Pergamon

European Journal of Cancer Vol. 33, No. 4, pp. 691–693, 1997

Printed in Great Britain
0959-8049/97 $17.00+0.00

PII: S0959-8049(96)00411-X

Short Communication

Prognostic Value of Basic Fibroblast Growth Factor and Its Receptor (FGFR-1) in Patients with Non-small Cell Lung Carcinomas

M. Volm, R. Koomägi, J. Mattern and G. Stammler

German Cancer Research Center, Department of Oncological Diagnostics and Therapy, Im Neuenheimer Feld 280, 69120 Heidelberg, Germany

Tumour specimens of 206 patients with untreated non-small cell lung carcinomas (NSCLC) were analysed immunohistochemically for the expression of the basic fibroblast growth factor (bFGF) and for its receptor (FGFR-1, Flg). Seventy of the tumours showed weak expression, 109 moderate and 27 high expression of bFGF. Thirty-eight tumours had low expression of FGFR-1, 116 had moderate and 52 cases high expression. Patients with high FGFR-1 expression had significantly shorter survival times than patients with weak or moderate expressions ($P < 0.05$), but there was no significant correlation between bFGF expression and patient survival. The results of the multivariate analysis demonstrated that FGFR-1 in the presence of stage is not an independent prognostic factor.

Key words: lung carcinomas, basic fibroblast growth factor, FGFR-1, immunohistochemistry, survival

Eur J Cancer, Vol. 33, No. 4, pp. 691–693, 1997

INTRODUCTION

BASIC FIBROBLAST growth factor (bFGF) and its receptor FGFR-1 (Flg) are involved in proliferation, differentiation, and angiogenesis [1]. Nanus and associates determined the expression of bFGF in renal cancers and found that patients whose renal cell carcinoma expressed bFGF had shorter survival times [2]. Ohta and associates [3] examined the expression of bFGF and its receptor by immunohistochemistry in pancreatic ductal adenocarcinomas and found that low expression of the receptor was significantly associated with a longer post-operative survival as compared with high FGFR-1 expression, whereas there was no significant difference in survival between the low and high bFGF expression groups.

The role of bFGF in the human lung has not been studied in detail yet. Therefore, in the present investigation, we examined bFGF and FGFR-1 in human non-small cell lung carcinomas by immunohistochemistry and determined the relevance of this growth factor system to prognosis of patients with non-small cell lung carcinomas (NSCLC).

Correspondence to M. Volm.
Received 21 Jun. 1996; revised 30 Aug. 1996; accepted 19 Sep. 1996.

PATIENTS AND METHODS

206 patients with previously untreated NSCLC were entered into the study. The tumours were resected completely. All patients were staged at the time of surgery. The classification of the stage (pTNM) was made according to the guidelines of the American Joint Committee for Cancer Staging and End Results Reporting [4]. Of the 206 patients, 56 had stage I or II, and 150 had stage III tumours. The morphological classification of the bronchogenic carcinomas was based on the WHO study [5] and comprised 114 epidermoid carcinomas, 60 adenocarcinomas, and 32 large cell carcinomas. The age distribution of the patients (185 men, 21 women) included 120 patients younger than 60 years and 86 older than 60 years. 78 patients did not have lymph node involvement, whereas 127 patients had lymph node involvement (one patient could not be defined). 144 patients were treated only by surgical procedures, 26 patients were additionally treated by cytotoxic drugs, and 36 patients (mainly epidermoid carcinomas) were treated with irradiation. The additional radiation treatment and chemo-

therapy had no significant effect on the survival time of the patients ($P = 0.24$). Follow-up data were obtained through hospital charts and correspondence with the referring physicians. The survival times were determined from the day of surgery. The minimum follow-up time was 5 years.

The biotin–streptavidin method previously described was used for the detection of bFGF and FGFR-1 [6–8]. Staining for bFGF was carried out using a rabbit polyclonal antibody raised against a peptide corresponding to amino acids 40–63, mapping within the amino terminal region of human bFGF (Santa Cruz Biotechnology, Heidelberg, Germany) [9]. Flg (C-15) is also an affinity-purified rabbit polyclonal antibody raised against a peptide corresponding to amino acids 808–822, mapping at the COOH terminus of human FGFR-1 (Flg; Santa Cruz Biotechnology) [10]. Flg specifically recognises the FGFR-1 receptor and is not cross-reactive with FGFR-2, FGFR-3 or FGFR-4. Three observers independently evaluated the results of immunohistochemical staining without knowledge of the clinical data of each patient. For evaluation of protein expression, a score corresponding to the sum of (*a*) percentage of positive cells (0 = 0% immunopositive cells; 1 = <25% positive cells; 2 = 26–50% positive cells; and 3 = >50% positive cells) and (*b*) staining intensity (0 = negative; 1 = weak; 2 = intermediate; 3 = strong) was established. The sum $a + b$ reached a maximum score of 6. Scores of 0–2 were regarded as low, scores 3 and 4 as moderate, and scores 5 and 6 as strong.

