among the elderly ones.[13] The major side effects resulting from its use in BC patients include myelosuppression and neuropathy.[13] Paclitaxel induce neuropathy primarily by injuring the dorsal root ganglia (DRG) neurons leading to a sequence of Neuropathological alterations in the DRG, dorsal horn of the spinal cord and peripheral nerve.[16] When comparing the levels of peripheral neuropathy toxicities between paclitaxel and docetaxel in rats, paclitaxel showed more severe side effects in nerve fibers.[17] However, the incidence of neutropenia and peripheral neuropathy was found to be dose dependent, and the association of neuropathy with paclitaxel was mainly sensory.[18] Toxic effects were evident between 24-72h following the administration of single doses above 250mg/m^2, or following the intake of several doses between 135-200mg/m^2.[18] The clinical manifestation of neuropathy included burning or tingling sensation in the glove and stocking areas, and can progress to motor weakness when drug administration is continued.[19] According to previous clinical studies and research, there are a number of clinical scales available for the assessment of taxane induced peripheral neuropathy.[20] These measures are combination

of objective and subjective metrics that are important to grade the severity of peripheral neuropathy.[21] The most commonly used scale rating system assessed by the World Health organization (WHO), US National Cancer Institute Common Toxicity Criteria (NCI-CTC) and Eastern Cooperative Oncology Group (ECOG) scales are shown in Table 1.[20–24]

Table 1 The NCI CTC grading system for peripheral neuropathy

Grade No	Symptoms
Grade I	Asymptomatic-clinical or diagnostic observations only
Grade II	Moderate symptoms- limiting activates of daily basis
Grade III	Sever symptoms limiting self-care and activates of daily basis
Grade IV	Life-treating consequences- require urgent intervention indicated
Grade V	Death

Recently, a new generation of taxane based drugs have been developed and are known as nanoparticle albumin bound taxane (nab-paclitaxel).[25,26] This modification was reported to exhibit less side effects than that normally produced from the use of taxane, and shows enhanced drug delivery into the targeted cancerous cells.[25,27,28] Nab-paclitaxel has been subjected to several phases of clinical trials. The results of those trials showed an improved efficacy and promising outcomes in patients with BC.[26] This review focuses on the comparison of classical taxane to the new generation, nab-paclitaxel chemotherapy, with emphasis on their comparative efficacy in metastatic breast cancer (MBC) and triple negative metastatic breast cancer (TNMBC) treatment.

Classical taxane vs nanoparticle albumin-bound taxane (Nab-paclitaxel)

Chemical characteristics

Taxane are a class of microtubule inhibitors that are natural products extracted from the bark of the Pacific Yew *Taxus brevifolia* tree.[29] Two types of solvent based taxane have been developed, namely paclitaxel (Taxol), doxetaxel (Texture). Because of the hydrophobic nature of paclitaxel, it requires being administered in a solution containing alcohol and ChromophoreÒ EL 1:1 (polyoxyethylated castor oil) to enhance its delivery.[30] Docetaxel on the other hand, is a second generation of taxane, which is taken intravenously.[31] The established new generation of taxane is the nanoparticle albumin-bound paclitaxel (Abraxane; nab®-Paclitaxel- Celgene Corporation, Summit, New Jersey, USA).[32,33] In nanotechnology the size of particle ranges usually between 1 and 1000nanometers, hence are named nanoparticles.[34] Thus, the high surface to volume ratio of these nanoparticles enhances the interaction with other molecules and allows flexibility in augmenting drug transport across challenging biological barriers including blood- brain and blood-tumor barriers.[34] Furthermore, because of the hydrophobic nature of taxane such as paclitaxel, its solubility in aqueous media can be enhanced by enveloping it in albumin nanoparticles creating nab-paclitaxel,[34] which is a novel solvent free drug in colloidal suspension of 130nanometer particles with human serum albumin (3%-4%). This makes it easy to infuse in higher doses than the standard dose of paclitaxel, and with higher response and lower toxicities, as well as less infusion time (30minutes) in patients with advanced MBC and non small cell lung cancer (NSCLC).[30–35]

Molecular mechanisms

Both paclitaxel and doxetaxel share the same mechanism of action with different pharmacokinetics and side effects.[36] However, doxetaxel is poorly tolerated clinically and less effective than paclitaxel and is, therefore, not frequently used.[31,37] The exact cellular molecular mechanism of action of paclitaxel relies in its ability to bind to b-tub line (the taxane target site) in the mitotic spindle.[38] Thus, it stabilizes microtubules by inhibiting their depolymerization and interfering with their kinetochore attachment.[39] The net result is to change the tension through the kinetochore in mitosis, thus disrupting mitosis and casing checkpoint arrest then inducing programmed cell death "apoptosis" through the mitochondrial pathway (Figure 1).[39–41] However, drug dose and duration of usage play a critical role in the induction of cell death.[42]

