Successes and Challenges in Translational Research: The Development of Targeted Therapy for Gastrointestinal Stromal Tumours

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Abstract Gastrointestinal stromal tumors (GISTs) are mesenchymal neoplasms that most commonly affect the stomach or small intestine, but that can occur anywhere within the gastrointestinal tract. The annual incidence of GISTs is estimated to be 10 to 20 cases per million. Traditionally, the only effective treatment was surgical resection, and recurrences were common even with complete removal of tumor. Systemic therapy with standard cytotoxic chemotherapeutic agents was completely ineffective. A series of exciting laboratory developments led to the discovery that the small molecule tyrosine kinase inhibitor STI571 (imatinib mesylate) has significant clinical activity in GISTs, representing one of the first therapeutic uses of a targeted agent directed against a solid tumor. In this article we will describe the key steps that led to the initial clinical trials of imatinib in GISTs, and we will also discuss the process of incorporating this novel therapy into mainstream oncologic practice.

Advances in Basic Science

Gastrointestinal stromal tumors (GISTs) were initially thought to be of smooth muscle origin until it was noted that they had a unique staining pattern, with a combination of smooth muscle and neural features, similar to the Interstitial Cells of Cajal (ICC), the gut wall pacemaker cells (3). In 1995 Huizinga and associates reported that KIT is critical to the development of the ICC (4). KIT is a receptor tyrosine kinase whose ligand is stem cell factor (SCF) (ref. 5). Binding of SCF to KIT results in receptor homodimerization, activation of the tyrosine kinase activity, and phosphorylation of downstream substrates leading to signal transduction (6). In 1998, Hirota and colleagues confirmed that KIT is also commonly expressed in GISTs, and through sequencing of *KIT* DNA they found mutations in five of six tested GISTs, in the region between the transmembrane and tyrosine kinase domains (7). These mutations led to activation of KIT without the requirement for binding of SCF (i.e., constitutive activation). This group also showed that transfection of lymphoid cells with a mutant *KIT* gene led to malignant transformation of these cells. These findings suggested that *KIT* mutations contribute to GIST development and/or maintenance of the potentially malignant phenotype (7). The majority of GISTs have mutations in *KIT*, but there is a subset of GISTs that are *KIT* wild type. In 2003, Heinrich and colleagues showed that a proportion of *KIT* wild type GISTs have mutations in a separate receptor tyrosine kinase known as platelet derived growth factor receptor alpha (PDGFRA), thus discovering a second oncogene involved in GIST pathogenesis (8).

Translation to the Clinic

Surgical extirpation is the mainstay of treatment for resectable GIST and complete surgical removal is the only potential curative therapy. A case series describing the various outcomes of surgery noted that even with complete surgical resection disease free survival was only 67% at 2 years and 45% at 5 years (9). Other reports detailed recurrence rates of as high as 90%, if patients were followed long enough (10). Patients who presented with unresectable disease or who recurred following surgery had no options offering long-term survival. Salvage surgery was ineffective (11), and GISTs proved to be impervious to chemotherapy, including agents effective in morphologically similar seeming soft-tissue sarcomas. Indeed multiple trials have been undertaken examining the role of cytotoxic chemotherapy in GIST. Single and multiagent combinations have been attempted (12–16) and failed to yield meaningful response rates or any clinical benefit.

The role of systemic therapy for GIST emerged from drug development in chronic myelogenous leukemia (CML), albeit in a later time frame. Treatment for GIST changed dramatically with the development of imatinib mesylate. Imatinib is a small molecule originally designed to inhibit Abl and PDGFR (17), and first used clinically to inhibit the bcr-abl fusion gene product present in CML (18). Trials in CML showed that this molecule had significant activity, with a complete remission rate of nearly 100% (19, 20). In addition to its activity against

