Is There Clinical Value to Prognostic Signatures in Early-Stage NSCLC?

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pAMPK and pmTOR favorably predicted outcome in early non–small cell lung cancer (NSCLC). The differences were small. Phosphoprotein lability makes routine clinical use and validation difficult. Protein immunohistochemistry is unlikely to be clinically useful, and numerous efforts to create predictive models to select resected patients for therapy have been unsuccessful. Clin Cancer Res; 20(7); 1727–9. ©2014 AACR.

In this issue of Clinical Cancer Research, Gold and colleagues report on their study in which they attempted to define prognostic signatures to predict outcomes in patients with early-stage lung cancer who undergo surgical resection but are at risk for recurrence following the surgery (1). This study not only took on this difficult challenge but also attempted to develop a signature based on analysis of protein and/or activated protein expression by immunohistochemistry, targeting proteins identified through gene array data. The authors report that they were able to find several proteins that were significantly associated with either progression-free or overall survival, some of which were associated with improvement in both endpoints. However, the magnitude of the differences was small and there are many technical difficulties to the routine assessment of activated (phosphorylated) proteins highlighting the difficulties in creating predictive and prognostic risk models. Among these were pmTOR and pAMPK. These findings will add to evidence of their role in non–small cell lung cancer (NSCLC) and could lead to an explanation of why high mTOR expression was associated with a favorable outcome. However, the magnitude of the differences in progression-free and overall survival was small. As acknowledged by the authors, there are many technical difficulties to the routine assessment of activated (phosphorylated) proteins by immunohistochemistry. Furthermore, the study was complicated by a heterogeneous patient population, which could theoretically result in the impact of this approach being understated. Thus, the authors appropriately concluded that their findings were consistent with the Squamous Lung Cancer Consortium supported by the National Cancer Institute’s (NCI) Specialized Program for Evaluation of Cancer Signatures is reevaluating many published gene signatures under standardized circumstances in terms of tissue processing, RNA extraction, histology, and clinical features both in a large prospective test set and a defined validation set.

The major question is what is the clinical relevance of these differences. Are any of these prognostic signatures predictive of benefit from adjuvant chemotherapy? Would the knowledge that a resected patient has a high or a low risk of relapse be associated with benefit (or lack thereof) from chemotherapy and thus affect the subsequent management? If this knowledge would affect the treatment plan and improve survival, there would be value to the patients and the health care system.
A, a prognostic signature can separate patients into those with a superior survival “good signature” compared with the entire group as illustrated. The signature may divide the patients into three or four groups if this is clinically desirable, compared with a division into two groups. The signature performance may differ by histology and stage, and generally the differences are less prognostic in validation sets. B, a signature that is prognostic and predictive requires a prospective randomized trial in which those with both a “good” and a “poor” signature would be separately randomized to receive or not receive adjuvant chemotherapy following surgical resection. Survival would be superior in those randomized to the chemotherapy.

subsequent follow-up or therapy, then the utility of such an approach is clear. Figure 1 illustrates the differences between a signature that is prognostic only and one that is prognostic and predictive. Proof that one of the prognostic signatures is predictive would require a prospective randomized trial with randomization to adjuvant or no adjuvant chemotherapy.

Current therapeutic guidelines recommend that patients with completely resected stage I NSCLC receive no adjuvant therapy and that patients with stage II and IIIA NSCLC receive adjuvant chemotherapy (14, 15) Unfortunately, there is no convincing evidence that current gene signatures that predict a poor outcome in stage I would also indicate that such patients would have their poor outcome reversed by adjuvant chemotherapy. And there is no convincing evidence that stage II or III patients with a good signature would fail to benefit from adjuvant chemotherapy. Moreover, none of the signatures developed to date were designed to predict the best therapy that might be given in the adjuvant setting. Thus, there is a need for separating prognostic and predictive signatures, even if overlap may occur.

The design issues of these trials can be overcome, but it is unclear whether such trials are feasible with our current clinical trial infrastructure and accrual rates. The NCI-supported alliance attempted such a trial but it was closed for lack of accrual. We must hope that we can develop therapeutic choices that are less toxic and biomarker/signatures that better predict outcomes from these therapies and are also associated with prognosis. Currently, there are no prospective trials that are likely to identify signatures that are prognostic or predictive, although it is possible that the ALCHEMIST trials evaluating specific molecular changes with specific molecular therapies could serve some of this functionality. Obstacles include the potential need to evaluate multiple prognostic approaches from one source of tissue, controlling for adjuvant therapy selected with appropriate planned subgroup analysis, controlling for the prognostic information inherently seen in well-defined driver alterations and the need to evaluate single-analyte approaches as well as complex “signatures.” The difficulties seen in this and other studies highlight the need for additional worldwide early-stage lung cancer clinical trials.

Disclosure of Potential Conflicts of Interest

P.A. Bunn Jr is a consultant/advisory board member for Myriad Genetics and Life Technologies. F.R. Hirsch is a consultant/advisory board member for Myriad Genetics. D.L. Aisner reports receiving speakers bureau honoraria from Illumina, Inc. and Abbott Molecular and is as a consultant/advisory board member for Boehringer Ingelheim.

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