EXPERT REVIEW

Imatinib Mesylate: Past Successes and Future Challenges in the Treatment of Gastrointestinal Stromal Tumors

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Abstract: Just over a decade ago, gastrointestinal tumours were a poorly understood mesenchymal neoplasm unsuccessfully treated with chemotherapy. Cytotoxic therapy for advanced disease yielded response rates of 10% and median survival of just 18 months. However, the discovery of *KIT* and platelet derived growth factor receptor alpha (*PDGFRA*) mutations as oncogenic drivers of most gastrointestinal tumours, paved the way for targeted therapy. Imatinib mesylate, a tyrosine kinase inhibitor, produces a clinical benefit rate (complete response, partial response, and stable disease) of more than 80% in metastatic setting and a median survival of 57 months. Imatinib is now also approved in adult patients following resection of KIT-positive GIST. Major insights into the mechanism of action of imatinib, unique pharmacokinetics, drug resistance, and management of low grade but chronic adverse effects continue to be made.

Keywords: Gastrointestinal stromal tumor, imatinib, metastatic, adjuvant

Introduction

Gastrointestinal stromal tumours (GIST) are the most common mesenchymal neoplasms, with an incidence of 14.5 cases per million.[1] While most GIST occur in the stomach (50%) or small bowel (25%), a minority are esophageal (5%) or colorectal (10%) in location.[2] The median age at diagnosis is 58 years and pediatric cases account for only 2% of all GIST.[3,4] Pediatric GIST are characterized by female prevalence, multiple gastric tumours, and wild type KIT and PDGFRA genotype.[4] Despite complete surgical removal of all macroscopic disease, 5 year disease free survival is about 45%.[53] Chemotherapy for advanced disease (typically doxorubicin based) has limited efficacy with response rates of 0%–10% and median survival of 18 months.[5,6] In comparison, the phase II B2222 study examining two dose levels of imatinib mesylate (Glivec; Novartis Pharma AG, Basel, Switzerland) in unresectable or metastatic patients, reported a median overall survival of 57 months.[7]

Mechanism of Action

KIT, a member of the type III receptor tyrosine kinase (RTK) family, is structurally similar to platelet-derived growth factor alpha (PDGFA), colony stimulating factor-1 receptor (CSF1R), and fms-related receptor (FLT3).[8] KIT is important for the development of melanocytes, germ cells, mast cells, hematopoietic stem cells, and the interstitial cells of Cajal (the so-called pacemaker cells of the gastrointestinal tract that GIST cells most closely resemble).[9] The KIT transmembrane receptor is composed of an extracellular region with five immunoglobulin-like domains (the second and third domain are involved in ligand recognition), a transmembrane hinge, a juxta-membrane domain (JM), and a cytoplasmic region with two tyrosine domains. The proximal kinase domain anchors ATP while the distal kinase domain binds and phosphorylates downstream substrates; importantly, an activation loop which stabilizes the activated KIT receptor, is localized to the distal kinase. Binding of stem cell factor to KIT results in prompts receptor homodimerization, activation of tyrosine kinase activity, and stimulation of signal transduction pathways such as the Ras/Raf/mitogen activated protein kinase (MAPK), phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR), and Src kinase pathways. The net result is cell cycle activation, proliferation, and inhibition of apoptosis.

A seminal paper by Hirota and colleagues in 1998 made a number of pivotal discoveries: GIST express KIT protein, 5 of 6 tumor specimens had KIT mutations, and KIT mutations resulted in constitutive kinase activity.[10] Further work clarified that KIT contains 21 exons; mutations are most commonly located in exon 11 (70%) which encodes the juxtamembrane domain, exon 9 (13%) which encodes the fifth extracellular immunoglobulin-like region, and less frequently in the tyrosine kinase domain 1 encoded by exon 13 (1%) and the phosphotransferase domain encoded by exon 17 (1%). Approximately 5% to 7% of GIST harbour oncogenic mutations in PDGFRA, typically in the juxtamembrane domain (exon 12) or activation loop (exon 18);[11] the D842V substitution in exon 18, is highly resistant to imatinib. GIST tumours with PDGFRA mutations tend to be of epitheliod morphology, display weak or no CD117 staining, and are usually localized to the stomach.[12] The remaining 10%–15% of GIST tumours lack known mutations and their pathophysiology is unclear. Possible mechanisms of oncogenesis in so called wild type tumours include: mutations involving IGF1R or BRAF, inactivation of KIT-inhibitory phosphatases, up-regulation of the KIT ligand, and KIT heterodimerization with other activated receptor-tyrosine kinase proteins.[13]

Carney Triad is characterized by GIST, extra-adrenal paragangliomas, and pulmonary chondromas.[14] GIST associated with Carney Triad share clinical and pathologic features with paediatric GIST and are distinctly different from adult GIST; patients are typically young females with multifocal tumours, lack KIT and PDGFRA mutations, and respond less often to imatinib.[14] Succinate dehydrogenase (SDH), an enzyme bound to the inner mitochondrial membrane that is involved in the Krebs cycle, is a tumor suppressor gene. Inactivating mutations of SDH have been associated with GIST and paraglioma tumours (so-called Carney-Stratakis syndrome).[15] Gill and colleagues were the first to demonstrate that pediatric and Carney-Stratakis associated GIST tended to have negative staining for SDH.[15] Janeway and colleagues detected SDH germline mutations in 4 of 34 (12%) patients with wild-type GIST by immunohistochemistry.[16] This observation is important as SDH protein expression detected by immunohistochemistry could

be a cost effective method of identifying a proportion of wild-type patients.

