Pharmacogenetics and cost-effectiveness of systemic treatment in soft tissue sarcoma

Verboom, M.C.

Part I: Pharmacogenetics of systemic GIST-treatment

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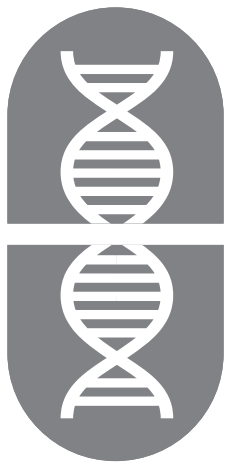
Systemic treatment of advanced gastro-intestinal stromal tumors

Michiel Verboom, Hans Gelderblom



Summary

The treatment of advanced gastrointestinal stromal cell tumors (GIST) includes three lines of tyrosine kinase inhibitors: imatinib, sunitinib and regorafenib. Each of these agents bind intracellular to KIT and PDGFRA receptors, that may cause unlimited cell proliferation due to a somatic mutation in the tumor. Sunitinib and regorafenib also inhibit angiogenesis. Imatinib and sunitinib have been registered for some years; in July 2014 regorafenib was registered as well. The development of nilotinib has been terminated after a negative phase III trial. In this chapter the development of these drugs in GIST are reviewed, as well as their respective mechanisms of resistance. Furthermore, new developments in systemic therapy are evaluated, and current and future clinical trials with GIST patients in the Netherlands are highlighted.

Introduction

Gastrointestinal stromal tumors (GIST) is a rare mesenchymal tumor, that can arise in the entire digestive tract.[1] It is estimated that up to 35% of the population have microscopic small GISTs, but only 250 patients are diagnosed in a clinically relevant stage in the Netherlands each year.[2,3] In case of advanced disease multiple options for systemic therapy can be considered. This chapter aims to review the developments in the systemic treatment of GIST, as well as current clinical studies in the Netherlands.

GIST is characterized by immunohistochemical staining of CD117 (KIT) and the even more specific DOG1 (Discovered On GIST 1).[4] Malignant transformation from the interstitial cells of Cajal, that function as a pacemaker in intestinal peristalsis, occurs due to mutations in the tyrosine kinase receptor KIT in the majority of cases.[5,6] In physiologic conditions, this receptor can be activated by the stem cell factor, for instance in melanocytes, gametogenesis, mast cells and in hematopoiesis. In GIST, a somatic mutation in the KIT receptor or in the platelet-derived growth factor receptor (PDGFRA) causes permanent activation of the downstream pathway through receptor autophosphorylation, leading to unbridled growth.[7] In a subset of GISTs a mutation in either of these receptors is not found. In this 'wild type' group more new mutations are found, for instance in NF1 and SDH*x*, making the term wild type possibly obsolete in the future.[8,9] For an overview of the prevalent KIT-, PDGFR- and so-called 'wild type mutations', see Table 1.

Imatinib (Glivec®, Novartis) has a clear position in the treatment of advanced GIST and the agent can also be used in the neo-adjuvant or adjuvant stage in locally advanced or high risk GIST, respectively.[10] Imatinib is an oral tyrosine kinase inhibitor (TKI) of KIT and PDGFR, among others. The drug is well tolerated, with gastro-intestinal adverse events, peri-orbital edema and muscle spasms as most frequent side effects.[11] Mutations in KIT exon 11 are sensitive to imatinib in the standard dose of 400 mg. For tumors with a mutation in KIT exon 9 an double dose of 800 mg is advised.[12]

The majority of patients have an objective response to imatinib.[11] Patients with stable disease as best response have an equal as good chance of long term efficacy. Very long term results have been published from a large randomized trial investigating the optimal imatinib dose. In the EORTC-Italian-Australasian trial, patients receiving imatinib 400 mg once daily had a median PFS of 20.4 months and median OS of 46.8 months at median 10.9 years of follow-up.[13] Sunitinib is indicated as second-line therapy after progression on imatinib.[10] Sunitinib (Sutent®, Pfizer) is a TKI and an inhibitor of KIT, PDGFR and vascular endothelial growth factor receptor (VEGFR) 1, 2, and 3 and so also has an anti-angiogenic effect. The most frequent adverse events are hypertension, hand-foot syndrome and gastro-intestinal symptoms.[14] Tumors with mutations in KIT exon 9 are relatively sensitive to sunitinib, which has two standard starting regimens; either 50

mg every four out of six weeks, or 37.5 mg continuously.[15] The median progression free survival is only 5.3 months, despite long term clinical benefit in some patients.[14]

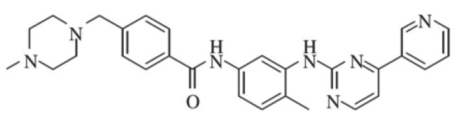
For an overview of published phase III studies with imatinib and sunitinib, see Table 2.

