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Mechanisms of taxane resistance in breast cancer: a systematic review

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Abstract

Background: Taxanes are established in the treatment of metastatic breast cancer (MBC) and early breast cancer (EBC) as potent chemotherapy agents. However, their therapeutic usefulness is limited by *de-novo* refractoriness or acquired resistance, which are common drawbacks to most anti-cancer cytotoxics. Considering that the taxanes will remain principle chemotherapeutic agents for the treatment of breast cancer, we reviewed known mechanisms of resistance to these drugs with an outlook of optimizing their clinical use.

Methods: We searched the PubMed and MEDLINE databases for articles (from inception through to 30th June 2011; last search 17th July 2011) and journals known to publish information relevant to taxane chemotherapy. We imposed no language restrictions. Search terms included: *cancer, breast cancer, response, resistance, taxane, paclitaxel, docetaxel, taxol*. Due to the possibility of alternative mechanisms of resistance all combination chemotherapy treated data sets were removed from our overview.

Results: Over-expression of the *MDR1* gene product Pgp was extensively studied *in vitro* in association with taxane resistance, but data are conflicting. Similarly, the target components microtubules, which are thought to mediate refractoriness through alterations of the expression pattern of tubulins or microtubule associated proteins and the expression of alternative tubulin isoforms, failed to confirm such associations. Little consensus has been generated for reported associations between taxane-sensitivity and mutated *P53*, or taxane-resistance and overexpression of Bcl-2, Bcl-xL or NFkB. On the contrary sufficient *in vitro* data support an association of spindle assembly checkpoint (SAC) defects with resistance. Clinical data have been limited and inconsistent, which relate to the variety of methods used, lack of standardization of cut-offs for quantitation, differences in clinical endpoints measured and in methods of tissue collection preparation and storage, and study/ patient heterogeneity. The most prominent finding is that pharmaceutical down-regulation of HER2 appears to reverse taxane resistance.

Conclusions: Currently no valid practical biomarkers exist that can predict resistance to the taxanes in breast cancer supporting the principle of individualized cancer therapy. The incorporation of several biomarker analyses into prospectively designed studies in this setting are needed. [MOJ 2011, 1:14-29](#)

Key words: Stathmin, P-glycoprotein, resistance, taxane, p53, HER2, BRCA1/2, MRP-1.

Introduction

Breast cancer remains the most common type of cancer in women, with more than one million reported new cases diagnosed per year [1]. Of those, 20-30% present with metastatic or locally advanced disease, and other 30% will develop recurrent or metastatic disease [2]. Treatment options include surgery, radiotherapy and systemic treatment. Among the most commonly used cytotoxic drugs for breast cancer are the taxanes; paclitaxel and docetaxel [3].

Taxanes were first introduced into clinical use during the 1990's. Both, paclitaxel and docetaxel compared favorably in terms of efficacy in metastatic breast cancer (MBC) and early stage breast cancer (EBC) when tested against older drugs [4-7]. Today, both taxanes have been established as a viable option in the treatment of MBC and have been incorporated into the management of EBC in association

with anthracyclins and trastuzumab where and when appropriate [3, 8-10].

Although improvements have been made, for virtually all therapeutic strategies, many patients have and eventually almost all patients will develop tumors that are non-responsive to our current treatment strategies whether they are of the so called 'targeted' or 'non-targeted' class [11]. Efforts to move more and more patients into adjuvant based therapeutic strategies has highlighted the need to either identify those that are less likely to be resistant and/or to develop strategies to circumvent such resistance mechanisms [12, 13].

In a more simplified view resistance can be *de-novo* (inherent insensitivity) or acquired (due to the emergence of resistant populations). The development of tumor resistance (acquired) is potentially a result of several alterations in the tumor including but not limited to protein isoform switching/ dysregulation/ mutations; alterations in drug efflux mechanisms, apoptotic modulation, and a number of other candidate mechanisms have also been suggested [14, 15].

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One of the most often studied mechanisms with regard to taxane resistance has centered on that of *de-novo* and acquired resistance with respect to drug efflux proteins. These are an ever-enlarging family of proteins that are known to limit drug efficacy by removal at their site of action. These proteins clear excessive extra- and/or intra-cellular concentrations of a variety of substrates and toxins. It is now well known that various cancer cell types express proteins of the adenosine triphosphate (ATP)-binding cassette (ABC) transporter family. The most well known member of the family is the P-glycoprotein (P-gp) membrane protein encoded by the *MDR1* gene, and other similarly functional transporters that have been correlated with reduced efficacy of a variety of different chemotherapeutics, including the taxanes [16, 17].

Circumvention or blocking resistance mediated by these mechanisms has been both a therapeutic target, but also a clinical challenge [18]. The synthesis of low susceptibility to resistance mechanism analogues of several chemotherapeutic agents has been a continual process [17]. Furthermore, several small molecule inhibitors of Pgp and MRP1 have entered clinical development, unfortunately with limited success [19-21]. Other strategies have included the development of alternative forms of taxanes that are poor substrates to Pgp, the most clinically advanced of which are the epothilones [22, 23].

Whatever agents or strategies we develop will ultimately depend upon our understanding of the mechanism of action of each of the therapeutic agents we develop and administer to our patients. Classification of all patients tumors based upon several measures will hopefully achieve this goal [24-30]. Considering that the taxanes will remain a principle chemotherapeutic agent for the treatment of breast cancer, a rational understanding not only of predictors of response but also potential predictors of resistance (*de-novo* or acquired) may assist in this personalized approach. This review aims to document our current best evidence regarding mechanisms of taxane resistance and propose potential avenues for circumvention.

Research Methodology

The information for this review was obtained by searching the PubMed and MEDLINE databases for articles published until 30th June 2011 (last search 17th July 2011). Electronic early-release publications were also included. We searched journals known to publish information relevant to our topic and cross-referenced the reference lists of recovered articles. We did not impose language restrictions. Search terms included: *cancer, breast cancer, response, resistance, taxane, paclitaxel, docetaxel, taxol*. Cell line and other *in-vitro* data have been used for mechanistic descriptions; however, precedence has been given to clinical evidence. Data was limited by treatment or pre-treatment strategies, wherein data included in the tables are derived solely from studies with taxane resistant populations or single agent taxane treated populations, i.e. studies with polychemotherapy inclusive of a taxane have not been included due to unknown characterization of 'other' agent(s) effect(s) on resistance. Therefore, due to the possibility of alternative mechanisms

of resistance all combination chemotherapy treated data sets were removed from our overview. Observations conveyed to the authors by personal communication and unpublished observations were also included. We also contacted experts in the field to broaden our yield of potentially eligible articles. Studies published exclusively in abstract form were not considered (they were considered open to subsequent modification).

