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Prognostic factors versus predictive factors: Examples from a clinical trial of erlotinib[☆]

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ABSTRACT

It would be helpful to have factors that could identify patients who will, or will not, benefit from treatment with specific therapies. Ideally, these should be molecular-based factors. When results with molecular-based factors are disappointing, physicians often use clinical characteristics to make treatment decisions. Several characteristics have been suggested to predict sensitivity to epidermal growth factor receptor inhibitors in patients with non-small lung cancer, including gender, histology, smoking history. This report demonstrates that gender and histology are actually prognostic, rather than predictive factors. Before biomarkers or clinical characteristics are included in guidelines for selecting patients for specific treatments, it is imperative that the prognostic effects of these factors are distinguished from their ability to predict a differential clinical benefit from the specific treatment.

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1. Introduction

Targeted therapies provide opportunities for identifying subsets of patients who will derive the most benefit, providing that the target can accurately be measured in patients and that the patient's tumor depends on activity of the target for its growth and survival. Recently, several agents that inhibit the epidermal growth factor receptor (EGFR) or the EGF pathway have been evaluated in clinical trials. Unfortunately, efforts to develop and validate the clinical utility of companion, tumor-based assays that measure abnormalities in the EGF pathway (e.g., protein overexpression by immunohistochemistry, gene copy number by in situ fluorescence hybridization, gene mutation by sequencing) have been

disappointing. None of the currently available assays accurately identifies patients who will definitely not benefit from EGFR inhibitors, and none accurately identifies patients who will definitely benefit from these treatments. Therefore, patients and their physicians are turning to clinical characteristics to make treatment decisions.

It has been observed that women with non-small cell lung cancer (NSCLC), patients with adenocarcinoma, and never smokers are more likely to have major objective responses when treated with EGFR inhibitors than other patients (Birnbau and Ready, 2005; Shah et al., 2005; Goodin, 2006). It has also been observed that patients whose tumors have activating mutations in the EGFR tyrosine kinase domain also are more likely to have tumor responses, and that these mutations

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are more frequent among Asians, nonsmokers, women, and patients with adenocarcinoma (Hsieh et al., 2005; Tsao et al., 2006; Matsuo et al., 2007). As a result, many physicians require patients to have one or more of these characteristics to be considered good candidates for treatment with EGFR inhibitors.

Before any factor is included in guidelines for treatment selection, it is important to distinguish its prognostic effects from its ability to predict a differential clinical benefit from the specific treatment. This is true for both clinical characteristics and molecular-based biomarkers.

The terms “prognostic” and “predictive” have been used in numerous publications to describe relationships between biomarkers and clinical outcomes; however, these terms are seldom defined and are often used interchangeably. In this report, we will use the definitions proposed by Clark et al. (2006b). A *prognostic factor* is a measurement that is associated with clinical outcome in the absence of therapy or with the application of a standard therapy that patients are likely to receive. It can be thought of as a measure of the natural history of the disease. A control group from a randomized clinical trial is an ideal setting for evaluating the prognostic significance of a biomarker. A *predictive factor* is a measurement that is associated with response or lack of response to a particular therapy. Response can be defined using any of the clinical endpoints commonly used in clinical trials. A predictive factor implies a differential benefit from the therapy that depends on the status of the predictive biomarker. In statistical terms, this constitutes an interaction between treatment benefit and biomarker status that is best evaluated in a randomized clinical trial with a control group.

These concepts will be illustrated by examples from National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) Study BR.21, a randomized, placebo-controlled study of erlotinib (Tarceva®, OSI Pharmaceuticals Inc., Melville, NY) versus placebo for the second- or third-line treatment of patients with advanced NSCLC (Shepherd et al., 2005). The placebo control arm provided a unique opportunity to evaluate the prognostic significance of various clinical characteristics in these patients, and the randomization between placebo and single-agent erlotinib permitted assessment of the predictive significance of the same factors in this setting. Treatment with single-agent erlotinib eliminates the confounding effects of chemotherapy and/or radiotherapy that may be present when EGFR inhibitors are combined with other treatment modalities.

2. Results

As reported by Shepherd et al. (2005), objective response rates among patients who were randomized to the erlotinib arm in NCIC CTG Study BR.21 were significantly higher among females, patients with adenocarcinoma, and never smokers compared with males, patients with other histological subtypes, and current or former smokers, respectively (Table 1). These results are consistent with the published literature (Birnbaum and Ready, 2005; Shah et al., 2005; Goodin, 2006).