For the structure of imatinib, sunitinib, regorafenib, sorafenib and nilotinib, see Figure 1.[37]

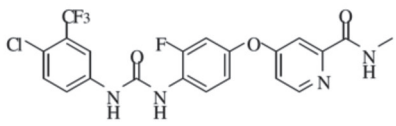
Table 1: overview of oncogenic mutation in GIST

KIT		
	exon 8	± 0.2 %
	exon 9	9 - 10 %
	exon 11	60 - 70 %
	exon 13	1 - 2 %
	exon 17	1 - 2 %
KIT total		70 - 80 %
PDGFRa		
	exon 12	1 - 2 %
	exon 14	± 0.6 %
	exon 18	10 - 14 %
PDGFRa total		11 - 15 %
'wild-type'		
	NF1 associated	± 1.1 %
	SDHx associated	1 - 4 %
	BRAF associated	1 - 2 %
	unknown	3 - 12 %
'wild-type' total		10 - 15 %

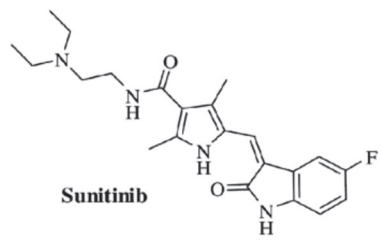
Figure 1: structure of imatinib, sunitinib, regorafenib, sorafenib and nilotinib



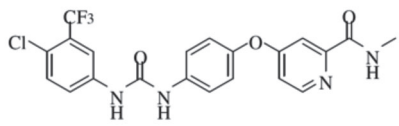
Imatinib



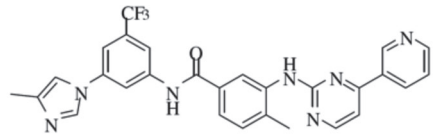
Regorafenib



Sunitinib



Sorafenib



Nilotinib

Mechanisms of resistance

Tumor growth continues in around 15% of patients, despite start of imatinib treatment, which is referred to as primary resistance.[11] In a similar proportion of patients, the (remaining) GIST remains sensitive to imatinib for a very long time, often more than 10 years, and it poses the question if those are cured by then. In the remaining 70% of patients secondary resistance develops over time.
Primary resistance occurs more often in wild-type GIST, in which a mutation in KIT or PDGFR is not found.[16] Possibly, mutations in other pathways play a part in this. Primary resistance also occurs frequently in case of a specific PDGFRa D842V mutation.[16]

Imatinib blood levels are reduced by 30% during the first three months of treatment, which could lead to so called pharmacokinetic resistance.[17] In a subset of patients, the blood level drops 1.100 mg/ml, which is the retrospectively defined target value.[18,19] These cases indicate a possible role for therapeutic drug monitoring and dosage adjustment.[19] Patients with extensive gastric surgery also have lower imatinib and sunitinib blood levels.[20,21] Furthermore, intracellular levels of imatinib can in theory decrease due to an increase of efflux transporters in GIST cells.

Secondary resistance most commonly happens due to growth of tumor clones with a second mutation in KIT or PPDGFR, after which imatinib is unable to bind to the receptor. Possible locations of the secondary mutations are the ATP-binding part (KIT exon 13 or 14), or the kinase activation loop (KIT exon 17 or 18).[22] Secondary mutations can lead to KIT hyperactivation and strong activation of the PI3-K/AKT pathway.[23] Separate tumor clones can have different secondary mutations and this heterogeneity can also occur within a single metastasis. A biopsy taken from a progressive lesion may very well not be representative for the tumor as a whole.[24] Other possible mechanisms of resistance include KIT gene amplification, increasing the quantity of this kinase, and the loss of wild-type GIST, losing the healthy allele.[25] Loss of KIT expression is another possibility, after which the tumor keeps proliferating due to overexpression of other kinases.[26]

In sunitinib treatment resistance also occurs. In around 40% of the patients, the agent does not have effect on tumor growth in the second line after imatinib.[14] Sunitinib is more frequently active if the secondary KIT mutation is located in the ATP-binding part (KIT exon 13 of 14), but much less active if the extra mutation has arisen in the KIT activation loop (KIT exon 17 or 18).[22]