The taxanes

Paclitaxel is a plant derivative of the Pacific Yew (*Taxus brevifolia*) and a potent cytotoxic microtubule-stabilizing agent [31]. It has been found to be efficacious in the treatment of a number of human cancers including ovarian cancer, breast cancer, NSCLC, and other malignancies [32-38]. However, it has become obvious that many patients treated with paclitaxel present *de-novo* or will acquire resistance to this agent.

Docetaxel is regarded as a second-generation taxane. It is semi-synthetically derived from the esterification of a side chain to 10-deacetyl-beccatin III [39]. The chemical status of the two taxanes is however, almost identical. Docetaxel is typically administered in a vehicle with low hypersensitivity. They both share similar, but not identical, pharmacokinetics and related side effects [40]. Reported mechanisms of resistance are typically if not identical for both.

A list of some of the taxane formulations available in clinical practice or under investigation is shown in Table I.

Mechanisms of taxane action

Classically taxanes exert their action through binding to β -tubulin, components of microtubules resulting in the formation of stable microtubules [39, 41-43]. Subsequent arrest at the mitotic checkpoint results in apoptosis presumably through G₂/M arrest and the mitochondrial pathway [44-46]. Paclitaxel can also cause disruption of microtubules during interphase, thereby disrupting growth and metabolism.

Some of the most well characterized mechanisms of molecular action include (Figure 1):

- activation of cell division control-2 kinase (*cdc-2*) [47],
- stabilization of cyclin B-1 [48, 49],

Table I – Formulations of taxanes for cancer therapy

Paclitaxel (Taxol®)
Docetaxel (Taxotere®)
Paclitaxel poliglumex (CT-2103), paclitaxel linked to a biodegradable polyglutamate polymer (OPAXIO™)
OncoGel (a biocompatible, biodegradable, controlled release depot formulation of paclitaxel in ReGel)
Vitamin E based paclitaxel emulsion (Tocosol®)
Liposomal paclitaxel (LipoTaxen™)
Cationic PEGylated liposomal paclitaxel (EndoTAG-1)
Nanoparticle albumin-bound (NAB) paclitaxel (Abraxane®)
Liposomal docetaxel (ATI-1123 PSN™)
Liposomal docetaxel (ThermoDox®)
Incomplete list of several of the most widely known taxane formulations

- c) activation of the spindle assembly checkpoint [50],
- d) induction of apoptosis through phosphorylation of bcl-2 [51, 52],
- e) inhibition of cell proliferation [53].

Both the dose and the duration of exposure appear to be important in triggering apoptosis. At sub-nanomolar concentrations paclitaxel favors microtubule assembly through reduction of the critical concentration of tubulin dimers, GTP and microtubule associated proteins (MAPs) [54, 55]. At picomolar concentrations it also exerts its effects on interphase microtubules and genes controlling apoptosis [56]. Increasing concentrations result in shifting the equilibrium of dimers to polymers thereby preventing disassociation even under conditions of extreme stress [41,

57]. As a result of the increasing number of patients being treated with taxanes the development of taxane resistance is becoming a clinically important issue. Therefore, the elucidation of resistance are not only important for the development of strategies to overcome it, but also in possibly predicting response of patients to taxane based regimens.

Molecular Mechanisms of Taxane Resistance

Although numerous mechanisms of drug resistance have been recognized we focus on those specifically reporting on taxane resistance. Several mechanisms have been identified in breast cancer cell lines, while characterization of resistance has proven more difficult in clinical specimens. We primarily

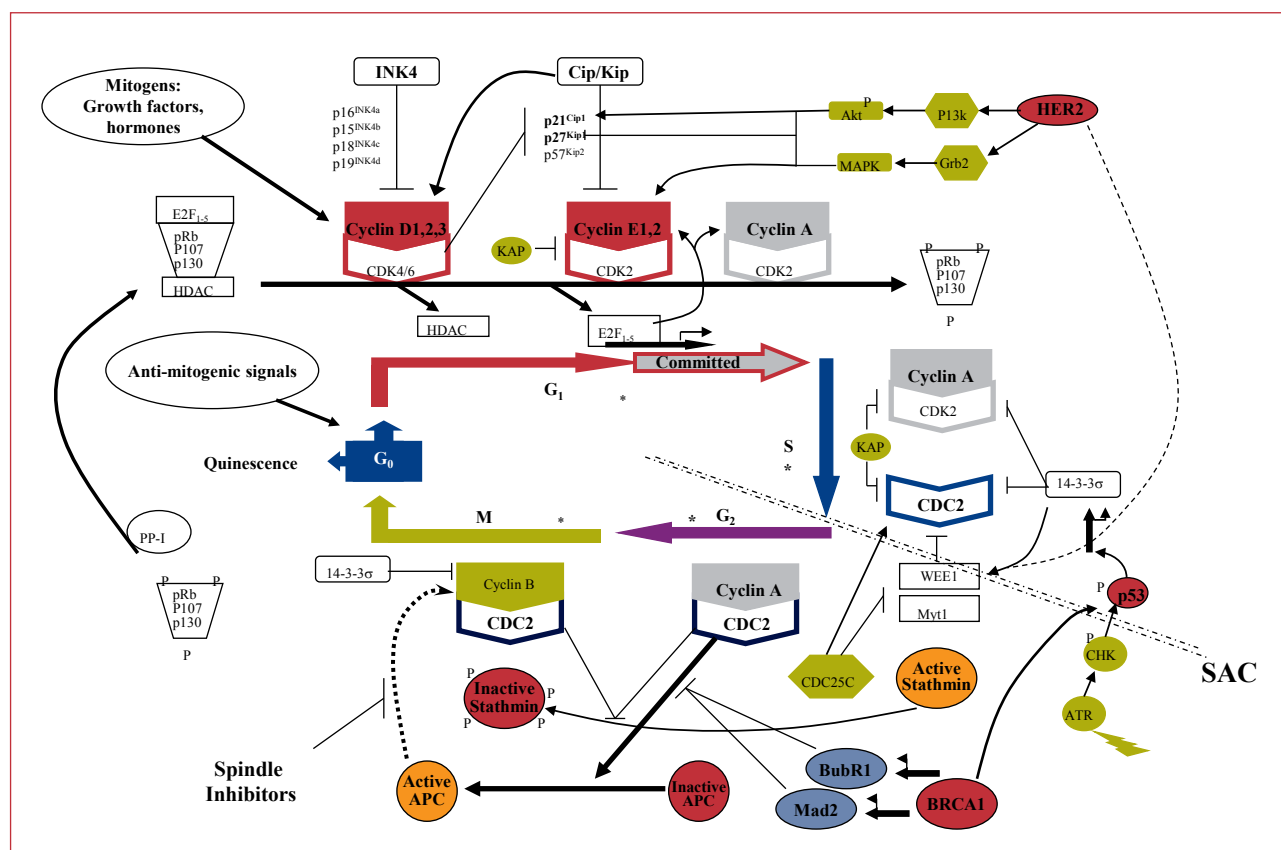


Figure 1.
Regulation of cell cycle in relation to taxane resistance.