Imatinib mesylate was initially developed for the treatment of chronic myelogenous leukemia, (CML), due to its ability to inhibit the BCR-ABL fusion protein. The phase III International Randomized Interferon versus STI571 (IRIS) study compared clinical efficacy of imatinib versus interferon and cytarabine for newly diagnosed chronic-phase CML.[17] Monotherapy with imatinib proved superior to standard therapy with improved hematologic and cytogenetic response rates, longer progression-free survival, and lower toxicity. This success prompted use of imatinib therapy in GIST. In vitro GIST cell lines with mutant *KIT* and *PDGFRA* treated with imatinib demonstrate reduced MAP kinase, PI3K dependent Akt activity, and enhanced apoptosis.[18] Importantly, the extent of KIT immunostaining does not seem to correlate with either the type of KIT mutation or the likelihood of response to imatinib, although, immunonegative or weakly staining tumours are more likely to be KIT wild type.[19]

Pharmacokinetics
Absorption
Imatinib is formulated in hard capsules or tablets as a salt (imatinib methane sulfonate, molecular weight: 589.7 g/mol).[27] Imatinib is a quadrivalent base and readily dissolves in solution with a pH of 5.5; this property contributes to the excellent bioavailability of 98%.[21] The predominant location of imatinib absorption is unknown and reports of patients with resected small bowel and rectum had lower plasma imatinib levels.[22] Food has no relevant impact on the rate or extent of bioavailability. After oral administration, the maximal plasma concentration of approximately 1.6 µg/mL is reached after 1.5–6 hours.[20] In the steady state, peak plasma concentration (Cmax) and area under the concentration time curve (AUC) are 2.9 µg/mL and 61.9 µg. h/mL, respectively.[20] Considerable interindividual variability of pharmacokinetics at steady state has consistently been observed, with a coefficient of variation for AUC of 40%. In CML patients, there is a dose proportional increase in AUC from time 0 to 24 hours for doses ranging from 25 mg to 1000 mg.[21]

Distribution
Imatinib undergoes rapid and extensive distribution into tissues, but does not cross the blood brain barrier in sufficient concentrations.[26] Over 95% of serum imatinib is protein bound either to albumin or α1-acid glycoprotein (AAG.) Only the unbound portion of imatinib is biologically active.[26] As AAG is an acute phase reactant and may fluctuate during the course of the disease, it has been used to explain interindividual variability in imatinib clearance and hematologic toxicity.[23]

Metabolism
Imatinib is metabolised by the cytochrome P450 (CYP) 3A4 enzymes in the liver, with minor contributions from CYP1A2, CYP2D6, CYP2C9.[26] The major metabolite formed, CGP74588, has similar biologic potency to imatinib and represents approximately 20% to 25% of the parent drug level at steadystate in patients with GIST. Co-ingestion of particular medications and foods, have significant effects on imatinib metabolism. Drugs such as ketoconzaole and erythromycin and nonpharmalogic agents like grapefruit juice inhibit CYP 3A4 enzymes and raise imatinib plasma concentrations.[27] Conversely, inducers of CYP3A4 enzyme activity such as dexamethasone, phenytoin, rifampicin, and St. John's Wort lower imatinib plasma levels.[25] Equally important, imatinib can increase Cmax and AUC of CYP 3A4 substrates such as simvastatin and cyclosporine, therefore a careful inventory of a patient's medications is vital.[27]

Elimination
Imatinib has a terminal half-life of 19 hours (range, 14–23 hours).[24] Gschwind and colleagues collected detailed information on excretion of imatinib by administration of radiolabelled drug into healthy volunteers.[28] After one week from ingestion of 14C-radiolabelled imatinib, 80% of the dose had been excreted; the predominant mode of elimination was fecal (67%) with a minority being excreted via the kidneys (13%).[28] In imatinib treated patients with chronic myeloid leukemia, drug clearance has been noted to increase with increasing body mass index.[29]

Pharmacokinetics (PK) differences in GIST vs. CML patients
The PK properties of imatinib in patients with CML and GIST are similar. Altered absorption due to GIST-related surgeries in the stomach and small intestine or altered metabolism secondary liver metastases

might explain some of the differences.[26] The Cmax of imatinib at steady state in patients with GIST is 2.9 µg/mL compared with 2.3 µg/mL in patients with CML.[24] Also, the rate of clearance for imatinib is approximately 8% lower in patients with GIST than in patients with CML.[26]

Dose adjustments for renal and hepatic insufficiency

Gibbons et al recently published a phase I study of patients with unresectable or metastatic GIST and varying degrees of renal impairment.[30] Of sixty accrued patients, 14 had normal renal function (creatinine clearance, CrCL over 59 mL/min), 22 had mild renal impairment (CrCL 40 to 59 mL/min; group), 22 had moderate dysfunction (CrCL 20 to 39 mL/min), and 2 had severe renal impairment (CrCL less than 20 mL/min). Intraindividual dose escalation was permitted if no response or disease progression was observed, in the absence of dose limiting toxicity (DLT). A maximum tolerated dose was not reached in the trial. However, serious adverse events were more common in patients with renal dysfunction. Imatinib exposure, as expressed by dose-normalized $AUC_{0-\infty}$ (area under the curve from 0 to infinity) on day 1 and AUC_{0-24} (AUC from 0 to 24 hours) on day 15, was significantly greater in patients with impaired renal function than in those with normal renal function. The authors theorize that this phenomenon related to lower hepatic CYP activity and increase levels of AAG in patients with renal impairment.

