April 26, 2021

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Title:

Improving Resources and Support for Patients with Tenosynovial Giant Cell Tumor

Document Type:

White Paper

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Cancer*Care* researched and developed this manuscript with the support of a grant from Daiichi Sankyo.

IMPROVING RESOURCES AND SUPPORT FOR PATIENTS WITH TENOSYNOVIAL GIANT CELL TUMOR

ABSTRACT

Tenosynovial giant cell tumor (TGCT) is a rare, typically benign tumor that develops in the synovial lining of joints and tendon sheaths. There are two recognized subtypes of TGCT; a localized type and a diffuse type. Localized TGCT typically presents as a single, well-demarcated tumor affecting smaller joints, such as those of the hand, while diffuse TGCT presents as multiple nodules with unclear borders more commonly affecting larger joints, such as the knee, hip, shoulder, and ankle. Since the 2013 World Health Organization reclassification, the term localized TGCT encompasses giant cell tumor of the tendon sheath (GCT-TS) and nodular synovitis, while the term diffuse TGCT includes diffuse-type GCT-TS and pigmented villonodular synovitis. Diffuse TGCT is more likely to recur, and, though extremely rare, can become malignant. Traditionally, surgery has been the standard of care for TGCT management, although the development of new systemic therapies is shifting the treatment paradigm, particularly for diffuse TGCT. The symptoms of the disease and complications of repeated surgical interventions can negatively affect quality of life for patients. To better understand the patient journey with TGCT and the needs of patients, Cancer*Care* convened an advisory board of 2 clinical experts and 6 representatives from patient advocacy groups with an interest in TGCT, one of whom was a patient diagnosed with TGCT. With the aim to improve support for patients with TGCT, participants developed targeted recommendations to address delayed diagnosis and misdiagnosis of TGCT; promote individualized, patient-centered treatment planning; educate health care providers about TGCT; and create resources for patient education and awareness.

INTRODUCTION

On January 12, 2021, Cancer*Care* convened an advisory board that included 2 experts in tenosynovial giant cell tumor (TGCT), a medical oncologist and an orthopaedic oncologist, and 6 representatives from 4 patient advocacy groups with an interest in TGCT: Sarcoma Foundation of America, Sarcoma Alliance, TargetCancer Foundation, and The Life Raft Group. The objectives of this advisory board were to characterize the patient journey encompassing symptom onset, diagnosis, and treatment of TGCT; to identify gaps and opportunities for educating patients and health care providers (HCPs) about TGCT; and to discuss mechanisms to strengthen clinical and community support for patients with TGCT. Discussions during the advisory board served as a basis for this white paper focused on addressing the challenges faced by patients with TGCT as they navigate diagnosis and treatment of their disease. Herein, we identify opportunities for improving support for patients with TGCT and provide recommendations for development of resources to promote patient-centered treatment planning and improve education and awareness around this disease.

TGCT Is a Rare Tumor That Develops in the Tissues Surrounding Joints

TGCT is a tumor, typically benign, that develops in the soft tissues in or around joints, including the synovium, bursae, and tendon sheath.[1] It is a rare disease with an estimated prevalence of 11–50 people per million.[2-4] Although patients may present with TGCT at any age, a registry-based study found that most patients are <60 years of age at diagnosis (**Figure 1**).[3] The median age of disease onset is 47, and TGCT may be slightly more common in women than in men.[3-5]

