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REVIEW ARTICLE – MELANOMA

The Landmark Series: Non-melanoma Skin Cancers

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ABSTRACT Surgery with or without radiation has always been the mainstay of treatment for patients with non-melanoma skin cancers, including basal cell carcinoma, squamous cell carcinoma, and Merkel cell carcinoma. Until recently, there were no effective systemic therapies for patients with advanced disease. This review will focus on the landmark clinical trials that led to Food and Drug Administration (FDA) approval of Vismodegib for advanced basal cell carcinoma (ERIVANCE BCC) and pembrolizumab for advanced Merkel cell carcinoma (KEYNOTE-017). These trials have not only changed the landscape for patients with metastatic disease but also notably for patients with locally advanced disease that is either unresectable or resectable with high morbidity. Additional mention is made for the clinical trial that led to FDA approval of cemiplimab for advanced cutaneous squamous cell carcinoma (EMPOWER-CSCC-1), which is already changing practice patterns, but for which longer-term data are still needed.

The most common nonmelanoma skin cancers (NMSCs) are basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). Both are associated with ultraviolet (UV) radiation, and the mainstay of therapy is surgical (Mohs micrographic surgery or standard excision with 4- to 6-mm clinical margins). Merkel cell carcinoma (MCC) is a much rarer and more aggressive NMSC with a 5-year overall survival of 40%.[1] Surgical management with or without radiation for additional local control is sufficient to treat the majority of BCC, SCC, and early-stage MCC cases. The major landmark trials for NMSCs have occurred in the realm of systemic therapies for locally advanced or metastatic disease. This article will describe and discuss the major clinical trials that define the current management of advanced BCC, SCC, and MCC. For the surgical oncologist, knowledge of these treatments will better inform patient discussions regarding treatment of locally advanced disease where surgery is feasible but highly morbid.

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VISMODEGIB IN ADVANCED BASAL CELL CARCINOMA (ERIVANCE BCC TRIAL)

Purpose and Rationale

Basal cell carcinoma occurs in approximately 2 million Americans annually and accounts for approximately 80% of NMSCs.[2] The mainstay of treatment is either Mohs micrographic surgery or standard excision with adjuvant radiation therapy (RT) in the setting of extensive perineural or large-nerve involvement or persistently positive margins despite multiple excisions.[3] In the vast majority of cases, surgery is curative; however, despite aggressive local therapies, these can recur, be destructive, and even metastasize. Before publication of this trial in 2012, there were no FDA-approved therapies for advanced BCC.

Activation of the hedgehog (Hh) pathway is an important factor in BCC development, both sporadic and inherited (Gorlin syndrome).[4] Aberrant pathway activation is most commonly due to loss of function of patched homologue 1 (PTCH1), an inhibitor of smoothened homologue (SMO). Failure of this negative feedback mechanism leads to basal cell proliferation and development of BCCs.[5,6] Vismodegib (GDC-0449) is a first-in-class small molecule inhibitor of SMO. A phase I study of 33 patients with advanced BCC showed a 58% response rate and a median duration of response of 12.8 months.[7] This led to the phase 2 trial: ERIVANCE BCC.[8] The purpose of this trial was to evaluate fully the efficacy and safety of Vismodegib in patients with locally advanced or metastatic BCC.

Study Design and Endpoints

This phase 2 study was sponsored by Genentech. The study population included patients 18 years or older with an ECOG performance status of 2 or less. Locally advanced disease was defined as having at least one lesion that was 10 mm or more in longest diameter and was considered, in the opinion of a Mohs dermatologic, head and neck, or plastic surgeon, to be inoperable or inappropriate for surgery (recurrence after 2 or more surgical procedures with curative resection unlikely, or anticipated substantial morbidity or deformity). Metastatic disease required a tissue diagnosis and measurable disease (nodal metastases included) by RECIST guidelines. Per these guidelines, measurable disease must be accurately measured in at least one dimension (longest diameter) with a minimum size of 10 mm by CT scan or 20 mm by chest X-ray.[9] The two groups were analyzed separately. Patients who were pregnant, lactating, unable to swallow capsules, or had a life expectancy of less than 12 weeks or uncontrolled medical illness were excluded. Patients were treated with 150 mg of oral Vismodegib daily based on the pharmacokinetic properties determined in the phase 1 study.[10] There was no control group used due to a historical absence of spontaneous regression and a lack of approved systemic therapies.

