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CSF1 receptor inhibition of tenosynovial giant cell tumor using novel disease-specific MRI measures of tumor burden

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Aim: Monitoring treatment of tenosynovial giant cell tumor (TGCT) is complicated by the irregular shape and asymmetrical growth of the tumor. We compared responses to pexidartinib by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 with those by tumor volume score (TVS) and modified RECIST (m-RECIST). **Materials & methods:** MRIs acquired every two cycles were assessed centrally using RECIST 1.1, m-RECIST and TVS and tissue damage score (TDS). **Results:** Thirty-one evaluable TGCT patients were treated with pexidartinib. From baseline to last visit, 94% of patients (29/31) showed a decrease in tumor size (median change: -60% [RECIST], -66% [m-RECIST], -79% [TVS]). All methods showed 100% disease control rate. For TDS, improvements were seen in bone erosion (32%), bone marrow edema (58%) and knee effusion (46%). **Conclusion:** TVS and m-RECIST offer potentially superior alternatives to conventional RECIST for monitoring disease progression and treatment response in TGCT. TDS adds important information about joint damage associated with TGCT.

Tenosynovial giant cell tumor (TGCT) is a rare, locally aggressive neoplastic disease arising in synovial joints and tendon sheaths [1,2], characterized by abnormal synovial growth forming a discrete mass (localized TGCT) [3] or diffuse thickening of synovial lining (diffuse TGCT) [1]. Surgical resection is the treatment of choice for localized TGCT [4], whereas total synovectomy, joint replacement or amputation may be needed in diffuse TGCT [5]. These surgical treatment strategies are not optimal and carry a high risk of recurrence [6].

Pathophysiology of TGCT is driven by elevated CSF1 expression and translocations, resulting in the recruitment of several CSF1 receptor (CSF1R)-expressing cell types leading to the development of CSF1R-targeted therapies. Systemic therapies, particularly tyrosine kinase inhibitors (TKIs) targeting CSF1/CSF1 receptor (CSF1R) signaling pathways, have shown promising results as novel treatment options in TGCT patients [7–16]. However, objectively evaluating the benefit of these agents has been a technical challenge. MRI can visualize TGCT better than computed tomography or other imaging modalities can, but precisely delineating tumor margins – particularly

in diffuse TGCT – is complicated by the irregular shape and asymmetrical growth of these tumors, poor image contrast between the tumors and surrounding structures in certain anatomic locations, and variable enhancement by intravenous gadolinium-based contrast agents [14,17]. These challenges limit accurate linear measurements and the applicability of Response Evaluation Criteria in Solid Tumors (RECIST) [14].

Automated quantification of tumor volume correlates more closely with patient outcomes in numerous malignancies [18–21], but since tumor margins of diffuse TGCT are difficult to delineate in certain locations, automated segmentation of MR images for quantifying volume based on edge detection is unreliable. Visual scoring based on semiquantitative ordinal scales has been successful in assessing changes in synovial thickening with MRIs in clinical trials of arthritis [22–25]. We developed a semiquantitative, joint-specific and tendon sheath-specific tumor volume score (TVS) for TGCT, modeled after established methods used in arthritis [14].

We previously reported phase I results of pexidartinib in patients with TGCT [14]. Here, we compared centrally read conventional RECIST 1.1 to novel TVS and a modification of RECIST based on measurements along the short axis of tumors (m-RECIST). Tissue damage scoring (TDS), for assessing local structural damage in TGCT, is also presented as a potential tool for evaluating disease severity and treatment effects.

Materials & methods

Study design

An open-label, single-agent study enrolled patients who had a histologically confirmed diagnosis of inoperable progressive or relapsing TGCT or a potentially resectable tumor requiring highly morbid surgery and who demonstrated progressive disease within 12 months. They were assessed for safety and efficacy of pexidartinib (NCT01004861) [14].

MRI

Multiplanar MRIs of the involved joint (knee, ankle, foot, hip, forearm, elbow or wrist) acquired every two cycles (8 weeks) were available from 36 participating patients (31 evaluable [baseline and ≥1 postbaseline MRI]). Four patients were excluded due to metal artifacts from joint replacement hardware, and one patient was excluded due to myositis surrounding the tumor in the forearm obscuring the tumor margins. Images were assessed centrally for tumor size and associated damage to local joint tissues by two expert independent musculoskeletal radiologists who specialize in reading for clinical trials using RECIST and developed the m-RECIST, TVS and TDS methods used here. To maximize sensitivity to change, images were displayed side-by-side in random order with acquisition dates masked. No nontarget lesions or new lesions were observed; thus, no end points included nominal data. Accordingly, the two radiologists' values were averaged; discrepancies were not adjudicated.

