Clinical Trials

Dejka M. Araujo, MD
Associate Professor
Dept. of Sarcoma Medical Oncology
The University of Texas,
M. D. Anderson Cancer Center

Connective Tissue Oncology Society

SARc
Sarcoma Alliance for Research through Collaboration
GIST Overview

- GIST have an incidence of 3-6,000 annually and a prevalence of ~40,000 individuals
- 0.2% of all GI tumors, but 80% of GI sarcomas
- Highest incidence in the 40-60 year age group
- Similar male/female incidence
- Clinical presentation is variable
  - Pain, hemorrhage, anemia, anorexia, nausea, perforation
  - May be asymptomatic

GIST Overview

GIST may occur anywhere along the GI tract or elsewhere in the abdomen or retroperitoneum.

- 60% Stomach
- 25% Small intestine
- 8% Esophagus
- 5% Colon/Rectum
- 8% Other (mesentery, retroperitoneum)

Major sites of GIST metastases:
- Liver
- Peritoneum
- Bone
- Lung

## GIST: Chemotherapy Trials

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Number of Patients</th>
<th>Partial Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOX + DTIC</td>
<td>43</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>DOX + DTIC +/- IF</td>
<td>60</td>
<td>10 (15%)</td>
</tr>
<tr>
<td>IF + VP-16</td>
<td>10</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>15</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>17</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Liposomal DOX</td>
<td>15</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>DOX</td>
<td>12</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>DOX or docetaxel</td>
<td>9</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>High-dose IF</td>
<td>26</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>EPI + IF</td>
<td>13</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Various</td>
<td>40</td>
<td>4 (10%)</td>
</tr>
<tr>
<td>DTIC/MMC/DOX/</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDDP/GM–CSF</td>
<td>21</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Temozolamide</td>
<td>19</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>280</td>
<td>19 (6.8%)</td>
</tr>
</tbody>
</table>
GIST: Therapy

- KIT is expressed on GIST cells
- Gene mutation in most cases
  - KIT: 80%-85%
  - PDGFRA: 5%-7%
  - Wild Type: 12%
- Gene mutation results in constitutively activated receptor tyrosine kinase activity
- Imatinib is effective in CML

Marked Biologic Response Revealed by PET Scan

Multiple liver and upper abdominal A marked decrease in FDG uptake
18FDG-accumulating metastases 4 weeks after starting imatinib mesylate.

Kit Receptor Structure

- Extracellular Domain (exon 9, 10.2%)
- Juxtamembrane Domain (exon 11, 66.1%)
- Tyrosine Kinase Domain I (exon 13/14, 1.2%)
- Tyrosine Kinase Domain II (exon 17, 0.6%)

★ = common mutation site
Kit Receptor Phenotype

ADP + P → ATP

Proliferation
Survival
Adhesion
Invasion
Metastasis
Angiogenesis
Imatinib Mesylate

- Rational drug design
  - 2-phenylamino pyrimidine
  - Based on structure of ATP binding site
  - Highly water soluble
  - Oral bioavailability

Formula: $\text{C}_{30}\text{H}_{35}\text{N}_7\text{SO}_4$

MW: 589.7

Inhibitor of selective tyrosine kinases
  - bcr-abl
  - PDGF-R
  - c-kit

Potent ($\text{IC}_{50} \approx 0.1\mu\text{M}$)
Kit Receptor Phenotype

Proliferation
Survival
Adhesion
Invasion
Metastasis
Angiogenesis

= imatinib contact point
Low KIT Expression Correlates With Benefit From Imatinib

Chirieac, Trent. Cancer 2006
Apoptosis After Imatinib (5 DAYS)

Baseline

5 days post-imatinib
Progression-free Survival By Imatinib Dose

*Kit Exon 9 Mutation*
A Clinical Trial is a Scientific Study in Humans
A Clinical Trial Must Be Ethically and Scientifically Sound
A Clinical Trial Should Be Ethically and Scientifically Sound, While Providing a Therapeutic Option For Patients
Clinical Trial Elements

- Objectives
- Background
- Patient Eligibility
- Pretreatment Evaluation
- Treatment Plan
- Evaluation During and after Treatment
- Criteria for Response
- Criteria for Removal from Study
- Laboratory Correlates
- Statistical Considerations
- Informed Consent
What Are The Objectives of The Clinical Trial?
Objectives

- **Phase I**
  - To determine maximum tolerated dose
  - To assess safety
  - To assess efficacy

- **Phase II**
  - To assess efficacy
  - To assess safety
  - Laboratory Correlates

- **Phase III**
  - To assess small differences in efficacy between two therapies (drug, dose, formulation, BSC)
Maximum Tolerated Dose

- Highest dosage of a drug, drug combination or other treatment modality that patients can safely tolerate. Usually determined by Phase I Trial.

- The dosage level below the level of DLT is then defined as the maximum tolerated dose (MTD).

