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Long-term results of treatment of advanced dermatofibrosarcoma protuberans (DFSP) with imatinib mesylate – The impact of fibrosarcomatous transformation

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Abstract

Background: Dermatofibrosarcoma protuberans (DFSP) is rare, infiltrating dermal neoplasm, characterized by indolent growth and low probability of metastases. The first effective systemic therapy in DFSP introduced into clinical practice was imatinib, demonstrating high activity in advanced cases. The aim of the study was to perform an analysis of patients with advanced DFSP treated with imatinib, with or without surgery, in routine clinical practice with long-term follow-up.

Patients and methods: We analyzed the data of 31 Caucasian patients (14 male, 17 female; median age 56 years) with locally advanced/initially inoperable and/or metastatic DFSP who started therapy with imatinib at initial dose 800 mg daily between 12/2004 and 07/2014. All diagnoses were confirmed cytogenetically for the presence of specific COL1A1-PDGFB fusion. Median follow-up time was 5.3 years.

Results: Metastases were present in 15 cases (8 – lungs, 5 – soft tissue, 2 – lymph nodes). Fibrosarcomatous transformation (FS-DFSP) was confirmed in 16 patients (52%). 5-year progression-free survival (PFS) rate was 58% (median 6.8 years), 5-year overall survival (OS) rate was 64% (median time for OS was not reached). The shorter PFS and OS correlated with FS-DFSP and presence of metastatic disease. 5-year PFS rate was 93% for classic DFSP and 33% for FS-DFSP. The best overall responses were: 21 partial responses (68%, including 8 FS-DFSP, but the responses were shorter than for classic DFSP), 6 stable disease (19%) and 4 progressive diseases (13%). Thirteen patients (47%) underwent resection of residual disease and nine of them remained free of disease, although imatinib was discontinued. Median survival after progression on imatinib was 19 months, and longer survival were observed only in cases were rescue surgery/radiotherapy was possible.

Conclusions: Our results indicate the long-term activity of imatinib in therapy of inoperable and/or metastatic cases of DFSP, including FS-DFSP. Some DFSP patients initially evaluated as unresectable/metastatic or necessitating mutilating surgery turned resectable after imatinib therapy and this rational approach leading to complete remission maybe potentially curative.

Keywords: Dermatofibrosarcoma protuberans; Fibrosarcomatous transformation; Imatinib

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Introduction

Dermatofibrosarcoma protuberans (DFSP) is a rare soft tissue tumor, comprising approximately 1% of sarcomas, with typically indolent growth over years and probability of regional/distant metastases less than 5%, especially in DFSP with fibrosarcomatous transformation (DFSP-FS).[1–8] The standard treatment of localized primary or recurrent cases is radical, wide local excision with clear margins, which may require reconstructive techniques and may cause functional and cosmetic disfigurement.[2,9,10]

From molecular point of view DFSP is typically characterized by a specific rearrangement of chromosomes 17 and 22 in the form of translocation t(17; 22) (q22; q13) that leads to the fusion of collagen type I A1-chain gene (*COL1A1*) to the platelet-derived growth factor B-chain gene (*PDGFB*) – often visible in supernumerary ring chromosome. The result of this rearrangement is upregulation of the COL1A1-PDGFB fusion protein, processing to a mature homodimer PDGF-BB, and consequently continuous autocrine activation of the PDGFB receptor (PDGFRB), a protein tyrosine kinase acting as a potent growth factor.[2,11–13] These mechanisms contribute directly to development and growth of DFSP, but also of giant cell fibroblastoma (GCF), which from a pathogenetic point of view can be called the juvenile form of DFSP.[14]

Advances in the understanding of the molecular mechanisms of DFSP have resulted in the introduction to clinical practice targeted therapy acting on PDGFRB. The first effective systemic therapy in DFSP introduced into clinical practice was imatinib mesylate.[2,15–18]

Due to the rarity of the disease and the lack of ongoing prospective trials we have decided to assess therapeutic activity of imatinib in the largest presented group of patients with locally advanced and/or metastatic DFSP expressing COL1A/PDGFB fusion treated in one cancer center outside clinical trials with long-term follow-up. The aim of the study was to analyze distant outcomes (survival and recurrences) of imatinib-treated advanced DFSP and scopes of neoadjuvant strategies in routine practice.