When survival of patients who were randomized to the erlotinib arm was analyzed by gender, histology, and smoking history, similar results were observed. Females survived

longer than males (Figure 1A), patients with adenocarcinoma lived longer than patients with squamous cell carcinoma (Figure 2A), never smokers lived longer than current or former smokers (Figure 3A). These results, together with the response rates in the erlotinib arm, seem to confirm the impression that erlotinib is particularly effective in females, patients with adenocarcinoma, and never smokers. However, before drawing this conclusion we need to know results from the placebo arm. Is it possible that these purported treatment benefits are really just the result of prognostic effects that are independent of treatment?

The same survival patterns observed in the erlotinib arm were also observed in the placebo arm for gender and histology. Females survived longer than males (Figure 1B) and patients with adenocarcinoma lived longer than patients with squamous cell carcinoma (Figure 2B). These results are classic examples of prognostic factors, where length of survival depends on gender and histology. In contrast, the survival curves were very similar for never smokers and current or former smokers (Figure 3B), indicating that in this clinical trial, smoking history was not a strong prognostic factor among patients on the placebo arm.

To establish predictive significance, it is necessary to determine if the survival benefit of patients on the erlotinib arm relative to patients on the placebo differs by patient characteristic or biomarker status. When survival curves by treatment arm among females are displayed next to survival curves among males, it becomes apparent that the relative treatment benefit, as measured by the hazard ratio (HR) for death, is nearly identical (Figure 1C and D). This is further illustrated in Figure 1E, where survival curves for all four combinations of treatment and gender are displayed. The test for interaction between gender and treatment is not statistically significant ($P = 0.76$), indicating that although gender is a strong prognostic factor, it does not predict a differential survival benefit from erlotinib compared with placebo that depends on gender.

A similar pattern can be seen for histology when survival curves by treatment arm among patients with adenocarcinoma are displayed next to survival curves among patients with squamous cell carcinoma (Figure 2C and D). Again, the HRs for death are nearly identical for the two histological subtypes, and the test for interaction between histology and treatment is not statistically significant ($P = 0.97$, Figure 2E). Similar

Table 1 – Tumor response in selected subsets of patients on the erlotinib arm in NCIC CTG Study BR.21

Subset	Response rate	P-value
Female	14.4%	0.0065
Male	6.0%	
Adenocarcinoma	13.9%	0.0020
Squamous cell carcinoma	3.8%	
Other histologies	4.5%	
Never smoker	24.7%	<0.0001
Current/former smoker	3.9%

Figure 1 – Survival of patients in NCIC CTG Study BR.21 by gender. (A) Survival of patients on the erlotinib arm by gender. Median survival for females was 8.4 months ($n = 173$); median survival for males was 5.7 months ($n = 315$); Hazard ratio (HR) for death (females:males) = 0.85 (95% confidence interval 0.69–1.05). (B) Survival of patients on the placebo arm by gender. Median survival for females was 6.2 months ($n = 83$); median survival for males was 4.5 months ($n = 160$); HR for death (females:males) = 0.80 (95% confidence interval 0.60–1.07). These results indicate that gender is a prognostic factor for survival in this study. (C) Survival of female patients by treatment arm. Median survival in the erlotinib arm was 8.4 months ($n = 173$); median survival in the placebo arm was 6.2 months ($n = 83$); HR for death (erlotinib:placebo) = 0.80 (95% confidence interval 0.59–1.07). (D) Survival of male patients by treatment arm. Median survival in the erlotinib arm was 5.7 months ($n = 315$); median survival in the placebo arm was 4.5 months ($n = 160$); HR for death (erlotinib:placebo) = 0.76 (95% confidence interval 0.62–0.84). (E) Survival of patients by gender and treatment arm. Test for interaction between gender and treatment benefit was not statistically significant ($P = 0.76$) indicating that gender was not a predictive factor for differential survival benefit from erlotinib relative to placebo in this study.

