Anti-tumour Treatment

Best clinical management of tenosynovial giant cell tumour (TGCT): A consensus paper from the community of experts


* Corresponding author at: Adult Mesenchymal and Rare Tumour Unit, Cancer Medicine Department, Fondazione IRCCS Istituto Nazionale Tumori, Via G Venezian 1, 20133 – Milan, Italy.
E-mail address: silvia.stacchiotti@istitutotumori.mi.it (S. Silvia).

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A B S T R A C T

Tenosynovial giant cell tumour (TGCT) is a rare, locally aggressive, mesenchymal tumor arising from the joints, bursa and tendon sheaths. TGCT comprises a nodular- and a diffuse-type, with the former exhibiting mostly indolent course and the latter a locally aggressive behavior. Although usually not life-threatening, TGCT may cause chronic pain and adversely impact function and quality of life (QoL). CSF1R inhibitors are effective with benefit on symptoms and QoL but are not available in most countries. The degree of uncertainty in selecting the most appropriate therapy and the lack of guidelines on the clinical management of TGCT make the adoption of new treatments inconsistent across the world, with suboptimal outcomes for patients. A global consensus meeting was organized in June 2022, involving experts from several disciplines and patient representatives from SPAGN to define the best evidence-based practice for the optimal approach to TGCT and generate the recommendations presented herein.

Introduction

Tenosynovial giant cell tumour (TGCT), previously called pigmented villonodular tenosynovitis (PVNS) or giant cell tumour of tendon sheath, is a rare mesenchymal neoplasm arising from the synovium of joints and tendon sheaths. It is molecularly characterized by recurrent genomic aberrations often involving the colony-stimulating factor 1 gene (CSF1). [1–5] The 2020 WHO Classification of Soft Tissue and Bone Tumours defines TGCT as a locally aggressive neoplasm. [6] Sarcomatous transformation with metastatic spread is exceedingly rare. [7,8] Most patients affected by TGCT are young and, although usually not life-threatening, the disease and its treatment may impact quality of life (QoL). Recent clinical trials for advanced TGCT have raised awareness of the challenges that patients endure. Treatment is mostly decentralized with variation in practice, and many physicians do not appreciate the risks of suboptimal treatment. Furthermore, effective systemic treatment options are not available in most countries.

Therefore, an international consensus meeting was held on June 21, 2022, in Frankfurt, Germany, involving international multidisciplinary sarcoma experts in collaboration with patient representatives from the Sarcoma Patient Advocacy Global Network (SPAGN) to define best clinical practice in TGCT and generate the recommendations presented herein.

Methods, level of evidence and grade of recommendation

A data literature search (literature search strategy and selection criteria available in the Appendix) was conducted and in conjunction with expert opinion, the group reached consensus on key aspects of TGCT management. Due to the lack of prospective data on local phase TGCT and only a few prospective trials in advanced disease, current practice is mainly based on retrospective reports (level IV-V evidence). Consequently, a degree of uncertainty needs to be accepted in clinical management and regulatory matters. [9,10] We graded levels of evidence from I to V and used recommendation grades from A-D adapted from the Infectious Diseases Society of America-US Public Health Service Grading System 2 (Table 1).

Nodular-type TGCT (N-TGCT) versus diffuse-type TGCT (D-TGCT): definition

TGCT comprises two clinically distinct subgroups, N-TGCT and D-TGCT. [11,12] N-TGCT corresponds to the pathological definition of localized-type TGCT (see Section 6). We chose “nodular” instead of “localized” as the preferred term, as it better reflects imaging findings. Consequently, “N-TGCT” is used throughout the text. N-TGCT usually presents as a single lesion, often evolving over years. N-TGCT arises in soft tissue, near tendons or interphalangeal joints. [6] Occasionally, N-TGCT can erode bone or involve the overlying skin. Large joints are infrequently affected by N-TGCT. [13] In contrast, D-TGCT shows...
extensive and infiltrative involvement of the synovium of the joint and/or tendon sheath and extends into extra-articular structures. D-TGCT can cause haemorrhosis, destruction of bone and cartilage with severe disability, as well as frequent local relapse (LR).

TGCT can cause substantial morbidity, but it is not fatal. An exception is malignant TGCT (M-TGCT), that can arise de novo or following multiple recurrences of conventional TGCT. [8,14-16].

Epidemiology and prognosis

Epidemiological data on TGCT are scarce and heterogeneous and therefore difficult to compare. In nation-wide studies, incidence rates for N-TGCT varied from 30 to 34/1,000,000 for N-TGCT affecting digits and 11/1,000,000 for N-TGCT located in the extremities. Incidence rates for D-TGCT ranged from 5 to 8.4/1,000,000. [1,17] Hospital-based studies reported a higher proportion of D-TGCT (70–90%) compared to N-TGCT, likely due to expert centers attracting complex cases. [11,12,19,20].

A Danish study reported the prevalence of N-TGCT and D-TGCT as 44/100,000 and 11/100,000, respectively. [18]. N- and D-TGCT are more common in females than males. Mean age at diagnosis is 35–50 years, with slight gender and subtype differences. [1,11,12,19,20].

TGCT can involve any joint. However, most N-TGCT affect the hand and wrist followed by knee, while most D-TGCT arise from the knee followed by the ankle and hip. [1,6,17] N-TGCT of the elbow is exceedingly rare. [20].

Recurrences are lower in N-TGCT (9–14%) than in D-TGCT (23–72%). The LR rate (LRR) for patients initially treated outside an expert centre was 44% versus 92%. [19] The 5-year recurrence-free survival (RFS) for N-TGCT is 70–90% and 30–80% for D-TGCT.

Information on the frequency of paediatric TGCT can be found in the Appendix.

M-TGCT has an incidence < 1/1,000,000/year, so rare as to be case reportable, with a mortality of ~30%, and about 50% develop metastases. [8,11,12,14–19].

Imaging

Magnetic Resonance Imaging (MRI) is the preferred technique for detection and characterization of TGCT [IV, A]. Conventional radiography does not establish the diagnosis, it should be obtained to rule out calcifications, which are rarely seen in TGCT but may be found in other potential diagnoses.

The recommended minimal MRI protocol includes T1-weighted, T2-weighted and a fluid-sensitive sequences [IV, A]. The choice of primary imaging plane (sagittal or coronal) depends on tumour location. Sagittal images are preferred for the knee, ankle and elbow, and coronal for the hand-foot region, shoulder, hip, wrist. Spectral fat suppression is preferred over inversion recovery unless metal artefact is present. Although gradient echo imaging is not part of routine soft tissue imaging protocols, T2-weighted imaging should be performed to depict hemosiderin. Gadolinium contrast administration is recommended, and subtraction of pre- and post-contrast T1-weighted images performed [IV, A]. Dynamic contrast enhancement studies for evaluation of lesion vascularityization may be used, especially if non-surgical treatment is planned. Baseline and follow-up examinations should be performed in the same manner. TGCT is FDG-avid, however, there is insufficient evidence to recommend routine PET-CT or PET-MR. [21].

N-TGCT

Intra-articular N-TGCT

Conventional radiography/CT are usually normal or show a dense soft tissue nodule related to iron content. Osseous pressure erosion may be seen in tight joints.

Ultrasound shows a well-circumscribed focal mass with heterogeneous echogenicity and increased Doppler signal.

The lesion is of low signal on T2-WI without fat saturation, but of relatively high SI on fluid-sensitive sequences with intralesional foci of low SI, which are more conspicuous on T2-weighted images for the presence of hemosiderin (“blooming”) (Fig. 1). [22-24] Compared to D-TGCT, blooming has a lower sensitivity for N-TGCT and there is high interobserver variability. [25] Intralesional areas of high T2 signal may correspond to necrosis. [22] Joint effusion is typically absent in N-TGCT. Tumour tissue usually shows moderate/ marked heterogeneous enhancement. [26,27].

