5 Combinations of Hypoxia-Targeting Compounds and Radiation-Activated Prodrugs with Ionizing Radiation

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CONTENTS

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5.1 Targeting Tumor Hypoxia

Tumor hypoxia was first postulated from histological studies of human lung adenocarcinomas by Thomlinson and Gray (1955). They reasoned that, because of unrestrained growth, tumor cells are forced away from blood vessels beyond the effective diffusion distance of oxygen (O_2) in respiring tissues, hence becoming hypoxic and eventually necrotic (Fig. 5.1a). Given the typical values for intracapillary O_2 tensions and consumption rates, they calculated that O_2 diffusion distances would be approximately 150 μm and this was consistent with their histological observations (Thomlinson and Gray 1955). This type of hypoxia has come to be termed "chronic," or "diffusion-limited," hypoxia.

Acute hypoxia also develops in tumors through temporal (reversible) cessation or reduction of tumor blood flow resulting from highly disorganized tumor vasculature (Fig. 5.1b; Brown 1979). Definitive evidence for acute hypoxia and fluctuating blood flow has been demonstrated in transplanted tumors in mice injected at some time apart with two different diffusion limited fluorescent dyes showing mismatch of labeled cells (Chaplin et al. 1986; Trotter et al. 1989); however, acute and chronic hypoxia are in fact the two ends of a continuum with fluctuations in blood flow without total occlusion, which are common in both experimental (Kimura et al. 1996) and human tumors (Hill et al. 1996), producing a dynamic situation with fluctuating oxygen diffusion distances in many parts of tumors.

Tumor hypoxia is a major factor contributing to the failure of radiotherapy (Fig. 5.2). This is largely because DNA damage produced by ionizing radiation, which would otherwise become fixed and lethal to cells by reacting with O_2 under well oxygenated conditions, can be restored to its undamaged form under hypoxic conditions (Brown and Wilson 2004). Clinically hypoxia predicts poor local control and survival of patients undergoing radiotherapy

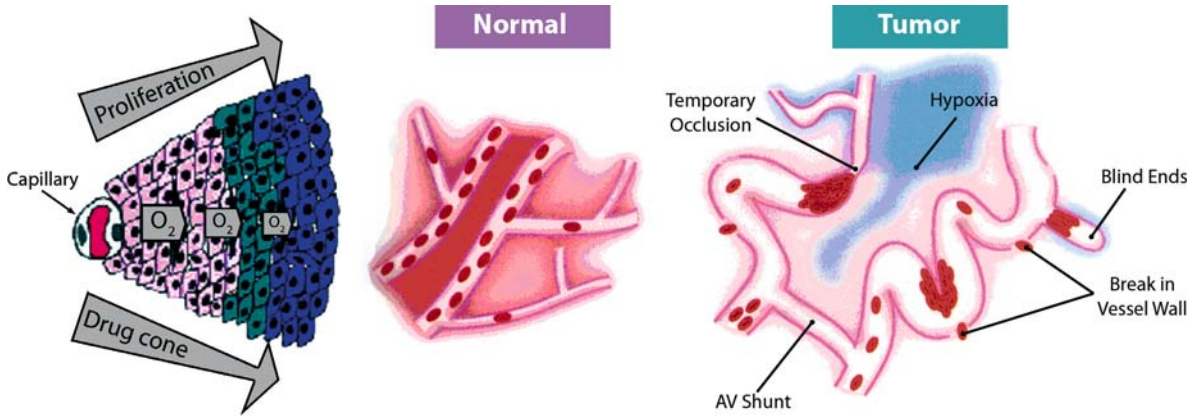

Fig. 5.1. a A diagram of a tumor capillary and surrounding tumor cells at decreasing oxygen concentrations (*in the direction of arrows*). Cells become hypoxic (*green*) and eventually necrotic (*blue*); chronic hypoxia. Cellular proliferation and chemotherapeutic drug concentration are also decreasing in the same direction, as a function of distance from the capillary. (From Brown 1999). **b** A diagram of normal (*left*) and tumor (*right*) blood vasculature. The tumor vasculature is highly disorganized resulting in acutely hypoxic regions in the tumor. (From Brown and Giaccia 1998)

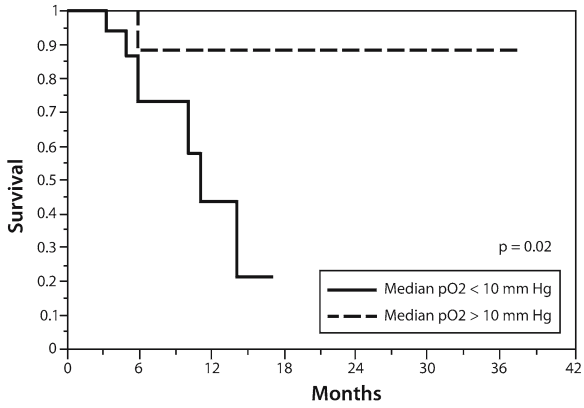

Fig. 5.2. A Kaplan-Meier plot of overall survival of patients with head and neck carcinoma undergoing radiotherapy. Well-oxygenated tumors (pO_2 >10 mmHg; *dotted line*) showed better prognosis than poorly oxygenated (pO_2 <10 mmHg; *solid line*) tumors. (From Brizel et al. 1997)

for carcinoma of the head and neck (Nordsmark et al. 1996; Brizel et al. 1997), and cancer of the cervix (Hockel et al. 1993; Fyles et al. 1998).

Hypoxia further complicates cancer management by limiting the access of conventional chemotherapeutic drugs (Fig. 5.1a; Brown and Wilson 2004). Hypoxia also increases genomic instability by increasing mutation frequency (Reynolds et al. 1996) or selecting for cells expressing an anti-apoptotic phenotype such as mutated p53 (Graeber et al. 1996). This leads to a more metastatic phenotype as has been observed clinically (reviewed by Rofstad 2000). In addition, expression of proangiogenic proteins, such as vascular endothelial growth factor (VEGF), are increased under hypoxic conditions, potentially resulting in increased tumor angiogenesis (Shweiki et al. 1992; Fang et al. 2001). Thus, there is substantial evidence that hypoxia both interferes with the effective therapy of solid tumors and contributes to a more malignant phenotype; however, hypoxia may also prove to be a therapeutic advantage: because it is virtually unique to tumor cells, therapies that target hypoxic regions may have the potential to kill malignant cells while leaving non-malignant cells relatively untouched. This chapter discusses some examples of hypoxia targeting compounds and approaches for combination with ionizing radiation in experimental or clinical settings.

5.2 Oxygen-Level Enhancers

One of the earliest attempts to overcome the problem of the resistance of hypoxic cells in tumors to radiotherapy was to increase O_2 levels in the blood stream, thereby increasing the diffusion distance of O_2. A number of trials were performed with patients breathing 100% O_2 at a pressure of 3 atmospheres, but the results were mixed (Watson et al. 1978; Dische et al. 1983; Henk 1986). One potential reason for such failures is that increasing the diffusion distance of O_2 would not be expected to reduce the levels of acute hypoxia. In some systems, the use of carbogen (95% O_2/5% CO_2) appears to have