CLINICAL VIGNETTE

Targeted Therapy for Advanced Basal Cell Cancer

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A 93-year-old man with paroxysmal atrial fibrillation and recurent skin cancers presented to oncology for evaluation. Approximately 6 months prior to presentation he developed a basal cell cancer in the right axilla and, instead of attempting local resection, his dermatologist referred him for radiation therapy (RT). He completed RT with some shrinkage of the area but developed persistent pain and a recurrent mass both in the axilla and the right supraclavicular fossa confirmed to be basal cell cancer on biopsy. PET-CT showed intensely PET positive 1.7 cm right axillary mass and a 2.4 cm right supraclavicular and 3.2 cm right external iliac lymph node and 1 cm area in the right biceps without evidence of visceral or bone metastases. Chest MRI demonstrated both a 1.9 cm right axillary and 4.2 cm bilobed right supraclavicular mass. His main complaint on presentation was persistent right axillary pain.

Since he clearly had metastatic basal cell cancer he was started on vismodegib 10 mg orally daily. He initially tolerated vismodegib well with mild fatigue, nocturnal hand cramps, decreased appetite and diminished taste. By serial exams his right supraclavicular mass resolved and his right axillary mass diminished by 50 % and his pain completely resolved. Repeat PET-CT and chest MRI after 5 months of therapy showed resolution of the right biceps and right supraclavicular masses and decreased size and FDG avidity of the right axillary and right external iliac lymph nodes. However he had completely lost his sense of taste and had worsening anorexia with a 25 lb weight loss and progressive fatigue. After completing 6 months of vismodegib, we held therapy for 3 months with return of his taste, appetite and energy. He regained the lost weight but axillary pain increased and his right axillary mass increased from 1.5 to 2 cm by palpation. His right axillary mass was deemed unresectable by an oncologic surgeon due to prior RT and the challenge of successful skin grafting with any resection. We decided on an intermittent 3 month on and 3 month off schedule of vismodegib.

Discussion

Basal cell cancer is the most common skin malignancy and the most common type of cancer overall. Basal cell skin cancers are almost always treated by dermatologists with either surgery or other local ablative measures. RT is generally reserved for un-resectable lesions or patients who could not tolerate surgery. As in our patient, basal cell cancer can metastasize. Given the rarity, past treatment was empiric with chemotherapy generally platinum based regimens with some short responses, there was one report of a complete response reported.[1] However, recent molecular studies of basal cell cancer showed the importance of the hedgehog signaling pathway in basal cell cancer cell proliferation.[2] After identification of this potential critical driver, pharmaceutical industry developed hedgehog pathway inhibitors, including Vismodegib. This was shown to have substantial activity in both locally advanced and metastatic basal cell cancer.[3]

The hedgehog signaling pathway, first discovered in Drosophila experiments, is involved in cell differentiation during embryogenesis and in adult stem cells.[2] In humans there are 3 hedgehog homologs including Desert (DHH), Indian (IHH) and Sonic (SHH). SHH, which is the best studied and the relevant pathway in cancers, binds to a cell surface receptor patched homolog 1 (PTCH 1) which then relieves the inhibition by PTCH 1 on another cell surface receptor smoothened homolog (SMO) which induces changes in gene expression. The majority of basal cell cancers have either activating mutations in SMO (10%) rendering it constitutively active or loss of function mutations in PTCH 1 (90%) which prevent inhibition.[2,3]

Vismodegib inhibits SMO, wild type of mutated. In a large international open label study, vismodegib had a 68% overall response rate (RR) and 33% complete response rate (CR) in locally advanced and a 37% RR and 4% CR in metastatic basal cell cancer.[3] Primary resistance occurred in 21% of patients. Median progression free survival (PFS) was 24.5 months with locally advanced and 13.1 months with metastatic basal cell cancer.[3] As with other therapy, however, there are significant side effects with vismodegib including, in diminishing frequency, muscle spasms 64%, alopecia 62%, altered taste in 54%, weight loss in 33%, generalized weakness in 28%, decreased appetite in 25 %, complete loss of taste in 22% and diarrhea in 17%, for most patients the side effects were tolerable but in 22% were severe and often led to stopping treatment.[3] Our patient experienced progressive anorexia, loss of taste and fatigue which, after 6 months, led to a treatment interruption for 3 months with resolution of the side effects and regained weight and energy. Given the frequency of side effects significantly interfering with activities of daily living in patients on vismodegib, intermittent dosing of vismodegib was shown to be feasible and appeared to result in a similar PFS with apparently improved side effects.[4] Our patient was placed on a 3-month on/3-month off schedule with continued cancer control.

A second hedgehog pathway inhibitor, sonidegib, has been compared to vismodegib in a systematic study review and meta-

analysis of clinical trials and appears to have similar activity and side effects.[5] Interestingly the anti-fungal drug itraconazole, which also suppresses hedgehog pathway signaling, had clinical activity in basal cell cancer in patients resistant or intolerant to vismodegib.[6] This provides another treatment option. Vismodegib illustrates both the promise of targeted therapy for advanced malignancy when key molecular drivers are identified and the inevitable off target side effects due to the physiological role of the targeted pathway in normal cells.

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