

Paclitaxel - Development, Properties, Toxicity/Safety Evaluation and the Scope of Improvement

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Abstract: Paclitaxel is a miraculous drug that is being extensively used against ovarian and breast carcinomas. Since its approval as a chemotherapeutic agent against breast and ovarian carcinomas, in April 1994, paclitaxel has been studied extensively leading to the tremendous development of its efficacy and alleviating its toxicity potential. It has been encapsulated in nanoparticles and emulsified with different types of solvents to observe its pharmacokinetics, toxicity, anticancer effects and resistance at a whole different level. Paclitaxel has shown significant activity in a broad range of solid tumors including non-small cell and small cell carcinomas, squamous cell carcinomas of head and neck, prostate, bladder, oesophageal cancers, ovarian carcinoma and advanced breast carcinoma but drug is capable of producing acute and delayed toxicity and since the commercial formulation of paclitaxel contains cremophor EL as a vehicle, the formulation exerts variety of biological effects as cremophor EL is not an inert molecule and has serious clinical implications. The following review provides insights regarding the development of paclitaxel, its properties, toxicity/safety evaluation and the scope of improvement.

Keywords: Carcinoma, cremophor EL, encapsulation, toxicity, paclitaxel.

I. Introduction

Paclitaxel (5beta, 20-epoxy-1,2alpha, 4beta, 7beta, 10beta, 13alpha-hexahydroxy tax-11-en-9-one 4, 10-diacetate-2-benzoate-13-ester with (2R, 3S)-N-benzoyl-3-phenylisoserine, is a white to off-white crystalline powder with empirical formula of C₄₇H₅₁NO₁₄ [1], insoluble in water, and melts at around 216-217° C. It is a complex, oxygen rich diterpenoid [2][3], consisting of benzene rings and other hydrophobic structures, which are responsible for its high lipophilicity (log P 3.5), practically insoluble in water (0.3 ± 0.02 µg/ml) and therefore has very slow dissolution rate and low oral bioavailability (<8%) [4][5]. Taxol[®], the current marketed parenteral formulation of paclitaxel is associated with poor patient compliance, severe hypersensitivity reaction and rapid elimination from blood circulation [6][7].

Abraxane[®], another parenteral formulation of paclitaxel is a colloidal suspension of drug in human albumin. It doesn't pose hypersensitivity but cost is comparatively high. Besides, the efficacy of Abraxane[®] is only marginal, therefore lacks patient compliance [7].



Taxus brevifolia

II. History

The first report about paclitaxel dates back to the beginning of 1900's when a British official in the Indian subcontinent noted that parts of *Taxus baccata* were used to treat cancer. Some 60 years later, in 1962, a program of the National Cancer Institute (USA) evaluating domestic plants for their anticancer activity revealed that crude extracts of the Pacific (or Western) yew (*Taxus brevifolia*) showed cytotoxic activity against several tumours. It took another 10 years before the active compound paclitaxel was isolated and fully characterized [8]. In 1979, Horwitz and colleagues elucidated the unique mechanism of paclitaxel discovering that paclitaxel promoted the polymerization of tubulin. The disturbance of the dynamic balance caused cells to undergo apoptosis [9].