Ramanathan conducted a similar phase I study of patients with liver dysfunction and various advanced malignancies (most commonly colorectal cancer or hepatocellular carcinoma).[31] Hepatic dysfunction was classified by National Cancer Institute Organ Dysfunction Working Group criteria using serum aspartate aminotransferase and total bilirubin. Unlike the previous study, no intrapatient dose escalation was allowed. Dose escalation occurred until two or more patients had DLT at a particular dose level. Plasma pharmacokinetics and urinary excretion of imatinib and its metabolite CPG74588 were similar regardless of liver function. The maximum tolerated dose (MTD, defined as one dose level below DLT) of imatinib for patients with mild liver dysfunction was 500 mg. While MTD was not determined for the moderate

and severe liver dysfunction groups, imatinib was tolerated up to 300 mg/d in both groups. As such, the authors suggest the initial dose for patients with hepatic impairment should be 300 mg per day and increased to 400 mg per day if there is no evidence of adverse effects.

Radiologic Assessment of Treatment Response

Standardized classification systems such as Southwestern Oncology Group (SWOG) criteria and Response Evaluation Criteria in Solid Tumors (RECIST), are based on uni- or bidimensional changes in tumor size. At the cellular level, GIST responding to treatment may undergo necrosis, intratumoral haemorrhage, or myxoid degeneration regardless of volumetric changes.[32] Radiologic correlates of positive response to treatment can include: disappearance of enhancing nodules and tumor vessels, enhanced tumor homogeneity and hypoattenuation, or darkening of the tumor due to decreased tumor density. Moreover, the time to onset of response can evolve slowly over months to years; in B2222, one quarter of patients required 5.3–39 months to reach SWOG-defined response.[7]

Positron emission tomography using 18-fluorodeoxyglucose ([18]FDG PET) is sensitive in detecting both early response to imatinib and predicting long-term outcomes in patients with metastatic GISTs.[33] Van den Abbeele et al demonstrated that absolute value for SUVmax of 3.4 and a 40% reduction in SUVmax one month after initiation of treatment was predictive of improved time to treatment failure.[33] Unfortunately, routine use of PET is limited by a lack of scanner availability and cost constraints. Choi and colleagues noted that imatinib sensitive gastrointestinal stromal tumours, demonstrate decreases in tumoral density on computed tomography (CT).[34] The so-called 'Choi criteria', a 10% decrease in unidimensionaltumor size or a 15% decrease in tumor density on contrast-enhanced CT correlate well with positive response by PET and is more predictive of time to tumor progression than RECIST.[35] As such, it should be remembered that all of the trials described below utilized radiologic response criteria designed for traditional cytotoxic drugs and probably resulted in lower reported response rates.

Efficacy

Preclinical

Using a *KIT* expressing human myeloid leukemia cell line, M-07e, Heinrich et al determined that 100 nmol/L of imatinib decreased ligand stimulated tyrosine kinase phosphorylation by 50%.[18] Furthermore, imatinib inhibited stem cell factor dependent growth in a dose dependent manner. Tuveson et al created a GIST cell line with a missense mutation (K642E) in exon 13 causing constitutive KIT activation; after incubation with imatinib, there was a decrease in level of phosphorylated tyrosine, amelioration of cell proliferation, and evidence of apoptosis.[36]

Unresectable/metastic GIST

The initial pilot study of imatinib in advanced GIST occurred in the year 2000 with a Finnish patient.[37] After presenting with abdominal pain in 1996, she underwent curative resection of two large gastric GISTs. Two years later she developed metastases to the peritoneum and liver which progressed despite multiple lines of chemotherapy. Based on clinical experience with CML, the Finnish patient received imatinib at 400 mg daily. Positron emission tomography performed 1 month after initiation of treatment, showed no abnormal uptake of ^{18}FDG

in the previously metabolically active liver lesions. After 8 months of treatment, six of twenty-eight liver metastases were no longer detectable by magnetic resonance imaging (MRI). Repeated biopsies during the course of treatment revealed a reduction in tumor cell density, myxoid degeneration, and scarring. The drug was well tolerated with minimal toxicity and response continued for two years.[6] In retrospect, as the tumor contained a *KIT* exon 11 mutation, there was a high likelihood of treatment response. The successful treatment of the first patient with metastatic GIST sparked a rapid succession of pivotal trials, described in Table 1.

The European Organization for Research and Treatment of Cancer subsequently initiated a phase I trial.[38] Of forty patients accrued, 36 had gastrointestinal stromal tumours; dosing levels ranged from 400 mg to 1000 mg daily. Treatment with 500 mg bid led to dose-limiting toxicities in five patients: severe nausea, vomiting edema or rash. Of note, three patients experienced intratumoral bleeding. 25 of 36 GIST patients met criteria for an objective response, with nineteen (53%) having a confirmed partial response and seven (19%) had stable disease. In addition, response assessed by PET imaging 8 days after treatment began, predicted objective response

Table 1. Summary of key GIST trials in metastatic and adjuvant setting.

Trial	Phase/ setting	Primary endpoint	Treatment (number patients)	ORR	PFS	Overall survival	Comment
B2222[7]	II, Metastatic	ORR	400 mg daily (n = 73) 600 mg daily (n = 74)	78.9% 78%	20 months* 26 months*	55%** 55%**	No statistically significant difference
EORTC[39]	II, Metastatic	ORR	400 mg bid (n = 27)	71%	73%***	n/a	
US-CDN[45]	III, Metastatic	OS	400 mg daily (n = 345) 400 mg bid (n = 349)	45% 45%	18 months* 30 months*	55 months**** 51 months****	No statistically significant difference
EU-AUS[46]	III, Metastatic	PFS	400 mg daily (n = 473) 400 mg bid (n = 473)	45% 45%	50%*** 56%***	85%***** 86%*****	Statistically significant PFS
ACOSOG Z9001[56]	III, Adjuvant	RFS	400 mg daily × 1 year (n = 359) No adjuvant therapy	n/a	98%+ 83%+	98.6%++ 97.7%++	Statistically significant RFS
SSG XVIII/ AIO[59]	III, Adjuvant	RFS	400 mg daily × 3 years (n = 200) 400 mg bid × 1 year (n = 200)	n/a	65.6%+++ 47.9%+++	92%+++ 81.7%++++	Statistically significant RFS and OS

