New Horizons GIST

2019 CONFERENCE REPORT

May 8-10, 2019

Wayne, New Jersey, USA

Contents

Acknowledgments

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The idea, conception, planning, preparation, management and summary of the New Horizons GIST 2019 conference are the responsibilities of the Steering Committee and GIST patient community without any influence from the sponsors.

We would like to thank our colleagues from the GIST expert community who travelled to speak at our conference. We are grateful for their time and insight during the discussions at the conference.

Finally, we would like to thank the other external speakers who attended the meeting to provide valuable insight on real world data and treatment access.

Introduction

Every year country leaders gather to discuss scientific updates, regional issues, and unmet needs for the global GIST community. This international meeting was launched by Novartis Oncology in 2003 with the title, "New Horizons in Treating CML and GIST," with the goal of uniting patient organizations representing people living with CML and GIST.

A few years ago, the conference divided into two separate meetings—one focused on GIST and the other on CML. Since then, the New Horizons GIST Conference has been organized by a GIST Steering Committee that aims to unify the global GIST patient advocacy community with key opinion leaders and facilitate ways to increase survival worldwide. What you may not know is that these advocates have over the years become lifetime friends. We celebrate happy occasions together and commiserate when we lose dear friends. We have walked through GIST history together.

In May, the LRG happily reunited these advocates and hosted the large annual global conference called New Horizons GIST near our headquarters in Wayne, NJ. We had 45 participants from 18 countries. One of the meeting's most important goals was to share relevant medical and scientific information about GIST, but just as important is the exchange of ideas and experiences that each one has had in their countries around topics such as collecting real world information, mutational testing, and advocacy efforts with health authorities.

NEW HORIZONS GIST Steering Committee

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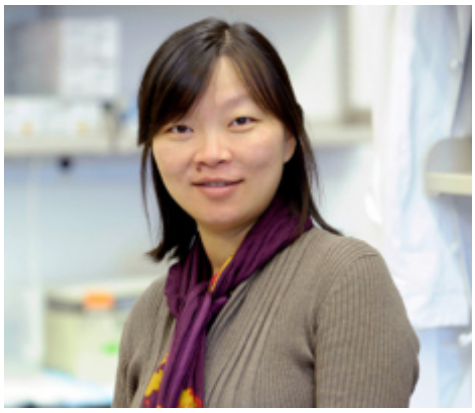
PRESENTATIONS

GIST Research Updates and Future Direction of Research

Dr. Ping Chi
Memorial Sloan Ketting Cancer Center

Dr. Chi is a medical oncologist and researcher. She began by reviewing the basic science and medicine of GIST. She noted that before the "KIT era", histopathological diagnosis of GIST was difficult because of the wide variety of appearances of the tumors under the microscope. GISTs originate with ICCs and the tumors express KIT highly (Hirota et al 1998). The introduction of imatinib therapy for GIST (2001) has been a paradigm for drug therapy of solid tumors.

Aberrant KIT signaling activates specific genes, mediated by specific transcription factor proteins in the nucleus, leading to uncontrolled growth. Dr. Chi reviewed the known mutational types in GIST: KIT, PDGFRA, BRAF, RAS, etc. Until recently, therapy research has focused on KIT and PDGFRA, but the other targets are now being studied.



Dr Chi explained the multiple challenges of imatinib resistance. 14% of patients show primary resistance, but many more develop resistance during treatment.

Multiple resistance mechanisms have been identified, including: secondary mutations (50-65%); gene amplification of RTKs (such as KIT and PDGFRA); activation of alternative signaling pathways (other than the expected STAT, PI3K, and MAPK pathways); KIT-low imatinib-resistant stem cells; and possibly other mechanisms.

The consequent clinical challenges include the heterogeneity of resistant tumor clones, even in a single patient; the problem of imatinib-resistant wild-type GIST; and adaptive responses (resistance) to TKIs.

Dr Chi asked whether, if we "hit the disease harder up-front", we might prevent the later development of resistance. And if we intervene early, as soon as resistance starts to develop, could we eradicate the disease?

She noted that the analysis of circulating DNA ("liquid biopsy") should help in monitoring the development of resistance, but this technology is still under development.

Dr Chi outlined a possible workflow for implementing precision therapy to target imatinib-resistant GIST clones (progression): use either tissue or liquid biopsies to identify targets; classify the mutations and use our knowledge of their properties to assign patients to the most promising therapy, e.g., for imatinib-resistant KIT mutations developing after primary exon 11 mutation: PLX9486 + PLX3397; for imatinib-resistant KIT mutations developing after primary exon 17 mutations: choose PLX9486 or BLU-285 or DCC-2618 as appropriate; for wild-type (e.g., SDH-deficient): try either imatinib or PLX3397, combined with MEK162/binimetinib.

Dr. Chi explained aspects of the basic biology of KIT. We now recognize that the KIT gene regulates the development of four different cell lineages: ICCs, melanocytes, germ cells, and mast cells. Nevertheless, GISTs develop from only one of these four, the ICC lineage - and this is true even for the (very rare) cases of familial (inherited) KIT mutations - the patients get GISTs only, not tumors from the other lineages. And bear in mind that tumors arising from those other lineages (melanomas, germ cell tumors, leukemias) are well-known cancers - they just aren't associated with KIT mutations! So, why not? There must be some special characteristic of the ICC lineage that makes them particularly susceptible to the effects of KIT mutations. This question was the starting point for Dr. Chi's research.

