Evaluating The Latest Trends and Research in Non-Melanoma Skin Cancer

BY GARY GOLDBERG, MD

Over the last several years, the status of non-melanoma skin cancer (NMSC) in dermatology, both from a research and a treatment standpoint, has shifted considerably. With increased knowledge and awareness regarding the pathology of NMSCs and associated conditions, as well as new therapies on the market, treatment options continue to emerge. Ahead I will examine the latest trends in research and therapeutic avenues for treating NMSCs.

**BASAL CELL CARCINOMA**

Arguably the most significant development the scope of basal cell carcinoma (BCC) in the last several years is the approval of vismodegib (Erivedge, Genentech), an agent that inhibits the hedgehog pathway in advanced BCCs. Since it has been on the market, vismodegib has taught us much about the role of the hedgehog pathway in BCCs. Hedgehog, a key regulator of cell growth and differentiation during development, controls epithelial and mesenchymal interactions in many tissues during embryogenesis. The hedgehog pathway is inactive in normal adult tissues. However, most basal-cell tumors have mutations in the hedgehog signaling pathway that inactivate PTCH1 (loss-of-function mutation) or, less commonly, constitutively activate SMO15 (gain-of-function mutation). These mutations cause constitutive hedgehog pathway signaling, which in BCCs can mediate unrestrained proliferation of basal cells of the skin. Therefore, blocking the hedgehog pathway represents a significant avenue in treating patients with BCC.

In a Phase I clinical trial, vismodegib demonstrated activity in patients with locally-advanced BCC (lBCC) and metastatic BCC (mBCC), with an overall response rate of 58 percent and a median duration of response measured at 12.8 months (as of January 2010) and ongoing. These promising observations prompted design of another trial called ERIVANCE BCC, a pivotal Phase II study that focused on patients with metastatic BCC (that had to be measurable by imaging) and locally advanced BCC. Patients were treated with vismodegib at 150mg daily until disease progression, intolerable toxicity, or withdrawal from study for other reasons. Responses in the metastatic cohort were measured by imaging, using Response Evaluation Criteria in Solid Tumors (RECIST) criteria, which allow researchers to determine if the cancer responds, stabilizes, or progresses. In the lBCC cohort, responses were measured using a novel composite endpoint that included measurable diameter and ulceration of visible tumor, as well as RECIST measures of the deeper tumor component when present. Researchers defined locally advanced BCCs as those that were “either inoperable or where surgery was inappropr...
ate, with the tumors being over 1cm in diameter and characterized by two or more recurrences after surgery, rendering curative resection unlikely and/or anticipated substantial morbidity and/or deformity from surgery.”

The primary endpoint of the study was objective response rate by independent review, with a hypothesis that overall response rate confidence intervals are significantly greater than 10 percent in patients with mBCC or greater than 20 percent in patients with laBCC. Secondary endpoints included objective response rate by investigator, progression-free survival, duration of response, and absence of residual BCC on biopsy in patients with laBCC.

Rate of objective response in metastatic BCC was 30 percent by independent review facility and 46 percent by investigator. Another 64 percent of patients had stable disease or progression. In laBCC, objective response rate was measured at 43 percent by independent review facility and 60 percent by investigator. Another 38.1 percent of patients had stable disease, while 12.7 percent had progression. Of note, the response rate observed by investigators in this study is identical to that observed by investigators in the Phase I study.

Clinical benefits have also shown to be durable in mBCC and laBCC. Patients on average experience a 9.5-month median progression-free survival and a clinical benefit rate of 76 percent in mBCC and 75 percent in laBCC. The most common adverse events are muscle spasms, alopecia, dysgeusia, weight decrease, and fatigue. In addition, four percent of patients experienced serious adverse events possibly related to vismodegib.

More recently, vismodegib has shown potential utility in the off-label treatment of patients with operable nodular BCCs. In a single-arm study to assess the ability of vismodegib to produce complete histological clearances in cases of operable nodular BCCs, 24 patients were treated for 12 weeks with oral vismodegib 150 mg qd, followed by an assessment for Mohs micrographic surgery. All but one patient showed clinical response (96 percent), while 42 percent had complete histological clearance by pathologic assessment (21 percent complete response; 17 percent partial response; four percent SD). Adverse events were mostly grade 1 or 2, similar to those described in previous studies.

Taken together, the current data on vismodegib have shown substantial clinical benefit for patients with advanced BCCs, with potential utility in other forms of BCC, as well.