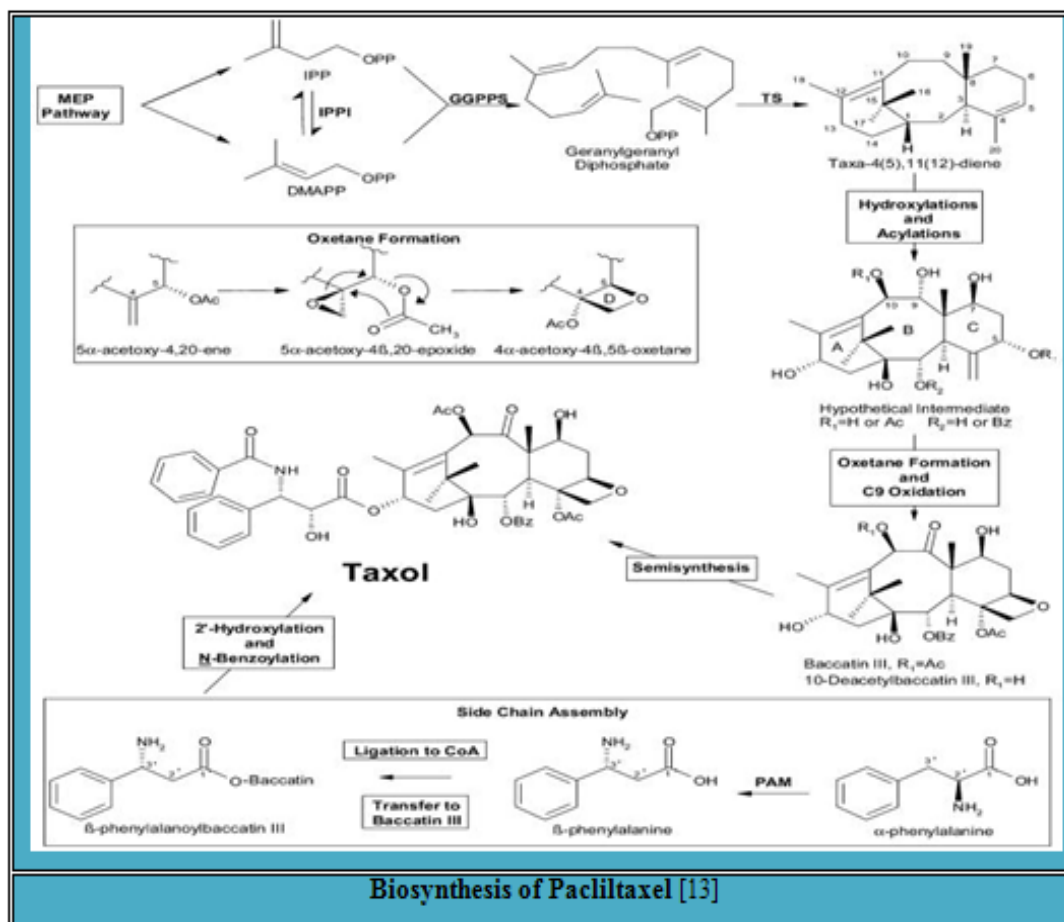
Initially, a major problem was the scarcity of the crude plant material and consequently of paclitaxel, but finally a semi-synthetic process using 10-deacetylbaaccatin III as precursor allowed production of sufficient amounts of paclitaxel and the first phase I clinical trials were initiated in 1983. Its poor water solubility further hampered the development of a commercially available formulation, until a collaboration between the National Cancer Institute and Bristol-Myers-Squibb[®] resulted in a formulation (Taxol[®]) where paclitaxel was dissolved in a 50/50 (v/v) mixture of Cremophor EL[®] and ethanol. This concentrate (6 mg/ml) is diluted to the appropriate concentration and administered through an infusion set to the patient. Finally, in 1992 and 1994, the Food and Drug Administration (FDA) approved Taxol[®] for the treatment of ovarian and breast cancer, respectively. Since then the interest in paclitaxel and other taxanes increased tremendously. They are considered as one of the most important additions to the chemotherapeutic arsenal in the late 20th century.

Table 1 Chronology of paclitaxel discovery and important development [10].

