Chapter 10

Angiogenesis: a potential target for therapy of soft tissue sarcomas

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1 INTRODUCTION

Tumors depend on neo-vascularisation (angiogenesis) during development (Folkman, 2002). The use of curative therapy in the treatment of soft tissue sarcomas (STS) is generally only possible in the initial stage of the disease, where surgery plus or minus adjuvant radiotherapy is used, and in a minority of cases where metastasectomy is possible. In advanced metastatic disease, treatment with the chemotherapeutic agents, adriamycin and ifosfamide, is associated with low response rates (20-35% when given as single therapy and up to 45% when given in combination) and with short progression free intervals. This means that there is a high need for additional chemotherapeutic compounds or effective alternatives. Tumor vascularisation might be a new target for anti-tumor therapy. The questions to be asked are therefore:

- what evidence is there that STSs are dependent on angiogenesis, and which factors are involved in STS-associated angiogenesis?
- which agents are available for anti-angiogenesis therapy, and what is the optimal strategy for using these compounds in patients with STS?

2 ANGIOGENESIS

Angiogenesis, the proliferation, migration and tube formation of endothelial cells, is a process regulated by many stimulating and inhibiting factors. In the tumor situation these factors are produced or generated by tumor cells and by activated stromal cells, such as fibroblasts and immune cells. The balance between pro and contra angiogenic factors determines the presence and activity of the angiogenesis process. While these factors may be found in the circulation, it is the local presence in tumor tissue that is of major relevance.

Different families of proteins are involved in angiogenesis which can be classified into three main groups. The first group comprises several stimulating growth factors (vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), angiopoietins, e.g., and cytokines (interleukin-6, e.g.) and several inhibiting factors such as thrombospondin, IL-12 and fragments of collagen and circulating proteins. VEGF, for instance, is an outstanding angiogenesis factor that is produced by all sorts of cells, with a unique characteristic, namely, the targeting of cancer endothelial cells. This growth factor induces the proliferation and migration of endothelial cells, and, at the same time, it is a survival factor and a permeability inducing factor for those cells (Ferrara, 2002). The second group comprises proteolytic enzymes belonging to the family of metalloproteases (MMPs) or plasminogen activators (uPA and tPA). These proteases are responsible for the degradation of the basal membranes and proteins of the extracellular matrix (ECM) during the migration of endothelial cells. The third group comprises adhesion molecules, e.g. integrins and cadherins. These molecules are a critical factor in the communication between cells, and in the communication between cells and constituents of the ECM, and determine largely the outcome of endothelial