Cell cycle and phase commitment. Mitogenic stimuli converge to activate cyclin D complexes; these allow E2F to activate the expression of genes required for S-phase entry in a pRb dependant fashion. Antiproliferative signals, by means of as yet unclear mechanisms, affect p27^{Kip1} that in turn antagonizes cyclin E-CDK2 activity. The cyclin dependent kinases (cdk1 (cdc2), cdk2, cdk4/6) bind to and regulate cyclin function. Phosphorylation of the complexes regulates various transcriptional events in cell cycle progression. The spindle assembly checkpoint (SAC) appears to be the principal site for taxane induced cell death signals to take effect. As indicated in the text, taxanes have been correlated with differential regulation of a number of key genes (proteins) associated with the cell cycle. Many of these are considered to specifically regulate the S/ G₂ transition preceding M. Resistance to taxanes is thought to occur through a variety of mechanisms, many of which have been linked to defects in the SAC. Several chemotherapeutic agents act in distinct phases of the cell cycle: G1 (alkylating agents, platinum, cytotoxic antibiotics), S (anti-metabolites, topoisomerase inhibitors, docetaxel), and M (paclitaxel, docetaxel, epothilones, vinca alkaloids). CDK, cyclin-dependent kinase; Cip, CDK interacting protein; HDAC, histone deacetylase; Ink4, Inhibitor of CDK4; Kip, Kinase inhibitory protein, PP-I, protein phosphatase 1; pRb, product of the retinoblastoma susceptibility gene. * = cell cycle checkpoint.

report on *in vivo* data and supplement with *in vitro* data for a number of the best-characterized mechanisms.

P-glycoprotein (Pgp)

A feature common to most cancer types is multi-drug resistance, i.e. cross resistance of cancer cells to structurally unrelated cytotoxic agents [58, 59]. Several mechanisms of variable drug and cancer specificity have been associated with the study of cancer cells to cytotoxic xenobiotics [60-64].

One of the most well known mechanisms relates to drug resistance associated with the over-expression of the MDR1 gene product Pgp (permeability-glycoprotein) in cancer [65-67]. Increased expression (as assessed by immunohistochemistry) of this protein has been extensively studied in taxane resistant breast carcinomas [68]. However, it remains an elusive marker for clinical implementation due to conflicting data and a lack of standardization in light of consensus recommendations that date back to the mid 1990's [69]. Pgp is a member of a growing family of at least 51 adenosine triphosphate (ATP) binding cassette (ABC) transporters [70, 71]. Proteins in this family include Pgp/ABCB1, breast cancer resistance protein (BCRP)/ABCG2 and multi-drug resistance related protein (MRP-1)/ABCC1, all of which confer an MDR phenotype [72-76]. The family is broken down into 8 subgroups, Table II, with each having a general structure as indicated in Figure 2.

The gene for Pgp is the most widely studied of all resistance mechanisms in breast cancer [77-79]. It is localized on chromosome 7, encoding a 170kDa protein containing two ATP-binding sites and two transmembrane domains [80]. Pgp expression is correlated with acquired and *de-novo* resistance to natural amphipathic products including taxanes, vinca alkaloids, epipodophylotoxins and anthracyclines, confounding separation of taxane specific resistance in light of most therapeutic schedules being polychemotherapy based [65].

Tubulin

Microtubules, the target components of taxanes, are composed of a backbone of tubulin heterodimers consisting

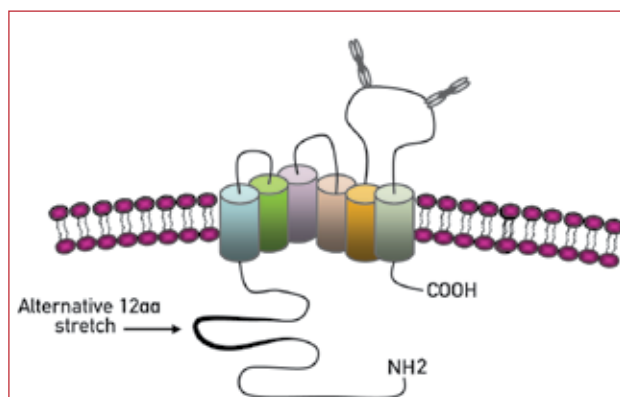


Figure 2.
Cartoon structure of ABC transporters.

There are currently 51 different human ABC transporters classified into 7 families (Table II). Due to the vast variety of such transporters as indicated in the Table, we include a cartoon of the ABCG family that is most representative of data pertaining to taxane resistance. Note here that not all transporters have similar structures. This family currently includes 8 members (1-8), ABCG2 is also known as ABCP and BCRP1 which is known to be expressed in the breast.

Typical structure consists of 6 transmembrane beta-barrels; both N- and C- termini are intracellular; a 12 amino acid stretch confers family divergence.

of α - and β - tubulin subunits that combine stoichiometrically to form tubulin dimmers in association with microtubule associated proteins (MAPs). The integrity of these tubules is essential for the separation and segregation of chromosomes during cell division wherein microtubule dynamics are critical for the proper alignment of chromosomes and kinetochores, the movement of chromosomes during metaphase and their segregation in anaphase and telophase. They are also involved in development and maintenance of cell shape, the transport of vesicles, mitochondria and other cellular components, and are also involved in signaling [81-83].

Throughout the cell cycle levels of tubulin heterodimers and polymerized microtubules are considered to be highly

Table II – ABC transporter subfamilies

Family	Members	Function	Examples
ABCA	Largest family, 5 located on 17q24	Transport cholesterol and lipids.	ABCA1, ABCA12
ABCB	Consists of 4 full and 7 half transporters	Located in blood-brain barrier, liver, mitochondria. Transport peptides and bile.	ABCB5
ABCC	Consists of 12 full transporters	Function in ion transport, as cell surface receptors and excrete toxins.	ABCC6
ABCD	Consists of 4 half transporters	All located in peroxisomes	ABCD1
ABCE/ ABCF	Consists of ABCE and 3 x ABCF transporters	These are ATP binding domains derived from the family lacking transmembrane domains. They regulate protein synthesis and expression.	ABCE
ABCG	Consists of 6 reverse half transporters	Transports lipids, drug substrates, bile cholesterol and steroids	ABCG1-8

There are 51 known ABC transporters in humans, classified into 7 families.

dynamic [84]. Polymerization is influenced by a number of factors such as GTP (binds to one exchangeable site on β -tubulin and on one non-exchangeable site on α -tubulin), and MAPs. MAPs in themselves constitute a complex family of proteins including MAP2, MAP4, Mip-90, tau and STOP [85]. Both ends of the microtubules are in a dynamic flux of what are called positive and negative states, wherein the microtubules often appear to treadmill (i.e. elongate, grow, move) [86] (Figure 3).

