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DRUG DELIVERY APPROACHES FOR PACLITAXEL FORMULATION

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ABSTRACT

Paclitaxel is a potent anticancer agent that inhibits cell division, employed in oncology and cardiology. In oncology, paclitaxel-eluting coated metal stents are employed to prevent tumor ingrowth, leveraging their anti-proliferative, pro-apoptotic, and anti-angiogenic properties. In cardiology, paclitaxel-eluting stents reduce in-stent restenosis significantly, maintaining arterial patency. Liposomal formulations encapsulate paclitaxel into minuscule carriers, enhancing targeted delivery, pharmacokinetics, and therapeutic effectiveness. Liposomal paclitaxel increases medication concentrations at the target site and has a more potent anti-tumor impact compared to traditional formulations. The amalgamation of paclitaxel with additional medicines, such as sirolimus, in stents may yield synergistic effects in the prevention of restenosis and tumor suppression. Liposomal formulations, when combined with adjunctive drugs, present compelling opportunities for improved accuracy and efficacy in therapies. Liposomal paclitaxel significantly improves targeted drug delivery, offering potential for enhanced outcomes in cancer therapy and cardiovascular interventions, including drug-eluting stents and drug-coated balloons in interventional radiology. New drug delivery systems of the clinical application of Paclitaxel has been fundamentally transformed by advanced delivery technologies that overcome its inherent limitations of poor solubility and systemic toxicity. Nano-Formulation Superiority: Modern nanotechnology, particularly nanocrystals and liposomes, has established a new standard by eliminating toxic solvents such as Cremophor EL. Those carriers enable 100% drug loading and precise targeted delivery, significantly improving the safety-efficacy balance.

KEYWORDS: paclitaxel, drug-eluting stent, paclitaxel carriers, controlled drug release, nano-formulations.

1. INTRODUCTION

Paclitaxel is a prominent natural compound used for the treatment of refractory cancers. It was discovered as part of a National Cancer Institute program where extracts of thousands of plants were screened for anticancer activity more than half a century ago.[1-2]

Paclitaxel is derived from Taxus brevifolia, also known as the yew tree, a rare and slow-growing evergreen found in the old-growth forests of the Pacific Northwest. Humanity has made use of the yew since the beginning of time in order to make spear points and other weapons; household implements and diverse tools. Although throughout history it had mythological associations with death, today yew is responsible for one of the most widely used anticancer agents in the world.[3-5]

2. Discovery of paclitaxel

Samples of the Pacific yew's bark were initially collected in 1962 by Arthur Barclay and other investigators from the US Department of Agriculture, contracted by the National Cancer Institute to find natural products that might treat cancer. They were then sent to Wisconsin Alumni Research Foundation in order to prepare crude extracts to be tested on oral epidermoid carcinoma cell culture – a cell line derived from human cancer.[6-9]

Two years later, doctors Monroe Wall and Mansukh Wani, together with their colleagues at the Research Triangle Institute's Natural Product Laboratory in Research Triangle Park of North Carolina discovered that extracts from that bark showed significant cytotoxic activity. Wall decided to name the substance "taxol" because they were sure it was alcohol, and also because it was a common practice to name a discovered molecule after the genus of the originating plant.[10-14]

In 1965 more samples of bark were collected and sent to Wall's group for identification and subsequent purification of the active component. Even though the isolation of paclitaxel (or "taxol") in pure form took several years, the chemical structure was finally published in 1971.[14]

Antitumor activity of paclitaxel was confirmed in 1977 in mouse melanoma B16 model, after which it was selected as a candidate drug for clinical development.[10, 13-16]

In August 1978, researcher Susan Horwitz successfully demonstrated that paclitaxel was able to prevent cell division via an interesting mechanism – stimulating the development of microtubules (cell's ultrafine filaments). While previous compounds killed cancer cells by preventing the production of microtubules and thus inhibiting the division, the overproduction of microtubules disrupts proper coordination of cell division.[10, 13-16]

Paclitaxel is a hydrophobic mitotic inhibitor with a powerful anti-cancer effect. It belongs to the group of taxanes, which are potent cytotoxic diterpenes derived from yew trees. Paclitaxel is active against a spectrum of malignancies that are generally considered to be refractory to conventional chemotherapy.[15, 17]

3. Structure and nomenclature

Paclitaxel is in a form of whitish crystalline powder which is highly lipophilic, thus very insoluble in water. It contains a heptadecane (17-carbon) skeleton with a molecular weight of 853.9 Da and a melting point around 216°C. The antitumor activity of the drug is mainly due to the side chain, A ring, oxetane ring and C2 benzoyl group (Figure 1).