Date	Event
June 1960	Beginning of NCI Plant Programme contracts
August 1962	Collection of <i>Taxus brevifolia</i> in Washington
April 1964	Cytotoxicity of bark extract to KB cells
October 1966	Isolation of pure Taxol (K172) and cytotoxicity activity of pure Taxol to KB cells
1968-69	Study of plant parts of <i>Taxus brevifolia</i>
May 1971	Chemical structure of Taxol published
April 1977	Taxol accepted for development as Stage 2A
August 1978	Taxol published as antimetabolic drug
February 1979	Taxol published as promoter of microtubule assembly
October 1980	Taxol passed Decision Network Stage 2B; approved for toxicology
November 1982	Decision Network stage 3 passed; Taxol [®] approved for Investigational new drug application (INDA) filing
September 1983	Investigational New Drug Application filed
April 1984	Investigational New Drug Application approved
April 1984	Phase I clinical trial began
April 1985	Decision Network stage 4 passed; approved for Phase II with the use of 24-h continuous infusion and pre-medication regimen
August 1989	Johns Hopkins group published activity in advanced ovarian cancer
December 1991	M.D. Anderson group published activity in metastatic breast cancer
1990-1993	Large scale production by Huaser/Bristol-Myers Squibb
July 1992	New Drug Application filed with FDA
December 1992	New Drug Application approved for refractory ovarian cancer
April 1994	Supplemental approval for metastatic breast cancer

III. Biosynthesis Of Paclitaxel

As a natural diterpenoid, taxol is formed exclusively from geranylgeranyl diphosphate (GGPP) which is synthesized from three IPP molecules and the isomer dimethyl diphosphate (DMAPP) by the enzyme geranylgeranyl diphosphate synthase and after a series of biological reactions baccatin III is formed. An essential step in the taxol biosynthesis is the esterification of the C13 hydroxyl group of baccatin III with the beta-phenylalanoyl-CoA side chain. The side chain is obtained from the amino acid beta-phenylalanine by the action of phenylalanine aminomutase (PAM) [11]. An unknown ester CoA ligase probably activates the compound so it can bind to baccatin III. The enzyme that catalyzes the conjugation of the beta-phenylalanoyl-CoA side chain to baccatin III is C-13-phenylpropanoyl-CoA transferase (BAPT), yielding the compound 3'-N-debenzoyl-2'-deoxytaxol. This compound, by the action of an unknown cytochrome P450-dependent hydroxylase that hydroxylates the C2 position and the enzyme 3'-N-debenzoyl-2'-deoxytaxol N-benzoyl transferase (DBTNBT) that conjugates benzoyl-CoA to 3'-N-debenzoyl-2'-deoxytaxol, yields taxol as the final compound. The enzyme can be exploited to improve the production of taxol in genetically engineered systems [12].



IV. Mechanisms Of Action And Resistance

The binding site for the taxanes on microtubules is different from those of GTP, colchicine, podophyllotoxin, and vinblastine. Paclitaxel binds to the N-terminal 31 amino acids of the beta-tubulin subunit of tubulin polymers [14]. Unlike the vinca alkaloids, which prevent microtubule assembly, the taxanes decrease the lag time and shift the dynamic equilibrium between tubulin dimers and microtubules toward polymerization, thereby stabilizing microtubules [15]. These effects occur even in the absence of GTP- and microtubule-associated proteins, which are usually essential for the function. Docetaxel has a 1.9-fold higher affinity for the site than paclitaxel does and it induces tubulin polymerization at a 2.1-fold lower critical tubulin concentration [16]. The initial slope of the assembly reaction and the amount of polymer formed is also greater for docetaxel. In addition, docetaxel is more potent than paclitaxel at inducing cytotoxicity *in vitro* and in tumor xenografts [17]. These differences do not imply that docetaxel has a greater therapeutic index because greater potency may also portend greater toxicity, and pharmacologic differences between the agents must be considered. The taxanes inhibit cell proliferation by inducing a sustained mitotic block at the metaphase/anaphase boundary, as well as formation of an incomplete metaphase plate of chromosomes and an abnormal organization of spindle microtubules, which occur at much lower drug concentrations than those required to increase microtubule mass [18]. Aberrant mitotic spindles and mitotic block due to stabilization of microtubule dynamics results from inhibitory drug effects on intrinsic microtubule processes involving the equilibrium between tubular dimers and microtubule polymers such as dynamic instability and treadmilling. After the disruption of microtubules, particularly those comprising the mitotic spindle apparatus, the precise means by which cell death occurs are not clear. However, morphologic features and DNA fragmentation patterns characteristic of programmed cell death or apoptosis have been documented in tumor cells after taxane treatment [18]. These apoptotic effects have been associated with phosphorylation of *bcl-2*, an antiapoptotic protein, resulting in a disruption of the balance between the dimerization of *bcl* and *bax* proteins [19].