Table 2: overview of clinical studies with imatinib and sunitinib in advanced GIST patients

Trial	Study type	Previous TKI treatment	Drug	No. of patients	Dose	Median PFS (months)	Median OS (months)	Median follow-up (months)	CR (%)	PR (%)	SD (%)	ORR (%)	CBR (%)
Verweij et al. 2003 [55]	phase II	none	Imatinib	27	800 mg	not reached	not reached	> 13	3.7	66.7	18.5	70.4	88.9
Demetri et al. 2002 [56], Blanke et al. 2008 [57]	phase II	none	imatinib	73	400 mg	20.0	57.0	63.0	0.0	68.5	13.7	68.5	82.2
				74	600 mg	26.0			2.7	64.9	17.6	67.6	85.1
Verweij et al. 2004 [11], Casali et al. 2017 [13]	phase III	none	imatinib	473	400 mg	20.4	46.8	40.0	5.1	45.0	31.7	50.3	81.8
				473	800 mg	24.0			5.9	48.4	31.7	54.3	86.0
Blanke et al. 2008 [58]	phase III	none	imatinib	345	400 mg	18.0	55.0	54.0	4.9	39.7	24.6	44.6	69.3
				349	800 mg	20.0	51.0		3.4	42.4	21.8	45.8	67.6
Nishida et al 2008 [59]	phase II	none	imatinib	28	400 mg	17.0	40.1	Not specified	0.0	60.7	39.3	60.7	100.
				46	600 mg	24.7	not reached		0.0	73.9	17.4	73.9	91.3
Ryu et al. 2009 [60]	phase II	none	imatinib	47	400 mg	40.0	65.0	62.0	0.0	68.1	19.1	68.1	87.2
Yeh et al. 2011 [61]	phase II	none	imatinib	171	400 mg	37.6	71.0	33.6	2.3	55.0	29.8	57.3	87.1
Schlemmer et al. 2011 [62]	compas-sionate use trial	none	imatinib	95	400 mg	not reached	not reached		4.6	29.9	47.1	34.5	81.6
Demetri et al. 2009 [63]	phase I-II	imatinib	sunitinib	97	25-75 mg every 4 out of 6 weeks	7.8	19.0	not specified	0.0	7.2	46.4	7.2	53.6

Shirao et al. 2010 [64]	phase I-II	imatinib	sunitinib	36	50 mg every 4 out of 6 weeks	6.5	not specified	not specified	0.0	11.1	27.8	11.1	38.9
George et al. 2009 [15]	phase II	imatinib	sunitinib	60	37.5 mg continuously	7.9	24.7	not specified	0.0	13.3	66.7	13.3	80.0
Demetri et al. 2006 [14], Demetri et al. 2012 [65]	phase III	imatinib	sunitinib	243	50 mg every 4 out of 6 weeks	5.3	16.8	41.7	0.0	6.6	52.7	6.6	59.3
			placebo	118	placebo	1.4	15.0		0.0	0.0	42.4	0.0	42.4
Reichardt et al 2015 [66]	compas-sionate use trial	imatinib	sunitinib	1124	50 mg every 4 out of 6 weeks	8.3	16.6	34.6	0.0	8.0	60.0	8.0	68.0

PFS = progression free survival, OS = overall survival, CR = complete response, PR = partial response, SD = stable disease
CBR = clinical benefit rate (at least stable disease), ORR = objective response percentage

Third line agents

Regorafenib

Regorafenib (Stivarga®, Bayer) is an oral multiple TKI and derived from sorafenib. In this 'fluoro-sorafenib' an extra fluorine-atom protrudes halfway the molecule from the carbon ring, expanding the list of target receptors. Next to VEGFR 1, 2 and 3 the agents inhibits tyrosine kinase with immunoglobin and epidermal growth factor domain 2 (TIE2), the fibroblast growth factor receptor (FGFR) and PDGFR. The oncogenic kinases KIT, RET and RAF are also inhibited.[27] The standard dose regimen is 160 mg each day during 3 weeks in cycles of 4 weeks.[28]

