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Letters to the editor

Interferon-β does not change the level of O^6-alkylguanine-DNA alkyltransferase in cancer patients' lymphocytes

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Interferon (IFN) can induce the DNA repair enzyme O^6-Alkylguanine-DNA alkyltransferase (AT) in the liver of rats or mice.[1,2] Treatment with the IFN inducer polyinosinic–polycitidylic acid or with the cytokine inducer lipopolysaccharide also caused this induction. Since AT plays an important role in the repair of the DNA lesions induced by some alkylating antineoplastic agents, such as chloroethylnitrosureas or methyltriazenes,[3,4] it can be important to know whether IFN raises the levels of AT in human tissues, thus modifying the pharmacological effects of these drugs.

In order to elucidate this point we studied AT levels in lymphocytes of cancer patients before and after IFN-β treatment. Fourteen patients entered the study, all women aged from 47 to 76 years suffering from endometrial adenocarcinoma. They received IFN-β (Frone, Serono, Italy) as a dose of 3×10^6 IU/day i.m. every other day for 3 weeks. Blood was sampled before treatment and on the second and ninth day (i.e. after one and four doses) from the start of therapy. Lymphocytes were separated by density gradient centrifugation over Ficoll-Hypaque, washed in phosphate buffered saline and stored at −80 °C until AT activity assay.

AT was determined in lymphocytes by measuring the removal of the ^{3}H-methyl adduct from O^6-[^{3}H]methylguanine in [^{3}H]methyl DNA as previously described.[5] Several samples of the same cell extract were used to obtain results in the linear range. The reaction mixture was incubated for 60 min at 37°C, acidified by adding perchloric acid and incubated for 40 min at 75°C to completely hydrolyze DNA. The protein was collected by centrifugation, washed and assayed for its radioactivity content. The results were expressed as fmol methyl transferred per mg of DNA content in each sample.

Figure 1 shows the levels of AT in each patient. As previously described, the basal level of AT varied widely in the different individuals with no apparent relation to age or to the disease stage (data not shown). The mean levels (±SD) of AT were 2.40 ± 1.54 at time 0, 2.13±1.31 on day 2 and 2.07 ± 0.98 fmol/mg DNA on day 9. The differences were not significant. This finding suggests that IFN can be combined with chloroethylating or methylating agents without reducing these drugs' antitumor potency.

This cannot be considered a definitive conclusion since AT levels were determined in peripheral lymphocytes and not in neoplastic tissues where the

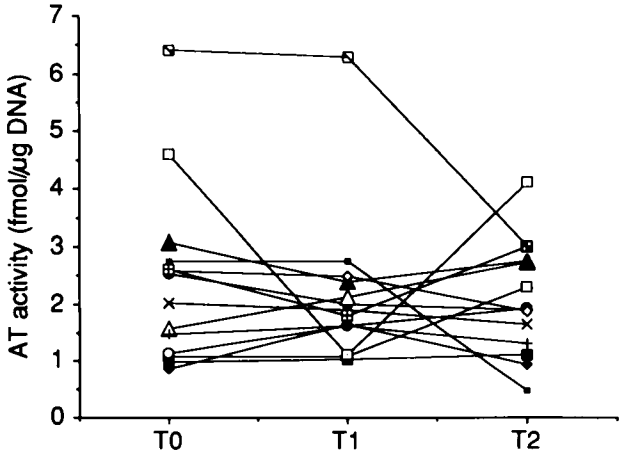

Figure 1. AT activity in patients sampled before IFN-β treatment (T0) and on day 2 (T1) and day 9 (T2) after starting therapy.

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drugs exert their effects. On the other hand, medical and ethical considerations make it virtually impossible to obtain repeated biopsies of tumor tissues from the same patient and recent studies indicate the lymphocytes are a good surrogate for measuring AT levels and for investigating changes in the activity of this DNA repair enzyme induced by chemotherapeutic agents.[6]

References

1. Bertini R, Coccia P, Pagani P, *et al.* Interferon inducers increase O^6-alkylguanine-DNA alkyltransferase. *Carcinogenesis* 1990; **11:** 181–3.
2. Coccia P, Bertini R, Pagani P, *et al.* O^6-Alkylguanine DNA alkyltransferase is induced by human recombinant interferon-aA/D in mouse liver. *J Interferon Res* 1992; **12:** 173–6.
3. D'Incalci M, Citti L, Taverna P, *et al.* Importance of the DNA repair enzyme O^6-alkylguanine DNA alkyltransferase (AT) in cancer chemotherapy. *Cancer Treat Rev* 1988; **15:** 279–92.
4. Pegg AE. Mammalian O^6-alkylguanine-DNA alkyltransferase: regulation and importance in response to alkylating carcinogenic and therapeutic agents. *Cancer Res* 1990; **50:** 6119–29.
5. Margison GP, Cooper DP, Brennand J. Cloning of the *E. Coli* O^6-methylguanine and methylphosphotriester methyltransferase gene using a functional DNA repair assay. *Nucleic Acids Res* 1985; **13:** 1939–52.
6. Lee SM, Thatcher N, Crowther D, *et al. In vivo* depletion of O^6-alkylguanine-DNA-alkyltransferase in lymphocytes and melanoma of patients treated with CB10-277, a new DTIC analogue. *Cancer Chemother Pharmacol* 1992; **31:** 240–6.

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Safe administration of oral etoposide after hypersensitivity reaction to intravenous etoposide

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Introduction

Etoposide, a semi-synthetic derivative of podophyllotoxin, is commonly used in the treatment of malignant disease. It has been available clinically for over 20 years. A well known but rare toxicity is manifested by dyspnea, chest discomfort, hypotension, bronchospasm or skin flushing and is typical of a type I hypersensitivity reaction (HSR).[1] It has been variably suggested that this reaction may be due to either the active drug or the solvent.

We report for the first time the details of a patient who despite experiencing an anaphylactic reaction to intravenous etoposide, tolerated the subsequent use of oral etoposide without any allergic problems. We conclude that in this case at least, the solvent and not the active drug was responsible for this toxicity.

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Case report

A 76 year old female with limited small cell lung carcinoma was treated with intravenous etoposide (120 mg/m^2) and carboplatin (100 mg/m^2) daily for 3 days. The patient had a previous history of a penicillin allergy which occurred almost 20 years ago.

The etoposide infusion was prepared immediately prior to administration using standard aseptic techniques. The dose of etoposide (190 mg) was added to 500 ml of normal saline. Within minutes of the administration of etoposide, the patient complained of generalized discomfort, pruritus, shortness of breath, wheeze, erythema and was very distressed. The infusion was immediately stopped and intravenous hydrocortisone (100 mg) and promethazine (12.5 mg) were administered, along with nebulized salbutamol. After 1 h, the patient had markedly improved. Carboplatin was not administered. Treatment was changed to vincristine