Expression of Epidermal Growth Factor Receptor Correlates with Disease Relapse and Progression to Androgen-independence in Human Prostate Cancer

Giuseppe Di Lorenzo, Giampaolo Tortora, Francesco P. D’Armiento, Gaetano De Rosa, Stefania Staibano, Riccardo Autorino, Massimo D’Armiento, Michele De Laurentiis, Sabino De Placido, Giuseppe Catalanò, A. Raffaele Bianco, and Fortunato Ciardiello


ABSTRACT

Purpose: The transforming growth factor α-epidermal growth factor receptor (EGFR) autocrine pathway has been implicated in prostate cancer cell growth. Amplification and/or overexpression of c-erbB-2, a receptor closely related to the EGFR, has been recently involved in prostate cancer progression. We investigated EGFR and c-erbB-2 expression in primary androgen-dependent and in advanced androgen-independent prostate cancer and their potential role as markers of disease progression.

Experimental Design: EGFR and c-erbB-2 expression were evaluated by immunohistochemistry in a consecutive series of 74 prostate cancer patients with the following characteristics: 29 patients (group 1) treated with radical prostatectomy; 29 patients (group 2) treated with luteinizing hormone-releasing hormone analogues and antiandrogen therapy followed by radical prostatectomy; and 16 patients with hormone-refractory metastatic disease. In all patients we evaluated: association between EGFR and/or c-erbB-2 expression and clinicopathological parameters; and disease-free survival according to EGFR and c-erbB-2 expression in univariate analysis (Kaplan-Meier product-limit method) and in multivariate analysis (Cox proportional hazards regression model).

Results: EGFR expression was found in 12 of 29 (41.4%) group 1 patients, in 22 of 29 (75.9%) group 2 patients (P < 0.0005), and in 16 of 16 (100%) metastatic patients (P < 0.005), whereas c-erbB-2 expression was found in 11 of 29 (37.9%) group 1, in 10 of 29 (34.5%) group 2 patients, and in 9 of 16 (56.3%) metastatic patients. A significant association was found between EGFR expression and a high Gleason score (P < 0.01) and between EGFR expression and higher serum prostate-specific antigen values (P < 0.02) in all groups of patients. Among the 58 patients treated with radical prostatectomy, 23 of 34 EGFR-positive patients (67.6%) relapsed, whereas only 2 of 24 EGFR-negative patients (8.3%) relapsed (P < 0.00004). c-erbB-2 expression did not significantly correlate with disease relapse (P = 0.07). In a Cox multivariate analysis, the only parameter with an independent prognostic effect on disease-free survival was EGFR expression (relative hazard, 11.23; P = 0.0014).

Conclusions: EGFR expression increases during the natural history of prostate cancer. Correlation with disease progression and hormone-refractory disease suggests that EGFR-targeted drugs could be of therapeutic relevance in prostate cancer.

INTRODUCTION

Complete surgical resection or radiotherapy is the only potentially curative treatment for patients with localized prostate cancer. Pathologic staging of prostate cancer, including evaluation of histological grade according to the Gleason score, represents the most accurate evaluation currently available for clinical outcome in patients that have undergone radical treatment. Approximately 25% of patients with early stage disease will relapse within 5 years (1). The majority of patients with relapsed or with metastatic prostate cancer are initially responsive to hormonal manipulation. In this respect, treatment with luteinizing hormone-releasing hormone analogues, with or without the combined treatment with antiandrogens, determines objective responses in most of these patients with a time to progression of ~18 months (1). Once a patient has failed first-line hormonal therapy, therapeutic options are limited and survival is in the order of 6–12 months for patients with androgen-independent, hormone-refractory prostate cancer (2). Although preliminary results on the activity of novel chemotherapy regimens are encouraging (3), Phase III clinical trials are needed to demonstrate if chemotherapy can improve patient survival.