Patients and methods

We analyzed all consecutive patients with locally advanced/metastatic DFSP treated with imatinib mesylate, from December 2004 to July 2014. Patients were treated at one reference center for treatment of soft tissue sarcomas. All patients provided a written informed consent to the treatment with imatinib. Approval by Institutional Review Board was also required.

All patients met the following criteria for imatinib therapy:

1) histological diagnosis of DFSP;
2) cytogenetic confirmation of presence of COL1A1/PDGFB (by fluorescence in situ hybridization – FISH);
3) metastatic and/or locally inoperable lesions or advanced tumor possible only to remove with significant functional/cosmetic consequences (as assessed by multidisciplinary team)
4) measurable disease with photographic imaging of superficial lesions and or CT scans in case of visceral metastases;
5) WHO performance status $\leq$3;
6) adequate renal and liver function.

Adverse events during therapy were evaluated by Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

Objective responses were evaluated by serial measurements with photographic documentation of superficial lesions and contrast enhanced spiral CT in case of deep structures involvement according to RECIST 1.1.[19] Possibility of resection of residual disease after response to therapy was assessed during every evaluation by two oncological surgeons. In case of such resection, as well as if postsurgical pathological evaluation confirmed microscopically, radical resection therapy with imatinib was stopped.

Progression-free survival (PFS) time was calculated from the date of the start of imatinib treatment to the date of the most recent follow-up, or progression or death due to the disease. Overall survival (OS) time was calculated from the date of the start of imatinib treatment to the date of the most recent follow-up or death due to the disease. Median follow-up time from the start of imatinib therapy was 5.3 years. The Kaplan–Meier method was used for analysis of survival curves, with the log-rank test for univariate comparison of the survival between groups. Differences were considered statistically significant if p-values were <0.05. These statistical computations were performed using Statistica 7.1 software [Statsoft ®; Tulsa, OK].

Results

We retrospectively identified 31 patients treated with imatinib in initial dose 400 mg bid, except one patient who started therapy from 400 mg daily. Table 1 summarizes patient characteristics and clinical findings. Metastases were present in 15 cases (eight – lungs, five – soft tissue, two – lymph nodes). Fibrosarcomatous transformation (FS-DFSP) was confirmed in 16 patients (52%) and metastases occurred only in FS-DFSP cases.

In terms of efficacy overall clinical benefit of imatinib therapy (counted as the sum of complete remissions – CR, partial remissions – PR and stable disease – SD rates) was 87% (Table 2). The best overall responses were: 21 partial responses (68%, including eight FS-DFSP, but the responses were shorter than for classic DFSP), six stable disease (19%) and four progressive diseases (13%).

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Table 1
Patient characteristics and clinical findings.

	N = 31 (%)
Gender	
Male	14 (45%)
Female	17 (55%)
Age – median (range) [years]	56 (20–71)
Primary tumor location	
Trunk	17 (55%)
Head	7 (22.5%)
Extremities	7 (22.5%)
Primary tumor	7 (23%)
Recurrent tumor	9 (29%)
Metastatic	15 (48%)
Classic DFSP	15 (48%)
Fibrosarcomatous DFSP	16 (52%)
Location of metastases	
Lungs	8 (54%)
Soft tissues	5 (33%)
Lymph nodes	2 (13%)

5-year progression-free survival (PFS) rate was 58% (median 6.8 years), 5-year overall survival (OS) rate was 64% (median time for OS was not reached) [Fig. 1A and B]. The shorter PFS and OS correlated with FS-DFSP ($p < 0.01$) and presence of metastatic disease ($p < 0.05$) [Fig. 2A and B]. 5-year PFS rate was 93% for classic DFSP and 33% for FS-DFSP ($p < 0.01$).

