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

Asian Pacific J Cancer Prev, **12**, 837-851

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 infact 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

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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 formulations derived like Abraxane not using CrEL (cremophor EL®), Taxoprexin® (Docosahexaenoic acid- paclitaxel) bounded to natural fatty acids, XytotaxTM (paclitaxel polyglumex), TOCOSOL (R) palitaxel, 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 homolgs 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 expressions 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 isoforms 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-*k*B (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-*k*B 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 CDK4 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 (Blagoskionny et al., 1995; Chang et al., 2006) and downregulate the proto-oncogene c-myc (Yim et al., 2004; El Khyari 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 conjugates, anti-oestrogens, cyclosporine-A and many others (Wang and Weider, 2004; Kucukzeybek et al., 2008; Rabi and Bishayee, 2009; Nehme et al., 2001; Sun et al., 2007; Nakahara et al., 2003; Bryan et al., 2010; Ferlini et al., 1998; Kim et al., 2006) in order to look for a competent therapeutic strategy for cancer patients. Moreover, the

efficacy of the taxanes alone or in combination can be determined using apoptosis serum biomarkers like cyt-c, nucleosomal DNA and caspase-cleaved cytokeratin 18 (CK18-Asp396) (Kramer et al., 2006) which can help oncologists to know how many cycles are needed before resistance is achieved in patients or whether the clinical treatment is effective or not. Through the decades, we have come to know that the sensitivity and level of apoptosis 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; Sgadari 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, Kaposi's sarcoma, transitional cell carcinoma 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 (Tsui 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 anti-angiogenic 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), GSTπ 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, NF*k*-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 if not eliminate chemotherapy induced 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; Sissung 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

cell lines (McGuire et al., 1989; Katsumata 2003); the YY1 gene expression (Matsumura et al., 2009) was found to be correlating with ovarian cancer survival and somehow, taxanes used in conjuction with knock out of some genes (Sood et al., 2004; Halder et al., 2005), platinum agent or other drugs (Katsumata 2003; Ma"enpa"a 2003) could greatly prevent metastasis and improve the quality of life of affected patients (Guastalla III and Die'ras, 2003) in proper clinical trials. However, resistance in advanced cases easily follows and accounts for less than 50% of 5 year survival rate; so the need to develop methods like intraperitoneal chemotherapy (De Breea 2006) or newer molecules (Mcdaid and Horwitz, 2001; Strobel et al., 1998) capable of preventing, reversing resistance or increasing taxane sensitivity may throw some light in cancer trials.

Melanoma

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), progession 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 canrcinoma. 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 have 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 chemotherapeutic 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/m^2 to 200mg/m^2 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 taxotere; 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 chemonaïve 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 (Ma"enpa"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 doxorubicin; 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/m^2, cyclophosphamide 500mg/m^2 and docetaxel 75 mg/m^2 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/m^2 and gemcitabine 800-900 mg/m^2 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 secluded 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/m^2 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

(Ryan and Grossbard, 1998); along with radiotherapy as both drugs are known to be potential radiosensitizers improving treatment in thoses cases that are inoperable. Recently, a final phase II trial of Docetaxel with Capecitabine had 53.9% who remained alive for more than 6 months, 14.7% for more than a year and better quality of life (Katopodis et al., 2010) could be used rather in first line of treatment than second line where it was not so favorable. Head and neck cancers with taxanes was described as being relevant by Schrivjers and Vermorken whilst, patient friendly combination was found to be with 5-FU, cisplatin and docetaxel in the treatment of such cancers (Al-Sarraf 2002; Posner et al., 2005). A phase II trial involving taxotere in unresectable cholangiocarcinoma had made a phase III warranted (Pazdur et al., 1999) proving its efficacy; however docetaxel in advanced hepatocellular carcinoma had some disappointing evidences (Hebbar et al., 2006) and has no effect in colon cancer which says that taxanes may not respond so well in all types of cancers but the majority of outcomes has definitely been a true blessing for cancer patients.

Abraxane®

Already approved by FDA for breast cancer wherever there has been failure of chemotherapy or relapse has occurred; several countries like Canada are implementing it as first line of treatment in breast cancer patients. Moreover, a phase III trial of lung cancer reports success with improved ORR in NSCLC patients and further studies are still ongoing in other types of carcinomas to relate its superiority over its predecessors; as it is a great formulation of the future.

Others

Like Taxoprexin® and Xytotax TM (Hennenfent and Govindan, 2006) have been used in phases I-III trials in different cancer treatment either as single or combination with standard chemotherapeutic medications, having good results of RR, ORR and PFS in NSCLC, MBC and prostate along with less side effects obtained with routinely used taxanes, but more trials are necessitated to confirm their activities in cancer management.

On the other hand, there are many ongoing trials (Clinical Trials.gov, 2010) at the moment, some are active, currently recruiting and others have been completed for innumerable number of carcinomas; showing that the patients' beliefs in taxanes are founded from previous studies and this should be continuing till an exceptional cure is exhumed.

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 24hours prior are administered while for docetaxel, dexamethasone 8mg bd for 3 days is given (Guastalla III and Die'ras, 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'ras, 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 Taxotere 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.

Acknowledgements

This work was supported all the way through by the Major State Science and Technology Special Project of Chongqing Innovative Medicine Incubation Base; Platform for New Drug Design and Screening (2010ZX9401-306-1-1).

We dedicate this review article to all cancer patients under treatment, my late daughter and on the other hand also deeply thank Dr. Mandarry M. Tasleem (Department of General Surgery, First Affiliated Hospital, Chongqing Medical University, China), Dr. Fauzee A. Raffick (Department of Public Health, SSRN Hospital, Mauritius), and Ms Fauzee F. B. Ayeshah (Department of Pharmacy, Rhodes University, South Africa) for their support, critical reading of our manuscript and suggesting new relevant items to be included.

References

Al-Sarraf M (2002). Treatment of Locally Advanced Head and Neck Cancer: Historical and Critical Review. *Cancer control*, **9**, 387-99.