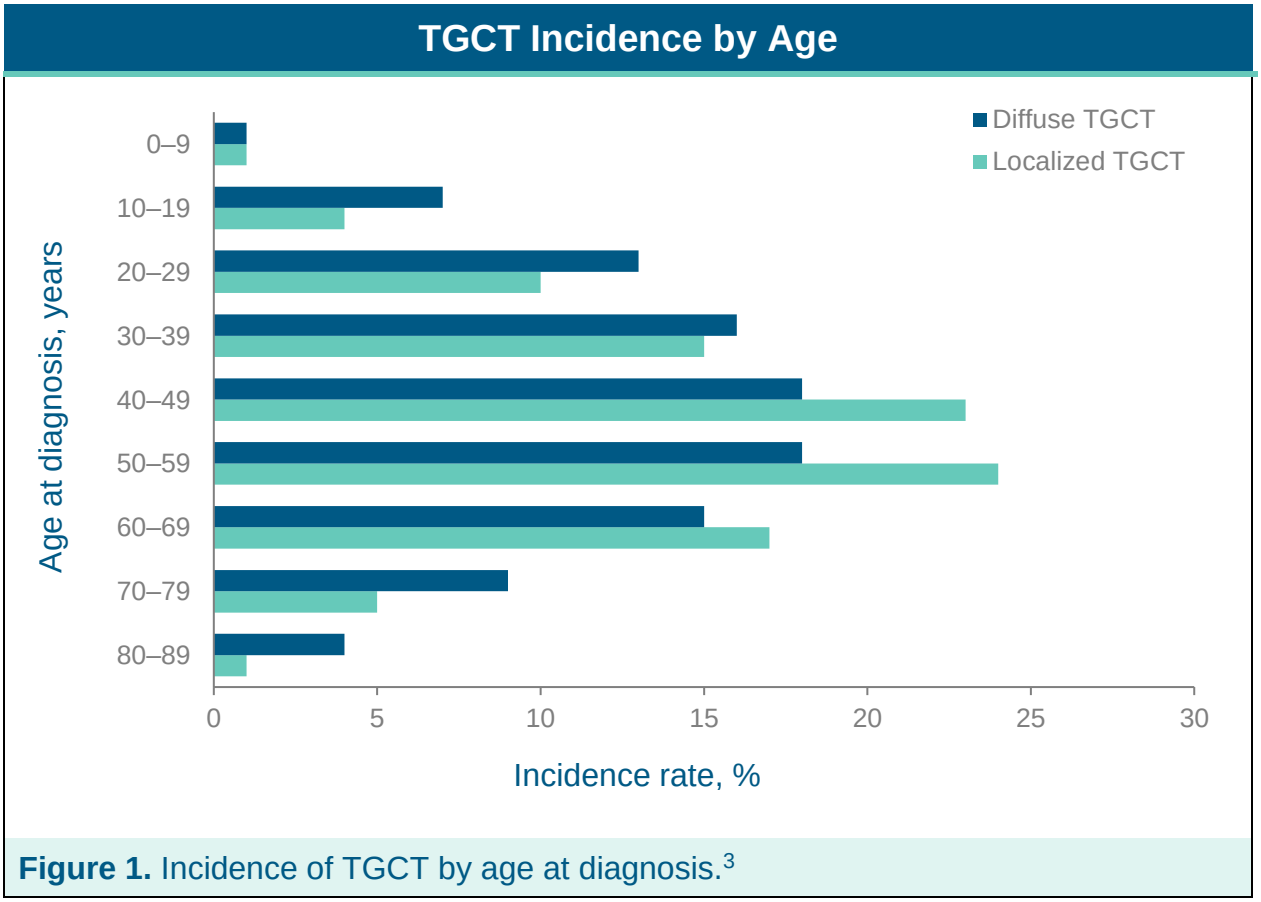

Figure 1. Incidence of TGCT by age at diagnosis.[3]

Historically, TGCT has been referred to as pigmented villonodular synovitis (PVNS) and giant cell tumor of the tendon sheath (GCT-TS); however, TGCT is now the preferred standardized term that encompasses both types of tumors.[6] The disease can be divided into two subtypes that differ in both frequency and presentation: localized and diffuse TGCT. Localized TGCT is the most prevalent subtype and accounts for 80%–90% of TGCT cases, with diffuse TGCT making up the remainder.[1,3,4] Smaller (<5 cm), rounded, single tumors are typical of localized disease, while patients with diffuse disease may have multiple, large (>5 cm) nodules with boundaries that are not well demarcated. Localized TGCT more frequently affects smaller joints, such as those of the hand. Patients generally present with painless swelling, though pain may develop later, and joint function may be affected. In contrast, diffuse TGCT is more likely to affect larger joints, such as the knee, hip, shoulder, and ankle. Presentation often

includes joint pain, swelling, and tenderness, as well as joint stiffness, instability, or limited motion. While the lifetime risk of recurrence is only 15% for localized TGCT, recurrence occurs in up to 55% of diffuse TGCT cases.[1,3,4,7,8] In rare instances, diffuse TGCT can become malignant, metastasizing to regional lymph nodes and the lungs.[1,9] Even with aggressive management comprising surgery, chemotherapy, and radiation, prognosis of malignant TGCT is poor with a median survival of 22.5 months after diagnosis.[9]

Elucidating the underlying biology of TGCT has greatly improved our understanding of the disease behavior. A translocation involving the colony stimulating factor 1 (*CSF1*) gene has been identified as a causative event in TGCT that results in overexpression of the CSF-1 protein.[10,11] CSF-1 regulates the proliferation and function of inflammatory cells through activation of its receptor (CSF1R). In TGCT, overexpression of CSF-1 by neoplastic cells harboring the *CSF1* translocation recruits inflammatory cells expressing CSF1R to form the tumor (**Figure 2**).[10-12]

