ATM Status of the Clinically Radio-Hypersensitive.

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AIMS: To characterise the response to ionising radiation of normal tissues from patients that display early and acute hypersensitivity to radiotherapy.

INTRODUCTION: It is now well appreciated that standard clinical doses (1.8-2 Gy per fraction per day) produce predictable acute and late toxicity in most patients. Occassionally, however, the standard clinical dose produces acute and late toxicity which can exceed the norm both in their extent and timing. Such individuals can be said to be radio-hypersensitive. For example, the first sign available to the clinician of this radiosensitivity may be early or excessively severe mucositis when the oral cavity or the gut is treated, or early and severe skin changes (erythema, moist desquamation).

METHODS: Methods included Cell proliferation assays using MTT, Induced chromosomal aberration testing, Cell cycle response to radiation via FACs, mutation analysis of the Ataxia Telangiectasia (AT) gene, p53 and AT Western analysis.
RESULTS: Lymphocyte cell lines from all five clinically hypersensitive patients retained a significantly higher degree of induced chromosomal aberrations when compared to normal. This was in contrast to non-definitive cell proliferation results after radiation. A number of the patients also showed differences in the induction of G_2 cell cycle delay and p53 induction after radiation. Differences were observed in the proportion of the 350kd and 200kd AT protein hybridising fragment in Western analysis using an AT specific polyclonal - the importance of this result is under further investigation. There were no AT gene truncation mutations evident in any of the hypersensitive patients.

DISCUSSION: Our analyses confirmed the innate cellular radiosensitivity of the clinically radio-hypersensitive patients used in this study. This could in turn help to explain the good outcomes that most of these patients appear to have experienced from radiotherapy on the basis of complementary tumour radiosensitivity.

While a number of response indicators in the radio-hypersensitive patients point to some degree of overlap with the reported response observed in AT heterozygotes we found no indication of AT gene truncation mutations.