The primary endpoint was an independently assessed objective response rate (ORR) based on photographs (locally advanced BCCs) or radiographic scans (metastatic or measurable locally advanced BCCs). Clinical response for locally advanced disease was defined as a decrease of 30% or more in the externally visible or radiographic dimension or complete resolution of ulceration (if present at baseline). Residual scarring was counted as visible tumor. Progression of locally advanced disease was defined as an increase of 20% or more in externally visible or radiographic dimensions, new ulceration, or a new lesion. Response and progression for metastatic patients were defined by RECIST criteria. Based on phase 1 results, the authors hypothesized that the ORR would be greater than 20% for locally advanced and greater than 10% for metastatic patients. The major secondary endpoint was duration of response.

Results: Primary and Secondary Endpoints

In total, 104 patients (71 locally advanced and 33 metastatic) were enrolled from 31 sites in the United States, Europe, and Australia. Both site investigators and an independent review committee evaluated patients. Only the latter are reported here, but concordance was 60% for locally advanced patients and 79% for metastatic patients, with site investigators generally reporting higher response rates.

The independent review committee reported an ORR of 43% for locally advanced patients and 30% for metastatic patients, which was greater than predicted. A complete response (defined as absence of residual BCC on biopsy) was seen in 13 (21%) locally advanced patients, and 10 of these had no progression during the study period. All responses in the metastatic group were partial responses. In the initial data set (9 months after accrual completion), both groups had a median duration of response of 7.6 months and median progression-free survival of 9.5 months. Long-term follow-up data (39 months after accrual completion) was reported in a separate study.[11] With a median follow-up of 39 months, there was a median duration of response of 14.8 months in metastatic patients and 26.2 months in locally advanced patients. Median overall survival was 33.4 months in the metastatic cohort and not reached in the locally advanced cohort.

Results: Safety

All patients had at least one adverse event (AE) during the study period. Serious AEs (grade 3 or 4) were reported in 26 (25%) patients. There were seven fatal events noted; however, the investigators note that these patients had clinically significant coexisting baseline conditions, and the deaths were considered by site investigators to be unrelated to the study drug. The most common AEs were muscle spasms (68%), alopecia (63%), dysgeusia (51%), and decrease in weight (46%). The most frequent serious AEs were decrease in weight (5%), muscle spasms (4%), and fatigue (4%). With longer follow-up, the incidence of AEs increased with longer exposure to the drug and 22 patients (21.2%) discontinued treatment due to adverse events.

Conclusions

Vismodegib is associated with tumor response in locally advanced/unresectable and metastatic BCC and is a new treatment option for these advanced BCC patients.

Commentary

Although rare, advanced BCC has always been a therapeutic challenge and Vismodegib represents the first FDA-approved (2012) systemic therapy for advanced BCC. Genentech sponsored this clinical trial, and five of the authors worked for Genentech. In this trial, response rates were higher than anticipated with follow-up reports demonstrating a median duration of response of 14.8 months for metastatic patients and 26.2 months for locally advanced patients. Overall, site investigators reported higher response rates with lower concordance rates in the locally advanced cohort. This may have been

due to independent reviewers only having photographs to review and being unable to examine the patients themselves. However, the independent reviewers also found significant tumor response in both groups, confirming the efficacy of the drug.

These data suggest that Vismodegib is a potentially beneficial option for patients who are inoperable or for whom surgery and/or radiation is highly morbid. However, all patients reported some AE and 21.2% discontinued treatment due to them. The subsequent SafeTy Events in VismodEgib (STEVIE) trial (n = 1215) demonstrated that 98% of patients had at least one AE with 23.8% having serious AEs. Exposure of greater than 12 months did not lead to increased incidence or severity of symptoms and the majority resolved after discontinuation of treatment.[12] For patients on chronic Vismodegib, even grade 1/2 AEs could cumulatively make the drug intolerable. Developing strategies to help patients cope with AEs and remain on treatment will be important when managing quality of life concerns or weighing the risks/benefits of Vismodegib versus further surgery/radiation for locally advanced disease.

More recently, the BOLT trial demonstrated the efficacy of sonidegib, another SMO inhibitor, in locally advanced and metastatic BCC and led to its FDA approval in 2015.[13] This reemphasizes the importance of the hedgehog signaling pathway in BCC. Data are limited on the use of cytotoxic chemotherapy; however, there are reports of responses to platinum-based chemotherapy, and this should be considered in advanced cases that are unresponsive to hedgehog pathway inhibition.[14]

PEMBROLIZUMAB IN ADVANCED MERKEL CELL CARCINOMA (KEYNOTE-017)