Linear measurements (RECIST 1.1 & m-RECIST)

Longest- and short-axis linear dimensions of up to two tumors or tumor regions per joint or tendon sheath were measured using electronic calipers. Short-axis measurements, analogous to the m-RECIST method used in pleural mesothelioma [26], were made approximately perpendicular to the long-axis of the tumor or tumor region as well as a reproducible adjacent anatomical landmark, such as the femoral cortex or a tendon, when such landmarks were available. Measurements were made where the tumor appeared largest and most reliably measurable with respect to margin delineation and follow-up assessment. Only tumors completely covered by scans were measured. The longest dimension and short-axis dimension measurements were each summed (sum of longest diameter [SLD]; sum of short-axis dimension [SSD], respectively).

Based on change in the SLD and SSD, RECIST 1.1 outcomes were calculated: complete response (CR; no viable tumor or residual scar ≥5-mm thick evident), partial response (PR; ≥30% decrease relative to baseline), progressive disease (PD; ≥20% and ≥5 mm increase relative to the shortest length during the study) or stable disease (SD; no prior criteria met) [17]. All classifications were verified on at least two consecutive visits.

Tumor volume score

TVS is a novel method developed specifically for TGCT and has been previously described [14]. It is an adaptation of scales used in the Whole-Organ MRI Scoring (WORMS) [25], Outcome Measures in Rheumatology (OMERACT), Rheumatoid Arthritis MRI Scoring (RAMRIS) [24], Psoriatic Arthritis MRI Scoring [22] and Hand Osteoarthritis MRI Scoring [23] methods to assess synovial thickening in clinical trials of arthritis. TVS expresses tumor volume as a percentage (10% increments) of the estimated volume of the maximally distended normal synovial cavity of
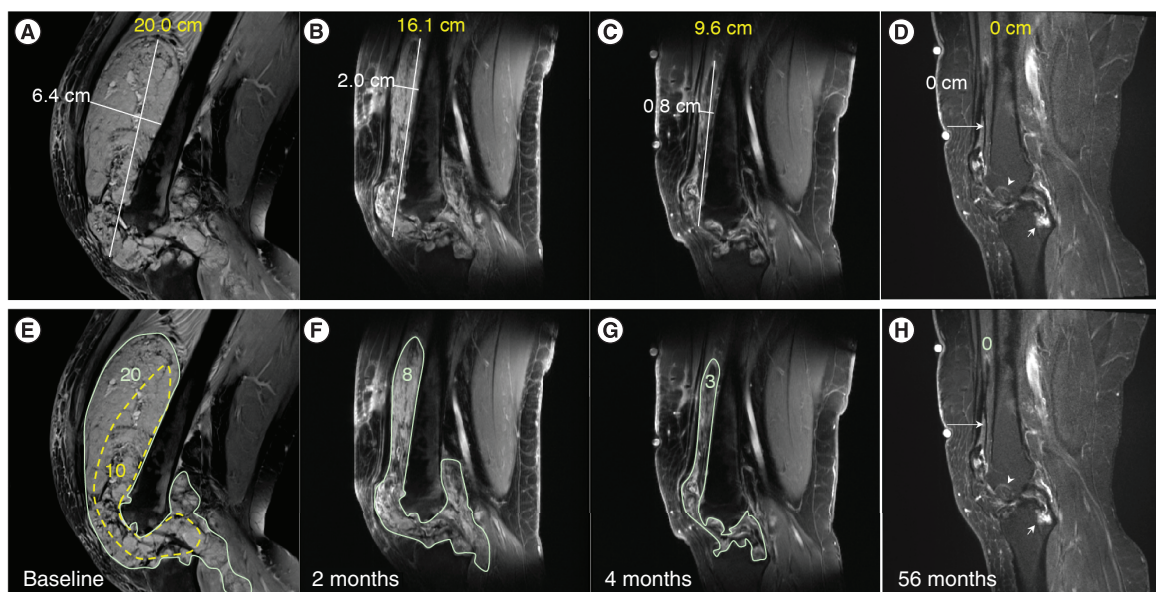
Figure 1. Tumor response measured by Response Evaluation Criteria in Solid Tumors, modified-Response Evaluation Criteria in Solid Tumorsand tumor volume score following treatment with pexidartinib. Mid-sagittal MRI shows a large tumor in the synovial cavity of the knee at baseline and after 2 and 4 months of treatment. The tumor is irregularly shaped and extends vertically in front of the femur, horizontally through the femorotibial joint space and posteriorly down the leg. **(A)** The longest measurable linear dimension is 20.0 cm at baseline. **(B)** After 2 months of treatment, this measure decreased by 19% to 16.1 cm, corresponding to stable disease by RECIST. By 4 months **(C)**, it had decreased by 52% to 9.6 cm, corresponding to PR, and, **(D)** from 24 months until the last visit at 56 months, only a thin, hemosiderin-containing scar (long arrow) in the suprapatellar recess remained without any significant local mass effect or other imaging evidence of a viable tumor, corresponding to CR.
The short-axis dimension (modified-RECIST) decreased much more: from 6.4 cm at screening **(A)** to 2.0 cm (-69%) at 2 months **(B)** PR, 0.8 cm (-87%) at 4 months **(C)**, PR and 0.0 cm (-100%) from 24 to 56 months **(D)**, CR.
Tumor volume score, which scores tumor volume (solid outline) in increments of 10% of the estimated maximum volume of the involved synovial cavity (dashed outline), also showed greater responsiveness than did RECIST, decreasing from a score of 20 at baseline **(E)** to 8 (-60%) at 2 months **(F)** PR, 3 (-85%) at 4 months **(G)** PR and 0 (-100%) from 24 to 56 months **(H)** CR.
Tissue damage score comprises multiple ordinal scales for bone erosion, cartilage loss, subchondral bone marrow edema/infiltration, joint effusion, meniscal and ligamentous integrity, and periarticular bursae and cysts. The extensive bone erosion and cartilage loss visible at baseline in this example did not progress during the 56 months of treatment, and the erosions, which originally contained intermediate-signal tumor, filled in with low-signal fat (arrowhead) or high-signal fluid (short arrow) **(D & H)**.
CR: Complete response; PR: Partial response; RECIST: Response Evaluation Criteria in Solid Tumors.
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the involved joint or segment of tendon sheath (Figure 1). A tumor equal to the volume of a maximally distended synovial cavity or tendon sheath would be scored 10. Thus, a tumor 70% of that volume would be scored 7, one twice the volume would be scored 20, etc. There is no theoretical maximum to the score.

