PURPOSE: Tirapazamine (TPZ) reportedly enhances the tumor cell killing effect of cisplatin up to fivefold and it is an attractive drug for combination with radiotherapy. We evaluated the toxicity of a fractionated combined treatment. METHODS: Murine RIF-1 fibrosarcomas growing on the right hind foot of C3-H mice were used. Within 2 weeks, animals were treated with six i.p. injections of TPZ (43.2-172.8 mg/kg total), and/or cisplatin (24 mg/kg total) and ten fractions of 2 Gy to the tumor. All treatments were carried out under anesthesia. Maximum follow-up was 35 days. The local tumor control was determined by calculating the tumor doubling time \( t_{2\alpha} \). In addition to standard toxicity assessment, the major inner organs were examined histologically. RESULTS: The administration of low TPZ doses to the cisplatin/radiotherapy treatment caused only little changes in tumor doubling time \( t_{2\alpha} \) and led to a lethality rate of 15-30%. Higher TPZ doses caused an increase in \( t_{2\alpha} \), but also a further increase in lethality and toxicity in particular to the heart, liver, kidney and stomach. Cisplatin/radiotherapy treatment without TPZ produced no severe toxicity. CONCLUSIONS: This is a detailed study of both the acute and delayed toxicities of combined TPZ treatment in a mouse model. In our study the addition of TPZ to the cisplatin/radiotherapy treatment caused a significant increase in...
toxicity with only moderate effect on the tumor.

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