Purpose and Rationale

Merkel cell carcinoma is a rare, but aggressive, cutaneous malignancy for which cytotoxic chemotherapy only offers a progression-free survival of 3 months in patients with advanced MCC.[15] MCC has been associated with UV radiation and the Merkel-cell polyomavirus (MCPyV).[16] Additionally, MCC has often been considered an immunogenic cancer and immunosuppression has been associated with worse prognosis. The mutational burden is 100 times higher in UV-induced, MCPyV-negative MCCs compared with MCPyV-positive MCCs.[17,18] Because elevated mutational burden has been associated with tumor regression in response to anti-PD1 therapy in other cancer subtypes, a clinical trial for immunotherapy in advanced MCC was a logical step for a disease in need of effective systemic therapy.[19,20] The purpose of the KEYNOTE-017 trial was to assess the efficacy of pembrolizumab, a humanized monoclonal antibody that blocks PD-1, in patients with advanced MCC without prior systemic therapy, and to correlate outcomes with PD-L1 and MCPyV status.[21]

Study Design

This phase 2 multicenter study was sponsored by the National Cancer Institute (NCI) and Merck. The study population included patients 18 years and older with distant metastatic or recurrent locoregional MCC not amenable to definitive surgery or radiation therapy who had an ECOG performance status of 0 or 1 and normal organ and bone marrow function. Patients with prior systemic therapy for MCC, active autoimmune disease, a diagnosis of immunodeficiency or ongoing systemic immunosuppressive therapy, concurrent second cancer, or active central nervous system metastases were excluded. Pembrolizumab was administered intravenously at a dose of 2 mg/kg every 3 weeks. Treatment continued until complete response, progression of disease, dose-limiting toxic effects, or a maximum of 2 years of treatment. In the event of asymptomatic, nonrapid progression of disease, treatment was permitted to continue, and the patient was reevaluated 4 weeks later. Patients were assessed by CT scan of the chest, abdomen, and other target lesions at the time of screening, 12 weeks after starting therapy, and then at 9-week intervals for the first year and 12-week intervals for the second year. Scans were assessed at the institutional level with NCI central radiologic review for patients with a response. Time intervals were measured from the first dose of pembrolizumab. Tumor MCPyV status was determined by IHC expression of MCPyV large T-antigen oncoprotein in tumor specimens or presence of serum antibodies or circulating T-cells specific for MCPyV oncoproteins. PD-L1 expression was determined by IHC in pretreatment tumor specimens. The primary endpoint was objective response rate as measured by RECIST criteria. The secondary endpoints were progression-free survival (PFS), overall survival (OS), and duration of response.

Results: Primary and Secondary Endpoints

In the initial trial, a total of 26 patients with stage IIIB or IV MCC were enrolled over the course of 1 year and received at least one dose of pembrolizumab, with 25 patients having at least one tumor assessment. Nine (35%) were classified as MCPyV-negative tumors. At a median follow-up of 33 weeks (range 7–53), there was an ORR of 56% (4 complete responses and 10 partial responses). Based on these promising results, the cohort was expanded to 50 patients and the longer-term follow-up was reported

in 2019.[22] With a median follow-up of 14.9 months, the ORR for the expanded cohort was 56% (24% complete response and 32% partial response). Five patients (10%) had stable disease and 16 (32%) progressed on therapy. The 24-month PFS was 48.3% and 24-month overall survival was 68.7%. Median PFS was 16.8 months, and median OS was not reached. Tumor viral status did not significantly correlate with ORR, PFS, or OS; however, there was a trend toward improved PFS ($p = 0.1284$) and OS ($p = 0.0570$) in patients with > 1% PDL1 positivity in tumor cells.

Results: Safety

Treatment-related AEs occurred in 48 (96%) of the 50 patients, with 14 (28%) experiencing grade 3 or higher events. Seven patients (14%) ultimately discontinued therapy as a result of AEs. There was one treatment-related death due to worsening pericardial and pleural effusions in a patient with a history of atrial fibrillation. The most common AEs were fatigue and abnormal laboratory results, whereas the most common immune-related AEs were hypothyroidism (6%) and pneumonitis (6%).

Conclusion

Pembrolizumab was associated with an objective response rate of 56% in patients with advanced MCC, with responses observed in both MCPyV-positive and negative tumors.

