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Phase II AIDS Malignancy Consortium (AMC) trial of topical halofuginone in AIDS-associated Kaposi's sarcoma (KS): clinical and biological effects using a novel intra-patient control design

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Background

KS is a disease of multifocal vascular proliferation. Matrix metalloproteinases (MMPs) and type I collagen play critical roles in angiogenesis and are potential targets. Halofuginone (Tempostatin™), a synthetic quinazolinone alkaloid derivative, induced anti-angiogenic, anti-metastatic and anti-proliferative effects in preclinical studies. It inhibits several essential stages of angiogenesis: endothelial cell proliferation, MMP2 expression, BM invasion, ECM deposition by newly formed vessels, synthesis of type I collagen during angiogenic sprouting, and bFGF-induced neovascularization. These data suggested that halofuginone might have activity in KS.

Methods

The AMC developed a novel trial design with a blinded intra-patient vehicle control. Halofuginone was supplied by Collgard Biopharmaceuticals Ltd (Atlanta, GA) to the NCI-DCTD under a CRADA as a 0.01% w/w ointment. Twelve KS lesions were divided into two groups of six, designated Group A and Group B. Tubes designated A and B containing either halofuginone or matching placebo ointment were supplied in a blinded fashion. Ointment A was applied to Group A lesions and ointment B to Group B lesions twice daily. Lesion response was assessed every 4 weeks for Group A and Group B lesions individually, and global response assessed both treated and untreated disease. Tumor biopsies obtained at baseline and from both Group A and B lesions during treatment were studied for expression of type I collagen by ISH and of MMP2 and VEGF by IHC. A patient subset had blood sampling after 8 weeks to evaluate systemic absorption.

Results

Twenty-three patients were treated. Median CD4 count was 322 (2-693); 68% had undetectable HIV RNA. Treatment was well tolerated. Of 14 patients who completed 12 weeks of treatment, 26% (95% CI, 10%-48%) showed partial response in halofuginone-treated lesions and 17% in placebo-treated lesions (95% CI, 5%-39%), (P=0.689). Global response was 30% (95% CI, 13%-53%). None of 10 subjects showed detectable blood levels. Type 1 collagen message decreased significantly in halofuginone-treated lesions at week 4, whereas vehicle-treated lesions showed no change. VEGF protein expression decreased significantly in vehicle-treated lesions at week 4, whereas halofuginone-treated lesions showed no change. There were no differences in levels of MMP2 or VEGF protein between halofuginone- and vehicle-treated lesions. No changes in HIV RNA levels or CD4 counts were observed.

Conclusion

Although topical halofuginone appears ineffective for KS treatment, this study presents a novel design that could be applied to future studies using the patient as his own control to test a topical, non-absorbed agent.

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