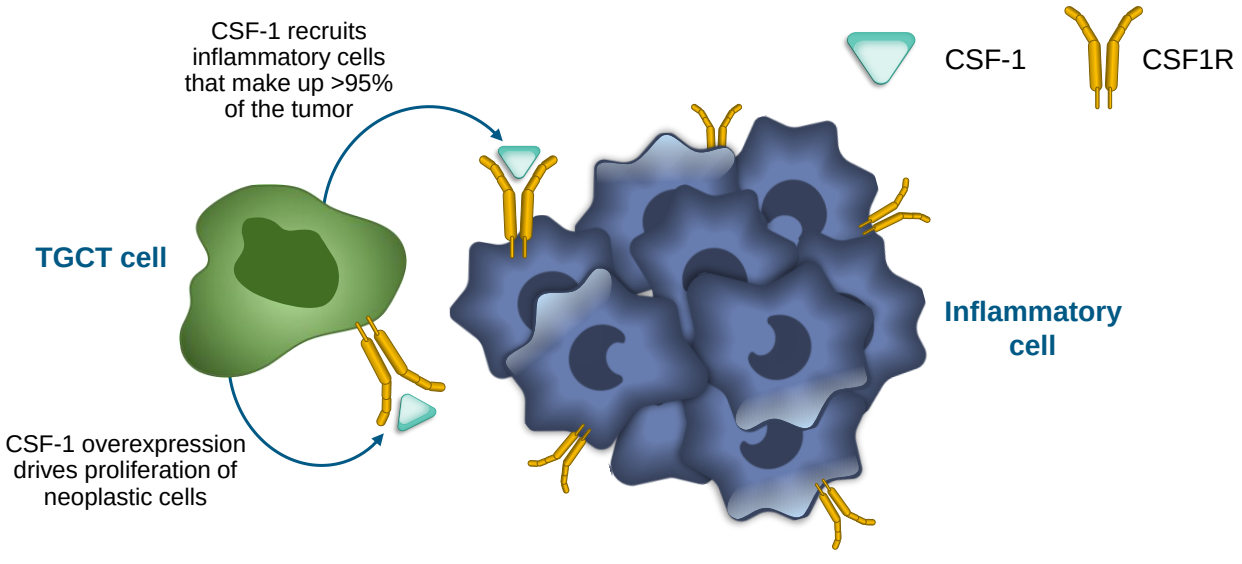

Figure 2. CSF-1 drives proliferation of neoplastic cells and recruits inflammatory cells to form tumors in TGCT.[10-12]

Diagnosis and Local Management of TGCT

Tumors involving the synovial joints often present with non-specific symptoms, such as pain, joint effusion, stiffness, and limited motion,[13,14] making diagnosis challenging.[15,16] Joint enlargement and accumulation of fluid caused by TGCT can resemble the symptoms of more common pathologies, such as arthritis.[16] As a result, diagnosis of TGCT is frequently delayed, with a mean delay of 2.9 ± 3.7 years, which can be associated with joint degeneration and erosion of bone or cartilage.[7,14,15,17]

Magnetic resonance imaging (MRI) is the most common modality that leads to a suspected TGCT diagnosis. Localized TGCT often presents as a nodular mass with well-demarcated borders, while diffuse TGCT usually has extensive joint involvement without clear borders. Additionally, both forms often exhibit hemosiderin deposits upon pathologic examination.[15] The differential diagnosis for TGCT includes synovial chondromatosis, synovial hemangioma, tuberculous arthritis, amyloidosis, and hemophilic arthropathy,[13] but for most patients with an intra-articular tumor, the diagnosis is either TGCT or synovial chondromatosis.[18]

Traditionally, surgery has been the standard of care for TGCT management, although the type of surgery may vary based on the location and extent of disease.[6,19,20] For patients with localized disease, surgery is often curative.[6] Arthroscopic (keyhole) synovectomy is a minimally invasive procedure using small incisions and an arthroscope; a benefit of using this surgical technique is minimized trauma to healthy tissue, potentially resulting in less pain and faster recovery.[6,19,20] However, in cases involving areas not easily accessible by arthroscopy, open synovectomy may be required. Open synovectomy can also be of use in cases with extra-articular extension of disease.[6,19,21] Less commonly, joint replacement may be required due to extensive joint destruction or development of secondary arthritis.[6] Severe, recurrent diffuse TGCT may require joint fusion, or in rare cases amputation, after failure of all treatments or severe complications.[6,22]

Radiation therapy is sometimes used in the management of TGCT but is not considered standard treatment. It is mainly used for inoperable disease, persistent recurrences, or as an adjuvant treatment to surgery.[6,23] Pre-operative radiotherapy may be considered to achieve local control of diffuse TGCT; however, based on the low risk of local recurrence, localized TGCT generally does not require adjuvant treatment.[6] Both external beam radiation and radiosynovectomy have been used for management of TGCT. For patients receiving external beam radiation, the preferred use is for potential improvement of local control and delayed recurrence after primary surgery in the early stages of treatment before irreversible joint damage has occurred.[24,25] Radiosynovectomy involves injection of radioisotopes directly into the joint, which can result in cell death in the joint.[6,24]

Both the treatment of TGCT and the symptoms of the disease can negatively affect quality of life for patients. Because of the chronic nature of the disease, clinical symptoms may span months to years, which can also negatively affect quality of life due to pain, swelling, joint stiffness, and restricted joint movement.[24,26] In severe cases, advanced disease can lead to joint destruction and severe functional impairment.[24] Given that diffuse TGCT has been reported to recur in 14% of patients after open synovectomy and 40% of patients after arthroscopic synovectomy, repetitive surgical interventions may be needed, with each surgery carrying the risk of complications and post-operative infections, delayed wound healing, joint stiffness, and loss of function.[6,21,23,27] Similarly, radiotherapy can cause skin reactions, impaired wound healing, decreased joint mobility, osteonecrosis, and a risk of radiation-induced malignancy.[6,28,29]