The efficacy in GIST was demonstrated in a phase II study with 34 GIST patients, who had progressive disease on imatinib and sunitinib, of whom 27 patients (79%) had stable disease for at least 3.7 months. The median progression free survival was 10 months in the original publication.[29] Efficacy data have also been updated and the median PFS went to 13.9 months with the longer follow-up, and median OS was 25.0 months instead of not being reached.[30] In a subsequent randomized placebo controlled phase III GRID study with 199 GIST patients, who were progressive after imatinib and sunitinib, regorafenib gave a median progressive free survival of 4.8 months versus 0.9 for placebo (P= 0,0001).[31] After progression on placebo patients switched to regorafenib. In part due to this, the overall survival was not significantly different (hazard ratio 0,77, P= 0.199). The drug has a considerable toxicity profile and in the majority of patients (72%) the dose had to be reduced, but in only 6% of patients was it stopped. The most frequent grade 3 adverse event was hypertension (23%), which is a class effect. Hand-foot syndrome is also prevalent (20%), but could be treated adequately.[31]

In July 2014, regorafenib was approved by the EMA for the treatment for imatinib and sunitinib resistant GIST, following FDA approval in February 2013. The CieBOM has published a positive advice in February 2014 and called the drug an effective third line therapy for GIST with manageable toxicity.[32]

Nilotinib

Nilotinib (Tasigna®, Novartis) is an oral inhibitor of Bcr-Abl, KIT and PDGFR. The recommended dose is 400 mg twice daily, as was found in a phase I study, which also demonstrated efficacy in imatinib-resistant CML.[33] The intracellular concentration of nilotinib in GIST cell lines is higher than of imatinib, and as such pharmacologic resistance would pose a smaller risk.[34]

A phase III study in which nilotinib and imatinib were evaluated in the *first* line was terminated prematurely after 397 patients, because the risk of progressive disease was twice as large for the nilotinib treatment versus imatinib treatment (Hazard ratio 2.032).[35]

To test the clinical value of nilotinib in GIST patients in the *third* line a phase III study was performed with 248 patients.[36] Nilotinib was compared to best supportive care, with the option to prescribe imatinib and sunitinib in the latter arm. To be eligible for inclusion patients had to either have progressive disease on imatinib and sunitinib, or to be intolerant for both of these agents. Due to this study design nilotinib was not consistently assessed as third line agent.

The median progression free survival at central radiologic review, the primary end point, was not different in either treatment group (3.6 months, p= 0.56); at local evaluation of progression nilotinib was superior to the best supportive care group with 3.9 months versus 2.3 months, respectively (p=0.0007). In a subgroup analysis, in which only 197 imatinib and sunitinib *resistant* patients were compared, nilotinib had a 4 months longer overall survival (13.2 months versus 9.2 months).[36] Unfortunately, this was not the primary end point, meaning further development of nilotinib for the indication GIST was ceased.

For an overview of clinical studies with nilotinib and regorafenib as third line treatment, see Table 3.

Other agents

A large number of other agents have been tested in phase II studies in GIST, most of which are TKI's. For an overview of clinical studies with drugs that have tested in advanced GIST patients, see Table 4.

Combination therapies

Despite the success of TKI monotherapy, new treatment options are needed for patients with progressive disease after treatment with registered agents. As previously mentioned, GIST metastases are often heterogeneous at progressive disease and a treatment is desired that interferes at a lower point in the downstream pathway of KIT, such as the PI3-K/AKT pathway. This concept is investigated in studies that combine simultaneous PI3-K inhibitors and imatinib.

Phosphatidylinositol 3-kinases (PI3-K) comprises a group lipase kinases in the PI3-K/AKT pathway, which in physiologically conditions are involved in protein synthesis, glucose metabolism, angiogenesis and cell proliferation and migration.[38] PI3-K activity can be inhibited by PTEN, a tumor suppressor enzyme. Activation of the PI3-K/AKT pathway is an important step in tumor genesis and cell growth in a large number of tumors. This can lead to inhibition of PTEN and overexpression of AKT. In GIST, it can be activated dependent or independent of KIT.[39] There are three different classes of PI3-kinases, and generic and specific inhibitors of PI3-kinas are being explored. The new agents are tested as monotherapy and in combination with other drugs in different tumors, including GIST.

