Radioprotectant combinations spare radiation-induced damage to the physis more than fractionation alone

Introduction: Radiotherapy in skeletally immature patients frequently results in asymmetric limb growth arrest, angular deformities, and resultant limb length discrepancy. The radioprotectant compound amifostine (S-2-[3-aminopropylamino] - ethylphosphorothioic acid, AMF) has previously demonstrated protection of normal growth plate function from the damaging effects of ionizing radiation. The amifostine mediated relief of this effect is incomplete, suggesting the need for other novel radioprotectants. Pentoxifylline (PTX), a clinically available vasodilator, has been shown to decrease the PTHrP lowering effect of irradiation in chick growth plate chondrocytes. Misoprostol (MISO), a prostaglandin E1 analog, has shown selective radioprotection to other tissues in mice and humans, and an additive effect has been demonstrated when administered in combination with amifostine. Pilot work showed efficacy of these agents individually and in combination in ameliorating the adverse effects of a single 17.5 Gy irradiation dose. The aim of this study is to determine if any combination of these radioprotectant drugs can protect normal growth from the damaging effects of a 25 Gy irradiation dose more than fractionation alone in the rat model.

Methods: Forty-two weanling Sprague-Dawley rats were randomized into 7 treatment groups: one group receiving a single 25 Gy fraction to the right limb and the remainder receiving a total 25 Gy irradiation divided into three equal fractions administered on consecutive days. One group received fractionated radiation and each of the other groups received either a single radioprotectant drug (pentoxifylline 50 mg/kg, misoprostol 20 mg/kg, or amifostine 150 mg/kg) or a combination of two radioprotectants (pentoxifylline and amifostine or misoprostol and amifostine). Doses for each of the drugs were based upon pilot work examining a range of doses for each drug alone and each of the combinations. Femoral and tibial lengths were measured from scanned digitized radiographs of the disarticulated limbs. The femur and tibia lengths of each animal were added to give total limb length. Data is presented as the percentage difference (discrepancy) in length between the non-irradiated left limb and irradiated right total limb length for each animal. ANOVA was used to compare the mean L-R limb length differences of each treatment group vs. the control animals, where significance is defined as p<0.05.

Results: Effects on femoral length differences paralleled those of the tibia for all treatments. The radiation dose of 25 Gy alone caused a mean femoral length discrepancy of 24.4%. Fractionation alone significantly decreased this to a mean 18.8% difference (p<0.001). Beyond fractionation alone, the mean femoral length discrepancies were significantly decreased by each of the individual and combination radioprotectant drugs (p<0.05 to 0.0001). Among the individual radioprotectants, amifostine yielded the best results, significantly better than pentoxifylline alone (p<0.01) and with a strong trend (p=0.05) compared to misoprostol. While the smallest absolute femoral length discrepancy (11%) was achieved with the combination of amifostine and misoprostol, this difference lacked statistical significance (p=0.20) when compared to the mean femoral discrepancy resulting from amifostine treatment alone (12.7%). There was no significant difference in growth of the left unirradiated limbs, regardless of treatment.

Discussion: The selective radioprotectant drug amifostine has been previously shown to provide significant reduction in growth arrest beyond the sparing effects of fractionated irradiation alone using the same model. Combinations of amifostine with other radioprotectants have also shown significant additive effects in protecting versus the damaging effects of a single 17.5 Gy dose. This is the first demonstration of significant growth plate radiation sparing effect beyond fractionation alone using misoprostol and pentoxifylline alone and in combination with amifostine. While the combinations in this study failed to protect significantly more than the amifostine alone, the protection afforded by misoprostol and pentoxifylline beyond fractionation suggests possible alternative growth plate radioprotectors with differing and possibly improved side effect profiles, based upon clinical usage of each of these drugs for other purposes. Despite the use of these drugs with fractionation, the amelioration of the damaging effects of irradiation is still incomplete, suggesting the need for alternate and potentially complementary strategies, such as selective stimulation of growth plate recovery.

References:

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