Thirteen patients (47%) underwent resection of localized residual disease (after median time of 4 months of preoperative imatinib, 1 was FS-DFSP) and nine of them remained free of disease, although imatinib was discontinued. Minimal macroscopic assessed margins were 1 cm (measured from the residual tumor after imatinib therapy) and contained the tattoo points (if marked) of initial tumor. Postoperative assessment revealed macroscopically negative margins (R0) in 8 cases, three of five patients with microscopically non-radical resection (R1) continued imatinib therapy postoperatively. Disease relapsed in 3 patients after R1 resection (two of them continued imatinib postoperatively and recurrence was re-resected in 2 cases) and in 1 patient in R0 group. Additionally two metastatic FS-DFSP patient underwent metastasectomy and continued imatinib postoperatively.Median survival after progression on imatinib was 19 months, and longer survival were observed only in cases were rescue surgery/radiotherapy was possible.

Table 2
The clinical efficacy of imatinib, progression and survival status for entire group of patients.

	Total (N = 31)
	N (%)
Progression status	
Progression free	19 (61)
Progression	12 (39)
Survival status	
Alive	22 (71)
Dead	9 (29)
Best overall response	
Partial response	21 (68)
[including FS-DFSP]	8 of 16
Stable disease	6 (19)
Progressive disease	4 (13)

Adverse events were relatively common during imatinib therapy, but no new toxicities were reported (Table 3). Eleven patients (35%) treated with initial imatinib dose 400 mg bid had finally reduction of the dose to 400–600 mg daily due to adverse events as recommended by manufacturer or required by patient.

Discussion

In this study we have presented the largest one institution series of advanced DFSP patients treated with imatinib with the longest follow-up. The results of this study confirmed that majority of advanced DFSP patients benefit from imatinib therapy with median PFS exceeding 5 years.

Taking into account all limitations related to retrospective analysis, these results seem to be comparable to outcomes of reported small prospective trials, but also they provide new information on the activity of imatinib in daily clinical practice, especially in the subgroup of FS-DFSP patients with more aggressive course of disease. Moreover, our series comprise unique homogenous group of patients with confirmed cytogenetically presence of *COL1A1-PDGFB* fusion gene, which is especially important as a target of imatinib therapy in FS-DFSP.

Although rarely DFSP is present as inoperable or metastatic, imatinib mesylate has become a gold standard treatment in such cases.[2,20,21] Until now reports of several cases and small phase II trials demonstrated the usefulness of imatinib in metastatic and localized unresectable DFSP.[15–18,22–25] We have confirmed that FS-DFSP still have sensitivity to imatinib, although responses last shorter[26] with median PFS approximately 1.5 years in our series of patients. Moreover, metastatic disease is closely related to fibrosarcomatous transformation.[27,28]

Majority of patients treated with imatinib experience adverse events during treatment, but almost all toxic effects are mild and manageable. There are no disease-specific side effects and these are similar to those observed in patients with gastrointestinal stromal tumor (GIST). Although imatinib is well tolerated but if used in initial dose of 800 mg daily, the dose reduction is required in significant proportion of patients (35% in our series).

The preoperative imatinib strategy for tumor downstaging and decreasing of excision morbidity by tissue-sparing leading to diminish cosmetic disfigurement or functional impairment appears very attractive. Kerob et al.[29] presented report on 25 resectable DFSP (median size – 4.5 cm) treated in phase II trial with neoadjuvant imatinib at the dose of 600 mg daily for two months, objective partial

