Paclitaxel is an important anticancer agent used in the treatment of a variety of malignancies including breast, ovarian and non-small-cell lung cancers. The mechanism of action is unique in that it promotes irreversible polymerization of tubulin leading to microtubule stabilization and cell cycle arrest\(^1\). The use of paclitaxel is restricted by several dose limiting side effects such as neutropenia, neurotoxicity and hypersensitivity reactions related to formulation\(^2\). Due to poor water solubility, paclitaxel is formulated with Cremophor EL, a polyethoxylated castor oil. This detergent releases histamine, requiring long infusion times, and premedication with antihistamines and steroids\(^3\). One strategy to overcome these challenges is the creation of paclitaxel prodrugs. Early attempts at prodrug design sought to increase water solubility by adding small molecules like amino acids, sulfonates, and sugars to paclitaxel. Although water solubility was increased, the compounds had poor activity and were unstable in aqueous solution. More promising small molecule prodrugs include amino esters, pyridinium salts and carbonates. All had improved water solubility and similar \textit{in vitro} and \textit{in vivo} activity compared to the parent drug although results from human trials were less promising\(^4\). Other prodrugs lack a promoiety and rely on N-O intramolecular acyl migration to reveal the active drug\(^5\). Another strategy aims to reduce nonspecific side effects and increase drug concentration by targeting tumor cells. Some agents are activated by overexpressed enzymes while others exploit hypoxic tumor tissue. The least developed tumor targeting method is ADEPT. This approach has potential but requires further study to adequately release the drug under physiologic conditions. The last category of prodrugs consists of macromolecules that accumulate in tumor cells due to enhanced permeability. Although many paclitaxel prodrugs have been synthesized, the complexity and challenges of prodrug design is proven by the lack of prodrug availability in the clinical setting. The prodrug must be stable to ensure proper drug delivery but also release the active drug efficiently. \textit{In vivo} testing is important with prodrugs since \textit{in vitro} data does not always correlate. The most valuable prodrugs are those that target malignant tissue as they may lead to more effective and less toxic anticancer agents.

References:


