Updates on the Treatment of Tenosynovial Giant Cell Tumor (TGCT)

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**Recommended Citation**  
Chan, Abigail S.; Katiyar, Vatsala; Dy, Paul; and Singh, Vikas (2022) "Updates on the Treatment of Tenosynovial Giant Cell Tumor (TGCT)," *Hematology/Oncology and Stem Cell Therapy: Vol. 16 : Iss. 4 , Article 2.*  
Available at: [https://doi.org/10.56875/2589-0646.1032](https://doi.org/10.56875/2589-0646.1032)

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Updates on the Treatment of Tenosynovial Giant Cell Tumor

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Abstract

Tenosynovial giant cell tumor (TGCT) is a rare inflammatory disorder affecting the joint synovium, bursae, and tendon sheaths that causes non-specific and often insidious joint discomfort. The application of systemic chemotherapy has been limited due to poor and unsustained disease responses. Surgery with or without adjuvant radiation is the primary treatment modality for TGCT. With its locally destructive nature and increased recurrence, multiple surgical interventions become necessary throughout the course of the disease, leading to disfigurement, decreased quality of life, and increased mortality. However, owing to recent evidence demonstrating the overexpression of colony-stimulating factor 1 (CSF-1) in TGCT, selective tyrosine kinase inhibitors targeting CSF-1 receptors are being developed. Pexidartinib is the first CSF-1 receptor inhibitor approved for the treatment of TGCT. Here, we discuss various available treatment strategies and ongoing investigations and trials targeting diffuse TGCT, which include nilotinib, lacnotuzumab, cabiralizumab, vimseltinib, and emactuzumab.

Keywords: Tenosynovial giant cell tumors, Pigmented villonodular synovitis, Surgery, Radiation therapy, CSF-1 receptor inhibitors

1. Introduction

Tenosynovial giant cell tumor (TGCT), also known as pigmented villonodular synovitis (PVNS), is a rare benign inflammatory disorder with an estimated incidence of 10 and 4 per million person-years for localized TGCT (L-TGCT) and diffuse TGCT (D-TGCT), respectively. It is more commonly observed in an age range of 20–50 with a median age of 47 years with a slight female predilection [1].

As a disease of the tendon sheaths, bursae, and joint synovium, patients with TGCT present with non-specific and insidious joint discomfort. The tumors progression, limits the range of motion in the joints, resulting in swelling, effusion, stiffness, pain, and hemarthrosis [2]. TGCT is mainly characterized into two types: L-TGCT or nodular and D-TGCT. L-TGCT shows single nodules affecting the digits in 85% of patients. D-TGCT forms multiple nodules that proliferate in the larger joints, such as the knees (75%), and are likely to be locally destructive [3]. Owing to its slow growth and nonspecific presentation, its diagnosis and treatment are often delayed. X-rays of the involved joints are the most commonly performed initial imaging modalities, characteristically showing bony erosions with distinct borders. Magnetic resonance imaging (MRI) is the gold standard and better demonstrates joint effusion, synovial proliferation, and joint bulging, which are typical features of TGCT. Joint effusion and a paucity of signal intensity due to hemosiderin deposition in the joint space can be observed in T1 and T2 images captured with MRI [4].

The accepted treatment strategies for TGCT include surgery, radiation, and systemic targeted therapy. Aggressive surgical interventions, such as synovectomy, open surgical excision, and amputation of the affected joints are the mainstays of treatment [5]. Owing to a propensity for local
recurrence (rates up to 55%), repeated surgical interventions performed for treatment contribute to disfigurement, decreased quality of life (QoL), and increased mortality [6]. Adjuvant radiation is administered to delay locoregional recurrence. Furthermore, it is considered for patients with relapsed or recurrent diseases unable to undergo further resection [7]. Chemotherapy is sparingly used in this population because of inconsistent and unsustained responses. Some of the chemotherapy regimens include doxorubicin/ifosfamide, gemcitabine/docetaxel, and gemcitabine/vinorelbine [8,9]. In 2006, West et al. described the translocations on chromosome 1p13 position in TGCT. This engenders the fusion of colony-stimulating factor 1 (CSF-1) with collagen type VI alpha-3 (COL6A3) at 2q35 along with the overexpression of CSF1, resulting in hyperplasia of synovial cells around joints and tendon sheaths [10]. This discovery revolutionized the role of systemic therapy in this subset of patients.