Table 3: overview of clinical studies with regorafenib and nilotinib in advanced GIST patients

Trial	Study type	Previous TKI treatment	Drug	No. of patients	Dose	Median PFS (months)	Median OS (months)	Median follow-up (months)	CR (%)	PR (%)	SD (%)	ORR (%)	CBR (%)
George et al. 2012 [29], Ben-Ami 2016 [30]	phase II	imatinib and sunitinib	regorafenib	33	160 mg every 3 of 4 weeks	13.2	25.0	41.0	0.0	18.1	57.6	18.1	75.6
Demetri et al. 2013 [31]	phase III	imatinib and sunitinib	regorafenib	133	160 mg every 3 of 4 weeks	4.8	not reached	not specified	0.0	4.5	71.4	4.5	75.9
			placebo	66	placebo	0.9	not reached		0.0	1.5	33.3	1.5	34.6
Montemurro et al. 2009 [67]	compassionate use trial	imatinib and sunitinib	nilotinib	52	400 mg twice daily	2.8	7.8	6.5	1.9	7.7	36.5	9.6	46.2
Kim et al. 2011 [68]	compassionate use trial	imatinib and sunitinib	nilotinib	17	400 mg twice daily	5.4	17.1	not specified	0.0	11.8	58.8	11.8	70.6
Sawaki et al. 2011 [69]	phase II	imatinib and sunitinib	nilotinib	35	400 mg twice daily	3.7	10.2	not specified	0.0	2.9	65.7	2.9	68.6
Cauchi et al. 2012 [70]	phase II	imatinib and sunitinib	nilotinib	13	400 mg twice daily	2.0	not specified	not specified	0.0	0.0	30.8	0.0	30.8
Reichardt et al. 2013 [36]	phase III	imatinib and sunitinib	nilotinib	165	400 mg twice daily	3.6	10.9	not specified	0.0	0.6	52.1	0.6	52.7
			Best supportive care, TKI's allowed	83	BSC, including TKI treatment	3.6	9.2		0.0	0.0	44.6	0.0	44.6
Blay et al. 2015 [35]	phase III	none (first line)	nilotinib	324	400 mg twice daily	25.9	not reached	not specified	-	-	-	-	-
			imatinib	320	400 mg	29.7	not reached		-	-	-	-	-

PFS = progression free survival, OS = overall survival, CR = complete response, PR = partial response, SD = stable disease
CBR = clinical benefit rate (at least stable disease), ORR = objective response percentage, BSC = best supportive care

Table 4: overview of clinical studies with (combinations of) drugs that have been tested in advanced GIST patients (continued on next pages)

Trial	Study type	Previous TKI treatment	Drug	No. of patients	Dose	Median PFS (months)	Median OS (months)	CR (%)	PR (%)	SD (%)	ORR (%)	CBR (%)
Bendell et al. 2016 [71]	phase II	imatinib and sunitinib	AUY922	25	70 mg/mg^2	3.9	8.5	0.0	4.0	60.0	4.0	60.0
Leahy et al. 2007 [72]	phase II	imatinib	brostallicin	21	10 mg/m^2 every three weeks	2.2	9.9	0.0	0.0	42.1	0.0	42.1
Edmonson et al. 2002 [73]	phase II	none	combination chemotherapy	21	a cycle every three weeks	7.3	16.7	0.0	4.8	-	4.8	-
Dickson et al. 2013 [74]	phase II	imatinib and sunitinib	BIIB021	25	400 or 600 mg thrice per week	1.2	not specified	0.0	0.0	43.5	0.0	43.5
Judson et al. 2014 [75]	phase II	imatinib and sunitinib	cediranib	24	45 mg once daily	2.0	not specified	0.0	0.0	45.8	0.0	45.8
Trent et al. 2011 [76]	phase II	imatinib	dasatinib	50	70 mg twice daily	2.0	19.0	0.0	31.9	-	31.9	-
Montemurro et al. 2018 [77]	phase II	none	dasatinib	42	70 mg twice daily	13.6	not reached	33.3	40.4	14.3	73.8	88.1
Kang et al. 2013 [78]	phase II	imatinib and sunitinib	dovitinib	30	500 mg every 5 of 7 days	3.6	9.7	0.0	3.3	70.0	3.3	70.0
Joensuu et al. 2017 [79]	phase II	imatinib and sunitinib	dovitinib	38	500 mg every 5 of 7 days	4.8	not specified	0.0	2.6	50.0	2.6	52.6
Kang et al. 2013 [80]	phase II	imatinib and sunitinib	imatinib	41	400 mg once daily	1.8	8.2	0.0	0.0	41.4	0.0	41.4
Schöffksi et al. 2010 [81]	phase II	imatinib	imatinib and everolimus	28	600 mg/ 2.5 mg once daily	1.9	14.9	0.0	0.0	35.7	0.0	35.7