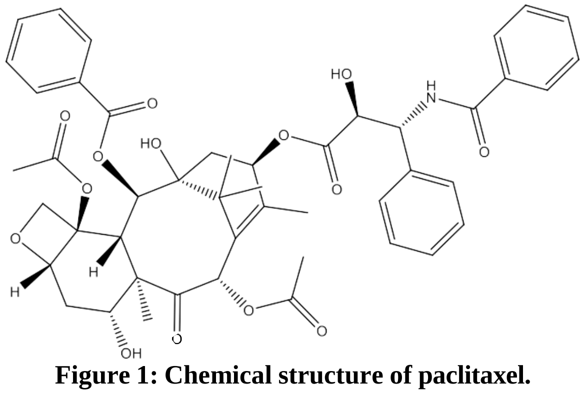

Figure 1: Chemical structure of paclitaxel.

The drug was approved by the US Food and Drug Administration (FDA) and has been marketed since 1992.[10,18] In 2005, the FDA approved a nanoparticle paclitaxel (also known as nab-paclitaxel). That form of the drug showed better effectiveness and lesser toxicity when compared to original paclitaxel.[15, 18, 19]

4. Range of activity

Paclitaxel is an effective anticancer agent against ovarian, lung, breast, prostate, liver, gastric and pancreatic cancer. It has also shown beneficial effects on melanoma, head and neck squamous cell carcinoma, anaplastic thyroid carcinoma and some other types of malignant tumors.[7, 20]

Although the list of cancers targeted by paclitaxel is still expanding, its main role to date is treating metastatic carcinoma of the ovary, non-small cell lung carcinoma, metastatic breast cancer and as a second-line agent in AIDS-related Kaposi's sarcoma.[18, 20, 21]

Paclitaxel can also act as an anti-proliferative agent. Stent-based elution of paclitaxel considerably reduces neointimal hyperplasia, angiographic restenosis and the need for repeated revascularization in patients undergoing percutaneous coronary interventions.[21,22]

Paclitaxel is currently being studies for other diseases that require stabilization of microtubules and the avoidance of angiogenesis and cell proliferation. One example is psoriasis, one of the most baffling and persistent skin disorders. As there is an ongoing research of paclitaxel as a potential treatment for Alzheimer's or Parkinson's disease, the magnitude of the drugs' usefulness could be even bigger.[24]

5. Methods of paclitaxel production

Throughout the development of paclitaxel, which is one of the most successful anticancer drugs of the past 50 years, adequate supply has remained a major challenge. The drug has been very complex to synthesize economically from first principles and cumbersome to isolate from natural sources. In addition, paclitaxel represents only a minor proportion of the total taxoid content of the Taxus species.[11, 22]

The first commercial company to accomplish large-scale production of paclitaxel was Polysciences, Inc.

Clinical trials were possible when a methodology was derived to extract a precursor of the drug, 10-deacetyl-baccatin III, from the common evergreen yew tree Taxus baccata, which is often found in people's gardens. By chemical synthesis procedures, the precursor was subsequently converted to paclitaxel.[26, 27]

Since the discovery of paclitaxel, a sustainable increase of its extraction was the principal goal of the pharmaceutical industry. A serious obstacle is the aforementioned low proportion of paclitaxel, even in the most productive species, Taxus brevifolia (0.001-0.05%).[3, 4, 8, 14]

In 2004, the company Yewcare began to plant Taxus chinensis in the Chinese province of Yunan, currently covering more than 30 km^2 in monoculture.

