



THE QUALITY ONCOLOGY PRACTICE INITIATIVE



Advertisement

JOURNAL OF CLINICAL ONCOLOGY
Official Journal of the American Society of Clinical Oncology

Search for: **GO**

Limit by: All Topics All Years

Browse by **Subject** or **Issue**

Home Search or Browse JCO Subscriptions PDA Services My JCO Customer Service

Journal of Clinical Oncology, Vol 26, No 18 (June 20), 2008: pp. 3015-3024
© 2008 American Society of Clinical Oncology.
DOI: 10.1200/JCO.2007.15.7164

Stem Cell-Related "Self-Renewal" Signature and High Epidermal Growth Factor Receptor Expression Associated With Resistance to Concomitant Chemoradiotherapy in Glioblastoma

Anastasia Murat, Eugenia Migliavacca, Thierry Gorlia, Wanyu L. Lambiv, Tal Shay, Marie-France Hamou, Nicolas de Tribolet, Luca Regli, Wolfgang Wick, Mathilde C.M. Kouwenhoven, Johannes A. Hainfellner, Frank L. Heppner, Pierre-Yves Dietrich, Yitzhak Zimmer, J. Gregory Cairncross, Robert-Charles Janzer, Eytan Domany, Mauro Delorenzi, Roger Stupp, Monika E. Hegi

From the Laboratory of Tumor Biology and Genetics, Centre Universitaire Romand de Neurochirurgie; Division of Neuropathology; Multidisciplinary Oncology Center, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Lausanne; the National Center of Competence in Research Molecular Oncology at the Swiss Institute of Experimental Cancer Research; the Swiss Institute of Bioinformatics, Epalinges; the Centre Universitaire Romand de Neurochirurgie, the Service of Oncology, University Hospital Geneva, Geneva; the Department of Clinical Research and Radiation Oncology, Inselspital and University of Berne, Berne; the Institute of Neuropathology, University Hospital Zurich, Zurich, Switzerland; Data Center, European Organisation for Research and Treatment of Cancer (EORTC), Brussels, Belgium; Department of Physics of Complex Systems, Weizmann Institute of Science, Rehovot, Israel; the Department of General Neurology and Hertie Institute for Clinical Brain Research, University of Tübingen, Tübingen; Department of Neurooncology, University Clinic Heidelberg, Heidelberg; Institute of Neuropathology, Charité –Universitätsmedizin Berlin, Berlin, Germany; Department of Neurology, Erasmus, Rotterdam, the Netherlands; Institute of Neurology, Medical University of Vienna, Vienna, Austria; and the Department of Clinical Neurosciences, University of Calgary, Calgary, Canada

Corresponding author: Monika E. Hegi, PhD, Laboratory of Tumor Biology and Genetics, Centre Universitaire Romand de Neurochirurgie, Centre Hospitalier Universitaire Vaudois and University of Lausanne, 46, rue du Bugnon, Lausanne 1011/Switzerland; e-mail: Monika.Hegi@chuv.ch

Purpose: Glioblastomas are notorious for resistance to therapy, which has been attributed to DNA-repair proficiency, a multitude of deregulated molecular pathways, and, more recently, to the particular biologic behavior of tumor stem-like cells. Here, we aimed to identify molecular profiles specific for treatment resistance to the current standard of care of concomitant chemoradiotherapy with the alkylating agent temozolomide.

Patients and Methods: Gene expression profiles of 80 glioblastomas were interrogated for associations with resistance to therapy. Patients were treated within clinical trials testing the addition of concomitant and adjuvant temozolomide to radiotherapy.

Results: An expression signature dominated by *HOX* genes, which comprises *Prominin-1* (CD133), emerged as a

This Article

- ▶ Full Text
- ▶ Full Text (PDF)
- ▶ Purchase Article
- ▶ View Shopping Cart
- ▶ Alert me when this article is cited
- ▶ Alert me if a correction is posted

Services

- ▶ Email this article to a colleague
- ▶ Similar articles in this journal
- ▶ Similar articles in PubMed
- ▶ Alert me to new issues of the journal
- ▶ Save to my personal folders
- ▶ Download to citation manager

Google Scholar

- ▶ Articles by Murat, A.
- ▶ Articles by Hegi, M. E.

PubMed

- ▶ PubMed Citation
- ▶ Articles by Murat, A.
- ▶ Articles by Hegi, M. E.

predictor for poor survival in patients treated with concomitant chemoradiotherapy (n = 42; hazard ratio = 2.69; 95% CI, 1.38 to 5.26; $P = .004$). This association could be validated in an independent data set. Provocatively, the *HOX* cluster was reminiscent of a "self-renewal" signature ($P = .008$; Gene Set Enrichment Analysis) recently characterized in a mouse leukemia model. The *HOX* signature and *EGFR* expression were independent prognostic factors in multivariate analysis, adjusted for the *O*-6-methylguanine-DNA methyltransferase (*MGMT*) methylation status, a known predictive factor for benefit from temozolomide, and age. Better outcome was associated with gene clusters characterizing features of tumor-host interaction including tumor vascularization and cell adhesion, and innate immune response.

Conclusion: This study provides first clinical evidence for the implication of a "glioma stem cell" or "self-renewal" phenotype in treatment resistance of glioblastoma. Biologic mechanisms identified here to be relevant for resistance will guide future targeted therapies and respective marker development for individualized treatment and patient selection.

Supported by the Swiss National Science Foundation (Grant No. 3100AO-108266/1; M.E.H.); Jacqueline Seroussi Memorial Foundation for Cancer Research (M.E.H.), Translational Research Fund of the EORTC (M.E.H.); the Nélia and Amadeo Barletta Foundation (M.E.H., R.S.); National Center of Competence in Research (NCCR) Molecular Oncology at the Swiss Institute for Experimental Cancer Research (ISREC) (M.E.H., M.D.); Ridgefield Foundation (E.D.); EC FP6 (E.D.); and the VITAL-IT project of the Swiss Institute of Bioinformatics (E.M., M.D.).

A.M. and E.M. contributed equally to this article.

Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

About
JCO

Editorial
Roster

Advertising
Information

Librarians &
Institutions

Rights &
Permissions

Site Map

Copyright © 2008 by the American Society of Clinical Oncology, Online ISSN: 1527-7755. Print ISSN: 0732-183X

[Terms and Conditions of Use](#)



HighWire Press™ assists in the publication of JCO Online