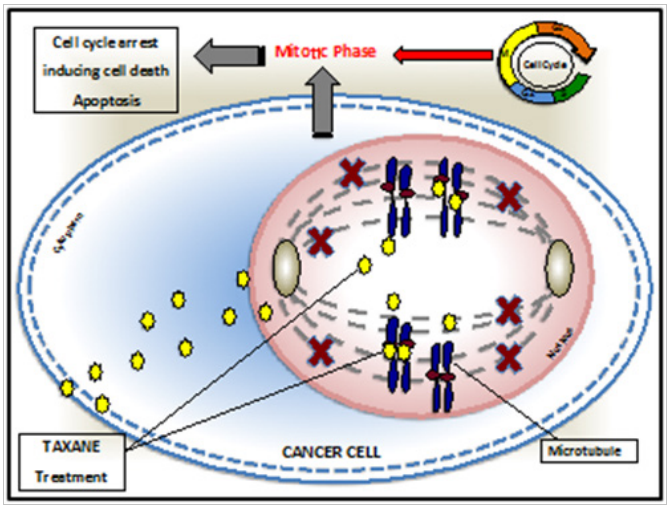

Figure 1 Cellular mechanism of taxane treatment on cancer cell.

On the other hand, nab-paclitaxel molecular mechanism is dependent on increased transport of paclitaxel to the tumor by albumin specifically binding to gp60 and facilitating caveolin-mediated transcytosis to enhance delivery across the blood vessels endothelial cells, thus transporting paclitaxel into extra vascular space to the tumor cells, hence inducing apoptosis, and resulting in an advantageous pharmacokinetic (PK) profile (Figure 2).[25,43] Indeed, several preclinical studies reported an approximately 10-fold endothelial binding of nab-paclitaxel, and 4-fold higher levels of transocytosis through endothelial cells in contrast to the solvent based paclitaxel allowing for a dose dependent antitumor activity.[43,44]

Dosage, bioavailability and therapeutic index in MBC

According to clinical and oncology standards, taxane are usually used in combination with anthracycline regimen, or after anthracycline treatment in order to improve efficacy and reduce the relapse risk.[47] A multicenter randomized phase III clinical trial was conducted on MBC patients where paclitaxel (175mg/m^2), or (135mg/m^2) was administrated for a period of 3weeks (q3w).[48–50] The results of this study indicated that higher doses of paclitaxel produced a superior overall response rate (ORR) as compared to using lower doses, and longer overall survival (OS) with a median time of tumor progression (TTP).[48–50] Two similar previous studies were conducted on BC patients where four cycles of doxorubicin and Cyclophosphamide were initially administrated every 3weeks, followed by the administration of four cycles of paclitaxel every 3weeks.[51,52] The obtained results

revealed an endorsement for the use of paclitaxel in treatment with positive axillary lymph node, and thus established new standards for BC care.[51,52] Furthermore, in another study, the efficacy of the administration of deoctaxel with doxorubicin and Cyclophosphamide in the management of positive node BC patients was investigated, and the results showed a higher efficacy of the above combination compared to fluorouracil, doxorubicin and Cyclophosphamide.[32]

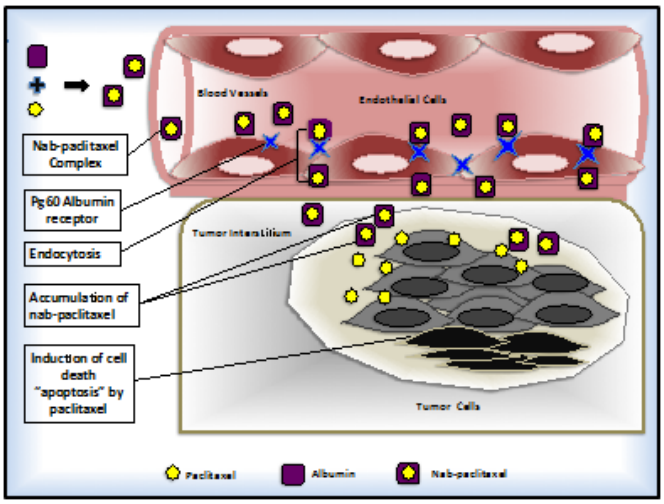

Figure 2 Cellular mechanism of nab-paclitaxel on cancer cell.