ETV1 is a transcription factor (a protein that regulates gene expression).

The "ExpoO" (Expression Project for Oncology) study had revealed that ETV1 expression is highly elevated in GIST, but much less so, or not at all, in other cancers (breast, lung, colorectal, and even in other sarcomas). This suggests that ETV1 is a "lineage-specific survival factor" for ICCs and GISTs.

Tumor adaptation & resistance

Dr. Chi discussed the role of ETV1 as activator of upstream cell-signaling pathways, such as the MAPK pathway. Her hypothesis is that simultaneous targeting of both the KIT and MAPK pathways could be synergistic in killing GIST cells. (The precedent for this approach is the use of combinations of MEK and BRAF inhibitors in melanoma treatment.) This idea was verified by studies (in vitro and in mice) combining imatinib with a MEK inhibitor (MEK162/ binimetinib); GIST882 cells and xenografts were studied (2010 and 2015 publications). Complete tumor eradication was seen in mice treated with high doses of the MEK inhibitor.

Can we forestall resistance?

Proof-of-principle clinical trials were undertaken to target both ETV1 and KIT. The GIST trials under way are a Phase Ib/II trial of MEK162 (binimetinib) + imatinib (NCT01991379); and a Phase Ib/II trial of MEK162 (binimetinib) + PLX3397 (pexidartinib) (NCT03158103).

NCT01991379: The Phase Ib (safety assessment) component has been completed. Clinically, most patients did not respond very well (but one must bear in mind that they had already exhausted other therapies). However, there was at least one very encouraging response in an SDH-deficient GIST patient, who remains on the trial after >5 years. Dr. Chi noted that eye toxicity (central vein occlusion) may be a side effect to this regimen. A manuscript describing the results is in preparation. Overall, the approach seems to be promising at least for some advanced patients

GIST Treatment Updates

Dr. Ciara Kelly
Memorial Sloan Kettering Cancer Center

Following on from Dr. Chi, Dr. Kelly emphasized the importance of the molecular classification of GISTs (see page 8). She showed a "pie chart" of the distribution of mutations (see page 9).

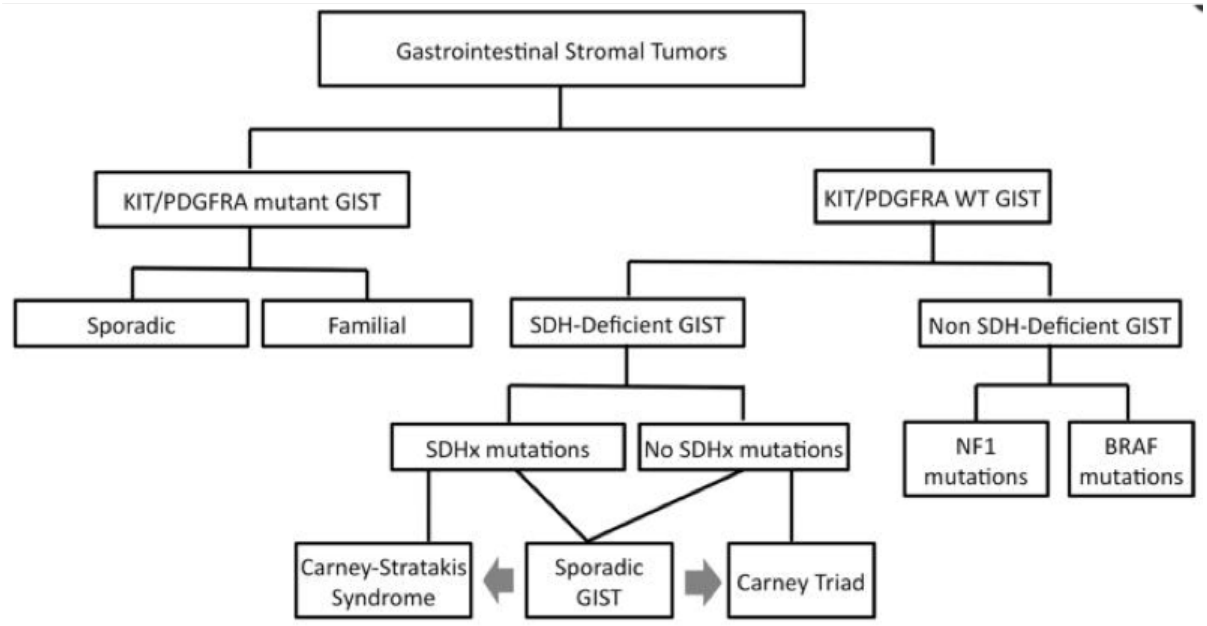
She reviewed the use of imatinib as first-line treatment. Imatinib is cytostatic but not cytotoxic; residual disease can give rise to resistance; this was shown by the results of Dr. Blay's clinical trial of imatinib interruption. Sunitinib and regorafenib are the approved second- and third-line drugs. Secondary resistance mutations in KIT exons 13 and 14 ("ATP-binding pocket") and exons 17 and 18 ("kinase activation loop") are the major causes of therapy failure.

Dr. Kelly considered the options beyond standard care. She said, "We [at Sloan Kettering] are huge proponents of clinical trials and compassionate access programs." Then she reviewed the results of their recent and ongoing trials.