Ajani JA, Mansfield PF, Crane CH et al (2005). Paclitaxel-Based Chemoradiotherapy in Localized Gastric Carcinoma: Degree of Pathologic Response and Not Clinical Parameters Dictated Patient Outcome. *J Clin Oncol*, **23**, 1237-44.

Amerongen RV, Berns A (2006). TXR1-mediated thrombospondin repression: a novel mechanism of resistance to taxanes? *Genes Dev*, **20**, 1975-81.

Antonello Calderoni, Thomas Cerny (2001). Taxanes in lung cancer: a review with focus on the European experience. *Crit Rev Oncol Hematol*, **38**, 105–27.

Armstrong DK, Bundy B, Wenzel L et al (2006). Intraperitoneal Cisplatin and Paclitaxel in Ovarian Cancer. *N Engl J Med*, **354**, 34-43.

Balcer-Kubiczek EK, Attarpour M, Jiang J et al (2006). Cytotoxicity of docetaxel (Taxotere) used as a single agent and in combination with radiation in human gastric, cervical and pancreatic cancer cells. *Chemotherapy*, **52**, 231-40.

Balcer-Kubiczek EK, Attarpour M, Wang JZ et al (2008). The Effect of Docetaxel (Taxotere®) on Human Gastric Cancer Cells Exhibiting Low-Dose Radiation Hypersensitivity. *Clinical Medicine: Oncology*, **2**, 301–11

Bissery MC, Guénard D, Guéritte-Voegelein F et al (1991). Experimental antitumor activity of taxotere (RP 56976, NSC 628503), a taxol analogue. *Cancer Res*, **51**, 4845-52.

Blagosklonny MV, Schulte TW, Nguyen P et al (1995). Taxol Induction of p21WAF1 and p53 Requires c-raf-1. *Cancer Res*, **55**, 4623-26.

Blagosklonny MV, Schulte T, Nguyen P et al (1996). Taxol-induced Apoptosis and Phosphorylation of Bcl-2 Protein Involves c-Raf-1 and Represents a Novel c-Raf-1 Signal Transduction Pathway. *Cancer Res*, **56**, 1851-54.

Blagosklonny MV, Giannakakou P, El-Deiry W et al (1997). Raf-1/bcl-2 Phosphorylation: A Step from Microtubule Damage to Cell Death. *Cancer Res*, **57**, 130-5.

Boer K, Lang I, Juhos E et al (2003). Adjuvant Therapy of Breast Cancer with Docetaxel-Containing Combination (TAC)- A Hungarian experience in the BCIRG 001 trial. *Pathol Oncol Res*, **9**, 166-9.

Braakhuis BJ, Hill BT, Dietel M et al (1994). In vitro antiproliferative activity of docetaxel (Taxotere), paclitaxel (Taxol) and cisplatin against human tumour and normal bone marrow cells. *Anticancer Res*, **14**, 205-8.

Brown I, Shalli K, McDonald SL et al (2004). Reduced expression of p27 is a novel mechanism of docetaxel resistance in breast cancer cells. Breast Cancer Res, 6, R601-R607. Doi: 10.1186/bcr918

Brown J, Shvartsman HS, Deavers MT et al (2004). The activity of taxanes in the treatment of sex cord-stromal ovarian tumors. *J Clin Oncol*, **22**, 3517-23.

Bryan M, Pulte ED, Toomey KC et al (2010). A pilot phase II trial of all-trans retinoic acid (Vesanoid) and paclitaxel (Taxol) in patients with recurrent or metastatic breast cancer. Invest New drugs, doi: 10.1007/s10637-010-9478-3.

Bseiso A, Verschraegen CF, Balat O et al (2002). Feasibility of Intrahepatic Arterial Paclitaxel in Two Patients http://www.ispub.com/ostia/index.php?xmlFilePath=journals/ijo/vol1n2/taxol.xml. Accessed 20 November 2010

Callagy GM, Pharoah PD, Pinder SE et al (2006). Bcl-2 Is a PrognosticMarker in Breast Cancer Independently of the Nottingham Prognostic Index. *Clin Cancer Res*, **12**, 2468-75.

Canfield SE, Zhu K, Williams SA et al (2006). Bortezomib inhibits docetaxel-induced apoptosis via a p21-dependent mechanism in human prostate cancer cells. *Mol Cancer Ther*, **5**, 2043-50.

Caraglia M, Giuberti G, Marra M et al (2005). Docetaxel induces p53-dependent apoptosis and synergizes with farnesyl transferase inhibitor r115777 in human epithelial cancer cells. *Front Biosci*, **10**, 2566-75.

Chan DC, Earle KA, Zhao TLM et al (2002). Exisulind in Combination with Docetaxel Inhibits Growth and Metastasis of Human Lung Cancer and Prolongs Survival in Athymic Nude Rats with Orthotopic Lung Tumors. *Clin Cancer Res,* **8**, 904–12.

Chan A, Miles DW, Pivot X (2010). Bevacizumab in combination with taxanes for the first-line treatment of metastatic breast cancer. Ann Oncol, doi:10.1093/annonc/mdq122

Chang HM, Kim TW, Ryu BY et al (2005). Phase II Study of Paclitaxel and Carboplatin in Advanced Gastric Cancer Previously Treated with 5-Fluorouracil and Platinum. *Jpn J Clin Oncol*, **35**, 251–55.

Chang JT, Chang GC, Jiunn-Liang Ko, et al (2006). Induction of tubulin by Docetaxel is associated with p53 status in human non small cell lung cancer cell lines. *Int J Cancer*, **118**, 317–25.

Chun E, Lee KY (2004). Bcl-2 and Bcl-xL are important for the induction of paclitaxel resistance in human hepatocellular carcinoma cells. *Biochem Biophys Res Comm*, **315**, 771-9.

