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Original Research

Impact of imatinib rechallenge on health-related quality of life in patients with TKI-refractory gastrointestinal stromal tumours: Sub-analysis of the placebo-controlled, randomised phase III trial (RIGHT)

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Abstract ***Introduction:*** The RIGHT trial demonstrated that resumption of imatinib significantly improves progression-free survival in patients with tyrosine-kinase inhibitor-refractory gastrointestinal stromal tumours. The impact of imatinib on health-related quality of life (QoL) was assessed in a preplanned sub-analysis.

Method and materials: QoL was assessed at baseline and every 4 weeks using European Organization for Research and Treatment Quality of Life Questionnaire C30, version 3.0. QoL data were collected only during the double-blind treatment period. The evolution of QoL parameters over time was assessed by analysis of variance with repeated measures, and comparisons between the two arms at each treatment cycle were performed by analysis of covariance after adjusting for baseline values.

Results: At baseline, 4 weeks, and 8 weeks after treatment, 35 (88% of enrolled patients), 32 (82%), and 21 (95%) patients in the placebo arm and 37 (90%), 33 (85%), and 25 (83%) patients in the imatinib arm, respectively, were evaluable for QoL analysis. In the longitudinal comparison, no differences in global health status/QoL, functioning and other symptom scales were observed between the two groups, although insomnia was significantly worse in the placebo group ($p = 0.02$). Cross-sectionally, at 8 weeks, pain was better ($p = 0.04$) and nausea/vomiting, appetite loss, and diarrhoea were worse ($p = 0.002$, $p = 0.01$, and $p = 0.04$, respectively)

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in the imatinib group than in the placebo group, with no differences in global health status/QoL and functional scales.
Conclusion: Despite the toxicity of imatinib, QoL was not impaired in this fragile patient population. The benefits of imatinib rechallenge outweigh its toxicities, supporting its clinical relevance for patients without active treatment options.

1. Introduction

Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal tumours of the digestive tract and commonly occur in the stomach and small intestine [1]. The molecular characteristics of GISTs include *KIT* or platelet-derived growth factor receptor alpha (*PDGFRA*) driver mutations, which are detectable in >90% of cases [1]. Although localised resectable disease is potentially curable with surgical resection only, the prognosis of patients with unresectable and/or metastatic GISTs was extremely poor before the emergence of imatinib.

Imatinib mesylate is an oral tyrosine-kinase inhibitor (TKI) with activity against *KIT*, *PDGFRA*, *ABL*, and *DDR*. The efficacy of imatinib was first demonstrated in the pivotal B2222 trial [2], which showed that the median time-to-progression (TTP) with imatinib was 2 years in the extended follow-up report [3]. For patients with disease progression or intolerance to imatinib, sunitinib is the approved second-line therapy, with a median TTP of approximately 7 months, as determined in the phase III trial [4]. Although many novel agents have been tested in the setting of failure of both imatinib and sunitinib [5–7], regorafenib is the only approved drug as standard third-line therapy based on the success of a randomized phase III trial (GRID) that showed a median progression-free survival (PFS) of approximately 5 months in the regorafenib arm [8].

Despite current advances in the management of advanced GISTs, most standard therapies eventually stop working because of the polyclonal evolution of the disease, which results in TKI resistance and ultimately overall disease progression. Because tumours progress rapidly after discontinuation of TKIs, many experts recommend resumption of previously effective TKIs to delay progression and relieve tumour-related symptoms by controlling the remaining sensitive tumour clones [9–11].

The RIGHT trial was a randomized, placebo-controlled, phase III trial comparing imatinib rechallenge and placebo in patients who had progressed on at least imatinib and sunitinib [12]. The trial demonstrated that the resumption of imatinib significantly improves PFS in patients with TKI-refractory GISTs who had shown no evidence of primary resistance to initial first-line imatinib therapy.

Given the heavily pre-treated patient population enrolled in the RIGHT trial and the palliative nature of imatinib rechallenge, the impact of imatinib on health-related quality of life (QoL) is an important parameter when measuring the benefit of imatinib rechallenge. Therefore, a health-related QoL analysis was pre-planned in the RIGHT trial. Here, we report the results of this analysis.

2. Materials and methods

2.1. Participants

Fig. 1 shows the design of the RIGHT study (ClinicalTrials.gov identifier, NCT01151852). Patients were enrolled in the study if they had documented clinical benefits (i.e. lack of primary resistance) with previous first-line imatinib treatment, defined as complete response, partial response, or stable disease for at least 6 months, an Eastern Cooperative Oncology Group performance status of 0–3, and at least one measurable lesion. Additional details regarding the eligibility criteria were presented elsewhere [12].

The trial was approved by the Institutional Review Board of Asan Medical Center, Seoul, Korea, and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. Informed consent for this QoL analysis was obtained before enrolment in the trial.

2.2. Treatment and assessment

Eligible patients were randomized in a double-blind manner to receive once-daily imatinib (400 mg) or matched placebo. Doses of study drugs were modified or interrupted in cases of grade III–IV haematological toxicities (excluding anaemia) and grade II–IV non-haematological toxicities. Other anticancer treatments, such as chemotherapy, radiotherapy, other targeted therapies, and surgical resections, were not permitted during the period in which the study treatment was masked. Best supportive care was given to all patients in both trial groups. Masked study treatments continued until patients showed disease progression according to a local investigator assessment, unacceptable toxicity, or withdrew consent.

Toxicities were assessed via physical examination and laboratory tests at 2 and 4 weeks and every 4 weeks