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The outcomes of patients with metastatic/inoperable gastrointestinal stromal tumors (GIST) treated with imatinib – an interim multicenter analysis of Polish Clinical GIST Registry

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The aim. of the study was to analyze the clinical outcomes of imatinib treatment in inoperable/metastatic gastrointestinal stromal tumors (GIST) CD 117(+) in Polish institutions collaborating in the Clinical GIST Registry.
Material and methods. Complete basic demographic and clinical data was available in 165 advanced (inoperable/metastatic – M1) patients treated with imatinib in a dose of 400-800 mg (155 patients for survival analysis) between 09/2001 and 01/2005 and registered in the Clinical GIST Registry in Warsaw. This data was compared with that of 107 patients without evidence of recurrent disease (M0) followed-up at the M. Sklodowska-Curie Memorial Cancer Center – Institute of Oncology in Warsaw.
Results. We observed the prevalence of male patients in the M1 group as compared to M0 patients (p=0.001). We found significantly higher median tumor size (11 cm) and median mitotic count value (10/50 HPF) in M1 patients as compared to the M0 group (5.5 cm and 2/50HPF, respectively) [p<0.001]. The percentage of gastric location (together with the lower esophagus and duodenum) was significantly lower in the M1 group than in the M0 group, 36% and 61% respectively (p=0.01). In the group of 155 patients treated with imatinib due to inoperable/metastatic lesions, 141 (91%) were alive at the time of the last evaluation in 01/2005. Ten patients (6.5%) demonstrated complete remission of disease and the other 102 pts (66%) remained on imatinib treatment and have maintained disease with partial response (40%) or stabilization (26%) only according to RECIST criteria. The estimated 3-year overall and progression-free survival was 75% and 64.5%, respectively.
Conclusions. It has been shown that it was possible to achieve a satisfactory clinical outcome in patients with such a rare malignancy as GIST treated with new molecular targeted therapy in different regional cancer centers in Poland. Direct multidisciplinary collaboration between specialists caring for patients with GIST in Poland has shown and confirmed the outstanding role of the Polish Clinical GIST Registry.

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Przeżycia chorych na rozsiany i nieoperacyjny GIST leczonych imatinibem – analiza etapowa Klinicznego Rejestru GIST

Celem badania była analiza wyników leczenia chorych na nieoperacyjny/rozsiany nowotwór podścieliskowy przewodu pokarmowego (GIST) CD 117(+), leczonych imatinibem w polskich ośrodkach współpracujących w Rejestrze Klinicznym GIST.

Materiał i metody. Kompletne podstawowe dane demograficzne i kliniczne uzyskano u 165 chorych z zaawansowanym GIST (nieoperacyjnym/rozsianym – M1), leczonych imatinibem w dawce 400-800 mg (155 chorych poddano analizie przeżycia) w okresie 09/2001 – 01/2005 i włączonych do Rejestru Klinicznego GIST w Warszawie. Dane te porównano ze 107 chorymi bez cech nawrotu choroby (M0), poddanych obserwacji w Centrum Onkologii – Instytucie w Warszawie.

Wyniki. Obserwowano przewagę płci męskiej w grupie M1 w porównaniu z M0 (p=0,001). Stwierdzono istotnie większą medianę wielkości guza (11 cm) i indeksu mitotycznego (10/50 HPF) u chorych w stopniu M1 niż u chorych w grupie M0 (odpowiednio: 5,5 cm i 2/50 HPF) [p<0,001]. Odsetek chorych na GIST, których pierwotny guz umiejscowiony był w żołądku (łącznie z dolnym odcinkiem przełyku i dwunastnicą), był znacząco mniejszy w grupie M1 niż M0 (odpowiednio: 36 i 61%; p=0,01). W grupie 155 chorych leczonych imatinibem z powodu rozsianych/nieoperacyjnych zmian 141 (91%) żyło w 01/2005. U 10 chorych (6,5%) obserwowano całkowitą odpowiedź na leczenie, a dalszych 102 (66%) było leczonych imatinibem po uzyskaniu częściowej remisji (40%) lub stabilizacji (26%) choroby zgodnie z kryteriami RECIST. Oszacowane 3-letnie przeżycia całkowite i wolne od progresji choroby wyniosły odpowiednio 75% i 64,5%.

Wnioski. Wykazano, że możliwe jest uzyskanie satysfakcjonujących klinicznych wyników leczenia chorych z tak rzadkim nowotworem, jak GIST za pomocą nowoczesnej terapii celowanej molekularnie w różnych regionalnych ośrodkach onkologicznych w Polsce. Ścisła wielodyscyplinarna współpraca specjalistów zajmujących się chorym na GIST w Polsce potwierdziła istotną rolę Rejestru Klinicznego GIST.