Extra-articular N-TGCT

Imaging findings are similar to intra-articular N-TGCT. MRI demonstrates the anatomical relationship with the tendon sheath with pre-dilection of the flexor tendons of the fingers and less frequently the synovial lining of a bursa or joint.

D-TGCT

Intra-articular D-TGCT

Extensive joint involvement, irregular margins, blooming artifacts, joint effusion, erosions and subchondral cysts are more frequent in D-TGCT. Erosions and cysts are predominantly seen in joints with a tight capsule, such as the hip, and may lead to joint destruction in longstanding disease (Fig. 2).

Extra-articular D-TGCT

D-TGCT shows an infiltrative growth pattern. Most lesions are in the peri-articular soft tissues, including muscle and subcutaneous tissue. [28].

![Fig. 1. Intra-articular nodular-type Tenosynovial Giant Cell Tumour (N-TGCT): MR imaging findings. Sagittal (a) T1-weighted TSE, (b) T2-weighted TSE, (c) T2*-weighted GRE, and (d) gadolinium subtraction images of the knee show well-defined nodular mass in Hoffa's fat pad. Note low signal intensity on T2-weighted image (b), focal areas of signal loss due to hemosiderin deposits on Gradient Spin Echo Sequences (GRE) image (c) as well as diffuse and inhomogeneous contrast enhancement (d).](image-url)
M-TGCT

Imaging features of M-TGCT are similar to benign disease and histopathology is required for diagnosis [IV, A]. [12].

Staging

Local staging evaluates articular and/or extra-articular involvement, ligamentous, muscular, tendinous tissue involvement, [29] tumour size, extent within the affected joint, articular cartilage loss, bone erosions, bone marrow edema and relationship with ligaments, muscles, tendons, and rarely neurovascular bundle. MRI is the technique of choice to evaluate the disease.

A thorax CT scan should be performed in M-TGCT or suspicion of malignant transformation to rule out metastatic spread [IV, A].

Radiologic assessment after local and/or systemic treatments

MRI is the technique of choice to detect recurrence [IV, A]. Surgical follow-up aims to evaluate LR and potentially progressive joint destruction in case of multiple recurrences of intra-articular D-TGCT. [30].

Response assessment to systemic treatment should include clinical, functional, and imaging assessments [IV, A]. MRI is recommended to evaluate dimensional changes. Systemic therapy trials currently use Response Evaluation Criteria in Solid Tumour (RECIST), version 1.1. [31] However, because of the typically irregular shape of TGCT, change in the longest diameter may underrepresent the degree of benefit. Volume-based assessments may better quantify the degree of change, but require validation.

Differential diagnosis

The main differential diagnoses are detailed in the Appendix.

Pathology and molecular biology

N-TGCT and D-TGCT share a common pathogenesis and are characterized by genomic aberrations disrupting the 3’-end of CSF1. [2–5] Detection of CSF1 rearrangement by cytogenetic or molecular genetic analyses is neither required for diagnosis nor has predictive value [IV, B]. Pathologic review by an expert pathologist is recommended, particularly in cases with discrepant imaging or clinical appearance [IV, B].

Morphology

N-TGCT are lobulated tumours with a variably yellow, tan, or whitish cut surface. D-TGCT can exhibit a villous pattern when intra-articular and multinodular growth with a variegated cut surface when extra-articular. TGCT has variable morphologic appearances depending on the composition of mononuclear cells, multinucleated osteoclast-like giant cells, foamy macrophages, and inflammatory cells (Fig. 3A). The mononuclear cells are either small histioyte-like cells with pale cytoplasm and round/reniform nuclei or epithelioid cells with amphophilic cytoplasm and round, vesicular nuclei. The larger cells often contain a rim of hemosiderin granules (“ladybird cells”) (Fig. 3B). The tumour cells are embedded in a collagenized and variably hyalinized stroma (Fig. 3B). N-TGCT is characterized by multinucleated giant cells and hemosiderin deposits. Xanthoma cells usually aggregate at the tumour periphery. [32–34] D-TGCT presents as an infiltrative mass with variable cellularity and cleft-like, pseudoglandular, alveolar, or cystic spaces. Multinucleated giant cells and stromal hyalinization are less...
CD45 are expressed in the smaller histocyte-like cells. [39] The multi
determinate mononuclear cells (Fig. 3D), whereas desmin is positive in 50 % of
cases and highlights large mononuclear cells. [37,38] CD68, CD163, and
Expression of clusterin and podoplanin (i.e., D2-40) is observed in the
this article.)
ences to colour in this figure legend, the reader is referred to the web version of
Fig. 4. Cytogenetic analysis in a case of Tenosynovial Giant Cell Tumour
(t(1;2) (p13;q37) (Fig. 4), leading to COL6A3::CSF1 fusion in a subset of
cases). [41].

Molecular profile

These are clonal neoplasms characterized by genomic aberrations, presumably all leading to truncation of the 3’ end of CSF1 with sub-
sequent overexpression of CSF1 and recruitment of non-neoplastic
chronic inflammatory cells through a paracrine “landscape” effect.

Karyotypic abnormalities include trisomy 5 and 7 and a recurrent
(t1;2) (p13;q37) (Fig. 4), leading to COL6A3::CSF1 fusion in a subset of
Cases. [41].

The CSF1 rearrangement is present in 2–16 % of tumour cells (i.e.,
the larger epithelioid cells) which can cause false-negative results from
chromosomal analyses. The two most common patterns of CSF1 rearrange-
ment are those near CSF1 exon 8/9 junction or within exon 9 (3’UTR),
which usually partners with intergenic sequences, often downstream of
CSF1, and gene fusions of CSF1 exon 5/6 junction with exons of various
other genes. [5] CSF1 overexpression is typically seen regardless of CSF1
fusion status. These results suggest that somatic CSF1 alterations may
provide a mechanism of sustained CSF1 production and explain the
activity of CSF1R inhibitors. [42].

Pathologic differential diagnosis and diagnostic pitfalls

The main pathological differential diagnoses are detailed in the
Appendix.

Principles of treatment

Patients affected by TGCT should be managed within expert centers or
reference networks, by a dedicated, experienced sarcoma multidisci-
plinary treatment team, including a pathologist, radiologist, ortho-
paedic surgeon, pain specialist, surgical, radiation and medical
oncologists [III, A]. Other specialists, such as neurosurgeons and phys-
ical therapists, should be involved as required.

Diagnostic procedures

For suspected D-TGCT, a biopsy is recommended either by image-
guided biopsy or arthroscopy [IV, B]. If a core biopsy is indicated and
there is a mass, a 14/16-gauge needle should be used with coaxial
 technique [III, B].

Biopsy may be avoided if radiological assessment in an expert center is
highly suggestive of TGCT and resection is planned [V, C]. Patho-
logical diagnosis will then be confirmed on the surgical specimen.

Indication for active surveillance (AS) versus active treatment.

Symptoms can include pain, swelling, limitation in range of motion,
joint instability or locking, or numbness, although many patients may be
asymptomatic. In N- and D-TGCT, the decision for active treatment
should balance the possible curative impact with the benign nature of
TGCT, its potentially indolent course in some patients, the risk of LR
after complete resection and the potential for surgery-related morbidity
[IV, B]. The decision for AS vs active treatment should be shared with
the patient after a thorough discussion of the risk/benefit ratio within
the multidisciplinary tumour board (MTB). AS should be considered as
the first option for asymptomatic patients. For symptomatic patients, AS
should also be considered if there is risk of major morbidity from surgery
or medical treatment (e.g., chronic hepatitis or history of severe toxicity
from previous treatment). When AS is selected, the frequency of follow-
up should be individualized, based on tumour growth pattern, anatomic
location, and symptoms [V, B].

