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Heterogeneous Interaction of Interferon-β and Taxol in Human Ovarian Cancer Cells *In vitro*

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INTERFERONS (IFN) ARE active against some human tumours by acting either directly on the cancer cell or indirectly on the immune system [1]. The combination of IFN and conventional chemotherapeutic agents offers a challenging new approach to the treatment of cancer [2]. However, it is still not clear how and when to combine antineoplastic agents with IFN in order to improve the therapeutic results. Taxol has recently been found to be active against several human ovarian cancers [3], and it has been shown that IFN can be effective in ovarian cancer [4–8]. We have evaluated whether, and to what extent, the cytotoxicity of taxol is potentiated by IFN-β.

Four human ovarian carcinoma cell lines—SW626, IGROV1, SK-OV-3 and OVCAR 3—were used. The cells were cultured in RPMI 1640 medium (Gibco, Irvine, U.K.) buffered with sodium bicarbonate and supplemented with 10% fetal bovine serum (batch 669141, Biological Industries, Israel) and 2 mM glutamine. After standard trypsinisation of exponentially growing cultures, 1500 live cells were seeded in 60 mm diameter Petri dishes in 3 ml of medium. Forty-eight hours after seeding, to assess the modulatory role of recombinant human IFN-β (rHu IFN-β) on taxol treatment, one set was incubated with 1000 U/ml rHu IFN-β (InterPharm Laboratories, Israel; batch 9300052, antiviral activity 9.73 million U/ml) for 24 h and then treated for 24 h with different doses of taxol (batch 80635592B, lot 906; Bristol-Myers Squibb, Wallingford, Connecticut, U.S.A.; rHu IFN-β pre-incubation), or incubated with rHu IFN-β for 24 h

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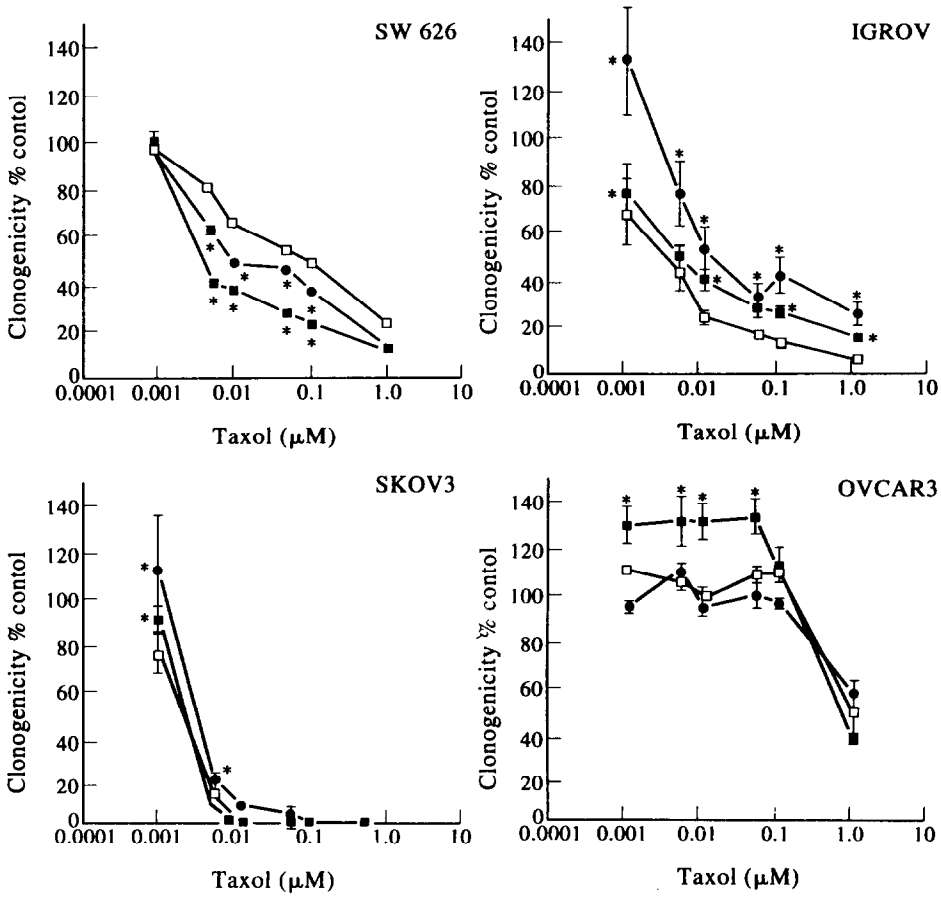

