REVIEW ARTICLE

Tenosynovial giant cell tumor: Better molecular understanding revolutionizes treatment outcome

Emad Shash
Medical Oncology Department, National Cancer Institute, Cairo University, Cairo, Egypt

Abstract: Tenosynovial giant cell tumors (TGCTs) are rare tumors, which are primarily treated via surgery with a low likelihood of metastasis. Although wide excision is an excellent choice for local control, tumors located within or close to major joints, along with the benign nature of the disease, make such resection impractical. An increase in local recurrences and the need for multiple surgical procedures promoted the interest in targeted-therapies for this disease. TGCTs contain a mixture of giant cells, mononuclear cells and inflammatory cells, with clonal cytogenetic abnormalities through rearrangements involving 1p11–13. Colony stimulating factor (CSF1) gene encodes for the ligand of CSF1 receptor (CSF1R). The CSF1 gene is located at the chromosome 1p13 breakpoint and is found to be translocated in 63%–77% of patients with TGCTs. Selective CSF1R inhibitors yield high response rate and disease control, demonstrating the integration of a new drug development technology that could revolutionize treatment outcomes.

Keywords: Tenosynovial giant cell tumor; colony stimulating factor receptor

Citation: Shash E. Tenosynovial giant cell tumor: Better molecular understanding revolutionizes treatment outcome. Adv Mod Oncol Res 2016; 2(1): 2–4; http://dx.doi.org/10.18282/amor.v2.i1.48.

Introduction

Tenosynovial giant cell tumors (TGCTs) are rare tumors that are classified according to their locations and growth patterns. Localized giant cell tumors of the tendon sheath are classified as localized types, while the diffuse types include diffuse giant cell tumors of the tendon sheath. Tumors involving joint space are known as intra-articular pigmented villonodular synovitis (PVNS). The differences are possibly due to the anatomic location influencing the pattern of growth rather than differences in pathogenesis. In fact, insights into the molecular biology of these tumors indicated the presence of a clonal population of cells that harbor a characteristic recurrent to chromosomal translocation, which reflects a common mechanism of pathogenesis. This understanding has enabled researchers to design and use specific targeted-therapies to inhibit the tumors.

Similar to most neoplastic processes with a low likelihood of metastasis, the tumors are primarily treated via surgery. Although wide excision is an excellent choice for local control, tumor locations within or close to major joints, along with the benign nature of the disease, make it impractical. Moreover, local recurrences are also high. Patients with PVNS or diffuse type TGCTs commonly have multiple recurrences and require several surgical procedures during their lifetime. This locally recurrent pattern and requirement for multiple surgical procedures advocated the use of targeted-therapies for this disease.

Molecular biology of TGCTs/PVNS

TGCTs and PVNS both contain a mixture of giant cells, mononuclear cells and inflammatory cells. Previous studies have demonstrated clonal cytogenetic abnormalities with rearrangements involving 1p11–13 in these tumors. A study conducted by West et al. proved that the colony stimulating factor (CSF1) gene encodes for the ligand of the CSF1 receptor (CSF1R). The CSF1...
gene is located at the chromosome 1p13 breakpoint and is translocated in 63%–77% of patients with TGCTs/PVNS\(^5\). Mononuclear and multinucleated cells that make up the bulk of TGCTs and PVNS express high levels of CSF1R. However, only a minority of tumor cells (2%–6%) carry the translocation and express CSF1. A majority of the tumor bulk is made up of CSF1R-bearing cells that are reactive and polyclonal in nature, recruited as a result of CSF1 production by neoplastic cells. This phenomenon is described as a tumorm-landscaping effect\(^5,6\). RNA-expression profiles of these tumors indicated that gene expression is associated with macrophage function and biology. It also suggested that a majority of the cells are likely to be reactive macrophages recruited by the CSF1 expression of neoplastic cells. Double staining with CD163 (macrophage marker) and CSF1 showed that the CSF1 expressing population and reactive macrophages are distinct. Synovial lining cells and CSF1 expressing neoplastic cells are known to express CD68, suggesting a link between neoplastic cells and synovial lining cells\(^5,6\). In summary, PVNS and TGCTs are neoplastic processes arising from synovial lining cells in which tumor cells overexpress CSF1, and this results in the recruitment of macrophages bearing CSF1R.

