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Primary Hypothyroidism Associated with Interleukin-2 and Interferon Alpha-2 Therapy of Melanoma and Renal Carcinoma

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Four patients out of twenty with renal cancer and melanoma undergoing cancer immunotherapy with interleukin 2 (IL-2) and interferon alpha-2 (IFN-α_2) had laboratory evidence of hypothyroidism starting at cycle three to six, with a decline in serum thyroxine below normal and, in three cases, a rise in serum thyrotropin and thyroglobulin. One hypothyroid patient had elevated serum antimicrosomal antibody titres before the start of treatment and two others responded similarly during therapy. Three of the sixteen euthyroid patients also developed elevated titres of this antibody. Partial or complete remission was observed in seven of the patients—three of the four with hypothyroidism showed tumour regression. Thus IL-2 and IFN-α_2 can cause hypothyroidism, presumably via induction or exacerbation of autoimmune thyroid reactions. The occurrence of hypothyroidism may be mediated by high-dose IL-2 (rather than by LAK cell therapy as previously suggested) and potentiated by IFN-α_2.
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INTRODUCTION

INTERLEUKIN-2 (IL-2) stimulates the *in vitro* tumoricidal activity of peripheral blood mononuclear cells (PBMC) via induction of lymphokine-activated killer (LAK) cells, which are capable of lysing natural killer (NK) resistant tumour targets [1, 2]. Trials with IL-2 alone or with LAK cells have reported promising results in patients with advanced renal carcinoma and melanoma [3]. Previous studies reported little correlation between laboratory and clinical variables and the response to IL-2 and/or LAK cell therapy [4], except for clinical response and HLA-DR expression by tumour cells [5] and the occurrence of autoimmune hypothyroidism [6]. Autoimmune hypothyroidism was observed in a fifth of patients receiving high-dose IL-2 with LAK cells. Most of these hypothyroid patients had thyroid autoantibodies before therapy. Within 6–11 weeks after therapy, thyroxine (T4) levels declined with an inverse rise of thyroid-stimulating hormone (TSH); in some cases, clinical hypothyroidism was observed. In contrast, 11 melanoma patients receiving IL-2 alone by the same schedule showed no hypothyroidism. It was suggested that LAK cells are required for the development of hypothyroidism in these patients. Furthermore, tumour regression rate was higher in patients who developed hypothyroidism than in euthyroid patients (71% vs. 19%).

We report primary hypothyroidism in four (three responders and one non-responder) out of twenty renal cancer and melanoma patients undergoing immunotherapy with IL-2 and interferon alpha-2 (IFN-α_2). The results suggest that combined treatment with these cytokines, rather than LAK cell administration, is required for the development of hypothyroidism in these patients.

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PATIENTS AND METHODS

Study design

Patients were treated in the clinical oncology unit of the Istituto Regina Elena, Rome, as part of a multicentre trial with

*Table 1. Patients' details**

	Hypothyroid (n =4)	Euthyroid (n = 16)
Age (yr)	41–63	21–70
F/M	2/2	7/9
Type of tumour		
Melanoma	2	11
Renal cell carcinoma	2	5
Tumour regression†	3 (75%)	4 (25%)
Thyroid autoantibodies		
Anti-Tg	0	0
Antimicrosomal	2	3

*Before start of therapy all were euthyroid, and four became hypothyroid as consequence of immunotherapy.
†Includes partial and complete remissions.

IL-2 and IFN-α_2 (Roche). The protocol had been approved by the human investigation review committee of the institute and informed consent was obtained from all patients.

IL-2 and IFN-α_2 were administered as follows: all patients received at least four cycles of therapy, each consisting of 4 days of IL-2 continuous infusion (3×10^6 IU/m^2 per day from day 1 to 4) and 2 days of IFN-α_2 (6×10^6 U/m^2 per day on days 1 and 4) by subcutaneous injection. After 10 days of rest, a new cycle was started. At the end of the fourth cycle, patients were evaluated for clinical response.

Patients whose tumours progressed were withdrawn from the study. Those whose tumours remained stable or responded received four additional cycles. This procedure was repeated at the end of each cycle for a maximum of thirteen cycles.

