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Pexidartinib upfront in a case of tenosynovial giant cell tumor: proof of concept for a treatment paradigm shift

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PURPOSE

- Surgery is the primary treatment for patients with tenosynovial giant cell tumor (TGCT); however, surgical resection is associated with high rates of disease recurrence, particularly for patients with diffuse TGCT
- Pexidartinib, a colony-stimulating factor 1 (CSF-1) receptor inhibitor, is approved by the US Food and Drug Administration (FDA) for the treatment of adult patients with symptomatic TGCT associated with severe morbidity or functional limitations and not amenable to improvement with surgery
- Here, we report the case of a patient with TGCT who achieved a complete response after 2 years of pexidartinib treatment, including reduced pain, restored mobility, and no side effects to treatment

CONCLUSIONS

- This case report detailing the upfront use of pexidartinib highlights the importance of multidisciplinary care and an individualized treatment approach based on the patient's tumor location and type, symptoms, functional impact, extent of response to treatments, and needs specific to young adults, including reproductive health and timing
- This case is unique because it provides support for pexidartinib use as upfront therapy for TGCT instead of surgery in select cases

INTRODUCTION

- TGCT is a rare, locally aggressive tumor of the joints, bursa, and tendon sheath that can cause considerable pain and substantial morbidity and is driven by overexpression of CSF-1[1-3]
- Although surgery is the primary treatment for patients with TGCT, surgical resection is associated with high rates of recurrence, particularly for patients with diffuse TGCT[4]
- Pexidartinib is an orally administered, small-molecule tyrosine kinase inhibitor with selective activity against the CSF-1 receptor[2,3]
- Pexidartinib was approved by the US FDA in 2019[5] and by the South Korean and Taiwanese authorities in 2021 and 2022,[6,7] respectively, for the treatment of adult patients with symptomatic TGCT associated with severe morbidity or functional limitations and not amenable to improvement with surgery (or other treatment [eg, local radiotherapy] in Taiwan)
  - Approvals were based on results from the phase 3 ENLIVEN study (ClinicalTrials.gov Identifier: NCT02371369)[3,5]
- Pexidartinib is only available in the United States through a Risk Evaluation and Mitigation Strategy (REMS) Program, TURALIO® REMS (tREMS), due to the risk of serious and potentially fatal idiosyncratic hepatotoxicity[5]

CASE STUDY

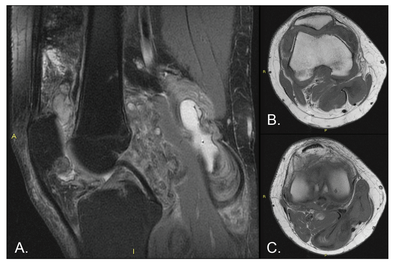
Patient History

- A 32-year-old man with a history of hypertension presented in 2014 with pain and swelling in his right knee
- A biopsy and magnetic resonance imaging (MRI) were conducted and revealed intra-articular diffuse TGCT
- After a discussion with an orthopedic surgeon at a different center, the patient did not undergo surgery at this time due to limited symptoms. Instead, a wait-and-see approach was used from the 2014 biopsy until the 2016 biopsy
- In 2016, the patient underwent arthroscopic biopsy with partial removal of tumor tissue and injection of intra-articular corticosteroids; this treatment was not intended to be curative
- Two years later, in 2018, the patient was treated with methotrexate, hydroxychloroquine, and etanercept for 3 months; these treatments were suggested by a rheumatologist

Treatment Plan

- The patient presented to the clinic in October 2019, and MRI scans showed a large tumor and substantial swelling around the knee (**Figure 1**)
  - At this time, the patient was generally in good health, had a numeric rating scale (NRS) pain score of 5, and was using nonsteroidal anti-inflammatory drugs as needed to manage pain
  - The patient had functional limitations and a range of motion of 10° to 100°
- Due to the extent of the disease, the patient's case was discussed with a sarcoma Multidisciplinary Tumor Board (MDTB) to determine a treatment approach
  - The patient had no prior surgery, except for arthroscopic biopsy of the knee, and had significant disease
  - The consensus of the MDTB was that surgery was expected to cause significant morbidity for this patient, with the intraoperative risk of neurovascular damage and possible postsurgical joint stiffness, and the patient was unlikely to obtain complete relief from the disease
- Given the patient's symptomatic disease and the tumor not being amenable to improvement with surgery, treatment with pexidartinib was considered

Figure 1. Sagittal (A) and axial (B-C) MRI scans of the patient's knee show a large tumor and significant swelling prior to treatment with pexidartinib



MRI, magnetic resonance imaging.
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Pexidartinib Treatment

- Due to the extent of disease, young age, and otherwise good health, treatment with pexidartinib was started through a compassionate use program (**Table 1**)
- The patient achieved a complete response after 2 years of pexidartinib treatment (September 2021)
  - The patient reported an NRS pain score of 1 to 2, with decreased pain frequency and intensity and a complete recovery of range of motion in the affected knee
  - No side effects related to pexidartinib treatment were reported
- After the profound response to pexidartinib, additional treatments were considered, including surgery, continuation of pexidartinib, and suspension of pexidartinib with possible rechallenge if symptoms returned
  - The MDTB recommended continued treatment with pexidartinib at a dose of 200 mg/day, and MRI scans were repeated every 3 months