The development of prostate cancer and the progression from normal prostate epithelium to androgen-dependent cancer and, eventually, to hormone-refractory prostate cancer is a multistep process involving several changes in the function of...
different growth regulatory signals. The understanding of the molecular mechanisms involved in prostate cancer development and progression could allow the design of novel therapeutic agents that are aimed to selectively target specific genes and gene products. The molecular mechanisms responsible for the development of androgen independence are not yet clear. However, experimental evidence has been provided on the role of peptide growth factors and their specific cell membrane receptors in such process (4–6). More specifically, growth factors of the EGF3 family, such as EGF, amphiregulin, and TGF-α could contribute through autocrine and paracrine mechanisms to prostate cancer cell growth and proliferation (7–10). TGF-α binds to a specific cell membrane receptor, the EGFR, with subsequent activation of the EGFR tyrosine kinase enzymatic activity that triggers the intracellular signaling pathway (11). The EGFR is part of a subfamily of four closely related receptors: EGFR (or ErbB-1); Her 2/neu (ErbB-2); Her 3 (ErbB-3); and Her 4 (ErbB-4; Ref. 11). The receptors exist as inactive monomers, which dimerize after ligand activation. This causes homodimerization and/or protein overexpression in prostate cancer have been reported. The difference in the results may be because of technical differences, including variability of tissue fixation protocols, different antibodies, lack of standardization of immunohistochemical assays, different scoring methodologies (14–22). Whereas, as opposed to breast cancer, c-erbB-2 gene is very rarely amplified in prostate cancer, three recent studies have shown experimental evidence of a significant increase in c-erbB-2 expression from hormone-independent to hormone-dependent disease (23–25).

To evaluate the role of EGFR and c-erbB-2 in prostate cancer progression, we studied by immunohistochemistry the expression of these growth factor receptors in primary and hormone-independent metastatic prostate cancer patients. The major aims of this study were: (a) to determine whether EGFR and c-erbB-2 proteins are expressed in human prostate cancer; (b) to assess whether EGFR and c-erbB-2 expression increases with cancer progression toward androgen independence; (c) to evaluate the association between patterns of EGFR and c-erbB-2 expression and standard clinicopathological parameters; and (d) to define the potential prognostic effect of EGFR and c-erbB-2 expression.

PATIENTS AND METHODS
Patients. A series of 74 consecutive prostate cancer patients that were referred to our university from 1996 to 2000 was studied. This cohort included 58 patients with localized disease and 16 patients with metastatic lesions and progressive, androgen-independent disease. The 58 patients with localized tumors were surgically treated with radical prostatectomy. Among these patients, 29 patients (group 1) received radical prostatectomy as initial treatment, whereas the other 29 patients (group 2) with clinically localized tumors received neoadjuvant androgen ablative therapy for 3 months based on the combination of a luteinizing hormone-releasing hormone agonist and an antiandrogen. The median follow-up for these 58 patients was 36 months. Table 1 summarizes the clinicopathological characteristics of the 74 patients. A cutoff value of 7 was used to distinguish between low and high Gleason score. For the 58 patients treated with radical prostatectomy, DFS was defined

Table 1  Clinicopathological characteristics of patients

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Hormone-refractory metastatic patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gleason score</td>
<td>29</td>
<td>29</td>
<td>16</td>
</tr>
<tr>
<td>&lt;7</td>
<td>14</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>≥7</td>
<td>15</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td>PSA values (ng/ml)</td>
<td>≤10</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>&gt;10</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>Tumor-Node-Metastasis</td>
<td>T2N0</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>T2/T3N+</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>M+</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

3 The abbreviations used are: EGF, epidermal growth factor; EGFR, EGF receptor; TGF-α, transforming growth factor α; PSA, prostate-specific antigen; DFS, disease-free survival; RH, relative hazard; CI, confidence interval; AR, androgen receptor.

