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Title

A literature review and database of how the primary *KIT*/*PDGFRA* variant of a gastrointestinal stromal tumour predicts for sensitivity to imatinib.

Short running title

GIST variants and imatinib sensitivity

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Abstract

It is well recognised that the primary *KIT* or *PDGFRA* variant of a gastrointestinal stromal tumour (GIST) can predict sensitivity to imatinib. However, these data are currently spread across a wide range of publications and have not been collated as one reference. A broad-ranging literature search was therefore performed to assemble such a database which should help optimise imatinib-based management of GIST patients henceforth. Having excluded wild type GISTs and results for imatinib used as adjuvant therapy, 79 publications (dated August 2001 to March 2022) underwent data extraction. These data on imatinib sensitivity were either derived from *in vitro* studies, predicted by *in silico* analysis or based on *in vivo* clinical patient response. Data interpretation carried some caveats: there was a potential for replication of patient-derived data between older and new publications; only predicted protein sequences were presented; the criteria used to record clinical response were not uniform across all publications; and imatinib dosage could vary between different clinical publications. However, these data showed broad agreement of imatinib sensitivity amongst similar subtypes of *KIT* or *PDGFRA* variant. There was also agreement between *in vivo* versus *in vitro/in silico* derived sensitivity data for most variants when both data types were available.

Keywords/phrases

Gastrointestinal stromal tumour, *KIT*, *PDGFRA*, imatinib, sensitivity.

Introduction

The use of *KIT/PDGFRA* genotyping of gastrointestinal stromal tumours (GISTs) to predict clinical response to imatinib therapy is an archetypal example of personalized medicine [1]. However, this use has been complicated by the great diversity of such tyrosine kinase (TK) variants harboured by GISTs. These range from point mutations to deletions or insertions to large indel variants [2], and new variants continue to be documented amongst these neoplasms. Because imatinib is invariably the first-line systemic drug for GIST in the adjuvant or advanced setting [1], it is especially crucial clinically that oncologists can access comprehensive data on how any one specific *KIT* or *PDGFRA* variant will determine sensitivity to the drug. These data are currently spread across a large and wide range of clinical trial reports, laboratory-based publications, cases series and even case reports but have not yet been all collated under a single reference. The following literature review was performed to serve as such a reference/database which should therefore help optimise imatinib-based management of GIST patients henceforth.

Material and methods

The literature search was performed using PubMed with the following strategy: (gist) OR (gastrointestinal stromal tumour) OR (gastrointestinal stromal tumor) OR (gastrointestinal stromal neoplasm)) AND ((mutated) OR (mutation) OR (variant) OR (genotype)) AND ((tyrosine kinase inhibitor) OR (imatinib).

Only primary *KIT* and *PDGFRA* variants were considered for this review because of current dogma that primary rather than secondary TK variants of a GIST predict for initial clinical response to first line imatinib therapy [1, 2]. Thus far amongst GISTs,

primary *KIT* variants have only been demonstrated in exons 8, 9, 11, 13, and 17 and primary *PDGFRA* variants in exons 5, 12, 14 and 18 [2-4]. Therefore, only variants in these *KIT* and *PDGFRA* exons were considered for this review. GISTs which lack primary *KIT* or *PDGFRA* variants - referred to as double-wild type GISTs – comprise up to 15% of all GISTs [1, 5, 6]. The associations between double-wild type GISTs and sensitivity to imatinib are well reported [1, 2, 6]. However, the definition of a double-wild type GISTs has varied between these publications based on how many *KIT* and *PDGFRA* exons were screened. The therefore heterogenous nature of double-wild type GISTs in the literature precluded inclusion of this GIST subgroup in this review.

Because most publications only reported the predicted protein phenotype for a variant (rather than the actual nucleotide sequence change), only protein phenotypes were collated for this review. The protein change reported for each variant was, as far as possible, cross-checked by the review authors and if any error (e.g. discordance between the reported amino acid and its position) was detected, that variant was omitted from the review.

Some publications have reported survival data for imatinib-treated patients with different *KIT* and *PDGFRA* mutated GISTs to reflect how the variants predicted for clinical response to the drug [7-9]. However, it is more difficult to compare survival data relative to genotype across different publications. Further, what is more applicable in a clinical setting, is a simple statement of whether a specific variant predicts for sensitivity to imatinib. Therefore, this review only considered sensitivity data in the two following ways.

For non-clinical investigations, these data were only collated if the publication explicitly stated that sensitivity/resistance to imatinib was predicted *in silico* and/or demonstrated *in vitro*. The latter was usually based on whether the drug could inhibit phosphorylation of *KIT* or *PDGFRA* for any one specific variant [10-12]. Some *in vitro* studies reported IC50 values without classifying them to mean sensitivity or resistance and these could not therefore be included in this review.

