The diffuse-type tenosynovial giant cell tumor (dt-TGCT) patient journey: a prospective real-world study

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Research
Abstract

**Background:** Tenosynovial giant cell tumor (TGCT) is a rare locally aggressive neoplasm arising from the synovium of joints, bursae, and tendon sheaths affecting small and large joints. It represents a wide spectrum ranging from minimally symptomatic to massively debilitating. The majority of findings to date are mainly from small, retrospective case series, and thus the morbidity and actual impact of this rare disease remain to be elucidated. This study explores prospectively the real-world management of TGCT.

**Methods:** The TGCT Observational Platform Project (TOPP) registry was a multinational, multicenter, prospective observational study involving 12 tertiary sarcoma centers in 7 European countries, and 2 US sites. This study enrolled for 2 years all consecutive \( \geq 18 \) years old patients, with histologically diagnosed primary or recurrent cases of diffuse-type TGCT. Patient demographic and clinical characteristics were collected at baseline and every 6 months for 24 months. Quality of life questionnaires (PROMIS-PF and EQ-5D) were also administered at the same time-points. Here we report baseline patient characteristics.

**Results:** 166 patients were enrolled between November 2016 and March 2019. Baseline characteristics were: mean age 44 years (mean age at disease onset: 39 years), 139/166 (83.7%) had prior treatment, 71/166 patients (42.8%) had \( \geq 1 \) recurrence after treatment of their primary tumor, 76/136 (55.9%) visited a medical specialist \( \geq 5 \) times, and 66/116 (56.9%) missed work in the 24 months prior to baseline, and 17/166 (11.6%) changed employment status or retired prematurely due to disease burden. Prior treatment consisted of surgery (i.e., arthroscopic, open synovectomy) (128/166; 77.1%), and systemic treatments (52/166; 31.3%) with imatinib (19/52; 36.5%) or pexidartinib (27/52; 51.9%). Treatment strategies at baseline visits consisted mainly of watchful waiting (81/166; 48.8%), surgery (41/166; 24.7%), or targeted systemic therapy (37/166; 22.3%). Patients indicated for treatment reported more impairment compared to patients indicated for watchful waiting: worst stiffness NRS 5.16/3.44, worst pain NRS 6.13/5.03, PROMIS-PF 39.48/43.85, and EQ-5D VAS 66.54/71.85.

**Conclusion:** This study confirms that diffuse-type TGCT can highly impact quality of life. A prospective observational registry in rare disease is feasible and can be a tool to collect curated-population reflective data in orphan diseases.

Introduction

Tenosynovial giant cell tumor (TGCT) is a rare, locally aggressive mesenchymal neoplasm arising from the synovium of joints, bursae, and tendon sheaths and affects both small and large joints [1]. Two subtypes of TGCT are defined based on clinical and radiological characteristics: localized- and diffuse-type TGCT (L-TGCT and dt-TGCT) [2, 3]. Although both subtypes share a common pathophysiology, they represent a wide spectrum of clinical entities, making TGCT behavior complex and hard to predict [4]. From the molecular point of view, both subtypes usually share the presence of a fusion involving the colony stimulating factor (CSF) gene, which drives tumor growth [5, 6]. The wide clinical spectrum ranges
from mildly symptomatic to extremely debilitating and may cause symptoms like pain, stiffness, swelling, and limitation in range of motion [7]. Disease severity is further characterized as mild localized, severe localized, moderate diffuse, or severe diffuse [8].

Although less prevalent, dt-TGCT is an aggressive multi-lobulated lesion located intra- and extra-articular, affecting various joints in the body (mainly the knee) and can have a detrimental effect on quality of life (QoL) [9, 10, 11, 12]. Dt-TGCT incidence rate is estimated at 5 per million person-years [9]. Due to non-specific symptoms and the rarity of this disease, a proper diagnosis can sometimes take years, which in turn may severely delay optimal treatment and care for TCGT patients [9, 13]. Patients with TGCT therefore have a high risk of overtreatment, undertreatment, or inadequate treatment, and in many countries referral to specialized centers is the absolute exception. Treatment options contain mostly surgical treatment, but recently CSF receptor (CSFR) inhibitors have been used for treatment of those cases in which surgery is not an option, shedding light on an otherwise neglected disease.

The morbidity and actual impact on quality of life (QoL) of this rare disease and its various treatment options are not well known because the majority of findings to date are mainly from small, retrospective studies that focus on oncological outcomes [1, 14]. There is a need for better knowledge of the natural history of this tumor in order to understand the burden of TGCT from a patient and a regulatory perspective, and of the treatment landscape beyond a single institution. Additionally, there is the need to explore the real-world management of TGCT, particularly of the diffuse type (including functional details measured pre- and post-treatment) to describe the spectrum of indications, challenges, and the actual impact on patient QoL and ability to work.

To this end a multinational, multicenter, prospective observational study, named the TGCT Observational Platform Project (TOPP), was launched in November 2016, involving hospitals and tertiary sarcoma centers from Europe and the United States. All patients included in the study were to be followed up for a minimum of 2 years. We report herein on patient characteristics at the time when they were entered in the registry (baseline).

**Methods**

**Study design and participants**

This global multi-center, prospective sponsored study included all consecutive patients from 12 tertiary sarcoma centers in 7 European (EU) countries from 2016 to 2018. Two sites in the United States (US) enrolled patients from 2017 to 2019. TOPP, the first non-interventional, observational disease registry, enrolled patients during a 2-year period with prospective follow-up of 24 months. Participating sites were selected based of their expertise in treatment of TGCT.