This study aims to review available treatment options and discuss novel systemic agents currently under investigation for the TGCT treatment.

2. Current treatment strategies

2.1. Surgery

The surgical approach for the management of TGCT depends on the extent of joint involvement. Localized TGCT has distinct and sharp margins that allow for sufficient macroscopic complete resection. The resection of diffuse TGCT is more challenging due to the lack of well-defined margins [6]. Recurrence rates for L-TGCT and D-TGCT are 0–15% [1,6,11,12] and 14–55%, respectively [6,13,14]. A meta-analysis by Mollon et al. suggested that while the recurrence of L-TGCT was independent of the surgical approach, D-TGCT relapse was observed more frequently in patients who underwent arthroscopic surgery than those who underwent open synovectomy or combined open and arthroscopic synovectomy [7].

Traditionally, the surgical approach for L-TGCT and D-TGCT involves marginal excision and total synovectomy, respectively [11,15]. However, complete synovectomy may be associated with postoperative complications, such as hemorrhosis requiring drainage [16], joint stiffness, loss of joint function [17], and secondary osteoarthritis [18], which highlights the morbidity and debility accompanying aggressive surgery. Palmerini et al. noted that despite macroscopic incomplete resection, 57% of patients did not show evidence of progression at the fifth year during follow-up [6]. Hence, subtotal synovectomy may preserve joint function and QoL. Another strategy to balance the risk of recurrence with postoperative complications involves the utilization of open posterior with arthroscopic anterior synovectomy compared to the posterior arthroscopic synovectomy approach [16]. Joint arthroplasty combined with synovectomy can help decrease flexion contractures and improve functioning in patients while ensuring a low recurrence rate. However, this may be associated with prosthesis-related complications and a risk of subsequent revision procedures [19,20].

Post-surgical isotopic synoviorthesis is another approach to prevent recurrence in D-TGCT. Radio-synoviorthesis involves the injection of a β-emitting radionuclide, usually 90-Yttrium (90Y) into the articular cavity. The cells of the synovial lining intake the isotope and release energy, which leads to irradiation of synovial tissues and subsequent cessation of proliferation and inflammation [13,21]. Ottaviani et al. showed relapses in 30% and 9% of 73 patients treated with synovectomy followed by isotopic synoviorthesis and relapses, respectively, with a mean delay of 2.6 and 2.4 years in knees (n = 50) and other locations (n = 23), respectively [16]. Other smaller studies noted a lower recurrence rate of 0–17% [22–24]. Unfortunately, osteonecrosis, intra-articular (IA) infections, skin necrosis, and chronic draining sinus have been reported with this approach. Hence, some clinicians have discontinued its use as a local adjuvant treatment [21,25].

2.2. Radiation therapy

Radiation therapy is a potential option for TGCT but its clinical use is limited by the significant long-term adverse outcomes. Very low-quality data reported in an individual patient meta-analysis showed that the recurrence rate of D-TGCT was reduced by peri-operative radiotherapy [7]. Its role has been established in a post-operative setting, especially after incomplete resection to enhance local control and as a salvage option for recurrent diseases [26,27]. Despite the promising results, its use has declined, especially in younger patients, owing to long-term toxicities like joint stiffness, tissue necrosis, skin reactions, pathological fractures, and transformation into malignant sarcoma (although no such cases have been reported) [3,26,28,29]. The availability of systemic therapies with a relatively more acceptable side effect profile...
further limits the use of RT. Hence, instead of routine use, RT is reserved for patients with recurrent disease, symptomatic residual disease, or when limb sparing is not feasible [29].