Key words: gastrointestinal stromal tumor, imatinib, clinical outcome
Słowa kluczowe: nowotwory podścieliskowe przewodu pokarmowego, imatinib, wyniki leczenia

Introduction

In August 2001 the EORTC trial No. 62005 at the Institute of Oncology in Warsaw for the recruitment of patients with inoperable/metastatic gastrointestinal stromal tumors (GIST) with positive immunostaining for c-KIT (CD117) was opened. At that time the trial was the third in the world (and the first conducted in Poland) – a prospective, randomized study evaluating the efficacy of molecular targeted treatment of GIST with small-molecule tyrosinase kinase inhibitor – imatinibe mesylate. Patient recruitment was finished in February 2002. The preliminary results of the study were published during the Annual Society of Clinical Oncology Annual Meetings 2003 and 2004, and finally were published in 2004 [1]. Soon after entering first patients we had realized that the treatment of GIST patients is an effort of many specialists throughout Poland: pathologists, surgeons, oncologists and radiologists. To strike up closure cooperation, the Polish Clinical GIST Registry was organised in 2002 as a multidisciplinary forum for exchanging information about GIST treatment and research. It holds national meetings twice a year in different centers in Poland. The main points of interest of the Clinical GIST Registry are: propagation of knowledge about GIST (diagnosis/treatment); clinical data collection, analysis of treatment outcomes, analysis of co-existence of other neoplasms in GIST patients, the evaluation of the role of surgery after imatinib treatment and co-operation in clinical trials and molecular research. The main achievement of our Registry is the extension of awareness of the GIST disease among doctors and the increase of newly diagnosed cases of GIST in Poland, as well as the implementation of new, effective treatment of this malignancy, as is the case in other European countries. The aim of this study is to analyze the clinical outcomes of imatinib treatment in inoperable/metastatic GIST CD 117(+) in Polish centers collaborating in the Clinical GIST Registry.

Material and method

We have collected data related to inoperable and/or metastatic GIST patients treated with imatinib from all institutions participating in the Clinical GIST Registry – oncological centers throughout Poland – at the beginning of January 2005. The information was obtained from the centers with the aid of a special questionnaire published on the web page (http://www.coi.waw.pl) and sent by e-mail (gist@coi.waw.pl) or fax. There were 98 patients treated at the Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology (CCIO) in Warsaw and 103 patients in other Polish centers. Complete basic demographic and clinical data was available in case of 165 advanced patients treated with imatinib and registered in the Clinical GIST Registry in Warsaw. These data were compared with that of 107 patients without evidence of recurrent disease followed-up in the CCIO in Warsaw (Table I).

The criteria of eligibility for imatinib treatment were as follows:
- histological diagnosis of GIST,
- c-Kit (CD117) positive staining (Dako polyclonal antibodies),
- metastatic and/or inoperable lesions,
- measurable disease on computed tomography scans,
- WHO performance status ≤3,
- no concomitant therapy for disease,
- adequate renal and liver function.

Table I. Patient characteristics (groups: M1 – patients with inoperable/metastastatic GIST lesions treated with imatinib; M0 – patients without evidence of disease, follow-up only)

Clinicopathological feature		M1	M0	Total	p-value
		165 pts	107 pts	272 pts	
Age [years]	Range	17-83 years	23-85 years	17-85 years	
	Mean	56 years	58 years	57 years	
	Median	56 years	60 years	58 years	n.s.
Gender	Female	69 (41.8%)	66 (61.6%)	135 (49.6%)	
	Male	96 (52.8%)	41 (38.4%)	137 (50.4%)	p=0.001
Primary tumor site	Esophagus	2 (1%)		2 (0.7%)	
	Stomach	50 (30%)	58 (54%)	108 (39.7%)	
	Duodenum	8 (5%)	7 (7%)	15 (5.5%)	
	Small bowel	60 (36%)	34 (31%)	94 (34.6%)	
	Large bowel/rectum	12 (7%)	2 (2%)	14 (5.1%)	
	Retroperitoneal space	14 (9%)	2 (2%)	16 (5.9%)	
	Others, intraperitoneally with Unknown primary origin	19 (12%)	4 (4%)	23 (8.5%)	p<0.001
Tumor size [cm]		104 pts	80 pts		
	Mean	13 cm	7 cm		
	Median	11 cm	5.5 cm		p<0.001
Mitoses number in 50 High Power Fields		48 pts	44 pts		
	Median	10	2		p<0.001
Time to recurrence after primary operation R0/R1		96 pts			
	Range	1 – 182			
	Mean	24 months			
	Median	13 months			
Follow-up time			104 pts		
	Range		1 – 132		
	Mean		18 months		
	Median		12 months		

Pts = patients

Imatinib treatment started from the dose of 400 mg once daily orally. The response to treatment was evaluated according to the RECIST criteria with computed tomography imaging examinations performed every 2-3 months. In case of progression the dose was increased to 600-800 mg daily. In case of further progression imatinib treatment was stopped. The imatinib dose was reduced to 300 mg daily due to recurrent grade 3 toxicity (neutropenia) in 2 cases.