Thyroid indices

Serum samples obtained before and during treatment were stored at − 40°C. Serum T4, triiodothyronine (T3) and thyroglobulin (Tg) were measured by radioimmunoassay; interassay coefficients of variation were below 10%. Anti-Tg and antithyroid microsomal antibody titres were measured by an immunoenzymatic method (Biscot, Livingston, UK). Both antibodies were assayed in serum samples at multiple dilutions up to 62 500; results were reproducible within one dilution. Titres were considered borderline up to 100 and elevated above 100.

Lymphocyte phenotype

Peripheral blood, drawn into sterile, heparinised plastic syringes and allowed to cool at room temperature, was mixed with an equal volume of sterile Iscove's medium (IMDM, Flow) at −20°C. Diluted blood (30 ml), layered on 20 ml Ficoll–Hypaque (Nyegaards) in a sterile plastic tube was centrifuged at 350 g for 40 min at 20°C. The buffy coat PBMC were removed, washed three times in IMDM and processed for immunofluorescence phenotype analysis.

Lymphoid cells were incubated for 60 min at 4°C with 100 µl of a 1:20 dilution (in Hank's saline solution containing 1 mg/ml bovine serum albumin) of the following monoclonal antibodies: anti-NK Leu 19 (Becton–Dickinson) and anti-T, including OKT3, OKT4 and OKT8 (Ortho Diagnostics). The cells were washed three times at 4°C in Hank's saline solution and incubated for 60 min at 4°C with fluorescein isothiocyanate-labelled F(ab')$_2$ fragments of immunoadsorbent-purified sheep antibodies against mouse immunoglobulins (Technogenetics, Turin). After three additional washes, the cells were analysed in a flow cytometer (FACScan, Becton–Dickinson).

RESULTS

Patients

Twenty patients were treated with IL-2 and IFN-α_2 up to twelve cycles (Table 1). All had a performance status of 0 or 1.

Thyroid indices

Four patients (20%) had laboratory evidence of hypothyroidism after IL-2 and IFN-α_2 treatment (Table 2). All showed a marked decline of serum T4 level, which was associated in three cases with an inverse rise of TSH. Furthermore, the decrease in T4 levels was always coupled with an increase in Tg. One of the four had elevated titres of antimicrosomal antibodies before

Table 2. Thyroid function, antithyroid antibodies and tumour response

	Serum levels				Antibody titres (IU/ml)		
Patients (sex/age)	T4 (µg/dl) (5–12)*	T3 (ng/dl) (80–100)	TSH (µIU/ml) (0.3–6.5)	Tg (ng/ml) (< 30)	Anti-Tg (< 600)	Antimicrosomal (< 20)	Clinical response
F/45, melanoma							
Before	5.6	30	0.68	14	–	–	PR
During	0.19	7.1	50	200	–	–	
M/41, melanoma							
Before	7.3	10	2.8	24	–	3125	PR
During	0.001	6.1	50	105	–	3250	
M/62, renal cancer							
Before	8.2	70	3.9	2.5	–	–	PR
During	0.04	0.001	50	210	–	–	
F/63, renal cancer							
Before	7.5	93	0.05	21	–	–	PD
During	0.001	0.001	0.39	200	–	250	

*Normal range. Peak or nadir values are presented during treatment. PR = partial remission and PD = progressive disease.

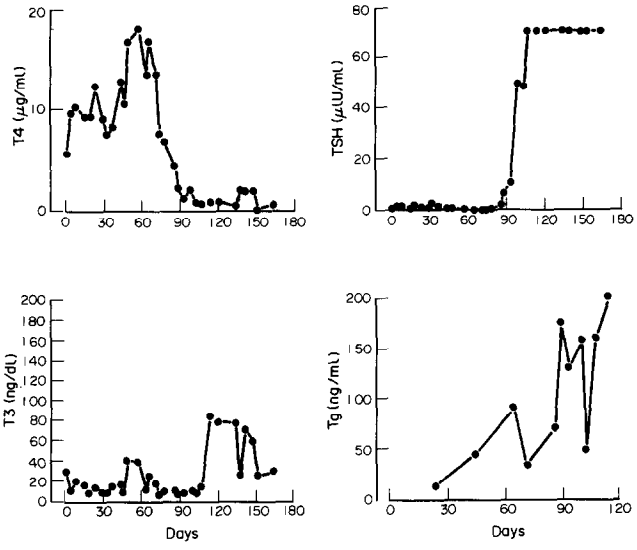

Fig. 1. Kinetics of development of hypothyroidism in first patient in Table 2.

