3 Combinations of Taxanes and Ionizing Radiation

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3.1 Introduction

For many decades radiotherapy has been a major treatment modality for locally or regionally confined cancers. Its curative success has commonly been high, yet treatment failures remain frequent particularly in large advanced disease, which adversely impacts overall cure rate and patient survival. Improvements in radiotherapy have continuously been made through a number of strategies including technological innovations that allow delivery of higher radiation doses to the tumor or lower doses to normal tissues, and in the implementation of radiotherapy strategies that modulate biological response of tumors or normal tissues to radiation, or by combining radiotherapy with chemical or biological agents. Among all these improvement strategies, combining chemotherapeutic drugs with radiation has, perhaps, had the strongest impact on current cancer radiotherapy practice. This combination has been in use for several decades, but has recently become a common treatment option in many clinical settings, particularly a combination approach in which chemotherapeutic drugs are administered during the course of radiotherapy (concurrent chemoradiotherapy). Recent clinical trials clearly demonstrated superiority of concurrent chemoradiotherapy to radiotherapy alone in controlling local–regional disease and in improving patient survival (Brizel et al. 1998; Furuse et al. 1999; Herskovic et al. 1992; Milas et al. 2003b; Morris et al. 1999).

There is a strong biological rationale for combining chemotherapeutic drugs with radiotherapy. By their independent cytotoxic action chemotherapeutic agents reduce the number of cells in tumors undergoing radiotherapy and in addition these agents may render the remaining tumor cells more sensitive to killing by ionizing radiation. This radiosensitizing property of chemotherapeutic agents constitutes a major rationale for concurrent chemoradiotherapy. Because of their systemic activity,

chemotherapeutic drugs may also act on metastatic disease, which is an additional benefit of combined chemoradiotherapy.

When combined with radiotherapy most chemotherapeutic agents are selected based on their known clinical activity in particular disease sites. Alternatively, agents could be chosen based on their efficacy in overcoming resistance mechanisms associated with radiotherapy. Recent clinical successes of concurrent chemoradiotherapy were made using traditional drugs, such as cisplatin and 5-FU that in addition to being strong cytotoxic agents on their own are also known for their potent radiosensitizing properties (Brizel et al. 1998; Furuse et al. 1999; Herskovic et al. 1992; Milas et al. 2003b; Morris et al. 1999). These clinical therapeutic achievements have led to extensive research on exploring newer chemotherapeutic agents including taxanes, nucleoside analogs, and topoisomerase inhibitors for their interactions with radiation. Some of these newer agents exhibit potent radioenhancing properties, and as such have already entered clinical testing in combination with radiotherapy. Preclinical research plays a critical role in developing effective anticancer agents as well as in obtaining full insight into the radiomodulating potential of such agents and their ability to increase therapeutic ratio when combined with radiotherapy.

In this chapter, we review preclinical findings on the interaction of taxanes with ionizing radiation.

3.2 Cytotoxic and Antitumor Activities of Taxanes

3.2.1 Origin and Chemical Structure

Compared with most common chemotherapeutic agents, taxanes chronologically belong to a newer class of anticancer agents. Paclitaxel and doxetaxel, as prototypes of taxanes, are the best known and most widely used in the clinic, but new agents, such as PG-Taxol and ABI-007, are rapidly emerging and may possess stronger antitumor activity and/or decreased normal tissue toxicity. Of these agents, paclitaxel was first to be discovered and is a natural product originally isolated from the bark of the Pacific Yew Tree (*Taxus brevifolia)* (Wani et al. 1971). Docetaxel is a semi-synthetic analogue of paclitaxel prepared from needle extracts of the European Yew Tree (Taxus baccata; Mangatal et al. 1989). Chemically, both paclitaxel and docetaxel are complex poly-oxygenated diterpine structures (Fig. 3.1). PG-Taxol is paclitaxel conjugated to polyglutamate polymer that allows increased and more selective uptake of paclitaxel by tumors (Li et al. 1999; Singer et al. 2005). ABI-007 is an albumin-stabilized, lyophilized, Cremophor-free, nanoparticle formulation of paclitaxel designed to overcome insolubility problems of paclitaxel (Sparreboom et al. 2005).

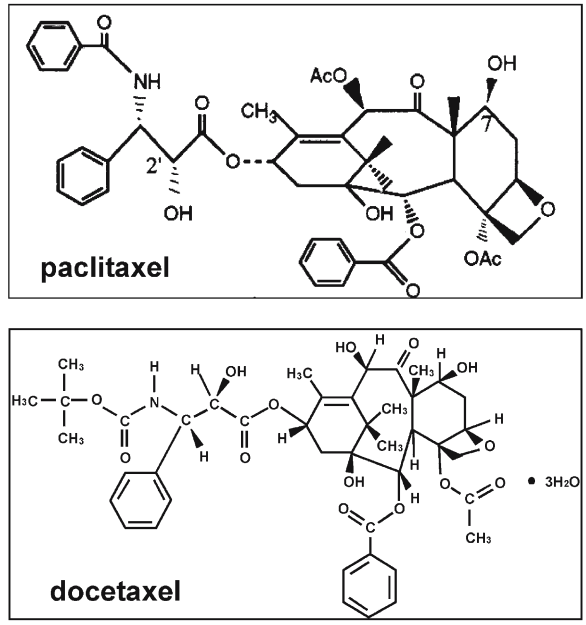

Fig. 3.1 Chemical structure of paclitaxel and docetaxel

3.2.2 Cytotoxic and Antitumor Activities

Taxanes have undergone extensive laboratory and clinical testing both for their cytotoxic and antitumor efficacy (Bissery et al. 1995; Choy et al. 1994; Liebmann et al. 1994a; Li et al. 1999; Milas et al. 1995a; Milross et al. 1996; Piccart et al. 1995; Rowinsky and Donehower 1995; Singer et al. 2005; Tishler et al. 1992a). The agents exhibit cytotoxic action in vitro against various tumor cell lines (Bhalla et al. 1993; Bissery et al. 1995; Hanauske et al. 1992; Kelland and Abel 1992; Liebmann et al. 1994a; Tishler et al. 1992a), show antitumor activity against many different experimental animal tumor systems and human tumor