Surgery

The preferred approach is resection either with marginal excision in
N-TGCT or with extensive synovectomy in diffusely involved joints or
tendon sheaths for D-TGCT, preferably when macroscopically complete
resection is achievable and it can be accomplished without significant
morbidity for durable local control and improved QoL [III, A].
The indication and expected outcome of surgery should be discussed with
the MTB and patient. M-TGCT should be treated as a soft tissue sarcoma
(STS). [43].

The preoperative MRI should be reviewed for concealed lesions not
visible with a standard surgical approach as under the menisci or
discontinuous growth in soft tissues.

The value of debulking surgery is controversial and should always be
discussed in an MTB balanced against other potential therapies. Whether
this should be done by extensive open synovectomy or by an arthro-
scopic approach, or a combination is debatable.

Traditional joint replacement effectively addresses joint pain and
alignment from degenerative disease and debulks disease intra-
lesionally. There is a high LRR. More radical oncologic resection and
reconstruction with megaprosthesis may be needed but has higher
failure rates [III, B].
Amputation may be considered for functional reasons in rare, selected cases within expert centers after full discussion with the patient, and having ruled other options [V, C].

Perioperative systemic therapy, aiming to reduce the morbidity of surgical resection and risk of LRR is investigational. [44].

Location and extent of disease, surgical experience and management in a MTB are major factors in choosing systemic therapy over resection. [45].

Surgery in recurrent cases has significantly higher risk of further LR. [12,34,45,46].

N-TGCT

N-TGCT can be managed by complete marginal resection, with low LRR.

**Intra-articular N-TGCT. Knee.**

In N-TGCT located anteriorly, treatment involves resection of the lesion by a mini-open incision [IV, B]. The lesion is exposed and the attachment of the nodule is dissected. Incidental findings during arthroscopy are resected or shaved away, LRR are low. Contamination of the joint in intralesional resections is rarely reported, but a large multicenter study of N-TGCT showed a lower LRR after open versus arthroscopic surgery (13 % versus 20 %). [47] In the posterior compartment, open resection is preferred [IV, B].

Hip.

Depending on location, either an anterior or posterior approach can be used [IV, B]. In 9 N-TGCT patients there was no LR. [48] The only necessity for joint luxation is a location attached to the ligament of the head of the femur with protrusion into the acetabular fossa.

Ankle and subtal joint.

In posterior lesions, either approaching from a posterolateral or medial approach, with attention to the posterior tibial vessels [V, B]. [49].

**Shoulder.**

Most N-TGCT may be resected by an anterior approach. Arthroscopy is an option [V, C].

Elbow.

The surgical approach is defined by the specific involvement of the joint. In expert centers arthroscopy might be used [V, C]. [20].

Other uncommon sites.

Locations such as midfoot, mandible or spine can only be treated surgically with partial resections of the joints/tumours. Other/ additional treatments may be considered.

**Extra-articular N-TGCT.** Most extra-articular N-TGCT originate in the tendon sheaths of the hand or foot, but also along tendons. Involvement of bursae is possible. In any case, macroscopic complete resection is necessary [III, B]. The LR risk is low. [50].

**D-TGCT**

Surgery for D-TGCT is associated with high LR risk and postoperative complications. All cases should be discussed by the MTB. [34].

**Intra-articular D-TGCT. Knee.**

A one- or two-stage procedure is required, unless one compartment is not (significantly) involved [IV, B]. Anterior synovectomy might be done arthroscopically. The LRR seems higher as compared to open synovectomy. A *meta*-analysis (630 patients D-TGCT of the knee) detected a lower LRR following open synovectomy or combination of open and arthroscopic synovectomy (24 % and 14 %) compared to arthroscopic synovectomy alone (38 %). [49] Two other studies found a lower LRR with open versus arthroscopic synovectomy. [33,51] By contrast, another *meta*-analysis (1,019 patients) showed a better LR after arthroscopic (16 %) than open surgery (23 %). [52].