Predetermined response criteria were CR (no viable tumor or residual scar of significant thickness), PR (≥50% decrease in volume score relative to baseline), PD (≥30% increase in volume relative to the lowest score during the study – baseline or other visit) or SD (no prior criteria met). The rationale for these criteria was as follows [17]. A 30% decrease in the longest diameter (PR based on RECIST) of a spheroidal tumor corresponds to a 66% decrease in volume, and a 20% increase in the longest diameter (PD by RECIST) corresponds to a 73% increase in volume, assuming symmetrical tumor change. If the tumor changes asymmetrically, along the short axes, which is the most common pattern observed with TGCT, identical linear changes would correspond to -49% and +44% changes, respectively, in volume [27]. Thus, the TVS response criterion of -50% would classify PR more sensitively than RECIST would for symmetrically changing tumors, but approximately the same as RECIST would for tumors that changed asymmetrically, along the short axes, as typically observed with TGCT. The TVS criterion for PD (+30%), on the other hand, would be more sensitive for tumor progression than RECIST would be, regardless of
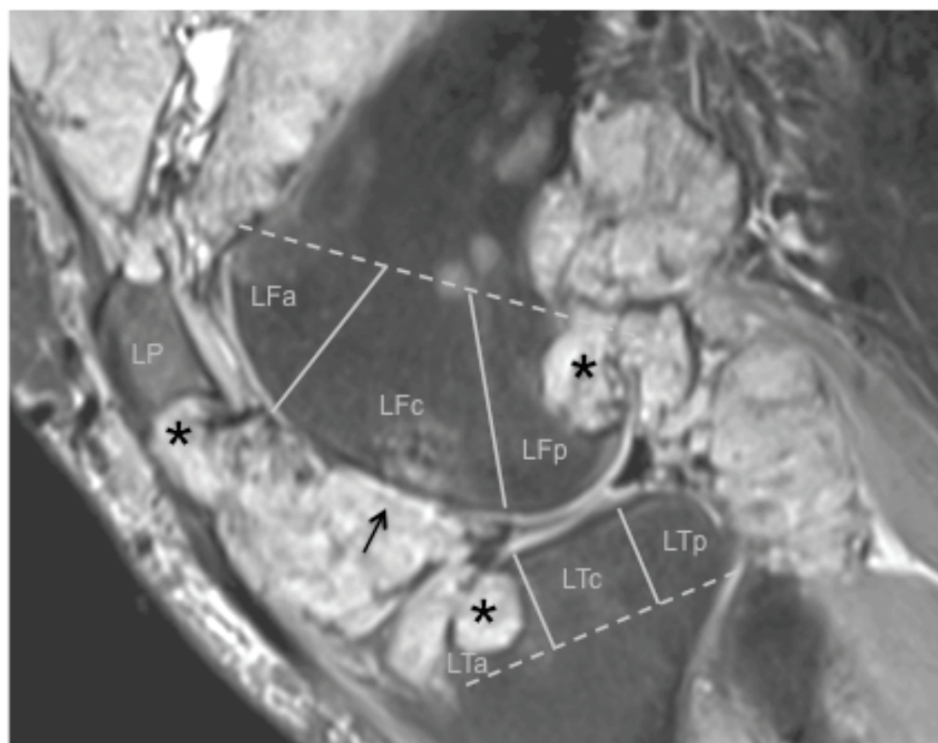
Figure 2.   Bone erosion and cartilage loss. Sagittal MRI of the knee shows extensive tumor-eroded cartilage (arrow) and bone (*) in the lateral femur, tibia and patella. Subdivisions of the lateral femoral condyle and tibial plateau by the tissue damage score method are shown.
LFa: Lateral femur anterior; LFc: Lateral femur central; LFp: Lateral femur posterior; LTa: Lateral tibia anterior; LTc: Lateral tibia central; LTp: Lateral tibia posterior; LP: Lateral patella.