Table 2  EGFR and HER/neu expression in prostate cancer patients

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Hormone-refractory metastatic patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>12/29 (41.4%)</td>
<td>22/29 (75.9%)</td>
<td>16/16 (100%)</td>
</tr>
<tr>
<td>Negative</td>
<td>17/29 (58.6%)</td>
<td>7/29 (24.1%)</td>
<td>0/16 (0%)</td>
</tr>
<tr>
<td>c-erbB-2</td>
<td>11/29 (37.9%)</td>
<td>10/29 (34.5%)</td>
<td>9/16 (56.3%)</td>
</tr>
<tr>
<td>Negative</td>
<td>18/29 (62.1%)</td>
<td>19/29 (65.5%)</td>
<td>7/16 (43.7%)</td>
</tr>
</tbody>
</table>
as the time from radical prostatectomy to the time of the first detectable serum PSA high value (>4 ng/ml). Three consecutive increases of PSA were required to confirm disease relapse, but the time to relapse was taken as the time of the first detectable PSA value increase, as reported previously (26).

**Immunohistochemistry and Evaluation of Immunoperoxidase Staining.** Formalin-fixed, paraffin-embedded tissue sections (5 μm) were deparaffinized in xylene and rehydrated in a graded series of ethanol. The slides were then treated for 30 min at 20°C with methanol containing 0.3% hydrogen peroxide to block any endogenous peroxidase activity. The Herceptest immunohistochemical kit (Dako, Milan, Italy) was used for the evaluation of c-erbB-2 expression according to the manufacturer’s procedures (27). Briefly, c-erbB-2 cell membrane-specific immunostaining was classified as undetectable or 0 to +3 categories. Score 0 was defined as undetectable staining or membrane staining in <10% of the tumor cells. Score +1 was defined as a weak membrane staining detected in >10% of the tumor cells. Score +2 was considered as a weak to moderate complete membrane staining observed in >10% of the tumor cells. Finally, score +3 was defined as a moderate to strong complete membrane staining observed in >10% of the tumor cells. c-erbB-2 expression was classified as negative (scores 0 and +1) or positive (scores +2 and +3), as recently reported by Osman et al. (23). For the evaluation of EGFR expression, an antihuman EGFR monoclonal antibody (clone H11; Dako) was used. EGFR cell membrane-specific immunoreactivity was scored by estimating the percentage of positive tumor cells as follows: score 0, no immunoreactive cell; score +1, positivity in <5% cancer cells; score +2, positivity in 5–50% cancer cells; and score +3, positivity in >50% of cancer cells. Specimens were considered positive for EGFR expression when the score was +2 or +3.

**Statistical Analysis.** The association between the different clinicopathological characteristics and the expression of EGFR and c-erbB-2 was studied by the use of contingency tables. Statistical significance was evaluated by the χ² test. Univariate analysis for the role of each prognostic variable on DFS was estimated according to the Kaplan-Meier product-limit method (28). The statistical significance of the differences in DFS distribution among prognostic groups was evaluated by the log-rank test (29). The Cox proportional hazards regression model (30) was used to determine among the different clinicopathological and biological characteristics, including T status, N status, Gleason score, EGFR, and c-erbB-2 expression, those parameters with an independent prognostic role. RHs with 95% CI were estimated. All Ps represent two-sided tests of statistical significance. Ps ≤0.05 were considered as statistically significant. All analyses were performed with the BMDP New System statistical package version 1.0 for Microsoft Windows (BMDP Statistical Software, Los Angeles, CA).