Eligible patients were 18 years or older, with a primary or recurrent diffuse type-TGCT (confirmed by histology and radiology). The institutional review board or ethics board provided approval in each center, and written informed consent was obtained from each patient who participated in this study.
Patient demographics, complete TGCT-related history and current status, including radiologic assessments and health resources used in the past 24 months, were collected at baseline.

TGCT-related patient-reported outcomes (PRO) for pain, stiffness, swelling, and limited range of motion were collected at baseline and every following year thereafter through electronic data capture (PPROM), administered at baseline consisted of the mean brief pain inventory (BPI), mean worst pain and stiffness numerical rating scale (NRS), the Patient-Reported Outcome Measurement Information System Physical Functioning® (PROMIS-PF), and the EuroQoL 5D (EQ-5D) (appendix). Admission status at baseline was categorized into patients with a primary diagnosis or recurrent disease. Primary diagnosis was defined as patients who were awaiting treatment or were treated and were without evidence for local progression at baseline. Recurrent disease was defined as tumor recurrence after complete resection or progression of residual tumor. Therapy-naïve patients received no therapy prior to baseline and were consequently admitted as primary diagnosed patients. Disease severity was in line with the TGCT severity classification by Mastboom et al, with severe dt-TGCT classified as intra- and extra-articular involvement with involvement of one or more ligaments or muscular/tendinous tissue observed on magnetic resonance imaging (MRI)[8]. This study presents the data of the TGCT patient journey collected at baseline, i.e., when patients entered the TOPP study.

**Statistical analysis**

Continuous data were described using either means and standard deviations (SD) or medians and interquartile ranges (IQR). Categorical variables were summarized as number of observations and percentages (%) of the observations in each category. Percentages do not include the missing category and are calculated over the number of subjects with available (non-missing) data. The whole analysis was descriptive only. Statistical analysis was performed using the Statistical Analysis System (SAS®) Version 9.4 under Microsoft Windows Operating System. Because dt-TGCT is an orphan disease, no formal sample size consideration has been performed, as recruitment of patients within the scheduled 2-year period was expected to be difficult.

**Results**

Between November 2016 and March 2019, 166 patients from EU and the US were enrolled in the TOPP registry. Patient demographics and clinical characteristics are described in Table 1. The mean age at diagnosis was 39.0 years (range, 14.4 – 75.6; SD ± 14.42) and median time from diagnosis until TOPP entry point was 29.7 months (IQR, 9.5–80.0). TGCT had a female predilection (n = 102; 61.4%), and the knee joint was predominantly affected (n = 112; 68.5%). Ninety-five patients (57.2 %) were primary diagnosed cases, and 71 patients (42.8%) had at least one recurrence prior to baseline, occurring after any treatment of their primary tumor.

**Diagnostic pathway**
A median of 16.9 months (IQR, 4.0–44.0) elapsed from onset of symptoms until diagnosis of TGCT (Table 2). MRIs closest to baseline of TOPP were commonly requested for postoperative follow-up (n = 56; 40.0%). Of all MRIs, dt-TGCT was generally located both intra- and extra-articular (n = 90/147; 61.2%) with involvement of ligaments (n = 88/134; 65.7%), and tendons and muscles (n = 99/141; 70.2%), classifying half of the patients (n = 83) with severe dt-TGCT at baseline (Table 2). Fourteen patients (8%) with severe dt-TGCT were still therapy naïve, illustrating a high percentage of severe dt-TGCT even after treatment (n = 69/166; 41.6%). Histological confirmation was primarily obtained after excision (n = 32; 41.6%), but several biopsy techniques were performed (e.g., core needle biopsy, arthroscopic biopsy, or fine needle aspiration). In 13% TGCT diagnosis was based on a surgical procedure undertaken for suspicion of a malignancy (Table 2).

**Treatments prior to baseline of TOPP**

Of 166 patients who entered the TOPP study, 139 (83.7%) had already received a TGCT-related treatment at baseline, while 27/166 patients (16.3%) were treatment naïve (Table 1). One hundred twenty-eight of 166 enrolled patients (77.1%) underwent surgery, 57 of 95 (60%) at primary diagnosis and 71 of 71 (100%) at recurrence time (Table 3).

Of 57 patients treated with surgery at the time of initial diagnosis, 30 (31.6%) were treated arthroscopically. At the time of relapse, 71 (100%) patients were re-operated, and in this case the surgical approach was open synovectomy in 49 (69.0%) and arthroscopic in 33 (46.5%). Five patients (3.9%) received a (tumor) prosthesis secondary to TGCT, in four cases due to a recurrent tumor. Fifty-two patients (31.3%) received systemic treatment; in 39.4% (28/71) this was indicated in recurrent cases and was still ongoing in 34.6% (18/52) at baseline. Thirty-two of 52 cases (62.7%) were indicated for systemic therapies because of locally advanced TGCT, 9.8% (5/52) as neo-adjuvant, 7.8% (4/52) for maintenance, and 7.8% (4/52) for palliative therapy. Eleven patients (21.2%) received systemic therapies as first treatment for TGCT. Tyrosine kinase inhibitors (TKI) imatinib (off label) or pexidartinib (in research setting) were most frequently administered as latest treatment prior to baseline (46/47; 97.9%) (Table 3). Radiation therapy, comprising external beam radiotherapy and radiosynoviorthesis with Yttrium⁹⁰, was administered in 15/166 (9%) and mostly performed as adjuvant therapy after surgery in refractory cases (10/15; 66.7%) (Table 3). Eighty-eight (53%) of all cases had received prior and concomitant therapies for TGCT-related symptoms.