Notes: *Median progression free survival; **5 year overall survival; ***1 year progression free survival; ****median overall survival; *****1 year overall survival; +1 year RFS; ++1 year overall survival; +++5 year RFS; ++++5 year OS.

by computed tomography after 8 weeks. Given the preliminary evidence of clinical efficacy and tolerable safety profile, three phase II studies were launched: the B2222 US-Finland study,[7] EORTC Soft Tissue and Bone Sarcoma Group trials,[39] and B1202 Japanese study.[40]

The EORTC Soft Tissue and Bone Sarcoma phase II trial examined the response rate and time to progression of various sarcomas to the maximum tolerated dose of imatinib (400 mg bid).[39] Of 27 patients with GIST, one (4%) experienced a complete remission, eighteen (67%) partial remission, five (18%) stable disease, and three (11%) disease progression. 73% of GIST patients were free from progression at 1 year. Side-effects were tolerable and no patient discontinued the drug due to adverse events.

The B2222 US-Finland study randomized 147 patients with unresectable or metastatic GIST to imatinib 400 mg (n = 73) or 600 mg daily (n = 74).[7] Patients on the lower dose experiencing progression were permitted to crossover to 600 mg daily and ultimately 400 mg twice daily. With 63 months follow-up, the overall response rates (68.1% overall, 68.5% [400 mg], 67.6% [600 mg]), median progression free survival (24 months overall, 20 months [400 mg], 26 months [600 mg]), and 1-year overall survival (88% for all patients) were similar between the treatment arms. Interestingly, one-quarter of patients required over 5 months to achieve either a partial or complete response as assessed by CT or MRI; with longer follow-up 23 patients (16% of all patients) initially classified as having progressive stable disease, achieved either a partial or complete response. Furthermore, overall survival was identical amongst patients who achieved either stable disease or a partial response (5 year overall survival, 55%). These observations highlight the pitfalls of traditional response criteria which measure volumetric changes as opposing to metabolic changes with PET scans. Now, with a median follow-up of 9.4 years, 26 pts (17.7%) remained on treatment and 9-year OS rate for all patients was 35%.[41] Baseline tumor bulk, as separated by quartiles, was predictive of long term overall survival: 9-year OS for patients in the lowest quartile was 53% compared to 23% for patients with the largest tumours.

Archival pre-treatment pathology specimens suitable for genotyping were available from 127 of the 147 patients enrolled in the B222 study: 112 had *KIT* mutations (85 in exon 11 and 23 in exon 9), 6 had *PDGFRA* mutations, and 9 were wild-type.[42] Patients whose tumor expressed an exon 11 mutant *KIT* were much more likely to have a partial response with imatinib therapy as compared to either exon 9 mutants or wild-type/*PDGFRA* (83.5%, 47.8%, and 0% respectively). In addition to being a predictive factor, *KIT* exon 11 mutation status was also a prognostic factor as median overall survival was superior compared to *KIT* exon 9 or other genotypes (63 months, 44 months, and 26 months respectively).[42] Imatinib therapy was approved for metastatic or unresectable GIST in November 2001 by the European Medical Association (EMA) and in February 2002 by the FDA, based on the findings of the B222 US-Finland and EORTC studies.[43,44]

Similar to the B2222 US-Finland study, the B1202 study was an open label randomized phase 2 study of patients with advanced GIST receiving imatinib at a dose of 400 mg/d (n = 28) or 600 mg/d (n = 46).[40] Again, no significant difference was found in response rate (69% overall), median progression free survival (96 weeks overall), and 3-year overall survival (73.6% overall) by dose. Side-effects were mild and included nausea (78% overall patients), diarrhea (70%), dermatitis (62%), facial edema (61%), and emesis (54%).

Due to lingering uncertainty regarding optimal dose for patients with advanced GIST (ie, 400 mg once or twice daily), two phase III trials were launched: the first conducted jointly in Europe and Australia by EORTC, Italian Sarcoma Group, and Australasian Gastrointestinal Trials Group (referred to as EU-AUS) and the second conducted in the United States and Canada by Southwest Oncology Group, Cancer and Leukemia Group B, National Cancer Institute of Canada, and Eastern Cooperative Oncology Group (referred to as US-CDN).[45,46] The primary endpoint of the US-CDN trial was overall survival; the investigators accrued an impressive 746 patients with unresectable or metastatic GIST in 9 months. With a median follow-up time of 4.5 years, there was no statistically significant difference by dose in response rate (45% confirmed complete and partial responses in both arms), progression free survival (18 months [400 mg] and 20 months [600 mg]), or median overall survival (55 months [400 mg] and 51 months [600 mg]). After progression on standard-dose imatinib, 33% of patients who crossed over to the high-dose imatinib regimen achieved either a partial response or stable disease. Serious adverse events and deaths were more

common in the high-dose imatinib arm, as were dose delays and reductions. Tumor samples were obtained from 447 patients of whom 368 were CD117 positive GIST.[47] 308 tumours had *KIT* mutations (269 in exon 11 and 31 in exon 9), 4 tumours had mutations in *PDGFRA* exon 18, and 56 were wild-type. Mutation status was found to be both prognostic and predictive of response to imatinib. *KIT* exon 11 mutation status as opposed to exon 9 or wild-type genotype correlated to higher response rates (71.7%, 44.4%, and 44.6%, respectively), improved progression free survival (24.7 months, 16.7 months, and 12.8 months) and median overall survival (60 months, 38.4 months, and 49 months). Treatment with high dose imatinib in patients with *KIT* exon 9 yielded improved response rates (CR/PR, 67% vs. 17%) but no statistically significant difference in progression free survival or median overall survival.

