REVIEW

Taxanes: Promising Anti-Cancer Drugs

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Abstract

Taxanes are amongst the most promising antitumor agents available at hand today, of increasing importance in Asia given that cancer is now one of the major public health problems which needs to be dealt urgently for the benefit of affected patients. Several ongoing experimental and clinical trials have supported the fact that even with their side effects and poor solubilities, taxanes are still the first lines of treatment chosen for breast, ovary, lung and other metastatic cancers. Prolonging the life of cancer patients is the main aim of all researchers, scientists, pharmaceutical companies and clinicians; therefore this review emphasizes the mechanisms of action of taxanes and how they can play an important role in palliative treatment if not applied for curative purposes, hence being considered a boon for cancer management.

Keywords: Taxanes - Taxol - Taxotere - cancer chemotherapy

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Introduction

Taxanes are the most recently solicited chemotherapeutic drugs of our era. During the past decades, these unique hydrophobic mitotic inhibitors have been thoroughly investigated through numerous experimental and clinical trials which have brought hope in breast, ovarian, lung, prostate (Tannock et al., 2004; Khan et al., 2003), pancreas, gastric (Cosimo et al., 2003; Roth and Ajani, 2003) and head and neck (Nabell and Spencer, 2003) cancer treatments.

In brief, the taxanes mainly group Paclitaxel (Taxol) and Docetaxel (Taxotere) as well as taxanes homologs, which are derived from natural sources; taxol (Wani et al., 1971) is derived originally from Taxus Brevifolia (bark of Pacific yew/Western yew conifers) while Docetaxel is a semisynthetic analogue of the latter; an esterified derivative of 10-deacetylbaccatin-III (10-DAB) extracted from Taxus Baccata (Bissery et al., 1991) (needles of European yew tree). During course of time due to poor oral bioavailability, solubility and numerous side effects; views for the development of new similar anti-mitotics have been encouraged and brought to light. Moreover, since there have been numerous multidrug resistance (MDR) (Patel et al., 2010) in patients, combination therapies are preferred over single drug therapy and taxanes also known to be having a radiosensitizing (Nabell and Spencer, 2003) effect have proved to be helpful in the palliative treatment of patients if not in the curative one. Despite, their side effects related mostly to their vehicles (Hennenfent and Govindan, 2006); they remain one of the most acceptable treatments for metastatic breast (Gudena et al., 2008), ovarian, prostate and lung carcinomas. The list for laboratory experiments and clinical oncological trials is very long concerning taxanes; but their outcome is of tremendous eagerness in the cancer field. So, here we have tried to underline their mechanism of action under the rationale of their use and current development in oncology.

Taxanes - Their Saga

Taxanes are remarkable cytotoxic diterpenes derived from natural products as described above. Taxol was in fact identified as the first member of a novel group of anti-cancer drugs. Arthur S. Barclay was a botanist who collected bark, twigs and leaves from the pacific yew tree in the 1962 as part of a National Cancer Institute program (Wani et al., 1971; Wall and Wani, 1995), its crude form was obtained and isolated with much labor in 1964 by Wall and Wani who gave it the name of Taxol in 1967 which they described in 1971. In the same year, it was found to be having cytotoxic effects on solid tumors and leukemic cells (Wani et al., 1971; Wall and Wani, 1995); later, Dr. Horwitz Susan and her group delineated its main mechanism of action (Schiff et al., 1979) and it was considered being worth for future development in cancer practice. The in vivo studies that followed were numerous, but however in 1989, the outstanding outcome in clinically treated patients with ovarian malignancies (William et al., 1989) brought further faith in our researchers to test it on other tumors and since then it has been a never ending process.

In 1992, Bristol-Myers Squibb marketed the drug as TAXOL® with the approval of the FDA (Food and Drug Administration) where it was used for treatment of breast, ovary and AIDS-related Kaposi sarcoma; furthermore, its combination with cisplatin is used in the treatment of advanced ovarian cancer and NSCLC (Pazdur 2011). Nevertheless, the fear that Paclitaxel was derived from ¹Department of Pathology, Molecular Medicine and Cancer Research Center; ²Department of Pharmacology, Pharmacy College, Chongqing Medical University, Chongqing, China *For correspondence: wangyalan074@126.com
an exhaustible source, made an urge to develop new semisynthetic taxol analogues-TAXOTERE® licenced by Sanofi- Aventis which was derived from Taxus Baccata, a European yew being a renewable source, was synthesized in 1981 by Pierre Potier a french pharmacist and chemist; then, american chemist Robert. A. Holton in 1992 further improved it. Approved by the FDA for breast, head and neck, prostate and gastric carcinomas; it is under clinical trials for other types of cancers (Pazdur 2011).

In 2005, FDA approved Abraxane® (Pazdur 2011), a nanoparticle paclitaxel (nab-paclitaxel) from Abraxis Bioscience in breast metastasis and in June 2010, outcome in NSCLC (non-small cell lung cancer) proved its efficacy in clinical trials (Gen news highlights 2010). During the course of time, many new taxanes from the parent molecule has been developed and entered clinical trials so as to give early diagnosed cancer patients a chance to live longer, remain cancer free and patients with advanced cancers some more months to live if not years. Recently, 3 new taxanes were isolated from the leaves of Japanese yew- Taxus Cuspidata (Ni et al., 2010) and therefore, encouragement is there for continuous discovery and exploration of new mitotic poisons inducing growth arrest.

**Their Nomenclature**

Taxol is a tetracyclic 17-carbon (heptadecane) skeleton. Whereas Taxotere differs from it at two positions in its chemical structure; a hydroxyl functional group on carbon 10 where instead Taxol has an acetate ester and a tert-butyl carbamate ester exists on the phenylpropionate side chain instead of bezyl amide in Taxol. Hence, it is the carbon 10 functional group that causes Taxotere to be more water soluble. Other formuliations derived like Abraxane not using CrEL (cremophor EL®), Taxoprexin® (Docosahexaenoic acid- paclitaxel) bounded to natural fatty acids, XytotaxTM (paclitaxel polyglumex), TOCOSOL (R) paclitaxel, BMS-184476, DJ-927, BMS-275183, RPR 109881A, Ortataxel, Genexol (co-polymer combination), LEP (liposomal-encalsulated paclitaxel) and taxol in vitamin E emulsion (Hennenfent and Govindan, 2006) have been designed to make them less hydrophobic, increase tumor permeabilities and enhance intracellular retention so as to make them more and more efficacious with less side effects related to their vehicles.

