10 Combinations of Ionizing Radiation and Other Sensitizing Agents

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CONTENTS

10.1 Introduction

Several chapters in this book cover broad classes of radiosensitizing agents. Two specific agents, recently used as "radiation enhancers," are addressed in the present chapter. They include the redox modulator motexafin-gadolinium (MGd), and the alkylating agent temozolomide. Each of these agents came to clinical testing through the recognition of unique preclinical radiosensitizing mechanisms and data that suggest enhancement of radiation cytotoxicity; they share the common theme of having been clinically tested primarily in tumors of the central nervous system (CNS), in a series of recent clinical trials, primarily because although radiation therapy (RT) has a central role in managing the majority of primary and secondary CNS neoplasms, outcomes for most patients afflicted by these tumors remain poor, and furthermore, these neoplasms, in many ways, present an ideal opportunity for enhancing the efficacy of RT in combination with radiosensitizers (Patel et al. 2004).

The major reasons for considering these neoplasms as candidates for radiosensitization are as follows:

1. The majority of CNS neoplasms cause death due to local progression, thereby underscoring the need for local control (Wallner et al. 1989).
2. Evidence exists that improving local control improves survival (Patchell et al. 1990; Noordijk et al. 1994; Mintz et al. 1996; Andrews et al. 2004).
3. A dose-response relationship for RT has been established (Walker et al. 1979).
4. These neoplasms reflect a rapidly growing population with high cell turnover in a milieu of slowly proliferating cells, thereby affording an opportunity for tumor-selective localization of several radiosensitizers (McGinn et al. 1996).
5. Linear (dose escalation linked to lengthening of treatment duration) radiation dose-escalation strategies have been limited by late normal tissue toxicity (Lee et al. 1999). Historically, several classes of radiation sensitizers, including S-phase halogenated pyrimidines (Phillips et al. 1995; Prados et al. 1999), oxygen mimetics (Evans et al. 1990), and others (Mehta et al. 2001a), have been tested without clear evidence of clinical benefit. Recently, agents with very different mechanisms of action have gained attention and are in clinical trials (Abraham et al. 1992; Rodrigus 2003; Mehta and Suh 2004). These agents, MGd, a redox modulator, and temozolomide, a DNA alkylator, are the focus of this chapter and each is addressed in sequence.

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10.2 Motexafin–Gadolinium

10.2.1 Structure and Chemistry

Motexafin-gadolinium (MGd) is an expanded metalloporphyrin, generally included in the family of compounds referred to as the texaphyrins (Fig. 10.1), and was previously referred to as gadolinium-texaphyrin. Motexafin-gadolinium, a redox active drug, specifically targets tumor cells and enhances the radiation response in several preclinical models (Xu et al. 2001; Magda et al. 2001; Biaglow and Miller 2005). As an avid electron acceptor, it catalyzes the oxidation of key intracellular reducing metabolites. These compounds, including glutathione, ascorbate, dihydrolipoate, protein thiols, and others, are necessary to maintain intracellular energy balance and play a key role in repairing cellular radiation injury. Irreversible oxidation of these reducing metabolites diminishes the cellular capacity for radiation-induced DNA damage. Furthermore, MGd inhibits thioredoxin reductase, a key enzyme in restoring the intracellular pools of these reducing agents. The oxidation of these compounds by MGd not only causes intracellular bioenergetic disruption, but also generates reactive oxygen species, a process known as futile redox cycling (Miller et al. 1999). As a consequence, cells irradiated in the presence of MGd are unable to adequately repair radiation damage, and cell death ensues (Donnelly et al. 1986).

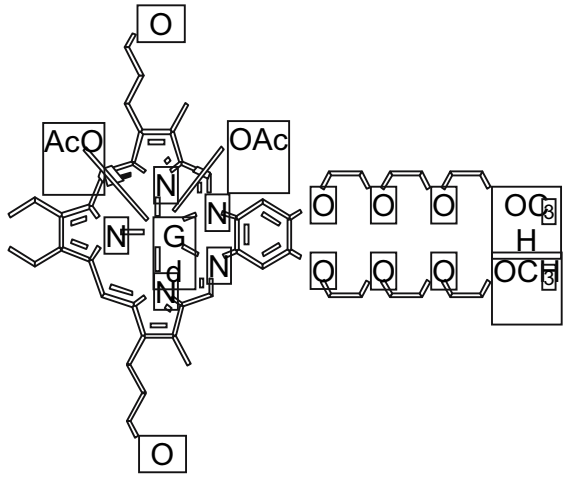

Fig. 10.1. Structure of motexafin–gadolinium (MGd)

10.2.2 Imaging Properties

It has been demonstrated that substitution of Gd by other lanthanides abrogates the radiation-sensitizing properties of MGd (Rockwell et al. 2002). The presence of trace amounts of Gd in this molecule [in significantly lower concentrations than the amount of Gd in magnetic resonance imaging (MRI) contrast agents] permits visualization of the drug on MRI, thus providing tumor-specific kinetic information (Fig. 10.2). Several preclinical (Woodburn 2001; De Stasio 2001) and clinical (Kesslering et al. 1998; Ford et al. 2003; Mehta et al. 2004) data have now confirmed this tumor-specific intracellular localization and visualization phenomenon. Ford et al. (2003) have effectively demonstrated the impact of dose and cumulative dose in this context through a phase-I trial in which intra-tumor Gd was estimated by co-imaging control vials containing known concentrations of Gd and verifying these data by obtaining tissue specimens for actual measurements.

10.2.3 Phase-I Results

An initial single-dose phase-I trial established the maximum tolerated dose (MTD) to be 22.3 mg/kg with reversible acute renal failure as the dose-limiting toxicity (DLT) at 29.6 mg/kg (Rosenthal et al. 2000). A subsequent multicenter phase-IB/II trial tested ten daily MGd injections with cranial RT in patients with brain metastases. This study established the MTD to be 6.3 mg/kg day^{-1} for 10 days with reversible hepatic transaminitis as the DLT at 8.4 mg/kg day^{-1} for 10 days (Carde et al. 2001). Subsequent testing of this regimen identified 5.5 mg/kg day^{-1} as the dose level associated with the least clinical toxicity and thus was established as the standard for further testing in the phase-II and phase-III setting using the 10-day regimen (Mehta et al. 2002).

A biodistribution study of C14-labeled MGd in SMTF tumor-bearing mice injected with 10 mmol/kg of drug demonstrated significant tumor uptake within 1 h, at which time the blood:tumor ratio is almost unity (Rodrigus 2003). Rapid and substantial blood/plasma washout follows, but MGd is retained in tumors at high levels ≥5 h, thereby substantially improving the tumor:blood ratio; therefore, the 2- to 5-h window following MGd administration is generally recommended for RT delivery.