Total synovectomy requires aggressive removal of the synovium commonly including the capsule [IV, B]. When possible, the periosteum is spared to prevent excess scarring and postoperative stiffness. Disease that undermines the coronary ligaments may require repair of the peripheral menisci. Bone invasion has to be considered. Any disease extending into the proximal tibial fibular joint should be removed and may require a separate arthrootomy [IV, B].

Posteriorly disease often dissect under the gastrocnemius tendons, which should be released or even obliquely cut to expose the tumour. Tissue dissection has to be done in relation to extent of disease on MRI. Bony destruction requires curettage.

Continuous passive motion after surgery, greatly enhances restoration of joint function.

Total joint arthroplasty may be indicated for secondary osteoarthritis. One option is total joint arthroplasty with a ventral synovectomy and posterior synovectomy if the posterior compartment is involved. D-TGCT undergoing joint replacement have an elevated risk of stiffness and subsequent procedures. [53].

**Hip.**

If there is joint destruction, total hip arthroplasty gives excellent outcomes with low LRR. [54] In the absence of joint destruction, joint dislocation might be considered. The approach(es) must allow synovectomy of all involved parts of the joint.

Ankle and subtalar joint.

Most patients need at least two incisions (and in extended cases three). In this case a two-stage procedure should be considered. The LRR is high (28 % with open synovectomy; 44 % with arthroscopic approach) [V, B]. [49].

Shoulder and elbow.

Arthroscopic approaches might be adequate if allowed by disease extent. At the elbow one incision might not be enough.

Other.

Locations in the spine and around the jaw rely on the experience of spinal and head/neck surgeons.

**Extra-articular D-TGCT.** Marginal resection is the method of choice but requires more extended incisions of the involved muscles or soft tissue spaces [IV, B].

**TGCT in children**

We did not address the approach to TGCT in skeletal-immature children. Treatment of adolescents should follow the same principles as adults.

**Radiotherapy**

The available literature provides insufficient data to propose reliable recommendations for the use of radiotherapy as a standard treatment for TGCT, including the neoadjuvant, adjuvant, or relapsed setting, even though some retrospective series reported a positive impact. Most of the expert panelists do not use this modality. Published reports are limited by small size, short follow-up, and non-randomized, retrospective design, leading to challenges in interpreting data. As TGCT patients are generally young with non-life-threatening disease, the long-term risk of malignant transformation and fibrosis, joint stiffness, or other sequelae are of significant concern. Whether radiotherapy should be considered in select cases with no alternative treatment options is a matter of debate.

A more detailed description of currently available data on radiotherapy is presented in the Appendix.

Radio-synoviorthesis has not shown to be effective in D-TGCT so far. It is not a method to compensate for suboptimal surgery. [55] Prospective studies are needed to better understand which is the potential role of this treatment modality for TGCT patients.
Cryotherapy

Cryotherapy is investigational as available data are insufficient to support the value of this procedure in TGCT.

Systemic treatment

Symptomatic TGCT resectable with acceptable morbidity

Standard treatment for symptomatic TGCT is surgery when it can be accomplished without significant morbidity.

TGCT resectable with unacceptable morbidity

The potential benefits of any systemic treatment need to be carefully weighed against side effects and impact on QoL. In contrast to malignancies where tumour shrinkage is often a surrogate for improved survival, assessment of treatment benefit in TGCT must also include changes in symptoms and/or functional status. TGCT can remain stable for prolonged periods. Consequently, in the later stages of disease several different scenarios can be encountered:

In asymptomatic disease, AS is the initial preferred approach, as the risk of over-treatment appears to outweigh the potential harm of delaying systemic treatment [IV, B]. However, an active systemic treatment may be justified in the rare asymptomatic cases in which anatomic location is potentially life-threatening (e.g., cervical spine).