Clinical Trials.gov (2010). http://www.clinicaltrials.gov. Accessed 3 January 2011

Cunha KS, Reguly ML, Graf U et al (2001). Taxanes: the genetic toxicity of paclitaxel and docetaxel in somatic cells of Drosophila melanogaster. *Mutagenesis*, **16**, 79-84.

De Breea E, Theodoropoulosb PA, Rosingc H et al (2006). Treatment of ovarian cancer using intraperitoneal chemotherapy with taxanes: From laboratory bench to bedside. *Canc Treat Rev*, **32**, 471-82.

Derry WB, Wilson L, Jordan MA (1995). Substoichiometric Binding of Taxol Suppresses Microtubule Dynamics. *Biochem*, **34**, 2203-11.

Di Cosimo S, Ferretti G, Fazio N et al (2003). Docetaxel in Advanced Gastric Cancer Review of the Main Clinical Trials. *Acta Oncol*, **42**, 693–00.

Du Bois A, Lu¨ck HJ, Meier W et al (2003). A Randomized Clinical Trial of Cisplatin/Paclitaxel Versus Carboplatin/Paclitaxel as First-Line Treatment of Ovarian Cancer. *J Natl Cancer Inst*, **95**, 1320-30.

El Khyari S, Bourgarel V, Barra Y et al (1997). Pretreatment by tubulin agents decreases C-MYC induction in human colon carcinoma cell line HT29-D4. *Biochem Biophys Res Commun*, **231**, 751-4.

El-Sayed MI, Maximous DW, Aboziada MA et al (2010). Feasibility of breast conservation after neoadjuvant taxene based chemotherapy in locally advanced breast cancer: a Prospective Phase I trial. *Annals of Surgical Innovation and Research*, **4**, 5.

Fabbri F, Carloni S, Brigliadori G et al (2006). Sequential events of apoptosis involving docetaxel, a microtubule-interfering agent: a cytometric study. *BMC Cell Biol*, doi:10.1186/1471-2121/7/6.

Feng Z, Zhao G, Yu L et al (2010). Preclinical efficacy studies of a novel nanoparticle-based formulation of paclitaxel that out-performs Abraxane. *Cancer Chemother Pharmacol*, **65**, 923–30.

Ferlini C, Di Stefano M, Marone M et al (1998). The synergistic anti-tumour activity of ICI 182,780 in combination with docetaxel is mediated by P-glycoprotein inhibition. *Endocr Relat Canc*, **5**, 315-24.

Ferlini C, Cicchillitti L, Raspaglio G et al (2009). Paclitaxel Directly Binds to Bcl-2 and Functionally Mimics Activity of Nur77. *Cancer Res*, **69**, 6906.

Ferlini C, Raspaglio G, Mozzetti S, et al (2003). Bcl-2 Down-Regulation Is a Novel Mechanism of Paclitaxel Resistance. *Mol Pharm*, **64**, 51–8.

Fujita K, Sano D, Kimura M et al (2007). Anti-tumor effects of bevacizumab in combination with paclitaxel on head and neck squamous cell carcinoma. *Oncology Rep*, 18, 47-51.

Galaup A, Opolon P, Bouquet C et al (2003). Combined Effects of Docetaxel and Angiostatin Gene Therapy in Prostate Tumor Model. *Molecular Therapy,* **7**, 731-40.

Gen news highlights (2010). Abraxis Reports Phase III Success with Abraxane in First-Line NSCLC.http://www.genengnews.com/gen-news-highlights/abraxis-reports-phase-iii-success-with-abraxane-in-first-line-nsclc/81243495/. Accessed 4 November 2010

Geng CX, Zeng ZC, Wang JY (2003). Docetaxel inhibits SMMC-7721 human hepatocellular carcinoma cells growth and induces apoptosis. *World J Gastroenterol*, **9**, 696-00.

Giannakakou P, Gussio R, Nogales E et al (2000). A common pharmacophore for epothilone and taxanes: molecular basis for drug resistance conferred by tubulin mutations in human cancer cells. *PNAS*, **97**, 2904-09.

Giannakakou P, Robey R, Fojo T et al (2001). Low concentrations of paclitaxel induce cell type-dependent p53, p21 and G1/G2 arrest instead of mitotic arrest: molecular determinants of paclitaxel-induced cytotoxicity. *Oncogene*, **20**, 3806-13.

Gonçalves A, Braguer D, Kamath K et al (2001). Resistance to Taxol in lung cancer cells associated with increased microtubule dynamics. *PNAS*, **98**, 11737-42.

Gore ME, Levy V, Rustin G et al (1995). Paclitaxel (Taxol) in relapsed and refractory ovarian cancer: the UK and Eire experience. *Br J Cancer*, **72**, 1016-19.

Grant DS, Williams TL, Zahaczewsky M et al (2003). Comparison of antiangiogenic activities using Paclitaxel (TAXOL) and Docetaxel (TAXOTERE). *Int J Cancer*, **104**, 121-9.

Gudena V, Montero AJ, Glück S (2008). Gemcitabine and taxanes in metastatic breast cancer: a systematic review. *Therapeutics and Clinical Risk Management*, **4**, 1157–64.

Guastalla III JP, Die´ras V (2003). The taxanes: toxicity and quality of life considerations in advanced ovarian cancer. *Br J Cancer*, **89**, S16 – S22.

Guo WJ, Chen TS, Wang XP et al (2010). Taxol induces concentration-dependent apoptotic and paraptosis-like cell death in human lung adenocarcinoma (ASTC-a-1) cells. *J X Ray Sci Tech*, **18**, 293-08.

Guo XL, Lin GJ, Zhao H et al (2003). Inhibitory effects of docetaxel on expression of VEGF, bFGF and MMPs of LS174T cell. *World J Gastroenterol*, **9**, 1995-8.

Haass NK, Sproesser K, Nguyen TK et al (2008). The Mitogen-Activated Protein/Extracellular Signal-Regulated Kinase Kinase Inhibitor AZD6244 (ARRY-142886) Induces Growth Arrest in Melanoma Cells and Tumor Regression When Combined with Docetaxel. *Clin Cancer Res*, **14**, 230-9.

