From molecular biology to Lazarus responses

Rembrant, approximately in 1630

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The “Lazarus Response” in Treatment-Naïve, Poor Performance Status Patients With Non–Small-Cell Lung Cancer and Epidermal Growth Factor Receptor Mutation

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BACKGROUND: PERFORMANCE STATUS 2 PATIENTS WITH NON-SMALL-CELL LUNG CANCER

In a series of more than 500 non–small-cell lung cancer (NSCLC)
Lazarus responses may be durable

A patient with many bulky GIST metastases at presentation

The same patient with ongoing response; 4 years on imatinib
Survival prior to the era of targeted therapies

• Patients with metastatic disease had median survival of only 10 to 20 months in the 1990’s

• Conventional chemotherapy had little efficacy

Gastrointestinal stromal tumour (GIST)

• The first solid tumour where a tyrosine kinase inhibitor proved highly effective (imatinib)

The most common type of soft tissue sarcoma

Annual incidence 10 cases per million

GISTs frequently give rise to metastases

- 10-20% of patients present with distant metastases
- 40% of local GISTs give rise to metastases during follow-up

Mutations in *KIT* oncogene discovered

- Hirota et al. found activating *KIT* mutations in GIST at Osaka University in 1998\(^1\)
- *KIT* encodes KIT receptor tyrosine kinase (ligand, stem cell factor)

Prof. Seiichi Hirota

STI-571 (inhibitor of BCR-ABL and KIT) found highly effective for chronic myeloid leukemia
Brief Report

Effect of the Tyrosine Kinase Inhibitor STI571 in a Patient with a Metastatic Gastrointestinal Stromal Tumor

Heikki Joensuu, M.D., Peter J. Roberts, M.D., Maarit Sarlomo-Rikala, M.D., Leif C. Andersson, M.D., Pekka Tervahartiala, M.D., David Tuveson, M.D., Ph.D., Sandra L. Silberman, M.D., Ph.D., Renaud Capdeville, M.D., Sasa Dimitrijevic, Ph.D., Brian Druker, M.D., and George D. Demetri, M.D.

Phosphatidylinositol 3-kinase and mitogen-activated protein kinases. Gastrointestinal stromal tumors are notoriously unresponsive to cancer chemotherapy, and there is no effective therapy for advanced, metastatic disease.8

We used STI571 (Glivec, Novartis, Basel, Switzerland),7 an inhibitor of the tyrosine kinase activity of c-kit, in a patient with a gastrointestinal stromal tumor.

CASE REPORT

In October 1996, a 50-year-old, previously healthy woman presented with mild abdominal discomfort and a large mass in the upper abdomen. Two tumors, 6.5 and 10 cm in diameter, were removed from the stomach by proximal gastric resection, and the greater omentum and mesocolic peritoneum were removed because of the presence of multiple metastatic nodules 1 to 2 mm in diameter. Histologic examination of the specimens revealed more than 20 cells undergoing mitoses per 10 high-power fields and identified the masses as a gastrointestinal stromal tumor. The diagnosis was confirmed by immunostaining for CD117, and a c-kit mutation consisting of a deletion of 15 bp from exon 11 was de-
Imatinib (STI-571) proved to be the first highly effective agent for advanced GIST

The B2222 (the U.S. – Finland trial)
• 120 (85.7%) out of the 140 evaluable patients responded or had stable disease
• Most responses were durable
• Therapy was generally well tolerated

Demetri GD et al.
N Engl J Med
A randomised trial comparing imatinib to chemotherapy was never conducted

- Comparisons with historical data suggested substantially improved outcome in advanced GIST

Comparison of 2 imatinib groups with historical GIST controls treated with doxorubicin-based chemotherapy (from the EORTC database)

Up to 30% of patients with advanced GIST survive for ≥10 years in the era of targeted therapy

<table>
<thead>
<tr>
<th>Series</th>
<th>Overall survival (OS) estimate</th>
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<tbody>
<tr>
<td>B2222 trial(^1)</td>
<td>9-year OS 35%*</td>
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<tr>
<td>S0033 trial(^2)</td>
<td>10-year OS 22%</td>
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<tr>
<td>Helsinki series</td>
<td>10-year OS 29%</td>
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</table>

*58% of patients with the tumour bulk within the lowest quartile survived for 9 years

• A small tumour bulk identified as a favourable prognostic factor for long-term survival

\(^1\) von Mehren et al. JCO 2011; 29:609s; \(^2\) Demetri et al. JCO 2014; 32:670s
Secondary *KIT* mutations are the most important cause for treatment failure

- Interfere with imatinib binding to the kinase
- Most frequent in *KIT* exons 13, 14 and 17

Heinrich MC et al. JCO 2006;24:4764-74
Secondary mutations leading to drug resistance

• May occur by chance
• The time to drug resistance likely the shorter the greater the number of tumour cells
  – Early and long enough TKI treatment leads to survival benefits?
Adjuvant imatinib in GIST: Randomised trials

- ACOSOG Z9001\textsuperscript{1,2}
  - 1 year of imatinib vs. placebo
- EORTC 62024\textsuperscript{3}
  - 2 years of imatinib vs. observation
- SSG/AIO XVIII\textsuperscript{4}
  - 1 vs. 3 years of imatinib

ACOSOG, American College of Surgeons Oncology Group
EORTC, European Organisation for Research and Treatment of Cancer
SSG, Scandinavian Sarcoma Group
AIO, Arbeitsgemeinschaft Internistische Onkologie

\textsuperscript{1}DeMatteo et al. Lancet 2009; 373:1097-1104; \textsuperscript{2}Corless et al. JCO 2014; 32:1563-70; \textsuperscript{3}Casali et al. JCO 2013; 31:632s; \textsuperscript{4}Joensuu et al. JAMA 2012; 307:1265-72.
ACOSOG Z9001 trial

- Patients had GIST ≥3 cm in size (low or high risk tumour)
- RFS favoured imatinib, but no overall survival benefit

Median follow-up time
74 months

**SSGXVIII/AIO trial in high-risk GIST**

**Recurrence-free and alive (%)**

<table>
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<tr>
<th>Years since randomisation</th>
<th>36 months of imatinib</th>
<th>12 months of imatinib</th>
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<tr>
<td>0</td>
<td>198</td>
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<tr>
<td>1</td>
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<td>177</td>
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<td>10</td>
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<tr>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Number at risk

- 36 months of imatinib: 198, 184, 173, 133, 82, 39, 8, 0
- 12 months of imatinib: 199, 177, 137, 88, 49, 27, 10, 0

Hazard ratio 0.46 (95% CI 0.32-0.65)

*P* < 0.0001

Median follow-up time 54 months

SSGXVIII/AIO trial: Overall survival

Hazard ratio 0.45 (95% CI 0.22-0.89)

P = 0.019

Number at risk

36 Months of imatinib
- 198
- 192
- 184
- 152
- 100
- 56
- 13
- 0

12 Months of imatinib
- 199
- 188
- 176
- 140
- 87
- 46
- 20
- 0
Next steps

• Advanced setting
  – Novel agents with improved inhibition of KIT and PDGFRA kinases
  – Combinations of targeted agents
  – Rotation of targeted agents

• Adjuvant setting
  – Longer (> 3 years) adjuvant treatments will be tested
Cancer research can produce magnificent results

- Even patients with bulky GIST metastases may now survive for many years
- GIST recurrence can be postponed/prevented in the adjuvant setting
Thank you!

Scandinavian Sarcoma Group

Finnish Breast Cancer Group

AIO
Arbeitsgemeinschaft Internistische Onkologie

Patients