Patient survey results confirm that both localized and diffuse disease are associated with significant detriments to daily living and quality of life. In a survey of 337 respondents, 13% of patients with localized disease and 11% of patients with diffuse disease reported that they were unable to fully perform their jobs. Similarly, 58% percent of respondents with localized TGCT reported that they are limited in sports-

related activities, compared to 64% of patients with diffuse TGCT. While treatment was associated with decreased pain and swelling, patients reported that stiffness and range of motion worsened. Diffuse-type TGCT, recurrent disease, and ≥2 surgeries were associated with greater detriments to quality of life.[30]

The continuum of patient experiences with TGCT ranges from complete surgical resection of a single, local tumor with no recurrence and minimal detriment to quality of life, to long-term management of diffuse, recurrent disease requiring repeated surgical interventions, joint replacement, joint fusion, or amputation that can severely affect quality of life.[3,4,6,20,28] As a result, patients with TGCT may require support from a multidisciplinary team involving a variety of specialties and expertise in treating TGCT, including orthopaedic surgery, medical oncology, radiation oncology, radiology, pathology, advanced practice providers, and physical therapy.[14,19,20,28] Effective management of TGCT requires balancing the potential benefits and harms of surgery or treatments with the risk of recurrence or disease progression. Shared decision-making ensures that the care team works together with the patient to make decisions that are best for the patient.[19,28,31,32]

Advances in TGCT Treatment: Systemic Therapies

As our understanding of TGCT biology has improved, systemic therapies have emerged as a means to manage TGCT, particularly in patients with diffuse and/or recurrent disease. Small molecule tyrosine kinase inhibitors (TKIs) and monoclonal antibodies (mAbs) targeting the CSF1/CSF1R axis and anti–tumor necrosis factor-alpha (TNF-α) therapies have been explored for treatment of locally advanced or relapsed diffuse TGCT as a means to block the pro-inflammatory pathways that drive the disease (**Table 1**).[6,14,33-35]

Table 1. Systemic therapies evaluated for treatment of locally advanced or relapsed TGCT. [6,14,33-35]

Anti-CSF1R TKIs	Anti–CSF-1/CSF1R mAbs	Anti–TNF-α agents
• Imatinib mesylate • Nilotinib • Pexidartinib*	• Emactuzumab (receptor) • Cabiralizumab (receptor) • Lacnotuzumab (ligand)	• Infliximab (mAb) • Adalimumab (mAb) • Etanercept (fusion protein inhibitor

*Pexidartinib is the only systemic therapy currently approved for treatment of TGCT.

Experience with TNF-α–targeted therapies has been limited to a few promising case reports, but agents targeting the CSF1/CSF1R axis have shown promising activity in several clinical studies.[36,37] Phase 1 studies of the anti-CSF1R antibodies emactuzumab and cabiralizumab have shown encouraging clinical activity and no dose-limiting toxicities.[38,39] With respect to CSF1R-targeted TKIs, long-term follow-up of a retrospective, multi-institutional study of imatinib mesylate in patients with locally advanced, metastatic, or recurrent TGCT resulted in an overall response rate (ORR) of 31% (17/55), with 78% of patients (40/51) reporting an improvement in symptoms. Adverse events were reported in 78% of patients (45/58), with 5 patients experiencing grade 3–4 toxicities, including neutropenia, acute hepatitis, facial edema, skin toxicity, and fatigue.[33,40] A phase 2 study evaluating the TKI nilotinib in patients with progressive or relapsing TGCT, or with disease not resectable by conservative surgical treatment, demonstrated a 96% (49/51) disease control rate at week 12 and an ORR of 6% (3/51) at 1 year. Forty-one percent (23/56) of patients experienced adverse events leading to treatment modification, including 6 patients with at least 1 grade 3 event (headache, dizziness, hepatic disorders).[41]

In 2019, pexidartinib, a TKI targeting CSF1R, became the first systemic therapy approved for treatment of TGCT based on demonstration of a robust tumor response and improved patient symptoms and functional outcomes.[34,42] Pexidartinib is indicated for treatment of adult patients with symptomatic TGCT associated with severe morbidity

or functional limitations and not amenable to improvement with surgery[43], and is recommended for treatment of indicated patients in clinical practice guidelines.[44]