The chemical synthesis of paclitaxel was first achieved by Holton and Nicolau in 1994; however, the low yield limit combined with the complexity of its biosynthesis hampered its applicability. An alternative approach is producing paclitaxel by semisynthesis through the use of intermediates from the needles of the European yew. Plant cell cultures represent an alternative and environmentally sustainable source of paclitaxel. Some advantages of that method include the growth of the material that is independent of its original location, thus preventing those materials from being subject to seasonality or weather.[17, 21]

In 1993, an endophytic taxol-producing fungus was found in Taxus; however, fungal fermentation was shown to give low yields of paclitaxel. Nevertheless, Cytoclonal Pharmaceutis, Inc. patented the process and, in 2001, signed a contract with Bristol-Myers Squibb for the development of new methodology based on microbial fermentation for paclitaxel and other new taxane therapeutics.[4, 8, 1415]

6. Pharmaceutical products

Paclitaxel is available in several intravenous (IV) dosage forms for oncological treatment, designed to address the drug's poor water solubility and formulation challenges.[18]

Figure 2: Example of paclitaxel injection for cancer treatment.

The primary oncologic dosage forms are.

6.1. Solvent-based Injections (e.g., Taxol and generics)

The original formulation is a clear, colorless to slightly yellow viscous solution for injection, which is diluted before IV infusion. It uses a nonaqueous vehicle containing Cremophor EL (polyoxyl 35 castor oil) and dehydrated ethanol to solubilize the paclitaxel. Due to the potential for severe hypersensitivity reactions to the excipient Cremophor EL, patients require premedication with corticosteroids and antihistamines.[6, 15]

6.2. Albumin-bound Nanoparticle Formulation (e.g., Abraxane, nab-paclitaxel)

It is a newer, solvent-free dosage form where paclitaxel is bound to human serum albumin nanoparticles. That formulation (a lyophilized powder for injection, reconstituted into a suspension) eliminates the need for Cremophor EL, thus reducing the risk of hypersensitivity reactions and the necessity for premedication. It also allows for a higher dose to be administered over a shorter infusion time.[28, 19]

6.3. Liposomal Formulations (e.g., Lipusu, Genexol-PM)

Those formulations encapsulate paclitaxel within liposomes (lipid vesicles) or polymeric micelles to improve solubility and reduce toxicity. Those are administered by IV infusion and offer similar efficacy to the original paclitaxel with potentially fewer side effects.[29, 30]

All currently approved commercial formulations of paclitaxel are IV administered. Other dosage forms, such as oral formulations using self-microemulsifying drug delivery systems (SMEDDS) combined with P-gp inhibitors, are under investigation or used in specific clinical trials, but are not widely available commercially as standard oncological treatment.[21, 25]

7. Common Side Effects For Paclitaxel

Table 1: Side Effects For Paclitaxel.[12, 19, 30-34]

System/Category	Common Side Effects	Management/Notes
Blood & Immune System	Neutropenia (low WBC count) and infection	Requires frequent monitoring and preventative measures (hygiene, avoiding crowds) are essential.
	Anemia (low RBC count)	Can cause fatigue and weakness and may require blood transfusions in severe cases.
	Thrombocytopenia (low platelet count)	Increased risk of bruising and bleeding; avoid NSAIDs and rigorous activity.
	Hypersensitivity Reactions	Symptoms include flushing, rash, chest pain, and difficulty breathing. Premedication is necessary for solvent-based forms (Taxol).
Nervous System	Peripheral Neuropathy (numbness, tingling, pain in hands/feet)	A dose-limiting toxicity; usually reversible after treatment but can persist.
	Myalgia/Arthralgia	Can be managed with pain

	(muscle/joint pain)	relievers like acetaminophen.
Gastrointestinal	Nausea and Vomiting	Anti-nausea medications are typically prescribed; dietary changes can help.
Skin & Hair	Alopecia (hair loss, all body hair)	Hair typically regrows after treatment completion.
	Injection Site Reactions	Redness, swelling, pain, or hardening at the IV site. Report signs of extravasation immediately.
Cardiovascular	Bradycardia (slow heart rate) and Hypotension (low blood pressure)	Monitored during infusion; severe events are rare but possible.
Liver	Liver Toxicity (elevated liver enzymes)	Monitored via regular blood tests.