Table 1. Pexidartinib Dosing Timeline

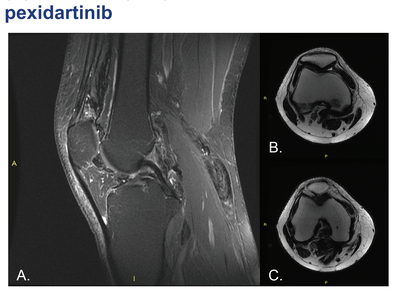
Timeline	Outcome	Pexidartinib dose
Started pexidartinib treatment	–	800 mg/day (400 mg twice daily)
After 4 months	• CPK levels had increased • Pexidartinib dose was reduced to 400 mg/day	400 mg/day
After an additional 2 months	• CPK levels continued to increase • Pexidartinib dose was further reduced to 200 mg/day	200 mg/day
Pexidartinib treatment continued at a reduced dose	• The tREMS program was followed • Elevations in CPK levels were discussed with the drug manufacturer (Daiichi Sankyo, Inc.) • Because there was no increase in the patient's bilirubin or creatinine levels, pexidartinib treatment continued at the reduced dose	200 mg/day

CPK, creatine phosphokinase; tREMS, TURALIO® Risk Evaluation and Mitigation Strategy.

Treatment Interruption

- Treatment was stopped in March 2022 for future family planning
  - After interrupting pexidartinib therapy, the patient's wife had a successful pregnancy and delivery
- In June 2022, minimal clinical progression was observed, with an NRS pain score of 0 and a decreased range of motion; these findings were validated by MRI scans showing progression of TGCT (**Figure 2**)
  - Three months after interrupting pexidartinib therapy, the patient showed a slow but constant clinical deterioration, with a decreased range of motion of the affected knee and an apparent increase in widespread TGCT nodules

Figure 2. Sagittal (A) and axial (B-C) MRI scans of the patient's knee at the end of treatment with pexidartinib



MRI, magnetic resonance imaging.
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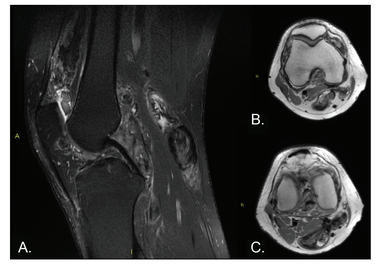
- In January 2023, the patient's pain had increased to an NRS pain score of 3; he had limitations in daily activities (eg, climbing steps of a staircase without pain, walking for long distances without stopping) and generally showed a worsening quality of life (**Figure 3**)
- At this point, because the pexidartinib compassionate use program was closed, the MDTB's recommendation was to resume systemic treatment with an investigational CSF-1 receptor inhibitor, which is currently ongoing within a clinical trial at the time of this report

Figure 3. Sagittal (A) and axial (B-C) MRI scans of the patient's knee 1 year after the end of treatment with pexidartinib



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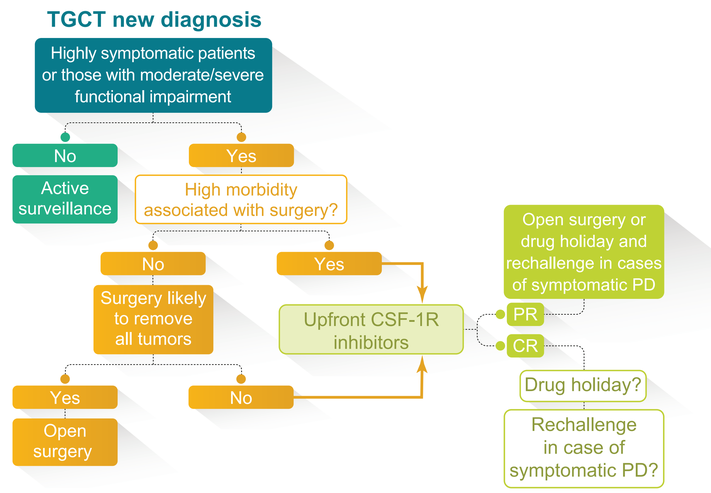
TGCT Treatment Paradigm

- Given the dramatic response in this patient with severe TGCT not amenable to surgery, future studies are warranted to investigate the benefits of CSF-1 receptor inhibitors (such as pexidartinib):
  - In reducing TGCT burden of disease prior to surgery OR
  - As the sole treatment option to reduce tumor size, reduce symptoms, and improve function of the involved joint or joints (upfront therapy), followed by treatment dose reduction or delays (maintenance treatment) or treatment interruption (drug holidays) and rechallenge (**Figure 4**)

Figure 4. Treatment paradigm for the use of neoadjuvant/upfront pexidartinib in patients with TGCT



CR, complete response; CSF-1R, colony-stimulating factor 1 receptor; PD, progressive disease; PR, partial response; TGCT, tenosynovial giant cell tumor.
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PRESENTING AUTHOR DISCLOSURES

Emanuela Palmerini has served on advisory boards for Daiichi Sankyo, Inc., Deciphera, EUSA Pharma, and SynOx Therapeutics.

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