1) Have you or know someone who participated in a clinical trial?

2) Have you had your chordoma genetically analyzed?

3) What does clinical trial mean to you?
When should you participate in a clinical trial?

- A) At time of initial diagnosis
- B) At time of recurrence
- C) At time of metastases (when tumor has spread)
- D) When all known therapies have failed
Two types of trials:

- Non-therapeutic trials: A clinical trial where tumor or blood is collected for research. Also trials of quality of life and other subjective assessments. No treatments are given here.

- Therapeutic trials: New drugs “first-in-man”, new combinations of FDA approved drugs, FDA approved drugs and radiation or new surgical devices.
The Long Path from Idea to Drug

**Full Development**
- Studies in 100-300 Patients (Phase II)
- Candidate Medicine Tested in 3-10,000 Patients (Phase III)
- Clinical Data Analysis
- NDA/MAA

**Registration**
- EU
- USA
- Japan

**Exploratory Development**
- Extenive Safety Studies
- Studies in Healthy Volunteers Phase I
- Early Safety Studies
- Large Amounts of Candidate Medicine Synthesized
- Formulations Developed
- In Vivo Efficacy & Safety
- Project Team and Plans
- Synthesis of Compounds
- Screening

**Project Concept**
- 100 Approaches

**Discovery**
- Complex Targets, Instability, PK, Safety, Efficacy, Selectivity, Synthesis & Manufacture, Commercial Failure is 75% cost of drug

1 New Medicine
- $800MM
- 12-15 yrs

Source: Burrill & Company
Therapeutic trials

- Phase I, if +
- Phase II, if +
- Phase III, if +
- FDA filing
Q2Dx7, 6 hr. I.v. infusion

(3/4 Complete Remission)

- Control (n=4)
- Taxol 20mg/kg (n=4)
Day 25

Drug.

Day 31

Control

Sacrificed on Day 31

Q3Dx1

Q3Dx3

Q3Dx5
Phase I: “First-in-man” or new combinations of FDA approved drugs or drugs + radiation

- New drug that appears to be promising.
- Is the drug safe?
- If safe, what is a safe dose?
- What are the side-effects of the compound?
- How does the body process the drug?
Example of a Phase I trials:

– Any patient with advanced cancer.

– Lung, breast, colon, prostate, ovary, bladder, brain tumors, sarcomas including chordoma

– 30 patients participated
Lung cancer and EGFR inhibitor

Rapid and dramatic response in lung lesions to afatinib-cetuximab combination. Each cycle = 28 days

PRIOR TO Rx

CYCLE 2, DAY 1
Phase II clinical trial: only lung cancer pts

Maximum % Reduction in Target Lesions

Max % Change Target Lesions

PR, SD/PD
Phase III trial: New drug vs placebo

A Progression-free Survival Population

- **Placebo** (N=110)
- **New Drug** (N=114)

P < 0.001

Months since Randomization
CONGRATULATIONS!!

On November 18, 2004, the U.S. Food and Drug Administration approved erlotinib or Tarceva for treatment of patients with lung cancer.
IPASS: Progression-free survival in EGFR-mutation + vs - patients

EGFR mutation-positive
- Gefitinib (n=132)
- Carboplatin/paclitaxel (n=129)
  HR (95% CI) = 0.48 (0.36, 0.64)
  p<0.0001
  No. events gefitinib, 97 (73.5%)
  No. events C/P, 111 (86.0%)

EGFR mutation-negative
- Gefitinib (n=91)
- Carboplatin/paclitaxel (n=85)
  HR (95% CI) = 2.85 (2.05, 3.98)
  p<0.0001
  No. events gefitinib, 88 (96.7%)
  No. events C/P, 70 (82.4%)

At risk:
- Gefitinib 132
- C/P 129
- 108
- 71
- 31
- 11
- 3
- 0

- Gefitinib 91
- C/P 85
- 21
- 7
- 2
- 1
- 0

Treatment by subgroup interaction test, p<0.0001

Incidence of EGFR mutation: 261/437 = 59.7%

Mok et al 2008
Different types of Lung Cancer

- **Unknown**: 36.4%
- **KRAS**: 25%
- **EGFR**: 23%
- **NRAS**: 0.2%
- **MAP2K1**: 0.4%
- **ERBB2**: 1%
- **MET**: 2%
- **PIK3CA**: 3%
- **BRAF**: 3%
- **EML4-ALK**: 6%
Q2Dx7, 6 hr. i.v. infusion

(3/4 Complete Remission)

- Control (n=4)
- Taxol 20mg/kg (n=4)
Phase I trial:

-- failed in humans.
35 yo male w/ artery and nerve entrapment. Heavily pre-treated. Forequarter amputation only surgical option.

