Chapter 4

An analysis of human equilibrative nucleoside transporter-1, ribonucleotide reductase subunit M1, ribonucleotide reductase subunit M2, and excision repair cross-complementing gene-1 expression in patients with resected pancreas adenocarcinoma: Implications for adjuvant treatment

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An Analysis of Human Equilibrative Nucleoside Transporter-1, Ribonucleotide Reductase Subunit M1, Ribonucleotide Reductase Subunit M2, and Excision Repair Cross-Complementing Gene-1 Expression in Patients With Resected Pancreas Adenocarcinoma: Implications for Adjuvant Treatment

Adjuvant chemotherapy improves survival in pancreatic adenocarcinoma (PAC). Still, studies for the identification of predictive/prognostic biomarkers of chemotherapy activity appear to be critical for better clinical management. Unfortunately, these studies obtained controversial results, and tailored treatments based on expression profiles are still far from being used. A possible explanation might reside in the analysis of a single factor versus several key determinants of drug activity.

Because only a few studies have tried to address this point, we appreciated the article by Fisher and colleagues [1], who used immunohistochemistry (IHC) to demonstrate that high tumor expression of ribonucleotide reductase subunit-M2 (RRM2) and excision repair cross-complementing group-1 was correlated with reduced overall survival (OS). Conversely, in our study on mRNA expression of 7 genes involved in gemcitabine activity in laser-microdissected PACs, we did not observe differences in RRM2 expression, and patients who had higher levels of human equilibrative nucleoside transporter-1 (hENT1) had significantly longer OS [2]. Consistent with our data, several studies have demonstrated that patients who have PAC with high hENT1 expression benefit from gemcitabine-based adjuvant chemotherapy [3-5]. However, recent press releases indicate a lack of correlation with hENT1 expression in the prospective multicenter NCT01124786 trial, which is testing a gemcitabine elaidate analog that enters tumor cells in an hENT1-independent fashion.

These discrepancies may be caused by differential methods, treatment heterogeneity, and relatively small sample size. IHC is a sensitive and versatile method, but it is largely empirical; the outcome depends on the antibody used and pathologists’ expertise. Fisher and colleagues used a polyclonal anti-hENT1 that differs from the antibody used in previous studies [3-5], and they evaluated patients who received different treatment regimens. We used a specific quantitative reverse transcriptase-polymerase chain reaction technique. Nevertheless, mRNA can differ from protein expression; hence, we believe that the optimization/standardization of both methodologies with appropriate controls that can be used for interlaboratory validation is crucial before larger prospective investigations in homogeneously treated patients can address the same pharmacogenetic question. Other critical points include: 1) evaluation of tumor heterogeneity and possible evolution of cancer cells after tumor relapse, which should be faithfully documented within multiple samples of the single tumor as well as repeated biopsies; and 2) analyses to clarify pharmacokinetic/pharmacodynamic interactions.

In conclusion, we agree that observational studies can provide a strong rationale for future trials, but we believe that standardized techniques of sample collection/processing, larger and uniformly treated populations according to powered statistical analysis, and integration with functional data are essential to validate the best markers for personalized treatment of patients with PAC.
References

Reply:

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We appreciate the letter from Avan et al regarding our study examining the prognostic value of excision repair cross-complementing gene-1 (ERCC1) and ribonucleoside reductase subunit M1 (RRM2) expression in patients undergoing resection for pancreas adenocarcinoma [1]. Observational studies have value in identifying potentially prognostic biomarkers that may help to risk stratify patients enrolled in trials and/or to guide the use of adjuvant therapy. A limitation of biomarker development using retrospective observational studies, as highlighted by Avan et al, is tissue heterogeneity and differences in techniques used for gene/protein analysis. In addition, the best method of assessment may differ by biomarker.

We agree with our colleagues that biomarker studies mandate expert selection of representative sections of tumor, as was done in our study and their previous works [2]. Immunohistochemistry (IHC), although widely available and cost effective, is subject to inter-rater variability. We attempted standardization by using a semiquantitative scoring system, as detailed in the article. Evaluating mRNA levels using a quantitative technique such as reverse transcriptase-polymerase chain reaction (RT-PCR) is attractive but is limited by the potential difference between mRNA levels and protein expression. A recent study of ERCC1 in nonsmall cell lung cancer compared RT-PCR with IHC in patients treated on trial. The authors observed no correlation between RT-PCR results and IHC results, and
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IHC-based ERCC1 expression accurately discriminated survival [3].
Our study identifies ERCC1 and RRM2 as potential prognostic markers; however, given the heterogeneity of adjuvant therapy regimens, further work is required to determine the predictive value of these biomarkers (and others; ie, hENT1) for response to therapy. We congratulate our colleagues on their work in this field regarding hENT1.2 We strongly support incorporating tissue-based correlative studies into clinical trials in pancreas cancer and other gastrointestinal malignancies [4], as well as collaborative efforts to thoroughly investigate both prognostic and predictive biomarkers

References