how the tumor changed (symmetrically or asymmetrically). Classifications were verified on at least two consecutive visits.

Tissue damage scoring

A multifeature scoring method was developed to assess local tissue damage by TGCT with respect to bone erosion, articular cartilage loss, bone marrow edema/infiltration (BME), synovial effusion, meniscal damage, ligamentous damage and periarticular bursitis and cyst formation. Bone erosion scoring was based on the OMERACT–RAMRIS erosion scale, originally developed for assessing rheumatoid arthritis of hands and wrists [24]. The scale ranged from 0 to 10, with each integer increment representing 10% of articular bone eroded, and was applied to each of the 14 regions in the knee specified in WORMS [25], a multifeature MRI scoring method originally developed for osteoarthritis in knees (Figure 2), or to each articular bone in the hip, ankle/foot, elbow or wrist. Articular bone was defined as bone within 1 cm of the articular cortex. Cartilage loss and BME were scored from 0 to 6 and 0 to 3, respectively, in each WORMS region in the knee and each articular surface in the hip, ankle/foot, elbow or wrist, based on the scales used in WORMS. TGCT in the ankle with bone erosions and extensive BME is shown in Figure 3. Integrity of menisci, cruciate ligaments and collateral ligaments, synovial effusion, and presence and severity of periarticular cysts and bursae were scored in the knee based on corresponding WORMS scales [25]. Destruction of local bones and joints in the ankle in TGCT is illustrated in Figure 4A–D. Semiquantitative scales used in TDS are summarized in the online Supplementary Appendix in Supplementary Table 1 (bone erosion), Supplementary Table 2 (cartilage loss), Supplementary Table 3 (BME) and Supplementary Table 4 (meniscus damage, knee effusion, popliteal cysts and bursitis).