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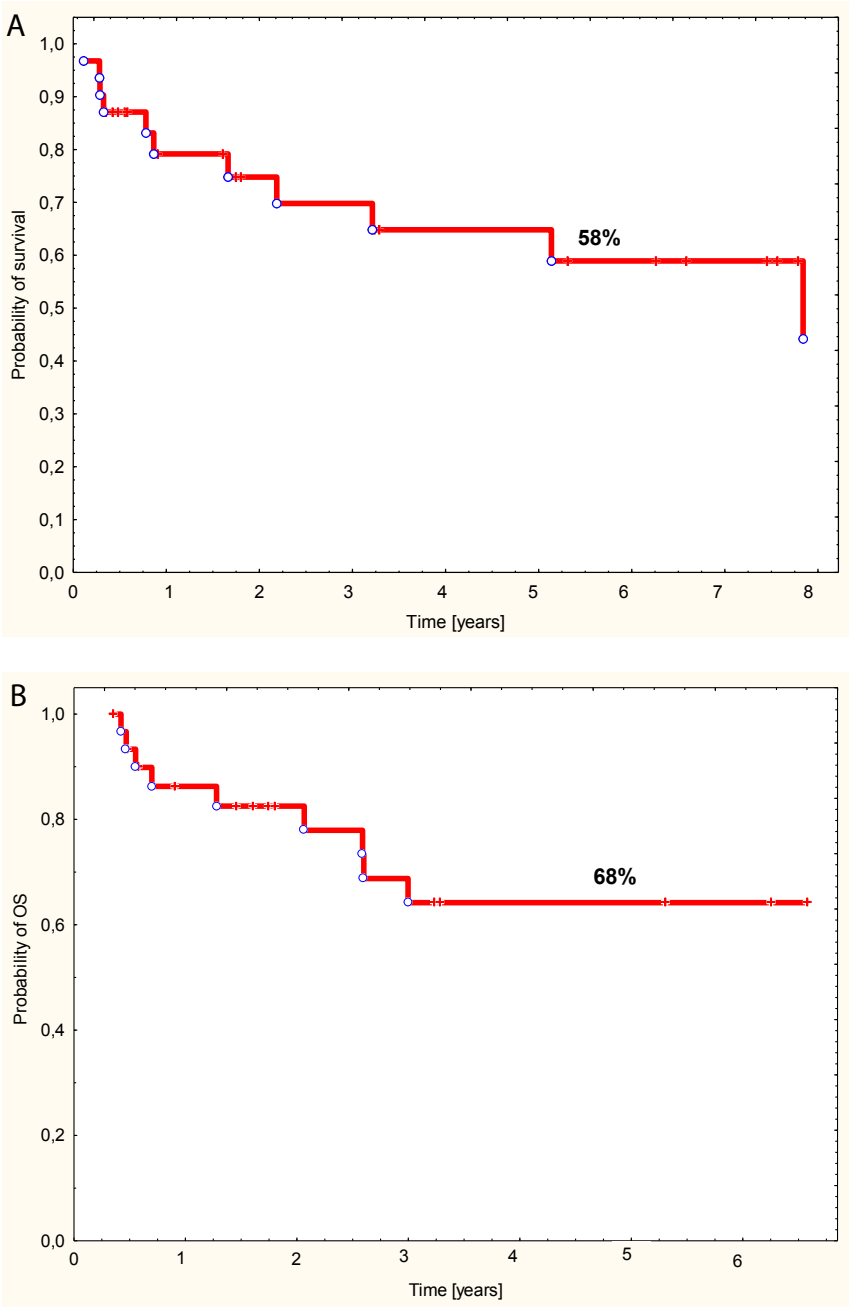

Figure 1. A. Progression-free survival from date of imatinib start. B. Overall survival from date of imatinib start.

response according to RECIST was observed in only 9 cases (36%). It is likely, that the response rate in this trial would have been significantly higher if the preoperative treatment duration would have been prolonged, as it was in our cases. Ugurel et al.[30] presented the results of multicenter phase II trial on neoadjuvant imatinib therapy at dose of 600 mg daily in locally advanced primary or recurrent DFSP with clinical benefit exceeding 90%. The definitive surgical resection of the tumor was performed in 13 of 14 patients.

In our 13 of 16 non-metastatic, locally advanced patients underwent resection of residual disease after partial response to imatinib therapy and nine of them had no disease recurrence during further follow-up. Current results indicate that some DFSP patient initially evaluated as unresectable/metastatic or necessitating mutilating surgery