Currently several members of the tubulin superfamily have been identified [87]. Of them α - and β -tubulin are structurally quite similar (Figure 4), and each has three functional domains. Tubulin γ exists but it is less abundant and is principally associated with the centromeres [88, 89].

The paclitaxel binding site lies in the so called intermediate domain of β -tubulin [90]. Taxanes, however, only bind to polymerized tubulin, as apposed to other tubulin poisons colchicine and vinca alkaloids that bind to soluble tubulin, therein altering the on and off rate constant of polymerization-depolymerization [41]. In the presence of the taxanes, hydrolysis of GTP to GDP occurs but subsequent depolymerisation is prevented. In the presence of purified tubulin, lateral polymerization and promotion of microtubule stability (and bundle formation) are favored [90]. In doing so these agents have been termed “microtubule stabilizing agents”, and in their presence cells are conditionally locked into G_2/M that typically results in death by apoptosis.

Data supporting the potential mechanisms of taxane

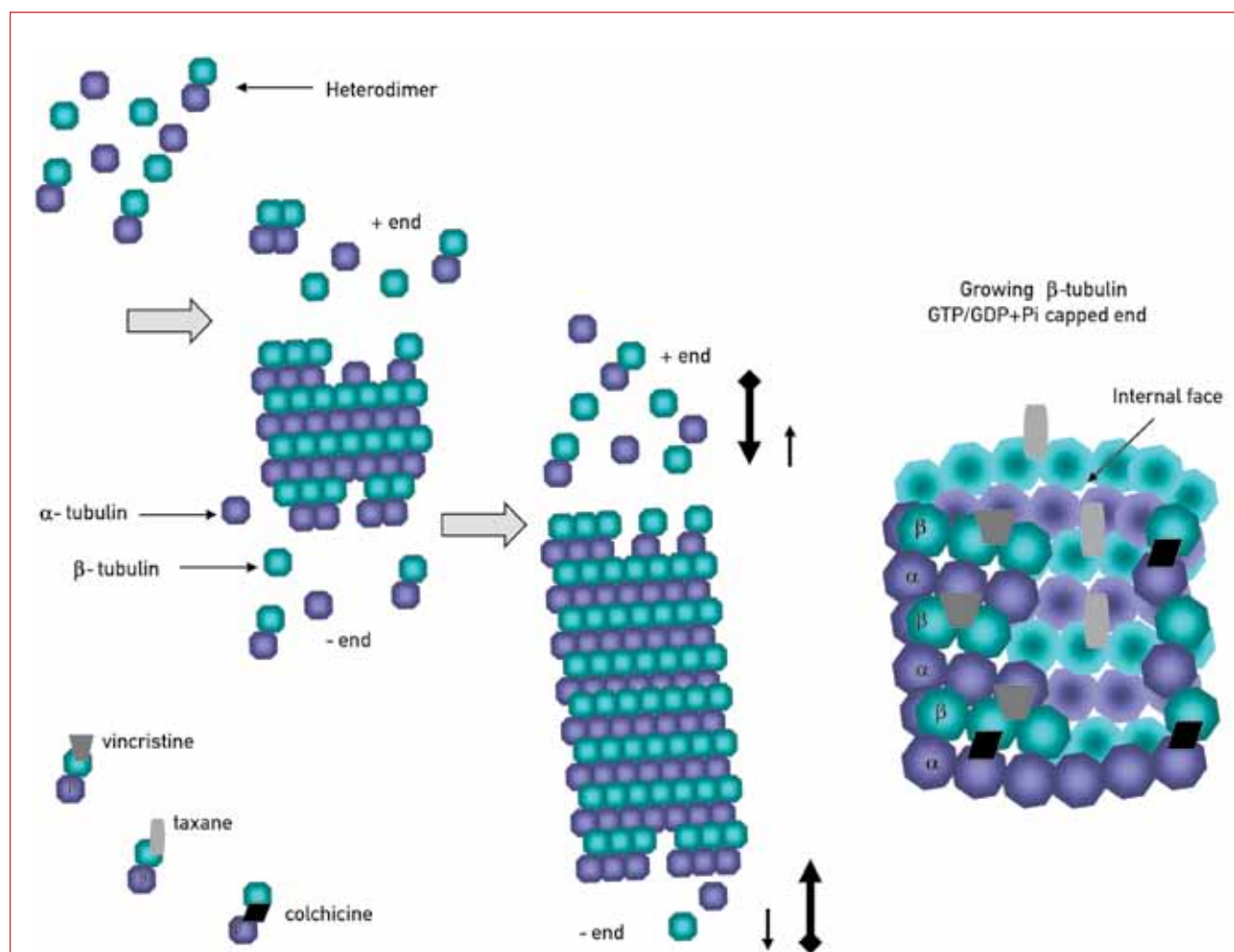


Figure 3.

Dynamic state of polymerization and depolymerization of microtubules.

Microtubules form when heterodimers of a 1:1 ratio of α - and β -tubulin units associate in a head to tail fashion. Cylindrical microtubules consist of 13 proto-fillaments with what are termed a plus (+) and minus (-) end. Tubes form and elongate at the plus end when GTP is hydrolyzed to GDP + Pi (inorganic phosphate) that generates a stable GTP cap. At the minus end the off rate is almost equivalent to the on rate, however, there tends to be more rapid elongation at the plus end. The motion of growth at the plus end has been termed 'treadmilling' wherein the plus end continues to grow and the minus end slowly recedes. The GTP cap stabilizes the plus end, allowing rapid elongation; this end is also further stabilized by the binding of paclitaxel or docetaxel promoting polymerization. The vinca alkaloids cause destabilization of the GTP/GDP+Pi cap and thus an increase in depolymerization. Colchicine binds at a domain located between the α - and β -subunits suppressing microtubule dynamics. The taxanes bind to the inner surface of the proto-fillament while the vinca alkaloids bind to the outer face.

resistance are reported to include:

- a) alteration of the expression pattern of α - and β - tubulin in various cell lines [91],
- b) increased expression of tubulin *per se* [92],
- c) the expression of alternative tubulin isoforms [93],
- d) alterations in the expression profile of MAPs [94].

There are, however studies that failed to confirm such associations [95]. Still our understanding of taxane-microtubule interaction(s) remains relatively naïve as we understand that microtubules are involved in numerous cellular functions [96], therein the effects of taxanes may be complicated by our snap-shot view of cellular processes leading to cell death.

