Modification of radiation-induced oral mucositis (mouse) by administration of mesenchymal stem cells

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Oral mucositis is a frequent and often dose-limiting side effect of radiotherapy for head-and-neck tumours. The ulcerative lesions develop on the basis of impaired proliferation of mucosal stem cells and a consequent reduction of the cellular flux into the post-mitotic epithelial layers, in face of continuing cell loss due to mechanical stress at the surface. Administration of bone marrow stem cells resulted in a significant reduction of mucosal radiation effects. The present investigation was initiated to characterise the modification of oral mucositis by application of mesenchymal stem cells (MSC)during daily fractionated irradiation. MSC were isolated from bone marrow of C3H/Neu mice. Six million cells were administered intravenously after cell separation and washing with PBS/FCS. All transplantation experiments were performed in C3H/Neu mice. Radiation-induced mucosal ulceration was analysed as a clinically relevant end-point. Fractionated irradiation with 5x3 Gy/week was given over 1 week (days 0-4) or 3 weeks (days 0-4, 7-11, 14-18). Each protocol was terminated (day 7 or day 21) by graded test doses in order to generate complete dose-effect curves. Based on results from previous bone marrow transplantation (BMT) experiments, MSC were administered on day -1, 2 or 4 during one week, and on day 8 during 3 weeks of fractionation. The ED50 (dose, at which ulceration is expected in 50% of the animals) for test irradiation after 1 week of fractionation was 7.5±2.2 Gy. MSC application on days -1, 2 or 4 yielded ED50s of 9.9±0.7 Gy (p=0.0109), 11.6±0.9 Gy (p=02), and 9.3±1.7 Gy (p=0.0804). For three weeks of irradiation, MSC administration on day 8 resulted in an ED50 of 11.8±0.7 Gy, compared to 7.2±3.5 Gy in the control experiment (p=0.0014). In conclusion, a significant reduction of oral mucositis by MSC was seen after application on days -1 and 8, which was comparable to that of BMT. A highly significant effect was also seen on day 2, where BMT was ineffective, and only a marginal effect was observed for day 4, where BMT was highly effective. This suggests, that the mechanism of action of MSC and haematopoietic stem cells from bone marrow is different.

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