Ripretinib

Ripretinib (DCC-2618) is a new "switch-pocket" KIT inhibitor, attacking KIT at a different site compared to the standard drugs, and it is hoped that it will be effective against a broad range of secondary KIT and PDGFRA mutations.

A Phase I clinical trial was conducted; this was a dose escalation/ safety study from 20-250 mg per day. It was followed by an expansion phase using 150 mg per day, allowing escalation to 2 x 150 mg per day if disease progression occurred. The new drug appears to be very safe



and tolerable, although there were some dose reductions (14%) and discontinuations (11%) due to adverse events. Promising activity was seen across all lines of therapy (2nd, 3rd, 4th); results were reported at ESMO in Oct. 2018. The ongoing clinical trials of the drug are the INVICTUS (4th line) and INTRIGUE (2nd line) trials.

Avapritinib

Next, Dr. Kelly discussed avapritinib (BLU-285). This drug is designed to bind to the active conformation of KIT/ PDGFRA, in contrast to imatinib, which binds to the inactive conformation. It is hoped that off-target side effects will be less likely, since the drug is highly specific for KIT/ PDGFRA. Dr. Kelly reviewed the NAVIGATOR Phase I clinical trial results.

The recommended phase II dose is 300 mg daily. Adverse events were usually low grade; only 8.7% of patients discontinued due to adverse events. However, memory impairment is a significant concern. Impressive clinical activity was seen, especially in the PDGFRA D842V subtype, with 84% objective response rate and 96% clinical benefit rate. Dr. Kelly stated that "This is a remarkable achievement." The responses are durable. Dr. Kelly reviewed one particular case where excellent tumor reduction was seen by both CT scan and circulating DNA analysis.

The complete data from the study were presented by Dr. Heinrich at CTOS 2018. In advanced GIST, the drug is much more effective for cases where the tumor is negative for exon 13/14 mutations than for cases where the tumor is positive for those mutations. Based on this study, the new drug was granted Breakthrough Drug designation by the FDA.

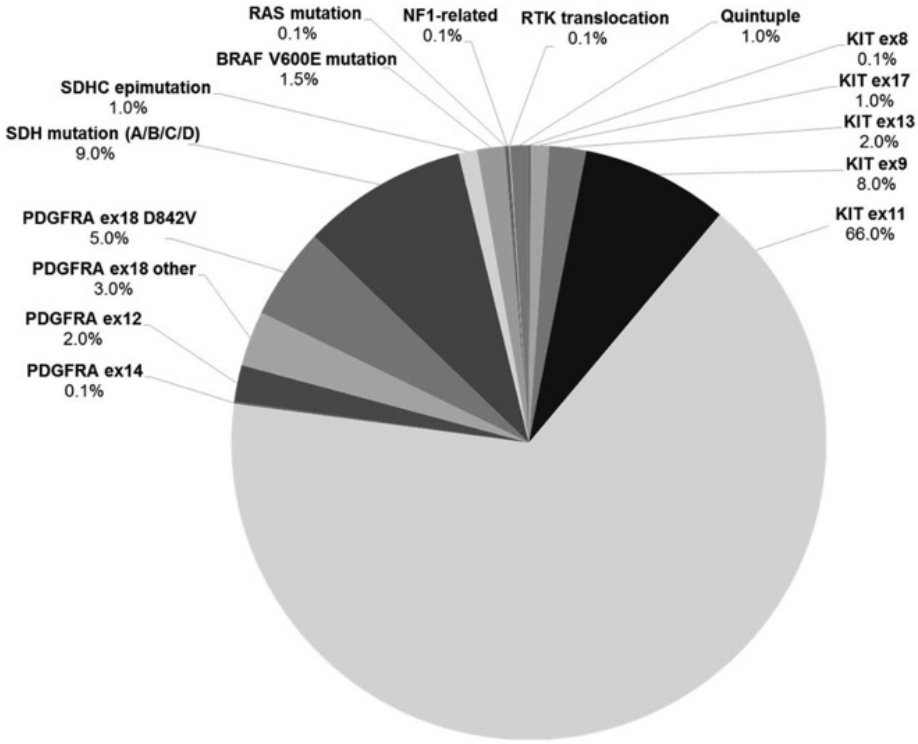
Immunotherapy in GIST

Finally, Dr. Kelly discussed the potential for immunotherapy in GIST. Preclinical work shows that GISTs are immunogenic tumors. Elevated levels of cytotoxic CD8 T-cells are seen in

pre-clinical studies of imatinib-sensitive GIST (DeMatteo). Greater imatinib activity is seen when CD8 T-cell levels are higher.

Inhibition of the IDO1 enzyme may sensitize the tumor microenvironment to the immune system and may provide a role for the use of immune-checkpoint inhibitor drugs. A clinical trial was done in sarcoma, where 20 of the 28 patients in the study were (heavily pretreated) GIST patients. Combination therapy was performed with dasatinib + ipilimumab. The results were disappointing. There were no partial or complete responses. The outcomes were similar to standard care (imatinib re-challenge).

Dr. Kelly indicated that future trials should use an immune-checkpoint inhibitor in combination with the newer TKI drugs. There is an ongoing trial with nivolumab + ipiluminab in advanced refractory GIST; interim data were reported at GI ASCO 2018 and full results are pending.



