Molecularly-guided therapeutic options beyond TKIs for Gastrointestinal Stromal Tumors (GIST)

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Abstract
Background: GISTs are characterized by KIT/PDGFRα mutations. A range of multi-targeted tyrosine kinase inhibitors (TKIs) are available for treatment, however, resistance mechanisms inevitably emerge. Recent data (Boichuk, et al 2014) suggests the potential efficacy of various cytokitic therapeutic agents identified as being able to effectively kill TKI-responsive and -resistant GIST cells. We sought to investigate the theranostic markers associated with non-TKI therapy options for their potential role in treatment of GIST.

Methods: 147 GIST cases were evaluated. A multiplex approach of biomarker testing was used and included a combination of sequencing (NGS), Sanger, protein expression (IHC) and gene amplification (ISH).

Results: Multidrug resistance phenotype was found in 52-68% (PGP, MRP1). Tubulin-binding agents (taxanes, vinca alkaloids) may be of potential use due to the high frequency of low TUBB3 expression (72% or 39/54). Anthracyclines and topoisomerase inhibitors may be of potential benefit in 1/3 of patients based on expression of TOP2A (33% or 32/97) and TOP1 (34% or 37/110). Cytotoxic agents used in non-GIST solid tumors, may also be considered, based on high frequency of low expression of MGMT (47% or 57/122), TS (70% or 78/112) and PDGFRA (5/55). Variants were detected in the following result in the detection of variants in only 10 genes, excluding KIT hot spot cancer panel (and Sanger sequencing for some genes) resulted in the detection of variants in only 10 genes, excluding KIT hot spot cancer panel (and Sanger sequencing for some genes).

Conclusions: A multi-platform approach of theranostic biomarkers identified therapy beyond TKIs for GIST. Various cytokitic and non-TKI/PDGFRα targeted therapies were identified based on protein expression or gene variations.

References
1. Boichuk S, et al. (Cancer Res 74:1200-1213) explored the sensitivity of GIST cells to various FDA-approved chemotherapeutic agents by performing a compound screening using the NCI-H69 Approved Oncology Drugs Set II. Using a pre-defined drug response score, they identified a number of chemotherapeutic agents that had high antitumor activity. We assessed the frequency distributions of GIST patients’ protein-expression and gene copy number data that associate with several chemotherapeutic agents. Agents highlighted in green below were shown to alter tumor on GIST cells in Boichuk’s study.

Results (contd.):

Table 2: Frequency distribution of protein and gene copy number changes. All biomarkers above are tested by immunohistochemistry (protein levels), unless indicated by “ISH” (gene copy status by in situ hybridization). Percent frequencies represent data collected from CMI database; highlighted rows correspond to drugs that effectively inhibit GIST cells in Boichuk’s study.

Table 3. Specimen site for profiling. 51% of patients received profiling from sites other than the primary tumor site listed, suggestive of metastatic (local and distant) disease.

Figure 1. Primary Tumor Location. 224 GIST were studied and grouped according to primary tumor site location.

Figure 2. Multitasking Resistance (MDR) - Frequency of GIST patients exhibit overexpression of ABC transporters which are drug efflux pumps.

Figure 3. Multiscale analysis in up to 100 GIST patients. Data demonstrates that beyond cKIT and PDGFRα, there is limited success at identifying a targetable gene through sequencing platforms.

Figure 4. Notable biomarker alterations in cKIT and PDGFRα wildtype GIST patients. Multiplex profiling including IHC, Sanger and NGS platforms revealed several potential therapeutic targets and protein expression status of multiple predictive biomarkers. Importantly, NGS identified only 2 alterations and Sanger did not identify any alterations. Data suggests potential therapeutic options based on protein expression status for cKIT/PDGFRα wildtype GIST patients.

Figure 5. Diagram of potential therapeutic options beyond tyrosine kinase inhibitors. Our data demonstrate GIST patients exhibit high frequency of low RRM1, low TUBB3, low TS and high TOP2A protein expression. These frequencies suggest the potential utility of cytotoxic agents that include DNA synthesis inhibitors, microtubule poisons, antimetabolites and topoisomerase inhibitors. GIST patients frequently exhibit high levels of drug efflux pumps. Further, treatment strategies that involve multidrug resistance, which lends support for the added benefit of identifying treatment options through molecular profiling. Multimodal platforms offer limited value in detecting targetable genes outside of cKIT and PDGFRα. Non-cKIT/PDGFRα targetable mutants are rare events (e.g. andesine or vandetanib).

Protein expression offers the most value for cKIT and PDGFRα wildtype patients (10-13% of GIST population), identifying multiple potential treatment choices based on expression status of predictive biomarkers (TOP2A, TUBB3, etc.)

*Data is updated to include an additional 67 GIST patients

Table 1. Tumor Attributes and Patient Demographics

*Data includes patients with confirmed primary tumors with 100% of all cases included. Tumors classified according to primary tumor site listed and included: metastases or adenomatous primary tumors.

Abstract

Methods

Results

Conclusions

References