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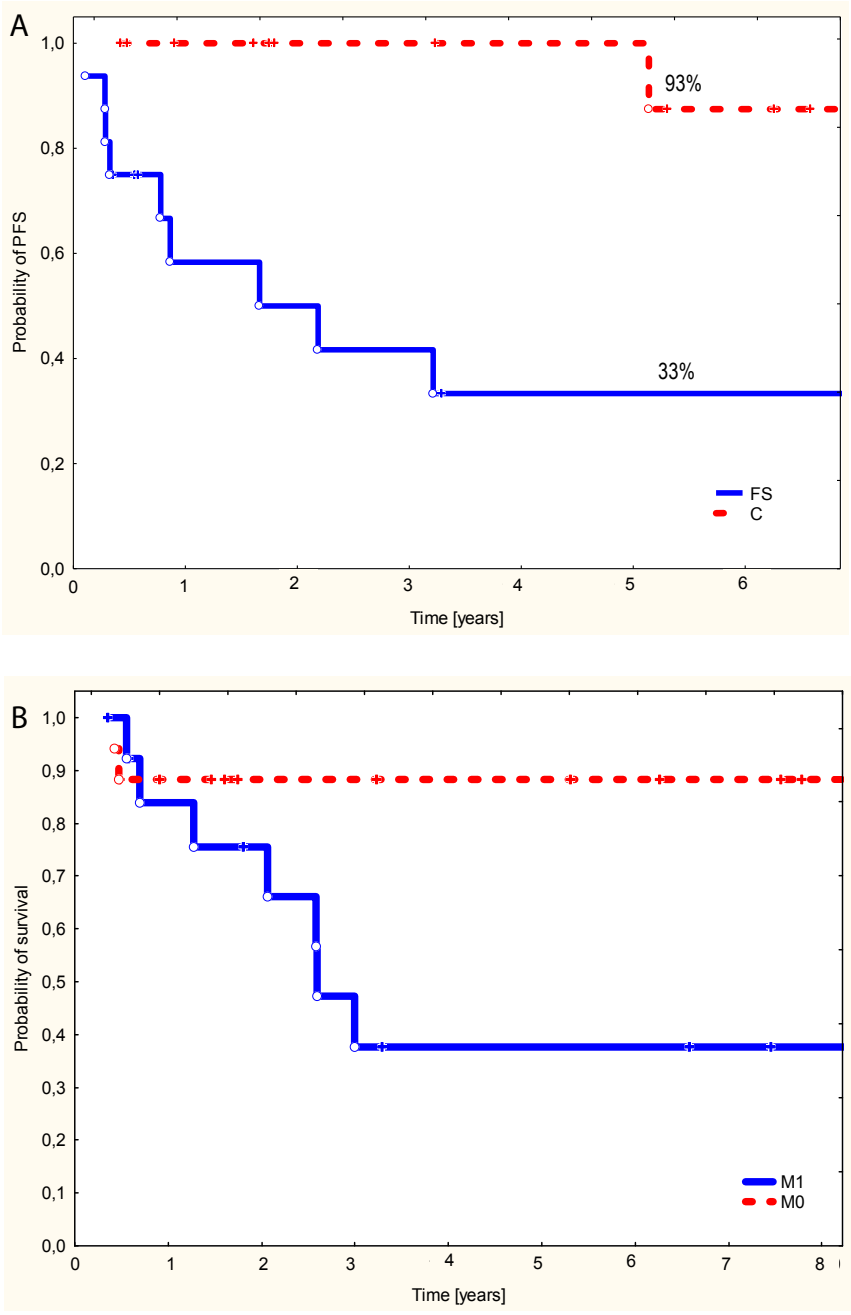

Figure 2. A. Progression-free survival according to fibrosarcomatous transformation ($p < 0.01$). B. Overall survival according to presence of metastases ($p < 0.05$).

turned resectable after imatinib therapy. This rational approach leading to complete remission maybe potentially curative (Fig. 3).[31–34] Further studies are necessary for elucidating whether preoperative imatinib therapy reduces the need for wide surgical margins or whether imatinib has activity as adjuvant therapy in cases of positive margins after excision (if re-excision is not feasible) or in other high-risk patients (e.g. FS-DFSP or located near critical anatomical sites).

It is little know about mechanism of resistance to imatinib. According to Ugurel et al. a weak PDGFRB phosphorylation seems to be associated with non-response to imatinib.[30] According to Eilers CDKN2A/p16 loss implicates CDK4 as a possible target in imatinib-resistant

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Table 3
Adverse events during imatinib therapy in DFSP.