Table 4: (continued)

Trial	Study type	Previous TKI treatment	Drug	No. of patients	Dose	Median PFS (months)	Median OS (months)	CR (%)	PR (%)	SD (%)	ORR (%)	CBR (%)
Schöffksi et al. 2010 [81]	phase II	imatinib and sunitinib	imatinib and everolimus	47	600 mg/ 2.5 mg once daily	3.5	10.7	0.0	2.1	42.6	2.1	44.7
Le Cesne et al. 2010 [51]	phase II	none	masitinib	30	7.5 mg/kg once daily	41.3	not reached	3.3	50.0	43.3	53.3	96.7
Adenis et al. 2014 [52]	phase II	imatinib	masitinib	23	12 mg/kg/day	3.7	29.8	-	-	-	-	-
			sunitinib	21	50 mg every 4 out of 6 weeks	1.9	17.4	-	-	-	-	-
Sawaki et al. 2010 [82]	phase II	imatinib	motesanib	35	125 mg once daily	3.7	not specified	0.0	2.9	54.3	2.9	57.1
Benjamin et al. 2011 [83]	phase II	imatinib	motesanib	102	125 mg once daily	3.7	14.8	0.0	2.9	58.8	2.9	61.8
Chugh et al. 2005[84]	phase II	none	9-Nitro-Camptothecin	13	1.25 mg/m^2 every 5 of 7 days	1.8	not specified	-	-	-	-	-
Trial	Study type	Previous TKI treatment	Drug	No. of patients	Dose	Median PFS (months)	Median OS (months)	CR (%)	PR (%)	SD (%)	ORR (%)	CBR (%)
Wagner et al. 2017 [85]	phase II	imatinib and sunitinib	olaratumab	21	20 mg/kg every 14 days	not specified	not specified	0.0	0.0	23.8	0.0	23.8
Ganjoo et al. 2014[86]	phase II	imatinib and sunitinib	pazopanib	25	800 mg once daily	1.9	10.7	0.0	0.0	48.0	0.0	48.0

Mir et al. 2016 [87]	phase II	imatinib and sunitinib	pazopanib	40	800 mg once daily	3.4	17.8	0.0	0.0	80.0	0.0	80.0
Heinrich et al. 2015 [88]	phase II	imatinib, sunitinib and regorafenib	ponatinib	45	45 mg once daily	2.0	13.5	0.0	4.4	48.9	4.4	53.3
Demetri et al. 2010 [89]	phase III	imatinib and sunitinib	retaspimycin (IPI-504)	32	400 mg/m^2 twice weekly	1.2	not specified	0.0	0.0	68.8	0.0	68.8
Kindler et al. 2011 [90]	phase II	imatinib and sunitinib	sorafenib	38	400 mg twice daily	5.2	11.6	0.0	13.2	55.3	13.2	68.4
Park et al. 2012 [91]	phase II	imatinib and sunitinib	sorafenib	31	400 mg twice daily	4.9	9.7	0.0	12.9	51.6	12.9	64.5
Trent et al. 2003 [92]	phase II	none	temozolomide	19	75 mg/m^2 once daily	2.3	26.4	0.0	0.0	22.2	0.0	22.2
Garcia del Muro et al. 2005 [93]	phase II	none	temozolomide	18	75 mg/m^2 once daily	2.4	19.4	0.0	0.0	-	0.0	-
Blay et al. 2004 [94]	phase II	none	trabectedin	28	1.5 mg/m^2 every three weeks	1.7	19.6	0.0	0.0	33.3	0.0	33.3
Ryan et al. 2012 [95]	phase II	none	trabectedin	20	1.5 mg/m^2 every three weeks	1.3	8.6	0.0	0.0	10.5	0.0	10.5
Joensuu et al. 2008 [96]	phase II	imatinib and sunitinib	vatalanib	15	1250 mg once daily	8.5	not specified	0.0	13.3	53.3	0.0	66.7
Joensuu et al. 2011 [97]	phase II	imatinib and sunitinib	vatalanib	45	1250 mg once daily	4.5	not specified	0.0	4.4	35.6	4.4	40.0

PFS = progression free survival, OS = overall survival, CR = complete response, PR = partial response, SD = stable disease
CBR = clinical benefit rate (at least stable disease), ORR = objective response percentage

BKM120 (buparlisib, Novartis) is an oral PI3-K inhibitor with high specificity for all classes of I PI3-kinases.[40] In GIST cell lines, synergy of imatinib and BKM120 has been established. Recently, an international phase I study was performed, wherein imatinib and sunitinib resistant patients were treated with imatinib and an escalating dose of BKM120. This study has been completed but the results have yet to be published (NCT01468688).

