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Microtubule-stabilizing agents: New drug discovery and cancer therapy

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ABSTRACT

Microtubule-stabilizing agents (MSAs) have been highly successful in the treatment of cancer in the past 20 years. To date, three classes of MSAs have entered the clinical trial stage or have been approved for clinical anticancer chemotherapy, and more than 10 classes of novel structural MSAs have been derived from natural resources. The microtubule typically contains two MSA-binding sites: the taxoid site and the laulimalide/peloruside site. All defined MSAs are known to bind at either of these sites, with subtle but significant differences. MSAs with different binding sites may produce a synergistic effect. Although having been extensively applied in the clinical setting, paclitaxel and other approved MSAs still pose many challenges such as multidrug resistance, low bioavailability, poor solubility, high toxicity, and low passage through the blood–brain barrier. A variety of studies focus on the structure–activity relationship in order to improve the pharmaceutical properties of these agents. Here, the mechanisms of action, advancements in pharmacological research, and clinical developments of defined MSAs during the past decade are discussed. The latest discovered MSAs are also briefly introduced in this review. The increasing number of natural MSAs indicates the potential discovery of more novel, natural MSAs with different structural bases, which will further promote the development of anticancer chemotherapy.

Contents

1. Introduction

Microtubules, composed of α- and β-tubulin heterodimers, are crucial to the function of eukaryotic cells as the key components of the cytoskeleton. In cells, microtubules are characterized by the high dynamics of polymerization/depolymerization, resulting in the net elongation/shrinkage of the filaments. The microtubule dynamics are precisely controlled to regulate several important processes in living cells, such as cell shape maintenance, intracellular transportation, signal transduction, cell division, and mitosis (Jordan & Wilson, 2004). Some intrinsic cellular factors, such as microtubule-associated proteins and microtubule motor proteins (kinesins) offer precise control of the microtubule dynamics (Bhat & Setaluri, 2007). Any disturbance in the microtubule dynamics may cause cell cycle arrest and lead to cell death.

Due to their crucial roles in dividing cells, microtubules have been considered a major target in cancer therapy. Microtubule-interacting drugs can be classified into two main groups based on their apparent mechanisms of action: microtubule-destabilizing agents (MDAs) and microtubule-stabilizing agents (MSAs). MDAs, for example, vinca

Abbreviations: MDA, Microtubule-destabilizing agent; MDR, Multidrug resistance; MSA, Microtubule-stabilizing agent; P-gp, P-glycoprotein; SAR, Structure–activity relationship.

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alkaloids and colchicines, prevent the polymerization of tubulin and promote the depolymerization of microtubules. By contrast, MSAs, such as taxanes and epothilones, prevent the depolymerization of microtubules and promote the polymerization of tubulin to microtubules (Ojima et al., 2014). Members of both groups have been proven successful in clinical anticancer chemotherapy.

Since the discovery of the first defined MSA paclitaxel in the 1960s, a variety of MSAs have been derived primarily from natural resources. At the molecular levels, all of the defined MSAs share two common features: i) at micromolar concentrations, MSAs reduce the equilibrated concentration of free tubulin (critical concentration) in the in vitro system of tubulin polymerization, and ii) at sub-micromolar or nanomolar concentrations, MSAs are considered to suppress the microtubule dynamics, thus leading to the formation of more stable filaments. It is worth noting that MDAs apparently share the same mechanism of microtubule dynamics suppression as that of MSAs at low concentrations (Jordan & Wilson, 2004). However, further studies on the binding modes of MSAs with microtubules have shown the presence of different binding sites and modes for various MSAs. To date, at least two MSA-binding sites have been confirmed: the taxoid-binding site located in β-tubulin at the luminal side of microtubules, and the laulimalide/peloruside site also located in β-tubulin but on the outer surface of microtubules (Prota et al., 2014). Moreover, an external pore type I site has been suggested in association with the taxoid site (Field et al., 2013). At the cellular levels, although the exact mechanism remains to be elucidated, MSAs apparently act by inducing mitotic block and causing subsequent apoptosis. Flow cytometry analyses showed that most apoptotic cells are blocked at the G2/M stage of the cell cycle, whereas some either undergo arrest in or reenter the interphase without undergoing cytokinesis (Chen & Horwitz, 2002; Chen et al., 2003; Jordan et al., 2002).

In a previous article, we summarized the structure and pharmacological activities of known MSAs, as well as the advancements and limitations in terms of their clinical use (Zhao et al., 2009). In this review, we focus on the advancements in pharmacological research and the clinical developments of MSAs during the past decade. Newly discovered MSAs from natural resources are also discussed to promote further discovery of new anticancer drugs.

2. Microtubule-stabilizing agents in clinical research and development

2.1. Taxanes

Paclitaxel (Taxol®, 1), a diterpene isolated from the Pacific yew tree (*Taxus brevifolia*), was the first MSA to be discovered (Schiff et al., 1979). Tests in the early stages demonstrated the antileukemic and antitumor activities of paclitaxel. In subsequent preclinical and clinical studies, paclitaxel showed significant activity against some solid tumors. In 1992, paclitaxel was approved by the Food and Drug Administration (FDA) for the clinical treatment of metastatic ovarian cancer. A semisynthetic analogue of paclitaxel, and docetaxel (Taxotere®, 2), was subsequently approved in 1996. Since paclitaxel was first approved in clinical settings, the two clinically available taxanes have been proven the most important first-line chemotherapeutic agents to treat solid tumor malignancies.