**Treatment strategies at time of TOPP study entry**

Treatment strategies at baseline visits of TOPP consisted of watchful waiting (n = 81/166; 48.8%), surgery only (n = 41/166; 24.7%), or targeted systemic therapy only (n = 37; 22.3%). A multimodality approach was administered in 7/166 (4.2%) of cases, comprising different therapy combinations (e.g. surgery, targeted systemic therapies, and/or radiation therapy) (appendix).

A conservative monitoring approach at baseline was primarily decided on for patients who received only surgery before baseline (n = 47/81; 58.0%) (Table 4). Most MRIs were conducted as regular postoperative
follow-up (n = 43/75; 57.3%), and this group comprised the lowest percentage of severe cases (n = 38/81; 46.9%). Non-invasive interventions were common in this group; 26.2% of the patients received rehabilitation (n = 17), and patients in need of physical therapy (n = 23, 28.4%) had a median of 18 (range, 4.0–200.0) sessions.

Patients indicated for surgery were most recently diagnosed with TGCT. A median of 6.7 (IQR, 1.2–59.8) months elapsed from TGCT diagnosis until baseline, and 65.9% (n = 27) had a primary diagnosis, of which 16/41 (39.0%) were therapy naïve at baseline. Furthermore, MRIs closest to baseline were primarily indicated to diagnose TGCT (n = 23; 57.5%) (Table 4).

Twenty one (56.8%) of the patients indicated for targeted systemic therapies at TOPP baseline already received multimodality treatment before baseline. None of these patients were therapy naïve at baseline, and just 7 (18.9%) patients had only surgery before. MRIs were predominantly obtained due to progressive complaints (n = 13; 37.1%), and in this patient group the highest percentage of recurrent (n = 18; 48.6%) and severe dt-TGCT (n = 21; 56.8%) was observed. These patients visited medical specialists at a median of 12 times (range, 2.0–65.0) in the 24 months prior to baseline. Patients indicated for systemic therapies had a median age of 48.0 years (range 20.0 – 73.0). In addition, algesics were most used by these patients (n = 9; 23.3%) and mean worst stiffness and pain NRS scores of 5.3 (SD ± 2.55) and 5.8 (SD ± 1.97), respectively, were reported. Physical functioning was limited with a median PROMIS-PF score of 39.98, and the lowest QoL scores were reported with an EQ-5D index score of 0.74 and VAS score of 70.0. At baseline, 33 patients (89.2%) had a current systemic therapy, of which 18 (54.5%) were started before. All current systemic therapies consisted of TKIs Imatinib (n = 14; 42.4%) and pexidartinib (n = 19; 57.6%).

Only 11 patients did not report complaints due to TGCT at baseline, resulting in 93.4% of patients with at least one complaint. Patients indicated for treatment reported TGCT-related symptoms (e.g., pain, stiffness, swelling, and limited range of motion) more frequently compared to those with a wait-and-see policy (Table 4), except for swelling, which was least experienced by patients treated with systemic therapies (51.4%), and. 68.3% indicated for surgery at baseline suffered from 3 or more TGCT-related symptoms. Both patient groups indicated for surgery and systemic therapies reported higher pain severity (4.25) and interference scores (3.00) compared to patients indicated for watchful waiting (2.25; 1.57). In addition, both treatment groups reported lower PROMIS-PF scores (39.54 and 39.98, respectively), EQ-5D index scores (0.80 and 0.74, respectively) and EQ-5D VAS scores (69.0 and 70.0, respectively).

**Health economics**

Thirty-three patients (23.9%) needed at least 5 visits from disease onset, before diagnosis of TGCT. In addition, 76 patients (55.9%) consulted a medical specialist 5 times or more to in the 24 months prior to baseline. Thirty-six patients (25.5%) had more than 10 physical therapy sessions in the 24 months prior to baseline. Hospitalization and rehabilitation were needed in 91.0% (151/166) and 18.6% (26/140), respectively, with a median of 3.0 (range, 1.0–184.0) and 15.0 (range, 1.0–120.0) days, respectively. Fifteen (9.9%) patients were hospitalized 5 or more times. Sixty-six patients (56.9%) missed work due to
their TGCT in the 2 years prior to baseline, with a median of 25.0 days (range, 1.0–75.0). More importantly, of 146 patients who were employed, 17 (11.6%) were forced to change their employment status or even retire prematurely due to disease burden. Domestic help was necessary in 26 cases (16.0%).

**Discussion**

TOPP represents the largest prospective, international, multi-center disease registry for dt-TGCT, being able to include 166 patients in slightly more than 2 years, and shows that conducting collaborative observational studies for rare tumor is feasible. Current literature is largely focused on the oncological outcomes of this often chronic disease [15, 16, 17, 18, 19, 20, 21, 22]. Data derived from this registry made it possible for the first time to describe the dt-TGCT patient journey and treatment decisions around disease onset and diagnosis of dt-TGCT patients. We believe that such study design can guide collection of high-quality data for other orphan diseases.

