7 Combinations of Cytotoxic Drugs, Ionizing Radiation, and Angiogenesis Inhibitors

Carsten Nieder and Nicolaus H. Andratschke

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7.1 Introduction

Many years after the fundamental hypotheses about delivery of oxygen and nutrients to malignant tumors via formation of new blood vessels (angiogenesis) were published, drugs developed to inhibit angiogenesis have now entered routine clinical practice, after landmark randomized trials have identified suitable combination regimens in metastatic colorectal cancer and advanced non-squamous non-small cell lung cancer (Table 7.1). Previously, monotherapy, e.g., with matrix metalloproteinase inhibitors, failed to improve the results. The fundamental principles of anti-angiogenic approaches and their consequences for the development and growth of solid tumors were published by Folkman (1971, 1986, 1995). Tumor angiogenesis results from imbalance between pro-angiogenic factors, e.g., vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF) and platelet-derived growth factor (PDGF), and endogenous anti-angiogenic factors such as angiostatin and endostatin (Folkman 1995; O'Reilly et al. 1996, 1997; Endrich and Vaupel 1998; Ferrara and Alitalo 1999; Kerbel 2000; Carmeliet and Jain 2000; Yancopoulos et al. 2000). A large body of experimental data indicate that application of either inhibitors of pro-angiogenic factors or administration of anti-angiogenic factors reduce the formation of new blood vessels. As a result, tumors grow at a slower rate or even decrease their size. However, in most cases no permanent tumor control can be achieved; therefore, the combination of anti-angiogenic strategies with cytotoxic agents such as chemotherapy, ionizing radiation, or both represents a promising approach to increase the cure rates of solid tumors (Folkman 1971; Teicher et al. 1992; Denekamp 1993; Folkman 1995; Siemann et al. 2000; Koukourakis 2001; Rosen 2002; Kal et al. 2004; Jain 2005; Xu et al. 2005). This chapter is focused on the VEGF pathways as an illustrative example of the therapeutic principles and efficacy. Further data can be found in the disease-specific chapters such as 15.6.4 (pancreatic cancer) and 20.4.3 (gynecological cancers).

Angiogenesis is not restricted to tumors but can also be found in many other physiological and pathological conditions, e.g., normal growth, wound healing, proliferative retinopathies, rheumatoid arthritis, and inflammation (for review see Folkman 1995; Carmeliet and Jain 2000); hence, inhibition of angiogenesis combined with other treatment may be associated with increased normal tissue reactions. In addition, several angiogenic growth factors were shown to reduce radiation-induced long-term toxicity, e.g., in the spinal cord and parotid glands (Andratschke et al. 2004, 2005; Thula et al. 2005); therefore, the therapeutic ratio of anti-angiogenic

C. Nieder, MD
N. H. Andratschke, MD
Department of Radiation Oncology, Klinikum rechts der Isar der Technischen Universität München, Ismaninger Strasse 22, 81675 München, Germany

Table 7.1. Randomized clinical trials of chemotherapy plus/minus anti-angiogenic agents

Reference	Compound	Tumor	Patient no.	Results
Leighl et al. (2005)	Paclitaxel/carboplatin plus BMS-275291 (MMPI) or placebo	NSCLC stage IIIB/IV	774	Outcome not improved, toxicity increased
Bissett et al. (2005)	Cisplatin/gemcitabine plus prinomastat (MMPI) or placebo	NSCLC stage IIIB/IV or recurrent	362	Outcome not improved, more treatment interruption
Sparano et al. (2004)	Marimastat (MMPI) or placebo after first-line chemotherapy	Metastatic breast cancer	179	Outcome not improved, toxicity increased
Bramhall et al. (2002a)	Gemcitabine plus marimastat or placebo	Unresectable pancreatic cancer	239	Outcome not improved, well tolerated
Bramhall et al. (2002b)	Maintenance marimastat vs placebo after max. 1 5-FU-based chemotherapy regimen	Non-resectable gastric and gastro-esophageal cancer	369	2-year survival 3 vs 9% in favor of marimastat (p=0.07), PFS sign. Longer
Stadler et al. (2004)	SU 5416 plus dexamethasone vs dexamethasone	Hormone-refractory prostate cancer	36	Outcome not improved
Szczylik et al. (2005)	Sorafenib vs best supportive care	Advanced renal cell carcinoma	769	PFS sign. improved (interim analysis)
Miller et al. (2005)	Capecitabine plus/minus bevacizumab	Metastatic breast cancer	462	Sign. higher response rate (20 vs 9%), PFS, and OS not improved
Sandler et al. (2005)	Paclitaxel/carboplatin plus/minus bevacizumab	Non-squamous NSCLC stage IIIB/IV	878	Sign. improvement in response rate, PFS and OS
Kabbinavar et al. (2005)	5-FU/LV plus bevacizumab or placebo	Metastatic colorectal cancer	209	PFS sign. better, OS better but not significant
Hurwitz et al. (2004)	5-FU/LV/irinotecan plus placebo vs bevacizumab	Metastatic colorectal cancer	813	Sign. improvement in OS, PFS, and response (first line)
Giantonio et al. (2005)	5-FU/LV/oxaliplatin (FOLFOX4) vs FOLFOX4 plus bevacizumab vs bevacizumab alone	Previously treated advanced colorectal cancer	829	Sign. improvement in PFS and OS

MMPI matrix metalloproteinase inhibitor, *NSCLC* non-small cell lung cancer, *5-FU* 5-fluorouracil, *LV* leucovorin, *PFS* progression-free survival, *OS* overall survival

strategies in combination with radiotherapy needs to be thoroughly determined for safe translation of this approach into clinical practice.

7.2 VEGFs in Tumor Angiogenesis

VEGFs are potent mitogenes for endothelial cells and key mediators of tumor angiogenesis (for review see Dvorak et al. 1995; Kerbel et al. 1998; Ferrara 1999; Carmeliet 2000; Carmeliet and Collen 2000; Carmeliet and Jain 2000; Karkkainen and Petrova 2000; Kerbel 2000; Veikkola et al. 2000; Yancopoulos et al. 2000; Byrne et al. 2005). The VEGFs represent a family of distinct proteins, e.g., VEGF (VEGF-A), VEGF-B, VEGF-C, VEGF-D, VEGF-E, and isoforms (e.g., $VEGF_{121}$ and $VEGF_{165}$). Some family members are involved in lymphangiogenesis (VEGF-C and VEGF-D). Down-regulation of VEGF-C, e.g., by endostatin, might therefore inhibit lymph node metastasis (Fukumoto et al. 2005). The VEGF expression can be demonstrated in the vast majority of tumors and is usually elevated above normal tissue levels. Until tumors reach a volume of about 1 mm^3, tumor cells are supplied by diffusion from the surrounding tissues (Folkman 1971; Ausprunk and Folkman 1977; Folkman 1986). At larger volumes, impaired supply with oxygen and nutrients and accumulation of metabolites occur in the tumor. This is accompanied by important changes in the tumor microenvironment, e.g., hypoxia, hypoglycemia, and acidosis, which result in up-regulated production and release of HIF-1α, VEGF, and other angiogenic factors by the tumor cells (angiogenic switch, see Chap. 20.3.1 for further details). These factors represent potential targets