Clinical investigations traditionally categorise, on radiological grounds, a patient's response to a drug therapy as: complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD). Some clinical trials on GIST defined responders as patients showing either CR or PR (versus SD and PD) [7-9]. Other trials included SD patients in this definition, sometimes referring to this parameter as a 'clinical benefit rate' [13-16]. In routine practice, an oncologist will usually be interested as to whether overall clinical benefit has been gained from the drug. In GIST, there may be tumour response to an agent without sufficient change in size to achieve a radiological RECIST response, hence use of other assessments such as the Choi criteria which came into use in 2007 [17, 18]. Therefore, for clinical investigations, our review defined *in vivo* sensitivity to imatinib as either PR, CR or SD (according to the radiological criteria used by the investigation, see below). Indeed, this wider definition became justified as it yielded closer agreement between *in vivo* and *in vitro/in silico* sensitivity data in the review (Tables). However, to retain the option to employ the more restricted definition of responders, SD data were presented separately in the Tables. Finally, data from published case reports were only collated if a clinical response had been explicitly categorised in the publication

as CR, PR, SD or PD, or adequately described to confidently permit such categorisation.

Results

The literature search was performed on two dates and the most recent was completed on 4 May 2022, i.e. just before preparation of the manuscript. The searches retrieved a total of 177 publications. Of these and after excluding one case report for perceived errors in the protein sequence of its reported *KIT* variant, 79 publications were deemed appropriate for data extraction and inclusion in this review. The publication dates of the included publications ranged from August 2001 to March 2022.

The data were presented only in table form to facilitate their access. To further aid access, the Tables were formatted, for each *KIT* and *PDGFRA* exon, by variant location from upstream to downstream, and the variants are subcategorised, in order, as substitutions, deletions, insertions or duplications and deletions/insertions. A germline variant was reported separately from its somatic equivalent, in case there was discordance in imatinib sensitivity between the pair.

Discussion

This review is the first known publication to comprehensively collate and present, in one document, how each primary *KIT* or *PDGFRA* variant associates with imatinib sensitivity for GIST. This review should therefore serve as a useful database and clinical tool both to laboratories that perform and report GIST genotyping, and to clinicians who use such reports to decide oncological management of GIST patients.

However, these users should be aware of a few caveats when referring to these data.

First, intentionally broad search terms were used for the PubMed searches but it is still possible that some publications relevant to the review were not detected. However, this seems unlikely because the data were extracted chronologically from the oldest to the most recent publications, and references were not found in the more recent publications which had not already been detected and data-extracted earlier. An opposite caveat to consider is whether data from earlier publications were included again in later publications. This would artificially inflate the number of patients listed in the tables of the review. However, while representing a methodological aberration, this would not be clinically significant if all publications for that variant reported the same *in vivo* sensitivity. For the few variants where the latter was not the case (e.g. p.(Asp842del) and p.(Ile843_Asp846del) of *PDGFRA*), review of the relevant publications was especially forensic and showed no definite replication of data between earlier and later publications.

Second, the clinical reporting of any variant should also include the reference sequence against which the genomic interpretation is based. This is to ensure consistency of variant nomenclature. The vast majority (>95%) of the publications used for this review did not report the reference sequences used. Although other transcripts exist, *KIT* NM_000222.2 (LRG_307t1) and *PDGFRA* NM_006206.4 (LRG_309t1) are well recognised as the canonical transcripts and it can only be assumed these have been used. Most of the publications also only reported the predicted protein phenotype for each variant and did not present the actual

nucleotide sequence change. Therefore in the absence of published nucleotide data, it can only be assumed the authors provided the correct protein predictions.

Third, the responses presented by clinical publications were based on radiological assessment, and the radiological criteria used to define CR, PR, SD and PD could differ between publications. The publications included in this review spanned from 2001 to 2022. While use of the RECIST criteria (published in 2000) [19] was more standard practice in earlier publications, the Choi criteria became increasingly used after their publication in 2007 [17]. A phenomenal effort would be required to retrospectively review all the radiology from older, RECIST-based publications for reclassification with Choi criteria. However, it is reassuring that we did not notice any consistent differences in sensitivity data for any one variant between publications before and after 2007. A second point related to response data is that the denominator groups varied between publications. Clinical trial papers would have reported from a 'complete' cohort (i.e. all patients treated with imatinib for the trial) whereas some studies only recruited more selective groups, e.g. solely patients who had initially shown response to imatinib. Further, some of the publications used in this review were only case reports or small case series. Therefore, some of the *in vivo* sensitivity percentages presented in this review's tables could represent overestimations.

Finally, the imatinib dose varied between different publications and sometimes even within the same publication. It would greatly complicate this review's data presentation if they were further subdivided by precise imatinib dose. The only variants which have thus far been reported to vary in sensitivity to different

doses/concentrations of imatinib are those residing in *KIT* exon 9 [7, 8, 20]. Otherwise, we did not notice any consistent differences in sensitivity data for any one variant between publications using different imatinib doses.