2.3. IA injections

In addition to radiosynoviorthesis, the effects of IA injections of drugs have been examined in monoarticular TGCT. Tumor necrosis factor (TNF)-α is a proinflammatory cytokine that promotes synovial proliferation, causing subsequent cartilage and bone damage [30]. Local injections of anti TNF-α drugs like infliximab and etanercept have demonstrated promising results in a small number of patients to exploit this mechanism of tumor growth. Praino et al. administered IA infliximab to three patients who had early recurrence after surgical synovectomy for knee TGCT. Clinical improvement, reduction of active synovitis, and sustained remission for more than 12 months were observed in two patients who underwent IA therapy followed by synovectomy. One patient refused surgery and continued local infliximab therapy [31]. In another study examining two patients with TGCT resistant to repeated IA steroid injections and arthroscopic synovectomy, administration of IA etanercept showed a marked improvement in functional recovery and regression of knee joint synovial proliferation [32].

Moreover, local use of antiangiogenic drugs like bevacizumab has been examined in a patient with multiple relapses after debulking arthroscopic synovectomy. Administration of 100 mg of bevacizumab every four weeks for 12 months showed a marked improvement in synovitis and functional outcomes [33]. Although no randomized controlled trials prove the efficacy of these drugs, they do offer potential options for patients with multiple recurrent monoarticular TGCTs.

Another novel agent, AMB-05X — a human immunoglobulin G2 (IgG2) monoclonal antibody directed against CSF1R with potential antineoplastic and immunomodulating properties is currently being studied in a phase II trial. The trial aims to evaluate the safety and efficacy of IA administration of AMB-05X. Patients will receive an injection of AMB-05X once every two weeks for 12 weeks (a total of six treatments) (NCT04731675). If found to be effective, AMB-05X could change the treatment paradigm of TGCT [34].

2.4. Systemic therapy

The identification of genetic aberrations associated with TGCT and enhanced understanding of tumor biology has led to an increased interest in the investigation and development of novel therapeutic options.

West et al. demonstrated that the majority of TGCT cases have translocations involving 1p13, and a subset of these fusions occur with 2q37. CSF1 or M-CSF1 and the COL6A3 located at 1p13 and 2q37, respectively, are involved in this translocation, resulting in the formation of the COL6A3-CSF1 fusion product. This leads to CSF1 overexpression. However, only a minority of tumor cells (2–16%) harbor the translocation and express CSF1. The tumor primarily comprises non-neoplastic reactive cells that express CSF1R and are recruited by the tumor cells via CSF1. Interestingly, the tumor cells also express CSF1R, which helps stimulate their own growth through an autocrine loop [10,35]. Hence, CSF1R inhibitors are used to control tumor proliferation.

2.5. Imatinib

Imatinib, a multi-kinase inhibitor, was the first CSF1R blocker showing activity against TGCT, with a complete response (CR) reported in a case [36]. This therapeutic benefit was later confirmed in two larger studies. In an observational study of 29 patients, 1 patient showed CR, 4 showed partial responses (PR), and the remaining had stable disease (SD). Common toxicities reported were fluid retention, skin rash, fatigue, and nausea, and six patients discontinued medication due to clinically significant toxicity [37]. Long-term outcomes presented by Verspoor et al. showed an objective response rate (ORR) of 31% with a disease control rate of 96% after a median follow-up of 52 months [38]. In another study examining 25 patients with D-TGCT, imatinib showed significant differences during tumor volume score (TVS) assessment performed using MRI and mean SUV differences examined using positron emission tomography-computed tomography (PET-CT). A majority (80%) of the patients had side effects similar to those observed in previous studies; three patients showed grade three adverse effects of creatinine increment, neutropenic sepsis, and liver dysfunction [39]. Hence, the authors suggest carefully weighing the risks and benefits of administering imatinib for a rarely lethal disease, such as TGCT.