Both paclitaxel and docetaxel have also been shown to enhance the cytotoxic effects of ionizing radiation *in vitro* at clinically achievable concentrations, which may be due to the inhibition of cell-cycle progression in the G₂ and M phases, the most radiosensitive phases of the cell cycle [20].

Two mechanisms of acquired resistance to the taxanes *in vitro* have been described. First, some tumors contain alpha- and beta-tubulin, which have an impaired capacity to polymerize into microtubules and an

inherently slow rate of microtubule assembly in the absence of the taxanes [21]. A second mechanism, multi-drug resistance (MDR) that involves amplification of membrane phosphoglycoproteins that function as drug efflux pumps, confers varying degrees of cross-resistance to diverse structurally bulky natural product cytotoxins [22]. MDR can be reversed by many types of agents, including the main components of the formulation vehicles of both paclitaxel and docetaxel, Cremophor EL (polyoxyethylated castor oil) and Tween 80 (polysorbate 80) [23][24]. The clinical relevance of these mechanisms of resistance is not known, but the early results of studies in breast cancer suggest a lack of complete cross-resistance between the taxanes and anthracyclines that would not be expected if MDR is an important mechanism of resistance for the particular tumor [25].

Taxane resistance has also been related to differential expression of various tubulin isotypes, decreased microtubule bundle formation, decreased expression of *bcl-2*, and other mechanisms that are unrelated to MDR [26][19][27].

V. Pharmacokinetics

Paclitaxel is primarily metabolized in the liver by the cytochrome P450 (CYP) enzymes, CYP3A4 and CYP2C8. CYP3A4 metabolizes paclitaxel to p-3'-hydroxypaclitaxel and CYP2C8 converts the drug to 6- α -hydroxypaclitaxel and these metabolites can be further oxidized to 6- α -p-3'-dihydroxypaclitaxel [28]. Other metabolites have been identified in smaller quantities [29]. Studies have shown that the major portion of unchanged paclitaxel and its metabolites are excreted in the faeces, indicating extensive non-renal clearance [30]. However, only paclitaxel has been shown to be toxic and to have an antitumor activity while its metabolites are considered to be inactive [31].

The pharmacokinetics of paclitaxel is best characterized by a three-compartment disposition profile. However, its pharmacokinetics is non-linear and is because of a saturation process in distribution and elimination. The nonlinearity appears to be associated more frequently with shorter infusions and/or higher doses. The time duration of paclitaxel concentrations maintained above 0.1 $\mu\text{M/L}$ ($T_{>0.1 \mu\text{M}}$) is associated with improved survival and development of toxicity. The pharmacokinetic relationship may change with antineoplastic agents and other agent administered concurrently, and necessitates additional pharmacokinetic-pharmacodynamic investigation [32].

VI. Formulation Of Paclitaxel

TAXOL[®] injection is a clear colourless to slightly yellow viscous solution. It is supplied as a non-aqueous solution intended for dilution with a suitable parenteral fluid prior to intravenous infusion. TAXOL is available in 30 mg (5 ml), 100 mg (16.7 ml), and 300 mg (50 ml) multi-dose vials. Each ml of sterile non-pyrogenic solution contains 6 mg paclitaxel, 527 mg purified Cremophor EL and 49.7% (v/v) dehydrated alcohol [4].