**Mechanism of Action of Taxanes**

**Effect on cell growth, differentiation and proliferation**

Taxanes currently known to suppress and inhibit cell growth, differentiation and proliferation in indefinitely known cancer cell lines are the most preferred anti-cancer drugs by physicians. Either it be in experimental or clinical trials, their mechanisms related to decrease cell growth has been thoroughly appreciated by everyone including patients in the oncological field. Taxanes main mechanism of action involves the inhibition of cell division, chromatid separation, growth and ultimately cell death. They are commonly known as mitotic inhibitors or microtubule inhibitors as they cause a frozen mitosis; hence they are also sometimes called as mitotic poisons.

In the past, some experimental conclusions made us believe that Taxotere was more potent and efficacious (Braakhuis et al., 1994; Vanhoefer et al., 1997), as it had greater potency to accumulate, remained intracellularly for longer periods of time and was hence more cytotoxic compared to Taxol; nevertheless, newer studies (Veitia et al., 1998; Calderoni and Cerny, 2001; Guastalla and Die’ras, 2003) have highlighted that they are equipotent drugs and that their main action lie in the microtubules that are essential components of mitotic spindles which are responsible for cell transport, division, transcription, post-translational modification and other cellular dynamics (Nogales 2000; Zhou and Giannakakou, 2005). Previously, it was stipulated that both compounds acted by either excessive polymerization or depolymerisation of microtubules (Calderoni and Cerny, 2001); however; after a series of experimental trials it was put forward that they reversibly and tightly bind to β-tubulin (Rao et al., 1999; Snyder et al., 2001), stabilize microtubules by enhancing rates of nucleation, growth and elongation phases of polymerization (Derry et al., 1995; Yvon et al., 1999; Jordan and Wilson, 1998); consequently leading to mitotic arrest and diminished cell growth. Moreover, inspite of their excellent anti-tumor activity they however are still not cell specific and not all concentrations have similar effects on the microtubules; higher concentrations of taxanes cause microtubule arrangement into bundles (Schiff et al., 1979; Schiff and Horwitz, 1980) while at lower concentrations, there is suppression and stabilization of microtubule dynamics without alteration of the polymer mass formed (Derry et al., 1995; Yvon et al., 1999; Jordan et al., 1993; 1996); further studies have even demonstrated that at very low concentrations, Taxol can inhibit cell proliferation with no mitotic arrest (Giannakakou et al., 2001). During course of time, they have shown to have different cytotoxic and anti-proliferative effects (Liebmann et al., 1993) on various cancer cell lines namely breast, lung, ovarian, leukemia, osteosarcoma, prostate, hepatic, lymphoma and several others (Liebmann et al., 1993; Wall and Mansukh, 1995; Zhou et al., 1999; Giannakakou et al., 2001; Chan et al., 2002; Wei et al., 2002; Geng et al., 2003; Okano et al., 2007; Ilgar and Arican, 2009). Besides, in most cancer cells they have caused growth inhibition in a concentration-dose dependent manner (Liebmann et al., 1993; Torres and Horwitz, 1998; Zhou et al., 1999; Giannakakou et al., 2001; Chan et al., 2002; Wei et al., 2002; Geng et al., 2003; Okano et al., 2007; Ilgar and Arican, 2009) and therefore, providing a rationale for clinical trials. The widespread clinical use of these anti-neoplastic drugs represents an advance in cancer treatment as cancer is a disease of uncontrolled mitosis; and being scientists or researchers, it is of our duty to sort out the most appropriate anti-mitotic treatments for the betterment of our cancer patients.

**Induction of Various Genes**

Besides, there is also evidence that the action of taxanes on cells can induce a whole spectrum of genes (Moos and Fitzpatrick, 1998) and cytokines (Lee et al., 1997) like tumor necrosis factor-α (TNF-α) and interleukins for proliferation, apoptosis, inflammation;
activate transcriptional pathways (Moos and Fitzpatrick, 1998; Perera et al., 1996); hence leading to inhibition of cell growth, apoptosis and angiogenesis. However, some studies have shown that even though taxol, taxotere and taxane homologs exhibit similar pharmacological traits, share a common primary mechanism of action but, due to structural activity restraints they cannot share similar mediation of all genes. Over past 15 years, several experimental researches have been carried out so as to know the genes related to taxanes; to date 85 genes are expressed by docetaxel (Noguchi 2006) and too many to be counted by paclitaxel; amongst which we have found the modulation of bcl-2/bax apoptotic pathway (Blagosklonny et al., 1997; Haldar et al., 1996; Blagosklonny et al., 1996) related genes by them; regulation of expression of several apoptosis related proteins like Yama protease (CPP32β) (Ibrado et al., 1996), P21WAF1, P53, c-raf-1 (Shah and Schwartz, 2001); activate P34cdc-2, cdc-like kinase, other cycline dependent kinases (CDKs) (Ilgar and Arican, 2009; Moos and Fitzpatrick, 1998) and protein kinase C isofoms which in turn mostly lead to programmed cell death which is the main mechanism to achieve a fruitful cancer therapy. However, sometimes taxanes can also activate genes like bax and p27 (Brown et al., 2004) which causes chemoresistance in malignant cells; hence leading to poor anticipated therapy but this has been overcome by using combination therapies. Moreover, taxanes have been shown to mimic LPS (bacterial lipopolysaccharide) where they have caused the translocation of NF-κB (Nuclear Factor-Kappa B) from cytoplasm to nucleus which has led to secretion of death gene TNF-α and interleukins IL-1 and IL-6 (Perera et al., 1996). Taxol can induce genes like CHUK (Moos and Fitzpatrick, 1998) that governs transcription factors like NF-κB important in the regulation of expression of inflammatory, adhesion, invasion, acute phase responses and checks on the activities of the caspase family which is the core to apoptotic processes. Furthermore, they can also increase the expressions of some cytokine genes; induce crg-2 and COX-2 (Moos and Fitzpatrick, 1998) important in inflammatory reactions; inhibit ERK2 kinase and downstream CK4 also found to be involved in the propagation of apoptosis (Ilgar and Arican, 2009; Shah and Schwartz, 2001; Moos and Fitzpatrick, 1998). In brief, taxanes mechanism of action in induction of certain apoptotic genes has proved efficacious in cancer treatment and pathways have been delineated to prevent chemoresistance.