Similarly, a number of preclinical studies were conducted on nab-paclitaxel, and reported that it accomplished higher intracellular concentration compared to standard paclitaxel with improved bioavailability, efficacy and therapeutic index on different animal's models.[43] Subsequently, nab-paclitaxel was licensed in Europe and approved by the FDA in 2005 for MBC patients who failed all first line treatments including anthracycline-containing therapy.[33] More recently, a phase III clinical trial on MBC patients was conducted where 260mg/m^2 nap-paclitaxel was applied every week compared to 175mg/m^2 of paclitaxel every 3week, and was found to show significant improvement in outcomes including overall response rate (ORR), time of tumor progression (TTP) and progression free survival (PFS).[11,53] According to this data, nab-paclitaxel dose of 260mg/m^2 every 3week has obtained an approval for use in MBC in more than 40countries.[54,55] Furthermore, nab-paclitaxel has been shown to reduce drug exposure to healthy tissue.[43] In addition, the intravenous infusion was reported to be controlled and safer compared with paclitaxel due to the use of standard plastic intravenous bags which are possible to reconstitute in smaller volume of normal saline.[56]

Clinical challenges in MBC- comparing taxane to nab-paclitaxel:

The major challenge that faces clinicians when treating BC patients is the severe toxic side effects that are produced by taxane, and especially among the elderly patients.[13] The major side effects include: myelosuppression, neutropenia and neuropathy.[13] A previous clinical trial investigated the efficacy of weekly administered paclitaxel compared to administering paclitaxel every 3weeks in 500BC patients.[31] Results showed that patients on paclitaxel weekly administration were susceptible to grad II, III and IV neuropathy (27%) more than patients with paclitaxel every 3weeks administration (20%).[31] However, regarding the efficacy they found that using adjuvant chemotherapy with doxorubicin and Cyclophosphamide, followed by weekly paclitaxel has improved disease-free and OS in females with BC.[31] Therefore, the number of paclitaxel infusion times and dose is strongly related to the severity and incidence of peripheral neuropathy.[18,19] Therefore, premedication requirement for patients receiving paclitaxel or doxetaxel is necessary, in order to reduce the neurotoxic side effects caused by these agents.[18] However, there is variation in the guideline recommendations for paclitaxel and doxetaxel.[57] Thus, patients receiving paclitaxel require intravenous antagonists of histamine H1 and H2 plus oral corticosteroids 24h prior to drug infusion, in contrast to patients receiving doxetaxel who are recommended to receive premedication regimen consisting of 3days of oral dexamethasone (8mg twice daily).[57] Moreover, corticosteroid medication is important and needed to prevent hypersensitivity reaction, and to delay the onset and reduce the severity of fluid retention, skin and nail changes.[57]

In contrast, the lack of solvent in the nab-paclitaxel formulation has lead to reduction of the acute toxicity reactions, and has assisted in escaping the use of corticosteroid and antihistamine premedication.[58] Furthermore, this new drug formula was shown to increase paclitaxel delivery and activity to tumors 4-5 folds because it combines with albumin receptors through the endothelial cells.[59,60] A study demonstrated the use of nab-paclitaxel in combination with lapatinib treatment for MBC patients (n=55).[26] In this study, the first ten patients were treated initially with 125mg/m^2 nab-paclitaxel every 3weeks for four cycles in combination with laptinib 1.25mg orally once a day for 4weeks.[26] However, the first five patients developed grade III toxicity (neutropenia), therefore the doses for both drugs were decreased.[26] Thus all following patients received (100mg/m^2) nab-paclitaxel every 3week for three cycles, and 1mg laptinib orally once a day for 4weeks. The RR was 53% and the PFS with TTP were 39.7%weeks.[26] Untch et al.[61] group conducted a phase III randomized trial, comparing the use of 150mg/m^2 nab-paclitaxel intravenous treatment for four 3week cycles to standard paclitaxel of 80mg/m^2 for four 3week cycles on two groups of MBC (n=1230).[61] After taxane treatment both groups were given intravenous epirubcin 90mg/m^2 plus Cyclophosphamide 600mg/m^2 for four 3week cycles. In addition patients with HER2 (human epidermal growth factor receptor 2) positive received subsequently herceptin (trastuzumab) therapy. The data from this trial revealed that complete pathological response was achieved in the nab-paclitaxel group (38%) compared to the standard paclitaxel group (29%). The incidence of grade III toxic effects; including anemia; was about 2% in nab-paclitaxel, whereas 1% anemia incidence was noted in paclitaxel group. In addition, peripheral neuropathy grade III-IV was noted in 10% of nab-paclitaxel group and 8% in paclitaxel group.[61]

Collectively, above data demonstrated that nab-paclitaxel shows better antitumor activity and efficacy with shorter infusion duration and higher concentration compared to paclitaxel that require pretreatment of patient and can cause drug resistance.[62] Thus, nab-paclitaxel drug can safely be offered to many women with MBC, with reasonable expectations of clinical benefit and without concern of significant toxicity.