2.6. Pexidartinib (PLX 3397)

Pexidartinib is another oral tyrosine kinase inhibitor (TKI) with strong selective activity against CSF1R. In addition, it also blocks c-kit receptor tyrosine kinase (KIT) and ms-like tyrosine kinase 3
internal tandem duplication (FLT3-ITD) [40]. It was approved by FDA in 2019 for the treatment of adults with symptomatic TGCT who show severe morbidity or functional limitations that cannot be improved with surgery, based on the results of ENLIVEN trial [41,42]. ENLIVEN was a placebo-controlled, randomized, and double-blinded Phase III trial that included 120 patients with unresectable TGCT. It demonstrated an ORR of 39% at week 25 compared to placebo. At the sixth month, no progression was observed in all responders. Moreover, it improved the functional outcomes, including the mean range of motion and physical function and decreased stiffness [42]. The recommended daily dose is 800 mg, with dose reductions recommended in renal or hepatic dysfunction or if administered simultaneously with CYP3A or UGT inhibitors [41]. The most concerning side effect is the risk of serious and potentially life-threatening hepatotoxicity, leading to a Black Box warning. In ENLIVEN trial, 3 of the 61 patients who received pexidartinib had aminotransferase levels three-fold higher than the upper limit of the normal range. Other adverse events included hair depigmentation (most common), fatigue, dysgeusia, rash, pruritus, periocular edema, nausea, vomiting, arthralgia, and hypertension [42]. PLX 108–01 is a phase I safety study of PLX3397 or pexidartinib for the treatment of advanced solid tumors refractory to standard of care therapy with pathophysiology linked to CSF1R, KIT, and FLT3 activity. In total 39 patients with TGCT were enrolled in this study. Examining the ENLIVEN patient population and the TGCT cohort in the PLX 108-01 study, Gelderblom et al. reported a pooled safety and efficacy analysis of 130 patients who received pexidartinib with a median follow-up of 39 months. Following Response Evaluation Criteria in Solid Tumors (RECIST) criteria, had an ORR of 60%, with 26% achieving CR, 34% showed PR, 20% had SD, 1% had progressive disease, and 19% were not evaluable. The TVS ORR was 65%, and the mean duration of response was 46.8 months. Safety analysis was similar to that of the ENLIVEN study. Hepatotoxicity was observed in 95% of the patients, majority of whom had ≥1 to <3-fold higher levels of alanine aminotransferase and aspartate aminotransferase than the upper limit of the normal range. Two patients had irreversible toxicity, leading to death and liver transplantation. Owing to these toxicity risks, a careful discussion with the patients is warranted prior to starting pexidartinib. Patients are required to enroll in the Risk Evaluation Management System (REMS) program to ensure the periodic monitoring of liver function with appropriate dose reductions [43].

2.7. Supportive care

Joint pain, stiffness, swelling, and reduced range of motion represent most of the symptoms of locally advanced disease. Physical therapy, occupational therapy, and analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids play important adjunct roles [2]. A randomized placebo-controlled double-blind phase II study of zaltoprofen, an NSAID that exerts possible anti-tumor effects by activating peroxisome proliferator-activated receptor gamma (PPARγ), is ongoing. A pilot study conducted by the same investigators included 10 patients (6 knees and 4 ankles) who received zaltoprofen for 48 weeks. Eight patients had SD, one had PD at 72 weeks, and three of the ankle patients underwent surgery during the planned treatment duration and subsequently had SD. Results of the phase II study are pending [44].

3. Investigational agents

3.1. Nilotinib

Originally studied for the treatment of Bcr-Abl chronic myelogenous leukemia, nilotinib is a TKI that acts against Bcr-Abl, KIT, platelet-derived growth factor receptor beta, and CSF-1 receptor. In a multicenter, open-label, single-arm, phase 2 trial (NCT01261429), eligible patients received 400 mg of nilotinib twice a day until one year of treatment completion, disease progression, or intolerance. After 12 and 24 weeks of the treatment, 93% and 90% of the evaluable patients were progression-free, respectively. However, no patients achieved CR at follow-up after one year; 90% showed SD, and 6% had PR [45]. A similar phase 2 trial (NCT01207492) with 17 patients is underway. The expected study completion date is December 2021 [46].

