Biomarkers in GIST: Partly Ready for Prime-Time Use

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Gastrointestinal stromal tumors, or GISTs, are now among the most treatable of solid malignancies. Assessing actual tumor response remains challenging; however, in this issue of Clinical Cancer Research, two articles discuss biomarkers potentially helpful in predicting response or other long-term benefits with standard tyrosine kinase therapy use. (Clin Cancer Res 2009;15(18):5603–5)

In this issue of Clinical Cancer Research, two articles address assessment of clinical outcomes in advanced gastrointestinal stromal tumor (GIST) patients treated with sunitinib malate after imatinib failure (1, 2).

GISTs have assumed oncologic importance far out of proportion to their incidence. Knowledge about their diagnosis and treatment has increased exponentially over the last decade, during which time advanced GISTs went from being a uniformly fatal disease to a malignancy that can be controlled 90% of the time. Currently, patients with advanced GIST survive an average of 5 years or more (3), and occasionally they remain without evidence of progression for periods up to 9 years or longer. GISTs were one of the first solid tumors treated successfully with a rationally applied, targeted biologic therapy, and they remain a relative rarity in being a malignancy for which experts recommend different doses of standard front-line systemic therapy, depending on underlying tumor mutational status. Interestingly, assessment of successful outcomes in treated patients, with the notable exception of overall survival, can be quite difficult. Standard Response Evaluation Criteria in Solid Tumors (RECIST) significantly under calls response in GIST patients actually benefiting from targeted therapy (4). Additionally, because successfully treated tumor masses occasionally undergo cystic degeneration and enlarge (progression under RECIST), patients may erroneously be thought to have failed tyrosine kinase inhibitor (TKI) treatment and be prematurely taken off therapy that is actually working well. Finally, standard radiographic responses may take a long time to evolve, leading to significant psychological stress for the patient or treating physician.

Demetri and associates published a phase I/II trial that used serial tumor imaging using 2-Deoxy-2-18F-fluoro-D-Glucose–positron emission tomography (FDG-PET), while also analyzing cell proliferation and KIT phosphorylation in serial tumor biopsies (1). DePrimo and colleagues looked at circulating levels of soluble KIT, to determine if they were valuable surrogates for standard outcome parameters (2). Thus, both groups tested potential predictive biomarkers of efficacy in similarly treated groups. At least one biomarker emerges at least partly ready for use in following advanced GIST patients treated with sunitinib, and possibly with imatinib or other TKIs.

The Demetri article described several potential schedules of sunitinib malate, an oral multitargeted TKI with activity against KIT, platelet-derived growth factor receptor (PDGFR), vascular endothelial growth factor receptors (VEGFR), and other receptor tyrosine kinases (RTK), tested mostly in patients resistant to imatinib (1). Computer-assisted tomography (CT) or magnetic resonance imaging (MRI) scans (assessed with RECIST), were done at the end of every even-numbered cycle, whereas serial PETs were done at baseline, after the first week of sunitinib, at the end of the first cycle, and once during subsequent cycles. Tumor biopsies were collected at baseline, and “where possible” at other time points for conventional histology; correlative studies looking at phosphorylated and total proteins of interest; tumor genotyping and proliferation rates were assessed as well. In brief, sunitinib was an effective and moderately tolerable drug, with about half of treated patients deriving clinical benefit (no immediate progression). Seventy-two percent of patients with PET data available at baseline and day 7 showed a ≥25% decline in standardized uptake value (SUV) max at the latter point, often “rebounding” during the drug-free period after the first cycle. Seventy-two percent of this group showed at least stable disease on sunitinib. Additionally, matched tumor biopsies showed little change in KIT expression with sunitinib treatment; proliferation was reduced by at least 25% in about half of cases (it increased by more than 25% in 21%); and one third undergoing immunoblotting showed reduction in activated KIT with decreased activation and/or expression in downstream cell proliferation effectors. The authors concluded PET changes indicative of response occurred months earlier than CT differences. They also stated the decreased phospho-KIT showed effective target modulation, and that changes in cell proliferation proteins were consistent with growth inhibition and correlated with clinical outcome.