therapy and two during therapy. In addition, none of these patients showed increased levels of serum anti-Tg antibodies, either before or during treatment. Before therapy two of these patients (the first two in Table 2) had low levels of T3, probably related to the fact that they were severely ill.

All euthyroid patients presented normal levels of T4, T3 and thyrotropin, although three patients showed a moderate rise of antimicrosomal antibody titre compared with pretherapy values.

Kinetics of hypothyroidism

Three of the four hypothyroid patients showed more than 50% tumour regression (i.e. partial response) after four cycles; the remaining case had tumour progression at the end of the first four cycles. In these four patients, T4 decreased at 30, 70, 90 and 100 days, respectively, after the start of IL-2 and IFN-α_2 treatment (a representative case is shown in Fig. 1). In three patients, the timing of the T4 decline essentially corresponded to that of the rise of TSH. The patient with a marked decrease in T4 without an increase in TSH was the only hypothyroid patient with tumour progression (Fig. 2).

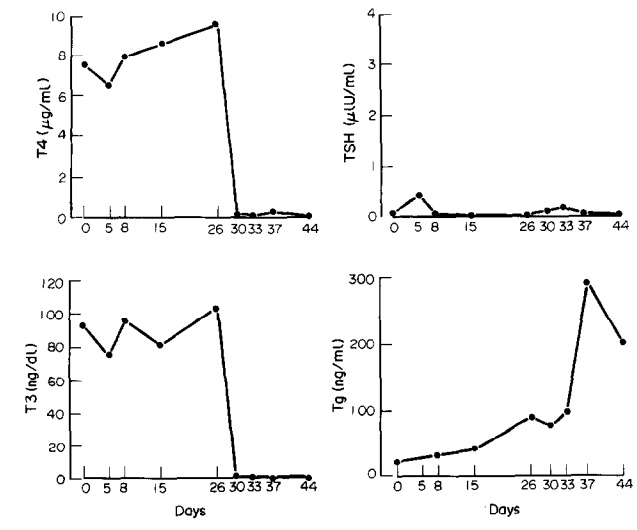

Fig. 2. Kinetics of development of hypothyroidism in fourth patient in Table 2.

Table 3. Characteristics of ten patients who received at least six cycles of therapy

	Hypothyroid (n = 3)	Euthyroid (n = 7)
Age (yr)	41–62	21–70
F/M	1/2	3/4
Type of tumour		
Melanoma	2	5
Renal cell carcinoma	1	2
Tumour regression*	3 (100%)	4 (43%)
Thyroid autoantibodies		
Anti-Tg	0	0
Antimicrosomal	1	2

*Includes partial and complete remissions.

In the hypothyroid patients, four to six cycles of therapy were required for development of hypothyroidism. It is of interest, therefore, to compare the clinical and laboratory characteristics of hypothyroid and euthyroid patients undergoing at least six cycles of therapy (i.e. ten out of the other sixteen patients and three out of the four hypothyroid cases) (Table 3). These two groups were similar in age, performance status and sex ratio. None of the euthyroid patients had elevated serum thyrotropin levels, but two of seven (29%) had elevated antimicrosomal antibody titres before therapy. Antithyroid antibodies were monitored in one of the three hypothyroid patients. More importantly, all three patients with hypothyroidism had evidence of tumour regression, compared with three out of seven (43%) in the euthyroid group.

