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Combination of Interferon and Prednisone in Human Cancer

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WE READ with interest the letter published in this Journal by S.D. Fosså [1] regarding improved tolerability of interferon when combined with prednisolone. We have similarly treated 11 patients with various malignancies (renal cell carcinoma 4, malignant melanoma 3, uterine carcinoma 1, adrenal cell carcinoma 1, nasopharyngeal carcinoma 1 and lymphoma 1). All of these patients had been on interferon alpha-2b (Intron®) s.c. 10×10^6 units 3 days/week for at least 4 weeks and were not showing evidence of tachyphylaxis despite the regular use of acetaminophen. To improve the subjective tolerability of interferon, oral prednisone 10 mg daily continuously was added to the previous IFN dose. Pre- and post-prednisone symptoms, weight, haematological and biochemical parameters and tumour status were recorded.

After 4 weeks of combined interferon and prednisone, nine out of 11 patients showed an improved tolerance to interferon, decreasing the subjective toxicity from grade 3–4 pre-prednisone to grade 1 post-prednisone and IFN combination. Two patients however showed no change and had their interferon discontinued. Prior to prednisone there was a median weight loss of 1.1 kg while these patients were on interferon alone; however, after 4 weeks of combined therapy there was a median weight gain of 1.3 kg; mild ankle oedema noted in a few patients might have accounted for some of this weight gain.

The median lymphocyte and leucocyte counts pre-prednisone were 1.2×10^9/l and 4.4×10^9/l; 4 weeks after interferon and prednisone these were 1.8×10^9/l and 4.7×10^9/l, respectively, indicating mild relative lymphopaenia. No other significant haemopoietic or biochemical alterations were noted.

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Two patients (one with adrenal cell carcinoma and one with renal cell carcinoma) demonstrated a partial (> 50%) tumour regression after several weeks therapy. In the absence of a concurrent 'control' therapy group, tumour responses in these patients cannot be definitely attributed to this combination therapy.

Prednisone *per se* may induce 'tumour regression' in a few cases with effects on the peritumoural oedema. Clinical anti-tumour activity of interferon has been reported in numerous studies but the mechanism(s) of this activity is not precisely known. Using clonogenic assay, direct anti-proliferative activity of interferons has been suggested [2]. These anti-proliferative effects may be related to inhibition of the mitotic cycle or a prolongation of all cell cycle phases [3]. Host-mediated indirect (immune) anti-tumour activity has been shown with human tumour xenografts in nude mice [4]. The exact nature of this host-mediated immune response is not clear and other non-immune mechanisms, e.g. depletion of growth factors, induction of cellular differentiation of reversion from a transformed phenotype, may also play a role.

The possible biochemical and physiological effects of pharmacological doses of systemic corticosteroids in humans are numerous [5] and include immune suppression. In the present report we observed a mild lymphopaenia following combined interferon and prednisone; however, the specific lymphocyte subsets or NK cell change were not fully investigated. At least no patient developed accelerated tumour progression and two patients had a partial response after 8–10 weeks therapy, albeit short-lived responses.

We concur with Fosså that improvement in subjective tolerance to interferon with concurrent use of prednisone might permit the use of a higher, possibly more therapeutic, dose of interferon for greater anti-tumour activity. Further studies along

similar lines are suggested to fully explore the roles of various biological response modifiers in cancer therapy, either singly or in various combinations.

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