The present study confirmed that TGCT has its onset in a relatively young, educated, and working patient population with a female predilection [9, 10]. Time between onset of symptoms until diagnosis averaged more than a year, and in this time interval several medical specialists were frequently visited. An under- or overestimation could be introduced due to a recall bias. Nonspecific clinical signs and symptoms in TGCT patients often mimicked other mono-articular pathologies, resulting in frequent consultation of various healthcare professionals, e.g., physical therapists, rheumatologists, and sports doctors, and lag time in diagnosis (Fig. 1, 2) [23]. MRI was the non-invasive gold standard to diagnose TGCT type and distinguish between the localized and diffuse subtypes [24, 25]. In addition, this modality was frequently utilized for postoperative surveillance for recurrence, evaluation of worsening complaints (e.g. distinguishing degenerative arthritic symptoms or internal derangement of the joint), or pre-surgical planning (Table 2). Definitive diagnosis was predominantly obtained by histological confirmation through different forms of biopsies [26, 27]. In 10 cases, TGCT was coincidentally diagnosed after surgery for an initial suspicion of cancer. Disease mimicking and unfamiliarity could possibly introduce such misdiagnoses, with potential major consequences for a patient.

The primary form of care for TGCT is complete surgical removal of abnormal tissue, performed arthroscopically, open or combined, often requiring multiple incisions to access the disease thoroughly. However, there is a high risk for recurrence, especially in dt-TGCT, due to invasive growth both in and outside the joint [13, 16, 28, 29]. Synovectomies are generally relatively invasive, with a high recurrence rate and repetitive surgery causing significant impairment [16]. Multimodality treatments (e.g., external beam radiotherapy and radiosynoviorthesis) have been performed in an attempt to reduce the recurrence rate in dt-TGCT, leading to varied reported outcomes [17, 18, 19]. In addition to surgery, several CSF1-receptor inhibitors including TKIs showed promising results in tumor volume decrease and reduction of debilitating symptoms [20, 21, 22, 30, 31]. Of the TKIs, pexidartinib is an approved systemic therapy, recently added as a category 1 recommendation for the treatment of adult patients with symptomatic
TGCT/pigmented villonodular synovitis (PVNS) associated with severe morbidity or functional limitations that is not amenable to improvement with surgery.

Our results confirm that surgery was the mainstay of treatment (75%), which is consistent with other studies [13, 16, 29]. Furthermore, all patients with recurrent dt-TGCT disease had surgery, often combined with other treatment modalities (Fig. 3). Synovectomies were mostly performed open. To date, literature reported conflicting results regarding different surgical techniques, not favoring one over another [15, 32, 33]. However, we hypothesize that open surgery may allow for better overview of tumor, located intra- and extra-articular, with extension to surrounding tissues, possibly resulting in more complete removal of disease burden. Almost a third of the patients received systemic therapies, mainly TKIs such as pexidartinib (in research setting) and imatinib (off label)—a relatively high percentage, possibly due to a selection bias since sarcoma centers participating in TOPP were also involved in clinical studies on TGCT. Use of TKIs was mostly found indicated in locally advanced refractory cases, illustrating this modality being considered a last resort for patients who are not amenable for surgery (Fig. 2). An individual well-thought treatment decision made by a multidisciplinary team of medical specialists is therefore needed regarding both surgical and systemic treatment options with such rates of response, local recurrence, complications, and side effects.

Given the lack of understanding of this disease, the incidence of TGCT may be underestimated as disease awareness increases and diagnostic tools improve [11]. Diagnostic delay results in multiple visits to different health care practitioners (e.g., general practitioner, physiotherapist, sports medicine doctor, rheumatologist) and unnecessary or excessive treatments (e.g., use of painkillers or diagnostic arthroscopies) in the first and second line before referral to an orthopedic or sarcoma oncologist [13, 34]. If treated inadequately, aggressive dt-TGCT can become a chronic illness affecting an otherwise young, healthy patient population, leading to a significantly decreased QoL and concurrent high social costs (e.g., sick leave, medical costs) (Fig. 1) [11, 35].

Current literature lacks treatment guidelines and does not present relevant clinical findings that support clinical decision making. Creating insight on such important factors can be of great value in optimizing treatment strategies. Different treatment strategies were selected at baseline of TOPP, predominantly watchful waiting, surgery, or systemic therapies. The number and type of follow-up visits were not controlled, as they were influenced by patient and physician concerns. Systemic therapies were predominantly indicated for older patients with recurrent and severe dt-TGCT despite their having received multimodality treatment before. This patient group reported the highest decrease in QoL and experienced a major limitation in physical functioning. The use of systemic therapies in the setting of relapsed dt-TGCT might be justified in an attempt to avoid chronic disability [20, 21, 22]. Local experience and availability of TKIs during TOPP possibly influenced the choice for treatment in the tertiary reference centers, with a preference for surgery followed by TKI. Primary or refractory cases are predominantly treated at doctors’ preference. Improved disease-specific patient education, multidisciplinary discussion, and shared decision making would enable better treatment selection for each patient.
At baseline of TOPP, patients with a wait-and-see policy reported fewer TGCT-related symptoms, less frequent use of painkillers, and higher QoL, advocating that the lack of symptoms may be the driving force for choosing a more conservative approach. We therefore considered PRO to be important influencers in shared treatment decision making, which is consistent with the increasing role of patient-based care in chronic diseases, especially in a benign disease such as TGCT [36].

TOPP aimed to provide insight on health care utilization by dt-TGCT patients. In 2 years prior to baseline, medical professionals were often consulted, a fourth of the patients needed multiple physical therapy sessions, and medical specialists were frequently visited by more than half of the patients (Table 5). Hospitalization and, to a lesser degree, rehabilitation were common with varying duration. Like the study of Burton et al, this suggests that TGCT causes a high health economic burden. In a like manner, dt-TGCT increases social costs [35]. Illness often causes work absence, intermittently more than 5 weeks of work in total in 2 years’ time (Table 5). On top of that, several patients were forced to change their employment status from full-time to part-time, being unemployed, or even entering early retirement, due to dt-TGCT. The demand for domestic help illustrates the impairment in activities of daily living.