Pexidartinib was evaluated in the phase 3 ENLIVEN study in patients with histologically confirmed, advanced, symptomatic TGCT.[34] The 2-part study included a 24-week placebo-controlled, blinded phase, followed by an open-label extension phase in which patients (n=120) could continue on pexidartinib 400 mg bid until progression or discontinuation. At week 25, ORR was 39% by Response Evaluation Criteria in Solid Tumors (RECIST) evaluation and 56% by tumor volume score (TVS) evaluation in patients taking pexidartinib, compared with 0% in the placebo group for both assessments.[34] Common adverse events with pexidartinib include: increased lactate dehydrogenase (92%), increased aspartate transaminase (88%), hair color changes (67%), fatigue (64%), increased alanine transaminase (64%), decreased neutrophils (44%), increased cholesterol (44%), increased alkaline phosphatase (39%), decreased lymphocytes (38%), eye edema (30%), decreased hemoglobin (30%), rash (28%), dysgeusia (26%), and decreased phosphate (25%). Hepatic toxicity was identified as a rare, but potentially serious, complication that requires monitoring.[43] Long-term follow-up (median, 39 months) in a pooled analysis of the ENLIVEN study and the TGCT cohort of the PLX108-01 study identified no new safety concerns with pexidartinib and confirmed initial efficacy results, with an ORR of 60% by RECIST and 65% by TVS in patients with TGCT.[45]

The landscape of TGCT management is changing with the advent of systemic treatment options, but questions remain regarding how these agents should be incorporated into the treatment arsenal. Other agents targeting the CSF-1/CSF1R axis are under active investigation, and additional data are needed to determine the effects of long-term treatment and treatment interruption, clarify the role of systemic therapy for patients with earlier stages of the disease, and optimize the management of adverse events and the timing of surgery.[14] The approval of a systemic therapy for TGCT[43] has further underscored the need for patient-centered, multidisciplinary care that balances the

benefits and harms of available interventions with the risk of recurrence or disease progression.[19,28,31] Clinical and community support is needed to ensure that patients and providers are educated about new treatment options and to shift the paradigm toward patient-centered treatment planning approaches. The section below summarizes the findings from the TGCT advisory board regarding key gaps and opportunities to improve support for patients with TGCT.

FINDINGS FROM THE TGCT ADVISORY BOARD

Participants

The advisory board included 2 experts in TGCT, a medical oncologist and an orthopaedic oncologist, and 6 representatives from 4 patient advocacy groups with an interest in TGCT: Sarcoma Foundation of America, Sarcoma Alliance, TargetCancer Foundation, and The Life Raft Group.

Understanding the Patient Journey

Discussion about patient experiences revealed that TGCT is often a “lonely diagnosis.” In detailing the journeys of specific patients, advisors stressed that patients may be diagnosed as early as their childhood or teenage years, leading to a lifetime of effects on quality of life, particularly in those with recurrent disease.[3,6,21,26] Although patients may initially be told that the tumor is an isolated occurrence that can easily be addressed by surgery, patients with diffuse TGCT often undergo repeated surgeries due to recurrence. Few resources are available to help these patients find information about their disease, compounding the difficulty of navigating the health care system to find the care they need. Referral to a specialty center may not occur until long after initial treatment. Advisors noted that the pain associated with the disease and its treatment can affect everyday activities, such as sitting, driving, or cooking, as well as interfering with athletic pursuits. In addition to these personal challenges, an overarching challenge

in the patient community is that despite the profound effects of TGCT on quality of life,[30] severity of the disease is frequently underestimated because the tumor is only rarely malignant.[1] One participant noted that patients may feel that "no one cares because it's not cancer."

Advisors identified 4 key gaps that negatively affect the care of patients with TGCT: (1) delayed diagnosis and misdiagnosis of TGCT; (2) limited implementation of individualized, patient-centered treatment planning for TGCT; (3) lack of mechanisms to reach HCPs for education around TGCT; and (4) few resources for patient education and awareness. Based on their discussion, the advisory board developed recommendations to address these gaps and improve support for patients with TGCT. These recommendations are described in detail below. Participants noted that patient advocacy groups are well-positioned to support implementation of many of these recommendations, as they are experienced with educational campaigns and patient support, and in some cases, already have TGCT-related projects underway. Due to the inconsistent history of TGCT terminology and classification,[6] cross-organizational collaboration was noted as an important requirement to promote consistent messaging and avoid duplication of effort. In addition to patient advocacy groups, patients with TGCT have formed an active and engaged community to share insights, experiences, and educational resources, providing a strong foundation to ensure the success of new initiatives through targeted channels of distribution and feedback.

Gap 1: Delayed Diagnosis and Misdiagnosis of TGCT

Advisory board participants concurred with findings from the literature stating that delayed diagnosis and misdiagnosis of TGCT are common.[14,17] According to expert advisors, outside of specialty centers, most clinicians have limited experience with TGCT. Because the tumor is rarely malignant, inexperienced clinicians may underestimate the problematic nature of the disease. The broad age spectrum and nonspecific symptoms associated with TGCT[3,14,17] also contribute to delayed diagnosis.

Community-based providers may not consider TGCT as part of the differential diagnosis, especially for patients with common symptoms, such as knee pain in older patients or shoulder pain in younger athletes. TGCT can easily be mistaken for more common ailments, like arthritis or impingement syndrome,[16] and younger patients may not even seek medical care. Diagnosis may not occur until pathologic examination after exploratory surgery or debridement. Often patients are not referred to specialty centers until post-surgical recurrence, although approval of pexidartinib is leading to shifts in referral patterns. Because TGCT has historically been primarily managed surgically by community-based surgeons, participants recommended **driving educational initiatives targeting community-based surgeons to promote awareness of the disease among frontline providers**.