In symptomatic disease, AS can still be offered particularly if patients perceive the symptoms as manageable [IV, B]. However, anatomic location as well as location within the joint may affect the risk of permanent joint damage. These aspects may justify starting systemic treatment, particularly if disease progression may affect QOL [IV, B].

Patients with difficult to manage, symptomatic disease, or moderate/severe functional impairment may be candidates for systemic treatment if surgery would be associated with significant morbidity.

Conventional chemotherapy commonly used for patients affected by STS is not indicated in TGCT and should be limited to advanced M-TGCT (see below) [IV, B].

CSF1R inhibitors are considered standard and a detailed list of available data on this class of agent is presented in Table 2 [II, A]. When available clinical trials should be offered. In countries without approved active treatments, the preferred option should be clinical trial participation or off-label CSF1R inhibitors, when available [IV, A]. The optimal duration of treatment has not been defined and (outside clinical trial) should be based on patient tolerance and preferences.

CSF1 is highly expressed in all TGCT providing the basis for targeting the CSF1R pathway. CSF1R is mainly expressed by macrophages but not the neoplastic cells, suggesting that CSF1R inhibitors do not target neoplastic cells but rather the bystander monocytes. Inhibition of CSF1R signaling may be achieved by blocking the ligand using antibodies, or the receptor itself either by small molecules or antibodies. CSF1R pathway inhibitors have shown activity in TGCT with substantial tumour shrinkage, symptomatic and functional improvement, and long-term disease control. [56–60].

Pexidartinib represents the only approved treatment but is available only in few countries. [61] Pexidartinib is an oral selective CSF1R inhibitor. A randomized phase III trial showed a 39 % versus 0 % RECIST overall response rate (ORR) at Week 25 in the pexidartinib versus the placebo arm. [56] Four percent (5/140) of patients treated with pexidartinib experienced severe mixed or cholestatic hepatotoxicity, and all recovered between 1 and 7 months after discontinuation. [62] Pexidartinib was approved by Food and Drugs Administration in 2019 for adult patients with symptomatic TGCT associated with severe morbidity or functional limitation that were not amenable to improvement with surgery, but not by the European Medicines Agency. The findings of ongoing studies will hopefully provide further support to improve pharmacovigilance.

Imatinib inhibits CSF1R in the sub-micromolar level. In a retrospective series of advanced TGCT, imatinib showed a ~ 30 % RECIST ORR and symptomatic improvement. [57,58] With 52-month median follow-up, median progression-free survival (PFS) was 18 months. Imatinib has a favourable toxicity profile and is generally available.

Nilotinib shows a potent inhibition (IC50 < 1 µM) of the catalytic activity of CSF1R. In a phase II trial of inoperable TGCT, nilotinib achieved a RECIST ORR of 6 %, with a progression-free rate of 96 % and 53 % at 12 weeks and 5 years, respectively. [59,60] Nilotinib is currently under investigation in a randomized clinical trial (NCT02209901).

Vimseltinib is an oral, selective switch-control kinase CSF1R inhibitor. Based on promising Phase I/II data, a phase III randomized trial is recruiting (MOTION) (NCT05059262). [68] G3 AE were elevated blood CKP and transaminases, and hypertension.

Emactuzumab is a monoclonal antibody directed against CSF1R, showing an ORR of 85 % and symptomatic/QOL improvement in a phase

Table 2

<table>
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<tr>
<th>Study</th>
<th>n</th>
<th>ORR (%) by RECIST</th>
<th>ORR (%) by TVS</th>
<th>DCR (%) by RECIST</th>
<th>Median PFS (months)</th>
<th>Median DOR by RECIST (months)</th>
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ORR: overall response rate; TVS: tumour volume score; DCR: disease control rate; PFS: progression-free survival; DOR: duration of response.

- Phase I extension study, phase III randomized to pexidartinib study (including patients treated with pexidartinib at the time of randomization and after the cross-over).
I trial. [63,64] Grade (G) 3 adverse events (AE) were periorbital oedema, lupus erythematosus, dermohypodermitis and mucositis.