For statistical computations the contingency tables were analyzed by the chi-square test. Groups were compared for age differences using the t-test for normal distribution of parameters and for other parameters, with non-normal distribution the Mann-Whitney U-test was used. Differences were considered statistically significant if p-values were <0.05. The Kaplan-Meier method was used for the analysis of survival curves. Overall survival (OS) and progression-free survival (PFS) time were calculated from the date of start of imatinib treatment to the date of the most recent follow-up, progression or death (for PFS and OS, respectively). 14 patients were excluded from the survival analysis because of the lack of detailed dates of the start of imatinib treatment. We excluded further 32 patients because of a too short follow-up time (minimal follow-up time necessary for the evaluation of the results of treatment was 6 months, which means that imatinib treatment should have been started before June 31st, 2004). Finally, for the survival analysis, we included 155 GIST patients treated with imatinib from 09/2001 to 01/2005. Median follow-up time was 17.7 months for survivors and mean follow-up time – 19 months. For data collection the hospital information system ONCOsys and the Clinical GIST Registry databases were used.

Results

The characteristics of the group of c-KIT positive GIST patients with inoperable/metastatic lesions treated with imatinib (group M1) and patients followed-up without evidence of recurrent disease after radical operation (group M0) are shown in Table I. Median age in the M1 group was 56 years and in the M0 group – 60 years ($p=0.2$). Men comprised the majority of patients in the inoperable/metastatic group, but, on the contrary, women predominated among patients without recurrence of disease after primary surgery ($p=0.001$).

The median tumor size (11 cm) was significantly higher in the M1 group as compared to the M0 group (5.5 cm) [$p<0.001$]. Similarly, the median mitotic count value was significantly higher in the M1 group (10/50HPF) than in the M0 group (2/50HPF) [$p<0.001$].

The characteristics of GIST locations were different in the M1 and M0 groups. The percentage of gastric locations (together with the lower esophagus and duodenum) was clearly lower in the M1 group than in

the M0 group, 36% and 61% respectively. On the contrary, the percentage of bowel GIST locations (small and large together) is significantly higher in the M1 group as compared to the M0 group, 43% and 33% respectively (p=0.01).

The median time to GIST recurrence was 13 months in the M1 group and was comparable to the median time of 12 months of follow-up in the M0 group. It means that the lack of recurrence in the M0 group was not related to, or caused by, the shorter time of follow-up only (Table I).

We have also observed a relatively high ratio of a second co-existent malignant neoplasm (8.1%) in the past history of GIST patients (8.5% – 14/165 in M1 and 7.5% – 8/107 in M0 groups).

In the group of patients with inoperable/metastatic lesions (M1) only two cases of dissemination outside the abdominal cavity (one to the bones and one to the lungs) were found. All patients in this group have had liver metasteses or intraperitoneal dissemination and, sometimes, inoperable local recurrences or primary tumors (data not shown).

In the eligible for analysis group of 155 patients treated with imatinib due to inoperable/metastatic lesions, 141 (91%) were alive at the time of the last evaluation in January 2005. Ten patients (6.5%) demonstrated complete remission of disease and the other 102 pts (66%) remained on imatinib treatment and have maintained disease with partial response (40%) or stabilization (26%) only according to RECIST criteria. Disease progression was observed in 27.5% of patients. Detailed results of imatinib treatment are presented in Table II.

Table II. The evaluation of response to imatinib treatment in 155 GIST patients (median follow-up 17.7 months)

Result	No of patients	%
Complete remission (CR)	10	6.5%
Partial remission (PR)	62	40.0%
Stable disease (SD)	40	26.0%
Progressive disease (PD)	43	27.5%

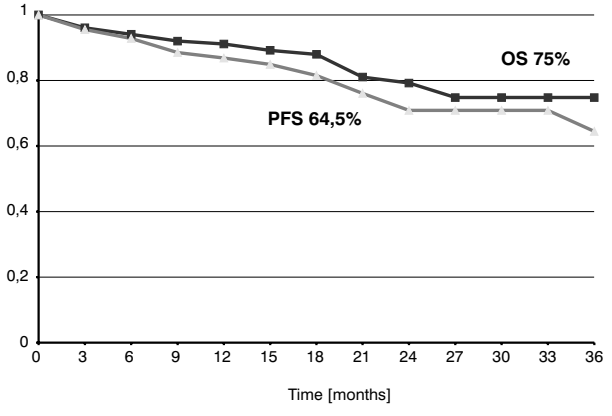

Figure. 1. Overall (OS) and progression-free (PFS) survival of patients treated with imatinib

Nineteen patients underwent adjuvant radical surgery after partial/complete response obtained during imatinib treatment. The estimated 3-year overall and progression-free survival were 75% and 64.5%, respectively (Figure 1).