Cremophor EL (CrEL) is a formulation vehicle used for various poorly-water soluble drugs, including the anticancer agent paclitaxel (Taxol). Cremophor EL is not an inert vehicle, but exerts a range of biological effects, some of which have important clinical implications. Its use has been associated with severe anaphylactoid hypersensitivity reactions, hyperlipidaemia, abnormal lipoprotein patterns, aggregation of erythrocytes and peripheral neuropathy. CrEL is an integral component of paclitaxel chemotherapy, modifies the toxicity profile of certain anticancer agents given concomitantly, by mechanisms other than kinetic interference [6]. The researchers have explored the following areas to overcome the solubility problem of paclitaxel in aqueous system.

VII. Application Of Suitable Co-Solvents And Surfactants

The weak electrolytes and non-polar drug molecules frequently have poor water solubility. Their solubility can be increased by the addition of water miscible solvent in which the drug has a good solubility. The solvents used in combination to increase the solubility of the solute are known as co-solvents [33].

The co-solvent system consisting of ethanol, polysorbate (Tween) 80, and the surfactant Pluronic L64, in the ratios of 3:1:6 (v/v/v) for paclitaxel formulations has been reported [34]. The drug was solubilized at a concentration of 5 mg/ml. No change in chemical and physical stability was observed over 3 months but the solution on dilution with water to a concentration of 3.45 mM was found to be physically stable for only 3 days.

VIII. Encapsulation Of Paclitaxel Drug In Liposome

The encapsulation in liposomes often results in distinct changes in the pharmacokinetic and the pharmacodynamic properties of the drugs, in some cases causing a marked decrease in toxicity or increase in potency [35]. Multilamellar vesicles employing different combinations of phospholipids like L-dimyristoyl phosphatidylcholine (DMPC) and L-dimyristoylphosphatidyl glycerol (DMPG) and cholesterol by the standard evaporation/hydration methods [36]. In general, mixtures of DMPC:DMPG, at a molar ratio 7:3 and 9:1, and the

addition of 5% cholesterol (w/w) gave the optimum results. *In vitro* cytotoxicity of liposomal drugs against L1210 cells was found to be more than that of a free drug in the case of paclitaxel. Later, the liposomal drug delivery systems containing paclitaxel and phospholipid in molar ratio of 1:33 from phosphatidylglycerol and phosphatidylcholine (1:9 molar ratio) was developed [37], and was found to be stable for more than 2 months at 4 °C, and for 1 month at 20 °C.

IX. Synthesis Of Paclitaxel Derivatives Which Are More Soluble

Paclitaxel is poorly soluble in an aqueous medium, but can be dissolved in organic solvents. Its solutions can be prepared in a millimolar concentration in a variety of alcohols, such as methanol, ethanol, tertiary-butanol as well as in DMSO. Non-aqueous solubility is found to be 46 mM in ethanol, 20 mM in methylene chloride or acetonitrile, 14 mM in isopropanol [38].

Prodrug synthesis has also been extensively studied to increase the aqueous solubility of paclitaxel (Burt *et al.* 1995). The preferred position for the preparation of prodrug of paclitaxel is 2'-position since many 2'-acyl-paclitaxel derivatives hydrolyze fairly rapidly back to paclitaxel in blood compartments [39]. Since the configuration of C-7 hydroxyl group does not seem to be a factor in determining cytotoxicity, C-7 prodrug ester has also been synthesized [40].

Polyethylene glycol (PEG) is an amphiphilic macromolecule that, in the molecular weight range of 2–12 kDa, it imparts greater aqueous solubility to conjugates of hydrophobic organic compounds or proteins, augmenting circulation half-life and increasing immunogenicity [41]. A prodrug strategy employing PEG as a solubilising agent has been successfully demonstrated in case of paclitaxel [42].

X. Search Of A Cyclodextrin (CD) Which Can Act As A Drug Solubilizer And Stabilizer

CDs are cyclic oligosaccharides, which have been used extensively to increase the solubility, dissolution rate and the bioavailability of poorly soluble drugs [43]. An enhancement in solubility of paclitaxel from an inclusion complex with hydroxy propyl- α -CD (HP α CD) was observed. The complex formed was more hydrophilic than the uncomplexed drug indicating that the solubility of the drug can be enhanced by HP α CD [44].