CASE PRESENTATIONS

BRAF V600E Mutation

Dr. Jason Sicklick

Case is a 68-year-old man with GIST. Next-gen sequencing revealed a BRAF V600E mutation (which is rare in GIST but common in melanoma). He was treated with dabrafenib (GSK 2118436) plus trametinib (Feb to April 2018). The patient responded, but underwent nine further lines of therapy and six surgeries! Facing rapid progression with lesions in the lung and pelvis, sequencing was done again and revealed a cell-cycle mutation, CDKN2A. This gene encodes two different proteins, p16 INK4a and p14, both of which act as tumor suppressors (cell cycle regulators). We added a drug that targets this cell-cycle mutation, palbociclib (Ibrance). There was a good response; the lesions shrank.

SDH-deficient GIST

Dr. Ciara Kelly

Dr. Kelly presented the case of a 20 year-old woman who presented with an upper GI bleed. Endoscopy revealed multiple gastric tumors. Gastrectomy was performed. Pathology showed multifocal GIST; the largest was lesion 7 cm. and the mitotic rate was high. KIT and PDGFRA mutation analysis was negative. A liver lesion (possibly just a cyst?) was seen by CT. The patient was placed on adjuvant imatinib for one year.

Five years later (2009), liver metastases were seen: recurrent GIST. She entered a clinical trial of imatinib vs nilotinib and was randomized to imatinib, 400 mg daily. Disease progressed in 2011 and she was switched to sunitinib; but there were complications, including high blood pressure.

She moved to NYC in 2012 and has since been treated at MSKCC. Further IHC analysis of the original (2003) surgical specimen revealed loss of SDHB expression: this is an SDH-deficient GIST. Next-generation DNA sequencing identified an SDHA mutation.

The patient continued on sunitinib but there was progression. Further surgery in 2013, including partial hepatectomy. From 2013-14, she was on a clinical trial of an IGF-1R inhibitor, but there was further slow progression after one year. In Jan 2014, she was enrolled in the imatinib + binimetrinib clinical trial mentioned earlier by Dr. Chi and Dr. Kelly. The dose had to be reduced. There was an initial response but (in 2015) a slight increase in the liver mets. Surgical debulking was attempted but failed due to the identification, at surgery, of extensive disease. Biopsy revealed strong necrosis of the peritoneal lesions. The patient is still on the study.

Rare Subtypes

Dr. Jason Sicklick
Moores Cancer Center, UCSD

KIT is not the only driver of GIST. Genetic testing is essential in GIST. We are not just looking for hot spots or single genes but more comprehensive panels are important to examine larger populations of genes, which allows us more ability to look at change in genes.

There are a lot of genetic alterations in GIST: 70% are kit mutant, 12% are PDGFRA, 10% NF1, 8% are SDHx, and the remainder are other.

According to a study Sicklick did with Foundation Medicine among the wildtype population, a large portion of patients have metastatic disease.

Among them, several genes were identified such as FGFR. Also, gene fusions were identified like ETV6-NTRK fusions from quadruple wildtype GIST patients. We are starting to understand that fusions can occur most commonly in small bowel but can occur in other places as well.

These past few years, there has been huge progress in drug development with a couple of companies finding therapies to target TRK fusions. This is a great example of how precision medicine targets a genetic alteration and one can see a dramatic response.

As a take home message, we are starting to learn a lot of pathways in these tumors, it is not just one single pathway. With that said, there may be some pathways that can be targetable with drugs in the market.

Pediatric & SDH-Deficient GIST Consortium Update: A Review with Experts & Advocates

Facilitators: **Sara Rothschild, Denisse Montoya, Jayne Bressington, Becky Owens, Dr. Jason Sicklick**

Traditionally, researchers and clinicians work independently on SDH-deficient GIST, a rare sub-type of GIST. Better collaboration is needed to bridge the gap among researchers to learn more about SDH-deficient GIST. The Pediatric & SDH-Deficient GIST Consortium was created to help close that gap. Ms. Rothschild discussed the aim of the consortium is to extend and sustain the work of the NIH Clinic and other research efforts, with the ultimate goal of finding a cure through global collaborations. As patients' survival and quality of life are dramatically impacted by this disease, it is critically urgent that the leading experts collaborate and share data and tissue, with the goal of finding successful targeted therapies that can help keep these patients alive.

The LRG has a paraffin tissue bank linked to a patient registry. Since the Consortium, we saw an increase in tissue from the SDH community. The need of tissue is critical to help advance research. We are encouraging patients in advance of surgery to contact advocates so that they can arrange fresh and viably frozen tissue to researchers to help grow cell lines and PDX models.

We have seen a successful model of biobanking SDH-deficient GIST tumors in the UK through the tireless work of the PAWSGIST UK Clinic. They have the largest collection of SDH-deficient GIST samples in Europe/world available to researchers. PAWSGIST is currently supporting five research projects on SDH-deficient GIST.

Dr. Jason Sicklick is one of the key researchers in the United States who has made significant progress on research in SDH-deficient GIST. He demonstrated some of the work he has done in growing cell lines in his laboratory. He also introduced a clinical trial of temozolomide for SDH-deficient GIST patients based on data found in his lab.

We look forward to continued collaboration among advocates and researchers as well as the learning exchange shared along the way.

Understanding the Concept of "Precision Oncology" in Patient-Friendly Language

Dr. Jason Sicklick
Moores Cancer Center, UCSD

When you look at tumors, there are lots of targets in these tumors. Systemic therapy sometimes hits targets and sometimes does not. Targeting multiple targets may be a better way to treat patients.