β -tubulin isotypes

Theoretically there are differences in paclitaxel binding dependent upon the tubulin isotype, suggesting that these may be important in terms of resistance [97]. Generally class III appears to be unique in that it destabilizes microtubules and thus much work has concentrated on taxane resistance associated with this isotype. This isoform along with that of isotype I are regarded as the most important for breast cancer as they are potentially clinically useful predictors of response to taxanes (Table III, Figure 4). To date, however, the vast majority of data derives from *in vitro* studies, and there are contradictory results between groups and differences between tumor types [98, 99]. Furthermore, most of the data available are derived from experiments in which taxanes are used at concentrations above that clinically available, and/or of much longer durations of exposure, and thus these data may not necessarily reflect the clinical setting.

Mutations of β -tubulin

The earliest report of somatic mutations in β -tubulin was in the amino acid stretch 250-300. Subsequent studies have reported mutations at nucleotides 810 and 1092 of the HM40 isotype of β -tubulin in paclitaxel resistant cell lines [95]. In order to explain why mutations occurring outside of the paclitaxel-binding domain correlate with resistance authors have speculated that they lead to alterations in microtubule dynamics. Little data exists regarding breast cancer except for a reported germ line polymorphism at codon 217 and another mutation, L215I resulting in enhanced binding of paclitaxel [96]. Mutations have also been reported in α -tubulin [72].

p53

The involvement of p53 in taxane resistance is very complex considering that wild type p53 leads to cell cycle arrest in the presence of DNA damage allowing for DNA repair. In the case of mutated p53 (mP53) it was expected that cells would be sensitive to DNA damaging agents, however, this is not always the case. Mutant p53 disables the apoptotic machinery often resulting in resistance to various drugs [100-103]. However, to complicate the issue further it appears from a variety of sources that mP53 does not lead to paclitaxel or docetaxel resistance [104]. There are several lines of thought on this matter derived from both *in vitro*

and *in vivo* data. In P53 KO (knock-out) mice increased sensitivity to paclitaxel is observed [105]. This is also seen in a number of p53 inactive cell lines [91]; however, the data are so varied and diverse there appears to be little if any consensus.

Apoptosis

Considerable interest has been placed on deciphering the events associated with taxane related sensitivity and resistance through the study of apoptosis. Early studies indicated that over-expression of Bcl-2 and Bcl-xL contributed to taxane resistance. Additional studies led to the suggestion that there may be a threshold at which specific genes confer resistance [106]. There are other studies that indicate over-expression of pro-apoptotic genes are associated with paclitaxel sensitivity [107], and yet others that show no correlation of Bcl-2 levels and response [104].

As most of the anti-apoptotic genes (*IAP*, *TRAF*, *Bcl-2*, *Bcl-xL*) are under the transcriptional control of NFkB this has also been studied. In fact it appears from a few studies that NFkB is constitutively activated in many breast cancers and that inhibition of NFkB may sensitize cells to taxanes [108-110]. In addition, it has been shown that approximately half of breast cancers have increased levels of Akt, which appears to activate Bcl-2 and also increase the activation of NFkB [111-113]. Akt is also activated by HER2 signaling and is implicated in chemoresistance mechanisms of taxanes [114, 115].

Cell cycle

The spindle assembly checkpoint (SAC) appears critical for taxane mediated cell death. Various mechanisms involved in this checkpoint appear to influence and be influenced by taxanes, and defects in the SAC correlate with resistance (Figure 1).

Various data sets seem to support this strong interaction: 1) Upon activation of the SAC both Mad2 and BubR1 interact with Cdc2 inhibiting its ability to activate APC [50]. Destruction of cyclin B and other regulators of mitosis by APC are responsible for proper metaphase-anaphase transition and mitotic exit. MAPs including Mad2 and BubR1 are thought to regulate SAC preventing anaphase until chromosomes are attached to bipolar spindles [116]. In the presence of spindle inhibitors cyclin B degradation is inhibited, cells arrest at pro-metaphase and maintain constitutive Cdk1 activity (destruction of cyclin B inactivates Cdk1) [50].

2) When Mad2 levels are low SAC is non-functional. Sensitivity is restored with re-establishment of Mad2 levels [50].

3) Over-expression of cyclins E and A have been associated with adverse outcomes. These cyclins are important mediators of G₁-S phase transition and subsequent S-G₂ phase transition. Cyclin A appears to be the more important as it is directly involved in regulating Cdk1 (cdc2) activity as activated Cdk1 is required for cells to enter mitosis and for SAC functionality, both key requirements of taxane sensitivity [117].

4) BRCA1 is also implicated in SAC control. BubR1

Table III – In vivo data correlating taxane resistance to molecular markers

Factor	Patient No	Patient Population	Treatment	Response	Comment	Reference
HER2	126	MBC	taxane	pHER2+1,2,3: 7CB vs 5PD pHER2-: 94CB vs 20PD P=0.046	IHC of p1248HER2	[156]
	66	MBC	docetaxel	HER2+: 16R vs 14NR HER2-: 19R vs 17NR P=0.5	IHC	[157]
	46	Neo-adjuvant primary	docetaxel	HER2+: 10R vs 5NR HER2-: 10R vs 5NR P=0.942	IHC	[158]
	62	Primary or recurrent	docetaxel	HER2+: 9R vs 4NR HER2-: 24R vs 25NR P=0.193	IHC	[104]
	67	Neo-adjuvant primary	taxane	HER2Amp: 3R vs 16NR HER2WT: 5R vs 43NR	FISH Response by pCR	[159]
	37	MBC	docetaxel	HER2+: 6R vs 3NR HER2-: 9R vs 18NR P=0.046	IHC	[160]
	100	Primary	docetaxel	HER2+: 7R vs 19NR HER2-: 13R vs 61NR P=0.305	IHC Response by pCR	[161]
	71	MBC	docetaxel	HER2Amp: 14R vs 21NR HER2WT: 20R vs 50NR	FISH	[162]
HER2 ECD	35	MBC	paclitaxel	HER2 ECD+: 40.9% HER2 ECD-: 38.5% P=0.4	ELISA	[163]
tau	41	MBC	docetaxel	Tau+: 19R vs 13NR Tau-: 2R vs 2NR P=0.99	IHC	[164]
	92	Primary	docetaxel	Tau+: 8R vs 5NR Tau-: 9R vs 40NR P=0.977	IHC Response by pCR	[161]
β-tubulin isoforms	39	Locally advanced, recurrent	docetaxel	Low β-I : 12R vs 7NR High β-I : 6R vs 14NR p<0.05 Low β-III : 13R vs 6NR High β-III : 5R vs 15NR p<0.01	RT-PCR	[165]
	41	MBC	docetaxel	β-II+: 7R vs 11NR β-II-: 11R vs 3NR P=0.04 β-III+: 11R vs 9NR β-III-: 7R vs 4NR P=0.72 β-IV+: 19R vs 12NR β-IV-: 3R vs 4NR P=0.43	IHC	[164]
	56	Primary or recurrent	docetaxel	β-III+: 4R vs 10NR β-III-: 25R vs 17NR P=0.05	IHC	[104]
	23	MBC	paclitaxel	β-I WT : 11R vs 9NR β-I Mut: 1R vs 3NR	β-I Mutational analysis (DHPLC-Seq)	[166]
BRCA1	61	Primary or recurrent	docetaxel	BRCA1+: 25R vs 22NR BRCA1-: 8R vs 6NR P=0.794	IHC	[104]
	63	Neo-adjuvant primary	docetaxel	Low: 5R vs 9NR High: 9R vs 37NR P=0.211	IHC	[172]

