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Suramin Therapy for Malignant Thymoma: a Case Report

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MALIGNANT THYMOMAS appear to originate from the epithelial cells that form the reticular matrix of the thymus gland [1]. The invasive variant of this neoplasm represents a relatively rare clinical entity often characterised by relentless locoregional spread and less frequently, distant metastases. In this report, we describe the use of suramin, a synthetic polysulphated naphtylurea with growth factor antagonist properties, in the treatment of a patient with invasive thymoma, refractory to conventional therapeutic modalities.

A 67-year-old man with a refractory mediastinal neoplasm was referred to the Medicine Branch of the National Cancer Institute for consideration of experimental salvage therapy. He was initially diagnosed after presenting with an anterior mediastinal mass on routine chest X-ray, biopsy from which revealed malignant thymoma. The patient received extensive external beam radiation and combination chemotherapy employing CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone). Subsequently, a combination of etoposide, Ara-C, bleomycin and procarbazine was given as well as a trial of α-interferon. In no instance did a significant objective tumour regression result. Upon referral to the National Institute of Health, the patient manifested signs of superior vena cava syndrome and indeed, restaging evaluation documented the presence of a large mediastinal mass extending into the right lung with extrinsic compression of the superior vena cava. No evidence of extrathoracic neoplasm was documented. He received parenteral suramin by continuous infusion at a dose of 350 $\mu g/m^2$/day for 22 days. This was discontinued upon achievement of a plasma suramin level of 336 μg/ml, in adherence to NCI suramin protocol treatment schedule guidelines [2]. Drug administration was tolerated reasonably well, resulting in diminished facial swelling as well as a decrease and eventual discontinuance of the patient's use of supplemental oxygen. He subsequently received two additional cycles of suramin, albeit at reduced dosage (280 $\mu g/m^2$/day). Evaluation subsequent to his second cycle of treatment revealed radiographic evidence of a minor response by strict criteria (Figure 1). This was

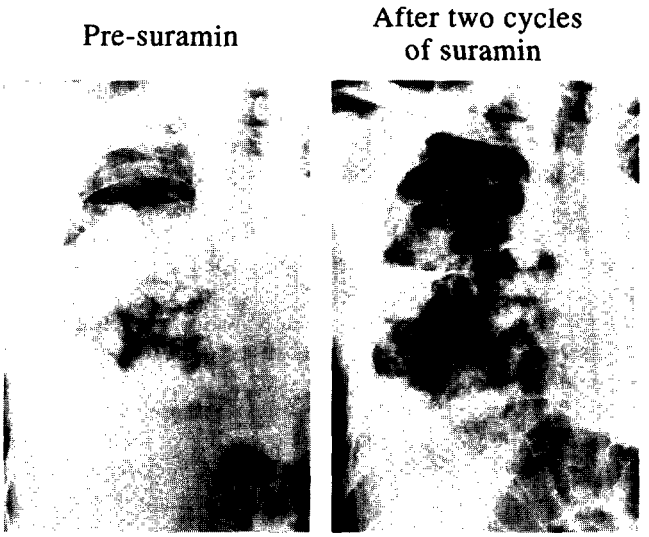

Figure 1. Minor tumour regression with suramin therapy.

accompanied by continued significant clinical improvement, with subsequent radiographical studies indicating disease stabilisation. The total suramin dose administered over three courses was 23.4 g, while the peak plasma suramin level achieved was 336 μg/ml, with the first course of therapy. In addition, a plasma suramin level obtained 175 days from completion of his last cycle of treatment was still detectable (16 μg/ml). His objective response duration was 8 months. Toxicities associated with suramin administration included: WHO grade 3 reversible thrombocytopenia, grade 3 anaemia requiring transfusion of pack red cells, and moderate fatigue. No significant neurological, renal or hepatic abnormalities resulted from therapy, and his total white blood cell count remained stable.

Suramin, an antiparasitic agent with recently described antitumour properties, has been the focus of ongoing clinical trials both in the U.S.A. as well as in Europe [2, 3]. Although its precise mechanism of action is yet to be elucidated, its growth factor and cytokine binding properties, as well as its ability to inactivate a variety of cellular enzyme systems, have been well described [2, 4, 5]. The ability of suramin to also inhibit angiogenesis *in vitro* has led investigators to postulate an additional antitumour mechanism through disruption of tumour-related neovascularisation [6]. Recently, investigators have identified a number of cytokines which may play important roles in thymic biology. Included among these are tumour necrosis factor α as well as the interleukins 1 and 2 [7, 8]. The latter has been shown by Mils and colleagues to be displaced from its receptor by suramin at clinically achievable concentrations [9].

