Expression and Prognostic Significance of Kit, Protein Kinase B, and Mitogen-activated Protein Kinase in Patients with Small Cell Lung Cancer

Fiona H. Blackhall, Melania Pintilie, Michael Michael, Natasha Leighl, Ronald Feld, Ming-Sound Tsao, and Frances A. Shepherd

Departments of Medical Oncology [F. H. B., N. L., R. F., F. A. S.], Biostatistics [M. P.], and Pathology [M-S. T.], University Health Network-Princess Margaret Hospital and Department of Laboratory Medicine and Pathobiology [M-S. T.], University of Toronto, Toronto, Ontario, MSG 2M5 Canada, and Division of Hematology and Medical Oncology, Peter MacCallum Cancer Institute, East Melbourne, Victoria, Australia [M. M.]

ABSTRACT

Purpose: The Kit receptor has been proposed as a key molecular target for the treatment of small cell lung cancer (SCLC). Protein kinase B (PKB/Akt) and mitogen-activated protein kinase (MAPK) are intracellular kinases that regulate cell survival and proliferation and may play a role in Kit signal transduction. This study was designed to examine the expression and importance of Kit, PKB/Akt, and MAPK relative to standard clinical prognostic factors in SCLC.

Experimental Design: Kit, PKB/Akt, and MAPK expression was assessed by immunohistochemistry in SCLC biopsies. Clinical data were collected on tumor stage, weight loss, hematology, biochemistry, response to treatment, and survival. Univariate and multivariate analyses were performed to evaluate prognostic significance.

Results: Biopsies from 42 patients were evaluable, and significant Kit expression (>35% cells) was detected in 51% of the tumors, phosphorylated PKB/Akt was detected in 62% of the tumors, and phosphorylated MAPK was detected in 48% of the tumors. Neither Kit nor PKB/Akt expression predicted for survival. Only increased expression of cytoplasmic MAPK was prognostic for survival (median, 1 year for negative staining versus 1.8 years for positive staining; P = 0.0054).

Conclusions: Kit, PKB/Akt, and MAPK are expressed in a high percentage of SCLCs, and our data suggest that MAPK is an independent positive predictive factor in this malignancy.

INTRODUCTION

Recent decades have witnessed progress in our understanding of the molecular biology of SCLC. There is almost universal loss of the tumor suppressors p53 and retinoblastoma protein and frequent amplification or up-regulation of oncogenes such as myc and bcl-2. Autocrine loops for growth have also been identified that include those mediated by gastrin-releasing peptide, IGF-I and -II, and platelet-derived growth factor. There is also recent evidence that the proliferation and survival of SCLC cell lines are dependent on a growth-stimulatory loop activated by SCF and its cognate tyrosine kinase signaling receptor, Kit.

The Kit transmembrane tyrosine kinase receptor is encoded by the c-kit proto-oncogene and is structurally similar to the platelet-derived growth factor and colony-stimulating factor 1 receptors. Binding of its ligand, SCF, induces receptor dimerization and autophosphorylation, which in turn activates multiple signal transduction components including PI3K, PKB/ Akt, Src family members, the Janus-activated kinase/signal transducers and activators of transcription pathway, and the Ras-Raf-MAPK cascade. Activation of Kit tyrosine kinase by somatic mutation has been documented in mastocytosis, seminoma, acute myelogenous leukemia, and at least 90% of gastrointestinal stromal tumors, and activation of aberrantly expressed wild-type Kit has been demonstrated in several malignancies including SCLC.

Coexpression of Kit and SCF has been demonstrated in 70% of SCLC cell lines and tumor specimens. Furthermore, increased proliferation and migration of SCLC cells in response to SCF have been demonstrated in vitro and in vivo. SCLC cell growth is suppressed when Kit is inhibited by antsense. Imatinib (STI571; Gleevec) is a p.o. bioavailable inhibitor of Bcr-Abl kinase activity that has demonstrated activity in chronic myeloid leukemia and gastrointestinal stromal tumors, and activation of aberrantly expressed wild-type Kit has been demonstrated in several malignancies including SCLC.