The disk shaped implants of polyanhydride P (FAD-SA, 50:50 w/w) loaded with 10% w/w of paclitaxel were developed. It was found that paclitaxel was released very slowly and only 15% of the drug was released in 77 days and based on first order kinetics, it can be predicted that 44 months will be required to release 100% of the drug from the device, which is too prolonged for any clinical condition [45]. However, the faster release of paclitaxel (45–65% in 30 days) was observed from a relatively more hydrophilic P (CPP-SA, 20:80 w/w) and the implants were found to be promising in an experimental malignant glioma model. Drug loaded polymeric disks using a biodegradable polyanhydride have been formulated for implantation into the cavity of resected brain tumors [46].

XI. Preparation And Administration Aspects Of Paclitaxel Injection

Paclitaxel must be diluted in 0.9% sodium chloride, 5% dextrose or 5% dextrose and 0.9% sodium chloride or 5% dextrose in Ringer solution to a concentration of 0.3-1.2 mg/ml before use. The solutions are physically and chemically stable for up to 27 hours at ambient temperature (approximately 25° C) and room lighting conditions. The use of PVC infusion bags and intravenous administration set is not recommended as Cremophor EL leaches di(2-ethylhexyl)phthalate {DEHP} plasticizers from PVC. In practice, paclitaxel is prepared in non-PVC container and a 0.22 μ m in-line filter is used to prevent the infusion of any particulates. In addition, non-PVC administration set is used for drug infusion [47].

XII. Patient Care Aspect

1.1 Retreatment Strategy for Patients Experiencing a Paclitaxel-Associated Hypersensitivity Reaction [48].

- 1) Immediate discontinuation of the paclitaxel infusion if a patient experiences any signs or symptoms of a hypersensitivity reaction (e.g. chest tightness, back pain, diffuse erythroderma, dyspnea, tachycardia, hypertension, hypotension, and sensation of extreme anxiety).
- 2) Rapid IV administration of diphenhydramine (50 mg) and hydrocortisone (100 mg).
- 3) Re-initiation of paclitaxel infusion approximately 30 minutes after initially stopping its administration (allowing for complete disappearance of signs and symptoms of the previous reaction).

1.2 Desensitization Protocol for Paclitaxel-Associated Hypersensitivity Reactions [48].

- 1) Dexamethasone 20 mg orally at bedtime approximately 36 and 12 hours before chemotherapy and morning of chemotherapy.
- 2) Thirty minutes before chemotherapy (all IV): dexamethasone 20 mg, diphenhydramine 50 mg, famotidine 20 mg.

- 3) Paclitaxel IV infusion: 2 mg in 100 mL normal saline over 30 minutes, followed by (if no reaction); 10 mg in 100 mL normal saline over 30 minutes, followed by (if no reaction); remaining full dose in 500 mL normal saline over 3 hours.
- 4) If the patient experiences a reaction to either test solution, discontinue infusion; administer IV diphenhydramine (50 mg) and hydrocortisone (100 mg).
- 5) Restart paclitaxel infusion approximately 30 minutes after symptoms subside.

XIII. Preclinical Studies Of Paclitaxel

Many of the preclinical biological activities of paclitaxel correlate well with *in vivo* antitumour activities, and when available, the specific clinical activities are observed. The spectrum of preclinical activity of paclitaxel is broad and the extent of tumour cell killing is typically several orders of magnitude, although curative effects against staged tumour models are not usual.