Lymphocyte analysis

The percentage of T lymphocytes (CD3+), T helper lymphocytes (CD4+), T suppressor/cytotoxic lymphocytes (CD8+) and NK lymphocytes (CD56+) was evaluated by immunofluorescence with specific monoclonal antibodies. In most cases the number of CD3+, CD4+, CD8+ and CD56+ lymphocytes decreased during IL-2 infusion, and rebounded to higher levels when IL-2 infusion was discontinued (Fig. 3). Similar lymphocyte subset values were observed in both euthyroid and hypothyroid patients, although slight differences were observed on particular days of observation.

DISCUSSION

IL-2 and IFN-α_2 induced hypothyroidism in a fifth of our patients treated for four or more cycles and in 30% of those treated for six or more cycles. Interestingly, tumour regression was observed in all three hypothyroid patients undergoing six or more cycles, indicating a link between tumour regression and hypothyroidism. However, study of a larger number of patients is required to substantiate this conclusion.

The pathogenesis of hypothyroidism after IL-2 and IFN-α_2 therapy is probably multifactorial. A previous study on cancer patients treated with IL-2, alone or combined with LAK cells, showed that in a fifth of the cases the combined therapy resulted in hypothyroidism, whereas treatment with IL-2 alone did not [6]. Furthermore, leucocyte-derived IFN-α_2 induced autoimmune thyroid disease in patients treated for breast cancer or carcinoid tumours [7, 8], but this effect was later ascribed to contamination with IFN-γ [8]. Sporadic cases of hyper-

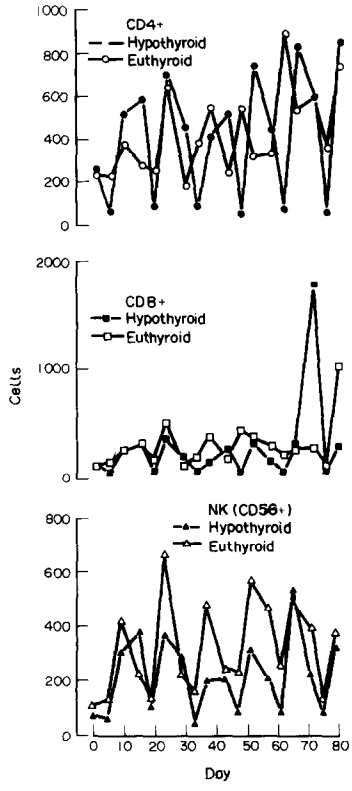

Fig. 3. Fluctuation in the number of lymphocyte subpopulations in hypothyroid and euthyroid patients.

thyroidism, but not hypothyroidism, have been reported in some cancer patients treated wtih recombinant IFN-α_2 alone [9]. Thus it appears that neither IL-2 nor IFN-α_2 alone can induce hypothyroidism when administered to cancer patients. Our study, however, indicated that combined treatment with these two agents may lead to this syndrome.

Possibly, the hypothyroidism was mediated by autoimmune mechanisms. The presence of antithyroid antibodies in two of our four hypothyroid patients suggests an autoimmune mechanism. However, antithyroid antibodies were also present in a few of our euthyroid patients similarly treated. IL-2 therapy includes secondary production of a series of cytokines, thus resulting in pleiotropic biological and clinical effects [10–12]. High levels of IFN-γ are consistently detected in the serum of patients undergoing adoptive immunotherapy with IL-2 alone or combined with LAK cells [10, 11]. Increased serum levels of tumour necrosis factor (TNF) alpha were observed in patients undergoing adoptive immunotherapy with IL-2 [12]. Interestingly, TNF-α acts synergistically with IFN-γ to induce HLA class II antigen on human thyrocytes [13], while TNF-α is produced by intrathyroidal T cells [14]. The Il-2 induced release of secondary cytokines, including IFN-γ and TNF-α, may act synergistically to induce HLA-DR antigen expression on thyrocytes; these cells may thus present thyroid-specific antigens to specific autoreactive T lymphocytes, thereby initiating an autoimmune response. This hypothesis is in line with other observations: the susceptibility to autoimmune thyroiditis is related to certain HLA class II antigens [15]; human thyroid epithelial cells express HLA-DR antigens in autoimmune thyroid disease [16, 17]; and recombinant IFN-γ can induce the expression of HLA-DR antigens on cultured thyroid epithelial cells [18].