Life table analyses according to Kaplan and Meier were performed for overall survival. The groups were compared by log-rank tests. The prognostic influence of clinical and molecular parameters was assessed by multivariate regression methods (Cox model) as described by Byar [11]. The inter-relationships of clinical and immunohistochemical data were assessed statistically by using Fisher's Exact test.

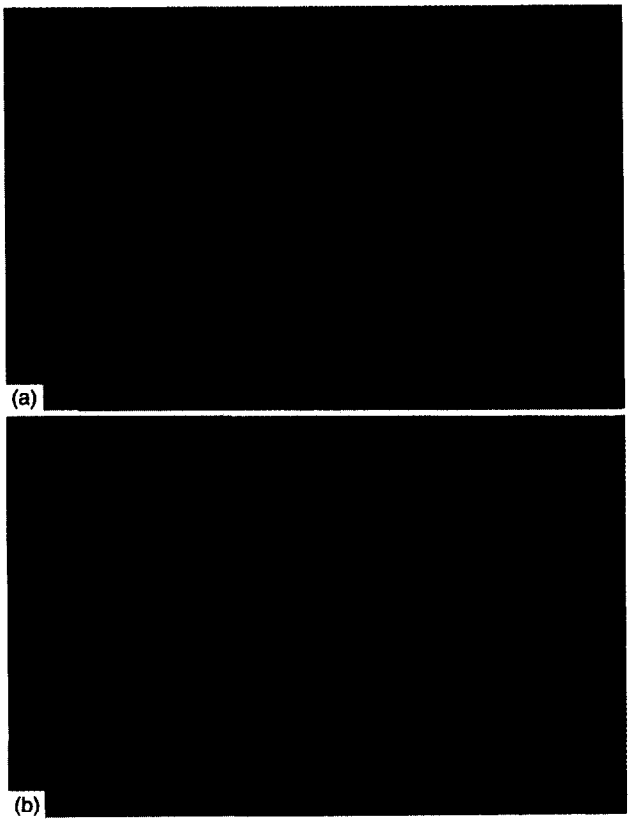

Figure 1. Typical immunohistochemical staining for (a) bFGF and (b) FGFR-1.

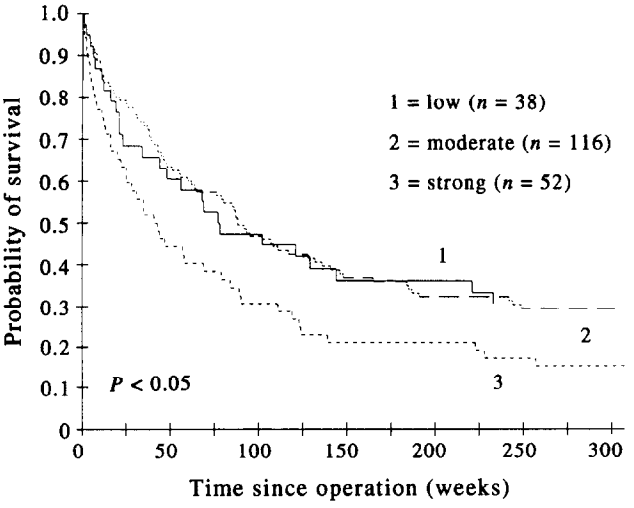

Figure 2. Survival curves (Kaplan–Meier estimates) of patients with NSCLC subdivided according to FGFR-1 (Flg) expression.

RESULTS

In the present investigation, tumour specimens of 206 patients with previously untreated NSCLC were analysed immunohistochemically for expression of basic fibroblast growth factor (bFGF) and its receptor FGFR-1 (Flg) (Figure 1). The purpose of the analysis was to find out whether these factors are additional prognostic factors for the patients' survival.

The prognosis of patients with NSCLC is largely determined by the stage of disease and this was confirmed by the present study ($P < 0.001$; data not shown). Nodal involvement is a well-known prognostic factor and its significance was also clearly established in our study ($P < 0.001$; data not shown). The histological type was only of weak prognostic value.