1.1 In Vitro Activities

Paclitaxel has exhibited several activities *in vitro* such as enhancing the polymerization of tubulin dimers to form microtubules, binding to microtubules to inhibit their disassembly, causing abnormal mitotic spindle production, microtubule bundling and inhibiting cell replication. These serve as indicators for its antitumour activities. Paclitaxel has been evaluated specifically for cytotoxicity against many tumour cell lines. It has been found to be quite potent at inhibiting the growth of both human and murine tumour cell lines. The concentration of paclitaxel needed to inhibit tumour cell growth by 50% (IC₅₀) was typically in the nanomolar range [49].

Rowinsky and colleagues studied the effects of paclitaxel at pharmacologically relevant concentrations (0.1-10 μ M for 2 to 22 hrs) on microtubules in four human ovarian and four human leukemia cell lines using electron microscope and immunofluorescent technique [26]. Paclitaxel-induced changes included formation of disrupted microtubule bundles and abnormal mitotic asters. The human ovarian cell lines were found to be less sensitive than the human leukemia cell lines. The cytotoxicity, as determined using a clonogenic assay, was directly proportional to the fraction of ovarian cells displaying paclitaxel-induced changes in microtubule formation. It was noted in both experiments that the induction of microtubule-related effects was dependent more on the exposure duration than its concentration.

Paclitaxel was found to be a phase-specific agent and was much more cytotoxic to the mitotic cell than to the interphase cells during their evaluation of the cytotoxic effects of paclitaxel on the Chinese hamster and the human A2780 ovarian cells. Cell killing reached a plateau at specific concentrations per cell line, and the cells were more responsive to increased exposure time than to increased concentrations above the plateau levels [50].

In a phase I study of paclitaxel in refractory acute leukemia patients, Rowinsky and his team noted that the mean peak paclitaxel concentrations at all dose levels used were in the range of concentrations that had previously been found to induce microtubule bundling *in vitro* [51]. Although the sample size was too small to perform any meaningful analysis, the investigators commented there was an indication that the clinical antitumour activity was associated with varying degrees of sensitivity to paclitaxel-induced microtubule bundling.

National Cancer Institute (NCI) performed the most comprehensive evaluation of cytotoxicity of paclitaxel as part of the disease-oriented antitumour pre-screening organization. The test panel consisted of 60 cell lines including human leukemia, melanoma, and carcinoma of the central nervous system, lung, breast, kidney, ovary and colon. The cells were exposed to paclitaxel for 48 hr in each experiment and about a dozen such experiments were conducted. Nearly all of the cell lines for all tumour types were sensitive to paclitaxel. In majority of the cell lines, the IC₅₀ of paclitaxel was less than 2.5 nM and much higher concentrations were required to completely block cell proliferation or achieve a 50% cell kill end-point [52]. However, in almost every experiment, the 50% cell kill end-point could not be achieved at the maximum paclitaxel concentration tested, 25 μ M, and for the majority of cell lines, the paclitaxel concentration needed for even 100% growth inhibition was greater than or equal to 25 μ M.

1.1a Radiosensitizing Effect of Paclitaxel

Paclitaxel has been shown to be a potent radiosensitiser in the laboratory setting. Its main mode of action is microtubule stabilizing activity and ability to promote microtubule assembly, resulting in cell accumulating DNA content in G2/M phase. Researchers have recognized that G2 and M phases are the most radiosensitive phases of the cell cycle. The molecular basis is not well understood currently but the p53 tumor suppressor protein, which is involved in mediating apoptosis by radiation and chemotherapeutic agents, has a part to play in the process [53]. Radiation sensitizing activities have been noted in human breast (MCF-7), lung (A549), ovary (OVG-1) pancreas (PC-Sh), adrenocarcinoma cells [54].

