A Personalized Medicine Approach to Treat MPTT, Case Report


Abstract

Objectives: Proliferating Trichilemmal Tumors (PTT) are rare skin neoplasms arising from the hair root sheath. Although benign, PTT can be recurrent and locally destructive, rarely undergoing malignant transformation into Malignant PTT (MPTT), with potential for distant metastases. Current treatments for MPTT are largely anecdotal and poorly validated.

Methods: We report a patient who presented with multiple recurrences and distant metastases of MPTT. SNaPShot analysis utilizing multiplex PCR was performed on both mediastinal nodes and MPTT neck mass to detect cancer-related mutations. Cell culture and biochemical assays were performed to correlate with clinical response to targeted therapy.

Results: A PI3KCA activating mutation (H1047R) was found in a distant metastasis and MPTT neck tissue. Specific activating PI3K mutations have been found in many human epithelial tumors, including head and neck squamous cell carcinoma and lung cancer. The reported patient enrolled in a Phase IA trial using BYL719, a selective PI3Kα Tyrosine Kinase inhibitor. Primary cells derived from the patient tumor were very sensitive to multiple agents targeting the PI3K pathway (e.g., PI3K, PI3K/mTOR, and AKT).

Conclusion: There are no suggested treatment guidelines for patients with rare tumors like MPTT. They receive a variety of chemotherapeutic agents based on limited clinical data. We suggest that rare tumors be screened for common oncogenic mutations. This will allow clinicians to personalize medical treatment based on identified dysregulated molecular pathways.

Introduction

Proliferating Trichilemmal Tumors (PTT) are benign rare skin neoplasms arising from the external hair root sheath.

- Mean age = 62.4yo; 79.5% Female
- 85.4% from scalp; mean diameter = 3.3cm

Transformation into Malignant Proliferating Trichilemmal Tumors (MPTT) is exceedingly rare, but associated with significant morbidity and mortality.

- 3.7% Local Recurrence; 1.2% Regional LN Metastasis
- Poorly validated treatment with no trials, largely anecdotal
- Empiric chemoradiation for squamous cell carcinoma (SCC)

Case Report - Overview

Pt. 3400: A 62 yo Female with six MPTT recurrences

2008 – 2x Wide Local Excisions (WLE) at an outside hospital (OSH) - OSH: poorly differentiated SCC

2009 – 3x WLE, modified radical neck dissections (MRND), local muscle flap

2011 – Dermal lymphatic involvement, with perineural invasion - Extracranial extension and venous invasion

2010 Chemoradiation with Carboplatin, Taxol → Complete Response

2011 Metastatic to lungs - SNaPShot: +H1047R mutation of PI3KCA

2011 Chemotherapy with Cisplatin, Taxotere → Complete Response

2011 Recurrence after 3 months

2011 Enrolled in a Phase 1A PI3K inhibitor drug trial (oral BYL719)

2012 Partial response to inhibitor: RECIST = Decreased 39%

SNaPShot Analysis

- Fast, high-throughput mutational profiling method using formalin-fixed, paraffin-embedded tissue (FFPE)
- Multiplex reactions using fluorescently-labeled primer extension products followed by capillary electrophoresis
- High-sensitivity - detects mutant DNA as low as 5% of total DNA (Sanger sequencing requires 25% mutant DNA)
- Lung NSCLC panel investigates 38 point mutations within 8 genes. (AKT1, BRAF, EGFR, KRAS, MEK1, NRAS, PIK3CA, and PTEN)
- Panels also exist for melanoma, colon cancer, and breast cancer; each detects mutations common to those conditions.

Pathology

- On a continuum that starts with Pilar Cysts → PTT → MPTT
- Palisading basaloid cells at periphery becoming squamous centrally
- Focal areas of squamous eddies within solid components, and calcification within stroma
- Difficult to distinguish from SCC, especially with poorly-differentiated PTT/MPTT
- Degree of cellularity and atypia does not necessarily correlate with severity of disease in both PTT and MPTT

PI3K Mutations

- Phosphatidylinositol 3-kinases (PI3Ks) regulate signaling pathways involved in neoplasia
  - PI3K/PI3K/mTOR/PTEN signaling pathway is implicated in many human epithelial tumors, including Head and Neck Squamous Cell Carcinoma (HNSCC) and lung cancer
  - Cellular proliferation, survival, adhesion, and motility
  - PIK3CA encodes the p110α subunit and mutations found thus far are all activating mutations
    - Elevated lipid kinase activity → activation of downstream Akt pathway

Clinical Response to PI3K inhibitor

Phase 1A, open-label, dose escalation study of oral BYL719 (Novartis)

- Must have biopsy-proven PIK3CA mutation
- 3 treatment cycles of 28 days each and can continue drug after 3rd cycle if good response and no serious side effects

SNaPShot: +H1047R mutation of PI3KCA

Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease

Laboratory Studies

Cell Culture

- Currently Passage 10, Day 102 (KGM-5F)
- Slow-growing cells with abundant intercellular bridging, suggesting defects in mitosis, likely due to BRCA2 deficiency.
- Growth in 2% Hypoxia, in serum-free Keratinocyte Growth Media

Cell Viability Assay

- GDC-0941 is a p110α selective PIK3CA inhibitor (72hr incubation)
- Olaparib is a PARP inhibitor (72hr incubation)
- Both drugs significantly inhibited cellular proliferation in Pt. 3400 (MPTT) compared to Pt. 649 (HNSCC, control)

GDC-0941 (PI3K) Survival Assay

Olaparib (PARP) Survival Assay

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