Of the 206 tumours investigated, 70 (34%) showed a weak, 109 (53%) a moderate, and 27 (13%) a high expression of bFGF. Low FGFR-1 expression was found in 38 tumours (19%), moderate expression in 116 tumours (56%) and high expression in 52 cases (25%).

Patients with a high expression of the FGFR-1 had significantly shorter survival times than patients with weak or moderate expression. The median survival time for patients with weak expression was 77 weeks, for patients with moderate expression 88 weeks and for patients with high expression 41 weeks ($P = 0.025$). In contrast, there was no correlation between expression of bFGF and survival ($P = 0.67$).

Figure 2 shows the survival curves of the patients grouped according to the expression of FGFR-1. There was a significant difference in survival between the groups of patients with low or moderate and strong expression of FGFR-1. The results of the multivariate analysis (Cox regression model) demonstrated that FGFR-1 in the presence of the stage is not an independent prognostic factor for the survival of patients with NSCLC (stage: $P = 0.002$; FGFR-1: $P = 0.36$).

DISCUSSION

We found that NSCLC patients with a high expression of FGFR-1 had significantly shorter survival times than patients with weak or moderate expression. In contrast,

there was no inter-relationship between expression of bFGF and patients' survival. This finding is in agreement with data reported by Ohta and associates [3]. These authors examined immunohistochemically the expression of bFGF and FGFR-1 in 32 pancreatic adenocarcinomas and found that low FGFR-1 expression was significantly associated with a longer survival, whereas there was no notable difference in survival with bFGF expression. In our investigation, we found that there was a significant correlation between FGFR-1 expression and stage and the result of the multivariate analysis clearly demonstrates that FGFR-1 is not an independent prognostic factor for the survival of patients with non-small cell lung carcinomas. These data show that it would be premature to use the expression of bFGF and FGFR-1 as prognostic markers for non-small cell lung carcinomas.

1. Baird A, Klagsbrun M. The fibroblast growth factor family. *Ann NY Acad Sci* 1991, **638**, 403–477.
2. Nanus DM, Schmitz-Dräger BJ, Motzer RJ, *et al.* Expression of basic fibroblast human renal tumors: correlation with poor survival. *J Natl Cancer Inst* 1993, **85**, 1597–1599.
3. Ohta T, Yamamoto M, Numata M, *et al.* Expression of basic fibroblast growth factor and its receptor in human pancreatic carcinomas. *Br J Cancer* 1995, **72**, 824–831.
4. Carr DT, Mountain CF. Staging lung cancer. In Straus MJ, ed. *Lung Cancer: Chemical Diagnosis and Treatment.* New York, Grune and Stratton, 1977, 151–161.
5. World Health Organization. Histological typing of lung tumours. *Tumori* 1981, **6**, 253–272.
6. Volm M, Bak M, Efferth T, Lathan B, Mattern J. Immunocytochemical detection of a resistance-associated glycoprotein in tissue culture cells, ascites tumors and human tumor xenografts by Mab 265/F4. *Anticancer Res* 1988, **8**, 531–536.
7. Volm M, Mattern J, Samsel B. Relationship of inherent resistance to doxorubicin, proliferative activity and expression of P-glycoprotein, and glutathione S-transferase-π in human lung tumors. *Cancer* 1993, **71**, 3181–3187.
8. Volm M, Mattern J, Stammler G, *et al.* Expression of resistance-related proteins in nephroblastoma after chemotherapy. *Int J Cancer* 1995, **63**, 193–197.
9. Moscatelly D, Joseph-Silverstin J, Manejias R, Ritkin DB. Mr 25.000 heparin-binding protein from guinea pig brain is a high molecular weight form of basic fibroblast growth factor. *Proc Natl Acad Sci* 1987, **84**, 5778–5782.
10. Mohammadi M, Honegger AM, Rotin D, *et al.* A tyrosine-phosphorylated carboxy-terminal peptide of the fibroblast growth factor receptor (Flg) is a binding site for the SH2 domain of phospholipase C-γ1. *Mol Cell Biol* 1991, **11**, 5068–5078.
11. Byar DP. Analysis of survial data: Cox and Weibull models with covariates. In Mike V, Stanley KE, eds. *Statistics in Medical Research. Methods and Issues with Application in Cancer Research.* John Wiley, New York, 1982, 365–401.

Acknowledgements—We would like to thank J. Boldrin and A. Wittmann for their excellent technical assistance.