In 1987, Spigelman and colleagues first demonstrated *in vitro* growth inhibition of eight of 10 lymphoid cell lines by suramin at a concentration of 200 μg/ml [5]. In addition, these investigators documented significant thymic involution in mice exposed to suramin at these concentrations. We have recently published our clinical experience with suramin in patients with progressive refractory follicular lymphomas, observing a 56% objective response rate (in some cases durable) using a similar dosing schedule as in this case [10].

The potential role of suramin as an antitumour agent must take into account the considerable toxicity that can be associated with its administration, including a potentially debilitating sensorimotor neuropathy, nephrotoxicity, adrenal insufficiency,

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coagulopathy and a non-steroid-related malaise syndrome [2]. Accordingly, much of the recent work pertaining to suramin has focused on developing an optimal, clinician-friendly dosing schedule that would minimise interpatient variability in plasma suramin concentrations and permit its more widespread clinical use [11, 12]. The response seen in this case of resistant thymoma treated with suramin reiterates the role of this compound as a potential therapeutic alternative in a variety of neoplasms otherwise refractory to conventional treatment modalities.

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Effect of Overall Time and Dose on the Response of Glottic Carcinoma of the Larynx to Radiotherapy

J. F. Fowler and R. Chappell

A MAJOR ANALYSIS of 303 patients with glottic carcinoma treated in Glasgow by radiotherapy was published recently in the *European Journal of Cancer* [1], and presented statistical coefficients for the effects of total dose and overall time. The purpose of the present communication is to translate these into changes in local control in terms of per cent per gray (increase with dose) or per cent per day (decrease with overall time).

The statistical model used for the analysis was the standard Poisson distribution of surviving cells and the linear quadratic dependence of cell survival on dose:

$$\log[-\log(P)] = C + A \times D + B \times d \times D - G \times T \quad (1)$$

Here P is the probability of local control at 5 years, C is a constant (different for different T-stages), A and B are the linear quadratic coefficients of dose and dose-squared, respectively, D is total dose, d is dose per fraction, T is overall time and G is the rate of decrease of local control (LC) with increasing overall time, after taking account of dose variations [2–9].

The factor $A + Bd$ is proportional to the increase of LC with total dose (for constant T and d) and G/A is the "time–dose trade-off", which is the rate at which total dose should be increased, on the average, to compensate for the deleterious effect of prolongation. However, these coefficients, as listed in the tables of [1], are in the statistical units of "log [−log(P)] per gray" (for A and Bd) or "log [−log(P)] per day" (for G). The coefficients can each be converted to percentages (change in local control per Gy or per day) through the usual procedure which we have used before [1, 10, 11]. Table 1 lists the approximate multiplying factors for use with either the logit [4–7] or the double-log formula [1, 8]; the latter is used here. The multiplying factors are here applied to the coefficient estimates only, although they may also be used to convert the standard errors and confidence intervals.

Although there are some discrepancies between the numbers of patients in their Table 1 and the text of [1], and details of the "heavy censorship" are not given, their conclusions do not differ grossly from those of other publications [4–9]. We have, therefore, taken the coefficients as presented by the authors in Tables 3 and 4 of [1] as our starting point.

Our Table 2 shows the application of the multipliers in our Table 1 to the coefficients estimated in the analysis under discussion. From A and B the apparent slope of the dose–response curve for tumour control can be calculated, after allowing for differences in overall time. The linearised factors $A + Bd$ give the percentage increase of local control per Gy. Here the median value of d is 2.5 Gy, which gives the per cent per Gy increases for the three T-stages as 5.54, 6.54 and 1.83, respectively. To convert these to the commonly used slope parameter "gamma-50" (per cent increase in LC for 1% increase

Table 1. Multipliers of coefficients to convert from parameter estimate to percentage change [2, 10, 11]

Probability of event	Logit multiplier*	Double log multiplier†
0.1	0.09	0.23
0.3	0.21	0.36
0.5	0.25	0.35
0.7	0.21	0.25
0.9	0.09	0.095

*Logit (p) = ln [p/(1−p)]. †See equation (1).

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