BYL719 (Novartis) is another PI3-K inhibitor which specifically inhibits class I α PI3-kinases, and the β, γ and δ isoforms much less so.[41] Just as BKM120, it is an oral agent and it should in theory have less central nervous system toxicity. BYL719 has also recently been tested in a phase I study in combination with imatinib. This study has an estimated completion date at the end of 2018 (NCT01735968).

New tyrosine kinase inhibitors

The treatment of GIST has developed beyond histology driven therapy to mutation driven therapy. An early example of this, is the recommendation to treat patients with a KIT exon 9 mutation with imatinib 800 mg instead of the usual 400 mg.[12] The *PDGFR* D842V mutation is insensitive to imatinib and patients with this mutation should not be treated with imatinib.[42] In cell line studies, the TKI crenolanib was found to inhibit the kinase activity and cells with this mutation.[43] Based on these findings, a phase II trial was performed for patients with this specific mutation (NCT01243346) which has been completed, but results have not been published. Also, a phase III trial has been initiated for this population in which crenolanib is tested versus placebo (NCT02847429). GIST clones may also revert to different tyrosine kinases to promote proliferation, and GIST growth was found to be inhibited in several xenograft models by the TKI cabozantinib, which is also an inhibitor for MET, AXL and VEGF-receptors.[44] An EORTC coordinated phase II trial investigating the efficacy of cabozantinib has completed patient accrual and follow-up data is being collected (NCT02216578).

DCC-2618

Overcoming drug resistance due to secondary mutations is a challenge in GIST research. TKI's currently approved are only active against a number of possible secondary mutations. A new agent named DCC-2618 has been reported to confer activity against a broad set of mutations, including mutations in KIT exon 13 and 14, as well exon 17 and 18. In advanced pretreated GIST patients a dose-escalation study was performed and a dose of 150 mg per day of DCC-2618 tablets was selected for further studies (NCT02571036).[45] Partial responses were seen in a number of patients. This has prompted the initiation of a randomized, placebo-controlled, double-blind multi-center study in which DCC-2618

is compared to placebo in GIST-patients who already received imatinib, sunitinib, and regorafenib (NCT03353753). In a different study with DCC-2618, the drug is compared to sunitinib in an randomized open-label multicenter study in patients who had imatinib and now need second line systemic therapy (NCT03673501).

BLU-285

Another new agent with potency against the activity of KIT harboring a broad spectrum of exon mutations is BLU-285. This oral drug has been named avapritinib. This drug has shown activity against *KIT* D816V and *PDGFRA* D842V mutations that other TKI do not inhibit. The safety of BLU-285 has been studied in a phase I study, in which no dose limiting toxicities were seen while the drug did show anti-tumor activity (NCT02508532).[46] A dose of 300 mg per day was selected for further studies. Preliminary results showed that despite pretreatment, 9 of the 40 patients had an partial remission. These results lead to study expansion, aiming to enroll more patients in a phase II setting. An randomized open-label study has been started to investigate BLU-285 in a third line setting comparing it to regorafenib and is currently recruiting (NCT03465722).

Immunotherapy

As has been the case in other types of cancer, the successes of checkpoint inhibitors has prompted the use of immunotherapy in clinical trials with advanced GIST patients. A phase I trial sought to combine ipilimumab with imatinib in patients with various tumors including GIST.[47] The recommended phase II dose was determined at ipilimumab 3 mg/kg every 3 weeks with imatinib 400 mg twice daily. No dose limiting toxicities were observed among 35 GIST patients, one of whom with a wild-type GIST had a partial response.[47] A clinical trial investigating pembrolizumab in combination with metronomic cyclophosphamide showed limited activity in 10 GIST patients.[48] Based on post-treatment tumor samples the investigators concluded that macrophage infiltration led to an immunosuppressive tumor microenvironment. In a randomized phase II nivolumab is currently tested against the combination of nivolumab and ipilimumab.[49] After accrual of the first 14 of a projected 40 advanced GIST patients, the clinical benefit rate for both treatment arms is around 40% with a median PFS of 1.9 months (NCT02880020). Another study recruiting GIST patients is a phase II trial investigating epacadostat and pembrolizumab to assess the efficacy of combined IDO and PD-1 inhibition (NCT03291054).

