

Appendix A

The use of anti-tumor drugs such as sargramostim (recombinant human GM-CSF) or mifamurtide is cited merely as an example, as is the time interval required between the drug injection and the visualization, via color-Doppler ultrasound, of increased flow around the tumor mass. Other drugs or substances that stimulate macrophages or otherwise induce an increase in flow around the tumor, detectable by ultrasound, will have the same effect from a psycho-oncological perspective. Likewise, the time to allow to pass between drug administration and the visualization of the flow increase must be calibrated according to the pharmacodynamics of the substance used. Several pharmacological agents have been identified that can increase blood flow around solid tumors, a strategy actively researched to enhance the delivery and efficacy of conventional therapies like chemotherapy, radiation, and immunotherapy. Among the most studied are Angiotensin II Receptor Blockers (ARBs), particularly losartan, which reduces solid stress within the tumor microenvironment and decompresses collapsed blood vessels, reportedly doubling the fraction of perfused vessels in desmoplastic tumors such as pancreatic cancer, thereby improving oxygenation and drug delivery. Dopamine agonists have also demonstrated the ability to stabilize tumor vasculature, increase blood flow, and reduce hypoxia, while paradoxically, low-dose anti-angiogenic agents like bevacizumab can induce vascular normalization that temporarily improves perfusion before exerting their inhibitory effects. Additionally, nitric oxide donors and precursors such as nitroglycerin and L-arginine, along with phosphodiesterase-5 inhibitors like sildenafil, promote vasodilation through nitric oxide signaling, and prostaglandin analogs like iloprost relax vascular smooth muscle to boost tumor blood flow. Although these approaches show promise in preclinical models and early clinical trials by creating a therapeutic window for enhanced drug penetration, they remain largely experimental, with considerations regarding optimal timing to maximize therapeutic benefit while minimizing risks such as potential facilitation of metastasis, and their efficacy varies significantly across different tumor types.^{11,12} Ultimately, while various pharmacological agents—including macrophage activators, vasodilators, and stromal modulators—may differ in their molecular mechanisms, the primary objective of this protocol remains strictly psycho-oncological: to leverage the ultrasound-visible increase in peri-tumoral blood flow as an objective, tangible biofeedback signal that empowers the patient to transform inescapable stress into escapable stress, regardless of whether the specific agent used offers direct therapeutic benefits beyond facilitating this visual confirmation of immune or vascular engagement.