8. Drug Interactions

Table 2: Drug interactions and potential side effects.[21, 31]

Drugs	Potential Effect	Recommendation
CYP2C8 & CYP3A4 Inhibitors (Ketoconazole, Erythromycin, Clarithromycin, Fluoxetine, Grapefruit juice)	Increased paclitaxel levels, higher risk of toxicity.	Avoid or use alternate drugs/monitor closely.
CYP2C8 & CYP3A4 Inducers (Rifampin, Phenytoin, Carbamazepine, St. John's Wort)	Decreased paclitaxel levels, potentially reduced efficacy.	Avoid or monitor closely.
P-glycoprotein (P-gp) Inhibitors (Cyclosporin, Atorvastatin, Valspodar)	Increased intracellular accumulation of paclitaxel, enhanced neurotoxicity.	Use with caution and monitor for neuropathy.
Live Vaccines	Immunosuppression from paclitaxel may reduce vaccine effectiveness or cause infection.	Avoid live vaccines during treatment.
Doxorubicin	Increased risk of toxicity if given concurrently; reduced doxorubicin clearance.	A minimum 24-hour interval between administrations is recommended.
Palifermin	Increased severity and duration of oral mucositis.	Do not administer within 24 hours of paclitaxel.

Liposome formulations improve paclitaxel bioavailability by altering its pharmacokinetics and biodistribution, primarily through enhanced solubility, prolonged circulation time, and targeted accumulation in tumor tissues.[17, 24, 29]

9. Mechanisms of Improved Bioavailability

9.1. Enhanced Solubility

Paclitaxel is highly hydrophobic and poorly soluble in water, which limits its systemic availability. Encapsulating the drug within the lipid bilayer of liposomes effectively addresses the solubility issue, allowing for the creation of a stable, concentrated IV solution without the need for toxic cosolvents like Cremophor EL.[6, 29]

9.2. Avoidance of First-Pass Metabolism and Efflux Pumps

By being encapsulated within a nanocarrier, the drug is protected from rapid metabolism and inactivation in the plasma or the liver. The liposomes also help to bypass P-glycoprotein (P-gp) efflux pumps in cell membranes, which typically pump free paclitaxel out of cells and significantly limit its absorption and effectiveness.[5, 7, 15, 16, 19]

9.3. Prolonged Circulation Time

Standard paclitaxel is quickly cleared from the bloodstream. Liposomal formulations, especially those that are "PEGylated" (coated with polyethylene glycol), evade the body's immune system (mononuclear phagocytic system in the liver and spleen), which significantly increases their half-life in the bloodstream (from a few hours to nearly 50 hours in some studies).[13, 18, 29]

9.4. Passive Tumor Targeting (enhanced permeability and retention effect - EPR effect)

Tumors often have "leaky" blood vessels with wider gaps than healthy tissue, and inefficient lymphatic drainage. Liposomes, due to their size (typically 60-150 nm), can passively seep through those gaps and accumulate within the tumor microenvironment.[29, 35, 36]

9.5. Reduced Toxicity of Vehicle

The original paclitaxel formulation's excipient, Cremophor EL, is associated with severe hypersensitivity reactions and neurotoxicity, which requires patient premedication and limits the administered dose. Liposomal formulations replace the toxic vehicle, leading to a better safety profile and allowing for higher doses to be administered over shorter periods, enhancing overall drug delivery and efficacy.[6, 28]

10. Industrial Paclitaxel Formulations

Table 3: Industrial Formulations for IV administration of paclitaxel.[2, 5, 9, 13, 18-22]

Feature	Taxol (and Generics)	Abraxane (nab-paclitaxel)	Liposomal Formulations (e.g., Lipusu, Genexol-PM)
Formulation Type	Solvent-based IV solution	Albumin-bound nanoparticles (IV suspension)	Lipid vesicle encapsulation (IV suspension)
Excipients	Cremophor EL, dehydrated ethanol, citric acid	Human serum albumin	Phospholipids (e.g., phosphatidylcholine)
Premedication Required?	Yes (corticosteroids, antihistamines due to Cremophor EL)	No (Cremophor-free)	No (Cremophor-free, reduced toxicity)
Maximum Tolerated Dose	Lower (~240 mg/m²)	Higher (~300 mg/m²)	Higher (reduced systemic toxicity allows higher dose)
Hypersensitivity Risk	Significant risk	Very low risk	Very low risk
Availability	Globally approved	Globally approved	Approved in specific regions (e.g., China, South Korea)

In summary, liposomes act as protective, highly effective transport systems that fundamentally change how paclitaxel behaves in the body, ensuring more of the drug reaches the tumor site efficiently and safely.[6, 29]