The adverse events were rather frequent during imatinib treatment, but most of them were mild (grade 1-2). The most common were: fluid retention, edema, nausea, abdominal and muscle pain, diarrhea and anemia. We observed some cases of grade 3-4 toxicity: neutropenia (4 cases), ascites (2 cases), skin rash (2 cases), tumor hemorrhage requiring surgery (1 case) and soft tissue infection in 2 cases (data not shown).

Discussion

Gastrointestinal stromal tumors (GIST) comprise a recently defined entity of the most common mesenchymal neoplasms of the abdominal cavity. GIST is thought to arise from precursors shared with the normal interstitial cells of Cajal – the gut pacemaker cells. They are characterized by overexpression of mutated c-KIT receptor detected by CD117 immunostaining [2, 3]. The introduction of molecular targeted therapy with imatinib mesilate has focused attention on GIST patients [4-7]. The current study presents the first multicenter results of treatment of inoperable/metastatic GIST patients in Poland.

GISTs occur in both genders with a more or less similar frequency, but among patients with inoperable/metastatic disease we observed male predominance. The median age of patients was 55-60 years but, unexpectedly, patients with inoperable/metastatic GIST were slightly younger than those without disease recurrence after radical primary surgery. The tumor size and the mitotic count, considered to be the most important prognostic factors, were significantly higher in the metastatic/inoperable group as compared to the non-recurrent group. This "advanced patients" group also comprised a lower percentage of gastric GISTs, which are considered to possess a lower recurrence potential [3, 8]. In general, all the listed clinical and pathological factors could play a crucial role in GIST prognostification (Table III). Undoubtedly, the quality of GIST surgery

Table III. Probable prognostic factors in GIST patients

Parameter Category	.
tumor size	≤5 cm vs. >5 cm
mitotic rate	≤5/HPF vs. >5/HPF
tumor location	stomach vs. other
gender	female vs. male
age (as continuous variable)	older vs. younger
mutation type	KIT (exon 11,9, other, WT) vs. PDGFR
type of surgery	R0 vs R1

HPF – high power field; WT – wild type; PDGFR – Platelet-derived growth factor receptor

should also play a crucial role in GIST patients prognosis [9].

The incidence of the registered advanced and aggressive (inoperable/metastatic) cases in Poland may be estimated at approx. 3 new cases per million annually, which means that according to statistics 1 case per a million of inhabitants per year is still not registered. The reliable data on the incidence of GIST are still not fully available, but the real number of all GIST cases in many countries is underestimated [8, 10, 11].

Imatinib mesylate therapy is the first and only one effective nonsurgical treatment for GIST. Imatinib mesylate prevents kinase signaling by blocking (in GIST) the KIT-associated signaling cascade. Several clinical trials have now been conducted to confirm the dramatic efficacy of imatinib in the treatment of GIST in a majority of patients with inoperable/metastatic disease [4, 6, 10]. When compared to historical clinical data, in which the median survival of those patients was 10-12 months, the method is really superior (in our group of patients the median survival has not been reached after a median follow-up time of almost 18 months and the estimated 3-year progression-free survival was 64.5%). However, imatinib is not a panaceum for GIST patients – with a longer follow-up time the rate of patients who have progressive or are resistant to imatinib increases and complete remission is rare (<10%). This implies the necessity for further studies on new drugs in resistant cases (SU11248 and AMG 706 are currently evaluated in the clinical setting) and, what is more important, on the combination of imatinib therapy with surgery [10].

The most effective method of response evaluation is computed tomography imaging, but the criteria of response are rather controversial and unsatisfactory and should be reconsidered [1].

The role of imatinib therapy in the adjuvant and neoadjuvant setting has not yet been established and is being evaluated in clinical trials (ACOSOG Z900 and Z9001; RTOG 0132 and EORTC 62024). The optimal dose for this orally administered, well-tolerated agent is still under discussion. There are some arguments that dose dependency (400 mg vs 800 mg) of the response to imatinib is related to the mutational status of the tumors and their localization (stomach vs small bowel) [12]. In patients with disseminated bowel GIST not responding to the 400 mg dose it appears to be justified to administer 800 mg daily doses.

In our paper it has been shown that it is possible to achieve a satisfactory clinical outcome in patients with such a rare malignancy as GIST treated with new molecular targeted therapy in different regional cancer centers in Poland. Direct multidisciplinary collaboration between specialists caring for patients with GIST in Poland has shown and confirmed the outstanding role of the Polish Clinical GIST Registry.

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