**Cell cycle and Apoptosis**

Killing of malignant cells is the goal of all cancer therapists. Over the past decades innumerable methods for killing cancer cells by triggering of apoptosis has been on the run to attain successful cancer treatment. Taxanes achieving favorable apoptotic outcomes have been thoroughly investigated both in vitro and in vivo. Apart from taxanes’ abilities to bind to microtubules, they have been shown to stabilize them, inhibit depolymerization, interfere with the G2/M phases (Shah and Schwartz, 2001) which is achieved by blocking the cell cycle during mitosis in the transition from prometaphase to metaphase (Cunha et al., 2001) and hence, induce apoptosis programmed cell death (Lowe and Lin, 2000); confirmed through cytometric studies (Fabbri et al., 2006) which is a crucial checkpoint in cancer treatment. Moreover, they also initiate a whole cascade of cell death pathways (Moos and Fitzpatrick, 1998) related to a whole spectrum of “death” genes which are very much solicited in successful cancer management. Amongst the whole myriad of genes enhancing taxanes induced apoptosis, there is the Bcl-2 family where it is speculated that taxanes can interact and induce cytotoxicity via phosphorylation of Bcl-xL (B-cell lymphoma-extra large) and Bcl-2 (B-cell lymphoma 2) / BAX (Bcl-2-associated X protein) which are members of the apoptosis regulator proteins (Pienta 2001; Moos and Fitzpatrick, 1998); they are also known to cause resistance (Chun and Lee, 2004) in tumor cells but, nevertheless, play a pivotal role in both breast (Noguchi 2006; Callagy et al., 2006) and prostate (Haldar et al., 1996; Yoshino et al., 2006) cancer treated regimens. However, recently Bcl-2 has been found to enhance taxane chemosensitivity (Ferlini et al., 2009) in some solid tumors therefore, changing it from a protector to a killer which proves to be a completely novel strategy and a plus in cancer battle. Taxanes can also induce high levels of ROS (Reactive Oxygen Species) (Geng et al., 2003) involved in apoptosis; regulate c-Raf-1 kinase (Torres and Horwitz, 1998; Moos and Fitzpatrick, 1998) an important mediator of programmed cell death which is somehow concentration dependent; increase stabilization of protein by induction of wild-type p53 and p21WAF1 (Blagoskinny et al., 1995; Chang et al., 2006) and downregulate the proto- oncogene c-myc (Yim et al., 2004; El Khayri et al., 1997) thus, promoting apoptosis. Besides, inhibition of MAPK pathway including activation of signal pathways ERK, JNK and P38 kinases has been found to enhance taxanes mediated cell death (Okano et al., 2007; Mcdaid and Horwitz, 2001; Wang and Wieder, 2004) while prolonged exposure to taxanes cause DNA fragmentation (Torres and Horwitz, 1998) which is another characteristic of programmed cell suicide. Caspase3 (Torres and Horwitz, 1998; Moos and Fitzpatrick, 1998; Mahaffey et al., 2007) main executioner of apoptosis related to taxanes along with its orthologs caspases 8, 9 play a central role in the cleavage of PARP (Poly-ADP ribose Polymerase) also essential for apoptosis identified in lung (Mahaffey et al., 2007), ovarian (Solomon et al., 2008), thyroid (Meng et al., 2008), prostate and breast (Wang and Weider, 2004) cancer cell lines; however, it has been found recently that taxotere could cause caspase-independent lysosomal cell death which was increased dramatically (Mediavilla-Varela et al., 2009), hence showing that taxanes could induce multiple cell death pathways. Several apoptotic enhancers for taxanes have been undergoing trials over the past few years; including ATRA (all-trans retinoic acid), d-limonene a non-nutrient dietary component, octreotide (bacterial lipopolysaccharide) where they have caused the translocation of NF-κB (Nuclear Factor-Kappa B) from cytoplasm to nucleus which has led to secretion of death gene TNF-α and interleukins IL-1 and IL-6 (Perera et al., 1996). Taxol can induce genes like CHUK (Moos and Fitzpatrick, 1998) that governs transcription factors like NF-κB important in the regulation of expression of inflammatory, adhesion, invasion, acute phase responses and checks on the activities of the caspase family which is the core to apoptotic processes. Furthermore, they can also increase the expressions of some cytokine genes; induce crg-2 and COX-2 (Moos and Fitzpatrick, 1998) important in inflammatory reactions; inhibit ERK2 kinase and downregulate the proto-oncogene c-myc (Yim et al., 2004; El Khayri et al., 1997) thus, promoting apoptosis. Besides, inhibition of MAPK pathway including activation of signal pathways ERK, JNK and P38 kinases has been found to enhance taxanes mediated cell death (Okano et al., 2007; Mcdaid and Horwitz, 2001; Wang and Wieder, 2004) while prolonged exposure to taxanes cause DNA fragmentation (Torres and Horwitz, 1998) which is another characteristic of programmed cell suicide. 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Considering the fact that tumor growth and metastasis is different in different cell lines; so more and more effort has been put up by our researchers for bridging the gaps with the development of some new taxane analogues, combination therapies or gene inhibitors so as to promote taxanes-induced apoptosis which is the key to cancer treatment.

