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Microtubule Stabilizing Agents in Clinical Oncology

The Taxanes

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SUMMARY

The taxanes are a versatile and important class of drugs that target microtubules. Paclitaxel and docetaxel are some of the most widely used cancer chemotherapeutic agents in clinical oncology. In this chapter, we discuss the most common dose and treatment schedules, clinical efficacy, and the toxicity profiles of these agents in detail.

Key Words: Taxanes; paclitaxel; docetaxel.

1. INTRODUCTION

The taxanes represent one of the most important and clinically useful classes of anti-cancer agents in all of clinical oncology. Initial studies of the taxanes began in 1963 when natural product screening programs demonstrated that extracts of the bark of the Pacific yew tree (Taxus brevifolia) had antitumor activity (1,2). Several years later, Monroe Wall and colleagues (3) identified paclitaxel as the active component in these crude extracts. Early studies of the taxanes were limited by the difficulties in preparing sufficient quantities of paclitaxel for pharmacological testing and by its poor aqueous solubility. However, further interest in this novel agent was stimulated by pioneering studies by Horowitz and colleagues that characterized paclitaxel’s novel mechanism of action as a microtubule stabilizer (4,5). Subsequent studies of related compounds led to the synthesis of docetaxel, a semisynthetic derivative of 10-deacetylbbaccatin III, which is an inactive but much more easily isolated taxane precursor found in yew tree needles. The yew tree needles represent a renewable resource that is much more readily available than tree bark (6).
Paclitaxel and docetaxel are both complex ester derivatives that share a common taxane 15-ring structure bound to an oxetan ring. Structurally, paclitaxel and docetaxel differ in the nature of the substitutions on the C13 ester side chain and in the alkyl groups bound to the C10 carbon. These structural differences render docetaxel slightly more water soluble than paclitaxel; however, both taxanes share a common binding site on the β-tubulin subunit that localizes to the inner surface of the microtubule lumen. These binding regions are completely distinct from those used by colchicine and the vinca alkaloids. Taxane binding results in the stabilization of polymerized microtubules by promoting the nucleation and elongation phases of microtubule assembly; thereby reducing the tubulin protein concentration required for microtubule formation (1,2). Docetaxel has about a twofold higher binding affinity for β-tubulin and may have slightly higher in vitro potency. This taxane-induced stabilization alters microtubule dynamics, ultimately interfering with mitotic spindle formation. This disruption can induce p53 expression and inhibit cyclin-dependent kinases resulting in cell cycle arrest in mitosis, identified on fluorescent activated cell sorter analysis as arrest in the G2M phase of the cell cycle (G2M arrest). Subsequently, inactivation of the antiapoptotic Bclx1/Bcl-2 proteins occurs and apoptosis ensues. The similarity of action of paclitaxel and docetaxel raises the question of whether complete clinical cross resistance exists between the taxanes. The clear clinical activity of one taxane in cancer patients truly refractory to another has not been unequivocally demonstrated. A detailed discussion of the taxane’s mechanism of action is provided in Chapter 13.

Taxane resistance has been associated with enhanced drug efflux from cells mediated by the multidrug resistance gene, MDR1 that encodes for the membrane-associated drug efflux pump, P-glycoprotein (7). Other less well-characterized transporters may also be important in mediating clinical taxane resistance. In cell lines, mutations in the α- and β-tubulin subunits have been characterized that promote taxane resistance; however, the importance of these mutations in the clinical setting has not been determined (8,9). Finally, the increased expression of antiapoptotic proteins such as Bcl-2 may also confer a relative degree of resistance to the taxanes.

2. PACLITAXEL

2.1. Doses/Schedules

Paclitaxel has been administered as an intravenous infusion in schedules ranging in duration from 1-h to as long as 96-h. In early studies of 6 h infusion schedules, the pharmacokinetics of the drug in plasma was characterized by a biphasic process with dose proportional kinetics (1,2,10,11). However, detailed pharmacokinetics analyses of shorter 3 h paclitaxel infusions demonstrate nonlinear pharmacokinetics with saturable drug distribution and elimination. These shorter infusions are associated with higher plasma concentrations of the Cremophore™ vehicle, which may contribute in part to paclitaxel’s nonlinear kinetics (12).

Paclitaxel is the most commonly administered at doses ranging from 175 to 200 mg/m² infused during 3 or 24 h every 3 wk. Prophylactic administration of glucocorticoids and H1 and H2 antagonists to prevent hypersensitivity reactions is considered routine when administering paclitaxel chemotherapy. Because longer infusion schedules have not demonstrated clear superiority during shorter infusion durations, most oncologists administer 175 mg/m² of paclitaxel as a 3-h infusion. In addition, weekly drug administration