INTERLEUKIN-3 ENHANCES THE ENDOGENOUS LEUKOTRIENE PRODUCTION

To the Editor:

Interleukin-3 (IL-3) is a multilineage hematopoietic growth factor that is currently being tested for its potential to ameliorate or prevent hematopoietic failure.\textsuperscript{1,4} Several lines of evidence suggest that endogenous leukotrienes may play a role in IL-3 actions: leukotrienes are lipoxygenase metabolites that appear to be involved in inflammatory and proliferative reactions including hematopoiesis\textsuperscript{5-7}; IL-3 has been shown to prime cells in vitro for an enhanced biosynthesis of leukotrienes\textsuperscript{8,9}; IL-3 shares some functional characteristics with granulocyte-macrophage colony-stimulating factor\textsuperscript{3,8} which exerts actions in vivo apparently closely related to an increase in leukotriene generation.\textsuperscript{10,11} We studied the effects of IL-3 on the endogenous leukotriene production in patients to establish whether or not there
is direct evidence for an involvement of leukotrienes in IL-3 actions in vivo. The study was performed in 10 patients treated in a phase II study for relapsed aggressive lymphoma. Recombinant human IL-3, derived from Escherichia coli was provided by Sandoz (Basel, Switzerland). IL-3 was administered subcutaneously on days 5 to 14 after 3 days of chemotherapy (epirubicin 50 mg/m² on day 1, ifosfamide 2.5 g/m², and etoposide 100 mg/m² on days 1 to 3). The daily IL-3 doses were 2.5 µg/kg (n = 2), 5 µg/kg (n = 2), 10 µg/kg (n = 3), or 15 µg/kg (n = 3). The endogenous leukotriene production was estimated by determination of the urinary concentration of leukotriene E₄ (LTC₄) plus N-acetyl LTE₄ before chemotherapy (day 1), before IL-3 (day 3), during and after IL-3 (days 9 and 15, respectively, Fig 1).

In the patients studied, the pretreatment concentration of urinary LTC₄ plus N-acetyl LTE₄, corrected for urinary creatinine concentrations, was 96 ± 66 nmol/LTE₄ plus N-acetyl LTE₄/mol creatinine (mean ± SD, Fig 1), i.e., significantly higher compared with healthy controls (9.9 ± 8.3 nmol/mol creatinine, mean ± SD, n = 21; P < .01, according to the t-test). This difference might be caused by the underlying malignant disease or to its sequelae. After chemotherapy, the elevated urinary leukotriene concentrations were normalized (Fig 1). After 5 days of IL-3 administration significantly (P < .01) higher leukotriene concentrations were observed, but at the end of the IL-3 course leukotriene concentrations returned to pretreatment values (Fig 1). Two observations provide evidence that the increase in urinary leukotrienes was most likely caused by IL-3 administration: (1) The increase in urinary leukotrienes did not occur in nine lymphoma patients investigated on different days of cytopenia after chemotherapy in the absence of exogenous cytokines. The leukotriene production on the fifth day of IL-3 treatment was correlated with the IL-3 dose administered (product moment correlation coefficient, .68, P < .01). The increase in leukotrienes preceded the leukocyte regeneration considerably (Fig 1). Urinary leukotriene concentrations varied by a factor of 1.1 to 4.2 in five patients in which results from two subsequent therapy courses were compared. There was no apparent relation between leukotriene production and the serum concentrations of granulocyte-macrophage colony-stimulating factor, IL-6, or tumor necrosis factor-α, which were determined by enzyme-linked immunosassay. Inflammatory reactions related to IL-3, similar to those noticed by other investigators, were observed in 8 of the 10 (8/10) patients. They presented as fever (8/10) and erythema at the injection site (2/10). The two patients without IL-3-related inflammatory reactions produced comparably low amounts of leukotrienes (maxima of urinary leukotriene concentrations below 48 nmol/mol creatinine).

Our results provide direct evidence that leukotrienes are involved in IL-3 actions in vivo. They support the view that these lipid mediators may contribute significantly to the biologic effects of IL-3 treatment. Whether this contribution is primarily directed to inflammatory reactions or also involves the proliferative effects of IL-3 remains to be established.

ACKNOWLEDGMENT

We are indebted to Prof Dr B.A. Peskar, Bochum, Germany, for providing the leukotriene antibody used for the leukotriene determinations. The excellent assistance of S. Sagebiel is gratefully acknowledged. Supported by the Deutsche Forschungsgemeinschaft (De 397/1-3).

REFERENCES

Interleukin-3 enhances the endogenous leukotriene production [letter]

C Denzlinger, J Walther, W Wilmanns and HH Gerhartz