3.2. Lacnotuzumab

Lacnotuzumab (MCS-110) (Novartis Europharm Limited) is a recombinant humanized, high-affinity anti–CSF–1 monoclonal antibody of the IgG1 kappa class [47]. Phase 1 studies have shown that lacnotuzumab was well tolerated in healthy volunteers [48]. In 2014, the European Medicines Agency granted orphan designation (EU/3/14/1350) to lacnotuzumab for the treatment of L- or D-TGCT [49]. Lacnotuzumab is currently being evaluated for many other cancers, such as esophageal, gastric, and triple-negative breast cancer, and melanoma [50]. A randomized, double-blind, placebo-controlled phase II study (NCT01643850) was performed to
assess the safety, tolerability, and effect of MCS110 on the tumor size in patients with PVNS, giant cell tumor of the tendon sheath, and L- or D-TGCT. A total of 36 patients were enrolled in the study with seven patients each in the placebo group, low dose (3 mg/kg), and medium dose (5 mg/kg) groups, while 17 patients were included in the high dose (10 mg/kg) group. After a single dose, the tumor size was reduced by 7.7% in the placebo group, 7.4% in the low dose group (\(p = 0.915\)), 25% in the medium dose group (\(p = 0.117\)), and 33% in the high dose group (\(p = 0.01\)). At the end of the treatment, after multiple doses, the tumor size was reduced by 30% in the low dose group (\(n = 7\)), 56% in the medium dose group (\(n = 7\)), and 55% in the high dose group (\(n = 15\)). The drug was overall safe; 11 patients showed serious adverse events more in the high dose group. No mortality was reported in the trial [51].

3.3. Cabiralizumab

Cabiralizumab (FPA008) (Five Prime Therapeutics, Inc.) is a monoclonal antibody that inhibits the binding of CSF1 and IL-34 by attaching itself to the CSF1R. This leads to the decreased activation and survival of TAM and monocytes. In 2015, a phase 1/2 (NCT02471716) study was conducted to evaluate the safety, tolerability, and clinical activity of cabiralizumab in patients with D-TGCT. In the phase 1 study, 38 patients were administered 1 (\(n = 3\)), 2 (\(n = 3\)), and 4 (\(n = 32\)) mg/kg of intravenous doses every two weeks following a 3+3 dose escalation design. With 4 mg/kg, no dose-limiting toxicities (DLT) were observed. Serious adverse events and adverse effects leading to treatment discontinuation were observed in 4 and 11 patients, respectively. Preliminary results confirmed that 5 of the 11 evaluable patients receiving the 4 mg/kg dose showed a PR. No treatment responses were observed in the cohorts administered 1 mg/kg and 2 mg/kg. The final results of this study are pending [52].

3.4. Vimseltinib

Vimseltinib (DCC-3014) (Deciphera Pharmaceuticals, Inc.), an oral agent, is a highly selective CSFR1 inhibitor, binding to CSF1 receptors with a specificity of more than 100-fold compared to other similar kinases such as FLT3, PDGF, and KIT. In preclinical studies, vimseltinib decreased the amount of infiltrating TAMs and CD16+ monocytes [53]. A phase I study (NCT3069469) evaluated the safety and tolerability in patients with malignant solid tumors and TGCT. Cohort 1 patients received 10 mg of the study drug daily, with variations in dosing, frequency, and addition of loading doses (LD) in subsequent investigational cohorts. A total of 62 patients were enrolled; 25 had TGCT. TGCT patients were enrolled in cohort 5 (\(n = 7\), 30 mg LD one a day (QD) x 5 days, then 30 mg BIW), cohort 8 (\(n = 12\), 30 mg LD QD x 3 days, then 10 mg QD), and cohort 9 (\(n = 6\), 20 mg LD QD x 3 days, followed by 5 mg QD). On October 5, 2020 (efficacy cutoff date), only 22 patients reached their first efficacy assessment. ORR was 41%, one patient showed a CR, and eight showed PRs. At the time of reporting safety cutoff (Sept 23, 2020), 22 patients were still receiving DCC-3014, 2 patients withdrew, and 1 patient from cohort 8 showed an adverse event leading to treatment discontinuation. Pharmacokinetic profiles were similar between cohorts 5 and 8, and lower steady-state exposure was observed in cohort 9. Recommended phase 2 dose was 30 mg administered twice weekly with no loading dose [54]. The study will be completed in June 2023. A phase 3 placebo controlled trial (NCT05059262) is currently underway [55].