Despite the frequent causes of delay described above, a combination of multimodal approaches can inform a swift and accurate diagnosis. Pathologists with expertise in soft tissue and bone tumors may recognize characteristic white blood cells and hemosiderin deposits associated with TGCT,[15] although these features may also be observed with some other conditions, such as hemophilic arthropathy.[46] Hemosiderin deposits may also be observed on MRI by experienced HCPs, and location of the tumor inside a joint can lead to suspicion of either TGCT or synovial chondromatosis.[15,18] History, such as absence of trauma, can rule out some other conditions. Although none of these features individually are diagnostic for the disease, they may serve as a "flag" to refer patients to a multidisciplinary team with expertise in TGCT. Consequently, advisors recommended **reframing early management of TGCT through consensus guidelines emphasizing the importance of multimodal approaches and referral to specialty centers for diagnosis and treatment**.

In addition to a lack of understanding of the potential severity of the disease, other factors can also decrease the likelihood of referring patients with TGCT to expert centers. Advisors noted that patients with rare diseases may hesitate to seek a referral due to the cost of a second opinion or due to concerns related to seeking care in a

different state. To address these concerns, advisors recommended **developing geographic-specific lists of "Centers of Excellence" and specialists to share with patients and advocacy groups**. Given the active and engaged patient community, social media platforms may be a useful avenue to crowdsource information and distribute resources. In addition, although TGCT is not a sarcoma, there is likely some overlap with existing lists of sarcoma specialists from advocacy groups. Potential criteria for creating a robust list of centers/specialists could consider TGCT-related publications, roles in TGCT clinical trials, and clinical practices at National Comprehensive Cancer Network® (NCCN®)–designated institutions.

Gap 2: Limited Implementation of Individualized, Patient-Centered Treatment Planning

Although surgery has traditionally been recommended as the primary treatment for TGCT,[6,19,20] the development of new systemic therapies is causing experts to rethink that paradigm, particularly for patients with diffuse TGCT. Surgery can result in fibrosis and can have lasting effects on joint function,[6,23] and outcomes may vary based on the skill of the surgeon and use of adjuvant treatment. Expert advisors noted that we do not currently have clear data about the optimal type of surgery for TGCT. Although quicker recovery is a benefit of arthroscopic surgery,[6,19,20] recovery time may be less of a factor in younger patients who generally heal more quickly. Open surgery may be a better option for more thorough removal of diffuse disease, but recovery is typically longer.[6,19-21] In addition, one expert noted that because the joint is filled with fluid during arthroscopic surgery, tumor cells may be forced outside of the joint in patients with diffuse disease. Although extensive, much of the data regarding open vs minimally invasive surgery for TGCT are conflicting and vary by anatomic location, illustrating the need for individualized treatment planning. With respect to radiation therapy, many providers are moving away from its use, as side effects are similar to those of surgery, and radiation exposure can lead to secondary cancers.[6,28,29,47]

According to advisors, approval of pexidartinib may be shifting the treatment paradigm away from repeated surgical intervention. As familiarity with diffuse disease and use of pexidartinib grow, referrals to medical oncologists are likely to increase. Advisors noted that the efficacy data for pexidartinib were impressive, particularly since RECIST, a set of criteria not tailored for assessment of benign neoplasms,[48] was used as a measure of efficacy.[34] In addition, patients reported significant improvements in physical function, pain, and range of motion,[34] which may be more important from the patient perspective. Advisors agreed that hepatic toxicity related to pexidartinib requires close monitoring, but also noted that if it occurs, it is typically early, within the first few months of therapy.[34] Based on these ongoing changes, advisors recommended **educating around systemic therapies for TGCT to continue to shift the paradigm away from repeated surgeries towards referral to experts in TGCT**. In addition to traditional referrals to local specialty centers, advisors suggested that **conducting virtual tumor boards could expand access to experts for treatment planning**.

Because of the wide spectrum of disease, advisors stressed that individualized treatment planning is important for patients with TGCT. Surgery may affect joint function, but systemic therapies may not be right for every patient and may be used too early in some patients who would benefit from surgery. Shared decision-making should be used to weigh the benefits and risks of therapy. According to advisors, treatment decisions should be as individualized as they are for patients with malignant conditions and should consider comorbidities, patient-specific needs/lifestyle (fitness, desire for surgery), specific disease characteristics (location, intraarticular vs extraarticular, diffuse vs localized), and patient concerns related to quality of life. When approaching discussions about TGCT, patients should be made aware of the potential severity of the disease, which is sometimes described as a “locally aggressive” tumor. Currently, few patients are warned that the disease can progress to the point of requiring joint replacement, joint fusion, or amputation. To better guide these patient-provider discussions, advisors recommended **developing HCP-patient dialogue tools to frame**

discussions about surgical and nonsurgical treatment options at diagnosis and **empowering patients with Q&A resources to help guide shared decision-making**.