**RESULTS**

Table 1 summarizes the clinicopathological characteristics of all patients. As illustrated in Table 2, among the 29 patients that were treated with radical prostatectomy as first line therapy (group 1 patients), 12 cancers were positive for EGFR expression (41.4%). EGFR expression increased to 22 of 29 (75.9%) samples in group 2 patients (patients that received hormone therapy before radical prostatectomy). Finally, all cancers in the group of 16 metastatic and hormone-refractory prostate cancer patients were positive for EGFR expression. This difference was statistically significant among the three groups (P < 0.0005). In contrast, c-erbB-2 expression was not significantly different among the three groups of patients (Table 2). Fig. 1 illustrates the immunohistochemical patterns of EGFR and/or c-erbB-2 protein expression in representative tumors. We next evaluated whether any correlation could exist between EGFR and/or c-erbB-2 expression in cancer specimens and the clinicopathological characteristics of the 58 prostate cancer patients that were treated with radical prostatectomy (groups 1 and 2). As shown in Table 3, a significant association was observed between EGFR expression and higher Gleason scores (P < 0.01) and...
between EGFR expression and higher PSA plasma levels \((P < 0.02)\). In contrast, c-erbB-2 protein expression did not correlate with these parameters. Furthermore, we evaluated whether any correlation could exist between EGFR and c-erbB-2 coexpression in these two groups of patients. Both receptors were expressed in 13 of 58 (22.4%) prostate cancer patients. Coexpression of EGFR and c-erbB-2 was significantly correlated with a more advanced disease (Table 3). In fact, in \(T_2N_0\) cancers, only 6 of 42 (14.2%) cases were positive for both EGFR and c-erbB-2, whereas in \(T_3/T_4N^+\) cancers, 7 of 16 (43.8%) cases were positive for both EGFR and c-erbB-2 \((P < 0.01)\). Similarly, EGFR and c-erbB-2 coexpression significantly correlated with a higher Gleason score because only 3 of 28 (10.7%) double-positive tumors had a Gleason score <7, whereas 10 of 30 (33.3%) double-positive tumors had a Gleason score \(\geq 7\) \((P < 0.01)\). Table 4 illustrates the relationship between receptor expression and clinicopathological characteristics in metastatic, hormone-refractory prostate cancer patients. Coexpression of EGFR and c-erbB-2 was associated with higher Gleason scores \((P < 0.01)\) and high levels of serum PSA \((P < 0.01)\).

The prognostic impact of clinicopathological parameters and of EGFR and c-erbB-2 expression on DFS of group 1 and group 2 patients was evaluated at a univariate analysis. Twenty-five of 58 (43.1%) patients in these groups relapsed. As shown in Table 5 and in Fig. 2A, EGFR expression significantly correlated with disease relapse in these patients. In fact, among the 34 patients whose tumors were positive for EGFR expression,

### Table 3: Relationship between EGFR and c-erbB-2 expression and clinicopathological parameters in group 1 (radical prostatectomy) and group 2 (hormonal neoadjuvant therapy + radical prostatectomy) prostate cancer patients

<table>
<thead>
<tr>
<th>Tumor-Node-Metastasis</th>
<th>EGFR</th>
<th>c-erbB-2</th>
<th>EGFR</th>
<th>c-erbB-2</th>
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<tbody>
<tr>
<td>(T_2N_0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>(T_3/T_4N^+)</td>
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<tr>
<td>Gleason score (\leq 6)</td>
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<td>(\geq 7)</td>
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<tr>
<td>PSA values (ng/ml)</td>
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<td></td>
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<tr>
<td>(\leq 10)</td>
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<td>(&gt; 10)</td>
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### Table 4: Relationship between EGFR and c-erbB-2 expression and clinicopathological parameters in metastatic, hormone-refractory prostate cancer patients

<table>
<thead>
<tr>
<th>M+</th>
<th>EGFR</th>
<th>c-erbB-2</th>
<th>EGFR</th>
<th>c-erbB-2</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gleason score (\leq 6)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\geq 7)</td>
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<tr>
<td>PSA (ng/ml)</td>
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<tr>
<td>(\leq 10)</td>
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<tr>
<td>(&gt; 10)</td>
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### Table 5: Relationship between EGFR, c-erbB-2 expression, clinicopathological parameters and disease relapse in group 1 (radical prostatectomy) and group 2 (hormonal neoadjuvant therapy + radical prostatectomy) prostate cancer patients

Disease relapse was defined as described in “Materials and Methods.”