3.5. Emactuzumab

Emactuzumab (RG-7155) is another monoclonal antibody directed against CSFR1 (Genentech/Roche/Celleron). A total of 63 patients with D-TGCT were included in the phase I study (NCT01494688). Emactuzumab was administered intravenously at the doses of 900 mg, 1000 mg, 1350 mg, and 2000 mg every 2–4 weeks. Patients received 4 to 5 cycles of the treatment drug. No DLTs were reported, and the optimal biological dose was 1000 mg administered every two weeks. Treatment response was compared using MRI, PET-CT scans, and tumor biopsies analyzed for CD68, CD163, and CSF1R expression. Evaluation of tumor response based on the RECIST criteria showed 2 patients with CR, 43 with PR, and 17 with SD. The data of one patient were lost during follow-up. This drug appears promising, with an ORR of 71% and durable response of 64% observed after two years. Emactuzumab was generally well tolerated, with pruritus, asthenia, and facial/orbital/eyelid edema being the most frequently reported adverse events [56]. Future studies are awaited.
Table 1. Summary of investigational agents in the treatment of tenosynovial giant cell tumor.

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Route</th>
<th>N</th>
<th>Population</th>
<th>Major trials</th>
<th>Important outcomes</th>
<th>Ongoing/future trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pexidartinib</td>
<td>PO</td>
<td>21</td>
<td>TGCT</td>
<td>Phase II: NCT04703322 [57]</td>
<td>NCT04703322: DLT, ORR, AUC</td>
<td>NCT04703322: Completion date June 30, 2024</td>
</tr>
<tr>
<td></td>
<td></td>
<td>35</td>
<td></td>
<td>Phase IV: NCT04526704 [58]</td>
<td>NCT04526704: Proportion of treatment-free participants at 12 months, proportion of</td>
<td>NCT04526704: Completion date April 27, 2023</td>
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<tr>
<td></td>
<td></td>
<td>35</td>
<td></td>
<td>Phase III: NCT04488822 [59]</td>
<td>treatment-free participants at 24 months</td>
<td>NCT04488822: Completion date March 30, 2022</td>
</tr>
<tr>
<td>AMB-05X</td>
<td>Intra-</td>
<td>12</td>
<td>TGCT</td>
<td>Phase II: NCT04731675 [34]</td>
<td>Treatment-emergent adverse events, Tumor response</td>
<td>Completion date: March 2022</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>PO</td>
<td>50</td>
<td>TGCT</td>
<td>Phase II: NCT 01261429 [45]</td>
<td>NCT 01261429: no CR, 6% PR, 90% stable disease.</td>
<td>NCT 01207492: Completion date December 2021</td>
</tr>
<tr>
<td>Lacnotuzumab (MCS110)</td>
<td>IV</td>
<td>36</td>
<td>TGCT</td>
<td>Phase II: NCT01643850 [51]</td>
<td>Tumor size changes: reduced by 7.7% in. The placebo, 7.4% in the low-dose, 25%</td>
<td>Future studies pending.</td>
</tr>
<tr>
<td>Cabiralizumab (FPA008)</td>
<td>IV</td>
<td>66</td>
<td>TGCT</td>
<td>Phase I/II: NCT02471716 [52]</td>
<td>Phase I: OBD was 4 mg/kg. Phase II: ORR: 25% for 4 mg/kg cabiralizumab administered</td>
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<td></td>
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<td>every two weeks in 28 day cycles for up to 12 doses and 33.3% for 4 mg/kg cabiralizumab</td>
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<td>on days 1 and 15 of cycle 1 and then every 4 weeks up to 12 months after day 1, cycle 1</td>
<td></td>
</tr>
<tr>
<td>Vimseltinib (DCC-3014)</td>
<td>PO</td>
<td>120</td>
<td>TGCT, malignant solid tumors</td>
<td>Phase I/II: NCT03069469 [54]</td>
<td>NCT03069469: OBD: 30 mg 2x weekly, no loading dose. Preliminary results for 5% CR, 36% PR</td>
<td>NCT03069469: Completion date June 2024.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>120</td>
<td>TGCT</td>
<td>Phase III: NCT05059262 [55]</td>
<td>NCT05059262: ORR</td>
<td>NCT05059262: Completion date July 2026</td>
</tr>
<tr>
<td>Emactuzumab (RG-7155)</td>
<td>IV</td>
<td>63</td>
<td>TGCT</td>
<td>Phase I: NCT 01494688 [56]</td>
<td>OBD: 1000 mg, 3% CR, 68% PR, 27% stable, data of 2% patients lost during follow up</td>
<td>Future studies pending.</td>
</tr>
</tbody>
</table>