As eluded to above, the presentation of data in this review's tables would become cumbersome and confusing if they included all the details related to the above caveats. Therefore, to facilitate users accessing these details themselves, the Tables' data have been referenced as specifically as possible. This may be especially pertinent to the handful of variants whose imatinib data appeared to differ between studies, differ from very similar variants and/or differ between the *in vivo* and *in vitro*/*in silico* settings: p.(Leu576Pro), p.(Pro577_Tyr578del) and p.(Asn822Lys) of *KIT* and p.(Asp846Val), p.(Asp842del), p.(Ile843_Asp846del) and p.(Asp842_Asp846delinsGlu) of *PDGFRA*. Explanations of the sensitivity data differences for the above variants are beyond the scope of this review. However, these explanations could, at least in part, relate to the abovementioned caveats. Further, it is noted that they appear to disproportionately reside in *PDGFRA* exon 18 so this could be a particular focus of future efforts to understand these differences.

For reasons outlined earlier, this review did not consider survival data, which would therefore include those from adjuvant trials [21, 22]. It would seem plausible to extrapolate the sensitivity data of this review to predict imatinib's impact in the adjuvant setting. Indeed and for example, this is supported by one trial's demonstration that disease recurred amongst GIST patients with the *PDGFRA* p.(Asp842Val) variant but not those with exon 11 mutations [23]. However, adjuvant trials have reported more nuanced differences between different *KIT* exon 11

subtypes than the clinical response data collated by this review. For example, GIST patients with exon 11 deletions appear to show greater survival benefit from adjuvant imatinib therapy than those with point mutations [22]. Further, only patients with *KIT* exon 11 deletions involving codons 557 and 558 demonstrated worse recurrence free survival than the rest of the patients in the SSGXVIII/AIO adjuvant trial, whereas a similar difference was not shown by patients with other KIT 11 exon variants [24]. These survival differences may reflect the confounding effects of different genotypes on tumour behaviour independent of sensitivity to imatinib. Indeed, some more recent trials have shown that response to imatinib does not always equate to longer survival [25, 26].

Future work to better understand the relation between different variants and both imatinib sensitivity and patient survival will only help triage GIST patients for imatinib therapy and assist with their prognostication. Sunitinib and regorafenib are respectively licensed as second and third line agents for GIST [1]. However, it is difficult to collate how GIST genotype predicts patient response to these two drugs because these patients would, by definition, have progressed on imatinib therapy and for the most part, have therefore manifested secondary *KIT* or *PDGFRA* mutations [14, 27, 28]. Not only would it then be difficult to determine whether and how the primary and secondary mutations affected drug sensitivity but it is well recognised that secondary mutations may be heterogeneous between different tumour deposits and even within the same deposit [6, 29]. On the other hand, any future published data on primary *KIT* or *PDGFRA* variants in relation to imatinib sensitivity could be collated in a revision of this review/database. It is also anticipated or proposed that national GIST databases (e.g. the registry curated by the UK

National Cancer Registration and Analysis Service) will independently collate such data.

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NW conceived the idea for this review. All authors contributed to the literature review and/or the writing of the manuscript.

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Table Legends

Table 1

Relation of primary *KIT* exon 8 variant to imatinib sensitivity. *In vivo* sensitivity % is the proportion of patients showing CR, PR or SD out of all patients described in the publication(s).

Table 2

Relation of primary *KIT* exon 9 variant to imatinib sensitivity. *In vivo* sensitivity % is the proportion of patients showing CR, PR or SD out of all patients described in the publication(s).

Table 3

Relation of primary *KIT* exon 11 variant to imatinib sensitivity. *In vivo* sensitivity % is the proportion of patients showing CR, PR or SD out of all patients described in the publication(s).

Table 4

Relation of primary *KIT* exon 13 variant to imatinib sensitivity. *In vivo* sensitivity % is the proportion of patients showing CR, PR or SD out of all patients described in the publication(s).

Table 5

Relation of primary *KIT* exon 17 variant to imatinib sensitivity. *In vivo* sensitivity % is the proportion of patients showing CR, PR or SD out of all patients described in the publication(s).

Table 6

Relation of primary *PDGFRA* exon 5 variant to imatinib sensitivity. *In vivo* sensitivity % is the proportion of patients showing CR, PR or SD out of all patients described in the publication(s).

Table 7

Relation of primary *PDGFRA* exon 12 variant to imatinib sensitivity. *In vivo* sensitivity % is the proportion of patients showing CR, PR or SD out of all patients described in the publication(s).

Table 8

Relation of primary *PDGFRA* exon 14 variant to imatinib sensitivity. *In vivo* sensitivity % is the proportion of patients showing CR, PR or SD out of all patients described in the publication(s).

Table 9

Relation of primary *PDGFRA* exon 18 variant to imatinib sensitivity. *In vivo* sensitivity % is the proportion of patients showing CR, PR or SD out of all patients described in the publication(s).