Treating patients with non-precision targeted therapies does not work well (5% of the time). If one gives standard cytotoxic chemo (15% of time), and with precision medicine (30% of time).

Precision medicine trials are playing off the paradigm of GIST.

There are challenges, however, and it can be compared to the analogy of snow.

All snowflakes are a little different even though they all look like snow. These are the challenges to the targeted therapy approach. At UCSD, a personalized medicine program was initiated called I-PREDICT with treating patients with different diseases who had previously treated therapies in order to try and catch them early with a personalized approach.

This is an example that we will be seeing more among medical institutions.

Some of the lessons of the I-PREDICT study:

- Single agent matched therapy is often inadequate to treat many lethal cancers
- We can safely treat each malignant snowflake and its co-genomic alterations: customized, molecularly matched combination therapies
- We can increase matching rates: nearly 50% of patients treated with molecularly matched regimens
- Appreciate the pillars of precision medicine by combining both genomically targeted therapies and immunotherapies
- Continuing to enroll both previously treated and treatment naive patients to the study

In Summary:

- Personalized-precision medicine represents a paradigm shift in oncology
- We are just in the process of defining the true feasibility of this approach with NGS technology
- While it does not completely account for tumor heterogeneity, the potential exists for obtaining data from multiple distinct tumor sites or primary and metastasis
- Ultimately, we need to start somewhere…GIST, CML, and melanoma have been successful examples of matched targeted approaches
- Potential for applications in other fields including anesthesia, internal medicine, and surgery

The Role of ctDNA in GIST

Dr. Ciara Kelly
Memorial Sloan Kettering Cancer Center

Circulating Tumor DNA (ctDNA) is a component of cell free DNA (cfDNA). cfDNA are fragments of normal and cancer cells shed into the blood stream. ctDNA is tumor derived and the sources of ctDNA are from blood, urine, csf, respiratory secretions.

The role of ctDNA can be applied in the following ways:

- For localized disease: therapeutic selection and detection of recurrence.
- For metastatic disease: therapeutic selection and monitoring response.
- For refractory disease: Detection of mechanisms of resistance, therapeutic selection, and capturing tumor heterogeneity and subclone-specific response.

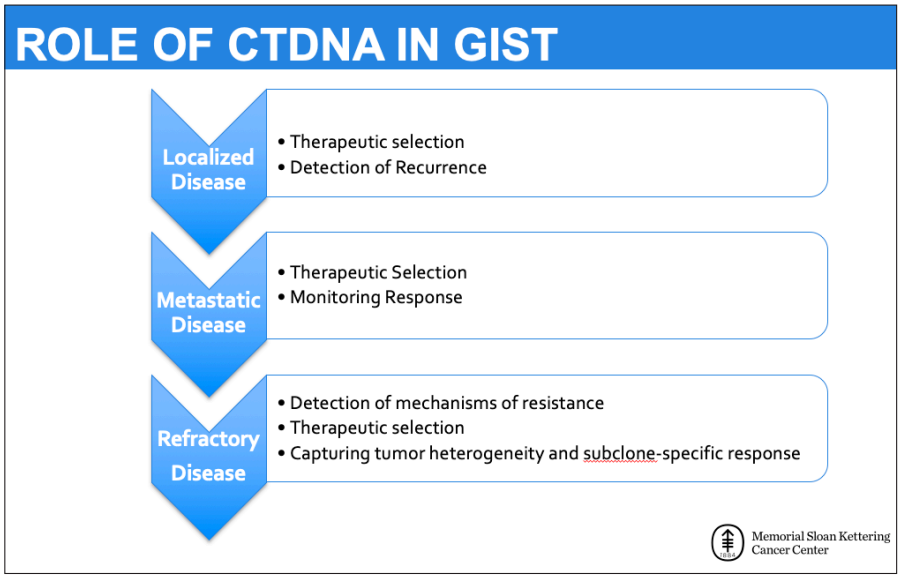
Several studies have shown the ability to detect somatic mutations in ctDNA collected from patients with GIST. Few studies have reported on the concordance rate between the molecular spectrum detected by sequenced ctDNA and tumor DNA from biospy/surgical specimens

- Detection of primary KIT mutations – high concordance rate (84%)
- Secondary KIT mutations – poor concordance
  - Plasma superior at detecting secondary mutations 47% vs 12% in tissue

Prospective studies have shown that changes in levels of mutational burden detected by sequenced ctDNA in GIST has been shown to correlate with

- Tumor volume
  - Higher levels with progressive disease
- Response to treatment
  - Lower levels with response to treatment

In summary, ctDNA is a potential blood biomarker of clinical and molecular behavior of GIST. Sequencing is evolving and we need to optimize the assay to improve sensitivity of detection. Routine collection of ctDNA in prospective clinical trials in GIST is necessary to advance this technology forward. Additionally, the integration of ctDNA into clinical trial design is important.



Bridging the Gap between Molecular Testing and the Patient & Physician Communities

Sue-Ann Woo
Foundation Medicine

Grounded in extensive experience, research, and partnerships in the cancer community, Foundation Medicine has been one of the leaders in providing comprehensive genomic profiling for the cancer community. This profiling can provide the genomic information that an oncologist can use to more quickly, confidently, and efficiently develop a personalized treatment plan, one based on the unique genomic profile of a patient's cancer.

Only about 15% of people with advanced cancer in the U.S. are getting this testing or multi-gene next generation sequencing, however in many cases, it's often too late in a patient's journey.