Statistical analysis

The statistics were descriptive and calculated based on the percentages of response rates for each method assessing tumor response and TDS.
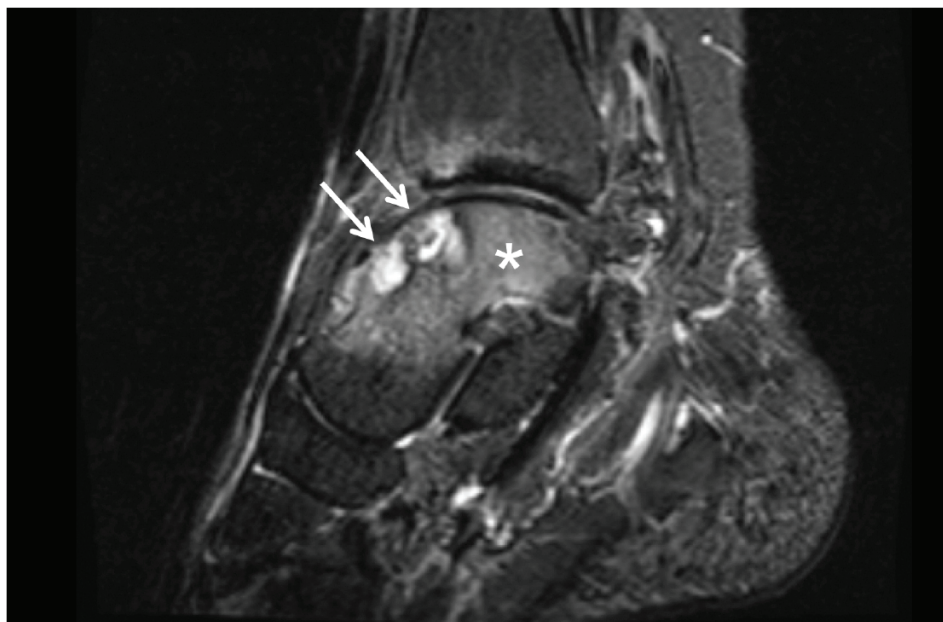
Figure 3. Bone marrow edema/infiltration. Sagittal MRI of the ankle shows two bone erosions (arrows) and extensive high-signal intensity BME (*) in the talus.
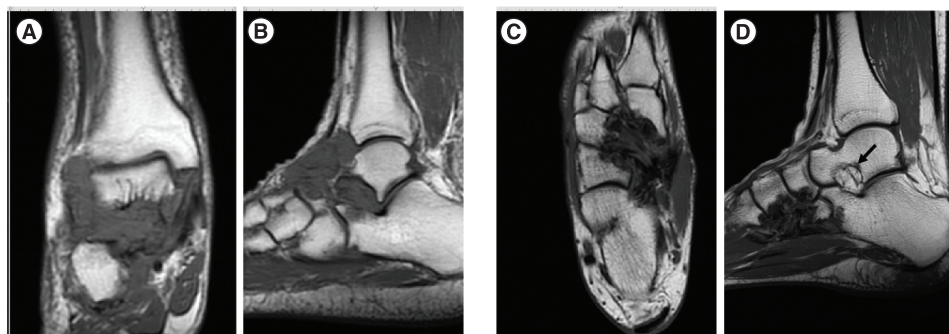BME: Bone marrow edema/infiltration.

Figure 4. Destruction of local bones and joints in the ankle by tenosynovial giant cell tumor. (A) Coronal and **(B)** sagittal MRIs of the ankle show tenosynovial giant cell tumor originating in the sinus tarsi and extending anteriorly into the soft tissues. Although the portion of the tumor in the sinus tarsi is just slightly larger than 3 cm in diameter, it has eroded the surrounding bones and effectively destroyed the joint. **(C)** Axial and **(D)** sagittal MRIs of the foot and ankle of a different patient show tenosynovial giant cell tumor of the tibialis posterior tendon eroding bone at the insertions of the tendon on the bones of the foot. Note the size of the normal sinus tarsi **(D, arrow)** for comparison with **(B)**.

Results

Of 31 evaluable patients, 16 had disease in the knee (52%). Baseline demographics are shown (Table 1). Response to pexidartinib by assessing median change in tumor size at the 2-month visit and the last available visit for each patient is summarized (Table 2). Most patients (29/31, 94%) showed a decrease in SLD (60%) and SSD (66%). TVS showed the greatest decrease in tumor size (-79%; Table 2).

The percentage of confirmed best response (CR, PR, SD, PD) in patients using the RECIST, m-RECIST and TVS methods is shown (Table 2). RECIST, m-RECIST and TVS had objective response rates (ORR = CR + PR) of 65, 81 and 71%, respectively. All methods showed 100% disease control rate (DCR = CR + PR + SD; Table 2).

The number of subjects with TVS ≥5 was 20 (65%) at baseline but only nine (29%) at the last visit. Of the 20 subjects with TVS ≥5 at baseline, TVS decreased to ≤5 in 11 (55%) by the last visit, and none of the 11 who had TVS ≤5 at baseline increased to >5. The number of subjects with TVS ≥3 was 24 (77%) at baseline and 13

Table 1. Patient demographics.

