Nilotinib Compassionate Use in Advanced GIST: A Retrospective Analysis

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INTRODUCTION

GIST

• GIST are rare, mesenchymal neoplasms that arise from the interstitial cells of Cajal or their precursors
• GIST express the CD117 antigen – an epitope of a TK receptor
• Pathogenetic mutations (c.1–11) that lead to constitutively activated, mutant receptor (KIT, PDGFRA) oncogenic signaling occur through the TK of the mutated receptor
• This has consistently improved the outcome of advanced GIST
  – First-line imatinib: OS 60–120 months, PFS 15–36 months1
  – Second-line imatinib: OS 27–72 weeks, PFS 14–24 months.2

GIST (formerly known as GIST) are rare, mesenchymal neoplasms that arise from the interstitial cells of Cajal or their precursors. They express the CD117 antigen, an epitope of a TK receptor. Pathogenetic mutations lead to constitutively activated, mutant receptor (KIT, PDGFRA) oncogenic signaling through the TK of the mutated receptor. This has consistently improved the outcome of advanced GIST. First-line imatinib leads to OS 60–120 months, PFS 15–36 months. Second-line imatinib shows OS 27–72 weeks, PFS 14–24 months.

METHODS

Study Design

• Patients during all available therapeutic options had access to nilotinib on a compassionate-use program. The starting dose of nilotinib was 400 mg twice daily with at least 1 h between doses for reduction to 400 mg every 48 h (day 8) for toxicity.
• Retrospective analysis of continuous enrollment of all patients treated with nilotinib compassionate use in Europe.
• 12 centers in 6 European countries participating; all consecutive patients of each center were included.

Prognostic Stratification

Compassionate care was approved in 60 countries; 23 of those were in Europe (World, number of GIST approvals/request: 365/384).

Europe, number of GIST approvals/request: 156/145

Inclusion Criteria

• Age ≥18 years
• WHO Performance Status 0–2
• Histologically confirmed GIST, unresectable and/or metastatic, not resectable to surgery or combined modality with curative intent
• Failure of all treatment options, including imatinib (up to 800 mg) and sunitinib
• Imatinib, sunitinib, investigational agents discontinued at least 8 days prior to start of nilotinib
• Normal renal function, electrolyte, and dopamine function
• Written informed consent

Exclusion Criteria

• Any investigational drug 6 weeks prior to nilotinib
• Impaired cardiac function
• QT interval prolongation and/or CYP3A4 inhibitors
• Severe and/or uncontrolled concurrent disease that, in the investigator’s opinion, could cause unacceptable risk or compromise compliance
• Pregnancy, breast feeding; no contraception
• Major surgery within 4 weeks or无限了 the last course of surgery
• Major radiotherapy at or within 4 weeks of nilotinib
• Known signing of alcoholic drug abuse
• Unresolved or inability to comply with the treatment protocol

Baseline Patient Characteristics (Table 1)

• All patients had failed imatinib and sunitinib and all other available therapeutic options
• Multimodal status was also determined for nearly half of study patients
• Study patients undergo a range of prior treatments including surgery, investigational agents, and additional

OBJECTIVES OF STUDY

To assess the efficacy of the second-generation TKI, nilotinib, in a compassionate-use program for patients with refractory advanced gastrointestinal stromal tumors, including surgery and investigational agents, and who had failed prior TKI therapy comprised of imatinib and sunitinib.

RESULTS

Safety

Treatment was discontinued in six patients (12%) due to the following reasons:
• Nausea/vomiting
• Arthralgia/arthritis/nausea/vomiting
• Muscle aches/tender/arthralgia
• Chest pain/cardiac
• QT prolongation

CONCLUSIONS

This is the largest series reported to date that assessed the efficacy of nilotinib, a second-generation TKI, in patients with imatinib- and sunitinib-refractory GIST. Nilotinib was well tolerated and displayed clinical activity in this heavily pretreated group of GIST patients.

Clinical benefit (PR+SD) was in 45% of the patients.

Median overall survival (mOS) with nilotinib was 263 days.

These results warrant further investigation of nilotinib in GIST, including its use in first- or second-line treatment.

REFERENCES


Table 1. Prior-Treatment Baseline Characteristics

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of Patients</th>
<th>Kaplan-Meier Survival Percentage (95% CI)</th>
<th>Hazard Ratio of Death (95% CI)</th>
<th>p Value of Log-Rank Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib</td>
<td>156</td>
<td>70% (65-74)</td>
<td>1.00 (0.82-1.22)</td>
<td>0.99</td>
</tr>
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<td>Sunitinib</td>
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REFERENCES


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• Switzerland
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Figure 2. Clinical Benefit in 45% of Patients Treated with Nilotinib

Figure 3. Overall Survival (OS) Since Nilotinib Start