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Nilotinib in the treatment of advanced gastrointestinal stromal tumours resistant to both imatinib and sunitinib

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ABSTRACT

Patients diagnosed with advanced gastrointestinal stromal tumours (GISTs) who are resistant or intolerant to both imatinib and second-line sunitinib have a poor prognosis and few therapeutic options. We evaluated the efficacy of nilotinib, a novel tyrosine kinase inhibitor (TKI) in patients pretreated with imatinib and sunitinib. Fifty-two consecutive patients treated with oral nilotinib, 400 mg twice daily, within the nilotinib compassionate use programme in 12 European cancer centres, were included in this retrospective analysis. Median age was 59 years (range 24–80), and all patients had WHO performance score better than 3. All patients had failed both imatinib and sunitinib pretreatment, either due to progressing GIST (96%) or intolerance (4%). Five patients (10%; 95% confidence interval (CI) 2–18) responded to nilotinib and 19 patients (37%; 95% CI 24–50) achieved a disease stabilisation. Nilotinib was generally well tolerated, but six patients (12%) discontinued treatment due to intolerance. Median progression-free survival of nilotinib treatment was 12 weeks (95% CI 9–15; range 0–104) and median overall survival was 34 weeks (95% CI 3–65; range 2–135). Nilotinib is active in GIST resistant to both imatinib and sunitinib. These results warrant further investigation of nilotinib in GIST.

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1. Introduction

Gastrointestinal stromal tumours (GISTs) arise from the interstitial cells of Cajal or their precursors[1] and are rare mesenchymal neoplasms, with an estimated incidence of 10–20 and a prevalence of 129 per million.[2–4] Median age at diagnosis is 60 years[2,4,5] and many patients have advanced disease at diagnosis, which precludes curative surgery.[6] During the last decade, novel treatment modalities have emerged as a result of an improved understanding of the disease and its molecular mechanisms.[7,8] Pathogenetic mutations encode for a constitutively activated mutant receptor, KIT or platelet-derived growth-factor receptor alpha (PDGFRα) which sustain oncogenic signalling. Tyrosine kinase inhibitors (TKIs), such as imatinib or sunitinib, inhibit the aberrant tyrosine kinase activity of KIT or PDGFRα and thus interrupt oncogenic signalling and further tumour growth.[9]

TKIs have significantly improved the outcome of GIST: imatinib extends the survival of advanced GIST from about 9 months[10] in historical series to nearly 5 years, but resistance to imatinib occurs after a median of 18–24 months of treatment and is the major reason for the need of second and further line treatment.[10–12] Secondary mutations of KIT or PDGFRα, and activation of alternate signalling pathways have been implicated as mechanism of resistance.[9] Sunitinib is the approved and recommended second-line treatment after imatinib progression or intolerance.[13–15] When both imatinib and sunitinib have failed, no established systemic third-line treatment is available.[14,16] One of the promising novel agents under evaluation is nilotinib (formerly AMN107), a second-generation oral TKI, engineered to specifically inhibit KIT, PDGFRα and BCR-ABL.[17] Nilotinib is currently approved for the treatment of chronic and accelerated phase Philadelphia chromosome-positive chronic myelogenous leukaemia in adult patients resistant or intolerant to prior therapy that included imatinib.[18,19] Human GIST cell lines (imatinib-sensitive or -resistant) may be more sensitive to inhibition by nilotinib than imatinib.[20] In one study, 7- to 10-fold greater intracellular concentrations of nilotinib than imatinib were achieved, while inhibitory activity was comparable.[21] Nilotinib monotherapy had clinical activity in a recent phase I study in a cohort of imatinib-resistant/intolerant patients. Eighteen patients received oral nilotinib monotherapy 400 mg twice daily, and 14 achieved disease control (either partial response or stable disease). The median progression-free survival (PFS) was 24 weeks, and the median time on treatment was 27 weeks.[22]

Patients failing both imatinib and sunitinib could receive nilotinib within a compassionate use programme. We report the treatment results of these patients herein.

2. Patients and methods

2.1. Study objectives and design

The primary objective of this retrospective analysis was to assess the efficacy of nilotinib in patients with advanced GIST who had failed prior therapy with both imatinib and sunitinib.

All patients were treated with nilotinib within a compassionate use programme organised by the drug manufacturer (Novartis Basel, Switzerland), open for participation since 25 September, 2005. This programme was reviewed and validated by local ethic committees and authorities according to national and European regulations. A written informed consent was required from all patients before starting nilotinib treatment. Patients aged 18 years or older with a histologically confirmed diagnosis of unresectable or metastatic GIST, after failure, i.e. progression or intolerance, of both imatinib and sunitinib, and a World Health Organisation (WHO) performance score of 2 or less could participate provided that they had normal electrolytes, organ and bone marrow function.