**Transferring molecular biology knowledge into clinical utility**

The work of West et al. on molecular pathogenesis of TGCTs/PVNS paved way to the introduction of targeted-agents that inhibit CSF1R for the treatment of this disease\(^5,6\). Small molecule inhibitors such as imatinib and sunitinib have the ability to inhibit CSF1R activation at therapeutic concentrations. Blay et al. initially reported a case of PVNS at the right elbow, treated with 400 mg/day of imatinib; resulting in partial response (PR) at 2 months and a complete response (CR) at 5 months\(^6,10\). Interestingly, when treatment was interrupted in the 7th month, disease recurrence was noted in the 9th month. Reintroduction of imatinib resulted in a second CR. Clearly, imatinib targeted an essential pathogenic process in this tumor, resulting in growth inhibition and locally invasive behavior.

Following this report, several groups began using this strategy to treat their patients with imatinib. Ravi et al. treated six diffuse TGCTs/PVNS patients with imatinib at 400 mg daily and reported clinical and radiological responses\(^6,11\). At the time of initial analysis, the median duration of therapy was 7 months, with over 80% of patients reporting an improvement from pain and swelling. Around 67% of patients showed a decrease in contrast enhancement and thickening at the joint surface. Among the six patients, four patients were evaluated for treatment responses via integrated positron emission tomography and computed tomography (PET/CT). All patients showed a decrease in 2\(^18\)F-fluoro-2-deoxy- D-glucose (FDG) avidity (mean decrease in standardized uptake value was 55% in the range of 37%–75%)\(^6,11\).

A report by Cassier et al. compiled experience from nine institutions, which included 16 patients treated with imatinib\(^6,12\). Treatment responses were measured using Response Evaluation Criteria In Solid Tumors (RECIST) and 50% of the patients indicated a stable disease (SD), PR in 13% and CR in 6%\(^,12\).

**New generation of molecules inhibiting CSF1R**

Tap et al. modified the molecule of an inhibitor (PLX647) of CSF1R to produce a new compound, PLX3397, which is a more potent inhibitor that binds to and locks the receptor in an inactive conformation\(^\cite{13,14}\). At a dose of 1000 mg per day, 23 patients exhibited a significant response rate (52%), and even more impressively, a median duration of disease control exceeding 8 months. All tumors from these patients had high levels of CSF1 expression. However, it remains undetermined whether the presence of specific translocation between chromosomes 1 and 2, which is found in some but not all patients with this tumor, correlates with the positive response\(^\cite{13,15}\).

X-ray crystallographic studies of PLX3397 revealed sites of potential interest in promoting strong drug-protein interaction. Key substitutions made in the initial CSF1R inhibitor, PLX647, produced a compound that interacted with the juxtamembrane (JM) domain, effectively locking the enzyme into an inactive conformation. This is a relatively new strategy in drug design, made possible in part by detailed structural studies. PLX3397 inhibits a relatively small subgroup of kinases as compared to the multiple targets of imatinib. Its selectivity may be attributed to its unique interaction with the JM domain. Selectivity and increased potency for CSF1R may be an important factor in its superior clinical activity in patients with CSF1-dependent TGCTs\(^\cite{13,15}\).

The design of PLX3397 represented an advancement of current drug-development research. Instead of just looking for inhibitors of enzymatic activity, new tools such as X-ray crystallography allows researchers to examine drug interactions with three-dimensional forms of key proteins. Besides, X-ray crystallography can also predict which modifications of an inhibitor will enhance the potency for a specific protein conformation. Despite its potency, PLX3397 causes a spectrum of toxic effects.
(e.g., liver-enzyme elevations and severe fatigue) that necessitated dose reductions or drug holidays in one-third of patients\textsuperscript{[13,15]}. Clearly, CSF1R inhibition using selective CSF1R inhibitors warrants further study in prospective randomized clinical trials and could potentially assist the improved management of such disease.

**Conflict of interest**

The authors declare no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

**References**