Inhibitors of Angiogenesis

Considering the fact that tumor growth and metastasis are fully dependent on angiogenesis- formation of competent new blood vessels; it is an important point of control in cancer progression and its inhibition is either by regulation of the main angiogenic cytokines VEGF (vascular endothelial growth factor) and bFGF (basic fibroblast growth factor) released by tumor cells or prevention of endothelial cell angiogenic processes. Microvessel disruption by taxanes has been appreciated in numerous experimental trials. In most they have been shown to inhibit VEGF, bFGF (Wang et al., 2003; Klauber et al., 1997; Sgdari et al., 2000), MMP-9, MMP-2, IL-8 (Lee et al., 1997; Inoue et al., 2003), upregulated E-cadherin and nm23 (Wang et al., 2003); hence suppressing angiogenesis, decreasing MVD (intratumor microvessel density), preventing spontaneous metastases, lymph node metastasis and angioproliferative lesions in melanomas, Kapo’s sarcoma, transitional cell carcinomas and others; moreover, some new facets of angiogenesis revealed that PMSA (prostate-specific membrane antigen) could present itself as a new target for angiogenesis detection (Tsiu et al., 2005) in prostatic malignancies; but deeper studies need to be done to further confirm its authenticity. Taxanes have been found to be potential angiogenic inhibitors either as single agents, together with chemotherapeutic drugs or combination therapies such as propapoptotis agents (Chan et al., 2002), endogenous estrogens (Klauber et al., 1997), angiogenic inhibitors (Inoue et al., 2003), Tyrosine kinase inhibitors (Naumova et al., 2006), anti-Erb-2 (Klos et al., 2003), thalidomide (Zhang et al., 2005), bevasizumab (Fujita et al., 2007) and angiostatin gene (Galaup et al., 2003) which regulated both VEGF and bFGF in an agonistic manner, have yielded some light in successful inhibition of neovascularization in solid tumors of breast, bladder, ovarian, lung, liver and prostate. Nevertheless, some other therapies such as taxanes with FITs (farnesyltransferase inhibitors) (Xu et al., 2001) affected different aspects of angiogenesis in vivo and further studies have even assessed the safety, merits and drug-drug interactions of combination therapy (Herbst et al., 2002) but still rendering them as being effective angiogenic inhibitors. However, some studies have proved Taxotere to be a more potent inhibitor of endothelial proliferation, migration, invasion and angiogenesis both in vitro and in vivo compared to Taxol (Grant et al., 2003; Polcher et al., 2010; Hotchkiss et al., 2002), somehow, several models have shown that both taxanes do have promising vascular targeting potential and antiangiogenic effects even at very low concentrations (Guo et al., 2003; Wang et al., 2003); therefore less side effects for the ultimate benefit of patients. Recently, a surprising discovery where VEGF gene (Kirchmair et al., 2007) was delineated as a treatment for taxanes caused neuropathy; as it is believed that angiogenesis is not the sole causative factor for tumorigenesis.

Resistance-a flaw of Taxanes

Acquired resistance to taxanes has become a serious clinical issue with increasing prescription. Though there have been a lot of successful outcomes with taxanes involved in the treatment of endless number of cancers but nevertheless, drug resistance remains a major obstacle which needs to be combated urgently. For years, profound researches have been going on just to understand the mechanisms related to MDR (multidrug resistance) in several carcinomas treated with taxol and taxotere. Few of the mechanisms that have been highlighted includes P-glycoprotein which pumps out intracellular accumulation of respective drugs (Ferlini et al., 1998; Pires et al., 2009; Goncalves et al., 2001; Sampath et al., 2003) being the most important as it increases resistance up to 1000 fold; involvement of mutational changes in microtubule dynamics including β-tubulin isotypes or drug binding sites (Chang et al., 2006; Goncalves et al., 2001; Sampath et al., 2003; Orr et al., 2003; Giannakakou et al., 2000) offers resistance up to 30 fold only; overexpression of certain proteins like bcl-xl, bcl-2, HER-2, Aurora-A (Noguchi 2006; Hu et al., 2008; Liu et al., 1999), survivin (Kucukzeybek et al., 2008; Hu et al., 2008; Jung et al., 2007), GSTT1 including redox system (Townsend and Tew, 2003; Iwao-Koizumi et al., 2005), p27 (Brown et al., 2004), annexin I, tubulin β-5 and knockdown of prohibitin1 (Patel et al., 2010); and TXR1, NFkB-B and PI3K/Akt pathways activation contributed to taxanes MDR (Jung et al., 2007; Amerongen and Berns, 2006; Jiang et al., 2009) as well as hypoxia. Though, it has been found that downregulation of bcl-2 (Yang et al., 2010) represents a novel mechanism for resistance, deeper studies are needed and furthermore, even at low concentrations of taxanes, drug resistance was found to be mediated (Amerongen and Berns, 2006); therefore, better combination therapies need to be forecasted to decrease risk of resistance which is a real headache not only for scientists but also for patients. However, during the course of time, long term effectiveness with less of acquired resistance displayed by taxanes has been appreciated with development of new taxane analogues (Sampath et al., 2003), proper vehicles, formulations (Ferlini et al., 2003), explicit experimental and clinical trials that have been on the run to overcome MDR.

Relevance of Taxanes in Experimental Trials

During the past decades, innumerable experimental...
studies on taxol, taxotere and their homologs have been carried out all over the world so as to try to carve a pathway for clinical oncological trials. Their mechanism of actions, pharmacokinetics, activation of signal transduction pathways, side effects are few of the characteristics that have been delineated through experimental trials. Laboratory based researches have been ongoing in numerous cell lines and have yielded quite appreciable outcomes to provide a rationale for ongoing clinical investigations, in order to optimize cytotoxicity of chemotherapy.

