The development of stem cell therapy to rescue radiation-induced damage to salivary glands

Nanduri, L.; Pringle, S.; van der Zwaag, M.; Stokman, M. A.; van Os, R.; Coppes, R.

DOI:
10.1016/S0167-8140(11)71763-7

pies should not be restricted arbitrarily for those over 70. In fact based on our treatment data, CyberKnife treatment appears preferable for this age group and above.

50 poster

TH2-LIKE IMMUNE RESPONSE IN IRRADIATION-INDUCED LUNG FIBROSIS

G. Han[1], H. Zhang[1], C. H. Xie[1], Y. F. Zhou[1]
[1] ZHONGNAN HOSPITAL, WUHAN UNIVERSITY, Department of Radio-Chemotherapy, Wuhan, China
[2] HUBEI CANCER HOSPITAL, Department of Radiotherapy, Wuhan , China

Purpose: Pulmonary fibrosis is a common delayed side effect of radiation therapy, since it's mechanism is almost unknown, little can be done to prevent it or treat it. Th2 cytokines have clearly been implicated as mediators of asthma, and evidence is mounting that type 2 immune responses may also promote the development of pulmonary fibrosis. The purpose of this study is to investigate if Th2-like immune response account for the development and progression of chronic radiation pulmonary fibrosis.
Materials: The thoraces of C57BL/6 mice were irradiated with 12 Gy X-rays, radiated and control mice were sacrificed at 1h, and 1, 2, 4, 8, 16 and 24 weeks post-irradiation (p.i.). Tissues were stained using HE and Masson to determine the histological changes. We assayed the expression of IL-13 in serum, and the expression of hydroxyproline and the mRNA and protein of GATA-3 and Arg-1 in lung tissue from each groups.
Results: mRNA and protein analysis revealed the expression of these Th2-immune response associated factors (GATA-3, IL-13 and Arg-1) in mice after irradiation. Without causing conspicuous fibrotic pathological changes, at the early post-irradiation phase (1 and 2 weeks p.i.), a Th2 profile was confirmed by significantly elevated expression of Th2-specific transcription factor GATA-3 mRNA (P0.01), and protein analysis confirmed the GATA-3 mRNA expression. And following obviously elevated expression of hydroxyproline (P0.01), at 16 weeks p.i., IL-13 and Arg-1 expression reached maximal value in serum and lung tissue and maintained high level to 24 weeks p.i. respectively (P0.01).
Conclusions: Our data indicate that lung irradiation induces Th2 polarization, and Th2-like immune response may take part in promoting radiation-induced pulmonary fibrosis. Although a causal relationship between Th2-like immune response and the pathogenesis of radiation-induced pulmonary fibrosis cannot be definitively established from this descriptive study, this can give us an indication that restoration of the immunological balance may be an important target for treatment.

51 poster

THE DEVELOPMENT OF STEM CELL THERAPY TO RESCUE RADIATION-INDUCED DAMAGE TO SALIVARY GLANDS

L. Nanduri[1], S. Pringle[1], M. van der Zwaag[1], M. A. Stokman[2], R. van Os[3], R. Coppes[1]
[1] UNIVERSITY MEDICAL CENTER GRONINGEN, Cell Biology, Section of Radiation and Stress Cell Biology, Groningen, Netherlands
[2] UNIVERSITY MEDICAL CENTER GRONINGEN, Oral and Maxillofacial Surgery, Groningen, Netherlands
[3] UNIVERSITY MEDICAL CENTER GRONINGEN, Cell Biology, Groningen, Netherlands

Purpose: Salivary glands are often exposed to radiation during radiotherapy for head and neck cancers. This may result in life-long salivary gland impairment, severely reducing the post-treatment quality of life of the patients. It is our hypothesis that radiation sterilizes salivary gland stem cells compromising the turnover of functional saliva producing cells. Thus, stem cell therapy may be an option to prevent hyposalivation in these patients. To obtain putative stem cells for therapy, dissociated salivary glands of both mice and human cells were cultured to form three-dimensional aggregates of cells termed salispheres [(1)]. In mice, we showed that transplantation of salisphere-derived c-Kit$^+$ stem/progenitor cells (SSCs) rescued the salivary glands from radiation-induced hyposalivation [(2)]. The aim of current study is to translate our findings from mice to humans.
Materials: Mice and human salispheres both contain cells expressing established stem cells markers such as CD49f, CD133, CD24, CD29 and c-kit cells, which also coexpress CD24/CD29. However, in humans salisphere-derived cells, a greater proportion of c-kit+ cells coexpress CD29 than CD24, in comparison to their murine counterparts. Cells from human salispheres were capable of forming secondary spheres in matrigel for more than 7 passages, suggesting self-renewal in vitro. Moreover, when placed in 3D collagen-matrigel, differentiatiation into functional cells of the salivary glands was observed. In order to determine which population of salisphere-derived cells is most potent, mouse salisphere cells expressing combinations of the above mentioned marker proteins were transplanted directly into salivary glands (intraglandularly) of 15Gy irradiated mice and functionality and morphology of the glands was assessed.
Results: In order to assess in vivo functionality of our putative human SSCs, isolated c-Kit$^+$ cells from human salispheres were transplanted under the kidney capsule of immune deficient mice. After a period of six weeks, transplanted cells showed features of serous and mucous salivary gland cells and amylase positivity was observed by immunohistochemistry, suggesting that SSCs have an innate potential for differentiation into saliva-producing cells in an in vivo environment.
Conclusions: Finally, a microarray study to determine expression of stem cell-associated genes in cultures enriched for putative salivary gland stem cells suggests some transcripts may be upregulated in salispheres,. This is exemplified by connexin 31, a cell-cell communication gene. Such candidate genes may be employed for future studies into the isolation or vitro cultivation of SSCs in mouse and humans.In conclusion, human salivary gland contain a similar potential stem cell population which can potentially be used for therapy in the near future.(1) Pringle et al (2010) Journal of Visual Experiments, in press. (2) Lombaert IM et al (2008). PLoS One ;3(4):e2063