Characteristic	PLX108-01, TGCT cohort, (1000 mg per day) n = 31
Median age, years (range)	41 (22–72)
Sex, n (%)	
– Male	13 (42)
– Female	18 (58)
Race, n (%)	
– White	25 (81)
– Asian	3 (10)
– Black	3 (10)
Disease location, n (%)	
– Knee	16 (52)
– Ankle	7 (23)‡
– Hip	5 (16)§
– Other†	3 (10)
Prior surgeries for TGCT, n (%)	
– 0	8 (21)
– 1	3 (13)
– 2	8 (26)
– ≥3	12 (41)
Prior systemic therapy,¶ n (%)	
– 0	28 (90)
– ≥1	3 (10)
Prior radiation therapy, n (%)	
– 0	29 (94)
– 1	2 (6)
– ≥2	0

†Included wrist, foot, shoulder, spine, finger and elbow.
‡Included foot/ankle.
§Included hip/thigh.
¶Included imatinib or nilotinib (n = 3) or sirolimus (n = 1). One patient received both imatinib and sirolimus.
TGCT: Tenosynovial giant cell tumor.

Table 2. Response to treatment.

End point	Median change, % (range)		Response, % (subjects [n])			
	Month 2	Last visit	CR	PR	SD	PD
RECIST	-35 (0, -78)	-60 (4, -100)	16 (5)	48 (15)	35 (11)	0 (0)
m-RECIST	-45 (-1, -79)	-66 (20, -100)	13 (4)	68 (21)	19 (6)	0 (0)
TVS	-50 (0, -75)	-79 (0, -100)	13 (4)	58 (18)	29 (9)	0 (0)

CR: Complete response; m-RECIST: Modified RECIST; PD: Progressive disease; PR: Partial response; RECIST: Response Evaluation Criteria in Solid Tumors; SD: Stable disease; TVS: Tumor volume score.

(42%) at the last visit. Of the 24 subjects with TVS ≥3 at baseline, TVS decreased to ≤3 by the last visit in 13 (54%), and none of the 13 subjects with TVS ≤3 at baseline increased to >3.

Regarding joint damage, metal artifacts associated with prior surgery prevented reliable assessment of BME in two patients. Twenty-two of 29 patients (76%) assessable for bone erosion or cartilage loss showed erosion of articular bone at baseline; scores ranged from 0.0 to 43.0 (mean, 8.0; median, 5.0). Two patients showed progression of bone erosion despite a tumor response to treatment (PR by all the methods). No patients without erosions at baseline developed erosions later. The erosion score improved in 7/22 patients (32%) who had erosions at baseline.

Severity of bone erosion in knees correlated with tumor size at baseline, based on TVS (Pearson correlation coefficient [p = 0.67], SSD [p = 0.70] and SLD [p = 0.63]). Correlation in other locations was poor, possibly because extra-articular TGCT involving tendons was more common in those locations.

Cartilage loss was present at baseline in 18/29 evaluable patients (62%). Average scores ranged from 0.0 to 60.25 (mean, 9.2; median, 2.3), improved in three patients, and progressed in five patients. No patients without cartilage loss at baseline developed cartilage loss later. Cartilage loss score in the knee correlated strongly with erosion score (p = 0.82) and tumor size based on TVS (p = 0.56) and SSD (p = 0.48) but weakly with tumor size based on SLD (p = 0.35).

Nineteen of 29 evaluable patients (66%) had BME noted by at least one reader. Averaged scores ranged from 0 to 18 (mean, 2.6; median, 1.0). Severity of BME correlated with volume of the tumor at screening in the knee based on TVS (p = 0.63) and SSD (p = 0.45), but it correlated poorly based on SLD (p = 0.24). No patients without BME at baseline developed it later. Eleven of 19 patients (58%) with BME improved; three (17%) worsened.

Thirteen (81%) of 16 patients with tumors in the knee had knee effusion at baseline (mean, 1.2; median, 1.0; range, 0.0–3.0). Effusion decreased in 6/13 (46%) patients; it did not increase or newly develop in any. Five of 16 knees (31%) evaluable had meniscal disease at baseline; one worsened; one improved. Nine knees (56%) had popliteal cysts at baseline. Averaged scores of 5 (56%) improved over the study; one worsened.

Discussion

All three methods of measuring tumor size demonstrated marked improvement in TGCT in 94% of patients treated with pexidartinib. The two novel measures – SSD (m-RECIST) and TVS – registered greater median decreases in tumor size than did SLD (conventional RECIST), and m-RECIST and TVS classified more patients as CR or PR than did RECIST.