The presenter, Sue-Ann Woo, demonstrated the global reach that Foundation Medicine/ Roche provides to ensure testing in different parts of the world. Unfortunately, it is not easily accessible or affordable in many parts of the world. During the presentation and afterwards during the discussion, we engaged in critical conversations between patient advocates and healthcare providers who were present to explore how to educate and advocate in our countries to make this testing a reality so that physicians can participate in better personalized care plans.

Interventional Radiology Approaches to Treat Recurrent GIST

Dr. Joseph Erinjeri
Memorial Sloan Kettering Cancer Center

Dr. Erinjeri focused on the radiological treatment of GIST metastases. What is the rationale for trying these methods? We have learned from sarcomas that resection of hepatic metastases improves patient survival!

He then surveyed the radiological treatment methods that are used. Both RFA (radio-frequency ablation) and microwave therapies kill tumors by heating them, causing proteins to denature and cells to desiccate, but the two technologies are different.

What is RFA?

Radiofrequency ablation uses an alternating current generator that transmits energy into the tumor by electrical conduction; the RFA electrical field causes ions in the cells to move (current flows) and thereby generates frictional heat. The tissue temperature is raised to 65-100 C near the tip of the RFA needle. The range that can be penetrated is 1-3 cm. Generation of the ionic current by the RFA requires forming a complete electrical circuit, so "grounding pads" are needed. These are placed on the legs.

Microwave ablation

Microwave ablation is similar, but uses a higher-frequency region of the electromagnetic spectrum, much like a kitchen microwave oven. The probe is targeted to the lesion and the microwave energy causes the water in the tissue to boil, killing the cells. The range is 1-5 cm. Because the energy is transmitted by radiation rather than by conduction, no grounding pads are needed. A larger region of tumor killing can be achieved with the microwave technique.

Hepatic artery embolization (HAE)

In this approach, the tumor cells are "choked": that is, their blood supply is cut off, causing the cells to die from ischemic damage. Small particles are injected through a micro-catheter into the tumors, causing a "tumor attack", much like a damaging "heart attack".

TACE

Trans-arterial chemo-embolization. In this technique, a chemotherapy drug (usually doxorubicin) is delivered directly to the tumor.

To disrupt the blood supply to a specific liver metastasis, the doctor identifies an individual "feeder" blood vessel, using real-time fluoroscopy. To do this, the doctor snakes a catheter up through the groin into the liver and injects dye directly into the hepatic artery. Then the doctor inserts a tiny micro-catheter, drives it right up to the tumor, and injects tiny particles

to block the blood supply to the tumor. After four months (for example, in the case study he presented), a CT scan shows necrosis of the metastases, not unlike what happens following imatinib treatment. Macrophages move in and digest the dead tissue, shrinking the metastasis and allowing the normal liver to occupy the volume liberated.

The doctor showed a case study of ablation of a GIST metastasis in the liver, a single lesion that would have been difficult to resect, located near the diaphragm. The needle is inserted right through the lung and into the tumor, heating the tumor.

In the doctor's practice, some recalcitrant GIST tumors are treated two ways - "double kill" - e.g., hepatic artery embolization, and then, later, ablation. GIST tends to respond particularly well to ablation, relative to other sarcomas.

In selected patients, RFA of GIST liver metastases can give an overall survival of 90 months, even after failure of systemic therapy.

The doctor reviewed published studies of survival statistics for GIST following these techniques. He noted that the presence of extra-hepatic lesions is a negative factor for their success. He suggested that designing embolization beads pre-loaded with TKIs would be an interesting idea for future development.

The doctor did a study to compare hepatic artery embolization as second line (post-imatinib) versus third-line (after imatinib and sunitinib) therapy. The answer is that HAE seems to be useful in both situations - "intervene early" or "intervene later".

The doctor asked, why would we bother to treat patients with HAE early on, when we still have second- and third-line drugs available?

Consider a situation where a localized GIST is treated, but then progresses. After metastasis, we could either go straight to systemic therapy; or, we could first try to do ablation, and hold off systemic therapy until later. This approach can provide the patient with a "chemo-free interval" - presumably with a better quality of life, even if only for a limited time.

Does this strategy work?

He studied this retrospectively, based on his patient data set. Indeed, he found that ablation can result in a prolonged chemo-free interval. He suggested that the length of this chemo-free interval is another valuable endpoint, besides PFS or OS - how long can we delay the need for systemic chemotherapy?

Conclusion

Ablation and embolization are good treatment options for GIST liver metastases!

Q&A

Q. *What about lesions elsewhere (other than the liver?)*

A: It's all a matter of location. You can't do ablations adjacent to a critical organ like the bowel or stomach; and, other than the liver, that is almost always where GIST metastases are.

Q. *What about freezing (cryo-ablation)*

A. This is not usually done in GIST. Cryo-ablation is less effective. However, it has the advantage that the radiologist can "watch the ice-ball grow", avoiding damage to a neighbouring structure. This technique is used in some other organs, e.g. the kidney.

Real World Evidence in Action

Piga Fernández
Fundación GIST Chile

Real world data and scientific evidence of GIST treatments have been instrumental in the achievement of three important goals that will help GIST patients in Chile access the health care services they need.

1. Access to GIST Treatment through the "Ricarte Soto Law"
2. National Cancer Law in Chile
3. Salud con Datos GIST Registry Project

Action and passion driven by vision.

