A New Aspect of Microtubule Targeting Agents as Anti-Cancer Drugs

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Microtubule targeting agents (MTA) such as taxoids have revolutionized the treatment of cancer and improved patient survival. However, in clinical use, several drawbacks were observed: ineffectiveness against MDR tumors; side-effects due to low selectivity; and low solubility for i.v. administration due to the drugs' hydrophobic nature. Consequently, there is a significant need to develop new and improved MTA so that they are suitable and practical in clinical oncology. An interesting aspect of MTA is that they induce tumor-selective vascular collapse, thus deviating blood supply from the tumor tissues. These MTAs are referred to as a "vascular disrupting agents" (VDAs). We are currently performing MTA research on two projects: the development of novel VDA and water-soluble taxoid prodrug (isotaxoid). From a natural diketopiperazine, phenylahistin, exhibiting colchicine-like anti-microtubule activity, we developed a highly potent VDA, NPI-2358, that is effective against MDR tumor cells. This VDA is now in Phase I clinical trial as an anticancer drug in the US. We also developed a series of novel water-soluble taxoids, "isotaxoids", that are the 2'-*O*-isoform of taxoids. Isotaxoids exhibited improved water-solubility and appropriate kinetics for parent drug formation via a pH-dependent O-N intramolecular acyl migration reaction. The fact that an auxiliary is not used and byproducts are not produced from this prodrug is useful in improving the problematic MTAs.