Commentary

The results of this clinical trial led to FDA approval of pembrolizumab for recurrent locally advanced or metastatic MCC, a rare disease with a poor prognosis. This trial was sponsored by Merck and the NCI with four authors from Merck but editorial oversight from the NCI. In this single-arm trial, median PFS far exceeds that of cytotoxic chemotherapy (based on historic control data). Interestingly, despite the MCPyV-positive tumors having a lower mutational burden, response rates between virus-positive and virus-negative tumors were very similar. This may be secondary to the presence of viral antigens leading to sensitivity to checkpoint blockade. Further research will need to be done to help identify which patients are more likely to respond to therapy. Although this trial found a high ORR, there was still one treatment-related death and almost all patients had some AE. Immune-related AEs are a known issue with all immunotherapies, and a recent meta-analysis of immune-related adverse events in clinical trials with anti-PD-1 therapy demonstrated an overall incidence of 22% for all grades, 4% for high-grade, and 0.34% mortality (primarily due to pneumonitis).[23] Management of these immune-related AEs is improving and will be critical to be able to maintain patients on these therapies to have a durable response.

More recent clinical trials have demonstrated the safety and efficacy of avelumab (JAVELIN Merkel 200 trial[24,25]), an anti-PD-LI antibody, in metastatic MCC. Prior studies with various chemotherapy regimens have demonstrated a high response rate but short median duration of response and rates of toxic death ranging from 3 to 10%.[26] Together, this led to the NCCN recommendation that immune checkpoint blockade with pembrolizumab, avelumab, or nivolumab be preferred over cytotoxic chemotherapy for patients with disseminated disease.[27] However, chemotherapy remains a treatment option in patients who cannot tolerate immunotherapy.

CEMIPLIMAB IN ADVANCED CUTANEOUS SQUAMOUS CELL CARCINOMA (EMPOWER-CSCC-1 TRIAL)

Cutaneous squamous cell carcinoma is the second most common NMSC. Similar to BCC, the majority of SCC patients have localized disease treatable with surgical excision ± radiation. However, advanced locoregional or metastatic disease has a poor prognosis and there was previously no FDA-approved systemic therapy. The association of cutaneous SCCs with UV radiation and immunosuppression, along with the high mutational burden, suggested that these patients may be responsive to immunotherapy. Migden et al. recently published the results of the phase 1 and early phase 2 studies for PD-1 blockade with cemiplimab in advanced cutaneous SCC (EMPOWER-CSCC-1 trial).[28] Although the data are not as mature as the above-mentioned landmark trials, it has already started to change clinical practice and deserves mention so that surgical oncologists are aware of its potential use and stay abreast of any upcoming data. The phase 1 study was an open-label, multicenter study of cemiplimab, an anti-PD-1 human monoclonal antibody, in patients with advanced solid-tumor cancers that included both metastatic and locally advanced patients who were not surgical candidates (recurrence after 2 or more surgical procedures or curative resection unlikely or resulting in substantial complications or deformity). This phase 2 study was a nonrandomized, multicenter study of cemiplimab in advanced cutaneous SCC; however, only the data on the metastatic patients were ready for analysis at the time of publication.

In both studies, the patients received cemiplimab intravenously at a dose of 3 mg/kg every 2 weeks and were assessed for response every 8 weeks. The primary endpoint

was response rate. Responses were seen in 13 of 26 patients (50%) in the expansion cohort of the phase 1 study and in 28 of 59 patients (47%) in the metastatic cohort of the phase 2 study. Median follow-up of the phase 2 metastatic cohort was only 7.9 months; however 23 of the 28 responders continued to have a response at the time of data cutoff. The most common AEs were diarrhea, fatigue, nausea, constipation, and rash with 7% of patients discontinuing treatment due to AEs. These data led to FDA approval of cemiplimab for advanced cutaneous SCC in 2018—the first systemic therapy approved for this disease. Further data will be necessary to validate these initial results and determine long-term outcomes. Due to the rarity of this disease, it will be difficult to directly compare cemiplimab with platinum-based chemotherapy, which previously had been shown to have efficacy, albeit also in small cohorts.[29–31] Long-term results will help clinicians to determine what the best choice of systemic therapy will be for individual patients.

CONCLUSION

While the majority of early stage BCCs and SCCs can be treated by dermatologists and the metastatic NMSC patients will be managed primarily by the medical oncologists, treatment planning for locally advanced NMSCs needs to be led by the surgical oncologist. A strong understanding of the biology of these diseases and FDA-approved effective systemic therapies is essential to guiding multidisciplinary care and creating a treatment plan with the patient. This is particularly relevant when locoregional disease may be feasible to resect but highly morbid and of questionable long-term benefit. Use in the neoadjuvant setting has yet to be studied but will be an area that needs to be explored with involvement of the surgical oncology community. With effective systemic therapy, a door has been opened that could make surgery for locally advanced disease less morbid as well as make unresectable disease potentially resectable. Further studies in these areas will be of great interest to surgical oncologists.

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