Piga Fernández, Executive Director of GIST Chile, was inspired and passionately motivated by the statement of Dr. Tedros, Director General of the World Health Organization.

"Health is a human right. No one should get sick and die just because they are poor or because they cannot access the health care services they need."

Action got results:

- Finding and working with the right people and organizations
- Advocating throughout the entire process, in meetings, conferences, the media as well as through marches to create awareness.
- Developing a new publication "Impact of GIST and its treatment in Chile" to raise awareness and to share a compelling story of improved patient outcomes.
- Being in the right place, at the right moment.

The National Cancer Law and the National Cancer Plan, both signed in December 2018, were the result of the collaborative efforts of politicians, researchers, academia and patient organizations, setting a way for improvement and development of current health policies.

Matías Munoz Medel, a data analyst from Catholic University of Chile, highlighted that the National Cancer Law is providing a necessary stepping stone to deploy a National Cancer Registry for rare cancers, including GIST. Preliminary results from this collaborative project were well received at a recent symposium held in Latin America. The aim is to leverage the Chilean GIST Registry to help with genomic analysis for GIST patients in order to improve both survivability and quality of life.

Rodrigo Salas
Fundación GIST Mexico

Over the years, Fundación GIST Mexico and Alianza GIST have learned that to help patients with better outcomes, real world data is needed on how patients are doing.

The Salud Con Datos GIST Registry Project began four years ago with the goal of establishing cancer registries throughout Latin America, in order to manage and leverage real world data. Information is gathered directly from GIST patients and analyzed to better understand the development of GIST in their countries.

The Registry has grown from 70 patients to 528 patients (in 4 years) and has significantly helped achieve some very important outcomes.

- Collaborating closely with physicians
  - Working as a team with the doctors has helped grow the Registry as there are now 55 specialists who refer patients to GIST Mexico
  - This cross-collaboration is also benefitting physicians because they now use Registry real world data to support their scientific publications in peer-reviewed journals and at conferences (ESMO &ASCO)
  - Encouraging special collaboration among physicians from different institutions to publish together. This has been so successful that there are now plans to have doctors from different countries publish together
- Empowering patients with information
  - Tracking patient appointments
  - Talking with patients before appointments to suggest what questions they should ask the doctors
- Following up with patients
  - Talking with patients after appointments to discuss status, side effects, diet etc.
  - Registry data shows that working closely with patients improves compliance and disease outcomes
- Monitoring patients on generic drugs
  - The Registry is capturing information about patients who are taking generic drugs; it is important to know how they are doing

- Tracking patients without drug funding
  - Helping them access programs providing public funding for GIST drugs
- Proposing to Congress that the health law be modified to state that it be mandatory to create and maintain a cancer registry.
  - Proposal accepted, budget approved and assigned
  - A population-based registry for all cancers is to begin in 2020
- Lobbying using reliable information regarding GIST costs and treatments.
  - Using Registry data, it was shown that patients who don't have access to GIST drugs have worse outcomes and that it is more less expensive to use GISTS drugs than to have multiple surgeries.
  - Partial approval obtained to support GIST drug therapies within the public health system.

Summary

Being in the right place at the right time and being very stubborn are all very important in making things happen.

LRG Platforms Update

Denisse Montoya
LRG Patient Registry Director

Pete Knox
LRG Senior Director, Research

The LRG hosts the largest GIST registry in the world with over 1900 patients from more than 67 countries. It is an ongoing research study where GIST patients and caregivers volunteer their information regarding GIST. Information is used to understand the natural history of GIST, treatment outcomes, and to help accelerate research with our Real World Evidence Data.

It is estimated that only 15-20% of GIST patients nationwide have mutational testing performed. By contrast 52% of LRG Patient Registry members know their mutation.

The LRG has used real world data from the registry to help change pathology guidelines as well as guide patients to get as much information about their disease to discuss with their physician. The LRG continues to encourage global advocates to collect data and use it to help shape policies in their respective countries.

SideEQ is a platform that allows users to track their disease, medications, and side effects, and see how they impact quality of life. It also allows for viewing and posting of tips. The platform enables us to collect data that will contribute to personalized side effect management.

The objective is to help patients live longer and improve their quality of life. By making side effect management more personalized, we can get closer to this goal. Global advocates were encouraged to get their patient communities

Understanding the Promises and Limitations of Real World Evidence

Lucinda S. Orsini, DPM, MPH

ISPOR

Real world data (RWD) gives us information that clinical trials cannot provide as clinical trial data is under controlled conditions with a narrowly defined population.

Real world data and real world evidence (RWE) comes from broader populations, under uncontrolled conditions, over the long term, versus all current standards of care. Patients do not always report side effects to doctors as they are afraid to be taken off the medication. RWD helps us understand how the patient is feeling on the med and gives us a better sense of patient perspective.

RWD and RWE are the principal tools patient advocates have to achieve their goals. Regulatory decision making is starting to use RWE to support decision making on treatments.

We can have a great advocacy project, but if we don´t justify it with data, and real world data, it is not worth submitting it.

To be heard when advocating for the "rights" of the patients, we need to know who the patients are, where they are, and how do they cope, not only with the side effects of their treatments, but also with quality of life and the costs involved. That is--how they are living in the real world. This is valuable information or real data that key decision makers need to know to evaluate our demands or proposals.

Challenges

There are challenges with RWD as data comes from a lot of different places and questions need to be asked if the data is reliable and trustworthy.