Figure 1. Effect of pre-incubation and postincubation of rHu IFN-β with taxol on ovarian cancer cell lines showing different sensitivity to taxol. Taxol alone (□); rHu IFN-β followed by taxol (●); taxol followed by rHu IFN-β (■). Points, mean of six independent replicates; bar, standard error of the mean. Bars are not visible if smaller than the symbols used. Representative experiments are shown for each cell line. Statistical significance of the data is shown by * at $P<0.01$ level using Dunnett's test. Incubation with rHu IFN-β did not alter the clonogenic potential of the cells. Number of colonies (mean ± S.D; $n=6$) of untreated control and rHu IFN-β incubated cells were 138±14 and 117±9 for the SW626 line, 213±96 and 289±87 for IGROV, 278±37 and 339±18 for SKOV3, 166±10 and 147±20 for OVCAR 3 cell line, respectively. Data are percentages of colonies with respect to untreated control cells normalised as 100%. The standard error of control values never exceeded 5% of the control value.

after taxol treatment (rHu IFN-β postincubation), or treated with the drug alone for 24 h. In all cases, the modulation of drug toxicity by rHu IFN-β was evaluated by clonogenicity assay. Colonies were allowed to develop for up to 14 days, then harvested, stained and analysed using an image analyser (Ibas20;Zeiss/Kontron, Germany).

Figure 1 shows the effect of pre- and postincubation with rHu IFN-β on the cytotoxicity of taxol on the four different cell lines. The cell lines differed in their sensitivity to taxol. Incubation with 1000 U/ml rHu IFN-β alone for 24 h did not reduce the clonogenic potential of the cells. Taxol, however, produced a clear, dose-dependent reduction in clonogenicity. In the SW626 cell line, consistent synergy was seen with both pre- and post-incubation with IFN-β ($P < 0.01$), for the IGROV1 cell lines, both pre- and post incubation with rHu IFN-β antagonised ($P < 0.01$) the effects of taxol. SK-OV-3 was highly sensitive to taxol treatment (panel C). OVCAR 3, in contrast, was comparatively resistant to taxol treatment (panel D). IFN-β post-incubation showed no evident interaction in these two cell lines.

It is thus apparent that IFN-β, at least at 1000 U/ml concentration, can either enhance or reduce the cytotoxicity of taxol in different cell lines, even though all are derived from human epithelial ovarian neoplasms. All four cell lines were growing almost at similar rates (doubling time around 22 h); SW626, in which IFN-β enhanced taxol cytotoxicity, showed an intermediate sensitivity to taxol compared to the other cell lines, SK-OV-3 and IGROV1 being more sensitive and OVCAR 3 less so. Therefore, the enhancement appears to be unrelated to either the cell kinetic features or the sensitivity to taxol. These data suggest the need for caution in generalising interpretations from single cell lines to clinical practice, and underline the likely complexity of the interactions between IFN and antineoplastic drugs.

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Poems Syndrome With High Interleukin (IL)6 and IL1β Serum Levels, in a Patient With Thyroid Carcinoma and Melanoma

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POEMS SYNDROME, a rare systemic disease, is characterised by a combination of polyneuropathy, organomegaly, endocrinopathies, monoclonal protein and skin changes. Myeloma and extra-medullary plasmacytoma are often found in the course of the disease [1]. Only anecdotal cases of Poems have been reported in patients with other malignancies. We report a documented Poems syndrome with elevated interleukin (IL)6 and IL1β serum levels, in a patient with thyroid carcinoma and melanoma. In 1955, a 27-year-old woman, with a follicular thyroid carcinoma, underwent a right lobectomy and lymph node dissection, followed by neck irradiation. She was then lost to follow-up. However, in 1982, her serum thyroglobulin level was elevated, a ^{131}I total body scan showed an uptake in the right lung and a computed tomography (CT) scan showed lung micronodules. She was treated with ^{131}I (100 mCi), and L-thyroxine treatment (100 μg/day) was given. At that time, tendon reflexes were diminished in her upper limbs and absent in lower limbs. In 1984, she was admitted for malaise and progressive neuropathy. Examination revealed symmetric motor and sensory deficits in the limbs, worse distally. A bilateral papilloedema, a hepato-splenomegaly and skin changes with hyperpigmentation and hypertrichosis were also noted. Serum immunoelectrophoresis disclosed a weak monoclonal IgA-λ spike, and urine immunoelectrophoresis was positive for λ light chains. Serum IgG and IgM levels were normal. Small sclerotic lesions were seen in the L2 lumbar vertebrae and in the right ischiopubic branch. A bone marrow biopsy and aspirate showed no plasma cytosis and a L2 vertebra biopsy, under CT guidance, discovered no plasmacytoma. At that time, a thrombocytosis (6.8×10^8/ml) was also present. No hormonal abnormality was found. Serum IL6 levels were moderately elevated (28 pg/ml, normally less than 15 pg/ml) and serum IL1β levels were high (120 pg/ml, normally less than 60 pg/ml). Cerebrospinal fluid (CSF) analysis showed high protein levels (120 mg/ml) with

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