Key exclusion criteria were treatment with any investigational drug or radiotherapy within 4 weeks, major surgery within 2 weeks prior study entry or treatment with any QT-interval prolonging medication or CYP3A4 inhibitors, impaired cardiac function, known ongoing alcohol or drug abuse, pregnancy or breast feeding. Minimal interval between previous treatment and nilotinib was five days. The starting dose of nilotinib was 400 mg twice daily, with the option of a dose reduction to 400 mg once daily in case of intolerance. Nilotinib capsules were swallowed with water 2 h or more after food ingestion, and 1 or more hours before eating again. Safety and tolerability assessments were performed on all patients who received at least one dose of nilotinib and included history, clinical status, blood count, chemistry and electrocardiograms. Adverse events were classified and graded according to the Common Terminology Criteria for Adverse Events version 3.[23] Tumour size assessments with CT or MRI were suggested to be performed at baseline, after the first and second month of treatment and every second month thereafter.

Response was assessed according to RECIST.[24] To avoid any selection bias in this analysis, the participating centres were required to include all their patients treated with nilotinib in the compassionate use programme to this analysis.

2.2. Statistics

All patients who received at least one dose of nilotinib were included in the intention-to-treat population and were assessed for safety, response rates and survival. Progression-free survival was defined as time from start of nilotinib treatment to progression or death from any cause, and overall survival calculated from the date of first nilotinib administration to death.[25] Survival curves were generated according to Kaplan–Meier.[26] SPSS® version 14 (SPSS Inc., Chicago, IL, USA), Statistica® version 4.1 (Statsoft Inc., Tulsa, OK, USA) and GraphPad Prism® version 3 (GraphPad Software Inc., La Jolla, CA, USA) were used for the statistical analysis.

3. Results

3.1. Patients

Fifty-two patients who entered the compassionate use programme from October 2005 to October 2008, were included in this analysis. The study participants were treated in 12 cancer centres located in 6 European countries. One centre contributed 10 patients, three centres 5–7, six centres 3 or 4,

and two centres contributed 1 patient each to the study. The median age at start of nilotinib treatment was 59 years (range 24–80), and median follow-up was 28 weeks (range 2–135 weeks). Baseline characteristics at initial diagnosis are given in Table 1. All except five patients had one or more surgical interventions for GIST in their history (range 0–8). Prior to study entry patients had been treated for a median of 127 weeks (range 8–304 weeks) with imatinib and 23 weeks (range 3–117 weeks) with sunitinib prior to study entry. The starting dose of imatinib was 400 mg/day (escalated usually to 800 mg/day at the time of disease progression), and the dose of sunitinib 50 mg/day (four weeks on/two weeks off). The most common reason for imatinib and sunitinib discontinuation was disease progression (imatinib, 94% and sunitinib, 92% of cases), adverse events in 4% (for both agents), and combined adverse events and disease progression in 2% and 4%, respectively. Four patients had received investigational systemic therapy prior to study entry (two PTK787,[27] one AMG706,[28] one AMG706 followed by imatinib/everolimus[29]).

3.2. *Efficacy*

The median treatment duration was 10 weeks (range 2 days–104 weeks). Six patients (12%) were treated longer than 52 weeks, 15 (29%) longer than 24 weeks, and 21 (40%) longer than 12 weeks. The reasons for nilotinib discontinuation were disease progression in 36 cases (69%), adverse effects in 6 patients (12%), and unspecified in 2 cases (4%). Eight patients (15%) continued with nilotinib at the time of data collection closure (January 2009).

Table 1 – Patient characteristics at initial diagnosis.

Gender	*n* = 52	%
Male	37	71.2
Female	15	28.9
Primary tumour site	*n* = 52	%
Stomach	18	34.6
Small intestine	17	32.7
Colon	2	3.9
Rectum	1	1.9
Peritoneum	2	3.9
Mesenterium	1	1.9
Extraintestinal	3	5.8
Unknown	8	15.4
Stage	*n* = 52	%
Localised	17	32.7
Advanced	7	13.5
Metastatic	26	50
Unknown	2	3.9
Primary mutation	*n* = 28	%
KIT Exon 11	15	53.6
Wild type	4	14.3
KIT Exon 9	3	10.7
KIT Exon 13	1	3.6
KIT Exon 17	1	3.6
KIT Exon 11 and 17	3	10.7
PDGFRα Exon 18 D842 V	1	3.6

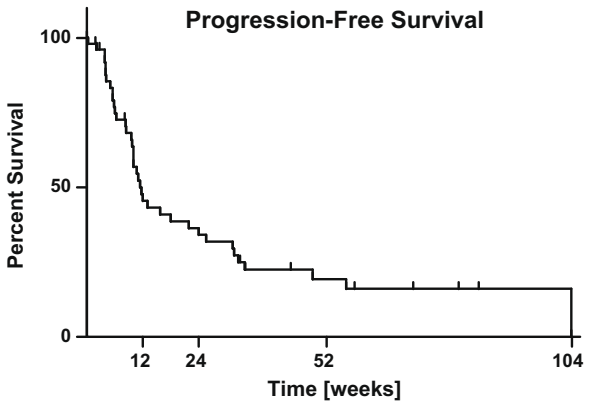

Fig. 1 – Progression-free survival since start of nilotinib treatment (Kaplan–Meier).