Other investigational CSF1R inhibitors, such as PLX7486, AMG820, IMC-CS4, and PD-0360324 are outside the scope of this study.

See Table 1 for a summary of investigational agents.

4. Conclusion

Although TGCT is a benign tumor, the locally aggressive and destructive nature of this disease can cause significant morbidity and functional impairment with a high impact on QoL. A multidisciplinary approach comprising surgical oncology or orthopedic oncology, medical oncology, radiation oncology, physical therapy, and occupational therapy is necessary at the period of diagnosis to avoid treatment delay, evaluation for subsequent therapy, and initiation of ancillary care. Surgery is the current standard of treatment. In recurrent disease, salvage resection is still employed when feasible. The use of radiation therapy, radiosynoviorthesis, and chemotherapy as adjunct therapies has declined due to long-term side effects. In the past, systemic treatments had little to no role in the management of TGCT. However, with an enhanced understanding of the biology and genetic aberrations associated with TGCT, the landscape of systemic therapy is rapidly evolving. Pexidartinib (PLX3397) is the first CSF1R inhibitor to undergo phase III clinical trials and has now been granted approval in the United States. The ENLIVEN trial showed promising clinical activity, with tumor shrinkage, functional improvement, and symptomatic relief across the cohort. Its use is limited by hepatotoxicity observed in most patients, requiring periodic monitoring of liver function tests and enrollment in the REMS program. Preliminary results of targeted CSF1R therapies and IA therapies are promising and would undoubtedly change the landscape of TGCT management.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contributions

AC, VK, and PD were involved in manuscript writing and critical suggestions. VS supervised and edited the final manuscript and provided expert opinion. All authors have read and agreed to the published version of the manuscript.

Declaration of Competing Interest

All authors have nothing to disclose.

References

[15] de Visser E, Veth RP, Pruszczynski M, Wobbes T, Van de Putte LB. Diffuse and localized pigmented villonodular...


Abbreviations:

- COL6A3: collagen type VI alpha-3;
- CSF-1: colony-stimulating factor 1;
- CSF1R: colony-stimulating factor 1 receptors;
- CR: complete response;
- DLT: dose-limiting toxicities;
- DTGCT: diffuse tenosynovial giant cell tumor;
- FLT3: FMS-like tyrosine kinase 3;
- LTGCT: localized tenosynovial giant cell tumor;
- MRI: magnetic resonance imaging;
- OBD: optimal biological dose;
- ORR: objective response rate;
- QD: once a day;
- PR: partial response;
- PDGFR: platelet-derived growth factor receptor;
- PVNS: pigmented villonodular synovitis;
- TGCT: Tenosynovial giant cell tumor.