Mechanism of action of Tigilanol tiglate (EBC-46), a novel anti-cancer agent

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Abstract
Intra-lesional chemotherapy for treatment of cutaneous malignancies has been used for many decades, allowing higher local drug concentrations and less toxicity than systemic agents. Here we describe a novel diterpene ester, Tigilanol tiglate (TT, also known as EBC-46), and provide preclinical data supporting its use as an intra-lesional treatment. A single injection of TT / EBC-46 caused rapid inflammation and influx of blood, followed by eschar formation and rapid tumor ablation in a range of syngeneic and xenograft models. TT / EBC-46 induce oxidative burst from purified human polymorphonuclear cells, which was prevented by the Protein Kinase C inhibitor bisindolylmaleimide-1. TT / EBC-46 activated a more specific subset of PKC isoforms (PKC-βI, -βII, -α and -γ) compared to the structurally related phorbol 12-myristate 13-acetate (PMA). Although TT / EBC-46 showed threefold less potency for inhibiting cell growth than PMA in vitro, it was more effective for cure of tumors in vivo. No viable tumor cells were evident four hours after injection by ex vivo culture. Pharmacokinetic profiles from treated mice indicated that TT / EBC-46 was retained preferentially within the tumor, and resulted in significantly greater local responses (erythema, oedema) following intra-lesional injection compared with injection into normal skin. The efficacy of TT / EBC-46 was reduced by co-injection with bisindolylmaleimide-1. Loss of vascular integrity following treatment was demonstrated by an increased permeability of endothelial cell monolayers in vitro and by CD31 immunostaining of treated tumors in vivo. Our results demonstrate that a single intra-lesional injection of TT / EBC-46 causes PKC-dependent hemorrhagic necrosis, rapid tumor cell death and ultimate cure of solid tumors in pre-clinical models of cancer.