While designed to show real-world information on dt-TGCT, TOPP study has the limitation that all participating institutions are among sarcoma referral centers. This might imply a selection bias as less severe cases will unlikely be referred to specialized centers. In addition, patients referred to such sarcoma centers are generally more impaired by dt-TGCT, and the lack of patients treated in non-specialized centers could give an overestimation of the disease burden and health care utilization. To avoid selection of patients and thus violation of the ‘real-life’ principle, no explicit non-eligibility criteria were defined. In addition, as data about medical history that were not considered essential or were difficult to remember were collected at baseline, an underreporting of data might occur.

In conclusion, the present study confirmed that dt-TGCT has its onset in a relatively young and working population. Diagnosis is often delayed, most likely due to disease unfamiliarity or misdiagnosis. In addition, both health economics and society are burdened by dt-TGCT. Finally, choice of treatment was mostly based on admission status, clinical experience, and PRO. Synovectomies are the mainstay of treatment, whereas TKIs are mostly restricted to severe and refractory cases, while a wait-and-see policy was applied for patients with less symptomatology. Developing multidisciplinary guidelines for the treatment of primary and refractory cases is therefore of the utmost importance.

**Declarations**

**Ethics approval and consent to participate**
| Country | City | Responsible Ethics Committee | Date of Submission | Date of EC approval |
|---------|------|------------------------------|--------------------|--------------------|
| Austria | Graz | Ethics committee of the Medical University of Graz Auenbruggerplatz 2 8036 Graz | 02-Feb-2017 | 24-Mar-2017 |
| France  | Nantes | CPP OUEST IV 53, Chaussée de la Madeleine 44000 Nantes | 27-Mar-2017 | 03-May-2017 |
| Germany | Essen | Ethikkommission der Medizinischen Fakultät der Universität Duisburg-Essen Robert-Koch-Str. 9-11 45147 Essen | 17-Feb-2017 | 24-Apr-2017 |
| Italy   | Bologna | Comitato Etico dell’Istituto Ortopedico Rizzoli via G.C. Pupilli, 1 40136 Bologna | 06-Oct-2016 | 14-Dec-2016 |
| Italy   | Milano | Comitato Etico della Fondazione IRCCS Istituto Nazionale dei Tumori Via Venezian 1 20133 Milano | 20-Oct-2016 | 23-Nov-2016 |
| Spain   | Barcelona | Comité Ético de Investigación Clínica Hospital de laSanta Creu i Sant Pau Sant Antoni Ma Claret, 167 08025 Barcelona | 02-Feb-2017 | 22-Mar-2017 |
| Country       | City          | Responsible Ethics Committee                                                                 | Date of Submission | Date of EC approval |
|--------------|--------------|-----------------------------------------------------------------------------------------------|--------------------|---------------------|
| Spain        | Sevilla      | Unidad de Gestión de Ensayos Clínicos, Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla Hospital Universitario Virgen Macarena Avda. Dr. Fedriani, 3 41071 Sevilla | 02-Feb-2017        | 20-Mar-2017         |
| The Netherlands | Nijmegen   | Concernstaf Kwaliteit en Veiligheid Commissie Mensgebonden Onderzoek Geert Grooteplein (route 629), Nijmegen | 24-Nov-2016        | 19-Dec-2016         |
| The Netherlands | Leiden      | Commissie Medische Ethiek LUMC Albinusdreef 2 2333 ZA Leiden                                                                                     | 06-Sep-2016        | 15-Nov-2016         |
| United Kingdom | London      | London - Hampstead Research Ethics Committee Barlow House 4 Minshull Street Manchester M1 3DZ | 30-Jan-2017        | 23-Mar-2017         |
| Country                  | City                  | Responsible Ethics Committee                                                                 | Date of Submission | Date of EC approval |
|-------------------------|-----------------------|---------------------------------------------------------------------------------------------|--------------------|---------------------|
| United Kingdom          | Oxford                | London - Hampstead Research Ethics Committee                                                | 30-Jan-2017        | 23-Mar-2017         |
|                         |                       | Barlow House                                                                                |                    |                     |
|                         |                       | 4 Minshull Street                                                                            |                    |                     |
|                         |                       | Manchester M1 3DZ                                                                            |                    |                     |
| United States of America| Los Angeles           | UCLA Institutional Review Board                                                               | 20-Dec-2017        | 30-May-2018         |
|                         |                       | University of California Los Angeles                                                           |                    |                     |
|                         |                       | 10889 Wilshire Blvd, Suite 830                                                                 |                    |                     |
|                         |                       | Los Angeles, CA 90095-1406                                                                    |                    |                     |
| United States of America| New York              | IRB Memorial Sloan-Kettering Cancer Center                                                    | 08-Jan-2018        | 23-Jan-2018         |
|                         |                       | 1275 York Avenue                                                                             |                    |                     |
|                         |                       | New York 10065                                                                               |                    |                     |

This non-interventional study was conducted according to the Declaration of Helsinki (October 2013) and Good Clinical Practice guidelines of the International Conference on Harmonisation. This study is registered with ClinicalTrials.gov (number NCT02948088), and the institutional review board at each participating center approved the study.

**Consent for publication**

All patients provided written consent.

