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ORIGINAL ARTICLE

Histamine reduces boron neutron capture therapy-induced mucositis in an oral precancer model

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OBJECTIVES: Searching for more effective and selective therapies for head and neck cancer, we demonstrated the therapeutic effect of boron neutron capture therapy (BNCT) to treat oral cancer and inhibit long-term tumor development from field-cancerized tissue in the hamster cheek pouch model. However, BNCT-induced mucositis in field-cancerized tissue was dose limiting. In a clinical scenario, oral mucositis affects patients' treatment and quality of life. Our aim was to evaluate different radioprotectors, seeking to reduce the incidence of BNCT-induced severe mucositis in field-cancerized tissue.

MATERIALS AND METHODS: Cancerized pouches treated with BNCT mediated by boronophenylalanine at 5 Gy were treated as follows: control: saline solution; His_{high}: histamine 5 mg kg^{-1}; His_{low}: histamine 1 mg kg^{-1}; and JNJ7777120: 10 mg kg^{-1}.

RESULTS: His_{low} reduced the incidence of severe mucositis in field-cancerized tissue to 17% *vs* CONTROL: 55%; His_{high}: 67%; JNJ7777120: 57%. His_{low} was non-toxic and did not compromise the long-term therapeutic effect of BNCT or alter gross boron concentration. Conclusion: Histamine reduces BNCT-induced mucositis in experimental oral precancer without jeopardizing therapeutic efficacy. The fact that both histamine and boronophenylalanine are approved for use in humans bridges the gap between experimental work and potential clinical application to reduce BNCT-induced radiotoxicity in patients with head and neck cancer.

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Keywords: boron neutron capture therapy; BNCT; oral cancer; hamster cheek pouch precancer model; mucositis; radioprotector

Introduction

Squamous cell carcinoma of the head and neck remains a major cause of morbidity and mortality worldwide (Jaiswal *et al*, 2013). The relatively poor overall 5-year survival rate for malignancies of the oral cavity (Mehrotra *et al*, 2011) poses the need for more effective and selective therapies. Studies in appropriate experimental models are pivotal to progress in this field.

Boron neutron capture therapy (BNCT) is a binary treatment that combines the administration of boron carriers that are taken up preferentially by neoplastic tissue and irradiation with a thermal/epithermal neutron beam. The high linear energy transfer (LET) α particles and recoiling lithium-7 (^{7}Li) nuclei emitted during the capture of a thermal neutron by a boron-10 (^{10}B) nucleus have a high relative biological effectiveness. Their short range in tissue (6–10 μm) would limit the damage largely to cells containing ^{10}B. In this way, BNCT would target neoplastic tissue selectively, sparing normal tissue (Trivillin *et al*, 2006). As BNCT is based on biological rather than geometric targeting, it would be suited to treat undetectable micrometastases (Pozzi *et al*, 2012) and foci of malignant transformation in field-cancerized tissue (Monti Hughes *et al*, 2013).

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