**SQUAMOUS CELL CARCINOMA**

Squamous cell carcinoma (SCC) is the second most common form of skin cancer; many treatment options are available. Given that the incidence of SCC continues to increase, several trends are worth noting.

In a study of 615 SCC excisions over an 11-year period, researchers noted several prognostic risk factors, including presence of desmoplasia on light microscopy: defined as fine branches of tumor cells at the periphery and a surrounding stromal reaction; findings of perineural or perivascular invasion were always associated with desmoplasia; all SCC in which at least a third of the representative tumor specimen met these criteria were classified as desmoplastic SCC. Also of note, 26 patients (four percent) developed metastasis, 19 of which occurred within the first year after surgery, with another six having local recurrence. Importantly, the first metastasis always affected a regional lymph node.

A univariate analysis showed statistical significance for all factors tested, except location at the lip and poor differentiation. The best Cox regression model (forward selection) consisted of tumor thickness, immunosuppression, location at the ear, and tumor size. This model was compared with the current model based on tumor size and differentiation. The predictive accuracy (C-index) of the best model was considered to provide higher predictive accuracy than the current model. In the exact logistic regression only tumor thickness and location at the ear were statistically significant predictive factors.

SCCs greater than 2mm in thickness are associated with a significant risk of metastasis. Additionally, tumors greater than 6mm are associated with a high risk of metastasis and local recurrence. Moreover, desmoplastic growth is an independent risk factor for local recurrence.

Regarding staging classification, the 7th edition of the American Joint Committee on cancer staging for cutaneous SCC noted several changes from the last edition. For example, size threshold no longer links 5cm with tumor (T) 3 classification, citing little evidence to support it as an important threshold. It also notes that both level and thickness of invasion are significant prognostic factors.

Kaposi’s Sarcoma and Merkel Cell Carcinoma

The pathogenesis of Kaposi’s Sarcoma (KS) is related to HHV-8, which is present in more than 95 percent of KS lesions. The origin of neoplastic cells is under current debate. It is worth observing that CD31, CD34, and von Willebrand factor are traditional endothelial markers found in KS. In addition, vascular endothelia growth fac-
The incidence of Merkel Cell Carcinoma (MCC) has been increasing in recent years. This may be due to more accurate diagnostic techniques as well as an increase in the chronically immunosuppressed population.

Data from NCI’s Surveillance, Epidemiology and End Results (SEER) database from 1973-2006 found 3,870 cases of MCC diagnosed in that period.10 Among the most common sites for MCCs are face (26.9 percent), upper limb and shoulder (22 percent), lower limb and hip (14.9 percent), and trunk (10.6 percent). As for tumor thickness and risk, one study found that Caucasian men over the age of 70 years old with tumors over 2cm fare the worst in terms of survival.11 However, some discrepancy remains on the matter of tumor thickness and survival rates, as another study found no correlation between the two.12 Despite this, the current data demonstrate the importance of checking all areas of the body for MCC, no matter how uncommon it is.

MCCs and Viruses. Also of note in the realm of MCC is its association with a previously unknown polyomavirus called Merkel Cell polyomavirus (MCV). In one study, six of eight MCC cases, viral DNA was integrated within the tumor genome in a clonal pattern and tested positive for MCV.13 The polyomavirus is a small double-stranded DNA virus that comes in three types: avian, mammalian related to simian virus 40 (SV40). The SV40 subgroup contains all human polyomavirus (SV40). The SV40 subgroup contains all human polyomavirus (SV40). The SV40 subgroup contains all human polyomavirus (SV40). The SV40 subgroup contains all human polyomavirus (SV40). The SV40 subgroup contains all human polyomavirus (SV40). The SV40 subgroup contains all human polyomavirus (SV40).

The reason to look for a virus in MCC patients is the fact that MCC is more common in immunosuppressed patients. For example, the ratio of malignant melanoma (MM):MCC in the general population is 65:1, whereas the ratio of MM:MCC in post-transplant patients is 6:1.15 In a literature review, 14.5 percent of MCC patients received or were receiving immunosuppressive therapy and 49 percent of post-transplant MCC cases were in patients under 50 years old.16

CONCLUSION

As our knowledge of NMSCs becomes more nuanced, our ability to treat them more effectively will become greatly enhanced. Staying abreast of the latest trends in data regarding the incidence and pathogenesis is therefore essential for all physicians treating patients with these conditions.

Article based on Dr. Goldenberg’s presentations at the 2013 Summer Meeting of the American Academy of Dermatology in New York.

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