11. Benefits of Liposomal Formulations

Liposomal formulations offer several key advantages over conventional, solvent-based paclitaxel: Table 4. Advantages of liposomal paclitaxel formulations for chemotherapy.[18, 29]

Benefit	**Description**
Reduced Toxicity	Eliminates the need for toxic solvents like Cremophor EL, significantly lowering non-hematologic side effects such as nausea, vomiting, alopecia, and neurotoxicity.
Improved Bioavailability/Efficacy	The nanoparticle structure allows the drug to accumulate preferentially in tumor tissues via the EPR effect, delivering a higher local concentration of the drug to the cancer cells.
Higher Maximum Tolerated Dose	The lower systemic toxicity profile allows for the safe administration of higher doses of paclitaxel.
Prolonged Circulation Time	Encapsulation protects the drug from rapid degradation and clearance by the body, extending its half-life in the bloodstream.
Enhanced Stability	The lipid encapsulation protects the active ingredient, improving its stability in vivo compared to free drug formulations.

12. Future approaches

Suprageneric versions of paclitaxel were developed, such as nanoparticle albumin-bound paclitaxel (Abraxis Oncology's Abraxane) and polyglutamate paclitaxel (Cell Therapeutics' Xyotax). Their advantages are in terms of drug delivery and a lower number of side-effects.[5, 29]

Recent insights into paclitaxel drug-eluting stents (DES) highlight a move toward polymer-free designs and a significant rise in the use of drug-coated balloons (DCBs) as alternatives. While paclitaxel remains effective for peripheral artery disease (PAD), new data emphasizes its limited efficacy in the specific hypoxic environment of coronary lesions compared to "limus" drugs (sirolimus and derivatives).[2, 9, 22, 23]

13. Key Insights in Paclitaxel DES and Drug-Coated Devices

13.1. Shift to Polymer-Free Designs

A major trend in paclitaxel stent technology is the development of polymer-free coatings. That approach aims to deliver the drug to the arterial wall without leaving behind a permanent polymer, which can cause long-term inflammation and delayed healing (reendothelialization), potentially leading to late stent thrombosis. Stents using microdrop spray crystallization for a polymer-free paclitaxel coating are being evaluated in clinical trials.[2, 9, 24]

13.2. Dominance of Limus Drugs in Coronary Arteries

In the treatment of coronary artery disease (CAD), second and third-generation DES predominantly use sirolimus or its derivatives (everolimus, zotarolimus). Recent research indicates that sirolimus has superior anti-proliferative effects in the hypoxic (low oxygen) microenvironment typical of advanced atherosclerotic plaques, where paclitaxel's efficacy is significantly weakened. That difference in mechanism makes limus drugs more suitable for preventing restenosis in the coronary arteries.[37]

13.3. Paclitaxel's Role in Peripheral Arteries (PAD)

Paclitaxel-coated devices continue to show positive outcomes in treating blockages in the femoropopliteal arteries (legs), reducing the need for repeat procedures. Five-year data released in 2024 reaffirmed the safety and effectiveness of paclitaxel in PAD treatment, finding no significant difference in all-cause mortality compared to non-coated devices in several large studies, which allayed previous safety concerns raised in prior meta-analyses.[5, 11, 27, 29]

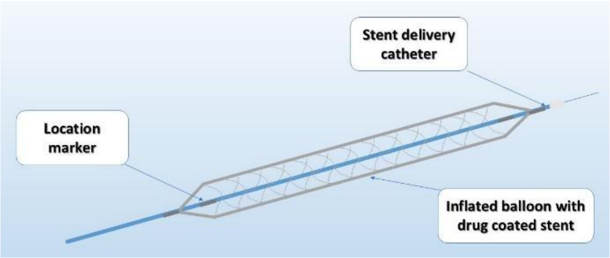

Figure 2: Drug Eluting Stent with paclitaxel.