Haldar S, Chintapalli J, Croce CM (1996). Taxol Induces bcl-2 Phosphorylation and Death of Prostate Cancer Cells. *Cancer Res*, **56**, 1253-55.

Halder J, Landen CN Jr, Lutgendorf SK et al (2005). Focal adhesion kinase silencing augments docetaxel-mediated apoptosis in ovarian cancer cells. *Clin Cancer Res*, **11**, 8829-36.

Hebbar M, Ernst O, Cattan S et al (2006). Phase II Trial of Docetaxel Therapy in Patients with Advanced Hepatocellular Carcinoma. *Oncology*, **70**, 154-8.

Hennenfent KL, Govindan R (2006). Novel formulations of taxanes: a review. Old wine in a new bottle? *Ann Oncol*, **17**, 735–49.

Herbst RS, Madden TL, Tran HT et al (2002). Safety and Pharmacokinetic Effects of TNP-470, an Angiogenesis Inhibitor, Combined With Paclitaxel in Patients With Solid Tumors: Evidence for Activity in Non–Small-Cell Lung Cancer. *JCO*, **20**, 4440-7.

Hotchkiss KA, Ashton AW, Mahmood R et al (2002). Inhibition of Endothelial Cell Function in Vitro and Angiogenesis in Vivo by Docetaxel (Taxotere): Association with Impaired Repositioning of the Microtubule Organizing Center. *Mol Cancer Ther*, **1**, 1191–00.

Hu H, Li GX, Wang L et al (2008). Methylseleninic Acid Enhances Taxane Drug Efficacy against Human Prostate Cancer and Down-Regulates Antiapoptotic Proteins Bcl-XL and Survivin. *Clin Cancer Res*, **14**, 1150-8.

Ibrado AM, Huang Y, Fang G et al (1996). Bcl-xL overexpression inhibits taxol-induced Yama protease activity and apoptosis. *Cell Growth Differ*, **7**, 1087-94.

Ichite N, Chougule MB, Jackson T et al (2009). Enhancement of docetaxel anticancer activity by a novel diindolylmethane compound in human non-small cell lung cancer. *Clin Cancer Res*, **15**, 543-52.

Ikeda H, Taira N, Hara F et al (2010). The estrogen receptor influences microtubule-associated protein tau (MAPT) expression and the selective estrogen receptor inhibitor fulvestrant downregulates MAPT and increases the sensitivity to taxane in breast cancer cells. *Breast Cancer Res*, **12**, R43.

Ilgar NN and Arıcan GO (2009). Induction of apoptosis and cell proliferation inhibition by paclitaxel in FM3A cell cultures. *Afr J Biotech*, **8**, 547-55.

Inoue K, Chikazawa M, Fukata S et al (2003). Docetaxel Enhances the Therapeutic Effect of the Angiogenesis Inhibitor TNP-470 (AGM-1470) in Metastatic Human Transitional Cell Carcinoma. *Clin Cancer Res*, **9**, 886–99.

Iwao-Koizumi K, Matoba R, Ueno N et al (2005). Prediction of Docetaxel Response in Human Breast Cancer by Gene Expression Profiling. *J Clin Oncol*, **23**, 422-31.

Jiang CC, Yang F, Thorne RF et al (2009). Human melanoma cells under endoplasmic reticulum stress acquire resistance to microtubule-targeting drugs through XBP-1-mediated activation of Akt. *Neoplasia*, **11**, 436-47.

Jiang J, Huang H (2010). Targeting the Androgen Receptor by Taxol in Castration-Resistant Prostate Cancer. *Mol Cell Pharmacol*, **2**, 1-5.

Joo WD, Lee JY, Kim JH et al (2009). Efficacy of taxane and platinum-based chemotherapy guided by extreme drug resistance assay in patients with epithelial ovarian cancer. *J Gynecol Oncol*, **20**, 96-100.

Jordan MA, Toso RJ, Thrower D et al (1993). Mechanism of mitotic block and inhibition of cell proliferation by taxol at low concentrations. *PNAS*, **90**, 9552-6.

Jordan MA, Wendell K, Gardiner S et al (1996). Mitotic block induced in HeLa cells by low concentrations of paclitaxel (Taxol) results in abnormal mitotic exit and apoptotic cell death. *Cancer Res*, **56**, 816-25.

Jordan MA, Wilson L (1998). Microtubules and actin filaments: dynamic targets for cancer chemotherapy. *Curr Opin Cell Biol*, **10**, 123-30.

Jung CS, Zhou Z, Khuri FR et al (2007). Assessment of apoptosis-inducing effects of docetaxel combined with the proteasome inhibitor PS-341 in human lung cancer cells. *Cancer Biol Ther*, **6**, 749-54.

Kang J, Wu X, Wang Z et al (2010). Antitumor effect of docetaxel-loaded lipid microbubbles combined with ultrasound-targeted microbubble activation on VX2 rabbit liver tumors. *J Ultrasound Med*, **29**, 61-70.

Katopodis O, Polyzos A, Kentepozidis N et al (2010). Second-line chemotherapy with Capecitabine (Xeloda) and Docetaxel (Taxotere) in previously treated, unresectable adenocarcinoma of pancreas: the final results of a phase II trial. *Cancer Chemother Pharmaco*, doi: 10.1007/s00280-010-1329-6.

Katsumata N (2003). Docetaxel: an alternative taxane in ovarian cancer. *Br J Cancer*, **89**, S9 – S15.

Kelly WK, Curley T, Slovin S et al (2001). Paclitaxel, Estramustine Phosphate, and Carboplatin in Patients With Advanced Prostate Cancer. *J Clin Oncol*, **19**, 44-53.

Khan MA, Carducci MA, Partin AW (2003). The Evolving Role of Docetaxel in the Management of Androgen Independent Prostate Cancer. *J Urol*, **170**, 1709-16.

Kim CH, Yoo JS, Lee CT et al (2006). FHIT protein enhances paclitaxel-induced apoptosis in lung cancer cells. *Int J Cancer*, **118**, 1692–98.

