Summary

As microtubules are important regulators of endothelial cell biology, it is not surprising that tubulin binding compounds have the potential to target the tumor vasculature. Two main uses of microtubule targeting compounds have been proposed. Tubulin binding agents can prevent the formation of new vessels (acting as inhibitors of angiogenesis) or damage the existing tumor vasculature (acting as vascular disrupting agents, VDA). Antiangiogenic and vascular disrupting microtubule targeting agents are hereby reviewed, with particular emphasis on their potentiality and limits in the clinical practice.

Key Words: Angiogenesis inhibitors; vascular disrupting agent (VDA); endothelial cells; tumor vasculature; combination therapy.

1. INTRODUCTION

In the recent years, the tumor vasculature has emerged as a promising target for cancer therapy. The development of a functional blood vessel network is critical for tumor growth, for the progression from a premalignant tumor to an invasive cancer, and for metastasis formation (1,2). The identification of agents affecting the tumor vasculature has become a highly active area of investigation from basic to clinical research. Theoretically, several advantages characterize this therapeutic approach. Damage to tumor vessels would have severe consequences on the hundreds of tumor cells that depend on them for survival, both at the early stage of tumor progression and later on advanced stage tumors (3). This therapy would be effective on all angiogenesis-dependent
solid tumors, independently on their histological type. The target endothelial cells are adjacent to the bloodstream, therefore easily accessible to the drug. Finally, as the target endothelial cells are a population of “normal”, nontransformed cells, the development of genetically driven resistance to therapy is unlikely.

Two approaches can be foreseen:

1. Antiangiogenic therapy, aimed at inhibiting angiogenesis, the formation of new vessels from pre-existing ones;
2. Vascular disrupting therapy, aimed at selectively destroying the already formed tumor vascular bed.

The mechanisms at the base of the two approaches, the effects on the tumors, and the therapeutic applications are very different (Fig. 1).

Antiangiogenic compounds prevent the formation of new vessels (1) either directly, by blocking endothelial cell functional response to stimulating angiogenic factors, or indirectly by interfering with the production, availability, or activity of angiogenic factors (2,4–6). The antiangiogenic approach exerts mainly a cytostatic effect, as it leads to prevention of tumor growth and metastasis, without eradicating the existing tumor. Therefore, the assumption is that these agents work best on small tumors, even before the angiogenic switch occurs. This therapeutic approach has been proposed to prevent the growth of the tumor mass and to maintain metastasis in a dormant state (7). The antiangiogenic effect is expected to last as long as the drug is present. Hence a chronic treatment is required, with obvious implications in terms of safety and side effects associated with the clinical use of these regimens.

In contrast, vascular disrupting agents (VDA, previously defined vascular-targeting agents, VTA) exploit the antigenic and functional differences between blood vessels in tumors and in normal tissues (8–11), to cause a selective damage of the vessel bed within the tumor (12–14). Strategies to affect the tumor vasculature are ligand-directed vascular targeting compounds (antibodies and peptides that deliver an effector to the endothelium) and small molecules, which include cytokine-inducer flavonoids flavone-8-acetic acid...