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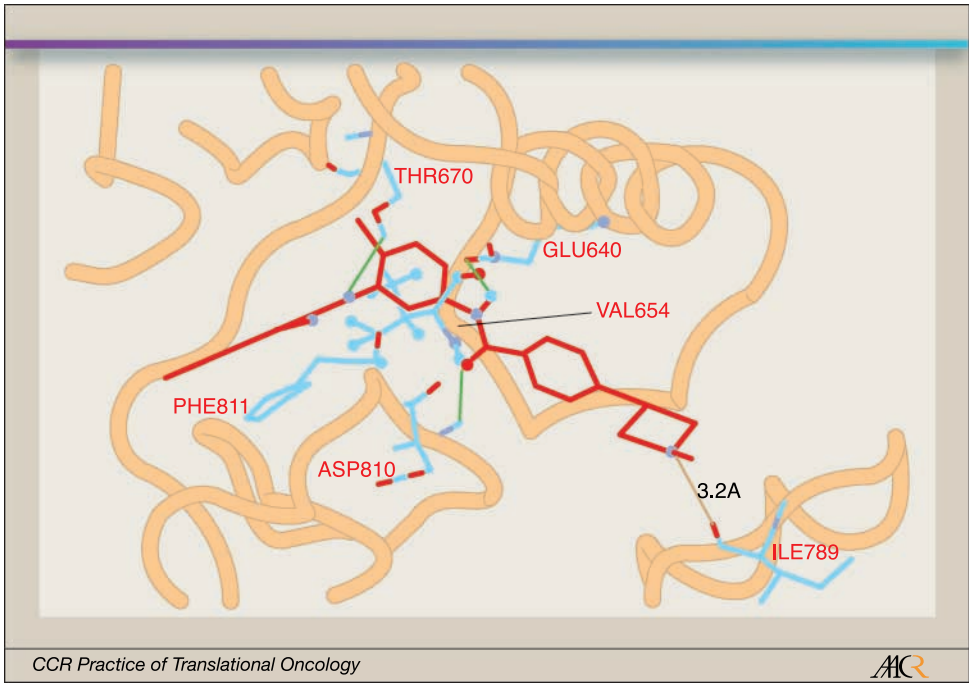

Fig. 1. Imatinib (red) shown binding within KIT (yellow). Adapted with permission from McLean et al, Molecular Cancer Therapeutics, 2005 (21).

ABL, imatinib was shown to inhibit KIT (Fig. 1) (ref. 21). At the time investigators did not suggest using imatinib in non-CML cancers, as malignancies driven by KIT or PDGFR had not been well described. In 2000, Heinrich and associates published a key study demonstrating that imatinib inhibits mutant KIT. Initially, a human myeloid leukemia cell line (M-07e) with a wild type KIT receptor was treated with imatinib and stimulated with SCF. Imatinib was found to inhibit SCF induced KIT autophosphorylation. Inhibition was noted to be dose dependent, with a concentration of 100 nmol/L causing 50% inhibition. Secondly, a human mast cell leukemia cell line (HMC-1) with a constitutionally active mutant KIT receptor was treated with imatinib. Again it was noted that KIT autophosphorylation was inhibited (through inhibition of KIT kinase activity). Near complete inhibition occurred at a dose of 100 nmol/L (a concentration that had previously been shown in CML studies to be obtainable in patients) (ref. 22).

Thus, at this time, there seemed to be strong biological rationale for the use of imatinib in GIST, given the limited standard therapeutic options, constitutive activation of KIT as a driving mechanism in this tumor, demonstration of activity in a GIST cell line (23), and the known fact that imatinib inhibited mutated KIT at clinically achievable doses. Trials of imatinib were proposed by Oregon Health Science University researchers, as well as scientists at the Dana-Farber Cancer Institute, and independently in Europe, but owing to the perceived rarity of GIST, the drug was not made available and studies did not initially move forward. This illustrates the challenge of obtaining support for trials of new therapeutics in rare diseases.

The first trial of imatinib in a human was undertaken in 2000 when a Finnish patient with metastatic GIST was given drug on a single-patient trial (this essentially represented granting of compassionate use access to the drug) (ref. 24). This patient had a remarkable clinical and radiographic response. Within several weeks metastases markedly decreased in size and six of 28 hepatic lesions were no longer detected on MRI after 8 months of therapy. There was a significant reduction in PET scan uptake. A post treatment biopsy showed marked decrease in density of the tumor cells, as well as myxoid degeneration and scarring. In addition the drug was well tolerated and cancer related symptoms disappeared. Of note, in hindsight it was very fortunate that this patient had an exon 11 *KIT* mutation, as this mutation has been shown to predict for a good response to imatinib. Had this patient possessed an imatinib-resistant mutation, or been *KIT* wild type, then she potentially would have not responded or progressed on imatinib, which would have decreased the enthusiasm to pursue further trials of imatinib in GIST and may have significantly delayed the development of targeted therapy in solid tumors.

