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Gastrointestinal stromal tumours in children and young adults: A clinicopathologic series with long-term follow-up from the database of the Cooperative Weichteilsarkom Studiengruppe (CWS)

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ABSTRACT

Background: Studies on gastrointestinal stromal tumours (GIST) in the paediatric population are limited to case reports or small case series.

Patients and methods: We conducted a retrospective study to describe the long-term outcome of children and adolescents with GIST registered in the database of the Cooperative Weichteilsarkom Studiengruppe (CWS).

Results: Sixteen patients (female, $n = 11$) were identified. Median age at diagnosis was 13.5 years. In four female patients presence of thoracic masses in addition to GIST led to the diagnosis of complete or incomplete Carney triad. Three female patients had metastatic disease at diagnosis, the remaining thirteen GIST were localised. The stomach was the most common primary site of the tumour, followed by the small bowel and colon/abdomen. All patients underwent tumour resection. Receptor tyrosine kinase inhibitors (RTKI) were administered in five patients. With a median follow-up of 96 months all patients are alive,

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nine of them in first CR. Four female patients developed local or distant recurrence; three of them achieved second CR and one a PR. Two individuals have extensive progressive ($n = 1$) or stable ($n = 1$) disease. Estimated progression-free survival at 5 years is 0.63 (95%CI: 0.50–0.86). *Conclusions:* Although long-term overall survival is favourable, approximately 30 percent of patients develop disease progression. International cooperation in registration, tissue collection and molecular studies are required to obtain reliable data on the clinical course of these rare tumours in the paediatric population. Biological studies are a prerequisite for initiation of studies with RTKI.

1. Introduction

Gastrointestinal stromal tumours (GIST), the most common mesenchymal tumour of the gastrointestinal tract are predominantly found in middle-aged or older adults with an incidence rate of 6.5–14.5 per million per year.[1,2] An annual incidence rate of 0.02 per million in children below the age of 14 years has been calculated from data of the UK National Registry of Childhood Tumours.[3] Gastrointestinal stromal tumours occur either sporadically or rarely in association with other syndromes such as neurofibromatosis type 1.[4] The association of gastric GIST (before the definition of GIST classified as leiomyosarcoma), extra-adrenal paraganglioma and pulmonary chondroma is termed Carney triad.[5] A familial occurrence of GIST due to germline mutations in either the KIT or the platelet-derived growth factor receptor alpha (PDGFRA) gene has been described in approximately 25 kindreds until now.[6] The characteristics and treatment modalities of paediatric GIST have recently been comprehensively reviewed.[7–9] Since studies on GIST in this population are rare, we have summarised data of children with GIST registered in the database of the Cooperative Weichteilsarkom Studiengruppe (CWS) of the German, Austrian, and Swiss Society of Pediatric Oncology and Haematology (GPOH).

2. Patients and methods

Patients <18 years with a histological diagnosis of gastrointestinal leiomyoma/leiomyosarcoma or GIST registered in the database of the prospective multicentre trials CWS-86, CWS-91, CWS-96 and CWS-2002 Pilot between 1988 and 2009 were subjected to analysis. Institutional review board approval was obtained for these studies. Initial staging and follow-up examinations included abdominal computed tomography (CT) or contrast-enhanced magnetic resonance imaging (MRI) scans and endoscopy. Fluorodeoxyglucose-positron emission tomography (FDG-PET) was done in selected patients since 2004. Tumour tissue specimens for histopathologic examination were obtained by tumour biopsy or tumour resection which was the primary approach of therapy for localised disease. In the pre-imatinib era adjuvant therapy was based on conventional chemotherapy. Patients diagnosed after 2001 – the year, in which imatinib was described effective in a patient with a GIST[10] – received treatment with receptor tyrosine kinase inhibitors (RTKI). Four patients were reported previously.[11] Two of them subsequently developed disease recurrence. In order to extend the follow-up, these four patients were also included in the present study.