Dr. Orsini summarizes these challenges in RWE:

- Bias and confounding factors
- Incomplete data or data gaps
- Data mining or data dredging -re-examining datasets to generate new information (RWE is vulnerable to manipulation via repeated analyses)
- Access to data – data sharing is not common in the US and privacy regulations make it difficult to link patients across data sets
- Universally accepted methods are needed to address the above and analyze RWE

And as there is a lot of promise in RWD with the rise of artificial intelligence and large data sets, we need to be prepared.

Dr. Orsini´s recommendations were:

- Know the strengths and challenges associated with RWE
- Design rigorous data collection and analysis plans
- Be transparent as possible about what was done with RWD and how it was analyzed.

Conclusion

In summary, global advocates learned about the latest clinical and lab-based research updates and walso gained insight on the power of real world evidence and how it can be applied in each of their countries.

The group left energized and unified with a renewed excitement to continue the dialogue on how to bring information to light in these changing times and how we can support one another with these efforts.

Agenda

Wednesday May 8

Time	Presentation/Activity
During the day	Arrival of Participants
18:00	Dinner at BRIO Tuscan Grille Meet in Hotel Lobby at 5:30 pm to take the hotel shuttle to restaurant

Thursday May 9

Time	Presentation/Activity
08:00	Breakfast in Fairfield meeting room (Lobby Level) **Registration**
08:55	**Official Start of Conference** Welcome & Thank You to Sponsors *Norman J. Scherzer, Executive Director* *Sara Rothschild, Vice President of Program Services, The Life Raft Group*
09:00 – 09:30	GIST Research Updates and Future Direction of Research *Dr. Ping Chi, Memorial Sloan Kettering Cancer Center* *Moderator: David Josephy*
09:30 – 10:00	GIST Treatment Updates *Dr. Ciara Kelly, Memorial Sloan Kettering Cancer Center* *Moderator: David Josephy*
10:00 – 10:30	Innovative Approaches to Prolong Survival: Case Studies *Dr. Ping Chi, Dr. Ciara Kelly, Dr. Albiruni Razak, and Dr. Jason Sicklick* *Moderator: David Josephy*
10:30 – 10:45	*Break*
10:45 – 11:15	Rare Subtypes *Dr. Jason Sicklick, University of California San Diego* *Moderator: Sara Rothschild*
11:15 – 12:00	Pediatric & SDH-Deficient GIST Consortium Update: A Review with Experts & Advocates *Facilitators: Sara Rothschild, Denisse Montoya, Jayne Bressington, Becky Owens, Dr. Jason Sicklick*
12:00 – 13:00	*Lunch*

Thursday May 8
continued

Time	Presentation/Activity
13:00 – 13:15	Understanding the Concept of "Precision Oncology" in patient-friendly language *Dr. Jason Sicklick, University of California San Diego* *Moderator: Sara Rothschild*
13:15 – 13:30	Precision Oncology: Opportunities & Challenges from a Patient Advocacy Perspective *Pete Knox, Senior Director of Research, The Life Raft Group* *Moderator: Sara Rothschild*
13:30 – 13:45	The Role of ctDNA in GIST *Dr. Ciara Kelly, Memorial Sloan Kettering Cancer Center* *Moderator: Sara Rothschild*
13:45 – 14:15	Bridging the Gap between Molecular Testing and the Patient & Physician Communities *Sue-Ann Woo, Foundation Medicine* *Moderator: Pete Knox*
14:15 – 14:45	Group Discussion on the Challenges of Precision Oncology in a Global Context *Facilitator: Sue-Ann Woo, Foundation Medicine* *Moderator: Pete Knox*
14:45 – 15:00	*Break (Coffee in back of meeting room during discussions)*
14:45–15:15	Interventional Radiology Approaches to Treat Recurrent GIST *Dr. Joseph Erinjeri, Memorial Sloan Kettering Cancer Center* *Moderator: Sara Rothschild*
15:15 – 15:45	Broad Analysis of Clinical Trials *Dr. Albiruni R Abdul Razak* *Princess Margaret Cancer Centre and Mount Sinai Hospital, Toronto* *Moderator: Sara Rothschild*
18:00	Dinner at Hudson Table Meet in Hotel Lobby at 4:30 pm to take transportation to restaurant

Friday May 10

Time	Presentation/Activity
08:00	*Breakfast in Fairfield Meeting Room (Lobby Level)*
09:00 – 10:00	RWE in Action *Piga Fernández, Fundación GIST Chile* *Rodrigo Salas, Fundación GIST México* *Moderator: Malcolm Sutherland*
10:00 – 10:30	LRG Platforms Update *Denisse Montoya, Patient Registry Director* *Pete Knox, Senior Director of Research* *The Life Raft Group* *Moderator: Malcolm Sutherland*
10:45 – 11:15	*Break*
10:30 – 10:45	Understanding the Promises and Limitations of Real World Evidence *Lucinda S. Orsini, DPM, MPH* *ISPOR (the professional society for health economics and outcomes research)* *Moderator: Piga Fernández*
10:45 – 11:15	Group Discussion on Different Approaches to Understanding RWE in Different Countries *Facilitators: Lucinda S. Orsini, ISPOR* *Pete Knox, Senior Director of Research, The Life Raft Group* *Moderator: Piga Fernández*
12:00 – 13:00	*Lunch*
Departures	

Participants

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