In one of our patients who developed hypothyroidism (Fig. 2), serum T3 and T4 levels decreased despite normal serum TSH. In this case the tumour progressed; this could correspond to a condition previously described [19] consisting of a failure of the normal negative-feedback control of the pituitary–thyroid axis due to illness-associated decreased secretion of thyrotropin. However, this interpretation is made difficult by two findings: at the moment of the lowering of T3 and T4 levels the patient had increased Tg thyroglobulin level and antimicrosomal antibodies. Thus, the most likely interpretation is that in this patient the genesis of hypothyroidism was multifactorial and mediated both by immunological and illness-related mechanisms.

Data from animal models [20, 21] as well as from human disease indicate that T lymphocytes play a major role in the pathogenesis of autoimmune thyroiditis [22, 23]. T-cell abnormalities in autoimmune thyroiditis are related to both regulatory [22] and effector function (direct cytotoxicity) [24]. The direct role of cytotoxicity as the primary effector mechanism in thyroid cell damage has been demonstrated in experimental autoimmune thyroiditis [22] and in Hashimoto's thyroiditis [25,26]. Analysis of cell-surface markers on the lymphoid cells infiltrating the thyroid glands of patients affected by autoimmune thyroiditis showed an increase of activated T cells mainly belonging to the CD8+ subset [27–30]. The presence of these cells strongly favours a potential role for cytotoxic T lymphocytes in the thyroid damage associated with autoimmune thyroiditis [31]. Interestingly, both IL-2 and IFN-α stimulate the cytotoxicity mediated by T lymphocytes [32, 33]. These results suggest that IL-2 and IFN-α may cooperate to induce the proliferation and stimulation of autoreactive antithyroid cytotoxic T clones in cancer patients undergoing therapy with these two cytokines.

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Toxicity, Pharmacokinetics and Metabolism of Iododoxorubicin in Cancer Patients

Klaus Mross, Ulrich Mayer, Tobias Langenbuch, Kirsten Hamm, Konrad Burk and Dieter Hossfeld

25 patients, mostly pretreated, received 55 courses of iododoxorubicin as a single intravenous bolus every 2 weeks. The starting dose was 2 mg/m² with seven steps to reach the dose-limiting toxicity level. 3 patients treated with 90 mg/m² had WHO grade 4 myelotoxicity; 2 of these patients had not had cytostatic chemotherapy. 3 of 7 patients treated with 75 mg/m² had grade 3–4 myelotoxicity; 4 had grade 1–2. Non-haematological toxicities were minor. Acute cardiotoxicity and objective tumour responses were not observed. Plasma and urine levels of iododoxorubicin and five metabolites were assayed in 16 patients. Metabolism to iododoxorubicinol was rapid and plasma clearance was dose-dependent and rapid. Plasma levels and the area under the curve for iododoxorubicin increased with dose. The mean residence time was 3.9 h in patients without liver metastasis and 10.4 h in patients with liver metastasis. Renal excretion was minor. The maximally tolerated dose was 90 mg/m².
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INTRODUCTION

THE INTRODUCTION of an iodine atom at the 4′ position of the daunosamine sugar of doxorubicin lowers the acid dissociation constant (p*K*a 6.4) of iododoxorubicin, which is therefore nearly unprotonated at physiological pH [1], and makes the drug more lipophilic than its parent [2]. Thus the penetration of cell membranes should be more rapid with iododoxorubicin. In preclinical screens iododoxorubicin had broad antitumour activity against several mouse and human tumours *in vivo* and *in vitro* [3,4] and against several human xenografts [5]. Additionally, the compound inhibited anthracycline-resistant tumour cells [6] and there was incomplete cross-resistance between iododoxorubicin and doxorubicin [7]. Preclinical toxicology showed that the major target organ for iododoxorubicin was bone marrow and the well-known side-effects of anthracyclines were reduced with this drug [5,8]. The reduction of the C-9 carbonyl by aldoketo-reductases yields iododoxorubicinol [9,10], which is also cytotoxic [11]. The parent as well as the