Factor	Patient No	Patient Population	Treatment	Response	Comment	Reference
BRCA2	25	Neo-adjuvant locally advanced, recurrent	docetaxel	Low: 5R vs 0NR High: 5R vs 15NR P=0.0022	RT-PCR	[119]
ER	69	Primary or recurrent	docetaxel	ER+: 18R vs 14NR ER-: 21R vs 16NR P=0.862	IHC	[104]
	45	Neo-adjuvant primary	docetaxel	ER+: 23R vs 9NR ER-: 8R vs 5NR P=0.502	IHC	[158]
	51	Neo-adjuvant primary	docetaxel	ER+: 30R vs 3NR ER-: 9R vs 9NR P=0.004	IHC	[167]
	100	Primary	docetaxel	ER+: 4R vs 48NR ER-: 16R vs 32NR P=0.002	IHC Response by pCR	[161]
p53	50	Primary or recurrent	docetaxel	<i>p53</i> Mut: 7R vs 9NR <i>p53</i> WT: 21R vs 13NR NS	39/136 additional tumors <i>p53</i> Mut	[168]
	63	Neo-adjuvant primary	docetaxel	<i>p53</i> high: 10R vs 22NR <i>p53</i> low: 5R vs 24NR NS	IHC	[169]
	64	Primary or recurrent	docetaxel	<i>p53</i> +: 16R vs 13NR <i>p53</i> -: 18R vs 15NR p=0.961	IHC	[104]
	114	Primary	paclitaxel	<i>P53</i> Mut: 14R vs 11NR <i>P53</i> WT: 36R vs 45NR p=0.1487	Whole gene sequencing	[170]
GSTP1	62	Primary	taxane	GST+: 0.31 ± 0.09 GST-: 0.73 ± 0.04 mean reduction rate p<0.001	IHC Docetaxel significant Paclitaxel was NS	[171]
Pgp	63	Primary or recurrent	docetaxel	Pgp+: 14R vs 12NR Pgp-: 20R vs 17NR P=0.987	IHC	[104]
Bcl-2	63	Neo-adjuvant primary	docetaxel	Low: 12R vs 34NR High: 3R vs 13NR NS	IHC	[169]
	63	Primary or recurrent	docetaxel	Bcl-2+: 12R vs 5NR Bcl-2-: 23R vs 23NR P=0.144	IHC	[104]
	92	Primary	docetaxel	Bcl-2+: 10R vs 39NR Bcl-2-: 7R vs 36NR P=0.611	IHC Response by pCR	[161]
Thioredoxin	63	Neo-adjuvant primary	docetaxel	Low: 15R vs 34NR High: 0R vs 14NR P=0.018	IHC	[169]
	63	Primary or recurrent	docetaxel	Thioredoxin+: 3R vs 11NR Thioredoxin-: 31R vs 18NR P=0.018	IHC	[104]
Ki67	100	Primary	docetaxel	Ki67+: 17R vs 52NR Ki67-: 3R vs 28NR P=0.108	IHC Response by pCR	[161]

MBC, metastatic breast cancer; R, response (generally CR + PR + SD); CB, clinical benefit; PD, progressive disease; NR, no response; IHC, immunohistochemistry; RT-PCR, reverse transcriptase polymerase chain reaction; NS, not significant, *p53*Mut, mutation present; *p53*WT, wild type *p53*; *p53*+, IHC positive according to criteria; *p53*-, IHC negative according to criteria; ELISA, enzyme linked immunosorbant assay; FISH, fluorescent in situ hybridization; ECD, extracellular domain; Amp, Jene copy number amplified; pCR, pathological complete response

Note: only studies in which a taxane (single agent) was administered in chemotherapy naïve patients have been included; including studies where <10% of the inclusive population were not taxane naïve

transcription is regulated by BRCA1, and also to some extent by p53. BRCA1 is a co-activator of p53 and positively regulates Mad2, thus inhibiting APC activity. Therefore, in BRCA1 deficient cells there is a premature onset of anaphase activated by APC by ubiquitination and degradation of cyclin B and subsequent activation of Cdk1 [118]. this being linked to paclitaxel resistance. Similarly there is data showing that decreased levels of BCRA2 correlate with better responses to docetaxel [119] (Table III).

5) Stathmin, a microtubule regulator, destabilizes microtubules by two mechanisms, catastrophic promotion and tubulin sequestration. It is active in G₂/M transition where it is inactivated by Cdk1 allowing for M phase entry. Stathmin over-expression has been correlated with resistance to taxanes [120]. More recently in a two-dimensional gel electrophoresis and MALDI-TOF peptide mass fingerprinting study stathmin was profiled as one of 9 proteins differentially expressed in paclitaxel resistant MCF-7 cells [121].

6) HER2 over-expression inhibits taxol induced apoptosis by transcriptionally up-regulating p21^{cip1} which associates with p34Cdc2 inhibiting taxol mediated p34 activation delaying cells from entering G₂/M and thereby inhibiting apoptosis [122]. HER2 may also directly phosphorylate Cdc2 leading to resistance. There is also evidence that HER2 positive tumors have low levels of Cdk1 resulting in delayed mitosis and paclitaxel resistance [123]. HER2 has also been shown to promote G₁/S progression and tumor cell proliferation by reducing p27^{Kip1} stability and reducing p27-cdc2 complexes. Stimulation through HER2 and other RTKs has also been shown to result in increased levels of Pgp, without affecting transcription, through the MEK-ERK-RSK pathway as inhibitors to this pathway decrease Pgp mediated resistance to paclitaxel [123].

Thus it appears that the microtubule composition of the mitotic spindle, the dynamics of microtubule assembly and the associated anaphase-metaphase block induced by anti-microtubule agents highlight the importance of the transition into M phase in determining their sensitivity and that deficits in any of the multitude of proteins that regulate the SAC would be sufficient for conferring resistance to taxanes.