Gap 3: Lack of Mechanisms to Reach HCPs for Education About TGCT

Although changing the decision point from "straight-to-surgery" to referral to expert centers is key to improving care of patients with TGCT, identifying optimal outlets for HCP education about the topic is a challenge given the different types of providers who may encounter patients with TGCT. Large meetings, like the American Society of Clinical Oncology Annual Meeting, are a common venue for disease-specific education; however, these meetings are likely too large to target most community oncologists. Therefore, advisors recommended **partnering with field-based medical science liaisons (MSLs) to share educational materials with community-based practitioners**.

Advisors also recommended specialty meetings as a venue for educating medical oncologists and orthopaedic surgeons. To inform medical oncologists in academic centers about the latest developments in caring for patients with TGCT, the Connective Tissue Oncology Society may be a useful resource. Educating orthopaedic surgeons was viewed as particularly important. Because TGCT is often grouped with sarcomas and only discussed in orthopaedic oncology specialty meetings, orthopaedic surgeons with limited exposure to TGCT may be more likely to operate themselves, rather than referring patients to a specialty center. Musculoskeletal meetings and the American Academy of Orthopaedic Surgeons may represent avenues for educating orthopaedic surgeons, and advisors suggested that **incorporating TGCT into the general orthopaedic curriculum could help change the initial decision point from arthroscopic surgery to referral to a specialty center**.

In addition to community-based and specialty-specific venues for HCP education, advisors also suggested **holding a TGCT summit for HCPs and patients**. A short

disease-focused conference would allow clinicians to learn about the latest developments in TGCT, while also providing an avenue for patients to connect with one another and with experts in the field.

Gap 4: Limited Resources for Patient Education and Awareness

According to advisors, feedback from patients has revealed a lack of educational resources around TGCT, particularly resources for diffuse disease. Patients are often confused when their presentation differs from what is most commonly described in the literature (such as tumors in the smaller joints of the hands), and inconsistent terminology related to TGCT makes it difficult for patients to educate themselves about their disease. Variable categorization of the disease (eg, benign tumor, rare disease, sarcoma, rare malignancy) makes finding information difficult, and current internet search results are limited to research articles and treatment-related sites. To help patients develop a clear understanding of their disease, advisors recommended **creating a uniform lexicon around TGCT that could be shared across organizations**.

Representatives from advocacy groups reported that patients are seeking guidance about what they should ask their doctors. They would like more information about different types of surgeries and treatments, and many recently diagnosed patients are unaware that sarcoma specialists can treat TGCT. Patients have many questions about systemic therapies, and conversations from discussion groups suggest that concerns vary by age and disease state. Older patients may be more comfortable with systemic therapy, while younger patients and patients of reproductive age may be interested in learning about the effects of pausing treatment, a topic currently under investigation in a phase 4 clinical trial (NCT04526704).[49] Resources designed to support patients initiating therapy are also needed; suggestions included a guide to common symptoms and their timing and a list of helpful tips for starting on systemic therapy, such as starting healthy habits and keeping a side-effect journal. To this end, advisors

recommended **developing patient resources related to initiation of systemic therapy and side effects that can shared by nurse navigators or posted on web-based outlets**.

Patients also need help to understand current research and identify clinical trials. Although resources are available on research-based sites, like Clinicaltrials.gov and Pubmed, many patients may not have the scientific background needed to navigate and interpret the information. Advisors highlighted a recent article in *Future Oncology* as a useful resource summarizing the ENLIVEN study for general audiences.[50] Advocacy groups also highlighted publication of patient registries as a valuable resource for aggregating real-world data related to treatments, scan results, and other health information. Advisors recommended **continuing development of patient registries and lay publications focused on pivotal studies**. To help patients easily access these resources and those described above, advisors recommended **establishing a patient-focused website about TGCT clinical trials to share patient-accessible educational resources and help patients identify clinical trials**.

Role of Patient Advocacy Groups

Representatives from the advocacy groups expressed strong support for working collaboratively to support patients with TGCT. The collective outreach power of the advocacy groups was noted as a key strength that could be leveraged to share information and tools for patients. Groups expressed enthusiasm for using their avenues of communication (eg, website, social media, education portals) to disseminate resources developed based on insights from patients and advocacy group experience.

Based on their wealth of experience, representatives from patient advocacy groups shared advice regarding how best to support patients and educate around a disease. Advisors noted that educating patients and providing resources to help guide their discussions with HCPs may be more feasible than educating the entire medical community about a rare disease. Patients need to know what questions to ask and what

information they need to understand the “whole picture” of their disease. Advocacy groups have found that educational initiatives are most effective when they employ consistent tactics, initiatives, and messaging across organizations. They also shared several other considerations for developing patient resources that are summarized in **Table 2**.

Table 2. Considerations for developing patient resources based on advocacy group experience.