<table>
<thead>
<tr>
<th>Total relapsed patients</th>
<th>EGFR</th>
<th>c-erbB-2</th>
<th>EGFR</th>
<th>c-erbB-2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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23 had a disease recurrence (67.0%), whereas only 2 of 24 (8.3%) EGFR-negative prostate cancer patients relapsed \( (P \leq 0.00004) \). Although not statistically significant \( (P \leq 0.07) \), a trend to a higher risk of relapse among the c-erbB-2-positive patients was observed (Fig. 2B). When coexpression of EGFR and c-erbB-2 was analyzed (Fig. 2C), patients whose tumors were positive for both receptors had a high probability of disease recurrence \( (11 \text{ of } 13 \text{ patients}, 84.6\%) \), whereas patients with tumors negative for both EGFR and c-erbB-2 had significantly lower risk of relapse \( (1 \text{ of } 16 \text{, } 6.3\%; \ P < 0.0001) \). Finally, a multivariate analysis was performed to define the variables with independent prognostic value with respect to serum PSA increase and to disease relapse. EGFR expression was the only independent parameter that was significantly associated to disease relapse when compared with Gleason score to T and N status and to c-erbB-2 expression (Table 6). In fact, the RH of disease relapse in these patients with EGFR expression was 11.23 \( (95\% \text{ CI, } 2.54–49.56), \ (P = 0.0014) \).

**DISCUSSION**

Despite advances in the management of prostate cancer, the development of hormone-refractory disease is generally the clinical outcome of advanced prostate cancer. The mechanisms responsible for the development of androgen independence are not yet completely understood. However, in the past few years, several experimental studies have proposed that AR mutations, AR gene amplification, and alterations in growth factor-activated pathways can modulate AR signaling and, therefore, may play a key role in the progression to androgen-independent, hormone-refractory prostate cancer \( (7–10) \). The majority of androgen-independent prostate cancers expresses AR, suggesting that the AR signaling pathway is activated also in absence of androgen \( (31) \). In this respect, a functional cross-talk between growth factors and growth factor receptors of the EGFR family and AR-activated pathways has been shown in preclinical models \( (32–36) \). Prostate cancer cells express the EGFR \textit{in vitro} and \textit{in vivo}, and TGF-\( \alpha \) is a potent mitogen for prostate cancer cell growth \( (37) \). Craft et al. \( (38) \) have shown that androgen-independent sublines of LAPC-4 prostate cancer cells express high levels of c-erbB-2 and that overexpression of c-erbB-2 in parental LAPC-4 cells causes androgen-independent tumor growth. Furthermore, c-erbB-2 activates the AR pathway in the absence of ligand and synergizes with low levels of androgen to increase AR signaling in this prostate cancer cell model \( (38) \).

In this study, we have evaluated by immunohistochemistry the expression of both EGFR and c-erbB-2 in three different groups of prostate cancer patients that are representative of different clinical stages of prostate cancer. Moreover, EGFR and c-erbB-2 were evaluated as potential prognostic indicators of disease progression. A significant increase in EGFR expression was observed from patients treated with radical surgery alone and not yet exposed to hormonotherapy \( (41.4\%) \), patients that received hormonotherapy as primary therapy before radical prostatectomy \( (75.9\%) \), and finally patients with metastatic and hormone-refractory disease \( (100\%) \). These results are in agreement with a report of Scher et al. \( (10) \) that shows a homogeneous-staining pattern for EGFR in 17 of 19 androgen-independent refractory metastatic prostate cancer specimens. A similar increase in EGFR expression has been demonstrated in a smaller series of prostate cancer patients: untreated, hormone-naïve \( (15\% \text{ positive}) \); and hormone-responsive \( (35\% \text{ positive}) \) and hormone-refractory \( (48\% \text{ positive}; \text{ Ref. 39}) \). No significant difference in c-erbB-2

<table>
<thead>
<tr>
<th>Variable</th>
<th>RH (95% CI)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>11.23 (2.54–49.56)</td>
<td>0.0014</td>
</tr>
<tr>
<td>c-erbB-2</td>
<td>1.98 (0.82–4.76)</td>
<td>0.13</td>
</tr>
<tr>
<td>Gleason score</td>
<td>0.92 (0.68–1.25)</td>
<td>0.6</td>
</tr>
<tr>
<td>T</td>
<td>1.14 (0.41–3.21)</td>
<td>0.8</td>
</tr>
<tr>
<td>N</td>
<td>1.22 (0.31–4.78)</td>
<td>0.78</td>
</tr>
</tbody>
</table>

Table 6: Multivariate analysis of DFS in group 1 (radical prostatectomy) and group 2 (hormonal neoadjuvant therapy + radical prostatectomy) prostate cancer patients.