Kirchmair R, Tietz AB, Panagiotou E et al (2007). Therapeutic Angiogenesis Inhibits or RescuesChemotherapy-induced Peripheral Neuropathy: Taxol- and Thalidomide-induced Injury of Vasa Nervorum is Ameliorated by VEGF. *Mol Ther*, **15**, 69–75

Klauber N, Parangi S, Flynn E et al (1997). Inhibition of Angiogenesis and Breast Cancer in Mice by the Microtubule Inhibitors 2-Methoxyestradiol and Taxol. *Cancer Res*, **57**, 81-6.

Klos KS, Zhou X, Lee S et al (2003). Combined Trastuzumab and Paclitaxel Treatment Better Inhibits ErbB-2-Mediated Angiogenesis in Breast Carcinoma through a More Effective Inhibition of Akt than Either Treatment Alone. *Cancer*, **98**, 1377-84.

Kobayashi M, Sakamoto J, Namikawa T et al (2006). Pharmacokinetic study of paclitaxel in malignant ascites from advanced gastric cancer patients. *World J Gastroenterol*, **12**, 1412-15.

Kramer G, Schwarz S, Hägg M et al (2006). Docetaxel induces apoptosis in hormone refractory prostate carcinomas during multiple treatment cycles. *Br J Cancer*, **94**, 1592-98.

Kucukzeybek Y, Gul MK, Cengiz E et al (2008). Enhancement of docetaxel-induced cytotoxicity and apoptosis by all-trans retinoic acid (ATRA) through downregulation of survivin (BIRC5), MCL-1 and LTbeta-R in hormone- and drug resistant prostate cancer cell line, DU-145. *J Exp Clin Cancer Res*, **27**, 37.

Lam WK, Tsang KWT, Ip MSM (1995). Chemotherapy for advanced non-small-cell lung cancer: role of paclitaxel and gemcitabine. *HKMJ*, **5**, 180-6.

Latimer P, Menchaca M, Snyder RM et al (2009). Aerosol Delivery of Liposomal Formulated Paclitaxel and Vitamin E Analog Reduces Murine Mammary Tumor Burden and Metastases. *Exp Biol Med*, **234**, 1244-52.

Lee LF, Haskill JS, Mukaida N et al (1997). Identification of Tumor-Specific Paclitaxel (Taxol)-Responsive Regulatory Elements in the Interleukin-8 Promoter. *Mol Cell Biol*, **17**, 5097–105.

Liebmann JE, Cook JA, Lipschultz C et al (1993). Cytotoxic studies of paclitaxel (Taxol) in human tumour cell lines. *Br J Cancer*, **68**, 1104–09.

Liu B, Staren E, Iwamura T et al (2001). Taxotere resistance in SUIT Taxotere resistance in pancreatic carcinoma cell line SUIT 2 and its sublines. *World J Gastroenterol*, **7**, 855-59.

Liu B, Staren E, Iwamura T et al (2001). Effects of Taxotere on invasive potential and multidrug resistance phenotype in pancreatic carcinoma cell line SUIT-2. *World J Gastroenterol*, **7**, 143-8.

Liu B, Staren ED, Iwamura T et al (2001). Mechanisms of Taxotere-Related Drug Resistance in Pancreatic Carcinoma. *J Surg Res*, **99**, 179-86 [abstract].

Liu R, Page C, Beidler DR (1999). Overexpression of Bcl-xL Promotes Chemotherapy Resistance of Mammary Tumors in a Syngeneic Mouse Model. *AJP*, **155**, 1861-7.

Liu Y, Huang L, Liu F (2010). Paclitaxel Nanocrystals for Overcoming Multidrug Resistance in Cancer. *Mol Pharmaceutics*, **7**, 863–69 [abstract].

Lowe SW, Lin AW (2000). Apoptosis in cancer. *Carcinogenesis*, **21**, 485-95.

Ma¨enpa¨a JU(2003). Docetaxel: promising and novel combinations in ovarian cancer. *Br J Cancer*, **89**, S29 – S34.

Mahaffey CM, Davies AM, Lara PN Jr et al (2007). Schedule-dependent apoptosis in K-ras mutant non-small-cell lung cancer cell lines treated with docetaxel and erlotinib: rationale for pharmacodynamic separation. *Clin Lung Cancer*, **8**, 548-53.

Markman M (2003). Managing taxane toxicities. *Support Care Cancer*, **11**, 144–7.

Matsumura N, Huang Z, Baba T et al (2009). YY1 modulates taxane response in epithelial ovarian cancer. *Mol Cancer Res*, **7**, 210–20.

Mcdaid HM and Horwitz SB (2001). Selective Potentiation of Paclitaxel (Taxol)-Induced Cell Death by Mitogen-Activated Protein Kinase Kinase Inhibition in Human Cancer Cell Lines. *Mol Pharmacol*, **60**, 290–01.

McGuire WP, Rowinsky EK, Rosenshein NB et al (1989). Taxol: A Unique Antineoplastic Agent with Significant Activity in Advanced Ovarian Epithelial Neoplasms. *Ann Intern Med*, **111**, 273-9.

Meera S, Philip J, Radheshyam et al (2008). A comparative clinical study of docetaxel-carboplatin and gemcitabine-carboplatin in patients with non small cell lung cancer. *Journal of Clinical and Diagnostic Research*, **2**, 946-51.

Mediavilla-Varela M, Pacheco FJ, Almaguel F et al (2009). Docetaxel-induced prostate cancer cell death involves concomitant activation of caspase and lysosomal pathways and is attenuated by LEDGF/p75. *Mol Cancer*, doi:10.1186/1476-4598-8-68.

Meng Z, Mitsutake N, Nakashima M et al (2008). Dehydroxymethylepoxyquinomicin, a Novel Nuclear Factor-κB Inhibitor, Enhances Antitumor Activity of Taxanes in Anaplastic Thyroid Cancer Cells. *Endocrinology*, **149**, 5357–65.