Figure 2 – Survival of patients in NCIC CTG Study BR.21 by histology. (A) Survival of patients on the erlotinib arm by histology. Median survival for patients with adenocarcinoma was 7.8 months ($n = 246$); median survival for patients with squamous cell carcinoma was 5.6 months ($n = 144$); HR for death (adenocarcinoma:squamous cell) = 0.66 (95% confidence interval 0.52–0.83). (B) Survival of patients on the placebo arm by histology. Median survival for patients with adenocarcinoma was 5.4 months ($n = 119$); median survival for squamous cell carcinoma was 3.6 months ($n = 78$); HR for death (adenocarcinoma:squamous cell) = 0.65 (95% confidence interval 0.48–0.88). These results indicate that histology is a prognostic factor for survival in this study. (C) Survival of patients with adenocarcinoma by treatment arm. Median survival in the erlotinib arm was 7.8 months ($n = 246$); median survival in the placebo arm was 5.4 months ($n = 119$); HR for death (erlotinib:placebo) = 0.71 (95% confidence interval 0.56–0.92). (D) Survival of patients with squamous cell carcinoma by treatment arm. Median survival in the erlotinib arm was 5.6 months ($n = 144$); median survival in the placebo arm was 3.6 months ($n = 78$); HR for death (erlotinib:placebo) = 0.67 (95% confidence interval 0.50–0.90). (E) Survival of patients by histology and treatment arm. Test for interaction between histology and treatment benefit was not statistically significant ($P = 0.97$) indicating that histology was not a predictive factor for differential survival benefit from erlotinib relative to placebo in this study.

Figure 3 – Survival of patients in NCIC CTG Study BR.21 by smoking history. (A) Survival of patients on the erlotinib arm by smoking history. Median survival for never smokers was 12.3 months ($n = 104$); median survival for current or former smokers was 5.5 months ($n = 358$); HR for death (never:current or former smoker) = 0.54 (95% confidence interval 0.41–0.71). (B) Survival of patients on the placebo arm by smoking history. Median survival for never smokers was 5.6 months ($n = 42$); median survival for current or former smokers was 4.6 months ($n = 187$); HR for death (never:current or former smoker) = 1.01 (95% confidence interval 0.71–1.45). These results indicate that smoking history is not a prognostic factor for survival in this study. (C) Survival of never smokers by treatment arm. Median survival in the erlotinib arm was 12.3 months ($n = 104$); median survival in the placebo arm was 5.6 months ($n = 42$); HR for death (erlotinib:placebo) = 0.42 (95% confidence interval 0.28–0.64). (D) Survival of current or former smokers by treatment arm. Median survival in the erlotinib arm was 5.5 months ($n = 358$); median survival in the placebo arm was 4.6 months ($n = 187$); HR for death (erlotinib:placebo) = 0.87 (95% confidence interval 0.71–1.05). (E) Survival of patients by smoking history and treatment arm. Test for interaction between smoking history and treatment benefit was statistically significant ($P = 0.006$) indicating that smoking history was a strong predictive factor for differential survival benefit from erlotinib relative to placebo in this study.

to gender, histology is a strong prognostic factor, but it has no ability to predict a differential survival benefit from erlotinib.

A quite different picture is observed when survival curves by treatment arm among never smokers are displayed next to survival curves among current or former smokers (Figure 3C and D). Here, the HRs are quite different for the two subsets, 0.42 and 0.87, respectively, and it is apparent that the survival benefit from erlotinib relative to placebo is considerably greater among never smokers. The test for an interaction between smoking history and treatment is statistically significant ($P = 0.006$), indicating that smoking history is a strong predictive factor for a differential survival benefit from erlotinib (Figure 3E).

It should be noted that a statistically significant interaction does not mean that current or former smokers derived no benefit from erlotinib; it simply means that the survival benefit differed by smoking history. Clark et al. (2006a) performed a thorough analysis of smoking history in this clinical trial, and concluded that erlotinib was beneficial in both subsets, but more effective in patients who had never smoked. For example, men with squamous cell carcinoma who were current or former smokers appeared to derive substantial survival benefit from erlotinib (HR = 0.66, 95% confidence interval 0.47–0.92). Note that this is precisely the subset of patients who would not be offered erlotinib if guidance that has appeared in the literature is followed (Birnbaum and Ready, 2005; Shah et al., 2005; Goodin, 2006).

3. Discussion

In NCIC CTG Study BR.21, gender and histology were strong prognostic factors, but neither was predictive of a differential survival benefit from erlotinib compared with placebo. Specifically, females and males derived the same relative survival benefit from erlotinib, and patients with adenocarcinoma derived the same relative survival benefit as patients with squamous cell carcinoma. Smoking history was the only predictive factor identified in this clinical trial, and never smokers experienced an enhanced benefit from erlotinib compared with placebo.