13.4. Rise of Drug-Coated Balloons (DCBs)

DCBs, which deliver paclitaxel without a permanent metallic scaffold, have emerged as a significant alternative, particularly for in-stent restenosis (ISR) and small vessel disease. Long-term data from trials like ISAR-DESIRE 3 found no significant difference in mortality endpoints between paclitaxel-eluting balloons and paclitaxel-eluting stents for ISR, demonstrating DCBs as a safe and effective "leave nothing behind" treatment strategy.[9, 11]

Recently, sirolimus and its derivatives have been used in the study of DCB. Compared with paclitaxel, the transfer rate of sirolimus and its derivatives is poor and needs to be retained in tissues for a long time. At present, several local balloon-based administration methods of sirolimus and its derivatives have been proposed. In the preclinical model, the biological effect of using zotamox instead of paclitaxel coating was confirmed.[24]

At present, paclitaxel is still the first choice for DCB, and the conventional dose is 2 ~ 3.5µg /mm^2.

Different coating formulation and coating technology can bring different pharmacokinetic characteristics, which is one of the key factors for successful drug transfer. Therefore, the interaction among drug dosage, preparation, release kinetics and lesion seem to be the key to the vascular response after DCB treatment.[9, 22-24]

For uncomplicated lesions, it is recommended to use hemispheric saccule or non-compliant balloon with the same diameter as the artery. In the case of expected vessel filling or potential insufficient size and difficult balloon delivery, we can start with a smaller balloon and reassess the vessel size after the use of vasodilators. If the standard semi-compliant balloon fails to expand, a high-pressure noncompliant balloon or cutting balloon is recommended.[29, 38]

13.5. Focus on Drug Release Kinetics

Innovations are exploring advanced coatings with programmable pharmacokinetic release capabilities to optimize drug delivery profiles.

In essence, new insights show that while paclitaxel DES remains an effective solution in peripheral applications, advancements in coronary intervention have largely favored limus-based therapies due to their superior performance in the specific coronary microenvironment, and the technology is generally trending towards polymer-free solutions or balloon-based delivery systems.[6, 37]

Standard paclitaxel contains Cremophor EL as a solvent, thus requiring premedication with high doses of antihistamines and corticosteroids, as well as prolonged infusion times. Albumin-bound or nab-paclitaxel was developed to overcome such limitations, ensure more convenient drug administration, and improved toxicity profiles.[7, 15, 19]

13.6. Hypersensitivity reactions

The early development of paclitaxel was hampered by the high incidence of major hypersensitivity reactions which, in some studies, approached 30%. Initial observations pointed to the histamine and other vasoactive substances as culprits in the development of those hypersensitivity reactions.[7, 11, 15]

A majority of affected individuals who have presented with type 1 hypersensitivity reactions have primarily shown signs of dyspnea, urticaria, and hypotension. Other common symptoms included chest or back pain, excess perspiration or sweating, and pruritus. Oral premedication with dexamethasone given orally at 12 and 6 hours before infusion of paclitaxel has been shown to significantly reduce the incidence of paclitaxel-induced hypersensitivity reactions. In addition, patients suffering from major hypersensitivity reactions rechallenged with paclitaxel after receiving high doses of corticosteroids have been free of recurrences, although the universal success of that approach has not been demonstrated.[20, 21, 25]

13.7. Neuropathies

Paclitaxel is able to induce peripheral neuropathy characterized by sensory symptoms such as paresthesia and numbness in a glove-and-stocking distribution. Symmetrical loss of sensations including proprioception, vibration, pinprick, and temperature, is also frequently noted.

Symptoms usually occur between 24 and 72 hours following paclitaxel treatment with higher doses of the drug (>250 mg per square meter), although they usually occur after multiple courses at conventional dosage protocols (< 200 mg per square meter). Severe neurotoxicity is quite rare when administering conventional doses, even in patients with prior exposure to neurotoxic agents such as cisplatin. When severe neurotoxicity ensues, it precludes further administration of high doses of the drug for up to 24 hours.[6]

Autonomic and motor dysfunction can also represent a problem of paclitaxel therapy, namely in patients with preexisting neuropathies caused by alcoholism, diabetes mellitus, and other pathological conditions. The optic nerve can be affected as well, denoted by scintillating scotoma. When it comes to nab-paclitaxel-induced sensory neuropathy, prior history of chemotherapy and dosing schedule are important factors in the development of the disorder.[33]

There is a common occurrence of transient myalgia (muscle pain), usually observed two to five days after therapy at doses above 170 mg per square meter. Insidious myopathy has been observed with high doses of paclitaxel, often in combination with the aforementioned cisplatin.[6]