Second pathologic review for the purpose of the present study according to the classification criteria for GIST was carried out in 15 patients by the CWS reference pathologists for Germany and Austria. In one patient diagnosis was based on local pathology only. The classification of GIST was based on the published spectrum of KIT-positive GIST with spindle cell or epitheloid features. The tumours were classified into three categories: (1) purely or almost purely spindle cell type tumours, (2) purely or almost purely epithelioid tumours, and (3) mixed spindle cell/epithelioid tumours. The cases were reviewed using H&E- and PAS-stained slides. Mitotic figures were counted by screening 50 high power fields (0,575 mm^2/HPF). Slides of paraffin-embedded tumour tissue were stained using antibodies against CD117/KIT (1:200), smooth muscle actin (clone 1A4, 1:400), anti-Ki-67 antibody MIB-1 (clone SP6, 1:300) (all from Lab Vision/Neomarkers, Fremont, CA, USA), PDGFRA (1:500, Santa Cruz Biotechnology, Inc., Santa Cruz, CA, USA), DOG-1 (1:100, Zytomed Systems, Berlin, Germany), CD34 (1:700, Beckman Coulter, Inc., Brea, CA, USA) and S-100 (1:1000, Dako Corp., Carpinteria, CA, USA).

All antibodies except against PDGFRA were stained by the Leica BOND-MAX™ system (Leica Microsystems, Wetzlar, Germany). As detection system either the BOND™ Polymer Refine Detection (Leica Microsystems) or – for PDGFRA antibody – the Histofine detection system (Nichirei Co. Ltd, Tokyo, Japan) was used. Staining intensity was evaluated and scored in a semi-quantitative way: (1) negative, (2) + (less than 25 percent of tumour cells weakly positive), (2) ++ (more than 25 percent weakly positive or less than 10 percent strongly positive), and (3) +++ (more than 10 percent strongly positive).

Molecular genetic analysis of paraffin-embedded tumour tissue specimens for the most common GIST-associated mutations was done at the Department of Pathology, University of Bonn Medical School, Germany or the Institute of Pathology, Medical University of Vienna, Austria. Overall survival (OS) and progression-free survival (PFS) was estimated by the Kaplan–Meier method.

3. Results

3.1. Patients' characteristics

Sixteen patients (female, $n = 11$; median age at diagnosis 13.5 years) with GIST were identified in the CWS database.

Histopathological and immunohistochemical characteristics of tumours are depicted in Table 1. Baseline clinical characteristics and treatment-related data are summarised in Tables 2 and 3. In seven patients the tumour was originally termed leiomyoma/leiomyosarcoma, but reclassified following reference pathology. Anaemia (median haemoglobin at diagnosis: 5.8 g/dl [range, 3.5–10.2 g/dl]) and anaemia-related symptoms caused by gastrointestinal bleeding were observed in thirteen patients. Three patients had other symptoms (ileus, $n = 1$; abdominal pain; $n = 2$). Upper gastrointestinal endoscopy at diagnosis was performed in 10 patients with additional endoscopic biopsies in seven of them. Biopsies were negative or inconclusive in 3 (treated in the pre-imatinib era) and revealed GIST in 4 patients. The most common tumour site was the stomach ($n = 11$), followed by the small intestine ($n = 3$), ascending colon ($n = 1$) and abdomen (between colon transversum and greater omentum; $n = 1$). Five patients (31.3%) were found to have bi- or multi-focal tumours. Three patients had already developed metastases at the time of diagnosis (liver metastases, $n = 1$; lymph node metastases, $n = 1$; liver and lymph node metastases, $n = 1$). Complete ($n = 1$) or incomplete ($n = 3$) Carney triad was diagnosed in four female patients because of the presence of additional thoracic masses (mediastinal paraganglioma, $n = 3$; pulmonary chondroma, $n = 2$). Three patients diagnosed with GIST in the pre-imatinib era were treated with conventional chemotherapy. Median follow-up of study patients (data missing in one patient) is now 96 months (range, 16–238 months). Estimated PFS and OS rates at 5 years are 0.63 (95%CI: 0.50–0.86) and 1.0, respectively (Fig. 1).

