hENT-1 Expression and Localization Predict Outcome After Adjuvant Gemcitabine in Resected Cholangiocarcinoma Patients

In the May 2016 issue of ***The Oncologist***, Brandi et al. [1] explored the expression and localization of human equilibrative nucleoside transporter 1 (hENT-1) in paraffin-embedded tissues from radically resected cholangiocarcinoma patients. They highlighted the prognostic role of this transporter and identified hENT-1 as a potential biomarker to predict outcome after adjuvant therapy with gemcitabine [1].

Curative treatment of cholangiocarcinoma is limited to surgical resection, but a recent meta-analysis supports the use of adjuvant chemotherapy [2]. However, few patients benefit from adjuvant treatment, as early recurrence or metastasis often occurs. Identification of biomarkers that can predict outcome and/or response to therapy is warranted. Hence we appreciated the findings by Brandi and colleagues, but believe that some key points should be carefully discussed.

Previous studies showed controversial results on the prognostic/predictive role of hENT-1 in pancreatic cancer. Although several retrospective studies, including the European Study Group for Pancreatic Cancer (ESPAC)-3, reported a significant correlation between high hENT-1 protein expression and longer survival after adjuvant gemcitabine treatment [3], the protein failed to predict outcome in metastatic patients in the prospective multicenter trial NCT01124786. These discrepancies might be caused by the relatively small sample size and several factors influencing hENT-1 levels, such as disease type and stage and hENT-1 localization, as demonstrated in the Brandi et al. study [1]. To overcome these limitations, the use of clinical trial data with well-annotated characteristics is vital.

A critical point is standardization of the technique to evaluate hENT-1 expression. Immunohistochemistry is a sensitive method widely used for the detection of specific proteins in tissue, but it largely depends on the antibody, as well as the pathologist's expertise. The hENT-1-specific rabbit polyclonal antibody of the Brandi et al. study differs from the mouse monoclonal antibodies of other studies, such as the NCT01124786 and ESPAC-3 trials, as reviewed by Ciccolini et al. [4]. Experiments comparing these antibodies in the same cholangiocarcinoma samples would allow for consensus on hENT-1 antibody expression and scoring. Furthermore, detailed procedures are needed to improve reproducibility and validate results.

As stated by Brandi et al., further work is required to determine the predictive value of hENT-1. To obtain a complete picture of the pharmacokinetics, pharmacodynamics, and effects of hENT-1 expression and localization, we also suggest additional studies investigating the active metabolites of gemcitabine, such as gemcitabine triphosphate [4].

Finally, a critical point is the evaluation of tumor heterogeneity and possible tumor evolution after relapse, which could be overcome by well-annotated documentation of multiple samples and repeated biopsies. Liquid biopsies are an appealing alternative because they offer the potential to characterize tumor heterogeneity and monitor tumor progression and response to treatment. Because recent studies have suggested that several microRNAs (miRNAs) play a key role in gemcitabine chemoresistance [5], future studies are necessary on modulation of hENT-1 expression by selected miRNAs, as well as monitoring of these miRNAs in liquid biopsies.

In conclusion, we are indebted to Brandi et al. and look forward to additional studies with standardized antibodies and techniques for sample evaluation, validation in larger populations with powered statistical analysis, and integration with new methodologies and biomarkers for pharmacological studies and liquid biopsies.

Acknowledgments

This work was supported by grants from the Bennink Foundation (to L.L. Meijer, J.R. Puik, G. Kazemier, and E. Giovannetti), Associazione Italiana per la Ricerca sul Cancro, Tuscany Region "Bando Fas Salute" 2014 (to E. Giovannetti), and CCA Foundation (to E. Giovannetti and G.J. Peters).

LAURA L. MEIJER*

JISCE R. PUIK*

Departments of Medical Oncology and Surgery, VU University Medical Center Amsterdam, Amsterdam, The Netherlands

GODEFRIDUS J. PETERS

Department of Medical Oncology, VU University Medical Center Amsterdam, Amsterdam, The Netherlands

GEERT KAZEMIER*

Department of Surgery, VU University Medical Center Amsterdam, Amsterdam, The Netherlands

ELISA GIOVANNETTI

Department of Medical Oncology, VU University Medical Center Amsterdam, Amsterdam, The Netherlands; Cancer Pharmacology Laboratory, Italian Association for Cancer Research Start-Up Unit, University of Pisa, Pisa, Italy

*Contributed equally.

Disclosures

The authors indicated no financial relationships.

References

1. Brandi G, Deserti M, Vasuri F et al. Membrane localization of human equilibrative nucleoside transporter 1 in tumor cells may predict response to adjuvant gemcitabine in resected cholangiocarcinoma patients. ***The Oncologist*** 2016;21:600–607.

2. Horgan AM, Amir E, Walter T et al. Adjuvant therapy in the treatment of biliary tract cancer: A systematic review and meta-analysis. J Clin Oncol 2012;30:1934–1940.

3. Greenhalf W, Ghaneh P, Neoptolemos JP et al. Pancreatic cancer hENT1 expression and survival from gemcitabine in patients from the ESPAC-3 trial. J Natl Cancer Inst 2014;106:djt347.

4. Ciccolini J, Serdjebi C, Peters GJ et al. Pharmacokinetics and pharmacogenetics of gemcitabine as a mainstay in adult and pediatric oncology: An EORTC-PAMM perspective. Cancer Chemother Pharmacol 2016;78:1–12.

5. Garajová I, Le Large TY, Giovannetti E et al. The role of microRNAs in resistance to current pancreatic cancer treatment: Translational studies and basic protocols for extraction and PCR analysis. Methods Mol Biol 2016;1395:163–187.

http://dx.doi.org/10.1634/theoncologist.2016-0262