Because of irregular shape, asymmetrical growth and poorly defined margins of diffuse TGCT, conventional RECIST does not provide an accurate measure of treatment response in TGCT [17]. In the knee, for example, TGCT often assumes a crescentic, S-shaped or 'catcher's mitt' form as it wraps around the front and sides of the femur and extends through the tibiofemoral joint from the suprapatellar recess anteriorly to the popliteal recess posteriorly. The longest linear dimension of the tumor, therefore, often cannot be measured for RECIST without crossing nontumor structures, such as the femoral bone. The m-RECIST method, analogous to the approach used in mesothelioma [26], obviates the need to include nontumor tissue, and thus offers greater accuracy, while also concentrating on the dimension (short-axis) along which TGCT tumors change most. This method accordingly classified a greater proportion of patients as responders (81%) than did conventional RECIST (65%).

Both RECIST and m-RECIST sampled only a small portion of any tumor unidimensionally, and were subject to variability when the tumor's shape was distorted by changes in joint flexion or extension, cystic areas within the tumor or degree of distension of the synovial cavity by effusion. Alternatively, TVS, a semiquantitative scoring method that estimates tumor volume directly, was able to incorporate all regions of the tumor, including those hidden from linear measurement behind normal anatomy, and could exclude cystic and nontumoral elements. Furthermore, whereas linear measurements were expressed in cm regardless of location, TVS expressed tumor size relative to the size of the joint or tendon involved and, therefore, related more closely to potential structural and functional effects of the tumor in that location. For example, a 3-cm tumor in the capacious synovial cavity of a knee may not cause any damage, disability or even discomfort, but in the sinus tarsi of the foot, a tumor of that size could be extremely destructive and disabling. RECIST and m-RECIST would consider tumor burden to be the same in both cases. By TVS, however, the 3-cm tumor may have a score of 1 in the knee but 10 in the foot. TVS may thus relate more closely to the potential clinical impact of a tumor than would absolute tumor volume.

Response criteria for TVS were inspired by, but slightly different from, those of RECIST and, as described in Materials & methods section, would be expected to classify PR similarly and PD more sensitively than RECIST under the most commonly seen pattern of change in TGCT. Despite this, TVS classified more patients as responders (ORR: 71%) than did conventional RECIST (ORR: 65%). Thus, TVS and m-RECIST each offered greater responsiveness than did conventional RECIST. Pexidartinib has been shown to be effective with high response rates utilizing RECIST (primary end point), TVS (secondary end point) and m-RECIST (exploratory analysis) scoring methods in patients with TGCT [13]. Follow-up studies showed increases in response rates via the RECIST and TVS methods in TGCT patients continuing pexidartinib treatment [28,29]. To put this into context with the present analysis, while RECIST has been the primary method for assessing tumor response in TGCT, TVS and m-RECIST can be potential alternatives to RECIST in measuring efficacy of pexidartinib in this disease.

Because TGCT rarely if ever metastasizes, local mass effect and tissue damage are important therapeutic priorities. The emphasis of RECIST, however, is more on tumor growth than on tumor size, as reflected by the criterion for PD, which looks at change in tumor size relative to the nadir rather than relative to baseline. While this may be appropriate for assessing cancers in which metastatic potential is the principal concern, it is less aligned with the therapeutic objectives in TGCT. A more relevant goal in TGCT would be to reduce tumor size relative to that of the involved joint or tendon sufficiently to eliminate local mass effect and prevent tissue damage. What the specific threshold for TVS value should be to accomplish this was not examined in this study and is yet to be determined, but a tumor that is, for example, four-times the volume of a knee joint (TVS = 40) at baseline and decreases by 50%

at follow-up would still be twice the volume of that joint (TVS = 20) and thus probably still interfere with normal joint function and continue to damage joint structure. The tumor may have to shrink to less than 30% of the volume of that joint (TVS ≤3), an absolute decrease of 93% of the original tumor volume in this example, to stop causing significant symptoms and damage. Had the tumor started at 100% of the volume of the knee (TVS = 10), it would need to shrink only 70% to reach a TVS of 3. Again, whether or not 3 is the optimal target threshold has not been determined. In this study, however, 77% of tumors had TVS ≥3 at baseline, and 54% of those shrank to TVS ≤3 by the last visit.