3.2. *Clinical course (non-relapsed patients with localised disease at diagnosis)*

With a median follow-up of 99 months (range, 41–238 months) eight patients (patients 1, 3, 5, 7, 9, 12–14) are in first continuous complete remission (CCR) following tumour resection. One patient (patient 2) was reported to be alive 10 years after diagnosis, but the remission status was not available. One female patient (patient 1) who was diagnosed with a gastric leiomyosarcoma (later reclassified as GIST) in 1988 received chemotherapy. This patient developed also multiple pulmonary chondromas and mediastinal paraganglioma. Patient 7 whose tumour carried a *KIT* exon 11 mutation (Table 3) was given imatinib for 2 months perioperatively.

3.3. *Clinical course (relapsed patients with localised disease at diagnosis)*

Four female patients (patients 4, 8, 10, 15) developed local ($n = 3$) or metastatic ($n = 1$) recurrence at a median of 41 months (range, 36–144 months) after diagnosis. Two patients underwent a second and one patient a second and third surgery for local recurrence. At last follow-up two of these patients were in complete remission 21, 96 months after second surgery. Unfortunately follow-up discontinued in the remaining third patient (patient 4) following third surgery. In this subgroup one patient (patient 8) was treated with dacarbazine and adriamycin for 6 months following relapse and one patient (patient 10) received adjuvant imatinib for 2 months at the time of diagnosis. Three years after diagnosis two liver metastases were detected and surgically removed in the fourth patient (patient 15). Despite treatment with imatinib she developed additional liver metastases which were again completely removed. Due to further progression nilotinib treatment was initiated. The patient is still receiving nilotinib at 2×400 mg per day for now 22 months. The sizes of the four detectable lesions which are 5–7 mm in diameter are stable/slightly decreased on follow-up MRI. Standardised uptake values (SUV) on FDG-PET decreased from a maximum of 10.8 to 4 at last follow-up.

Table 1 – Histopathologic and immunohistochemical characteristics of gastrointestinal stromal tumours of study patients.

Patient	Morphology	SMA	S-100	CD34	CD117	PDGFRA	DOG-1	Mitoses per 50 HPF	MIB-1 (%)
1	Epithelioid	–	–	–	++	++ (focal)	+	5	5
2	Mixed	–	–	–	+	+++	–	5	10, focal 20
3	Mixed	–	–	–	–	++	–	11	5, focal 10
4	Epithelioid	–	–	+++	+++	++	++/+++	6	5, focal 10
5	Mixed	–	+	++	+++	++	++	4	5, focal 10
6	Mixed	+	–	+++	++	++	++	5	2, focal 5
7	Epithelioid	–	–	+++	+++	+/++	++	9	5, focal 10
8	Mixed	+++	–	– (focal)	–	+/++	–	4	5
9	Spindle cell	++	–	–	–	–	–	2	5, focal 10
10	Epithelioid	–	N.d.	++	++	–	N.d.	5	5
11	Epithelioid	–	–	+++	++/+++	–	++	1	5
12	Spindle cell	–	++/+++	++/+++	(+)	–	–	4	10, focal 15
13[a]	Spindle cell	+++ (focal)	N.d.	++	++	N.d.	N.d.	low	N.d.
14	Mixed	–	–	++	+++	++	+++	19	N.d.
15	Spindle cell	–	–	+++	+++	+/–	+/–	15	5
16	Mixed	–	–	+++	+++	–	+++	4	2, focal 5

Abbreviations: DOG-1, abbreviated from discovered on GIST 1 – a cell surface protein selectively expressed in GIST; HPF, high power field; PDGFRA, platelet-derived growth factor receptor alpha; SMA, smooth muscle actin.

[a] Histology/immunohistochemistry from local pathology.

Table 2 – Clinical characteristics of study patients.

