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Letters

Suramin and Tumour Cell Radiosensitivity

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SURAMIN HAS been reported as an anticancer agent [1, 2], either alone or in combination. Suramin modifies growth factor transduction within cells by binding to, and therefore blocking, certain growth factor receptors (e.g. epidermal growth factor [EGF] and transforming growth factor-alpha [TGF-α]) [3, 4]. Suramin also inhibits phosphoinositide resynthesis [4] and reverse transcriptase [5]. Furthermore, suramin increases differentiation in several human tumour cell lines [6, 7].

Kwok and Sutherland [8] found that adding EGF *in vitro* to CaSKI human squamous cancer cells sensitised them to X-rays, and radiosensitisation has been reported in WiDR human colon cancer cells treated with TGF-α [J.L. *et al.*]. EGF and TGF-α bind to the same receptor, and probably exert their radiosensitising effects via the same signal transduction pathway. Therefore, blocking receptors might lead to a decrease in the effectiveness of radiation treatment. Notwithstanding, compounds inducing tumour cell differentiation often increase radiosensitivity [9]. Suramin has a long half-life, and might persist at sufficient concentrations to modify radiation response [10]. The drug is associated with the nervous system, kidney, liver, and skin, tissues which would be included in many radiation treatment fields [10].

We studied the effect of suramin, TGF-α and X-ray on HCT-8 human colon cancer cells [11]. This line has about 10^4 receptors for EGF/TGF-α per cell, and significant radiosensitisation is found at around 100 ng/ml TGF-α, which increases at 100–200 ng/ml. When suramin was added to the cultures, growth was inhibited starting at about 30 ng/ml. 40 and 250 ng/ml suramin were required to inhibit tumour cell growth by 10 or 50% of control values, respectively. We investigated the effects of 30 ng/ml of suramin, so that modification of HCT-8 tumour cell radiosensitivity by suramin could be interpreted unconfounded by potential cell selection or cell cycle effects.

Three protocols were used. First, suramin was added to HCT-8 cells 24 h before X-ray. Flasks were briefly placed on ice, irradiated, exposed, and trypsinised, counted, and replated (without suramin) for estimation of cell survival using a clonogenic endpoint. Secondly, cells were not exposed to suramin until after irradiation, trypsinisation, counting and reseeding procedures, when suramin-containing medium was left on the cell monolayers until tabulation (about 11 days). Radiation responses in both cultures did not differ from controls. In the third protocol, suramin (30 μg/ml) and TGF-α (100 μg/ml) were added to HCT-8 cells immediately after irradiation, and left there. Again, radiation sensitivity of the treated cells was not statistically different from that of controls, suggesting that suramin could block radiosensitisation produced by TGF-α.

Cooper *et al.* [10], using continuous suramin infusion in cancer patients, found tumour response at plasma levels of about 200 μg/ml or more. This level of suramin is near the *in vitro* IC_{50} in our studies with HCT-8 cells, and would saturate available EGF/TGF-α receptors. Typical serum levels of EGF are about 0.2 ng/ml, and at this low level, only a small percentage of available EGF receptor binding sites would be occupied. Because about 100 ng/ml (a factor of 500 times that in normal serum) TGF-α is required for radiosensitisation, it is unlikely that suramin could modify response.

Although we found that suramin did not affect tumour cell radiosensitivity, only one cell line and dose of suramin were studied. Agents such as steroids interact with suramin to potentiate growth inhibition of tumour cells, and with radiation treatments might provide different results.

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