10/28/08: Post Gadolinium (upper extremity)  
1/12/10: Post Gadolinium

SHRINKAGE. On Therapy: 25+ mo
Shrinkage Rates

Individual desmoid patients

Tumor shrinkage: 25%
Stable Disease: 70%
A multicenter, Phase III, double blind, randomized, placebo-controlled trial of sorafenib in desmoid tumors or aggressive fibromatosis.

Study Chair/PI: Mrinal Gounder
HUMANS ARE THE BEST MODEL OF HUMAN DISEASES

– Larry Baker, M.D.
Imatinib Mesylate in Chordoma

Paolo G. Casali, M.D.1
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Silvia Stacchetti, M.D.3
Elena Tambarini, Ph.D.2
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Raffaele Bertieri, M.D.9
Rossella Bertulli, M.D.10
Maurizio Colecchia, M.D.11
Elena Fumagalli, M.D.1
Angela Greco, Ph.D.12
Federica Grosso, M.D.1
Patrizia Olimi, M.D.13
Marco A. Pierotti, Ph.D.14,13
Silvana Pilotti, M.D.7

BACKGROUND. To the authors’ knowledge, no effective medical therapy currently is available for advanced chordoma. Imatinib mesylate is a tyrosine kinase inhibitor targeting platelet-derived growth factor receptor-β (PDGFRB), BCR-ABL, and KIT.

METHODS. Six patients with advanced chordoma were treated with imatinib mesylate at a dose of 800 mg daily. In all patients, the tumor was found to be positive for PDGFRB, and in four patients PDGFRB was shown to be hyperphosphorylated expressed.

RESULTS. After a treatment period of ≥6 months, a decrease in contrast enhancement (MRI) and a decrease in glucose uptake were detected. Similar signs on MRI an patients, who had a shorter treatment period removed from therapy and then was read with regard to tumor response assessed therapy, an over decrease in tumor de patient. In four of five symptomatic observed early in the course of treatment, with a sizeable, mostly liquefied mass. An unrelated causes. The remaining patient follow-up.

CONCLUSIONS. Imatinib mesylate has 1 patients with chordoma. This activity in FRB. Tumor response manifests through in patients with gastrointestinal stromal treated therapy, but evolves more slowly, pattern of tumor response in chordoma in the presence of significant local disease.

© 2004 American Cancer Society

KEYWORDS: chordoma, imatinib mesylate, tyrosine kinase inhibitor, platelet-derived growth factor receptor-β (PDGFRB), response.
Phase II Study of Imatinib in Advanced Chordoma
Silvia Stacchiotti, Alessandro Longhi, Virginia Ferroni, Giancarlo Cognolati, Alessandra Condamine, Roger Augé, Annalisa Barozza, Ilaria Fanciulli, Silvia Pilotti, Antonio Mecca, Concetta Greggio, Alessandro Grinch, Marco Amori, Valentina Vittale, and Paolo Giovanni Censi


ABSTRACT

Purpose
To explore the antitumor activity of imatinib in patients with advanced platelet-derived growth factor β (PDGFRB)-positive chordoma.

Patients and Methods
A prospective, single-arm, phase II study conducted from December 2001 to April 2009. Inclusion criteria included patients with advanced PDGFRB- and/or PDGFRB-positive chordomas 18 years of age, or greater, with measurable disease. Exclusion criteria included previous radiotherapy or surgery, and active neoplastic etiology of the disease.

Results
Among 60 patients enrolled, the overall response rate (ORR) was 48.3%, with a median overall survival time of 19.8 months. The median time to progression was 9.6 months. The most common adverse events were dermatitis, fatigue, nausea, and anemia.

Conclusion
Imatinib is an active treatment for patients with advanced chordoma and is worth further investigation.

