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Plasma Prostaglandins in Lung Cancer

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Abstract—*Plasma levels of three stable prostaglandin (PG) metabolites were measured in 29 patients with lung cancer. The mean level of 6-keto-$PGF_1\alpha$, the hydrolysis product of prostacyclin, was significantly elevated in cancer patients compared to a control group with non-malignant respiratory disorders, although an overlap in values between the groups was seen. Levels correlated inversely with survival and showed a significant fall in 14 patients with tumour regression. The mean level of 11-deoxy-3,14-dihydro-15-keto-11,16-cyclo-prostaglandin E_2 was also significantly elevated in cancer patients, but did not correlate with tumour response. 13,14-Dihydro-15-keto prostaglandin $F_2\alpha$ levels did not differ in lung cancer patients and controls. Contrary to previous reports we could not support a role for the metabolites of PGE_2 and $PGF_2\alpha$ as tumour markers in lung cancer but plasma 6-keto-$PGF_1\alpha$ should be further evaluated in this regard.*

INTRODUCTION

ELEVATED levels of prostaglandins (PG) or their metabolites have been found in extracts from several human tumours including those of the lung [1] and in the peripheral blood of normocalcaemic patients with lung cancer [2]. It has been suggested that PGs may have a role as tumour markers as elevated peripheral blood levels of PGE_2 and 13,14-dihydro-15-keto PGF_2 fell abruptly following surgical resection of lung tumours. A similar role has been suggested for 6-keto-$PGF_1\alpha$, a metabolite of prostacyclin in gynaecological and prostatic malignancy [3, 4]. We have measured plasma levels of these three prostaglandin metabolites in patients with lung cancer of different histological types, to see if there was a correlation with clinical status and support for their use as tumour markers.

MATERIALS AND METHODS

Twenty-nine patients with bronchial carcinoma (adeno- or large cell—11, squamous—9 and small cell—8) were studied at diagnosis. Mean age ± S.E.M. of patients was 65.4 ± 1.3 years and 20 were male. Serial values were obtained in 17 patients undergoing therapy with radiation, cytotoxics or surgery either alone or in combination. Eighteen patients with non-malignant respiratory disorders attending a chest clinic, 11 male, mean age 65.5 ± 2.4 years, served as a control group. The smoking habits of the two groups were similar: only one patient in each group had never smoked, 19 (66%) of cancer patients and 12 (67%) of controls were current smokers and the remainder had stopped smoking within the previous 5 years. No patient was receiving steroids or anti-inflammatory analgesics at the time of the initial valuation. Three patients were hypercalcaemic at diagnosis.

Stable metabolites of prostacyclin (6-keto-prostaglandin $F_1\alpha$, $6KPGF_1\alpha$), PGE_2 (11-deoxy-13, 14-dihydro-15-keto-11,16-cyclo-prostaglandin E_2, PGEM-II) and $PGF_2\alpha$ (13,14-dihydro-15-keto-prostaglandin $F_2\alpha$, PGFM), were assayed in peripheral blood. Ten millilitre blood samples were collected in chilled tubes at 0°C containing 0.1 ml EDTA (70 mg/ml) and 0.1 ml acetylsalicylic acid (5 mg/ml saturated solution). The samples were spun at 1500 ***g*** and stored at −20°C. Samples were assayed in one batch without prior extraction by specific radioimmunoassays (RIA) that have been described and validated in detail elsewhere [5, 6]. The limit of detection of these assays is < 4 pg/ml and intra-assay variation < 10%.

As the data distribution showed a positive skew, square roots were taken before using Student's *t* test to compare means. The log-rank test was used to compare survival in diffferent groups.

RESULTS

$6KPGF_1\alpha$ was elevated in the 29 lung cancer patients compared with 18 controls, $P < 0.002$ (see Fig. 1). Levels fell in the 14 patients with tumour regression assessed by chest radiography, from a

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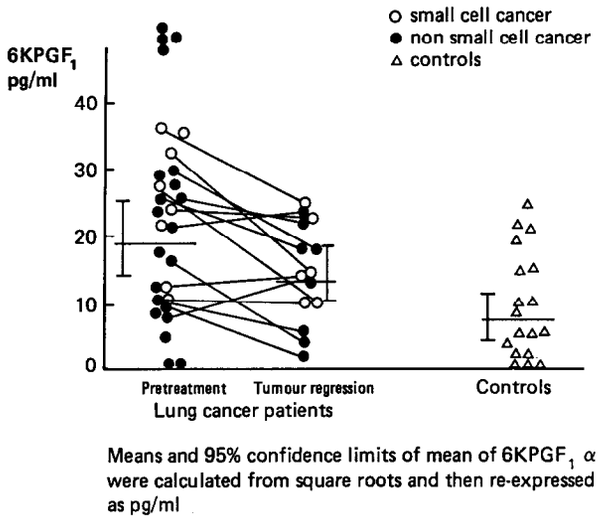