Gene signatures/ metagenes

Several groups have investigated high throughput screening of thousands of genes as a method to identify patterns of expression of single genes or gene combinations (gene signatures) that correlate with outcome to given therapies. A first study to investigate taxane related outcomes of response in breast cancer was reported by Chang, et al. [124]. They identified 92 genes that correlated with docetaxel response of primary breast cancer in the neo-adjuvant setting. Their RNA profile from 24 patients included higher expression of genes involved in cell cycle, cell adhesion, protein modification, transcription and apoptosis; while resistant

tumors showed increased expression of some transcriptional and signal transduction genes. The 92 gene predictor had positive and negative predictive values of 92% and 83%, respectively [124].

Utilizing another technique, adaptor-tagged competitive (ATAC)-polymerase chain reaction (PCR), Iwao-Koizumi et al, measured the expression of 2,453 genes in a series of 70 (44 learning set, 26 validation set) primary or locally recurrent breast cancers receiving docetaxel [125]. They identified an algorithm consisting of 85 genes that predicted clinical response to docetaxel with positive and negative predictive values of 73.3% and 90.9%, respectively. Non-responders were characterized as having elevated expression of genes controlling cellular redox, thioredoxin, glutathione-S-transferase and peroxiredoxin [125].

The utility of gene expression signature based predictive algorithms will advance as they allow, if standardized, potentially improved positive and negative predictive ability over single gene predictors. Similar algorithms of metagenes may also enter into clinical development as our knowledge base increases per predictive marker/signature.

Clinically Relevant Prediction of Taxane Resistance

While the majority of data presented relates to *in vitro* experimentation, limited hypotheses of taxane resistance have been investigated *in vivo*. Therefore, insufficient *in vivo* data exist to gain a clear picture of numerous hypotheses that have been generated for molecules of predictive/prognostic significance in breast cancer. To date studies have failed to indicate any particular mechanism or marker as immediately clinically relevant with respect to offering insights into patient stratification.

P-glycoprotein (Pgp)

Increased expression in breast cancers and in other cancer types has generally been correlated with MDR [68]. However, much of the data is conflicting. Some of the problems in assessing the predictive nature of Pgp may relate to the variety of methods used and lack of standardization of cut offs for quantitation, clinical endpoints measured and study/patient heterogeneity that exists across all studies. Furthermore, one of the main antibodies used for its detection has been reported to cross react with HER2 and also the heavy chain of myosin leading to distinct difficulties in interpretation [126].

Putting this aside Pgp expression (depending on the method of analysis and thresholds used) shows a broad range of expression. From 0-30% in newly diagnosed breast cancer rising to over 70% in many cases of relapsed BrCa [127]. Indeed in a meta-analysis of MDR1/Pgp expression in breast cancers Trock et al., showed that approximately 40% of breast tumors expressed Pgp at RNA level or protein assessed by IHC, and that in tumors analyzed post chemotherapy the incidence of Pgp positivity increased [128]. Furthermore, patients with Pgp positive tumors were three times less likely to achieve an objective response compared to those

with Pgp negative tumors. Nevertheless, a word of caution needs to be raised here as very few of the included studies represent patients treated with single agent taxane, there was great heterogeneity between study populations and the methods of expression were also inconsistent.

In one study examining the relationship between YB-1, a Y-box binding protein that targets the Pgp promoter, YB-1 localization and Pgp expression indicated that translocation of YB-1 from the cytoplasm to the nucleus was associated with increased expression of Pgp in breast cancers [129]. The authors claimed that nuclear localization of YB-1 was significantly correlated with resistance to paclitaxel. Their data confirmed previous reports indicating that YB-1 is important in drug sensitivity of cancers via increasing Pgp levels, offering another mechanism for increased Pgp in chemotherapy treated breast cancers.

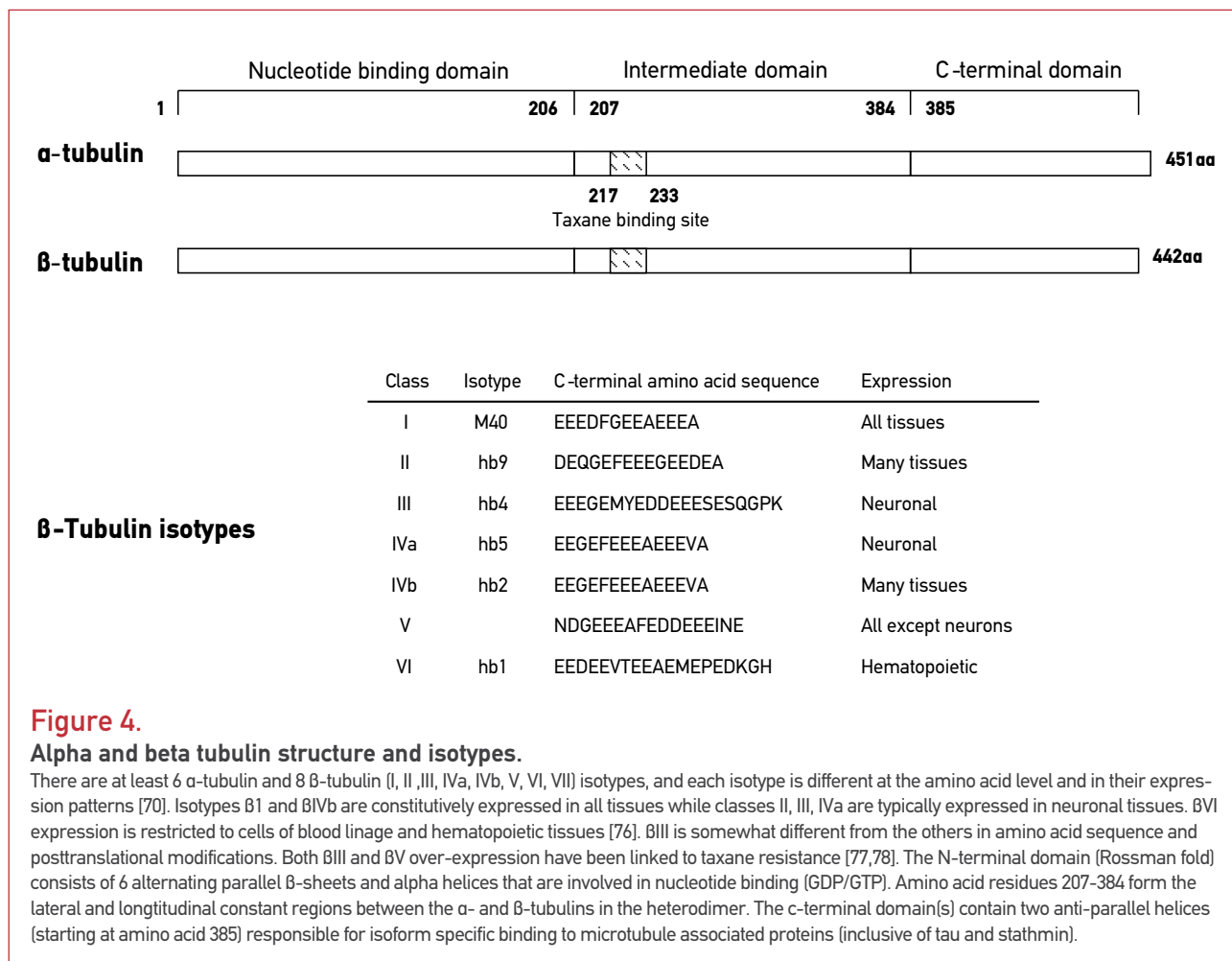
The development of alternative technologies for measuring P-gp expression real-time *in vivo* include Technetium-^{99m}-Sestamib radio-imaging, however, it has not as yet offered clinical prediction of response to paclitaxel [91]. Additional efflux pumps other than Pgp have also been investigated, again with limited predictive ability.