Typically, paclitaxel and docetaxel are administered intravenously. However, their clinical use has been limited as both agents are poorly water soluble, leading to their high toxicity partially induced by the excipient Cremophor EL and low bioavailability. Many nanoparticle delivery systems have been developed without Cremophor EL with the aim of improving the water solubility and in turn reducing the toxicity of clinical taxanes, such as albumin (Kundranda & Niu, 2015), PEG-PCL (Wang et al., 2014), liposome (Zhang et al., 2005), Genexol-PM (Kim et al., 2004), AI850 (Mita et al., 2007), chitosan (Battogtokh & Ko, 2014), poly(2-oxazoline) (He et al., 2015), and β-cyclodextrin (Shah et al., 2015). An albumin-bound paclitaxel, known as nab-paclitaxel or Abraxane, was developed to improve the water solubility of paclitaxel. The Cremophor EL-free formulation led to a significant reduction in severe allergic side reactions (Ibrahim et al., 2002). Moreover, nab-paclitaxel accumulates at a higher concentration in tumor tissues than paclitaxel. This may be attributed to the greater concentration of the acidic and cysteine-rich secreted protein in tumors than in normal tissues, which facilitates the easy binding of albuminized paclitaxel to tumor tissues (Desai et al., 2006; Yardley, 2013). In the in vivo test, nab-paclitaxel showed superior extravascular distribution and tumor penetration (Chen et al., 2015). Nab-paclitaxel was approved in 2005 by the FDA to treat metastatic breast cancer, in 2012 to treat local advanced or metastatic non-small cell lung cancer, and in 2013 to treat advanced or metastatic non-small cell lung cancer in combination with carboplatin.

In addition to new formulations, several novel paclitaxel analogues have also been developed to improve the solubility and oral bioavailability. Some have entered phase I or phase II studies, including IDN5109 (ortataxel, BAY 59–8862, 3) (Nicoletti et al., 2000; Tonkin et al., 2003), MAC-321 (milataxel, 4) (Lockhart et al., 2007; Ramanathan et al., 2008; Sampath et al., 2003), DJ-927 (tesetaxel, 5) (Saif et al., 2011; Shionoya et al., 2003), and BMS-275183 (6) (Bröker et al., 2006; Heath et al., 2011; Rose et al., 2001). Further novel taxoids for oral administration, such as MST-997 (7), are currently being investigated (Jing et al., 2014; Sampath et al., 2006). (See Fig. 1 for taxanes in clinical use or trials.)

Multidrug resistance (MDR) also hinders the clinical use of taxanes in cancer chemotherapy, often leading to clinical failure of the tumor therapy. It is well known that at least two main factors play a key role in MDR in the clinical setting: overexpression of the drug efflux pump, such as P-glycoprotein (P-gp), and of tubulin isotypes with increased dynamicity, primarily βIII tubulin (Cai et al., 2013). To overcome MDR, a series of novel taxoids, termed as second- and third-generation taxoids, have been developed by conducting structure–activity relationship (SAR) studies (Ojima et al., 2008; Ojima & Das, 2009; Otová et al., 2012). In general, the second-generation taxoids are highly potent against MDR cells, whereas the third-generation taxoids show similar potency against both drug-resistant and drug-sensitive cells.

Two strategies have been proposed to develop compounds capable of countering P-gp-mediated MDR: reducing the molecular affinity to P-gp and increasing the affinity to microtubules. Both strategies have been proven applicable. Some new-generation taxoids with greater efficacy against P-gp-mediated MDR cells, such as XRP9881 (larotaxel, 8) (Metzger-Filho et al., 2009) and XRP6258 (Jevtana®, cabazitaxel, 9) (Nightingale & Ryum, 2012; Vrignaud et al., 2013), have entered the clinical trial stage. In 2010, the FDA approved the use of cabazitaxel in combination with prednisone to treat metastatic castration-resistant prostate cancer. TPI-287 (10), a novel taxoid with poor P-gp-binding activity, was found to be capable of crossing the blood–brain barrier and to have significant activity against brain metastases of breast cancer (Fitzgerald et al., 2012), thus highlighting the potential new taxoids that can target brain tumors or metastases. A phase I trial of TPI-287 was recently conducted for the treatment of refractory or relapsed neuroblastoma or medulloblastoma (Mitchell et al., 2015).

Reports on the SAR of taxoids in terms of βIII tubulin-mediated drug resistance are scarce. IDN5390 (11), a seco-taxane, was found to have eightfold higher activity against resistant cells that overexpressed βIII tubulin than either paclitaxel-sensitive or P-gp-mediated drug-resistant cells (Ferlini et al., 2005). In addition, a series of novel C-seco-taxoids targeting βIII tubulin were synthesized (Pepe et al., 2009). However, to date, none of these βIII tubulin-targeting taxoids has entered the clinical trial stage.

2.2. Epothilones

Epothilone A (12) and B (13), two 16-membered macrolides in the myxobacterium *Sorangium cellulosum*, were first isolated and described for their antifungal activity in 1993. However, they were not extensively studied until their MSA-like activity was revealed in 1995. In vitro