A treatment strategy that requires patients to be female, or to have adenocarcinoma, or to be a never smoker would exclude males with squamous cell carcinoma who are current or former smokers. Clark et al. (2006a) demonstrated that this subset of patients experienced a statistically significant survival benefit in this clinical trial (HR = 0.66, $P = 0.016$). This result is certainly counter-intuitive to the guidance that has appeared in the literature (Birnbaum and Ready, 2005; Shah et al., 2005; Goodin, 2006). The studies that support these treatment recommendations were retrospective reviews of patients treated with single-agent gefitinib (Iressa®, AstraZeneca Pharmaceuticals, Wilmington, DE) or single-arm clinical trials that did not include a control group. As stated in Section 1, it is not possible to assess the predictive significance of a biomarker or clinical factor unless the study includes a control group. The prognostic and predictive significance of biomarkers are completely confounded in single-arm evaluations of a treatment.

Because NCIC CTG Study BR.21 included randomization between erlotinib and placebo, it was possible to separate the

prognostic effects from the predictive effects for the clinical characteristics. In this case, if “benefit” is defined in terms of tumor response and the focus is only on the erlotinib arm, then never smokers, females, patients with adenocarcinomas appear to have derived the most benefit. However, if “benefit” is defined in terms of survival relative to placebo, then all subsets of patients appeared to benefit, although never smokers derived the most benefit.

The discordance between response rates and survival benefit raises the question of the adequacy of tumor response as a surrogate endpoint for clinical benefit. Buyse et al. (2000) summarized several techniques for validating surrogate endpoints, and Fleming (2005) described three levels of statistical evidence that should be considered in such validations: (1) Is the biomarker correlated with the clinical endpoint? (2) Does evidence suggest that objective response rate fully captures the effect of treatment on survival? (3) In a meta-analysis of trials evaluating a class of agents in a clinical setting, does the treatment effect on response rate reliably predict the effect on survival? A complete discussion of surrogate endpoints is beyond the scope of this paper, however, it is apparent from both NCIC Study BR.21 and from the ISEL (Iressa Survival Evaluation in Lung Cancer) study of another EGFR tyrosine kinase inhibitor (Thatcher et al., 2005) that lack of tumor response does not preclude a survival benefit for this class of agents, and that it does not fully capture the effect of treatment on survival.

The differentiation between prognostic factors and predictive factors is applicable to any clinical endpoint, not just survival. Selection of the most appropriate endpoint may differ by disease state and class of agent. In some situations, tumor shrinkage may better reflect the biological effect of the drug, while survival may be affected by competing risks on which treatment has no effects. However, tumor response does not reflect disease stabilization, so progression-free survival might be an appropriate, albeit more subjective, endpoint than overall survival for some clinical trials.

Before biomarkers or clinical characteristics are included in guidelines for selecting patients for specific treatments, it is imperative that clinically relevant endpoints are evaluated and the prognostic effects of these factors are distinguished from their ability to predict a differential clinical benefit from the specific treatment.

4. Materials and methods

4.1. Patients

Details about the patients who participated in NCIC CTG Study BR.21 and the treatment arms were previously described by Shepherd et al. (2005). Briefly, 731 patients with stage IIIB/IV NSCLC after failure of at least one but no more than two previous regimens for advanced or metastatic disease were stratified by center, performance status, best response to previous therapy, number of previous regimens, and exposure to previous platinum agents and were randomized 2:1 to receive erlotinib 150 mg daily or placebo. The primary endpoint of the study was overall survival. A total of 587 patients (80%) had died at the time of database lock,

and the median follow-up of patients still alive was 15 months (range, 0.4–26 months).

4.2. Smoking history

Smoking history was retrospectively ascertained by asking the following question: Has the patient ever smoked cigarettes? The possible responses were: (1) No, <100 cigarettes in entire lifetime; (2) Yes, ≥ 100 cigarettes in entire lifetime; and (3) Unknown. Patients were classified as never smokers if they responded No, <100 cigarettes in their entire lifetime.

4.3. Statistical methods

All survival analyses were performed using PROC LIFETEST and PROC PHREG as implemented in SAS[®] version 9.1.3 (Cary, NC). Relative survival benefit was measured by the hazard ratio for death, defined as the ratio of the risk of death in the erlotinib arm relative to the risk of death in the placebo arm, assuming proportional hazards. The assumption of proportional hazards was evaluated by examining plots of residuals and by including time-dependent terms in the models. The assumption of proportional hazards could not be rejected for any of the models created for these analyses. All analyses performed for this report were retrospective, subset analyses. No adjustments were made for multiple hypothesis testing.

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