Due to the astounding success of imatinib in this single case, several phase I and II studies were reproposed and subsequently undertaken. These studies set out to examine the optimal dose and side effect profile of imatinib, while also attempting to confirm and quantify the degree of activity in GIST. The results of these trials were dramatic and exceeded all expectations. Van Oosterom and colleagues conducted a phase 1 study with 40 patients (36 with GIST) (ref. 25). The results indicated that 25 out of 36 patients had tumor regression. The dose of 400 mg twice daily was noted to be well tolerated. A larger multicenter phase II trial (CSTIB2222) was also undertaken by three U.S. academic centers and the University of Finland (the latter group, as well as one of the American investigators had treated the original Finnish patient described above) (ref. 26). This trial compared imatinib 400 mg versus 600 mg daily in patients with surgically unresectable GIST.

As strikingly positive results for this trial became known (see below), patient selection for the B2222 trial presented a unique challenge. Drug was available in the United States only to trial participants. Patients were primarily self-referred, with many

finding out about the trial through internet communication. Each of the three U.S. sites were initially allocated 10 patient slots. A waiting list of patients seeking the study drug grew rapidly, dramatically exceeding available slots. To accommodate the growing patient demand, the protocol had to be amended three times over a 4-month period to provide for increased accrual (the trial originally called for 36 patients but eventually expanded to include 147 patients) (ref. 27). The expansion related solely to making drug more available and was not necessary to answer the original scientific questions posed by B2222.

Long-term results for B2222 have been reported (28). Of 147 patients included, 68.1% achieved an objective response, significantly exceeding the 30% objective written into the original statistical section of the protocol. Additionally, 15.6% of patients had stable disease. Response rates were noted to be similar between arms. The median time to progression was 24 months and estimated overall survival was 57 months, significantly exceeding the 18-month figure expected with any other treatment available. Twenty-eight percent of patients were alive and well with median follow-up of 63 months, suggesting there may be long-term survival observed in advanced GIST patients treated with imatinib. On the basis of the results of this study imatinib was approved by the U.S. Food and Drug Administration (FDA) for the treatment of advanced GIST. Further analysis done on tumor tissue from this study revealed that the mutational status of *KIT* and *PDGFRA* is predictive of response to imatinib (29). Patients with exon 11 *KIT* mutations were found to have improved event free and overall survival compared with patients with exon 9 *KIT* mutations or no detectable mutations.

The aforementioned studies served to confirm the significant activity and tolerability of imatinib in the treatment of GIST, but numerous questions remained unanswered. To address the question of optimal dose, two phase III trials were undertaken (30, 31). These trials also served to increase access to imatinib as the only way to receive it at the time of accrual was through a clinical trial. Because of the high demand for imatinib these trials went from planning to initiation at a remarkable pace. The S0033 trial, for example, went from conception to activation in only 6 weeks and accrued 746 patients within months. The results of these trials and a subsequent meta-analysis (32) revealed no difference in overall survival between the two dosing arms, but patients with exon 9 mutation seemed to have a significantly improved progression free survival with higher dose imatinib.

Further research on imatinib in GIST is attempting to address several issues. One issue is the prognostic and predictive significance of the different *KIT* genotypes and the use of this molecular information to guide therapeutic decisions. Another important issue under investigation is the role of imatinib in the adjuvant and neoadjuvant settings. Studies have shown clinical activity for other target therapies in GIST, including the use of sunitinib in second line treatment for imatinib resistant patients (33). The role of other target therapies in GIST, both as salvage therapy, and upfront therapy in combination with imatinib is currently under investigation.

GIST is a unique disease in which advances in understanding the disease at the basic science level directly led to development of a targeted agent that was potentially clinically active. Whereas there is biological rational for most of the agents we use in oncology, rarely do we see such potent rationale for using a specific drug, nor do we often see such a significant response with a single agent, especially in diseases previously refractory to all systemic agents. The astounding results noted required an international collaborative effort to ensure studies were planned appropriately and as many patients as possible had access to this new therapy. The GIST story is an example of the success that is possible in translational research, and it also serves to show unique challenges that may accompany this success.

Disclosure of Potential Conflicts of Interest

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