Fig. 2 Kaplan-Meier DFS estimates of group 1 (radical prostatectomy) and group 2 (hormonal neoadjuvant therapy + radical prostatectomy) prostate cancer patients in relationship to EGFR expression (A), c-erbB-2 expression (B), and EGFR and c-erbB-2 coexpression (C). The \( P \)s for each estimate were as follows: \( A, \ P < 0.00004; \ B, \ P = 0.07; \ C, \ P < 0.0001 \). \( P \)s \leq 0.05 were considered as statistically significant.
expression was found in our series of prostate cancer patients. In this respect, three recent studies (23–25) have reported an increase in c-erbB-2 expression in prostate cancer progression defined in three groups of patients with similar clinicopathological characteristics to those described in this study. However, although not statistically significant (P = 0.07), a trend to a higher risk of relapse among the c-erbB-2-positive samples was observed in our series of prostate cancer patients. We have also found a significant association between EGFR expression and clinicopathological characteristics of advanced disease as high Gleason scores and higher serum PSA values in all groups of patients. Furthermore, EGFR expression was significantly associated with disease progression. In fact, among the 58 patients treated with radical prostatectomy, 23 of 34 EGFR-positive patients (67.6%) relapsed in comparison to only 2 of 24 EGFR-negative patients (8.3%). Furthermore, the evaluation of both EGFR and c-erbB-2 expression has a relevant prognostic impact. In fact, only 1 of 16 (6.3%) patients whose tumors were negative for both EGFR and c-erbB-2 had a disease relapse, whereas 11 of 13 (84.6%) patients with EGFR and c-erbB-2-positive tumors relapsed. Finally, when tumor stage, Gleason score, EGFR, and c-erbB-2 expression were evaluated as potential indicators of disease relapse in a Cox multivariate analysis, the only parameter with an independent prognostic effect on DFS was EGFR expression.

Collectively, these results strongly support a role for EGFR expression in the development of prostate cancer and, more specifically, in the progression to an androgen-independent, hormone-refractory clinical behavior. An important issue that needs additional investigation is whether EGFR and/or c-erbB-2 protein overexpression is accompanied by the activation of growth factor receptor-induced intracellular downstream signaling. In this respect, it will be interesting to evaluate the activation of the mitogen-activated protein kinase and phosphatidylinositol 3'-kinase-AKT pathways.

Because anti-EGFR selective agents are in advanced clinical development in different human epithelial cancers (40, 41), measurement of EGFR expression in prostate cancer could allow to identify subsets of patients with early stage disease at high risk of relapse after radical prostatectomy that could potentially benefit of adjuvant treatment with EGFR-targeted drugs in combination with hormonotherapy. Furthermore, anti-EGFR agents could be used in combination with hormonotherapy in an attempt to prevent the development of androgen-independent, hormone-refractory disease. In this respect, experimental evidence has been recently provided that inhibition of EGFR activation by ZD1839, a small molecule tyrosine kinase inhibitor, has a potent antiproliferative effect in human MCF-7 breast cancer cells that become estrogen independent and hormone refractory after chronic exposure to the pure antiestrogen ICI 182,780 (Faslodex; Ref. 42). Similarly, Sirotak et al. (43) have recently reported that ZD1839 treatment inhibits the in vivo growth of EGFR overexpressing, androgen-independent, human prostate cancer xenografts. Finally, prostate cancer patients whose tumors coexpress both the EGFR and c-erbB-2 could potentially benefit of a combined treatment with anti-EGFR and anti-c-erbB-2 agents. In this respect, preclinical studies have shown a supra-additive or synergistic antitumor activity of such combinations in human breast cancer cell lines (44–46).

ACKNOWLEDGMENTS

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EGFR and c-erbB-2 Expression in Prostate Cancer


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