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Prevention of fibroblast senescence by hyaluronic acid and clinical application to chemoradiation-induced oral mucositis

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Abstract

Purpose. Virtuallyallpatientsreceiving radio- and chemotherapy for head andneckcancerdeveloporalmucositis (1), a severe and highlydebilitatingcondition. Because the onset of mucositisisrelatedto the production of reactiveoxygenspecies (ROS) (2), hereweinvestigated a possibleprotectiveeffect of sodiumhyaluronateenriched with aminoacids (Mucosamin®) in the damageinduced by oxidative stress both*in vitro* and *in vivo*.

Methods. Normaloralstromalfibroblasts (NOF) and keratinocytes (NOK) wereused for the *in vitro*study. Oxidative stress wasinduced with H_2O_2 and senescencemarkerswereinvestigated by Western blot (p16),immunofluorescence (SA-□gal), andsenescence-associatedsecretory (SAS) molecules. MetaboliceffectsonNOK werestudied by MTT test. The clinicalstudywas a case-series of 11patientsundergoingchemiotherapy, radiotherapy, or both. Sodiumhyaluronate spray (Mucosamin®) wasused for thisstudy.

Results. Whilst H_2O_2wastoxic to NOK and inducedcelldeath*in vitro*, exposure of NOF to H_2O_2 led to long termsenescence, asdemonstrated by sustainedincrease in the levels of p16 and Sa□-gal and expression of SAS phenotype.Conditioned media from senescentNOF induceddetrimentaleffectson NOK, asshown by MTT. Pre-treatment with Mucosamin® couldpreventboth H_2O_2-induced fibroblastsenescence and reduction of metabolicactivity of NOK exposed to the conditioned media. The data from case-series of 11 patientsundergoing radio/chemotherapydemonstratedthatprophylactic use of Mucosamin®preventedoralmucositis in 9 out of 11 patients; the remaining 2 showedlow grade transientmucositis; 10 out of 11 patientsdevelopedradiodermitis.

Conclusion. SH preparations can preventcellularsenescence in NOF undergoingoxidative stress *in vitro*. Clinically, prophylactic use of SH virtuallyabrogates the incidence of oralmucositissecondary to chemoradiation, providing a safe and approachableintervention for thismostdebilitatingcondition.