**Lung Cancer**

Lung cancer is the first leading cause of cancer death in the United States, numerous anti-cancer drugs have been developed over years but somehow, taxanes tend to remain in the front line of chemotherapy for NSCLC (Non-small cell lung cancer) compared to squamous cell carcinoma of the lung. It usually displays as an inoperable disease due to multiple metastases with high degree of chemoresistance towards a broad spectrum of naturally occurring cytotoxic drugs and cross resistance to other drugs has also been identified (Wang et al., 2007), but however, both Docetaxel and Paclitaxel alone or in bitherapy have shown to inhibit cell growth, increase rate of apoptosis, parapoptosis newer form of cell death and significantly prolong survival of human lung adenocarcinoma cell lines and xenografts (Vanhoefer et al., 1997; Chan et al., 2002; Chang et al., 2006; Guo et al., 2010; Yamori et al., 1997). Also, several preclinical lung cancer evaluation models, have underlined the effectiveness of combination therapies; either by augmenting the activity of chemotherapy or by increasing entrance into apoptotic pathways (Patel et al., 2010; Chang et al., 2006; Mahaffey et al., 2007; Jung et al., 2007; Ichite et al., 2009). Moreover, newer formulations (Sun et al., 2007; Sampath et al., 2003; Feng et al., 2010) have shown to be having superior preclinical pharmacokinetics compared to parent taxanes in NSCLC; which infers that preclinical studies provide an impetus to test their hypotheses into clinical trials. Since, NSCLC has great sensitivity responses to taxanes irrespective of the drug concentrations (Giannakakou et al., 2001), further experimental studies are being carried out to find a most compliant and appropriate treatment for all types of lung carcinomas so as to decrease both mortality and morbidity rates.

**Breast Cancer**

During the past few years the issues concerning the quality of life in women with advanced breast carcinoma has become utterly important in the field of cancer treatment, as women are particularly sensitive concerning any harmful breast lesions. Despite the fact that there has been a decrease in the number of deaths related to breast cancer due to regular screening, novel surgical methods and better cytotoxic agents; there is still a lot of advancement to be done in the field of metastatic breast cancer (MBC). The taxanes; Taxotere and Taxol are two well established active agents representing the cornerstone for mammary tumors shown by the rate of response of docetaxel ranging from 30-50% in metastatic settings. Several new breast cancer experimental studies showed that upregulation of HER-2 by inhibition of CDK1 could act as a predictor of paclitaxel sensitivity as well as Aurora-A (Noguchi 2006; Nakayama et al., 2009; Shimomura et al., 2010) increasing docetaxel sensitivity. Even gene expression profiling has been carried out in order to meet up challenges for breast cancer management (Callagy et al., 2006; Iwao-Koizumi et al., 2005) while even monotherapy along with other adjuvant therapies showed promising anti-proliferative, anti-angiogenic and decreased metastatic activities of cancer cell lines (Brown et al., 2004; Wang and Weider, 2004; Ferlini et al., 1998; Shimomura et al., 2010; Chan et al., 2010; Latimer et al., 2009; Ikeda et al., 2010); recently, Abraxane and bevacizumab showed to have some action in triple-negative breast cancer which however needs clinical trial confirmation; hence, encouragement is there to continue digging out novel therapies for MBC management and alleviating tumor burden.

**Prostate Cancer**

Being an androgen-dependent tumor, hormonal therapy tends to be the primary line of treatment, nevertheless most patients tend to be refractory to it and the final outcome may be fatal. Therefore anti-neoplastic agents like Taxotere is solicited although the latter provides only some palliative treatment. Being the second leading cause of male cancer death in developed countries; it rings the bell that emergency measures should be taken for its treatment. Though both taxanes have been investigated (Obasaju and Hudes, 2001; Jiang and Huang, 2010), preferably Docetaxel has successfully inhibited growth, caused increased apoptosis through old and new pathways in both prostate sensitive and resistant cells in vitro either it be as a single agent therapy or with various adjuvants (Tannock et al., 2004; Khan et al., 2003; Mediavilla-Varela et al., 2009; Kucukzeybek et al., 2008; Rabi and Bishayee, 2009, Nehme et al., 2001; Kramer et al., 2006). Moreover, it has been found that there is rapid development of resistance (Jiang and Huang, 2010; Qian et al., 2010); with the taxanes in patients with HRPC (Hormone-refractory prostate cancer) or metastatic prostate cancers and thus, in order to improve their lives continuous experimental evaluations concerning new regimens (Rabi and Bishayee, 2009; Wu et al., 2009) or markers (Yoshino et al., 2006; Sisung et al., 2008) to assess their efficacies are being carried out. Besides, several Taxotere combinations in HRPC are currently undergoing clinical experiments, their preliminary results are promising, and this can increase the median survival rate for such cancer patients; however, caution should be taken during bitherapy (Canfield et al., 2006).

**Ovarian Cancer**

In the United States in year 2010, 21880 new cases were diagnosed and 13,850 died from it (Pazdur 2011), so it remains one of those cancers that affect most women amongst all the gynaecological malignancies in industrialized countries. Like in all other cancers, taxanes in ovarian preclinical studies have been found to bring a lot of promises in management of early and platinum resistant
Melanomas being the most severe form of skin cancer with high incidence of metastasis and resistance to conventional therapeutic modalities including chemotherapy; is continuously increasing throughout the world. Significant experimental efforts have been expanded to identify active anti-cancer agents in melanoma-amongst which taxanes have been reported to be having beneficial effects over melanoma cell lines. A growing body of evidence suggested that poor taxane sensitivity maybe due to activation of MAPK, ERK1/2, PI3/Akt pathways (Jiang et al., 2009; Haass et al., 2008; Mhaidat et al., 2007) in melanoma cells while activation of JNK and caspase-2 (Mhaidat et al., 2007; Mhaidat et al., 2007; Mhaidat et al., 2007) promoted apoptosis thus causing tumor shrinkage, inhibiting spread and preventing acquired resistance; suggesting that taxotere and taxol do have fruitful outcomes in the treatment of melanomas and more profound in vitro trials are to be inspired.

Hepatocellular carcinoma (HCC)

HCC is the 6th most common tumor worldwide, usually treated by surgical interventions. Since unresectable tumors shorten patient’s survival; it is of utmost importance to find appropriate treatments. Taxanes have shown to inhibit cell growth, induce apoptosis either alone or hand in hand with other cytotoxic agents (Geng et al., 2003; Okano et al., 2007; Zhang et al., 2005; Yuan et al., 2000) and besides, due to unfavorable outcome of administered drugs, targeted interventional therapies like Ultrasound and Intrarterial Paclitaxel (Kang et al., 2010; Bseiso et al., 2002) on localized or metastasized tumors using taxanes have been tried in preclinical and clinical investigations and therefore, they may represent novel strategies for chemotherapy in liver cancer.