The EU-AUS study accrued 946 patients and had a similar protocol to the US-CDN study, but the primary endpoint was progression free survival.[46] At initial publication with a median follow-up of approximately 25 months, progression free survival was slightly longer in the patient group receiving higher dose as opposed to standard dose imatinib (56% vs. 50%, $P = 0.026$). However, after a median follow-up time of 40 months, the difference in progression free survival was no longer statistically significant.[48] The higher imatinib dose caused increased adverse effects such as edema, rash, fatigue nausea, bleeding, diarrhea, and anemia. Of 247 patients with documented progression on standard dose imatinib, 133 patients crossed-over to the higher dose; impressively 29% achieved either a partial response or disease stabilization and 18% were still progression free at 1 year after cross-over. Debiec-Rychter et al published an accompanying paper attempting to correlate GIST genotype with clinical efficacy.[49] *KIT* exon 9 mutation status had prognostic (190% increased relative risk of death compared to patients with *KIT* exon 11 mutation) and predictive (61% relative decrease in risk of progression when treated with high dose imatinib) value. Interestingly, response to high dose imatinib upon progression was high in patients with wild type or *KIT* exon 9 mutations as opposed to *KIT* exon 11 mutants (83%, 57%, and 7%, respectively).
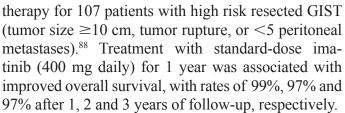
As selection criteria, protocol treatment, and follow-up were similar in the EU-AUS and US-CDN studies, a meta-analysis including all 1640 patients was undertaken-metaGIST.[50] In the pooled data set, a small but statistically significant improvement in progression free survival benefit at 3 years (34% [400 mg bid] vs. 30% [400 mg daily]) was observed. There was no difference in overall survival in the standard versus higher dose treatment arms. Seven factors had adverse prognostic value on multivariate analysis for overall survival: high neutrophil counts, poor performance status, advanced age, low albumin level, prior chemotherapy, large tumor size, and male sex. Having a *KIT* exon 9 mutation was the only factor predictive of benefit for high dose imatinib on multivariate analysis. As a result, for unresectable or metastatic GIST both the NCCN and ESMO guidelines recommend a dose of 800 mg daily for patients with *KIT* exon 9 mutation.[51,52]

Adjuvant

Despite resection of all macroscopic GIST, five year survival is 54% and disease free survival is 45%.[53] Accurate risk stratification is crucial for the selection of patients most likely to benefit from adjuvant imatinib therapy; factors that predict relapse after surgical resection include tumor size, mitotic index, primary site, microvessel density, and presence and site of *KIT* mutation.[87] The Gold nomogram predicts recurrence free survival at two and five years after surgery based on tumour size, location, and mitotic index; the predictive ability of the nomogram is superior to National Institute of Health consensus classification system and not statistically different from the Miettinen-Lasota/Armed Forces Institute of Pathology classification system.[54] Importantly, the Gold nomogram has never been prospectively evaluated and the agreement on mitotic index between pathologists varies.

Nilsson and colleagues treated 23 consecutive patients at a single centre with completely resected GIST at high risk for relapse (based on a risk score of tumor size and the Ki-67 maximum proliferative index) with one year of imatinib 400 mg daily.[55] After a median follow-up of three years, only one of the 23 (4%) patients developed recurrent disease compared to 32 out of 48 patients (67%) in the historical control group. The American College of Surgeons Oncology Group (ACOSOG) Z9000 conducted a single-arm phase II multicenter trial of adjuvant

therapy for 107 patients with high risk resected GIST (tumor size ≥10 cm, tumor rupture, or <5 peritoneal metastases).[88] Treatment with standard-dose imatinib (400 mg daily) for 1 year was associated with improved overall survival, with rates of 99%, 97% and 97% after 1, 2 and 3 years of follow-up, respectively.

The ACOSOG Z9001 trial, a multinational phase III trial, examined differences in recurrence free survival (defined as the time from randomization to the development of tumor recurrence or death due to any cause) based on assignment to 1 year of 400 mg imatinib daily (n = 359) or placebo (n = 354).[56] All patients were at least 18 years if age, had *KIT*-positive GIST tumours at least 3 cm in size, and had undergone complete gross tumor resection within 84 days of randomization. Importantly, patients were stratified by tumor diameter but not mitotic rate, tumour site, or rupture on the grounds that these prognostic indicators have not been validated prospectively. Treatment was stopped prematurely in 184 (25.8%) patients; discontinuation was more likely due to adverse events in the imatinib arm ($P < 0.0001$) and tumor recurrence in the placebo arm ($P < 0.0001$). With a median follow-up of 19.7 months, the one-year RFS was 98% (95% CI 0.96–1.00) on the imatinib arm versus 83% (95% CI 0.78–0.88) on the placebo arm; the overall hazard ratio was 0.35 (95% CI 0.22–0.53) with a *P*-value <0.0001. At the time of reporting, there was no significant treatment difference in overall survival (HR = 0.66 [95% CI 0.22–2.03]). On multivariate analysis, factors predictive of recurrence in the placebo group were mitotic rate ($P < 0.0001$), tumor size ($P < 0.0026$), small bowel location (vs. gastric location; $P < 0.0267$), and *KIT* exon 11 mutations (vs. wild type; $P = 0.042$). Subgroup analysis revealed that patients with large tumors (greater than 10 cm in diameter) derived the greatest benefit from imatinib treatment. Based on the findings of the ACOSOG Z9001 trial, the EMA and FDA approved adjuvant imatinib as a treatment option in patients at substantial risk of relapse.[57,58]