The DePrimo article described changes in circulating plasma levels of the extracellular domain of soluble KIT (sKIT), in patients receiving sunitinib or placebo on a phase III trial in

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imatinib failures (2). sKIT was measured on days 1, 14, and 28 of cycle 1 and days 1 and 28 of subsequent treatments (cycles were 6 weeks in duration). Formal statistical criteria were applied to test the validity of sKIT as a surrogate marker for efficacy. A "proportion of treatment effect" (PTE, the percent of the result explained by the surrogate versus the overall treatment effect, with unity representing a perfect surrogate) was generated by Freedman's method. The sunitinib-treated and placebo groups did not differ at baseline in terms of sKIT levels; following therapy, sKIT in the sunitinib group generally decreased, whereas it generally increased in the placebo group. Patients with increased levels relative to baseline had shorter time-to-progression (TTP) than those with decreases. The calculated PTE at cycle 3 was 0.98, suggesting the overall majority of the treatment effect was explained by sKIT. The authors hypothesized sKIT assays might be a useful surrogate marker in monitoring response, specifically identifying, after two cycles, patients who will derive benefit from sunitinib treatment.

Many potential uses for clinical biomarkers exist. Markers may be studied before therapy for their prognostic (offering patients important information on the likely outcome given the natural history of their particular disease) or predictive (giving information on whether patients are more or less likely to obtain benefit from said treatment) values. KRAS status in patients with metastatic colorectal cancer represents an important but not perfect recent example of the latter. Those with tumors possessing mutated KRAS derive no benefit from treatment with anti-EGFGR antibodies, and this class of targeted agent may reasonably be withheld from such patients. Unfortunately, the converse is not true; not having mutant status (i.e., being wild-type) does not guarantee success with usage of said antibodies. After a specific treatment has begun, there are several additional uses for biomarkers. They may serve as alternates or surrogates for the outcome endpoint of interest, allowing earlier determination of the potential benefit of therapy, or perhaps being easier or safer to use than standard means of assessing efficacy. Even a marker that suggests eventual therapeutic failure would be useful, allowing earlier intensification of dosing or a change to a different regimen that might be more effective.

It is helpful when changes in the proposed biomarker can be mechanistically tied to outcome, and this is the case for both PET and sKIT. Signaling pathways targeted by TKIs are related to tumor glucose metabolism, and marked decreases in GIST metabolic activity have been noted as early as 24 hours after patients have received their first imatinib dose. PET changes in GIST (Fig. 1) are already known to detect early response to imatinib, and they seem to correlate with long time-to-progression (4). sKIT declines with sunitinib therapy could certainly represent a decrease in tumor cell viability and/or bulk, though they may also merely represent differences in KIT synthesis or shedding, in the absence of cancer cell death. It is also possible a fraction of the sKIT shown could actually arise from normal tissues, and changes therein could be from drug effects occurring in non-neoplastic cells. Other investigators have shown sKIT levels decrease in GIST patients treated with imatinib regardless of whether they respond, suggesting changes reflect inhibition of KIT receptor turnover in normal tissues, rather than tumor response (5). Finally, it is satisfying to report a potential link between the two markers. Tying together the two articles, the DePrimo group has shown from their earlier phase sunitinib study that sKIT declines only occur in GIST patients with FDG-PET responses (6).

Neither PET nor sKIT is a perfect tool, though PET is more usable now. In the Demetri article, 28% of patients with PET responses did not show disease control on later CT/MRI scans. However, most experts believe PET progression invariably heralds classic radiographic progression, and thus truly represents drug failure. In DePrimo’s study, some patients on placebo still had decreases in sKIT, and a large fraction with increases in sKIT still enjoyed long TTP. Thus declines in either PET activity or sKIT levels will likely (but not absolutely) predict for good radiographic results and would definitely encourage the treating physician to continue sunitinib; increases in PET activity but not sKIT levels might call for a change to a different drug or action plan (increases in the latter might still call for more frequent or earlier radiographic testing.

![Fig. 1. A, fused 18F-FDG-PET/CT coronal image showing an intensively hypermetabolic left hepatic lobe metastasis. B, repeat scan after 1 mo of imatinib mesylate therapy shows complete resolution of the FDG-avid hepatic abnormality.](image-url)
however). Although not currently clinically useful, certainly the sKIT analyses described in the second article are very encouraging in terms of potential future development. When the assay itself is optimized, and results are prospectively confirmed, serial sKIT determination may move to routine clinical use.

Finally, we are reminded that correlative substudies in clinical trials involving rare diseases such as GIST remain necessary to make significant progress in treatment. Indeed, the National Cancer Institute (NCI)-designated GIST Task Force recently proclaimed all United States Cooperative Group GIST trials will mandate tissue collection for concurrent or future translational studies. The two articles in this issue of Clinical Cancer Research are exemplary of the type of correlative research that should accompany standard drug testing.

Disclosure of Potential Conflicts of Interest

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