SUMMARY

This chapter summarizes the preclinical and clinical development to date of investigational anticancer agents whose mechanism of action is thought to be via direct interaction with tubulin or microtubules. All of the compounds discussed are agents discovered or derived from screening natural materials for anti-cancer activity. The underlying theme for pursuit of these agents is that tubulin is a validated anticancer target and that novel interactions between new chemical entities and tubulin may overcome resistance, increase therapeutic index, or alter the spectrum of clinical utility against different cancer types.

Key Words: Epothilone; dolastatin; colchicine; investigational agents.

1. INTRODUCTION

Agents targeting the microtubule have been available in the clinic for more than four decades. Vinca alkaloids, originating from the periwinkle plant, were widely tested in the clinic during the 1960’s, and a decade later were incorporated into a number of combination chemotherapy regimens that are still in use today. The four major vinca alkaloids approved for use in various parts of the world are vincristine, vinblastine, vinorelbine, and vindesine. Owing to the unusually diverse spectrum of antitumor effects seen with this class, the vinca alkaloids remain in use as first- and second-line agents against a variety of malignancies. The nonclinical development of the taxanes
began in the 1960s as well. Because of difficulties in the isolation and purification of paclitaxel from the bark of the Pacific yew tree, it was not until the early 1990s that paclitaxel was widely studied in the clinic. Docetaxel, a semisynthetic taxane, became available for clinical use soon thereafter. Like the vinca alkaloids, taxanes have a diverse spectrum of activity, although the uses of these two classes in the clinic are divergent. Whereas both the vinca alkaloids and taxanes are natural products that bind tubulin, their molecular mechanisms and clinical spectra of efficacy differ in many ways. The tubulin binding sites of each are distinct; vinca alkaloids inhibit microtubule heterodimer polymerization, whereas taxanes stabilize the polymer. However, at low concentrations, both classes of agents can decrease the turnover rate, or “treadmilling,” of the tubulin heterodimers through microtubules.

There is little additional knowledge about the association between the site of tubulin binding, effect on microtubule dynamics and polymerization, and the ultimate clinically relevant anticancer effects of these agents. Is the relationship between altered microtubules and induction of apoptosis the most relevant? Or is suppression of antiapoptotic molecules paramount? How does modulation of microtubule dynamics of tumor-associated endothelial cells contribute to these agents’ anticancer activity? Why are these agents cancer specific? Whereas there are data that buttress one hypothesis or another, the link between the primary site of action at the microtubule and ultimate anticancer activity remains poorly understood. By extension, the link between the type of effect on the microtubule and spectrum of anticancer activity of a particular compound is perplexing. Therefore, drug discovery and development of agents directed against the microtubule remains empiric. It is no accident that the compounds discussed in this chapter are either natural products or their analogs. Investigators continue to rely on the creativity of evolution, which has provided a diversity of compounds that can screen for activity against this target. Pending a better comprehension of the process resulting in relatively selective anticancer (versus normal tissue) toxicity of these agents, and further understanding of the mechanism enabling each of these agents to have a unique clinically useful spectrum of activity, the investigational antimicrotubule agents in clinical trials are likely to share only two features. They will act on the microtubule, and they will be discovered by drug screening of molecular libraries mostly populated by the largess of nature.

Many of the agents discussed in this chapter exist naturally in some of the most isolated parts of the planet, in minute quantities, and in a highly impure form. A recurrent theme in drug development is the process of screening, isolation, purification, and synthesis of a lead drug candidate, which subsequently is subject to preclinical efficacy and toxicology evaluations. Despite extensive preclinical research, antimicrotubule agents continue to enter the clinic lacking adequate information concerning the relative likelihood of efficacy in a particular cancer type, which would allow clinical development targeted toward a particular tumor type, or with a specific molecularly defined phenotype. Therefore, phase one evaluation is usually a generic study of the human pharmacology of these agents, whereas phase two testing is necessarily broad, across many different schedules and tumor types. The extent of clinical testing may be primarily a result of business decisions concerning the identification of a potential registration niche. Without scientific rationale for pursuit of particular tumor types, there is usually no justification for restricted clinical evaluation.