One of the most compelling questions regarding adjuvant treatment of resected GIST, is the optimal duration of imatinib. The Scandinavian Sarcoma group's SSG XVIII/AIO trial is an open label phase III trial comparing 1 year (n = 200) versus 3 years (n = 200) of imatinib therapy after surgical resection.[59] All patients were high risk according to the modified Consensus criteria (based on tumor size, mitotic count, and tumor rupture).[60] 5 year recurrence free survival was significantly longer in the group treated for 3 years (65.6% [3 years] vs. 47.9% [1 year]); importantly, overall survival was also significantly higher at 5 years with longer duration of treatment (92% [3 years] vs. 81.7% [1 year]). However, 27 patients assigned to 3 years of imatinib discontinued treatment early due to adverse events, while only 15 patients treated for 1 year stopped treatment due to side-effects. All but two patients in the entire trial were free of any adverse effects; grades 3 and 4 adverse events more common in the group treated for longer duration (20% [1 year] vs. 33% [3-years]).

The SSG XVIII/AIO trial raises a number of significant issues. First, high risk according to the modified consensus criteria, includes patients with a risk of relapse ranging from 34% to 100%; it remains uncertain if all such patients actually benefit from adjuvant therapy, or if a higher cut-off value could be used. Second, in the ACOSOG Z9001 trial patients treated with one year of imatinib therapy experienced a high rate of relapse approximately six months after therapy cessation; whether longer duration of adjuvant therapy might actually increases overall survival or simply delays relapse, will become clearer with longer follow-up. Last, it is uncertain if *KIT* exon 9 mutants might benefit from imatinib 800 mg daily as is the case with advanced disease.

Neoadjuvant

At present, published literature on neoadjuvant imatinib therapy is limited to surgical series, two phase II trials, and retrospective subgroup analysis of a phase III trial. McAuliffe and colleagues randomized 19 patients to receive preoperative imatinib 600 mg daily for 3, 5, or 7 days followed by two years of imatinib at a similar dose; primary endpoint of the phase II study was tumor cell apoptosis and secondary endpoints were patient safety, disease free survival, and radiographic response.[61] Compared to historical surgical controls, there was no difference in surgical morbidity. Approximately two thirds of patients demonstrated responses as seen on PET scan or decreased tumor blood flow assessed by dynamic CT. Interesting, while the degree of apoptosis increased with longer duration of preoperative treatment, this did not correlate with prolonged disease free survival. In the phase II

Radiation Therapy Oncology Group 013/American College of Radiology Imaging Network 6665, preoperative imatinib 600 mg daily for 2 to 3 months was followed by postoperative therapy for two years at the same dose.[62] In the subgroup of patients with locally advanced disease (defined as tumors at least 5 cm in diameter) 2 year overall survival and progression free survival was 93% and 83% respectively. A retrospective sub-analysis of the BFR14 phase III trial, evaluated the efficacy of neoadjuvant imatinib in patients with locally advanced GIST (as defined by local multidisciplinary team).[63] Nine of the 25 assessed patients underwent complete resection following a median of 7.3 months of imatinib treatment; six of these patients had sufficient tumor shrinkage to facilitate resection while three patients went to surgery due to early signs of progression. A superior progression free survival was observed in patients who underwent surgical resection compared with those who did not who did not (not reached vs. 23.6 months, $P = 0.0322$). The optimal role of neoadjuvant imatinib therapy in daily practice is unclear at the moment; NCCN guidelines recommend initial treatment with imatinib for patients with marginally resectable tumours and for those who have potentially resectable disease but with the risk of significant morbidity.[64]

Side-effects

Virtually all patients treated with imatinib have at least one adverse event and 21%–43% experience a Grade 3 or 4 adverse events.[65] Most side effects occur early in the course of treatment and tend to reduce in frequency and intensity over time. This phenomenon has been correlated with increased imatinib clearance with long-term treatment.[66] Utilizing safety data from the EU-AUS phase III study of standard or high dose imatinib for advanced GIST, Van Glabbeke et al determined patient and tumor characteristics that predicted for grade 2 or higher non-hematologic toxicities (edema, fatigue, nausea, diarrhea, and skin rash) and grade 3 or 4 hematologic adverse effects (anaemia and neutropenia).[67] High dose was correlated with anaemia and all the previously listed non-hematologic adverse effects. Female patients were more likely to experience edema, fatigue, nausea, and diarrhea; this may relate to lower on average weight compared to male counterparts, leading to reduced clearance and higher AUC.[68] In the EU-AUS study, advanced age was associated with dermatologic toxicity and fatigue; lastly, fatigue and nausea were more common in patients with a poor performance status.

The most common hematologic toxicities are anaemia and neutropenia. Unlike neutropenia, anemia is dose dependent; in the S0033 phase III trial, about 20% of patients on standard dose imatinib and 27% on high dose imatinib experienced grade 3 or 4 hematologic toxicity.[45] Baseline low hemoglobin is a risk factor for anemia and neutropenia while on treatment, as the AUC is greater than in patients with a normal baseline hemoglobin level.