The principal signal transduction pathways activated by SCF/Kit are not well defined for SCLC. Experimentally, Kit

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2 To whom requests for reprints should be addressed, at FRGCP, Princess Margaret Hospital, Suite 5-104, 610 University Avenue, Toronto, Ontario, MSG 2M5 Canada. Phone: (416) 946-4522; Fax: (416) 946-6546; E-mail: frances.shepherd@uhn.on.ca.

3 The abbreviations used are: SCLC, small cell lung cancer; PKB, protein kinase B; MAPK, mitogen-activated protein kinase; SCF, stem cell factor; PI3K, phosphatidylinositol 3’-kinase; ECOG, Eastern Cooperative Oncology Group; p-, phosphorylated; IHC, immunohistochemistry; IGF, insulin-like growth factor.
activation induces phosphorylation of a variety of substrates including the intracellular kinases PKB/Akt and MAPK (18–22). These kinases promote cell survival by preventing apoptosis and increasing proliferation, respectively (23), and in vitro, PKB/Akt inhibition is synergistic with Kit inhibition in suppressing SCLC growth (20). This study was undertaken to determine the prevalence of these kinases in SCLC and to evaluate their prognostic significance relevant to standard clinical parameters (24–26).

**PATIENTS AND METHODS**

**Patients.** Patients with SCLC were identified retrospectively from the database of The University Health Network (Toronto, Ontario, Canada). Those with adequate histological material (obtained in the majority of cases by mediastinoscopy) and complete clinical data were eligible for inclusion. The study protocol was approved by the institutional ethics review board. Baseline data obtained from patient charts included ECOG performance status, history of weight loss, tumor stage, sites of metastases, baseline hemoglobin, WBC and platelet counts, serum sodium, albumin, alkaline phosphatase, and lactate dehydrogenase. Treatment, clinical response, and survival time were also recorded. Survival was calculated from the date of diagnosis until the date of death or last follow-up.

**IHC.** Paraffin-embedded tissue specimens were retrieved from the Department of Pathology at The University Health Network. Five-μm-thick tissue sections were stained with a polyclonal antibody to the intracellular domain of Kit (CD117; 1:200 dilution; Dako Laboratories), a monoclonal antibody to p-MAPK (1:100 dilution; New England Biolabs, Pickering, Ontario, Canada), and a polyclonal antibody specific for p-PKB/Akt at serine 473 (1:50 dilution; New England Biolabs). Tissue sections were incubated with primary antibodies overnight and visualized using the routine streptavidin-biotin-peroxidase method. The final dilution of each antibody was determined after preliminary serial dilution studies. These were chosen to yield an intermediate level of positive staining in control tissues. Slides were analyzed by two independent observers who had no prior knowledge of clinical and survival data. The sections were scanned at low magnification, and the percentage of positively stained tumor cells was estimated from 0–100% of the total tumor cells. The distribution of staining, either membranous, cytoplasmic, or nuclear, was also recorded and assessed at high magnification. For p-MAPK and p-PKB/Akt, the percentage of cells with nuclear staining was recorded separately from the percentage of cells with cytoplasmic staining. Positive expression of p-MAPK in stromal fibroblasts and endothelial cells of tumor sections was used as an internal standard of tissue quality and antigen preservation.