Patient	Gender	Age at diagnosis of GIST	Primary site	Size	Additional clinical characteristics
1	Female	17 years 11 months	Stomach (corpus, fundus)	3 cm/1.5 cm/1.5 cm (multifocal)	Multiple pulmonary chondromas, mediastinal paraganglioma (Carney triad)
2	Female	1 month	Distal Ileum	2 cm	–
3	Male	2 years 7 months	Stomach (greater curvature)	5.6 × 5.3 cm	–
4	Female	10 years 1 month	Stomach (lesser curvature)	3 cm/1.5 cm (bifocal)	–
5	Male	15 years 6 months	Jejunum	11 × 10 × 8 cm	–
6	Female	15 years 1 month	Stomach (greater curvature, pylorus)	8.6 × 5 cm/2 × 1.5 cm (bifocal)	Primary hepatic metastases, mediastinal paraganglioma (incomplete Carney triad)
7	Female	13 years	Stomach (lesser curvature)	6 × 2.8 × 3.2 cm	–
8	Female	7 years 8 months	Ascending colon	Not available	–
9	Male	16 years 9 months	Abdomen (between colon transversum and greater omentum)	6.5 cm	–
10	Female	13 years 2 months	Stomach (antrum)	6 × 3 cm (bifocal)	Mediastinal paraganglioma, right labial leiomyoma (incomplete Carney triad)
11	Female	14 years 1 month	Stomach (lesser curvature)	8 × 6 × 7 cm	Primary lymph node metastases
12	Male	2 years 5 months	Jejunum	6 × 3 × 3 cm	–
13	Male	16 years 7 months	Stomach (fundus)	5 × 4 × 3 cm	–
14	Female	6 years 9 months	Stomach (lesser curvature)	4 cm	–
15	Female	11 years 5 months	Stomach (lesser curvature)	3 × 2 cm/2 × 1 cm (bifocal)	Multiple pulmonary chondromas (incomplete Carney triad)
16	Female	13 years 10 months	Stomach (corpus)	8.1 × 7.1 cm	Primary hepatic and lymph node metastases

3.4. *Clinical course (patients with primary metastatic disease)*

Metastatic disease at diagnosis was observed in three female patients with GIST of the stomach (patients 6, 11, 16). One of them (patient 11) had lymph node involvement only. After complete tumour resection chemotherapy according to the CWS-96 trial was given. The patient is in first CCR with a follow-up of 14 years. Two patients (patients 6, 16) had large gastric GIST with multiple liver metastases at diagnosis, one with additional lymph node involvement. The first of these two patients was primarily put on imatinib at 400 mg/day. While the primary tumour and some metastases increased in size (assessed by MRI), FDG-PET uptake of metastases decreased. Despite further dose increase to 800 mg/day the size of the tumours remained unchanged. She underwent complete resection of the primary tumour with removal of seven liver metastases. Continuous RTKI treatment (Table 3) resulted in temporary disease stabilisation. RTKI were changed to motesanib and sunitinib following progression. Presently she is in good general condition on 2 × 400 mg nilotinib with stable liver metastases. In the other patient a minimal increase of the tumour size was noted after a 2-week treatment with imatinib (400 mg/day) leading to dose increase to 800 mg/day, followed by surgery. Several lymph nodes were found to be positive. Under continuous imatinib administration follow-up MRI showed now stable hepatic metastases with decreased contrast enhancement.

3.5. *Molecular genetics*

Molecular genetic analysis could be done in seven patients (Table 3). The number of definitely analysed exons in an individual patient was dependent on the amount of DNA extractable from tissue slides/blocks. In patient 7 an activating *KIT* exon 11 mutation (p.V560_L576del) was detected (Table 3).

4. Discussion

Guidelines for the management of paediatric GIST are presently not available. The recommendations for the management of adult GIST patients[12,13] are, therefore, generally applied to children and adolescents with GIST.[7–9] Thus far surgery is the mainstay of treatment in patients with local-

Table 3 – Molecular genetic findings, treatment and follow-up of study patients.