Mhaidat NM, Zhang XD, ChenJiang C et al (2007). Docetaxel-Induced Apoptosis of Human Melanoma Is Mediated by Activation of c-Jun NH2-Terminal Kinase and Inhibited by the Mitogen-Activated Protein Kinase Extracellular Signal-Regulated Kinase 1/2 Pathway. *Clin Cancer Res*, **13**, 1308-14.

Mhaidat NM, Wang Y, Kiejda KA et al (2007). Docetaxel-induced apoptosis in melanoma cells is dependent on activation of caspase-2. *Mol Cancer Ther*, **6**, 752–61.

Mhaidat NM, Thorne RF, Zhang XD et al (2007). Regulation of docetaxel-induced apoptosis of human melanoma cells by different isoforms of protein kinase C. *Mol Cancer Res*, **5**, 1073-81.

Miller K, Wan M, Gralow J et al(2007). Paclitaxel plus Bevacizumab versus Paclitaxel Alone for Metastatic Breast Cancer. *N Engl J Med*, **357**, 2666-76.

Minisini AM, Tosti A, Sobrero AF et al (2003). Taxane-induced nail changes: incidence, clinical presentation and outcome. *Ann Oncol*, **14**, 333–7.

Mok TS, Wu YL, Thongprasert S et al (2009). Gefitinib or Carboplatin–Paclitaxel in Pulmonary Adenocarcinoma. *N Engl J Med*, **361**,947-57.

Moos PJ and Fitzpatrick FA (1998). Taxane-mediated gene induction is independent of microtubule stabilization: Induction of transcription regulators and enzymes that modulate inflammation and apoptosis. *PNAS*, **95**, 3896-901.

Moos PJ, Fitzpatrick FA (1998). Taxanes Propagate Apoptosis via Two Cell Populations with Distinctive Cytological and Molecular Traits. *Cell Growth Differ*, **9**, 687-97.

Nabell L, Spencer S (2003). Docetaxel with concurrent radiotherapy in head and neck cancer. *Semin Oncol*, **30**, 89-93.

Nahleh Z, Pruemer J, Lafollette J et al (2010). Melatonin, a promising Role in Taxane-Related neuropathy. *Clinical Medicine Insights: Oncology*, **4**, 35–41.

Nakahara C, Nakamura K, Yamanaka N et al (2003). Cyclosporin-A Enhances Docetaxel-Induced Apoptosis through Inhibition of Nuclear Factor-κB Activation in Human Gastric Carcinoma Cells. *Clin Cancer Res*, **9**, 5409-16.

Nakayama S, Torikoshi Y, Takahashi T et al (2009). Prediction of paclitaxel sensitivity by CDK1 and CDK2 activity in human breast cancer cells. *Breast Cancer Res*, doi:10.1186/bcr2231.

Naumova E, Ubezio P, Garofalo A et al (2006). The Vascular Targeting Property of Paclitaxel Is Enhanced by SU6668, a Receptor Tyrosine Kinase Inhibitor, Causing Apoptosis of Endothelial Cells and Inhibition of Angiogenesis. *Clin Cancer Res*, **12**, 1839-49.

Nehmé A, Varadarajan P, Sellakumar G et al (2001). Modulation of docetaxel-induced apoptosis and cell cycle arrest by all- trans retinoic acid in prostate cancer cells. *Br J Cancer* **84**,1571-1576.

Ni ZY, Dong M, Cong B et al (2010). A Novel Taxane 13-Glucoside and Other Taxanes from the Leaves of Taxus cuspidate. *Planta Med*, doi: 10.1055/s-0030-1250333 .

Nogales E (2000). Structural insights into microtubule function. *Annu Rev Biochem*, **69**, 277-302.

Noguchi S (2006). Predictive factors for response to docetaxel in human breast cancers. *Cancer Sci*, **97**, 813–20.

Obasaju C, Hudes GR (2001). Paclitaxel and docetaxel in prostate cancer. *Hematol Oncol Clin North Am*, **15**, 525-45.

Okano JI, Nagahara T, Matsumoto K et al (2007). The growth inhibition of liver cancer cells by paclitaxel and the involvement of extracellular signal-regulated kinase and apoptosis. *Oncology Rep*, **17**, 1195-200.

Orr GA, Verdier-Pinard P, McDaid H et al (2003). Mechanisms of Taxol resistance related to microtubules. *Oncogene*, **22**, 7280–95.

Park SY, Oh DY, Kim DW et al (2004). A multi-center, late phase II clinical trial of Genexol® (paclitaxel) and cisplatin for patients with advanced gastric cancer. *Oncology Rep*, **12**, 1059-64.

Pectasides D, Pectasides M, Farmakis D et al (2005). Comparison of docetaxel and docetaxel–irinotecan combination as second-line chemotherapy in advanced non-small-cell lung cancer: a randomized phase II trial. *Ann Oncol*, **16**, 294–99.

Patel N, Chatterjee SK, Vrbanac V et al (2010). Rescue of paclitaxel sensitivity by repression of Prohibitin1 in drug-resistant cancer cells. *PNAS*, **107**, 2503–08.

Pazdur R (2011). Cancer Drug Information.http://www.cancer.gov/cancertopics/druginfo/fda-nanoparticle-paclitaxel. Accessed 3 November 2010

Perera PY, Qureshi N, Vogel SN (1996). Paclitaxel (Taxol)-Induced NF-kB Translocation in Murine Macrophages. *Infect Immun*, **64**, 878–84.

Piccart-Gebhart MJ, Burzykowski T, Buyse M et al (2008). Taxanes alone or in combination with anthracyclines as first-line therapy of patients with metastatic breast cancer. *J Clin Oncol*, **26**, 1980-6.

Pienta KJ (2001). Preclinical mechanisms of action of docetaxel and docetaxel combinations in prostate cancer. *Sem Oncol*, **28**, 3-7.