Adverse event and grade CTCAE	N (%)
Edema/fluid retention	
G1	24 (77%)
G2	3 (10%)
G3	1 (3%)
Fatigue	
G1	6 (20%)
G2	1 (3%)
G3	1 (3%)
Skin toxicity	
G1	6 (20%)
G2	2 (6%)
Nausea	
G1	5 (16%)
G2	2 (6%)
Diarrhea	
G1	4 (13%)
G2	2 (6%)
G3	1 (3%)
Anemia	
G1	8 (25%)
G2	3 (9.7%)
Neutropenia	
G3	3 (9.7%)
Thrombocytopenia	
G1	3 (9.7%)
G2	1 (3%)
G3	2 (6.4%)

DFSP.[35] Tazzari et al. imply the future utility of immunotherapy in advanced DFSP.[36]

In series from Memorial Sloan-Kettering Cancer Center[37] two patients were treated with sorafenib after failure on imatinib and one partial response was observed. Similar report was provided by Kamar et al.,[38] where locally invasive DFSP after failure of radiation therapy and imatinib (400–800 mg) was successfully treated with sorafenib 800 mg daily for 5 months. The single patient who developed secondary resistance to imatinib in German phase II trial responded transiently to second-line therapy with sunitinib, which may be explained by the binding capacity of sunitinib to PDGFRB, which is about 10 times more than that of imatinib.[30] Chinese study on 30 imatinib-resistant metastatic DFSP suggest also the efficacy of sunitinib in second-line therapy with median PFS and OS – 19 and 27 months, respectively.[39]

In conclusion, our results with median follow-up exceeding 5 years indicate the long-term activity of imatinib in therapy of inoperable and/or metastatic cases of DFSP harboring COL1A1-PDGFB fusion,[40–42] with an objective response rate exceeding 50%, and that imatinib is also active in aggressive fibrosarcomatous DFSP.[28,43] The activity of imatinib is limited in time, especially in FS-DFSP, and still no effective, proven options after progression exist. Some DFSP patient initially evaluated as un-resectable/metastatic or demanding mutilating surgery turned resectable after imatinib therapy and this rational approach leading to complete remission is potentially curative.

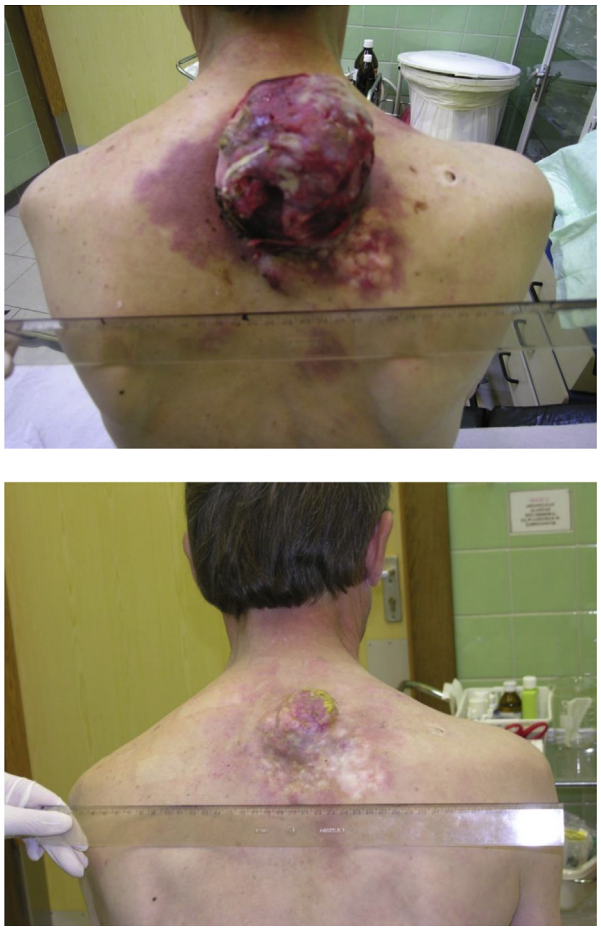

Figure 3. Photographs demonstrating the response of advanced multifocal DFSP on the back to imatinib (A. before therapy, B. after 3 months of imatinib therapy that was followed by microscopically radical resection of the tumor and no recurrent disease during 5 years of follow-up).

Current therapy of DFSP with t(17; 22) translocation should be definitively conducted by multidisciplinary team, including oncological surgeon, to consider the use of imatinib mesylate as initial therapy to decrease possible extent of surgery and related morbidity.

Conflict of interest

Piotr Rutkowski hasreceived honoraria and was a member of Advisory Board for Novartis.

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No external sponsors were involved into this study.

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