Dermatologic side-effects are common and include edema and maculopapular eruptions. Edema occurs in about 39%–74.1% of imatinib treated patients and is typically localized to the periocular or pedal regions.[69] While the exact physiology is unknown, a common explanation is increased capillary permeability and extravasation of fluid due to inhibition PDGFR signalling in dermal dendrocytes. Mild cases of periorbital edema may be treated with a low-salt diet, topical 1% hydrocortisone, 0.25% topical phenylephrine, or oral diuretics.[68] Rarely, severe periorbital edema may require drug cessation or surgical intervention with bilateral upper eyelid blepharoplasty. Imatinib induces self-limited non-specific maculopapular eruptions in 30%–40%; classic drug-associated skin manifestations, such as vasculitis, Stevens-Johnson syndrome, and toxic epidermal necrosis are documented in case reports.[69]

As several other tyrosine kinase inhibitors (ie, sunitinib) are known to have deleterious effects on cardiac function, recent studies have examined potential cardiotoxicity from long term imatinib therapy. Kerkela et al identified ten imatinib treated patients with CML who developed heart failure.[70] On transmission electron micrographs, mitochondrial abnormalities and accumulation of membrane whorls in the endoplasmic reticulum (ER) suggested a toxic myopathy. In vitro assays of imatinib treated myocytes revealed activation of ER stress pathways leading to mitochondrial collapse and apoptosis. While prospective studies are lacking, to date there is no conclusive evidence of imatinib directly causing cardiac damage in humans. Of 942 treated patients in the EU-AUS study, there were 7 documented episodes of cardiac failure and 3 deaths due to cardiac events.[71]

However, excluding patients with pre-exciting cardiac dysfunction or prior exposure to doxorubicin left only 2 patients (0.2% of all treated patients) where imatinib was the only potential cause of cardiac failure. Similarly, Trent el al reviewed cardiac safety data of 219 patients with GIST and other sarcomas treated with imatinib;[72] 5 patients had objective evidence of cardiac ischemia or chest pain, 2 patients had documented arrhythmias, and only 1 had objective left ventricular dysfunction by echocardiography. Until a causal association between imatinib exposure and cardiac damage can be excluded, patients with cardiac disease or risk factors for cardiac failure should be monitored carefully and those developing signs or symptoms suspicious for cardiac failure are evaluated and treated.

Resistance

Approximately 80% of GIST patients with advanced disease receive some benefit from imatinib therapy, but a significant proportion eventually become resistant with a median time to progression of 2 years. To better understand the mechanisms underlying the two patterns of resistance, it is important to appreciate the three dimensional structure of KIT. The intracellular portion of KIT consists of a juxtamembrane domain and proximal and distal kinase (including the activation loop) regions separated by a kinase insertion domain. These regions can either be configured in an "open/on" conformation which allows ATP to bind or a "closed/off" conformation which facilitates phosphorylation of substrates.[73] Trans-phosphorylation of two tyrosine residues in juxtamembrane domain (Y568 and Y570) causes: (1) a steric shift allowing ATP to bind to the proximal domain (2) release and phosphorylation of the activation loop which helps maintain an "open/on" conformation. Imatinib can only attach to the off conformation and functions to maintain the receptor in this state. However, most KIT mutations and PDGFRA mutations promote the open conformation, thereby reducing the efficacy of imatinib.

A potentially important mechanism of early resistance results from subtherapeutic imatinib plasma levels. In a retrospective analysis of 73 patients with advanced GIST from the B2222 trial, Demetri et al, correlated imatinib trough level (Cmin) on day 29 with long term outcome.[74]

Patients in the lowest Cmin quartile ($\geq$1,100 ng/mL) had a significantly shorter time to progression (11.3 months) when compared to patients in the upper three quartiles (30.6 months, $P = 0.0029$). In addition, amongst the subset of patients with KIT exon 9 mutation, the objective overall response rate (includes patients with complete and partial response and stable disease) was inferior in the lowest Cmin quartile compared to all others. No significant differences in median overall survival was found between different Cmin quartiles.

Acquired resistance, unlike primary resistance, typically involves secondary mutations (67% vs. 10%, respectively) in either the ATP binding pocket of the kinase domain (exons 13 and 14) or the kinase activation loop (exons 17 and 18).[75] Secondary mutations develop more often in tumours with a primary exon 11, rather than exon 9 mutated KIT (60% and 20% of the cases, respectively). Alternate mechanisms of delayed resistance include: amplification of KIT or PDGFRA gene, activation of alternate tyrosine kinases (AXL, or insulin-like growth factor-1 receptor), efflux of intratumoral imatinib via ABC drug pumps.[73]

Patient Preferences

While imatinib is well tolerated compared to cytotoxic therapy, patients will experience at least mild adverse effects. Drug holidays and dose reductions are not without risk as discontinuation of imatinib administration can results in rapid tumor progression. The French Sarcoma Group BFR14 study demonstrated that interruption amongst patients with disease control after 1 year of imatinib therapy, yielded a median time to progression of 6 months, and most patients had relapsed 1 year after treatment interruption.[76] Feng and colleagues attempted to quantify compliance in imatinib treated patients with CML (n = 286) and GIST (n = 34) and reasons for nonadherence.[77] Only 76% of all doses prescribed were filled within the first year and 28% of patients required at least a 30 day drug interruption. On multivariate analysis, factors associated with non-compliance included: increasing age, female gender, and patients with more cancer complications.

Place in Therapy

Although imatinib is unquestionably effective, other treatment options are inevitably necessary as

approximately 10%–15% of GIST patients show primary resistance to imatinib, 50% develop secondary imatinib resistance within 2 years and 4% of patients are intolerant to imatinib therapy. Metastatectomy is useful in a highly selected group of patients. The nodule-within-a-tumor phenomenon, is a common radiologic sign of progression and signifies the emergence of a resistant clone of cells.[78] Surgical excision of a few progressing lesions has yielded positive results in nonrandomized studies and imatinib can continued to be used to maintain pressure on sensitive clones.[79] However, individuals with multifocal progression require change in systemic therapy.