Pires MM, Emmert D, Hrycyna CA et al (2009). Inhibition of P-Glycoprotein-Mediated Paclitaxel Resistance by Reversibly Linked Quinine Homodimers. *Mol Pharmacol*, **75**, 92–100.

Pölcher M, Rudlowski C, Friedrichs N et al (2010). In vivo intratumor angiogenic treatment effects during taxane-based neoadjuvant chemotherapy of ovarian cancer. *BMC Cancer*, **10**, 137.

Posner MR, Hershock DM, Blajman CR et al (2005). Cisplatin and Fluorouracil Alone or with Docetaxel in Head and Neck Cancer. *N Engl J Med*, **357**, 1705-15.

Pushkarev VM, Starenki DV, Saenko VA et al (2008). Differential effects of low and high doses of taxol in anaplastic thyroid cancer cells: possible implication of the Pin! Prolyl isomerase. *Exp Oncol*, **30**, 190–4.

Qian DZ, Rademacher BLS, Pittsenbarger J et al (2010). CCL2 is induced by chemotherapy and protects prostate cancer cells from docetaxel - induced cytotoxicity. *Prostate*, **70**, 433–42.

Rabi T, Bishayee A (2009). d -Limonene sensitizes docetaxel-induced cytotoxicity in human prostate cancer cells: Generation of reactive oxygen species and induction of apoptosis. *J Carcinog*, **8**, 9.

Raitanen M, Pulkkinen J, Kulmala J et al (2004). Head and Neck Squamous Cell Carcinoma Cell Lines are Highly Sensitive to the New Taxanes, BMS-184476, BMS-188797, In Vitro. *Anticancer Res*, **24**, 3769-74.

Rao S, He L, Chakravarty S et al (1999). Characterization of the Taxol Binding Site on the Microtubule. Identification of Arg282 in b-tubulin as the site of photoincorporation of a 7-benzophenone analogue of taxol. *J Biol Chem*, **274**, 37990-4.

Rao RD,.Holtan SG, Ingle JN et al (2005). Combination of Paclitaxel and Carboplatin as Second-Line Therapy for Patients with Metastatic Melanoma. *Cancer*, **106**, 375-82.

Richard P, Melanie R, Gladys R (1999). Phase II Trial of Docetaxel for Cholangiocarcinoma. *American Journal of Clinical Oncology*, **22**, 78-81.

Ross HJ, Canada AL, Slater LM (1997). Cyclosporin A enhances paclitaxel toxicity against leukemia and respiratory epithelial cancers. *Clin Cancer Res*, **3**, 57-62.

Roth AD, Ajani J (2003). Docetaxel-based chemotherapy in the treatment of gastric cancer. *Ann Oncol*, **14** (Suppl 2), 41-44.

Ryan DP, Grossbard ML (1998). Pancreatic Cancer: Local Success and Distant Failure. *Oncologist*, **3**, 178-188.

Sarafraz M, Ahmadi K (2008). Paraclinical evaluation of side-effects of Taxanes on auditory system. *ACTA oto rhinolaryngologica italic*, **28**, 239-42.