**Availability of data and materials**
De-identified individual participant data (IPD) and applicable supporting clinical trial documents may be available upon request at https://vivli.org/ourmember/daiichi-sankyo/

**Competing interests**

NMB reports consulting fees from Daiichi Sankyo, Zimmer Biomet, and Onkos Surgical. GS reports research funding to his institution (LUMC) from Daiichi Sankyo. JHH reports consulting fees from Daiichi Sankyo. SS reports consulting fees from Bayer, Bavarian Nordic, Deciphera, Eli Lilly, Epizyme Inc, Daiichi Sankyo, Karyopharm, Immune Design, Intellisphere, Maxivax, PharmaMar, and Takeda; research funding to her institution from Amgen Dompé, Advenchen, Bayer, Bavarian Nordic, Blueprint, Deciphera, Eli Lilly, Epizyme Inc, Daiichi Sankyo, Karyopharm, Novartis, Pfizer, and PharmaMar; and travel coverage from PharmaMar. EP served on an advisory board for Amgen, Daiichi Sankyo, Lilly, Eusa Pharma, Deciphera; research funding from Bristol-Myers Squibb, Pfizer, PharmaMar, and travel support from Lilly, PharmaMar, and Takeda. SB reports advisory board fees for Deciphera, Blueprint Medicines, ADC Therapeutics, Nanobiotix, Bayer, Lilly, Novartis, Exelixis, Daiichi Sankyo, and Roche; CME honoraria from PharmaMar, Lilly, and Novartis; research funding from Incyte, Blueprint Medicines, and Novartis; and travel support from PharmaMar. HG reports research funding to his institution (LUMC) from Daiichi Sankyo. ELS has served on a steering committee for Daiichi Sankyo Europe GmbH and an advisory board for Daiichi Sankyo Inc. JLB declares no competing interests. EMF, PL, and XY are employees are Daiichi Sankyo. MAJvdS reports research funding from Daiichi Sankyo. The TOPP Study Group reports the following conflicts of interests: BS reports limited research administrative compensation from Daiichi Sankyo; AL reports institution education grants from Johnson and Johnson, Alphamed, and Globus; JMB reports research funding from Lilly, PharmaMar, Eisai, Novartis, GSK, LIXTE, Karyopharm, Celgene, Pfizer, BMS, Blueprint, Deciphera, Nektar, Forma, Amgen, and Daiichi Sankyo; FG reports consulting fees from Amgen, stock ownership in Atlanthera, and honoraria from Deciphera; ALP and TC declare no competing interests.

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**Authors’ contributions**

GS, NMB, JHH, PL, SS, EP, ELS and MAJvdS were responsible for the conception and design of the study. NMB, JHH, SS, EP, ELS, the TOPP Study Group, and MAJvdS collected the data. EMF assembled the data and performed the statistical analysis. GS, NMB, JHH, PL, EMF, SS, EP, ELS, and MAJvdS interpreted the
data. GS drafted the manuscript, after which NMB, JHH, SS, EP, SB, HG, ELS, JLB, and MAJvdS revised the manuscript with important intellectual content. GS, NMB, JHH, SS, EP, SB, HG, ELS, JLB, EMF, XY, PL, and MAJvdS all reviewed and approved the final version of the manuscript before submission.

The corresponding authors take responsibility for the integrity of work, from inception to published article. The TOPP Study Group consists of contributors taking part in the steering committee and/or responsible for patient inclusion and data collection. The TOPP Study Group members all have reviewed and approved the final version of the manuscript.

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Tables

Table 1. Demographic and clinical characteristics of patients included in the TOPP study at baseline.

| Features                                           | n = 166 (%) |
|----------------------------------------------------|-------------|
| Mean age [years] at diagnosis ± SD                 | 39.0 ± 14.42|
| Mean age [years] at baseline ± SD                  | 44.0 ± 14.12|
| Female, n (%)                                      | 102 (61.4)  |
| Level of education (n = 143)                       |             |
| University (bachelor or higher)                    | 63 (44.1)   |
| Time [months] since diagnosis, median (Q1, Q3)     | 29.7        |
|                                                     | (9.5-80.0)  |
| Localization, n (%)                                |             |
| Knee                                               | 112 (68.5)  |
| Ankle                                              | 19 (11.4)   |
| Hip                                                | 12 (7.2)    |
| Shoulder                                           | 8 (4.8)     |
| Foot                                               | 5 (3.0)     |
| Other                                              | 10 (6.0)    |
| Therapy prior to baseline, n (%)                   | 139 (83.7)  |
| Recurrent disease, n (%)                           |             |
| 1 recurrence                                       | 37 (52.9)   |
| 2 recurrence                                       | 15 (21.4)   |
| 3 recurrence                                       | 18 (25.7)   |

Q1, Q3 quarter 1, quarter 3; SD standard deviation; TOPPTGCT Observation Platform Project.
Table 2. Diagnostic pathway (%)

| Time [months] from onset symptoms until diagnosis, median (Q1, Q3) | 16.9 (4.0 – 44.0) |
|---|---|

Information on MRI

| Any closest* to BL MRI, n (%) | 157 (94.6) |
|---|---|

Indication of MRI closest to BL, n (%)

| Primary diagnosis | 36 (25.7) |
| Pre-surgery | 16 (11.4) |
| Regular postoperative follow-up | 56 (40.0) |
| Follow-up due to complaints | 32 (22.9) |
| Missing | 17 |

Characteristics of MRI, n (%)

| Both intra- and extra-articular (n = 147) | 90 (61.2) |
| Extra-articular tendon/muscle involvement (n = 141) | 99 (70.2) |
| Ligament involvement (n = 134) | 88 (65.7) |

TGCT severity, n (%)

| Moderate diffuse | 64 (38.6) |
| Severe diffuse | 83 (50.0) |
| Not assessable | 19 (11.4) |