J Clin Oncol 30, © 2012 by American Society of Clinical Oncology

INTRODUCTION
Chordoma is a rare tumor. After surgery, local recurrence is more than 50% of cases, with a risk of patients receiving adjuvant therapy. The study design is a phase II, single-arm, open-label, single-center study. The primary endpoint is the overall response rate (ORR) and secondary endpoints include time to progression (TTP), overall survival (OS), and adverse events. The study was conducted at the University of Turin, Italy, and included patients with advanced chordoma who had not responded to prior treatment. The study was sponsored by the European Organization for Research and Treatment of Cancer (EORTC) and the Italian Chordoma Society.
Resistance to Imatinib: mTOR inhibitors

Response to imatinib plus sirolimus in advanced chordoma


Department of Internal Medicine, Department of Oncology and Hematology, Department of Oncology, Department of Surgery, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy

Background: Imatinib (400 mg/die) is active in advanced chordoma. The evidence of upregulation of the downstream mTOR pathway and its potential role in resistance to imatinib has been recently shown. Stacchiotti et al., 2009

Results: We report on the use of mTOR inhibitors in advanced chordoma. All patients received sirolimus 2 mg/die plus imatinib 400 mg/die, with a median of 4 months of follow-up. All patients experienced disease stabilization or improvement in their disease, with a partial response in one patient. The median progression-free survival for all patients was 4 months. Markers of mTOR pathway inhibition were observed in all patients, including phosphorylation of p70S6K and S6.

Discussion: The combination of imatinib and sirolimus may be an effective treatment for advanced chordoma, providing clinical stability and disease control.

Key words: chordoma, mTOR, sirolimus, rapamycin, sarcoma, sirolimus

Introduction

Chordoma is a rare bone tumor with a high incidence of local recurrence and a high rate of distant metastases. It is often associated with pain and neurological deficits. The disease is characterized by the overexpression of transcription factors, including SOX9 and Wnt signaling pathway components.

The mTOR pathway is implicated in the pathogenesis of chordoma, and inhibitors of this pathway may be effective in treating this disease.

References


Potential targets in Chordoma

- PDGFR
- EGFR
- VEGF
- mTOR
- Hedgehog
- CDK2NA/B
- Hsp90
- PTEN
- Immunotherapy
Potential targets in Chordoma

- PDGFR – FDA
- EGFR – FDA
- VEGF – FDA
- mTOR – FDA
- Hedgehog – FDA
- CDK2NA/B
- Hsp90
- PTEN
- Immunotherapy – FDA
Navigating Clinical trials

- Must be taken care in a tertiary care sarcoma center with experience in chordoma.

- Make sure you meet a surgeon, radiation oncologist and a medical oncologist: multi-disciplinary approach.

- Off-label use of FDA approved drugs

- Phase I clinical trials or Phase II sarcoma trials.  www.clinicaltrials.gov
Navigating Clinical trials

- Clinical trials in chordoma are rare.

- Clinical trials in sarcoma are plenty and ask your sarcoma medical oncologist about this.
When to join a clinical trial?

<table>
<thead>
<tr>
<th>Stage</th>
<th>Event</th>
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<tr>
<td>Diagnosis</td>
<td>S R</td>
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<td>Cure!</td>
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Memorial Sloan-Kettering paradigm

- **Genetic analysis of your tumor**
- **Phase I/II or off label FDA**
- **Medical Oncology**
- **S + R + M**
- **Cure!**
- **S + R + M**
- **Cure!**
- **S + R + M**
- **Cure!**
- **S + R + M**
- **Cure!**
- **S + R + M**
- **Cure!**
- **S + R + M**
- **Cure!**

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Memorial Sloan-Kettering Cancer Center
Clinical trials at MSKCC

- **Hedgehog** – Phase II
- CDK2NA/B – Phase I
- Hsp90 – Phase I
- PTEN/P13K – Phase I
- Immunotherapy – Phase I

- PDGFR – off label
- EGFR – off label
- VEGF – off label
When should you participate in a clinical trial?  

- A) At time of initial diagnosis
- B) At time of recurrence
- C) At time of metastases (when tumor has spread)
- D) When all known therapies have failed

*National Cancer Institute guidelines*
“There is only one thing that makes a dream impossible to achieve: the fear of failure.”
— Paulo Coelho, *The Alchemist*

We must act, knowing that our work will be imperfect.

Barack Obama