Clinical studies in the Netherlands

In the five Dutch soft tissue sarcoma centers a number of trials are performed or prepared for the first, second and third line of treatment. Furthermore, studies are set up for the adjuvant setting and for long term responders, and work is being done into biomarkers like germ line DNA polymorphisms, circulating tumor DNA (the KWF sponsored GALLOP study) and blood level monitoring. Some studies are briefly highlighted below.

ALT GIST

In this randomized phase II trial patients with advanced GIST are treated with either standard imatinib treatment, or with imatinib alternated with regorafenib and a brief interval without medication. The idea is that cells re-enter the proliferation cycle during the treatment-free interval and then will be more sensitive to imatinib. Regorafenib should suppress imatinib resistant cells before these can grow to clinically relevant clones. The EORTC coordinates this study in the Netherlands. This study has been completed and results are to be reported shortly (NCT02365441).

Masitinib

Masitinib (AB1010, AB Science) is an inhibitor of KIT, PDGFRa and Lyn and preclinical research suggests that it has a stronger and more specific binding to KIT than imatinib does.[50] In a first line phase II study almost all of 30 patients (97%) had at least stable disease and a median survival of 41.3 months.[51] Recently, a randomized phase II study was published in which 44 imatinib resistant patients were treated with masitinib or sunitinib; the group of 23 patients who received masitinib had a longer progression free survival compared to the group of 21 patients who received sunitinib; 3.7 versus 1.9 months, respectively.[52] The median PFS of sunitinib is far shorter than the original trials designed to asses sunitinib efficacy. Two phase III trials were started; one study which compares masitinib with imatinib in the first line (NCT00812240), and a study in which masitinib is compared to sunitinib in the second line (NCT01694277). Both these studies have been closed for inclusion for some time and results have not yet been reported.

LOP628

A recent development in targeted therapy is the antibody drug conjugate (ADC). These conjugates use an antibody to guide a cytotoxic drug to malignant cells. This should result in less toxicity of non-sensitive cells and the delivery of a cytotoxic agent at or in the targeted cells. An ADC has been developed called LOP628, which consists of an anti-KIT antibody that is linked to a DM1 maytansinoid toxin. This toxin interferes in

microtubule assembly and thus prevents cell proliferation. A preclinical study showed anti-proliferative activity on c-KIT-positive cell lines, including some imatinib-resistant cell lines.[53] A phase I trial aiming to establish a maximum tolerated dose in patients with a KIT positive tumor has been performed (NCT02221505).[54] All three included patients suffered a hypersensitivity reaction requiring rescue medication in the form of steroids and antihistaminic drugs. Mast cell degranulation was determined as the cause for the reaction and the trial was subsequently terminated.

GALLOP study

On a different note, one noteworthy study currently performed in the Netherlands is the GALLOP study (NCT02331914). Collaborating in the Dutch GIST consortium, all five Dutch sarcoma referral centers participate in this study. This study aims to asses GIST mutation during treatment, as well as measure TKI serum. In a bio-database, clinical data, tumor and blood samples are collected. Blood samples are analyzed during treatment for TKI serum levels in order to adjust dosing and thus optimize anti-tumor treatment. Next to mutation analysis of the primary GIST , blood samples during treatment are used to routinely perform mutation analysis on circulating tumor DNA. In case of disease progression, patients are asked to have a biopsy of a progressive lesion taken in order to test for secondary mutations. Using circulating tumor DNA, disease progression may be discovered before CT scans show tumor growth or spread. Receiving optimal TKI treatment may influence whether secondary mutations in circulating tumor DNA emerge at all. The DNA collected in these blood samples may also serve as a validation set for the pharmacogenetic studies presented in the subsequent chapters.

Conclusion

In the past 18 years, the median survival of advanced GIST has risen from less than 12 months to more than 60 months. Factors that contribute to this include improved understanding of GIST pathogenesis, mechanisms of resistance to available TKI's and the opportunities that new (combination) therapies offer. The clinical introduction of imatinib, sunitinib and regorafenib facilitates long term treatment. This chapter highlights current developments in systemic treatment as well as current trials. Sadly, most patients with metastasized disease will eventually die of their disease. Therefore, patient participation in clinical trials is vital to discover new effective treatment strategies. These trials are performed in specialized centers, so patients will have to be treated at those hospitals. As shown, numerous trials have been and are currently performed to improve the systemic treatment of advanced GIST patients.

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