Information on biopsy

| Any biopsy prior BL* (restricted to the 95 patients with primary diagnosis), n (%) | 86 (90.5) |
|---|---|
| Excisional biopsy | 32 (41.6) |
| Core needle biopsy | 14 (18.2) |
| Arthroscopic biopsy | 11 (14.3) |
| Surgery for suspected cancer diagnosis | 10 (13.0) |
| Fine needle aspiration biopsy | 6 (7.8) |
| Other | 9 (11.7) |
| Missing | 9 |

*Defined as MRI with nearest date to Baseline visit date, with the date of MRI either before or equal to the Baseline visit date or – if no treatment yet performed - at the latest 30 days after the Baseline visit date. *Percentage calculation can sum to > 100% because patients can fall in more than one category. BL baseline; MRI magnetic resonance imaging; Q1, Q3 quarter 1, quarter 3; SD standard deviation; TOPPTGCT Observation Platform Project.
Table 3. TGCT-related therapies prior to baseline, N (%)

| Tumor status | Primary diagnosis (n = 95) | Recurrent diseases (n = 71) | Total (n = 166) |
|--------------|---------------------------|-----------------------------|-----------------|
| Any surgery prior to baseline | 57 (60.0) | 71 (100) | 128 (77.1) |
| Type of surgery prior to BL (if any)\(^a\) | | | |
| Arthroscopic synovectomy | 30 (31.6) | 33 (46.5) | 63 (49.2) |
| One-stage synovectomy | 22 (23.2) | 42 (59.2) | 64 (50.0) |
| Two-stage synovectomy | 6 (6.3) | 7 (9.6) | 13 (10.2) |
| (Tumor) prosthesis | 1 (1.1) | 4 (5.6) | 5 (3.9) |
| Any systemic treatment prior BL | 24 (25.3) | 28 (39.4) | 52 (31.3) |
| Type of last systemic treatment prior BL (if any) | | | |
| Tyrosine kinase inhibitors | 22 (91.7) | 25 (89.3) | 47 (90.4) |
| Monoclonal antibodies | 1 (4.2) | 3 (10.7) | 4 (7.7) |
| Other | 1 (4.2) | - | 1 (1.9) |
| Duration [days] until BL, median (Q1, Q3) | 307.00 (120.00 – 421.00) | 186.00 (88.00 – 345.00) | 236.00 (118.00 – 366.00) |
| Ongoing | 11 (45.8) | 7 (25.0) | 18 (34.6) |
| Possible side effects | 11 (45.8) | 19 (67.8) | 30 (58.8) |
| Any radiation therapy | 5 (5.3) | 10 (14.1) | 15 (9.0) |
| Type of radiation therapy prior to BL (if any) | | | |
| Radiotherapy | 2 (40.0) | 4 (40.0) | 6 (40.0) |
| \(^{90}\)Yttrium | 3 (60.0) | 6 (60.0) | 9 (60.0) |
| No prior therapy | 27 (28.4) | - | 27 (16.3) |
| Prior & concomitant therapies for TGCT-related symptoms | 50 (52.6) | 38 (53.5) | 88 (53.0) |

\(^a\)Sum of all therapies can be more than total, because a patient could have received \(\geq\) 1 therapies. BL baseline; MRI magnetic resonance imaging; Q1, Q3 quarter 1, quarter 3; TGCT tenosynovial giant cell tumor.
Table 4. Patients’ presentation and reported outcomes at baseline by treatment strategy, N (%)