1.2 In Vivo Activities

Different investigators worldwide have demonstrated the broad spectrum of paclitaxel's *in vivo* antitumour activity following NCI's initial success in identifying its activity in murine tumours in the 1960s as part of natural products screening programme. In these studies paclitaxel was commonly given as subcutaneous or intraperitoneal injection in various administration schedules and vehicles to mice implanted intraperitoneally with tumour models [55]. The tumour models used include murine leukemia tumours (L1210, P388, P1534) murine solid tumours (B16 melanoma, M109, M5076, Lewis lung carcinoma) and human tumour xenografts (CX-1, CX-2, CX-5, LX-1 LOX, MX-1, M109 and A2780). Ovarian and non-small cell lung tumours were more responsive to paclitaxel than were colon tumours, but the data from other investigators did not indicate any tumour of a particular histology with unusual insensitivity or greater susceptibility [56].

1.2a Toxicity and Safety

Intravenous administration of paclitaxel in adult Sprague Dawley rats caused hypoplasia of bone marrow and depletion of lymphoid organs on days, 6 and 12, respectively, with decreased reticulocyte count and differential count of neutrophils [57], but in pregnant rats lactation and gestation periods were unaffected, did not affect the organ weights in F0 generation, did not alter the pre-natal development in F1 and did not induce the skeletal and ossification variations but delayed the growth of hair in F1 [58].

Hepatotoxic effects of acute intraperitoneal administration of 3 doses; MTD (Maximum tolerated dose) 1.7 ID (Intermediate dose) 1.15 and MD (Medical dose) 0.6 mg/kg Taxol were studied. Ultrastructural changes included denaturation of hepatic and cellular organelles such as endoplasmic reticulum and mitochondria with ballooning of hepatocytes, lipid accumulation, cytoplasmic vacuolation and the frequency of micro-nucleated polymorphic erythrocytes was significantly increased after 24 and 48 hours with all doses [59].

The paclitaxel administration synergistically might potentiate doxorubicin induced cardiotoxicity. Preceding doxorubicin by paclitaxel might be less cardiotoxic combination in comparison with reverse order of combination. Doxorubicin treatment produced myocytolysis and myocardial necrosis. The administrations of paclitaxel following doxorubicin treatment showed extensive myocardial necrosis compared with rats treated with doxorubicin alone or reverse the order of sequence [60].

The nephrotoxic effects of taxol at different doses: MD, ID and MTD (0.6, 1.15, and 1.7 mg/kg), respectively, were studied, given by intra-peritoneal route to 54 adult mice with an average weight between 20-25 g. The kidney samples were taken 6, 24 and 48 hours after drug administration. Marked loss of renal tubular epithelial lining, damage to brush border and formation of epithelial casts in the damaged tubules was observed. The alterations were in the form of both necrotic and apoptotic changes. Focal atrophy of glomerular tufts was also observed. The proximal tubules showed loss of basal infoldings and increased formation of micronuclei proved genotoxic effects of taxol in mice bone marrow cells [61].

XIV. Conclusions

Taxanes have revolutionized the science of chemotherapy and are considered as one of the most significant compounds in the chemotherapeutic arsenal. The commercial formulation of paclitaxel containing polyoxyethylated castor oil as a vehicle has shown serious clinical complications and can markedly decrease the number of cells in mitosis. The need of more effective, safe and water soluble formulations of paclitaxel is increasing with each passing day as breast cancer is the most common invasive cancer in women and ovarian cancer is regarded as the most deadly gynecologic cancer because of high mortality rates.

Taxanes have shown significant activity against solid tumors but the cytotoxic potential of paclitaxel against gliomas has not been conclusively elucidated in comparison with ovarian and breast cancers. Gliomas account for majority of primary malignant brain tumors and are associated with very poor survival rates. After intravenous administration of paclitaxel, very poor concentrations are obtained in CSF. It is of utmost importance to formulate formulations achieving profound cytotoxic concentrations in brain against gliomas, with minimal damage to normal cells.

The available commercial formulation of paclitaxel is administered intravenously but in the advanced stage of ovarian cancer with metastasis the whole of abdominal/peritoneal cavity is involved and the intravenous formulation is not much effective against peritoneal ovarian carcinomatosis, unless less toxic formulations are made and given through the intra-peritoneal route to observe their effectiveness, toxicity and safety potential.

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