Gastric Cancer and Pancreatic Cancer

Since gastric carcinoma has been the first cause of cancer death of the 20th century, plenty of researches have been on the platform with some disappointing results; taxotere being a novel class of anti-cancer agent, was mainly used as a second line drug in chemotherapy which proved its beneficial outcomes on gastric carcinoma cell lines in laboratory experiments either as monotherapy, with other synergistic drugs or in combination with radiation; moreover, pancreatic cancer cells also displayed similar results (Nakahara et al., 2003; Balcer-Kubiczek et al., 2006; Balcer-Kubiczek et al., 2008). Pancreatic adenocarcinoma (PAC) is an aggressive disease with grim prognosis and MDR is mediated mostly by P-glycoprotein; but somehow neoadjuvant therapies have proved otherwise (Sherman and Fine, 2001; Liu et al., 2001; Lui et al., 2001); so better results are to be expected in clinical trials.

Others

Some other cancers that have underwent in vitro studies over past few years coming out with satisfactory results are cell lines of oropharyngeal epidermoid tumors (Caraglia et al., 2005) where Docetaxel and FIT caused substantial effects on cell suicide mechanisms; in head and neck squamous cell carcinoma (Raitanen et al., 2004) sensitivities varied in different cell lines though effectiveness of taxanes could not be ruled out; anaplastic thyroid carcinoma (Meng et al., 2008; Pushkarev et al., 2008) deepened the mechanism related to G1/S transition as well as expression of Pin1 which could be involved in drug induced cell death, thus discovering some new facets of taxanes; osteosarcomas (Wei et al., 2002) and lymphomas (Zhou et al., 1999) responded very well to Taxol, so in cases of refractory chemotherapy they could be futured in oncological studies; as for leukemias (Ross et al., 1997) enhancement drug therapy has shown to increase cellular toxicity in cancer cells resulting in anti-proliferation whereas in colonic cancer (Wang et al., 2005) radiation together with new formulation of Docetaxel lead to targeted action over Lovo adenocarcinoma cell line.

In brief, those experimental trials have provided a theoretical basis for the clinical treatment of several cancers. As without proper knowledge about taxanes mechanism of actions, pharmacokinetics and resistance protocols in those cancers, they would have never been able to be validated for clinical trials. So, laboratory studies are a must and they should be perpetually carried out so that newer treatment modalities could be unveiled for our patients’ sake.

Most Solicited Taxanes in Clinical Oncological Trials

Clinical studies are on the deck since the discovery of these anti-mitotic drugs; they have given oncologists, scientific researchers and drug companies a foresight for their future consideration and development in the field of cancer. Moreover, many trials in numerous countries have been carried out with outstanding and critical outcomes which have enlightened the pathway for proper treatment and care of cancer patients.

Taxol® (Paclitaxel)

For past two decades, Taxol has been undergoing infinite number of clinical studies in many cancer patients, in order to know about several factors regarding their usefulness as potential anti-neoplastic agents.

Accumulating evidence from clinical trials has shown
that Taxol alone in relapsed or platinum resistant patients was active but however, poor prognosis hampered its single use (Gore et al., 1995); but Taxol along with platinum are a blessing in ovarian cancer confirmed by the GOG (Gynaecological Oncology Group), European-Canadian Intergroup Study and AGO (Arbeitsgemeinschaft Gynaekologische Onkologie). A phase III study comparing cisplatin-paclitaxel with carboplatin-paclitaxel as first line of treatment (Du Bois et al., 2003), underlined that the latter was superior in all terms of response rate (RR), progression free survival (PFS) and median overall survival (OS) time; therefore showing its preference for effective cancer management and could be considered for an option in advanced ovarian carcinoma. Moreover, another phase III randomized control trial conducted by GOG in patients with stage III ovarian tumor where intravenous Taxol along with intraperitoneal injection of cisplatin and Taxol every 3 weeks for 6 cycles showed that intraperitoneal chemotherapy needs to be encouraged in patients who had transcoelomic dissemination due to its numerous advantages like increase OS from 18.3 to 23.8 and PFS from 49.7 to 65.6 months (Armstrong et al., 2006) which is quite significant; despite the fact that higher levels of toxicity was recorded. Moreover, doctors, paramedical staffs and families should talk the patients in completing their cycles as in most trials it was noted that there was poor compliance and this may have altered consequences. Sex cord-stromal ovarian tumor (SCSTs) is an indolent cancer whose outcome was acceptable with Taxol, 89% were disease free and in recurrent patients there was 42% RR; that showed it is a pretty active agent in this type of cancer (Brown et al., 2004). Another interesting trial was with EDRA (extreme drug resistance assay) (Joo et al., 2009) which is an independent predictor for improved survival rates, can also assess benefits of triple therapy and can guide in the selection of appropriate chemotherapy drugs, as maybe all individuals do not have the same responses to anti-cancer treatments.

Several monotherapies or conjoint therapies were used before introduction of taxanes into treatment regimen for breast cancer. Taxol plus anthracyclines increased RR, median follow up was > 40 months with absence of cross resistance with them (Piccart-Gebhart et al., 2008); thus patients’ survival rates were prolonged. In a phase III study for MBC (metastatic breast cancer) paclitaxel and nucleoside analogue-gemcitabine were found to be the most active systemic chemotherapeutic combination enhancing RR, PFS and even OS (Gudena et al., 2008) while in a phase II trial, triple therapy constituting of taxol, doxorubicin and gemcitabine even the overall response rate (ORR) and time to progression (TTP) was raised (Gudena et al., 2008) so pointing out efficacy of taxanes in combined therapy for breast cancer management; other striking three drug combinations were nab-paclitaxel, gemcitabine plus bevacizumab with frequent cycles representing a important selection as first line treatment for MBC; besides, even Taxol with bevacizumab, increased PFS and ORR (Chan et al., 2010; Miller et al., 2007). The latter presented at ASCO 2010 showed its efficacy alone in MBC; nevertheless, recently FDA stated that recent studies showed failure of bevacizumab in treatment of breast cancer. On the other hand; gemcitabine, nab-paclitaxel and trastuzumab combination, TTP was appreciated but OS saw failure; taxol combined even with tamoxifen (Wenzel and Steger, 2006) showed some favorable results; so it can be deduced that in order to achieve disease free survival taxol should be tried with several adjuvants to meet up to its expectancy. A recent publication, profiled breast conservation surgery after pre-operative chemotherapy (El-Sayed et al., 2010) in females with locally advanced non-metastatic breast cancer which is a completely novel facet in breast cancer management; anticipated to have good prospects for the future.