Fig. 1. 6-KPGF$_1\alpha$ in lung cancer patients and controls.

mean 21.3 (16.3–27.0) (means and 95% confidence limits of mean expressed as pg/ml after calculation from square roots) to 13.6 (9.3–18.7) pg/ml, paired t test, $P < 0.01$. No differences were seen between histological types. Patients with 6-KPGF$_1$ levels above 20 pg/ml (taken as the mean) had a shorter survival than those lower levels, median 5 versus 14 months, $P < 0.025$ (Fig. 2). Levels of PGEM-11 in cancer patients were also elevated with a mean 132.3 (113–152.8) pg/ml versus 99.4 (95.9–113.8) pg/ml in the control group, $P < 0.01$, but were unrelated to tumour response and survival. PGFM levels did not differ in patients and controls but a rise was seen in the five patients with small cell lung cancer after tumour regression, 136.9 (117–157) pg/ml prior to therapy and 193.8 (166.9–182.7) pg/ml post therapy, $P < 0.01$. PG levels did not differ in the three patients hypercalcaemic at diagnosis from the group as a whole.

DISCUSSION

Differences in RIA methodology have resulted in a variable range of 'normal values' of 6-KPGF$_1\alpha$ probably because of cross-reaction of the antibody with other PGs. It has been suggested, however, that for clinical studies, measurement of 6-KPGF$_1\alpha$ by RIA may better reflect changes in PGI_2 metabolism than the absolute values obtained by gas-chromatography/mass spectrometry [7]. In this study the control group was selected with similar smoking habits to the study group as smoking may reduce prostanoid synthesis although plasma levels are not significantly altered [8].

Khan *et al.* [4] suggested that plasma 6-PGF$_1\alpha$ may be a useful marker in prostatic cancer as high levels distinguished between benign and malignant disease, correlated with disease extent and inversely with tumour differentiation. In gynaecological tumours elevated levels did not differentiate between benign and malignant disease although they fell with tumour regression [3]. Although 6-KPGF$_1\alpha$ levels were elevated in approximately half our cancer patients there was considerable overlap with values in the control group, and thus not of diagnostic value. 6-PGF$_1\alpha$ levels fell in the majority of patients with tumour response thus supporting the findings in gynaecological and prostatic malignancy. Although we did not analyse for tumour differentiation, we did find an inverse correlation between survival and 6-PGF$_1\alpha$ levels. Elevated PG production in human breast and cutaneous tumour extracts has been associated with an aggressive growth pattern and thus may be a marker for a high neoplastic potential [9, 10]. The role of PGs in the interaction between tumour cells, stroma and neovasculature and in view of their vasoactive properties and effect on platelets against host defences has yet to be defined.

We failed to support the findings of Fielder *et al.* [2] of a fall in PGFM and PGEM-11 with tumour regression. All their patients underwent surgical resection, however, compared with only one patient studied serially in our group, the majority having only minor tumour regression after chemo-/radio-

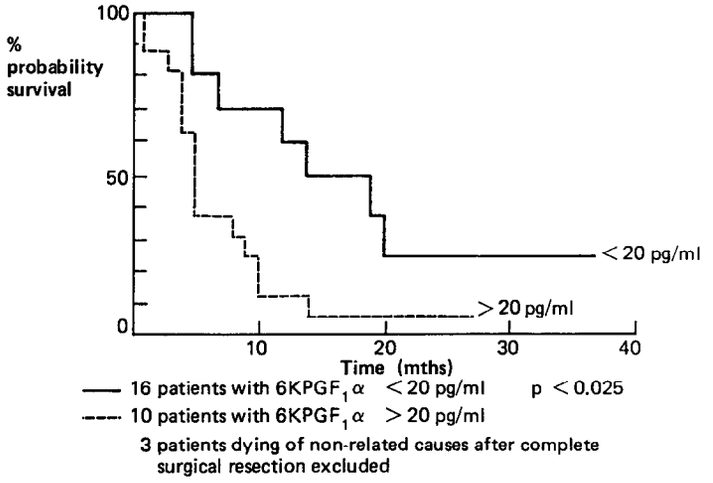

Fig. 2. Survival of lung cancer patients according to 6-KPGF$_1\alpha$ level.

therapy. We also had patients with small cell lung cancer in whom PGFM rose unexpectedly with tumour regression. This lack of sensitivity to the small alterations in tumour burden and variance with histological type suggest a limited use of these PG metabolites as tumour markers in clinical practice. 6-KPGF$_1\alpha$ shows more promise and should be further evaluated.

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