- MTD: Appearance of side effects during treatment that are severe enough to prevent further increase in dosage or strength of treatment agent, or to prevent continuation of treatment at any dosage level.
Background

- Provide an overview of the disease and the drug.
- Why are the objectives important?
- How will this improve patient care?
- What are the risks and benefits to the patients?
Phase II Study Design

- Patient population
- Selection of agent(s)
- Dose
- Definition of endpoints
- Statistical design
Eligibility Criteria

Selection of Patients

- Patient population
  - Type of cancer
  - Prior therapy
  - Stage of disease
  - Presence of drug target
Eligibility Criteria

Selection of Patients

- Select patients who have progressing disease
- Should not be overly strict on exclusion criteria
  - Prior therapy
  - Prior cancer history
Selection of Study Drug

- Phase II studies in advanced GIST
  - Perifosine (AKT/MapK/p21 inhibitor) + Imatinib
  - Nilotinib (Tasigna): Kit and Abl inhibitor
  - HSP90 inhibitor vs. Placebo (randomized)
Imatinib 400mg vs 800mg
Time to Progression on Crossover
Clinical Trial Evaluations

Measuring Efficacy

- Pre-treatment
  - Baseline measurement
- During Treatment
  - Response assessment (same method as baseline)
  - Survival
- Post-treatment
  - “on study” until event
Phase II Study

Design

- Endpoints
  - Response rate
  - Time to progression
  - Progression Free Survival (PFS)
  - Overall Survival (OS)
  - Improved Quality of Life
Progression Free Survival (PFS)

- Advantage over OS
  - PFS can reflect tumor growth and be assessed before the determination of a survival benefit
  - PFS is not confounded by subsequent therapy or crossover
  - Smaller sample size and shorter follow-up necessary compared with survival studies
  - Measurement of stable disease included
Temozolamide in GIST

Overall Survival

TTP 2 months

OS (28 months)

Trent et al, Cancer 2003
Phase II Study

Design

- Definition of response
  - Clinical
  - Radiographic
  - Histological
  - Molecular
  - Improved Quality of Life
CT Scan Results

Jun 27, 2000

Before Imatinib

Oct 4, 2000

After Imatinib
Effects of Imatinib on GIST: CT and PET findings
Response

Pre-Imatinib

Post-Imatinib (8 weeks therapy)
## Effect of Imatinib on Vascularity

<table>
<thead>
<tr>
<th>Perfusion Parameter</th>
<th>Pre-Imatinib</th>
<th>Post-Imatinib</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BF (mL/100g/min)</td>
<td>36.84</td>
<td>24.55</td>
<td>0.017</td>
</tr>
<tr>
<td>BV (mL)</td>
<td>3.90</td>
<td>2.84</td>
<td>0.005</td>
</tr>
<tr>
<td>MTT (s)</td>
<td>9.47</td>
<td>9.96</td>
<td>0.26</td>
</tr>
</tbody>
</table>
Toxicities

What are grade 1, 2, 3, and 4 toxicities:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL
Toxicities Continued

- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL
Toxicities Continued

- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.
Phase III Studies: Control Arm

- Phase III trials are designed to demonstrate the potential advantages of a new therapy over other therapies already on the market.

- Why do Phase I and II studies not have a control arm?
  - Phase I – Focus is safety of the new drug.
  - Phase II – Some do but cost can be an issue.
Statistical Considerations

Study Design
Statistical Considerations

- **Power:** The *power* of a *statistical test* is the probability that the test will reject the *null hypothesis* when the null hypothesis is false (i.e. that it will not make a *Type II error*, or a false negative decision).

- A *type II error*, also known as a *false negative*, occurs when the test fails to reject a false *null hypothesis*. For example, if a null hypothesis states a patient is healthy, and the patient is in fact sick, but the test fails to reject the hypothesis, falsely suggesting that the patient is healthy.
Statistical Considerations

- **Significance**: A result is called statistically significant if it is unlikely to have occurred by chance.
Statistical Considerations

- Allow quantitation of objectives
- Require “clinical considerations”
- When done properly ensure a safe, ethical, and successful study
Confidence Interval: A range around a measurement that conveys how precise the measurement is.

If independent samples are taken repeatedly from the same population, and a confidence interval calculated for each sample, then a certain percentage (confidence level) of the intervals will include the unknown population parameter. Confidence intervals are usually calculated so that this percentage is 95%, but we can produce 90%, 99%, 99.9% (or whatever) confidence intervals for the unknown parameter.
Phase II Study

Design

- Statistical design
  - 1-stage design
  - 2-stage designs
  - Newer Bayesian approaches
Clinical Trials

- Clinically Sound: Ensure the Best Patient Care
- Scientifically rigorous
- Ethical
- Offer a therapy to patients that have no other treatment options
- Learn about the disease and the therapy so that the next Clinical Trial is better.
Why Participate In A Trial?

- No other therapeutic options are available.
- Therapy or testing are free.
- To allow researchers to understand GIST and help future patients.
- Freireich’s Law #6: A good clinical trial offers the best patient care.
Clinical Trials

- A Study to Investigate the Safety and Efficacy of AT13387 (HSP inhibitor), Alone or in Combination With Imatinib, in Patients With GIST (phase II)
- Raf inhibitor – Phase II for Raf mutant GIST
- Pazopanib in Imatinib Refractory or Intolerant Gastrointestinal Stromal Tumors (GIST) (Phase II)
- A Study Evaluating STA-9090 in Patients With Metastatic and/or Unresectable Gastrointestinal Stromal Tumor (GIST) (Phase II)
How To Find a Clinical Trial

- Clinicaltrials.gov
Clinical Trials

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daraupo@mdanderson.org

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