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### Table 1 Patient characteristics at diagnosis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cohort with clinical data [N = 57 (%)]</th>
<th>Subset with molecular data [N = 42 (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median age (range)</td>
<td>63.3 (35–79)</td>
<td>63.1 (35–79)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>36 (63)</td>
<td>26 (62)</td>
</tr>
<tr>
<td>Female</td>
<td>21 (37)</td>
<td>16 (38)</td>
</tr>
<tr>
<td>Clinical stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limited</td>
<td>39 (68)</td>
<td>29 (69)</td>
</tr>
<tr>
<td>Extensive</td>
<td>18 (32)</td>
<td>13 (31)</td>
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<tr>
<td>ECOG performance status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0, 1</td>
<td>46 (81)</td>
<td>33 (79)</td>
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<tr>
<td>2, 3</td>
<td>11 (19)</td>
<td>9 (21)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>21 (37)</td>
<td>15 (36)</td>
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<tr>
<td><strong>Laboratory values</strong></td>
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<td></td>
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<tr>
<td>Hemoglobin level &lt; 120 g/liter</td>
<td>12 (21)</td>
<td>10 (24)</td>
</tr>
<tr>
<td>Leukocyte count</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;4 × 10⁹/liter</td>
<td>4 (7)</td>
<td>5 (12)</td>
</tr>
<tr>
<td>&gt;11 × 10⁹/liter</td>
<td>3 (5)</td>
<td>3 (7)</td>
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<tr>
<td>Platelet count</td>
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<tr>
<td>&gt;400 × 10⁹/liter</td>
<td>13 (23)</td>
<td>10 (24)</td>
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<tr>
<td>&lt;150 × 10⁹/liter</td>
<td>0 (0)</td>
<td>0 (0)</td>
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<tr>
<td>Serum sodium &lt; 135 mmol/liter</td>
<td>13 (25)</td>
<td>8 (22)</td>
</tr>
<tr>
<td>No. of patients</td>
<td>51</td>
<td>37</td>
</tr>
<tr>
<td>Serum albumin &lt; 38 g/liter</td>
<td>4 (11)</td>
<td>2 (7)</td>
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<tr>
<td>No. of patients</td>
<td>37</td>
<td>30</td>
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<td>Serum LDH &lt; 190 IU/liter</td>
<td>19 (61)</td>
<td>17 (65)</td>
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<td>No. of patients</td>
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<td>26</td>
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<tr>
<td>Serum ALP &gt; 110 IU/liter</td>
<td>5 (10)</td>
<td>3 (8)</td>
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<tr>
<td>No. of patients</td>
<td>50</td>
<td>37</td>
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</table>

* N = 57 (cohort with clinical data) or 42 (subset with molecular data) unless specified.

### Table 2 Treatment and response of patients with SCLC

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cohort with clinical data [N = 57 (%)]</th>
<th>Subset with molecular data [N = 42 (%)]</th>
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</thead>
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<tr>
<td><strong>Systemic chemotherapy</strong></td>
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<tr>
<td>EP</td>
<td>14 (25)</td>
<td>12 (29)</td>
</tr>
<tr>
<td>CAV</td>
<td>6 (11)</td>
<td>6 (14)</td>
</tr>
<tr>
<td>EP and CAV</td>
<td>33 (58)</td>
<td>20 (48)</td>
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<tr>
<td>Other</td>
<td>4 (7)</td>
<td>4 (10)</td>
</tr>
<tr>
<td><strong>Response to therapy</strong></td>
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<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>27 (47)</td>
<td>21 (50)</td>
</tr>
<tr>
<td>Partial response</td>
<td>17 (30)</td>
<td>11 (26)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>5 (9)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>8 (14)</td>
<td>6 (14)</td>
</tr>
</tbody>
</table>

* E, etoposide; P, cisplatin; C, cyclophosphamide; A, doxorubicin; V, vincristine.

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**Fig. 1** Overall survival curve of patients with SCLC.
Statistical Analysis. Two independent observers scored the percentage of cells stained for each variable. The agreement between the observers was analyzed by calculating the Spearman correlation coefficient and $\kappa$ statistics. To calculate $\kappa$ statistics, the parameters were dichotomized by using the median of the variable obtained by averaging the scores of the two observers for each parameter as a cutoff. Thus, Kit expression $\geq 35\%$ was established as positive, and any expression of p-MAPK and p-PKB/Akt was considered positive. Total p-MAPK and p-PKB/Akt were defined as positive if either the cytoplasm or the nucleus was positive.

The associations between the IHC parameters and between IHC parameters and clinical factors were investigated using scatter plots, correlation coefficients, and $\chi^2$ tests. The end point for the outcome analysis was survival defined as the time between diagnosis and death or last follow-up. All parameters were tested in univariate analysis using the log-rank test when dichotomous and the Cox proportional hazards model when continuous. The IHC parameters were tested when continuous...
(data not shown) and when dichotomized at the median. The results were similar. Survival at 2 years and the median survival were estimated using the Kaplan-Meier method.

