Expression profiling of Gastrointestinal Stromal Tumors
Biomarkers for Prognosis and Therapy

Akademisk avhandling

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Gabriella Arne

Fakultetsopponent:
Docent Anders Höög
Avdelningen för Patologi och Cytologi
Karolinska Universitetssjukhuset, Solna

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Gabriella Arne

Sahlgrenska Cancer Center, Department of Pathology,
Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden

ABSTRACT

Gastrointestinal stromal tumor (GIST) is a mesenchymal tumor of the gastrointestinal tract with a clinical spectrum ranging from indolent tumors to tumors with aggressive behavior and poor patient survival. The established model for prediction of prognosis for GIST is the NIH risk score, which is based on tumor size and mitotic index. Even so, there are difficulties in predicting the clinical outcome for individual GIST patients, which may lead to inadequate treatment. The majority of GISTs have activating mutations in the genes encoding the tyrosine kinase receptors KIT, or PDGFRA, which are considered to be pathogenic events in tumor development. Imatinib, a tyrosine kinase inhibitor (TKI) that inhibits KIT, has become an important therapeutic option in addition to surgery.

To identify biomarkers that accurately predict clinical outcome in GIST patients, global gene expression profiling was performed based on KIT mutations associated with poor prognosis. Tumor material from 16 GISTs was analyzed with expression microarray for identification of multiple candidate genes with differential expression related to mutational status. PROM1 was shown to be highly expressed in GIST with KIT exon 11 mutations. Detection of PROM1 protein with immunohistochemical staining of 204 GISTs arranged in a tissue microarray (TMA) showed that PROM1 expression was predominant in gastric GISTs of high-risk type. Multivariate Cox analysis showed that PROM1 expression was significantly associated with poor prognosis and short patient survival, independently of NIH risk score. To evaluate the usefulness of immunohistochemical biomarkers for prognostication of GIST, we performed a comprehensive study of 14 biomarkers in 205 GISTs in a TMA. There was a significant correlation between expression of CA2, CDKN2A, CXCL12, EPHA4, FHL1, and DPP4 protein and survival. Furthermore, survival analysis using Cox regression showed that CA2, EPHA4, and FHL1 provided prognostic information additional to that from the NIH risk score. Construction of a decision-tree model combining NIH risk and expression of biomarkers further improved the prediction of patient survival. GISTs are effectively treated with surgery and imatinib, but some patients are refractory and develop drug resistance. We have investigated the prerequisites for alternative treatment strategies with peptide receptor-mediated radiotherapy (PRRT), by analyzing the expression of somatostatin receptors (SSTRs) and uptake of radiolabeled somatostatin analogs in GIST. Analysis of 34 GISTs with pPCR and immunohistochemistry showed expression of SSTR1 and SSTR2. Primary cultures established from GIST showed specific binding and internalization of 177Lu-octreotate. Diagnostic imaging with 111In-octreotide showed tumor uptake of 111In in 3/6 GIST patients in vivo. Tumor-to-blood activity ratios for 111In measured in biopsies from excised tumor tissue showed ratios that may be adequate for therapy.

We conclude that the expression of PROM1 in GIST may be used as a prognosticator of patient survival and may provide a therapeutic target. Several immunohistochemical biomarkers provide additional prognostic information in addition to NIH risk score and may be useful in constructing decision-trees for improved prognostic accuracy for GIST patients. Binding and uptake of radiolabeled somatostatin analogs via SSTR enable tumor imaging and targeted therapy in selected GIST patients.

Key words: Gastrointestinal stromal tumor (GIST); KIT; Biomarker; PROM1 (CD133), Somatostatin receptor (SSTR); Peptide receptor-mediated radiotherapy (PRRT); Expression profiling; Immunohistochemistry; Tissue microarray (TMA); Survival analysis


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