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JOURNAL ARTICLE

Hormonal protection from cyclophosphamide-induced inactivation of rat stem spermatogonia

M. L. Meistrich, N. Parchuri, G. Wilson, B. Kurdoglu and M. Kangasniemi

Department of Experimental Radiotherapy, University of Texas M. D. Anderson Cancer Center, Houston, USA.

Studies of protection of testicular function from cyclophosphamide with hormonal pretreatment have been limited by the lack of a convenient model for cyclophosphamide-induced inactivation of stem spermatogonia. In the rat, the mortality from cyclophosphamide had prevented the administration of sufficient dosages to produce detectible damage to stem spermatogonia. To overcome this problem, we used bone marrow transplantation and sodium 2-mercaptoethanesulfonate (Mesna) treatment to raise the lethal dose for 50% of the animals (LD50) for cyclophosphamide from 275 to > 400 mg/kg body weight. In addition we used irradiation, 2 weeks prior to injection of cyclophosphamide, to greatly enhance the measured toxicity of cyclophosphamide towards stem spermatogonia. Whereas sperm counts at 9 weeks after a 300 mg/kg cyclophosphamide dose were reduced by only a factor of 1.6 without prior irradiation, they were reduced by a factor of 60 when 2.5 Gy of irradiation had been given. Dramatic protection against this toxicity was produced by hormone treatment with a gonadotropin-releasing hormone (GnRH) antagonist (Nal-Glu) and an antiandrogen (flutamide) following the radiation but prior to cyclophosphamide. This hormone treatment did not modify the stem cell toxicity of the radiation and it therefore must be protecting stem cells against cyclophosphamide-induced damage. Because GnRH antagonist-antiandrogen treatment can protect stem spermatogonial survival and/or function in the rat from cyclophosphamide-induced damage, if the same principles are applicable in human, hormonal pretreatment should be useful for preventing the prolonged azoospermia caused by chemotherapy with cyclophosphamide-containing protocols.

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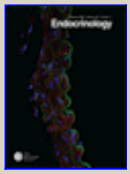

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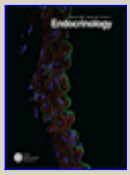

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