Sunitinib maleate (SUTENT, previously known as SU11248; Pfizer, New York, USA) is an oral multitargeted receptor tyrosine kinase inhibitor of KIT, PDGFR alpha and beta, vascular endothelial growth factor receptors (VEGFR-1, -2 and -3), FMS-like tyrosine kinase 3, colony-stimulating factor 1 receptor, and the glial cell line–derived neurotrophic factor receptor.[75] Due to its broader spectrum of activity, suntinib also causes a different spectrum of potentially serious adverse events such as hypertension, hypothyroidism, and heart failure. A phase I/II trial of GIST patients after imatinib failure due to resistance or intolerance, established a maximum tolerated dose of 50 mg/d for four weeks of a six week cycle.[80] Of ninety-seven treated patients, 7 (7%) achieved a partial response and 35 (46%) had stable disease as assessed by CT scan; dose limiting toxicities were fatigue, diarrhea, and nausea. Detailed genotype analysis of all treated patients by Heinrich and colleagues revealed improved outcomes in *KIT* exon 9 compared to exon 11 mutant tumours in terms of response rate (37% vs. 5%), progression free survival (19.4 months vs. 19.0 months) and overall survival (26.9 month and 12.3 months). Median progression free survival and overall survival were similarly improved in sunitinib treated wild type tumours in comparison to exon 11 mutant tumors.[81]

A placebo controlled randomized trial of sunitinib therapy for advanced GIST in patients resistant to or intolerant of imatinib, demonstrated an improved median time to progression (27.3 weeks for sunitinib versus 6.4 weeks for placebo) and progression free survival (24.1 weeks and 6 weeks).[82] Median overall survival using the Kaplan-Meier technique between sunitinib treated patients (73.9 weeks) and those receiving placebo (64.9 weeks) was not statistically significant. The most common grade 3 adverse events were palmar plantar erythrodysesthesia, fatigue, and diarrhea; 19 (9%) sunitinib treated patients discontinued therapy because of adverse events.

Enrolment in a clinical trial is recommended for patients with GIST who have progressed on imatinib and sunitinib; Table 2 lists many such agents currently being tested. In particular, a number of second generation tyrosine kinase inhibitors and novel proteins are being tested. Nilotinib (Tasigna®, Novartis Pharma AG, Basel, Switzerland) was formulated based on the crystal structure of imatinib, to have high efficacy against imatinib resistant BCR-ABL mutants.[83] In vitro studies have shown nilotinib to be a potent inhibitor of several *KIT* mutant cell lines: exon 11 $KIT^{V560del}$, exon 13 KIT^{K642E}, and double mutations involving *KIT* exons 13 or 17.[83] The Evaluating Nilotinib Efficacy and Safety in Clinical Trials (ENEST g3) compared nilotinib with best supportive care. Importantly best supportive care comprised a heterogeneous group of patients including: those still receiving imatinib (n = 54), sunitinib (n = 23), and patients who had progressed on both (n = 6).[84] No statistically significant differences in progression free survival or overall survival were found between the nilotinib and control arms. An exploratory post hoc analysis indicated that nilotinib provided a 4-month improvement in median OS in true third line patients (median overall survival, 57.8 weeks nilotinib vs. 40 weeks). As a result, a current

Table 2. Selected agents under study and their main targets.

Nilotinib (AMN107)	KIT, PDGFRA/B, Abl
Sorafenib (BAY 43-9006)	KIT, PDGFRB, VEGFR 2/3, Raf, Flt-3, RET
Vatalanib (PTK787/ ZK222584)	KIT, PDGFA/B, VEGFR1-3
IPI-504 (retaspimycin)	HSP90 inhibitor
STA-9090	HSP90 inhibitor
B11B021	HSP90 inhibitor
Bortezomib	26S proteosome inhibitor
Everolimus (RAD001)	mTOR inhibitor
Ridaforolimus (AP23573)	mTOR inhibitor
Vorinostat	Histone deacetylase inhibitor
CUDC101	Histone deacetylase inhibitor
Panobinostat	Histone deacetylase inhibitor
PF-04691502	PI3K, mTOR inhibitor

phase III study is underway, comparing nilotinib versus placebo in adult patients with advanced GIST resistant to imatinib and sunitinib.

Heat shock proteins (HSP) are molecular chaperones involved in posttranslational folding, stability, activation and maturation of many proteins integral to signal transduction and cell cycle progression.[85] HSP90 is essential for the stability and the function of many oncogenic proteins including: Her2, BCR-ABL, AKT/PKB, C-RAF, VEGFR, and FLT3. In GISTs, it was hypothesized that HSP90 inhibition would dampen growth signals emanating from the mutated receptor and ultimately inhibit cell growth. However, efficacy in clinical trials has been mixed and a phase III study with IPI-504, a water-soluble HSP90 inhibitor, was terminated early due to the occurrence of four on treatment deaths in the study drug arm.[86]

Conclusion

Just over a decade ago, GIST were a poorly characterized mesenchymal neoplasm with a guarded prognosis due to chemo and radioresesistance. However, with discovery that imatinib targeted mutant KIT and PDGRFA receptors, median overall survival tripled. The B2222 study, with 35% of patients alive at 9 years of follow-up, highlights the potential of long term survival. In fact, GIST has become a model for the development of other targeted therapies. However, management paradigms will continue to evolve as ongoing studies accrue. For instance, the optimal duration of adjuvant treatment at the present time is unknown. In the metastatic setting, further research will need to focus on management of low grade adverse effects which effect compliance in the long term. Last, the place of other tyrosine kinase inhibitors and novel proteins which target downstream signal transduction pathways in treatment algorithms will need to be clarified.

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