Cabiralizumab is an intravenous monoclonal antibody to CSF1R. A phase 1/II study showed a 45 % RECIST ORR. [65] G3 AE were creatine kinase elevation, periorbital oedema and hypertension.

Monoclonal antibodies directed against CSF1 administered into the affected joint are under investigation. [69] Among others, AMB-05X is under development in a phase 1/II study (NCT04731675).

M–TGCT

The optimal treatment for advanced M-TGCT remains to be defined. CSF1R inhibitors appear inactive and their use is not recommended outside of clinical trials. [16] Anthracycline-based chemotherapy is the preferred first-line approach, despite low response rate and short time to progression; there is a report of targeted therapy and radiation. [16].

Open questions regarding the optimal use of systemic treatments in TGCT are discussed in the Appendix.

QoL, symptoms management and physiotherapy

D-TGCT is commonly associated with joint destruction and pain, swelling, decrease range of motion, and stiffness. Surgical resection can also be accompanied by joint damage and life-long consequences. [70] These symptoms persist in about 50 % of patients even after active treatment. [71] Additionally, long-term systemic therapies may be accompanied by treatment-related toxicity. Consequently, D-TGCT often has a significant impact on QoL, patients’ activities of daily living, exercise and work activities, resulting in changing occupations or preemptively retiring, and overall healthcare costs. [72,73] Patients and their support systems lack help to cope with emotional, psychological, and financial obstacles related to their disease and care. They recount anxiety and often feel their experience is minimized by the perception of benignity.

Patient-reported outcome (PRO) data are an essential part of the assessment and can influence treatment decision making [III, A]. [74] Tools such as Visual Analog Scale or Numerical Rating Scales for pain-stiffness and PRO Measurement Information System-Physical function (PROMIS-PF) questionnaires have been identified as valuable instruments to assess TGCT-related symptoms. [11,75].

Patients should be referred to pain specialists depending on their disease and symptom burden, the psychosocial condition and individual/family-related factors [V, B]. Important physical and psychosocial distress, the initiation of tumour-specific therapies, patients’ or family concerns, serious comorbidities and multiple hospitalizations are all criteria warranting palliative care referral. [75,76].

There are no data that specifically address management of pain in TGCT, and so existing guidelines on chronic pain treatment should be followed [II, B]. [77] Pain management should be always part of a multidisciplinary assessment to identify surgical, rehabilitation or systemic interventions which can be temporarily supported by the use of low to moderate strength analgesics. anti-inflammatory drugs and opioids are among the most used medications. Eventual side effects or consequences of long-term pain therapies should also be weighed. The chronic use of opioid analgesics should be managed with a pain specialist. [75].

Future studies should elucidate the impact of TGCT site on symptom burden, physical therapy optimal schemes and the impact of the different therapeutic options on QoL.

Follow-up

There are no data to indicate the optimal length and frequency for follow-up of completely resected TGCT. Currently, routine follow-up schedules differ across institutions and may be symptom-driven and/or based on growth-patterns, tumour location and patient preferences. In D-TGCT, most centers recommend MR imaging every 6–12-month for patients with symptomatic disease. A more frequent disease assessment (e.g., every 3–4 months) is usually applied in patients receiving an active systemic therapy.

Future perspectives

While several open questions regarding the optimal treatment strategy in TGCT are left to be addressed by future studies (as discussed in Appendix), a global effort is needed to make active systemic treatments available to TGCT patients worldwide and avoid discrimination.

Contributors

Stacchiotti S and Bauer S planned and organised the consensus event, chaired the consensus meeting, and contributed to scientific literature review, drafting of the report, and final approval. Schuster K planned and organised the consensus event, and contributed drafting of the report, and final approval. All the other authors contributed to scientific literature review, drafting of the report, and final approval.

Declaration of Interest

None of the authors has any interest to report directly related to this manuscript.

Outside the scope of this manuscript:

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

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