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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 induced 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.