|                                      | Wait & See (n = 81) | Surgery only (n = 41) | Systemic only (n = 37) |
|--------------------------------------|---------------------|-----------------------|------------------------|
| **Mean age [years] ± SD**             | 44.3 ± 15.17        | 41.8 ± 14.94          | 47.7 ± 10.44           |
| **Time since diagnosis primary tumor [months] median (Q1, Q3)** | 34.3 (13.8 – 77.9) | 6.7 (1.2 – 59.8)      | 32.1 (18.2 – 89.6)     |
| **Treatment before baseline**        |                     |                       |                         |
| Therapy naïve                        | 11 (13.6)           | 16 (39.0)             | -                      |
| Surgery only                         | 47 (58.0)           | 20 (48.8)             | 7 (18.9)               |
| Systemic only                        | 2 (2.5)             | -                     | 9 (24.3)               |
| Multimodal treatment                 | 21 (25.9)           | 5 (12.2)              | 21 (56.8)              |
| **Admission status**                 |                     |                       |                         |
| Primary diagnosis                    | 47 (58.0)           | 27 (65.9)             | 19 (51.4)              |
| Recurrent diseases                   | 34 (42.0)           | 14 (34.1)             | 18 (48.6)              |
| **Indication MRI closest to baseline**|                     |                       |                         |
| Primary diagnosis                    | 7 (9.3)             | 23 (57.5)             | 4 (11.4)               |
| Pre-surgery                          | 5 (6.7)             | 8 (20.0)              | 2 (5.7)                |
| Regular postoperative follow-up      | 43 (57.3)           | 6 (15.0)              | 7 (20.0)               |
| Follow-up due to complaints          | 15 (20.0)           | 2 (5.0)               | 13 (37.1)              |
| **Severity**                         |                     |                       |                         |
| Moderate                             | 34 (42.0)           | 15 (36.6)             | 12 (32.4)              |
| Severe                               | 38 (46.9)           | 20 (48.8)             | 21 (56.8)              |
| Not assessable                       | 9 (11.1)            | 6 (14.6)              | 4 (10.8)               |
| **In last 24 months prior to baseline**|                     |                       |                         |
| Any rehabilitation                   | 17 (26.2)           | 5 (13.2)              | 4 (12.5)               |
| Specialist visits*, median (range)   | 5.0 (1.0 – 70.0)    | 3.0 (10 – 27.0)       | 12 (2.0 – 65.0)        |
| Physical therapy sessions*, median (range) | 18.0 (4.0 – 200.0) | 11.0 (1.0 – 100.0)    | 11.5 (3.0 – 90.0)      |
| **Symptoms**                         |                     |                       |                         |
| Pain                                 | 56 (69.1)           | 37 (90.2)             | 32 (86.5)              |
| Stiffness                            | 36 (44.4)           | 27 (65.9)             | 23 (62.2)              |
| Swelling                             | 44 (54.3)           | 34 (82.9)             | 19 (51.4)              |
| Variable                        | BL 1 | BL 2 |
|--------------------------------|------|------|
| Limited range of motion        | 39 (48.1) | 31 (75.6) | 30 (81.1) |
| ≥ 3 symptoms                   | 31 (38.3) | 28 (68.3) | 22 (59.5) |
| **Analgesics use**             | 8 (9.9) | 5 (12.2) | 9 (24.3) |
| **Worst stiffness NRS**<sup>a</sup> | 3.4 ± 2.57 | 5.2 ± 3.14 | 5.3 ± 2.55 |
| **Worst pain NRS**             | 5.0 ± 2.41 | 6.5 ± 2.27 | 5.8 ± 1.97 |
| **Pain severity score**        | 2.25 | 4.25 | 4.25 |
| median (Q1, Q3) (n = 147)      | (0.75 – 4.00) | (1.50 – 6.25) | (1.50 – 5.50) |
| **Pain interference score**    | 1.57 | 3.00 | 3.00 |
| median (Q1, Q3) (n = 146)      | (0.14 – 4.00) | (1.14 – 5.57) | (0.57 – 5.57) |
| **PROMIS-PF**<sup>b</sup>      | 44.43 | 39.54 | 39.98 |
| median (Q1, Q3) (n = 142)      | (37.30 – 49.29) | (34.95 – 44.42) | (34.79 – 43.69) |
| **EQ-5D Index score**          | 0.84 | 0.80 | 0.74 |
| median (Q1, Q3) (n = 153)      | (0.67 – 0.89) | (0.53 – 0.84) | (0.48 – 0.84) |
| **EQ-5D VAS**                  | 79.0 | 69.0 | 70.0 |
| median (Q1, Q3) (n = 154)      | (60.0 – 85.0) | (60.0 – 80.0) | (50.0 – 75.0) |

*Based on patients that had any. <sup>a</sup>Numeric rating scale. <sup>b</sup>Physical functioning. BL baseline; EQ-5D EuroQol 5D; MRI magnetic resonance imaging; PROMIS Patient-Reported Outcomes Measurement Information System; Q1, Q3 quarter 1, quarter 3; SD standard deviation; SD standard deviation; TGCT, tenosynovial giant cell tumor; VAS visual analog scale.
Table 5. Health economics prior to baseline, N (%)  

| Health Economics | Value |
|------------------|-------|
| **Any referral / specialists visits prior to diagnosis (n = 138)** | 135 (97.8) |
| ≥ 5 | 33 (23.9) |
| **24 months prior to baseline** | |
| ≥ 5 GP\(^a\) visits  
(n = 132) | 21 (15.9) |
| ≥ 5 specialists visits  
(n = 136) | 76 (55.9) |
| ≥ 10 PT\(^b\) sessions  
(n = 141) | 36 (25.5) |
| Rehabilitation  
(n = 140) | 26 (18.6) |
| Duration [days], median (range) | 15.0 (1.0 – 120.0) |
| **Hospitalization related to TGCT** | 151 (91.0) |
| ≥ 5 hospitalizations | 15 (9.9) |
| Duration [days], median (range) | 3.0 (1.0 – 184.0) |
| **Changed employment status from full-employment due to TGCT (n = 146)** | 17 (11.6) |
| Part-time employed | 5 (3.4) |
| Unemployed | 9 (6.2) |
| Retired | 3 (2.1) |
| **Work missed in 24 months prior to baseline (n = 116)** | 66 (56.9) |
| If work missed, number of [days], median (range) | 25.0 (1.0 – 75.0) |
| **Domestic help required at baseline (n = 162)** | 26 (16.0) |

\(^a\)General practitioner. \(^b\)Physical therapy. TGCT, tenosynovial giant cell tumor.

Figures
Figure 1

A typical timeline of dt-TGCT in a single TOPP patient. The disease had its onset in an 18-year-old patient who was forced to stop exercising and in need of physical therapy due to dt-TGCT-related complaints. Several recurrences occurred despite multimodality treatment, leading to secondary gonarthrosis at the age of 25.
Figure 2

This figure represents the general patient journey of patients with dt-TGCT. Non-specific symptoms and disease unawareness results in several visits to different health care practitioners and unnecessary or excessive treatment in first and second line before referral to an orthopedic or sarcoma oncologist.
PROMS Patient-reported outcome measurements; NRS Numeric rating scale; BPI Brief pain inventory; PROMIS-PF Patient-reported outcomes measurement information system physical functioning; EQ-5D EuroQol 5D; VAS visual analog scale.
Figure 3

This flowchart gives a schematic overview of the treatment types patients received prior to TOPP, according to tumor status: primary diagnosis or recurrent disease. In addition, the cohort is stratified into 2 patient groups according to treatment plan at baseline: watchful waiting and indicated treatment at baseline. Possibly important factors in treatment decision making are shown per subgroup.

Supplementary Files

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