13.8. Other common side-effects

One of the principal toxic effects of paclitaxel is non-cumulative neutropenia, which is an abnormally low count of neutrophils, suggesting that immature hematopoietic cells are not irreversibly damaged. The drug can also reduce the number of erythrocytes, resulting in anemia, as well as thrombocytes, which can result in bruising and bleeding.[32, 33]

Normal cardiac rhythm can be disturbed, and the most common manifestation is transient asymptomatic bradycardia. Cardiac monitoring is therefore advisable for patients with ventricular dysfunction and those who may not be able to fully tolerate the drug's potential bradyarrhythmia.[1, 34]

Gastrointestinal effects such as diarrhea and vomiting are also frequent, particularly upon administration of higher doses. Such conditions necessitate at least two liters of fluids every day. Patients with leukemia are especially prone to mucositis and breakdown of the mucosal barrier.[31] Inflammation at the injection site along the course of the vein and in areas where the drug leaves the blood vessel may rarely occur, as well as the consequent inflammatory skin reactions.[31]

14. Oncology Formulations and Bioavailability

14.1. Excipient Interference

The original solvent, Cremophor EL (CrEL), is essential for initial IV solubility but causes severe hypersensitivity reactions and significantly hinders oral bioavailability by forming micelles that trap the drug and influencing P-glycoprotein (P-gp) efflux pumps.[6]

14.2. Novel Formulations are Key

To improve bioavailability and safety, industrial innovations have moved beyond solvent-based systems to albumin-bound nanoparticles (e.g., Abraxane) and liposomal formulations (e.g., Lipusu, Genexol-PM). Those alternatives eliminate toxic solvents, enhance solubility, extend the drug's circulationtime, and facilitate passive targeting of tumors via the Enhanced Permeability and Retention (EPR) effect.[2, 9, 11, 22-24, 27, 29]

14.3. Oral Bioavailability Remains a Challenge

Achieving effective oral paclitaxel treatment remains difficult, requiring specialized systems (SMEDDS) often co-administered with P-gp inhibitors like encequidar to counteract intestinal efflux mechanisms.[39]

14.4. Side Effects and Interactions

14.4.1. Toxicity Mitigation

The primary conclusion regarding side effects is that modern, solvent-free formulations significantly reduce the risk of severe hypersensitivity reactions and associated premedication burdens compared to older formulations.[1]

14.4.2. Dose-Limiting Factors

Myelosuppression (low blood counts) and peripheral neuropathy remain the primary dose-limiting toxicities across all formulations.[31, 38]

14.4.3. Metabolic Interactions

Paclitaxel is extensively metabolized by liver enzymes (CYP2C8 and CYP3A4). Co-administration with inhibitors or inducers of those enzymes can dangerously alter drug levels, necessitating careful medication management.[40, 41]

14.5. Paclitaxel in Drug-Eluting Stents (DES)

14.5.1. Application-Specific Efficacy

A critical insight is that the effectiveness of paclitaxel is site-specific. It remains a valuable anti-proliferative agent for treating PAD, where data reaffirms its safety and long-term efficacy in preventing restenosis.[2]

14.5.2. Coronary Artery Limitations

In contrast, paclitaxel has largely been superseded by "limus" drugs (sirolimus, everolimus) for CAD. Limus drugs perform better in the hypoxic conditions typical of coronary lesions.[38]

14.5.3. Technological Shift

The field of vascular intervention is moving toward "leave nothing behind" technologies, such as drug-coated balloons (DCBs) and polymer-free stents, to reduce long-term inflammation risks associated with permanent polymers.[42]

15. CONCLUSION

In 2025, paclitaxel remains a foundational therapeutic agent**,** bridging the worlds of systemic oncology and localized cardiovascular intervention through its potent ability to stabilize microtubules and inhibit cell division. Despite historical concerns regarding a "late mortality signal" in peripheral devices, 2025 consensus suggests that the benefits in patency and quality of life often outweigh risks, especially with improved patient-level monitoring and modern device designs. Paclitaxel research highlights that paclitaxel may offer antiplatelet and antithrombotic effects within stents, potentially reducing the risk of local blood clots beyond its primary anti-proliferative role.

Conflict of Interest

The authors declare no conflict of interest.

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