Patient	Surgery	Chemotherapy/RTKI treatment	Molecular genetics	Clinical course and follow-up
1	Billroth II gastrectomy	Yes (not specified)	Insufficient DNA quality	GIST: 1st CCR (FU: 238 months); repeated thoracotomies, tumour embolisation, and thermotherapy for pulmonary chondromas
2	Segmental resection	No	N.d.	Alive 120 months after diagnosis, but disease status not available
3	Partial gastrectomy	No	N.d.	1st CCR (FU: 133 months)
4	Local excision, subtotal gastrectomy (1st relapse) remnant gastrectomy (2nd relapse)	No	Wild-type *KIT* (exon 9, 11), wild-type *PDGFRA* (exon 18)	Local relapse (2×, 3 years 4 months and 12 years after diagnosis) (FU: 144 months)
5	Segmental resection	No	N.d.	1st CCR (FU: 136 months)
6	Billroth II gastrectomy, lymphadenectomy, resection of liver metastases and mediastinal paraganglioma	Imatinib (4 months), motesanib (9 months), sunitinib (30 months), nilotinib (18 months)	Wild-type *KIT* (exon 9, 11, 13), wild-type *PDGFRA* (exon 12, 18)	Stabilisation/slow progression of hepatic metastases (FU: 60 months)
7	Local excision, partial gastrectomy	Imatinib (2 months)	*KIT* exon 11 mutation p.V560_L576del	1st CCR (FU: 19 months)
8	Segmental resection, right hemicolectomy (relapse)	Dacarbazine + adriamycin (relapse) (6 months)	N.d.	Local relapse (4 years after diagnosis) (FU: 144 months months)
9	Complete resection	No	N.d.	1st CCR (FU: 41 months)
10	Partial gastrectomy, local excision (relapse), resection of mediastinal paraganglioma and right labial leiomyoma	Imatinib (2 months)	Wild-type *KIT* (exon 11)	Local relapse (3 years 5 months after diagnosis) (FU: 62 months)
11	Billroth II gastrectomy, lymph node biopsy	CWS 96 (ifosfamide, dactinomycin, adriamycin, vincristine)	N.d.	1st CCR (FU: 168 months)
12	Segmental resection	No	N.d.	1st CCR (FU: 58 months)
13	Local excision	No	N.d.	1st CCR (FU: 102 months)
14	Billroth I gastrectomy	No	N.d.	1st CCR (FU: 111 months)
15	Billroth I gastrectomy, resection of liver metastases	Imatinib (8 months), nilotinib (22 months)	Wild-type *KIT* (exon 9, 11, 17), wild-type *PDGFRA* (exon 12, 18)	Repeated occurrence of liver metastases (3 years after diagnosis) (FU: 77 months)
16	Billroth II gastrectomy, lymphadenectomy	Imatinib (15 months)	Wild-type *KIT* (exon 9, 11, 13-15), wild-type *PDGFRA* (exon 10, 12, 18)	Disease stabilisation (FU: 16 months)

Abbreviations: CCR, continuous complete remission; FU, follow-up; N.d., not done; PDGFRA, platelet-derived growth factor receptor alpha; RTKI, receptor tyrosine kinase inhibitor.

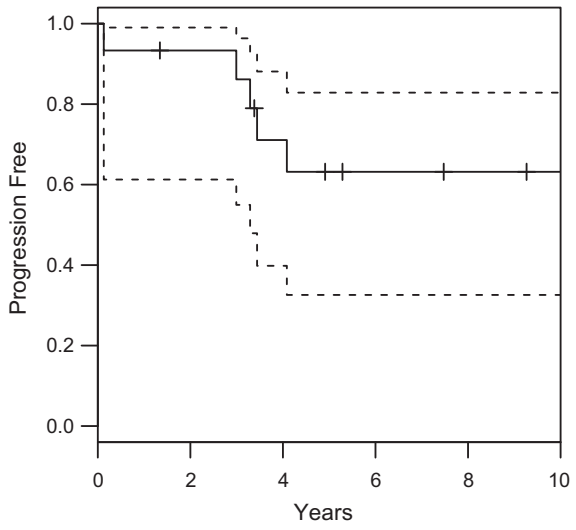

Fig. 1 – Kaplan–Meier estimates of progression-free survival (PFS) and 95% confidence intervals of study patients (*n* = 15).