Resource Attributes	Useful Formats
• Should be understandable and clearly explain general terminology • Must address different stages of the patient journey • Consider health literacy	• Downloadable tools and infographics • Videos that summarize the basics and direct viewers towards sources of additional information • Checklists that serve as a roadmap for patients

In addition to their experience, each advocacy group highlighted resources, both currently available and in development, that may be of use to support patients with TGCT. The Life Raft Group is already engaging in strategic work related to TGCT, and resources in development include: a TGCT lexicon; curated list of specialists with expertise in TGCT; a webinar series to educate around giant cell tumors; a website to host disease state education resources; a patient registry that includes treatments, scan results, and other health information, as well as an associated tissue bank; and disease stage-specific FAQs. The Life Raft Group has extensive experience with bringing specialists together to talk about a rare disease and with organizing live and virtual tumor boards. They also have a surveillance network of sarcoma specialists around the world who discuss cases, and they are experienced in partnering with leading experts to develop publications. Their side effect management platform (SideEQ) incorporates built-in criteria for patient-reported outcomes, an important aspect of TGCT treatment.

Currently, TargetCancer Foundation is leveraging their TCF-001 TRACK (Target Rare Cancer Knowledge) study to drive enrollment and promote awareness around the importance of participation in clinical trials early in the disease course of rare cancers. TRACK is currently targeted to enroll 400 patients to evaluate whether patients with rare tumors can benefit from matched molecular therapy. TRACK includes a virtual tumor board designed to connect patients and local physicians with specialists as proposed for TGCT. TargetCancer Foundation is working with other groups like the National Organization for Rare Disorders (NORD) Rare Cancer Coalition to leverage existing resources and co-promote to drive enrollment in their study.

The Sarcoma Foundation of America is experienced with developing clear and accessible tools that span the phases of the patient journey. They also have experience in working with medical schools and faculty to develop public service announcements to promote disease awareness.

The Sarcoma Alliance is experienced with providing guidance to patients along the cancer journey with a variety of tools, one-to-one support, and nurse navigation. They also connect patients with multidisciplinary specialist centers and provide financial assistance to support patients obtaining second opinion consultations from sarcoma specialists. They frequently work with experts to share information about clinical trials, new research, and innovative therapies.

Cancer*Care* recently hosted a webinar about TGCT to promote disease awareness. They are experienced at bringing together patients, advocates, experts, and industry to improve support for patients. Patients are referred to Cancer*Care* for psychosocial and emotional support, as well as practical needs (food, support, transportation, etc.).

Collectively, participating advocacy groups have a wealth of experience and a powerful network of resources that can be leveraged through partnership.

RECOMMENDATIONS

Recommendations from the TGCT Advisory Board

- Drive educational initiatives targeting community-based surgeons to promote awareness among frontline providers
- Reframe early management of TGCT through consensus guidelines emphasizing the importance of multimodal approaches and referral to specialty centers for diagnosis and treatment
- Develop lists of "Centers of Excellence" and specialists organized by geographic regions
- Educate around systemic therapies for TGCT to encourage shift away from repeated surgeries toward a paradigm of systematic referral to experts in TGCT
- Conduct virtual tumor boards to expand access to experts for treatment planning
- Develop HCP-patient dialogue tools to guide discussions about surgical and nonsurgical treatment options at diagnosis
- Empower patients with Q&A resources to encourage shared decision-making
- Partner with field-based MSLs to share educational materials with community-based practitioners
- Incorporate TGCT into the general orthopaedic curriculum to help change the initial decision point from arthroscopic surgery to a specialty center referral
- Hold a TGCT summit for clinicians and patients
- Create a uniform lexicon around TGCT and share across organizations
- Develop patient resources related to initiation of systemic therapy and side effects that can shared by nurse navigators or posted on web-based outlets
- Continue development of patient registries and lay publications focused on pivotal studies
- Establish a patient-focused website about TGCT to share patient-accessible educational resources and help eligible patients identify clinical trials

SUMMARY

Recommendations from the advisory board highlighted several key opportunities to provide support for patients with TGCT. To help patients find a swift and accurate diagnosis, early management should be reframed to emphasize the importance of multimodal diagnostic and treatment approaches and referral to specialty centers. To promote individualized patient-centered therapy over the “straight-to-surgery” approach for TGCT treatment, shared decision-making tools may help HCPs and patients feel more confident in approaching discussions about treatment. In addition, educating around systemic therapies and conducting virtual tumor boards may expand access to multimodal treatment approaches. Shifting the paradigm will require educating HCPs who may not be familiar with TGCT, including those in community practices. Resources for disease education may be shared through field-based MSLs or through specialty-specific curricula and guidelines. A TGCT summit could also expand awareness and help clinicians and patients learn about the latest research. Finally, to increase early awareness and patient education around TGCT, a patient-focused website could provide a centralized mechanism to share patient-accessible educational resources grounded in consistent terminology and up-to-date clinical research. Cross-organizational collaboration to leverage the experience and resources of patient advocacy groups, as well as engagement of the active TGCT patient community, will be important to achieve these goals and improve outcomes and support for patients with TGCT.

ACKNOWLEDGMENTS

Support for this advisory board and white paper development was provided by a grant from Daiichi Sankyo. Medical writing and editorial support were provided by Melanie Styers and Leslie Mitchell of Verascity Science.

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