Sandler A, Gray R, Perry MC et al (2006). Paclitaxel–

Carboplatin Alone or with Bevacizumab for Non–Small-Cell Lung Cancer. *N Engl J Med*, **355**, 2542-50.
Sampath D, Discafani CM, Loganzo F et al (2003). MAC-321, a novel taxane with greater efficacy than paclitaxel and docetaxel in vitro and in vivo. *Mol Cancer Ther*, **2**, 873-88.
Schiff PB, Fant J, Horwitz SB (1979). Promotion of microtubule assembly in vitro by taxol. *Nature*, **277**,665-7.
Schiff PB and Horwitz SB (1980). Taxol stabilizes microtubules in mouse fibroblast cells. *PNAS*, **77**, 1561-5.
Sgadari C, Toschi E, Palladino C et al (2000). Mechanism of Paclitaxel Activity in Kaposi's Sarcoma. *J Immunol*, **165**, 509–17.
Shah MA, Schwartz GK (2001). Cell Cycle-mediated Drug Resistance: An Emerging Concept in Cancer Therapy. *Clin Cancer Res*, **7**, 2168–81.
Sherman WH, Fine RL (2001). Combination gemcitabine and docetaxel therapy in advanced adenocarcinoma of the pancreas. *Oncology*, **60**, 316-21.
Shimomura T, Hasako H, Nakatsuru Y et al (2010). MK-5108, a Highly Selective Aurora-A Kinase Inhibitor, Shows Antitumor Activity Alone and in Combination with Docetaxel. *Mol Cancer Ther*, **9**, 157-66 .
Sissung TM, Danesi R, Price DK et al (2008). Association of the CYP1B1*3 allele with survival in patients with prostate cancer receiving docetaxel. Mol Cancer Ther, 7, 19-26
Snyder JP, Nettles JH, Cornett B et al (2001). The binding conformation of Taxol in b-tubulin: A model based on electron crystallographic density. *PNAS*, **98**, 5312-16.
Socinski MA (1999). Single-Agent Paclitaxel in the Treatment of Advanced Non-Small Cell Lung Cancer. *Oncologist*, **4**, 408-16
Solomon LA, Ali S, Banerjee S et al (2008). Sensitization of ovarian cancer cells to cisplatin by genistein: the role of NF-kappaB. *Journal of Ovarian Research*, **1**, 9 doi:10.1186/1757-2215-1-9
Sood AK, Coffin JE, Schneider GB et al (2004). Biological Significance of Focal Adhesion Kinase in Ovarian Cancer. *A J Path*, **165**, 1087-95.
Strobel T, Tai YT, Korsmeyer S et al (1998). BAD partly reverses paclitaxel resistance in human ovarian cancer cells. *Oncogene*, **17**, 2419-27.
Suk KT, Kim JW, Kim HS et al (2007). Human application of a metallic stent covered with a paclitaxel-incorporated membrane for malignant biliary obstruction: multicenter pilot study. *Gastrointest Endosc*, **66**, 798-803.
Sun ML, Wei JM, Wang XW et al (2007). Paclitaxel-octreotide conjugates inhibit growth of human non-small cell lung cancer cells in vitro. *Exp Oncol*, **23**, 186-91.
Tannock IF, De Wit R, Berry WR et al (2004). Docetaxel plus Prednisone or Mitoxantroneplus Prednisone for Advanced Prostate Cancer. *N Engl J Med*, **351**, 1502-12.
Torres K, Horwitz SB (1998). Mechanisms of Taxol-induced Cell Death Are Concentration Dependent. *Cancer Res*, **58**, 3620-26.
Townsend DM, Tew KD (2003). The role of glutathione-S-transferase in anti-cancer drug resistance. *Oncogene*, **22**, 7369–75
Tsui P, Rubenstein M, Guinan P (2005). Correlation Between PSMA and VEGF Expression as Markers for LNCaP Tumor Angiogenesis. *J Biomed Biotechnol*, **3**, 287–90.
Vanhoefer U, Cao S, Harstrick A et al (1997). Comparative antitumor efficacy of docetaxel and paclitaxel in nude mice bearing human tumor xenografts that overexpress the multidrug resistance protein (MRP). *Ann Oncol*, **8**, 1221-28.
Vasey PA (2003). Role of Docetaxel in the Treatment of Newly Diagnosed Advanced Ovarian Cancer. *J Clin Oncol*, **21**, 136s-144s.
Vasey PA, Jayson GC, Gordon A et al (2003). Phase III Randomized Trial of Docetaxel–Carboplatin Versus Paclitaxel–Carboplatin as First-line Chemotherapy for Ovarian Carcinoma. *J Natl Cancer Inst*, **96**, 1682-91.
Veitia R, Bissery MC, Martinez C et al (1998). Tau expression in model adenocarcinomas correlates with docetaxel sensitivity in tumour-bearing mice. *Br J Cancer*, **78**, 871–7.
Wall ME, Wani MC (1995). Camptothecin and Taxol: Discovery to Clinical-Thirteenth Bruce F. Cain Memorial Award Lecture. *Cancer Res*, **55**, 753-60.
Wang F, Cao Y, Zhao WZ et al (2003). Taxol Inhibits Melanoma Metastases Through Apoptosis Induction, Angiogenesis Inhibition, and Restoration of E-Cadherin and nm23Expression. *J Pharmacol Sci*, **93**, 197-03.
Wang J, Lou P, Lesniewski R et al (2003). Paclitaxel at ultra low concentrations inhibits angiogenesis without affecting cellular microtubule assembly. *Anti-Cancer Drugs*, **14**, 13-9.
Wang Q, Wieder R (2004). All-trans retinoic acid potentiates Taxotere-induced cell death mediated by Jun N-terminal kinase in breast cancer cells. *Oncogene*, **23**, 426–33.
Wang QW, Lu HL, Song CC et al (2005). Radiosensitivity of human colon cancer cell enhanced by immunoliposomal docetaxel. *World J Gastroenterol*, **11**, 4003-7.
Wang Z, Li M, Zhao W, Zhao G et al (2007). Establishment and characterization of lung adenocarcinoma cell lines with multidrug resistance. *Life Science Journal*, **4**, 13-6.
Wani MC, Taylor HL, Wall ME et al (1971). Plant antitumor agents. VI. The isolation and structure of taxol, a novel antileukemic and antitumor agent from Taxus brevifolia. *J AM Chem Soc*, **93**, 2325-27.
Wei G, Chun Z, Fengquan D, Wei L (2002). Paclitaxel-induced apoptosis in osteosarcoma cell line U-2 OS. *Chin Med J*, **115**, 1796-801.
Wenzel C, Steger GG (2006). Adjuvant Treatment of Breast Cancer with Taxanes. *Breast Care*, **1**, 171-5.
Wu Y, Fabritius M, Ip C (2009). Chemotherapeutic Sensitization by Endoplasmic Reticulum Stress: Increasing the Efficacy of Taxane Against Prostate Cancer. *Cancer Biol Ther*, **8**, 146–52.
Xu G, Pan J, Martin C, et al (2001). Angiogenesis Inhibition in the in Vivo Antineoplastic Effect of Manumycin and Paclitaxel against Anaplastic Thyroid Carcinoma. *J Clin Endocrinol Metab*, **86**, 1769-77.
Yamori T, Sato S, Chikazawa H, et al (1997). Anti-tumor Efficacy of Paclitaxel against Human Lung Cancer Xenografts. *Cancer Science*, **88**, 1205-10.
Yim EK, Bae JS, Lee SB, et al (2004). Proteome Analysis of Differential Protein Expression in Cervical Cancer Cells after Paclitaxel Treatment. *Canc Research and Treatment*, **36**, 395-99.
Yoshino T, Shiina H, Urakami S, et al (2006). Bcl-2 Expression as a Predictive Marker of Hormone-Refractory Prostate Cancer Treated with Taxane-Based Chemotherapy. *Clin Cancer Res*, **12**, 6116-24.
Yuan JH, Zhang RP, Zhang RG, et al (2000). Growth-inhibiting effects of taxol on human liver cancer in vitro and in nude mice. *World J Gastroenterol*, **6**,210-5.
Yvon AMC, Wadsworth P, Jordan MA (1999). Taxol Suppresses Dynamics of Individual Microtubules in Living Human Tumor Cells. *Mol Biol Cell*, **10**, 947–59.
Zhang ZL, Liu ZS, Sun Q (2005). Anti-tumor effect of thalidomide and paclitaxel on hepatocellular carcinoma in nude mice. *Chin Med J*,**118**, 1688-1694.
Zhou J, Giannakakou P (2005). Targeting Microtubules for Cancer Chemotherapy. Curr Med Chem - Anti-Cancer Agents, **5**, 65-71.
Zhou X, Xu L, Zhu W et al (1999). Effects of Taxol on three

different types of lymphoma cell lines. *Chin J Canc Res*, **11**, 105-10.