Taxol in lung cancer has been studied on different schedules and dosages for SCLC and NSCLC, whose dose ranged from 175 mg/m² to 200mg/m² and has been flattered even as single therapy in the first line of treatment (Calderoni and Cerny, 2001; Socinski 1999) in phase I, II and III where it accounted for 1 year survival rate rise and improved QoL (Quality of Life). Cisplatin and taxol demonstrated good activity in NSCLC but carboplatin with Taxol was far better in terms of RR and PFS and was easily administered even in outpatient department (Calderoni and Cerny, 2001); in stage III unresectable NSCLC success was reached with cisplatin, gemcitabine, taxol or carboplatin and chest radiotherapy resulting in RR of 66% while taxol, gemcitabine and cisplatin achieved RR of only 55%; hence showing relevance of radiation (Calderoni and Cerny, 2001); even bitherapy of taxol combined gemcitabine could palliate symptoms and improve OS (Lam et al., 1995). The Eastern Cooperative Oncology group (ECOG) trial (Sandler et al., 2006) had highlighted a tremendous increase in survival rate, RR and PFS with paclitaxel, carboplatin and bevacizumab hence could be of potential success in other anticipated trials. Nevertheless, a phase III study revealed that taxol and carboplatin were not as efficient as gefitinib in advanced pulmonary adenocarcinoma which greatly improved QoL (Mok et al., 2009); so we need to deepen our researches to find an optimal treatment protocol.

Gastric cancer if in its early stages, surgical resection with post operative radiotherapy is usually the step followed; nevertheless, a clinical study showed that pre-operative Taxol based chemoradiotherapy in stage II/III localized gastric or gastroesophageal adenocarcinoma had better pathological response with better control of metastasis where patients lived substantially for longer period of time (Ajani et al., 2005). On the other hand, a phase II study of Taxol combined with carboplatin in previously treated 5-fluorouracil and platinum in advanced gastric cancer (AGC) revealed to be feasible as the RR was good with an OS of 40 months in all responders to therapy (Chang et al., 2005); however, a new Taxol formulation derived from Taxus Chinensis (Genexol®) along with cisplatin in AGC had a 1-year survival rate of 50.2% which makes us think that this combination could be used as a first line of treatment in cases of failure with 5-fluorouracil (Park et al., 2004). Even control of malignant ascites from gastric cancers by Taxol has proved itself; thus it can be taken into consideration for future management of such cases (Kobayashi et al., 2006).

Other important features and results of Taxol’s efficiency
have come from studies related to metastatic melanoma where there are very few proper chemotherapeutic treatments but paclitaxel and carboplatin in low doses used weekly had good PFS (Rao et al., 2005); while advanced prostate cancer has been treated via various anti-cancer agents; nevertheless, due to its rapid refractory characteristics, there has been poor prognosis but newer regimens like combination of triple therapy with taxol, carboplatin and estramustine phosphate considered as safe with high RR are more warranted (Kelly et al., 2001) However, some cancers like advanced pancreatic carcinomas (Ryan and Grossbard, 1998) in phase II study with Taxol had poor RR and OS of only 5 months compared to tautomere; as well as metastatic and recurrent head and neck though being sensitive to paclitaxel and platinum with RR of 64% but best results was achieved while using taxotere combination (Al-Sarraf et al., 2002).

Hence, we can deduce that in some cancers the response to taxol may be less in comparison to taxotere, so it is an important finding which helps us to achieve explicit treatment in appropriate malignancies. Somehow, taxol coated stents for malignancy causing biliary obstruction has shown to be really efficacious (Suk et al., 2007).

**Taxotere®**

Docetaxel used either in phase I/II/III trials has been somewhat preferred over paclitaxel in several solid tumors including ovarian cancer since ongoing trials, as it retains an important degree of clinical activity. Besides, due to having a shorter infusion period than taxol with good RR and OS in even chemonaive patients (Katsumata 2002), it is much more accepted than its parent drug. Moreover, several studies using taxotere as single agent, in combination with platinum analogues or even as triple therapy (Mu¨enpaa¨a 2003) (docetaxel, carboplatin and epirubicin) has been having maximum activity in advanced ovarian carcinomas with promising data. A phase III randomized trial conducted to compare various aspects of docetaxel-carboplatin with paclitaxel-carboplatin revealed that they have similar PFS, RR and OS except that the difference lies in their toxicities (Vasey et al., 2003). Phases I/II studies found that ovarian cancers resistant to taxol or platinum as single agents were sensitive to docetaxel and the SCOTROC (Scottish Randomized Trial in Ovarian Cancer) notified its use even in newly diagnosed epithelial ovarian carcinoma (Vasey 2003), which shows that it has got great potency.

Breast cancer has been previously treated with anthracyclines regimen for a long time until the introduction of taxanes in management of MBC showed that both had similar effects when docetaxel was compared to doxorubin; besides, it was found that taxanes were of poor response as single agents but effective in combination with potential RR and PFS (Piccart-Gebhart et al. 2008). In fact, docetaxel has been a more wanted one than taxol due to favourable outcomes with cyclophosphamide and taxotere either pre-operatively or post-operatively in node positive MBC. Doxorubin 50mg/m², cyclophosphamide 500mg/m² and docetaxel 75 mg/m² as adjuvant therapy for MBC in a Hungarian multicentric phase III trial was found to increase PFS and OS in both advanced and early breast cancers (Wenzel and Steger, 2006; Boer et al., 2003) showing its high impact as well as combination of gemcitabine and taxotere in a phase II and III trials showing safety, QoL, ORR and OS (Gudena et al., 2008). Furthermore, AVADO phase III trial, ATHENA and RIBBON-1 phase III improved PFS was seen with EU approved bevacizumab and docetaxel combination therapy (Chan et al., 2010).