Using the whole cohort of 57 patients, a clinical model was developed with a stepwise selection technique. The clinical parameters considered were age, gender, stage, weight loss, hemoglobin, platelet count, and leukocyte count. The IHC parameters were then tested when adjusting for the significant clinical factors (stage and weight loss). The parameters Kit, cytoplasmic and nuclear p-MAPK, and cytoplasmic and nuclear p-PKB/Akt were tested as continuous and categorical (dichotomized) variables.

**RESULTS**

Clinical and laboratory data were obtained for 57 patients who were treated at The University Health Network from March 1982 to October 2001 and who had histological biopsies for diagnosis. (Table 1). Biopsy material was retrieved for 48 of 57 patients, and the quality of tissue (based on stromal and endothelial p-MAPK expression; Fig. 2) was adequate for further molecular testing in 42 of 48 patients. The baseline pretreatment characteristics of the 42 patients in the subset with molecular data are also shown in Table 1. The majority of patients (69%) had limited-stage disease, and 79% had an ECOG performance status of 0–1. The clinical and laboratory parameters did not differ significantly for the two groups (Table 1). The treatment regimens, response rates, and survival for both groups were similar (Table 2; Fig. 1). In the study cohort with IHC, the overall response rate was 76%, with complete and partial response rates of 50% and 26%, respectively. Their median survival was 1.2 years, and the 2-year survival rate was 12% (Fig. 1).

**Distribution of Kit, p-MAPK, and p-PKB/Akt by IHC.**

Typical IHC patterns obtained for Kit, p-MAPK, and p-PKB/Akt are shown in Fig. 2. The distribution of Kit was cytoplasmic and membranous, with no evident nuclear staining. Phosphorylated (i.e., activated) MAPK and PKB/Akt were detected in both the nucleus and the cytoplasm of the tumor cells. The scores from the two independent observers were in agreement with Spearman correlation coefficients of 0.9–0.97 and k statistics of 0.8–1.0 for all but nuclear p-MAPK staining (r = 0.7; k = 0.6). Kit, p-MAPK, and p-PKB/Akt expression are summarized in Fig. 3. One or more of the kinases was expressed in 81% of cases, with all three present in only 17% of the cases. Kit was detected in 51% of cases, p-MAPK was detected in 48% of cases, and p-PKB/Akt was detected in 62% of cases. There were no strong associations between expression of the kinases, although a weak association between expression of Kit and p-PKB/Akt was detected (r = 0.3). Tumor expression of p-PKB/Akt was significantly associated with limited clinical stage (38% for extensive stage and 72% for limited stage; χ² test, P = 0.04). When nuclear p-PKB/Akt expression and cytoplasmic p-PKB/Akt expression were considered separately, only cytoplasmic p-PKB/Akt staining remained significant (χ² test, P = 0.01).

**Prognostic Factor Analysis.** The significant clinical factors that adversely affected survival were extensive stage (P = 0.0018) and pretreatment weight loss (P = 0.0078; Table 3). Neither Kit nor p-PKB/Akt expression provided prognostic information, nor did we detect any significance when combinations of two or more variables were examined. Positive tumoral expression of p-MAPK (nuclear or cytoplasmic) was significant on univariate analysis (P = 0.018) but not on multivariate analysis when adjusted for the clinically significant parameters of stage and weight loss (P = 0.36). However, p-MAPK expression in the cytoplasm of the cancer cells was associated with better survival in both univariate analysis (P = 0.0054) and multivariate analysis (P = 0.05; Table 4). The median survival for patients negative for cytoplasmic p-MAPK was only 1 year compared with 1.8 years for positive expression (Fig. 4). With respect to response to treatment, none of the IHC variables studied provided predictive information.

