The perception that inhibition of cancer-associated angiogenesis would be an effective treatment strategy was based on the fundamental difference in cell cycle activity between neoplastic and normal endothelial cells. Selective targeting of tumor vessels could have additional benefits, such as circumventing development of acquired resistance to these types of agents, overcoming intrinsic tumor resistance, exhibiting broad anti-tumor activity and decreasing normal tissue toxicity. Successful translation of anti-angiogenic therapy into the clinical setting was achieved only 5 years ago with the approval of bevacizumab for metastatic colorectal cancer. Although the benefits demonstrated in clinical trials led to the approval of bevacizumab for treatment of colorectal, lung and breast cancers, and most recently glioblastoma, a number of serious soft-tissue and vascular toxicities have also been observed in patients receiving this anti-angiogenic agent. This review assesses the relationship between inhibition of VEGF and toxicity, and proposes the pathogenic mechanisms that lead to the adverse events.