β-tubulin

With regards to the possible alterations in tubulin levels or the dynamics of tubulin polymerization being related to taxane resistance in the clinical setting remains a more difficult challenge than demonstrated *in vitro*. Studies investigating both alterations in β-tubulin isoform expression levels and somatic mutations have proved to be technically demanding and have generated conflicting results in all tumor types investigated, one reason for these differences being the existence of 9 β-tubulin pseudogenes and all share substantial sequence homology with the functional gene [130-132].

Tau

Tau is a stabilizer of microtubule assembly. One interesting feature of tau is that over-expression is linked to ER expression. The gene for tau also contains an ER responsive element, thus questioning the predictive nature of tau expression with endocrine sensitivity. At a functional level tau binds to the same microtubule binding pocket that taxanes bind, indicating that low tau expression should correlate with taxane sensitivity, while high tau expression may indicate increased benefit from endocrine therapy [133]. Limited



data from clinical data sets exist regarding tau, see Table III.

BRCA

Recently “BRCAness” has come to the forefront with the correlation of triple negative (HER2, ER and PR negative tumors) breast cancers (TNBC) and hereditary breast cancers harboring germline mutations in *BRCA1* or *BRCA2* [134]. Following on from this several studies have indicated that chemo-sensitivity of TNBC may be higher to non-taxane and non-anthracycline containing regimens [94-96], although there is contradictory data [135-137]. At this early point in time it would be advisable to await additional and better designed analyses of appropriate studies before conclusions are made regarding the utility of BRCA status for guiding treatment with taxanes. Other groups are also investigating meta-genes for the identification of signatures that may predict response to taxanes in TNBC [138].

HER2

In vitro experiments of systems with HER2 over-expression indicate that down-regulation of HER2 using neutralizing antibodies (including HerceptinTM) can reverse the resistance observed with taxanes. Other reports indicate that HER2 may confer resistance independent of MDR-1. HerceptinTM demonstrates tumor inhibitory and chemosensitizing effects with paclitaxel [55], and docetaxel [104, 139]. The mechanism of resistance to taxanes in HER2 over-expressing tumors is unknown, however, it is suggested that HER2 over-expression induces resistance by increasing p21 expression leading to CDK1 inhibition, that results in blockade of taxane mediated apoptosis [140] (see Figure 1).

Several issues of HER2 status could lead to misinterpretation of the published data sets. It has long been recognized that HER2 amplification is associated with co-amplification of the Topoisomerase IIa gene in 40-50% of cases [141-143]. This could be a factor that biases results obtained from both standard IHC but also from FISH based analyses, and likewise any chemosensitivity/ resistance on behalf of the *TOPOII* gene would also need to be investigated independently from HER2 expression or gene amplification [144].

Other factors

While there are a number of other predictive factors for response to taxanes it is impossible to list all of those reported in detail [91, 104]. The principle mechanisms are highlighted in Table III along with some of the more interesting of the novel mechanisms.

Conclusions

Some of the most obvious limitations to understanding the clinical relevance of any of the aforementioned mechanisms of resistance relate to the lack of universally accepted guidelines for analytical and/or clinical validation, differences in methods of tissue collection preparation and storage, different target assays being utilized and the associated problems of sensitivity and specificity of currently used immunohistochemical analyses [145, 146]. Even in the most comprehensive meta-analysis to date of P-gp in breast cancer,

study heterogeneity, and sample and analytical heterogeneity significantly limited the extraction of reliable data [68].

As indicated from the data sets presented for taxane treated chemo-naïve breast cancer patients the cumulative best evidence for any suggested biomarker is limited but to a few studies. It is obvious that there are severe weaknesses such as retrospective analysis, sample size and lack of clinical information beyond that of response. For these reasons the real predictive value of any of the candidate biomarkers remains ill-defined. Furthermore the utility of individual biomarkers remains a limited approach as many of the agents do not have only one target, and thus multiple gene models or signatures may be more informative.

There are also several specific issues related to some of the individual candidate biomarkers and their rationale in light of our understanding of taxane function. If we consider that the taxanes function by stabilizing microtubules leading to cell cycle arrest at G₂/M (Figure 1) and subsequent apoptosis, biomarkers of resistance should have some functional interaction in this process. Taxanes attach to the β-subunit of tubulin and therein do not directly cause DNA-damage. With this in mind there is little supposed benefit from the study of p53 status as docetaxel induced cell cycle arrest occurs in a late phase of G₂/M. Mutational analysis of p53 is also thwart with errors simply as we do not know exactly what each mutant variant does. Some generate stable aberrant protein, and others generate no protein at all [147]. Furthermore, some mutation positive cases may generate mutant p53 that is undetectable by a given antibody clone used for IHC.

One trend that may be possible to discuss is that of the association between taxane efficacy and the proliferation index of the tumor. Indeed most chemotherapeutic agents work better in cancers with a high proliferative index [148-150]. This high proliferative index characterized by rapidly growing tumors may therein correlate with some of the candidate biomarkers indicated in Table III. Unfortunately there is little collaborative data associated with this possibility as only a few studies have examined a routine set of markers (e.g.: HER2, ER, Ki67) and grade is not one of the factors stratified in the studies reviewed herein.

It appears from the limited number of published studies that there are no valid practical biomarkers that could predict resistance to the taxanes. There remains an immediate clinical requirement for a biomarker of taxane resistance. The community will need to come together in addressing several consanguineous candidate biomarkers, however, there is also a need for the community to understand that eligible data sets will only be those that have received a taxane (or possibly a taxane containing regimen) in predefined chemotherapy naïve patient populations. Some examples of possible data sets that could be analyzed retrospectively include: ECOG 2100 [151], E1193 [152] and others [153-155]. However, it is only by the incorporation of such biomarker

analyses into prospectively designed studies that clinical practice will alter; such studies are awaited.

Conflict of Interest

None to declare.

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