**DISCUSSION**

Molecular targeted therapies, either alone or as adjuncts to standard chemotherapy, are under evaluation for many tumors (27–29). The Kit receptor is an attractive target due to the recent availability of selective, p.o. active inhibitors (7). PKB/Akt and MAPK are also the focus of novel drug development strategies (30, 31). However, data to support these kinases as valid targets in SCLC in vivo are lacking. This study was performed to determine the prevalence of Kit, p-MAPK, and p-PKB/Akt in clinical samples and to determine their significance compared with standard prognostic factors (24–26).

Although Kit is absent or expressed at very low levels in normal lung (32, 33), it is detected in 50–80% of SCLC cell lines and nude mouse xenografts (8, 9, 32–34). We identified significant Kit expression (indicated by ≥35% positive cancer cells) in 51% of tumors in this series, p-PKB/Akt expression in 62% of tumors, and p-MAPK expression in 48% of tumors (Fig. 3). These results are consistent with other small surveys of Kit expression in human primary SCLC tumors (9, 32, 34–37). We did not detect any prognostic significance of Kit for

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Univariate</th>
<th>Adjusted</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kit (n = 41)</td>
<td>0.89</td>
<td>0.84</td>
<td>1.1 (0.5–2.3)</td>
</tr>
<tr>
<td>Nuclear p-MAPK</td>
<td>0.11</td>
<td>0.6</td>
<td>1.3 (0.5–2.9)</td>
</tr>
<tr>
<td>Cytoplasmic p-MAPK</td>
<td>0.0054*</td>
<td>0.05</td>
<td>2.8 (1–8)</td>
</tr>
<tr>
<td>Nuclear p-PKB/Akt</td>
<td>0.51</td>
<td>0.82</td>
<td>1.1 (0.5–2.3)</td>
</tr>
<tr>
<td>Cytoplasmic p-PKB/Akt</td>
<td>0.77</td>
<td>0.76</td>
<td>0.9 (0.5–2.8)</td>
</tr>
<tr>
<td>No expression</td>
<td>0.15</td>
<td>0.63</td>
<td>1.3 (0.5–3.5)</td>
</tr>
</tbody>
</table>

* Forty-two patients, unless otherwise stated.

Significance of molecular variable after controlling for stage and weight loss. CI, confidence interval.

[Table 4 Results of univariate and multivariate analysis assessing the influence of clinical and molecular variables on survival]
survival or response to treatment when Kit was tested as a continuous variable, or when it was dichotomized at 35% or 15%. In another series of 104 patients, Kit (defined as $\geq 15\%$ cells stained) was detected in 37% of cases and correlated with poorer survival in patients with extensive stage disease (38). A study of 30 patients has also been reported in which Kit (defined as $\geq 50\%$ cells stained) was detected in 53% of patients and correlated with a nonsignificant trend toward poorer outcome in univariate analysis (35). It is noteworthy that our series had more patients with limited-stage disease (69%), whereas that of Micke et al. (38) had only 30% patients with limited-stage disease. Nevertheless, our univariate analysis showed that the known adverse prognostic factors of extensive stage and weight loss were significant, thus confirming that our cohort is representative of SCLC in general. Interestingly, increased cytoplasmic p-PKB/Akt expression was significantly associated with limited-stage disease in our series. This, together with the data of Micke et al. (38), raises the possibility of stage-specific heterogeneity of PKB expression and Kit function.

We also evaluated the expression of p-MAPK and p-PKB/Akt to determine their association with Kit expression. We detected significant expression of activated MAPK and PKB/Akt in 48% and 62% of tumors, respectively, demonstrating for the first time that these signal transducers are active in SCLC in general. Interestingly, increased cytoplasmic p-PKB/Akt expression was significantly associated with limited-stage disease in our series. This, together with the data of Micke et al. (38), raises the possibility of stage-specific heterogeneity of PKB expression and Kit function.

We identified an association between increased p-MAPK expression and better survival (Table 4; Fig. 4). This is counterintuitive, given that MAPK is a downstream component of the ras-raf pathway that is frequently activated in cancer cells and associated with increased cellular proliferation (31). MAPK signaling has not been studied extensively in SCLC, but there is evidence that Kit receptor autophosphorylation activates the MAPK pathway via a mechanism involving association with a Src family kinase, Lck (18, 19). However, in the absence of functional retinoblastoma protein (an almost universal molecular change in SCLC; Ref. 1), MAPK pathway activation is not essential for SCF/Kit-mediated growth (18). This may explain the lack of correlation between MAPK and Kit in the present study.