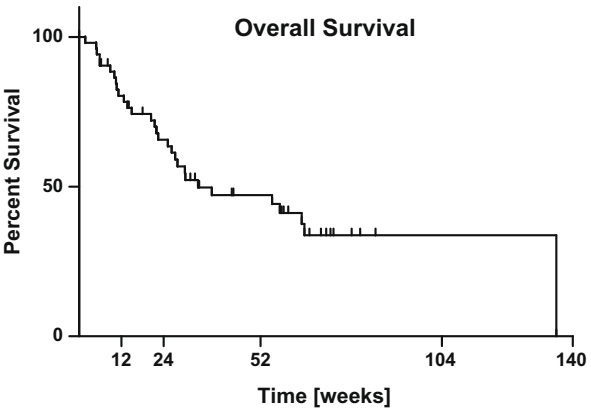

Fig. 2 – Overall survival since start of nilotinib treatment (Kaplan–Meier).

47 of the 52 patients were evaluable for response, four patients stopped treatment early due to toxicity and response data were missing for one patient. Five patients (10%; 95% confidence interval (CI) 2–18) responded to nilotinib, and 19 (37%; 95% CI 24–50) had disease stabilisation. One of the 5 responses was classified as a complete and 4 as a partial response. All patients have been evaluated for survival. The median PFS was 12 weeks (95% CI 9–15; range 2 days–104 weeks) and the median overall survival 34 weeks (95% CI 3–65; range 2–135 weeks) (Figs. 1 and 2). The median survival as calculated from the date of the first diagnosis of GIST to the last date of follow-up or death was 72 months.

The primary mutation did not influence survival (data not shown), but numbers per group were small (Table 1). Age at diagnosis, the primary tumour site, number of surgical interventions, duration of prior TKI treatments, or the participating centre were statistically not significantly associated with response to treatment or survival.

3.3. *Tolerability*

In general, most patients tolerated nilotinib well, and no dose reductions were done for toxicity. However, 6 (12%) patients discontinued treatment due to grade 2 or 3 adverse effects;

2 due to anorexia (one grade 2, one grade 3), one to diarrhoea (grade 2), one to abdominal pain (grade 3), one to cardiac ischaemia (grade 3), and one due to QT prolongation (grade 3).

4. Discussion

Patients diagnosed with advanced GIST who no longer benefit from imatinib or sunitinib generally have a poor outcome. They often receive best supportive care only, may be rechallenged with imatinib, or may be enrolled in clinical trials or compassionate use programmes.[16] Smaller phase I/II trials or retrospective series have suggested efficacy of nilotinib[22], sorafenib[33,34] and IPI-504[35] after imatinib and/or sunitinib failure.

In this retrospective analysis we investigated whether such patients might benefit from treatment with nilotinib. We found that a minority responded to nilotinib, a third achieved disease stabilisation and the median time to progression was approximately 3 months. These findings suggest that nilotinib does have activity in this heavily treated patient population. We included all patients treated with nilotinib in the participating centres within the compassionate use programme in this analysis to avoid any selection bias. The baseline patient characteristics with respect to age,[10,12] site of the primary tumour[6,14] and GIST primary mutational status[30] are similar to other series in this setting.

In a phase III trial of patients with advanced GIST intolerant or resistant to imatinib who were randomised to either sunitinib or placebo, the patients assigned to placebo had a median PFS of 6 weeks only and an overall survival of 36 weeks.[13,31] Although comparisons between series are notoriously difficult, the median PFS of 12 weeks achieved in the present series in a patient population whose disease was resistant to both imatinib and sunitinib compares well with the above-mentioned 6 weeks achieved in the placebo arm. These results may be viewed as encouraging, and are in line with the results obtained in a small phase I study of nilotinib monotherapy.[22]

The present study was not designed to collect detailed data on treatment toxicity, but our findings suggest that nilotinib is generally well tolerated. Few patients discontinued nilotinib due to adverse effects (12% of the 52 patients), which appears to compare well to some other agents.[32]

To the best of our knowledge, the present series is the largest series addressing nilotinib as treatment of GIST thus far. The study has, however, some limitations. The analysis was retrospective, which most likely did not allow to record all adverse effects. Due to a lack of a control group it was not possible to assess reliably whether nilotinib prolongs survival. The study size was too small to allow a meaningful analysis of some factors that influence drug efficacy, such as the effect of KIT and PDGFRα mutation status, on outcome.

We conclude that nilotinib has clinical activity in this heavily treated group of GIST patients, and that it was generally well tolerated. The results warrant further evaluation of nilotinib in the treatment of advanced GIST.

Conflict of interest statement

M. Montemurro, P. Reichardt and S. Leyvraz have attended advisory boards and received honoraria from Novartis. E. Weber is an employee of Novartis Pharma AG (Bern, Switzerland), the owner and producer of imatinib and nilotinib.

The authors declare no conflict with regard to the work described in this manuscript.

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