ised disease.[14–17] Long-term remission is achievable in the majority of patients by total tumour resection with microscopic free margins. However, since local recurrence may occur years after diagnosis long-term tumour-related follow-up is mandatory. Three female patients developed local recurrence. Analysis of medical records, however, did not allow differentiating whether or not these tumours were 'true' relapses or multifocal tumours that were initially not detected. In case of local recurrence only second or even subsequent surgeries are indicated having the ability to cure these patients. However, the consequences of more radical surgical procedures (total gastrectomy) should be critically discussed in an interdisciplinary group. In adult patients with large or unfavourably located tumours imatinib pretreatment is recommended to allow less mutilating surgery.[12,13]

Four female patients were diagnosed with complete or incomplete Carney triad. Given the fact that the time interval between diagnosis of first and diagnosis of second tumours in patients with Carney triad might be as long as 26 years,[5] these patients should be regularly screened for additional tumours.

The management of patients with extensive disease at diagnosis or metastatic recurrence is challenging and requires interdisciplinary cooperation including central reviews by designated reference experts who are familiar with rare paediatric tumours such as GIST. Hepatic resection should be considered in patients with isolated or a limited number of potentially resectable liver metastases and no extrahepatic disease. Imatinib at 400 mg daily is the recommended first-line drug therapy in adult patients with advanced, non-resectable or metastatic disease.[12,13] In case of tumour progression or lack of response a dose increase to 800 mg daily is appropriate, particularly in patients with *KIT* exon 9 – mutant GIST who are most likely to benefit from 800 mg imatinib.[12,13,18] However, since two large multicentre trials[18,19] have shown that the kinase genotype strongly correlates with response to RTKI in patients with metastatic GIST, one might consider to use other RTKI (e.g. sunitinib or nilotinib) as first-line treatment in paediatric GIST which in only 0–10% have an oncogenic *KIT* mutation.[7,8,20] Sunitinib is comparably active in patients whose tumours have a *KIT* exon 9 mutation or a wild-type genotype, whereas patients with a *KIT* exon 11 – mutant GIST are reported to respond less favourably to sunitinib.[19] In a study by Janeway et al. six children with advanced GIST were treated with sunitinib after failure of imatinib. One patient achieved a partial response and five patients had stable disease for 7 to 21+ months.[21] Nilotinib, a second generation RTKI has been found effective in adult patients with advanced GIST who failed prior imatinib and sunitinib therapy.[22] In this retrospective study nilotinib was administered at 400 mg twice daily. No data are presently available concerning nilotinib treatment in children. However, *in vitro* experiments have recently shown that nilotinib more effectively inhibits proliferation of murine Ba/F cells expressing wild-type *KIT* compared to other RTKI.[23]

The small and presently unknown number of paediatric patients treated with RTKI – both in our and in other series – does not allow to draw any meaningful conclusion in terms of efficacy or toxicity of RTKI in this population. Considering the fact that GIST in children and young adults often have an indolent clinical course despite development of metastases,[23,24] disease stabilisation may reflect the natural course of the disease rather than efficacy of RTKI.

The molecular mechanisms involved in the pathogenesis of wild-type GIST are not well understood. Recently it has been shown that insulin-like growth factor 1 receptor (IGF1R) is highly expressed in paediatric wild-type GIST compared to KIT–mutant GIST.[25] Furthermore defects in succinate dehydrogenase subunits B, C, D – originally identified in patients with the inherited Carney Stratakis syndrome (GIST and paragangliomas) – were also found in wild-type GIST not associated with paraganglioma.[26]

In order to facilitate evaluation of new drugs in rare diseases clinical trials should be based on collaborative academic platforms such as the CWS. Based on a paediatric investigation plan (PIP) approved by the European Medicine Agency in 2009 a clinical trial with sunitinib in children with GIST is now expected. For the registration of children and adolescents with soft tissue sarcomas and other rare soft tissue tumours including GIST in Germany, Austria, Switzerland, Poland and Sweden the soft tissue sarcoma registry of the CWS (CWS-SoTiSaR) has recently started accruing patients. Furthermore a European Working Group on paediatric GIST in association with the International Society of Pediatric Oncology (SIOP) has been established to promote international collaboration.

Conflict of interest statement

Martin Benesch: one-time consultant honorarium for an advisory board meeting (Pfizer), all other authors declare to have no potential conflict of interest.

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