Several polytherapies have been on the run to improve both cancer and patient outcomes. Some trials conducted have declared that docetaxel can either be used as first or second line settings in lung cancer. NSCLC phase II reported superior activity discerned by taxotere as single agent or even in platinum pre-treated cases (Calderoni and Cerny, 2001) while, several trials of carboplatin with docetaxel has revealed to be not only cost effective (Meera et al., 2008) but also reliable RR. Somehow, irinotecan and docetaxel as second line therapy has prolonged TTP, efficacy and was well tolerated with RR of 20% in NSCLC together with taxotere 60-90 mg/m² and gemcitabine 800-900 mg/m² having RR of 37% (Pectasides et al., 2005). Addition of radiotherapy has been discovered to be both feasible and well tolerated with RR of 81% (Calderoni and Cerny, 2001); nevertheless, there is lack of profiling for treatment of SCLC with docetaxel.

Men most touched type of cancer being prostate needs emergency sorting out of novel chemotherapies. Docetaxel tried in various studies has declared many good alternatives like as in monotherapy where it secludied an OS of 27 months in responders which underlines its efficacy; taxotere plus estramustine a phase III study showed a decrease of 80% PSA and its combination with radiotherapy had an OS of 13.5 months (Khan et al., 2003) in advanced prostatic carcinomas; however, taxotere and prednisolone in a comparative trial with prostatic metastasis of the bone showed an increase in RR, PSA decrease, improved QoL and subsided pain (Tannock et al., 2004); in others tritherapy was found to be an alternative treatment whereas there was complete pathological response in some. It has been deduced that an earlier and rapid use of docetaxel is bound to be having an outstanding prediction of results.

The world’s leading cancer death related to gastric cancer known to be cured by surgical intervention needs chemotherapeutic approaches in cases of distant metastases; amongst which Taxotere has been found to be a potentially active drug as single agent in a phase II where those who had partial response or stable disease had received 3 courses of 100mg/m² docetaxel every 3 weeks (Cosimo et al., 2003). Bitherapy of docetaxel with 5-fluorouracil (5-FU) or irinotecan or cisplatin or epirubicin had relevant overall response and clinical benefits in local or advanced gastric carcinoma. The three-drug regime constituting of 5-FU, docetaxel and cisplatin in phases I/II (Cosimo et al., 2003; Roth and Ajani, 2003) was of valuable interest to clinicians as RR was of 54% and all other parameters too were acceptable for inclusion in relevant phase III which was thus carried out and found to be profitable for cancer patients. Gemcitabine and Docetaxel have been considered to be targeted chemotherapeutic drugs for pancreatic cancers
Major Side Effects Associated with Taxanes

Hematopoietic and neurologic toxicities have been the most common problematic side effects encountered with taxol and taxotere. However, hypersensitivity reactions have been dealt with premedication like for paclitaxel, i.v histamine antagonists and oral corticosteroids at least 24 hours prior are administered while for docetaxel, dexamethasone 8 mg bd for 3 days is given (Guastalla III and Die’aras, 2003). Usually Taxol is frequently associated with sensory neuropathy/ peripheral neuropathy characterized by burning and tingling sensations of the fingers and toes. A study of cisplatin and taxol revealed that the increased rate of infusion caused more sensory neuropathy than a slower rate of drug administration (Guastalla III and Die’aras, 2003). and also carboplatin and taxol combination showed to be less neurotoxic; a trial demonstrated that melatonin (Nahleh et al., 2010) could represent a possible strategy for diminishing incidence of neuropathy while others like gemcitabine and paclitaxel lead to grade 3-4 neutropenia with thrombocytopenia along with fatigue, motor neuropathy and raised LFTs (Gudena et al., 2008; Calderoni and Cerny, 2001). But, gemcitabine and nab-paclitaxel prevented profound neutropenia (52% only) and addition of bevacizumab resolved untreated thrombocytopenia, so this could be preferred over other treatment modalities. Taxotere on the other side, causes high incidence of neutropenia including febrile neutropenia; where a gemcitabine and docetaxel combination caused 82% neutropenia of grade 3-4 with thrombocytopenia while with carboplatin it worsens and lead to grade 4 neutropenia; capecitabine with taxotere also lead to similar side effects including alopecia, hand and foot syndrome. Both Taxol and Taxotre lead to severe febrile neutropenia and bone marrow suppression but with taxol it usually recovers much faster than taxotere. Nowadays, with implementation of granulocyte-colony stimulating factor (G-CSF), this side effect has been found to be diminished in cancer patients. Taxanes and anthracyclines resulted in a lower hazard ratio and were so well appreciated in MBC (Piccart-Gebhart et al., 2008). Other drawbacks are alopecia which starts with 10-14 days of treatment but is reversible in nature and represents no clinical risks; fluid retention accounts for less than 10% of side effects and is easily resolved via early administration of diuretics and premedication of steroids; myalgias, arthralgias (Markman 2003) is more linked with paclitaxel toxicity; nail changes can be resolved using coolers (Minisini et al., 2003), some emotional unstability has also been there along with nausea and vomiting which might also be due to ototoxicity caused by taxanes but deeper investigations are needed (Sarafraz and Ahmadi, 2008). Despite these disadvantages, the utilities of taxanes in cancer cannot be disregarded as they present more good than bad.

Conclusion

“Taxanes” a 7 letter word which means a lot in the field of cancer treatment, though their mechanism of action is clear to us in numerous cancers but there still remains several facets of them to be unveiled. All those who contributed in the field of cancer in relation to taxanes are to be endlessly thanked including our patients who have helped researchers, doctors, pharmaceutical companies seen light at the end of the tunnel. But there are still miles to go before curative treatment for cancer patients are delineated; encouragement and faith is there to continue with those eternal “oncological explorations” which represent a blessing in cancer treatment.
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