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Original Research

Relationship between imatinib trough concentration and outcomes in the treatment of advanced gastrointestinal stromal tumours in a real-life setting

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KEYWORDS
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Abstract ***Background:*** Imatinib has dramatically improved the prognosis of advanced gastrointestinal stromal tumours (GISTs). Clinical trial data showed that patients with trough imatinib plasma concentrations (Cmin) below 1100 ng/ml (quartile 1) had shorter time to progression, but no threshold has been defined.

The main objective of this study was to investigate in advanced GIST whether a Cmin threshold value associated with a longer progression-free survival (PFS) could be specified. This would be the first step leading to therapeutic drug monitoring of imatinib in GIST.

Patients and methods: Advanced GIST patients (n = 96) treated with imatinib 400 mg/d (41 stomach, 34 small bowel, and 21 other primary site localisations) were prospectively included in this real-life setting study. Routine plasma level testing imatinib (Cmin) and clinical data of were recorded prospectively.

Results: Small bowel localisation was associated with an increased relative risk of progression of 3.09 versus stomach localisation (p = 0.0255). Mean Cmin (±standard deviation) was 868 (±536) ng/ml with 75% inter-individual and 26% intra-patient variability. A Cmin threshold of 760 ng/ml defined by log-rank test was associated with longer PFS for the whole population (p = 0.0256) and for both stomach (p = 0.043) and small bowel (p = 0.049) localisations when analysed separately. Multivariate Cox regression analysis found that Cmin above 760 ng/ml was associated with 65% reduction risk of progression (p = 0.0271) in the whole population independently of the anatomical localisation.

Conclusion: Concentration of imatinib significantly influences duration of tumour control treatment in GIST patients with a Cmin threshold of 760 ng/ml associated with prolonged PFS in real-life setting.

1. Introduction

Gastrointestinal stromal tumours (GISTs) are the most common sarcoma (mesenchymal tumours) of the gastrointestinal tract. Approximately 60% of these occur in the stomach, 30% in the small bowel, 5% in the colon and rectum, and 5% in the oesophagus [1]. Prognosis evaluation in GIST is currently based on tumour diameter, mitotic count and anatomic localisation [2]. Recent studies have also shown that primary site localisation should be considered as an independent risk factor [3,4]. Most GISTs show mutations in KIT or platelet-derived growth factor receptor alpha [5,6] that are targeted by the selective tyrosine kinase inhibitor imatinib mesylate (Glivec™, Novartis Pharmaceuticals). This molecule used as frontline therapy has dramatically improved the prognosis of patients with advanced GIST. In imatinib-treated patients it has been reported that 80% obtained clinical response [7] and that median survival was extended by nearly four times the historic values from the pre-imatinib era [8].

To improve imatinib treatment efficacy, dose-escalation has been investigated, and it was found that it could overcome imatinib failure, especially for patients with KIT exon 9 mutation [9,10]. These studies did not however investigate any relationship between this and plasma levels, even if pharmacokinetic studies have found a correlation between steady state trough imatinib plasma concentrations (Cmin) and efficacy. In chronic myeloid leukaemia (CML), a threshold of 1000 ng/ml has been significantly associated with better cytogenetic and molecular responses [11–13]. For GIST it has been reported in a clinical trial that patients with Cmin at 1 month below the first quartile of concentration values (1110 ng/ml) had shorter time to progression than patients in other quartiles [14]. This cannot preclude that the threshold of imatinib Cmin in GIST is lower than this concentration. A more recent study indicated that imatinib Cmin fall down of about 30% over the first 3 months of treatment [15], showing up that the proposed value determined at 1 month should not be used during all the follow-up. These studies also underline that dose cannot predict plasma levels owing to high inter-patient variability [12,14], which depends on numerous individual pharmacokinetics parameters including CYP polymorphisms, drug-transporters such as P-glycoprotein, protein binding and drug-drug interactions [16–18]. For gastric GIST patients, this is further complicated by surgery, those having undergone partial or total gastrectomy being reported to have significant lower Cmin than those who had not [19]. Taken together these studies on the pharmacokinetics and efficacy of treatment suggest that therapeutic drug monitoring (TDM) could be a useful tool for individual treatment management and optimisation. In advanced GIST, a Cmin threshold that could serve as reference to guide TDM in clinical practice remains to be defined.

The initial observations of a relationship between duration of treatment and concentrations in GIST