Assessing local tissue damage should be an important imaging goal for monitoring disease progression and treatment response in patients with TGCT. We, therefore, adapted MRI scoring methods used to assess structural joint integrity in degenerative and inflammatory arthritis to TGCT. Based on TDS, the majority of patients included in this study had structural damage, including articular bone erosions (76%) and articular cartilage loss (62%) associated with their TGCT. Erosions usually were contiguous with and frequently filled by tumor. Severity of bone erosion and cartilage loss correlated with the size of the tumor at baseline and improved in 32 and 17% of patients, respectively, over the study. BME and effusion scores improved in 58 and 46%, respectively, of patients who had those findings at baseline. This illustrates the value of including local tissue damage assessment in TGCT and supports a therapeutic strategy of decreasing tumor size early in the disease to prevent or stabilize potentially irreversible joint damage.

There were numerous limitations of this study. The MRI protocol was not standardized and varied among centers, patients and visits based on local standards of care. This was not a major problem, however, because of the redundancy of information across different pulse sequences in the MRI protocols used. Occasionally, portions of a tumor extended beyond the field of view and, thus, had to be excluded from the analysis. Typically, localizer images using larger fields of view showed that these excluded portions were minor and behaved similarly to the remainder of the tumor included within the field of view. Standardizing the imaging protocols and verifying complete tumor coverage on all serial visits are, thus, recommended for future studies. Metal artifacts in patients with prior joint replacement or other surgery obscured some areas of interest, particularly for assessments of BME. Therefore, prior surgery should be considered when selecting patients for studies, and methods for handling nonevaluable data should be prospectively defined.

Conclusion

In conclusion, the TVS method, based on estimated tumor volume relative to the size of the involved joint cavity or tendon sheath, and the m-RECIST method, based on linear short-axis measurements rather than the longest diameters, showed greater responsiveness to change than did conventional RECIST in assessing the effectiveness of pexidartinib in TGCT. These novel methods offer potentially superior alternatives to RECIST for monitoring disease progression and treatment response in clinical trials of TGCT. Furthermore, TDS adds important information concerning the severity of local tissue damage associated with TGCT and its response to pexidartinib treatment, which is not addressed by RECIST. Together, these MRI measures provide a more discriminative and comprehensive assessment of TGCT treatment. Further work is needed to correlate clinical outcomes in TGCT with changes in tumor size and tissue damage.

Future perspective

Due to the irregular shape, asymmetrical growth and poorly defined margins of diffuse TGCT tumors, objectively evaluating the benefit of CSF1R-targeted therapies has been a technical challenge. Conventional RECIST does not provide an accurate measure of treatment response in TGCT and is not optimally aligned with the therapeutic objectives for this disease.

Novel methods (TVS, m-RECIST and TDS) offer potentially superior alternatives to RECIST for monitoring disease progression and treatment response in clinical trials of TGCT. Further work is needed to associate clinical outcomes in TGCT with changes in tumor size and tissue damage.

Summary points

- Tenosynovial giant cell tumor (TGCT) is characterized by uncontrolled synovial growth in joints and tendon sheaths, associated with local swelling and tissue damage.
- Pathophysiology of TGCT is driven by elevated CSF1 expression and translocations, resulting in the recruitment of several CSF1R-expressing cell types.
- Systemic therapies, targeting CSF1R signaling pathways, have shown promising results as novel treatment options in TGCT patients.
- Monitoring treatment in TGCT using Response Evaluation Criteria in Solid Tumors (RECIST) is complicated by irregular shape and asymmetrical growth of the tumor and does not assess tissue damage.
- These challenges limit accurate linear measurements and the applicability of RECIST.
- The tumor volume score method, based on estimated tumor volume relative to the size of the involved joint cavity or tendon sheath, and the m-RECIST method, based on linear short-axis measurements rather than the longest diameters, showed greater responsiveness to change than did conventional RECIST in assessing the effectiveness of pexidartinib in TGCT.
- These novel methods offer the potential of enhanced alternatives to RECIST for monitoring disease progression and treatment response in future studies of TGCT.
- In addition, tissue damage score adds important information concerning the severity of local tissue damage associated with TGCT and its response to pexidartinib treatment, which are not addressed by RECIST.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fon-2021-1437

Ethical conduct of research

This was a retrospective analysis based off the original phase I study [Tap *et al. N. Engl. J. Med.* 373(5), 428–437 (2015)], so no institutional review board approval was necessary.

Open access

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Papers of special note have been highlighted as: ● of interest; ●● of considerable interest

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●   **Case Report measuring tumor response by conventional Response Evaluation Criteria in Solid Tumors (RECIST) in tenosynovial giant cell tumor (TGCT) patient treated with peixdartinib.**

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