52 poster

THE USE OF MUGARD(TM) AND CAPHOSOL(R) IN PATIENTS WITH LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

L. Pettit[1], G. Davis[2], S. Whitmarsh[3], P. Sanghera[4], A. Hartley[4]
[1] QUEEN ELIZABETH HOSPITAL BIRMINGHAM, Clinical Oncology, Birmingham, United Kingdom
[2] BIRMINGHAM SCHOOL OF DENTISTRY, Dental School, Birmingham, United Kingdom
[3] UNIVERSITY HOSPITAL BIRMINGHAM, Lead Cancer Services Pharmacist, Birmingham, United Kingdom
[4] HALL-EDWARDS RADIOTHERAPY RESEARCH GROUP, QUEEN ELIZABETH HOSPITAL, Clinical Oncology, Birmingham, United Kingdom

Purpose: Oral mucositis is a frequent complication of radiotherapy in patients with Head and Neck Cancer. Current products to treat symptoms are fairly inadequate. Two new products, MuGard^{TM} and Caphosol^{R} have been used in some UK hospitals. MuGard^{TM} is a viscous mucoadhesive rinse which provides a coating to the oral mucosa, (priced at 20 + VAT for a 250 ml bottle) and Caphosol^{R} is a supersaturated calcium phosphate oral rinse designed to moisten, lubricate and clean the oral cavity (priced at 32 + VAT for a weekly pack). We audited their effects in patients undergoing concurrent chemoradiation for squamous cell carcinoma of the head and neck.
Materials: Patients undergoing concurrent chemoradiation for locally advanced squamous cell carcinoma of the head and neck at University Hospital Birmingham were audited for eight consecutive weeks. Patients were reviewed in weekly on treatment clinics. Grade of mucositis, dysphagia, nausea and analgesia score were recorded and compared with standard mouth care (a 'cocktail' of aspirin, glycerin and sucralfate and Gel Clair (31.28 + VAT for 21 sachets)).
Results: Eighty-Five patients were identified. All underwent chemoradiation (55 Gray in 20 Fractions). Sixteen patients received MuGard^{TM}, 21 patients received Caphosol^{R} and 48 received standard first line mouth care. There was no significant reduction in analgesia score for either Caphosol^{R} or MuGard^{TM} compared with standard oral care. There was no observed difference between the groups for grade and duration of mucositis, nausea or dysphagia. Rates of oral Candida were similar between the 3 groups.
Conclusions: The majority of patients complied with MuGard^{TM} or Caphosol^{R} usage during treatment. There is no evidence from this series that Caphosol^{R} or MuGard^{TM} improves analgesia score. There is no evidence that dysphagia, nausea or mucositis is improved with either MuGard^{TM} or Caphosol^{R}.

Modelling and prediction of normal tissue response

53 poster

A NTCP MODEL FOR RADIATION-INDUCED HYPOTHYROIDISM BASED ON A PROSPECTIVE COHORT STUDY.

M. Boomsma - van Holten[1], H. P. Bijl[1], M. Christianen[1], I. Beetz[1], O. Chouvalova[1], R. Steenbakkers[1], B. van der Laan[2], S. Oosting[3], C. Schilstra[1], H. Langendijk[1]
[1] UNIVERSITY MEDICAL CENTER GRONINGEN / UNIVERSITY OF GRONINGEN, Radiation Oncology, Groningen, Netherlands
[2] UNIVERSITY MEDICAL CENTER GRONINGEN / UNIVERSITY OF GRONINGEN, Otorhinolaryngology, Head and Neck Surgery, Groningen, Netherlands
[3] UNIVERSITY MEDICAL CENTER GRONINGEN / UNIVERSITY OF GRONINGEN, Medical Oncology, Groningen, Netherlands

Purpose: To investigate the dose response relationship and establish a multivariate normal tissue complication probability (NTCP) model for radiation-