Taxane and nab-paclitaxel use in triple negative metastatic breast cancer (TNMBC)

The TNMBC has become one of the aggressive clinical cancers with poor prognosis among BC patients, being found in 15% to 20% of all BCs.[63–67] TNMBC is generally composed of heterogeneous group of cancers with high rate of proliferation and poorly differentiated cells.[68] Patients with TNBC present early disease recurrence, and reduced survival rate compared with other BCs.[68] This type of BC is

characterized by the lack of both estrogen and progesterone receptors (ER and PR), and lack of human epidermal growth factor 2 (Her2),[66] which limits the treatment options for females affected with it.[66] The standard treatment for TNMBC is chemotherapy, with taxane regimen being one of the effective therapies used with improved outcomes.[69] In general, the use of single agent chemotherapy is preferred in most cases of MBC.[48] However, the National Comprehensive Cancer Network guidelines suggested the use of combination treatments in TNMBC.[70,71] Platinum agents in combination with other chemotherapy has established an antitumor activity in TNMBC.[72,73] A small randomized phase II study for first line therapy was carried out on 53 female with TNMBC. Patients were given different combinations of chemotherapy: doxetaxel with capecitabine compared with doxetaxel with cisplatin. Results of the study indicated that the use of platinum agent plus taxane regimen produced grater efficacy than capecitabine regimen, with improved ORR, OS and progression-free survival (PFS).[74] However, there is a limitation in the availability of optimal care of regimen for TNMBC patients.[68] Hence, the lack of established molecular targets therapy and poor prognosis are still major obstacles for TNMBC patients and oncologists.[75]

Nevertheless, treating TNMBC patients with nab-paclitaxel was convenient, and hence proposed because of the therapeutic index of this drug that was investigated in a phase III trial.[53] Moreover addition of nab-paclitaxel to platinum based regimen in patients with TNMBC showed to be effective.[75] The phase II trial used nab-paclitaxel (100mg/m^2) every 3-4weeks in combination with carboplatin plus bevacizumab observed an effective antitumor activity in TNMBC patients producing 85% ORR.[75] Moreover, further retrospective analysis of data in phase II trials recommended the use of nab-paclitaxel in combination of therapy for patients with TNMBC who were treated with taxane previously.[62,74,76] In addition, a case study reported that a 48year female with TNMBC who was treated with first line adjuvant chemotherapy, experienced an excellent response to taxane treatment.[58] However, due to her apparent hypersensitivity reactions towards paclitaxel her treatment was terminated.[58] The patient was then recommended to start with nab-paclitaxel as a second line therapy, and showed a high response with limited toxicities.[58] Therefore, nab-paclitaxel may be particularly beneficial for patients with TNMBC. Continuing research to evaluate the different dosing schedules and combination regimens of nab-paclitaxel could broaden the clinical utility of this agent in the future.[77]

Conclusion

In this era of improved outcomes with molecularly targeted BC therapy, through better understanding of tumor biology, it has become possible to devise methods to improve drug delivery to a complex tumor microenvironment as in the case of BC. The development of nab-paclitaxel and its success in the treatment of MBC is a prime example of the interface between concepts of nanotechnology and the ingenious principles of drug development to target BC. In addition, nab-paclitaxel showed to be an effective treatment for TNMBC patients, and is recommended as second line chemotherapy. Though, several questions on this novel formulation are still unresolved such as the optimal dose and treatment schedule, which risk population subgroups in the adjuvant and neoadjuvant settings of BC, will benefit most, and whether it is possible to reverse prior resistance to taxane with nab-paclitaxel-paclitaxel. Therefore, it will be crucial and necessary to investigate these issues in the future findings. In conclusion, present data indicate that nab-paclitaxel has improved efficacy, safety data and with more convenient administration confirming an optimal treatment option for patients with MBC.

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Conflict of interest

The author declares no conflict of interest.

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