MAPK is activated in the cytoplasm and then translocated to the nucleus, where it induces gene expression and promotes cell cycle entry (41, 42). The factors governing nuclear translocation of p-MAPK are not well understood and have not been investigated in SCLC, but requirements for intact ras function (43) and neosynthesis of nuclear anchoring proteins (44) have been reported for other cell lines. Notably, in senescent fibroblasts that are irreversibly growth arrested, cytoplasmic activation of MAPK is not impaired, but the nuclear translocation of p-MAPK is inhibited (41). Therefore, although our observation is based on a small number of samples, SCLC cells with enhanced cytoplasmic p-MAPK expression may have altered kinetics of nuclear p-MAPK translocation, leading to a slower rate of cellular proliferation. Interestingly, among the few published studies specific to SCLC, MAPK activation by both Raf-1 and notch signaling has been shown in vitro to be associated with cell cycle arrest and suppression of growth (45–47). Therefore, p-MAPK may have a unique biological role in SCLC that warrants further investigation.

We did not detect any predictive value of Kit, p-PKB/Akt, or p-MAPK for response to chemotherapy. However, recent in vitro data implicate the PI3K-PKB/Akt pathway in chemoresistance (21, 48). The PI3K-PKB/Akt antagonist LY294002 inhibits SCLC cell growth and enhances sensitivity to etoposide in vitro (21), whereas imatinib, a Kit tyrosine kinase antagonist, does not enhance the

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Fig. 4 Overall survival curve of patients with SCLC expressing cytoplasmic p-MAPK (n = 11) relative to nonexpression (n = 31).
cytotoxicity of either carboplatin or etoposide (20). Therefore, PKB/Akt inhibition may be a promising adjunct to standard chemotherapy, and our data suggest that at least 50% of patients with SCLC would be eligible for trials addressing this hypothesis. This strategy is reinforced by expression of p-PKB/Akt in the absence of Kit and preclinical data that PKB/Akt is activated by a number of receptors in SCLC (3, 20, 39, 40). Also, imatinib-induced blockade of Kit signal transduction does not prevent PKB/Akt phosphorylation by IGF-I or stromal cell-derived factor 1α (21, 39). Although we did not detect a correlation between expression of PKB/Akt and clinical outcome, signal transduction is a dynamic process that may not be reflected in the “snapshot” of expression provided by an immunohistochemical study. The kinetics of PKB/Akt phosphorylation vary depending on the upstream activator (21); therefore, the timing and duration of activation may be a more important determinant of SCLC biology.

Although the expression and prognostic significance of a molecular marker are frequently used as evidence for a novel therapeutic target, it is not clear to what extent expression predicts for response. As a paradigm, the epidermal growth factor receptor is expressed in at least 80% of non-SCLC (49), yet it does not appear that expression can reliably predict for response to epidermal growth factor receptor inhibitors in the clinical trials reported to date (50). Nevertheless, clinical correlative studies are vital to ensure that trial protocols for novel targeted therapies are directed toward those most likely to benefit from treatment. As a case in point, a Phase II trial of imatinib in SCLC was recently reported in which there were no responses (51). However, retrospective immunohistochemical analysis of the tumors revealed that there was no expression of Kit in the majority (11 of 14) of patients. These results suggest that future trials of imatinib should be directed to patients with Kit-positive tumors.

In summary, we have demonstrated that Kit and p-PKB/Akt are expressed in approximately 50% of SCLC but do not predict for either response or survival in this series. These data do not preclude a therapeutic role for Kit and/or PKB/Akt inhibition in SCLC. However, our finding that increased expression of cytoplasmic p-MAPK is prognostic for a better outcome emphasizes that detailed in vitro and clinical studies are still required to unravel the molecular mechanisms driving SCLC cell growth and to identify the key signal transduction pathways for therapeutic intervention.

ACKNOWLEDGMENTS

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REFERENCES


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