The Impact of Inoperable Advanced Basal Cell Carcinoma: the Economic, Physical, and Psychological Burden of the Disease

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ABSTRACT

The development of vismodegib and its recent approval by the United States Food and Drug Administration for use in patients with locally advanced or metastatic basal cell carcinoma (BCC) carries with it a renewed sense of optimism. Once BCC has progressed to an advanced, or so-called inoperable stage, there has been a paucity of effective therapies, making the new small molecule inhibitors targeting the hedgehog pathway particularly hopeful prospects. In order to better understand the utility of these new treatments, it is important to assess the existing economic, physical, and psychological burden of advanced BCC. This review aims to recognize the impact of inoperable and metastatic BCC, as well as to better characterize the various types of advanced BCC. The use of vismodegib as a prophylactic treatment in patients with basal cell nevus syndrome is also addressed, including possible adverse events, tumor resistance, and new onset malignancies.

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INTRODUCTION

While the overwhelming majority of basal cell carcinoma (BCC) is effectively managed with surgery, causing minimal distress to the patient, individuals whose BCC has metastasized or progressed to an inoperable state are severely affected by their disease.[1] The physical disfigurement from advanced lesions as well as concern about life expectancy affect both quality of life (QOL) and the psychological state of the patient.[2] In interviews with clinicians, Shingler et al found that the most common symptom of patients with advanced BCC was embarrassment from either the dressings or the lesions themselves. Metastatic lesions may weep or bleed, have the potential to become infected, and consequently can become malodorous.[2] As a result, patients with advanced BCC may isolate themselves from family, friends, and the workplace, despite the fact that they may be physically able to carry on with the normal activities of daily life. Anxiety and depression can also often accompany this social isolation.[2]

Because BCC metastasis is extremely rare, with a reported incidence of 0.0028% to 0.5%, it is difficult to quantify the economic, physical, and psychological impact of the disease.[3,4] There has been very little in the medical literature that attempts to investigate how and to what extent the QOL is affected in patients with advanced BCC, as case reports only offer qualitative information regarding the burden of the disease. In an attempt to capture social utility values associated with different levels of advanced BCC, Shingler et al employed a newer methodology known as the time trade-off (TTO) measurement.[2] A representative sample of the general public in the United Kingdom was asked to choose between living in a particular health state with advanced BCC for 10 years vs living in a state of full health for 10-x years.[2] The TTO method was used to calculate utility values based upon the responses to these scenarios.[2] The health states of advanced BCC used in the valuation exercise included the following: complete response (CR), post-surgical state, partial response (PR) with small growth, PR with large growth, stable disease (SD) with small growth, SD with multiple growths (at 2 cm), SD with large growth, progressed disease (PD) with small growth, and PD with large growth.[2] Small growth was defined as 2 cm and large growth as 6 cm. While the study was limited in its ability to capture all possible presentations of advanced BCC, several important findings did emerge.

Not unexpectedly, the highest mean utility value, or amount of time participants were willing to trade for a full state of health, was for the complete response state (94%). The lowest utility value was progressed disease with large growth (67%).[2] The size and number of lesions was also found to be an important influence on QOL, and those states were accordingly valued. The most interesting finding of all was that the post-surgical state was valued second to last at 74%.[2] The post-surgical state was found to have even more impact on QOL than progressed disease with small growth, suggesting that the general public perceives the impact of disfigurement from extensive surgery for advanced BCC just as debilitating as the experience of progressed disease. From these data, Shingler et al concluded that patients with larger lesions as well as those with numerous lesions would benefit from non-surgical intervention.[2] Additionally, treatment efforts to reduce the size and number of lesions were also highly valued by patients.

In addition to the physical and psychological impact of advanced BCC, the financial burden of non-melanoma skin cancer

(NMSC) is also significant. As the prevalence of NMSC has globally increased over the past 3 decades, the costs involved in treatment and management have also risen.[5] Between 1992 and 2006, the number of procedures performed for NMSC in the United States rose by 76.9%.[6] Although treatment for an individual case of BCC is low compared with other malignancies (approximately $492 in a physician's office setting), NMSC ranks fifth for cancer cost in the Medicare population.[6,7] This equates to 4.5% of all Medicare cancer costs.[6,8]The cost of treatment for an episode of BCC is positively correlated with tumor size and anatomical site. Lesions on the head and neck or feet are associated with a higher cost.[6] In 2004, the total direct cost associated with treatment for NMSC was $1.5 billion.[9]

For patients with multiple BCCs requiring frequent and recurrent treatment, preventative management with a targeted molecular therapy offers promise. Genentech offers a one-month supply of once-daily capsules of vismodegib for $7,500, which comes out to $250 per capsule.[9] While the length of treatment may vary by patient, the expected length of therapy is 10 months. This is a conservative estimate since the endpoint for BCC treatment remains undefined. Thereby, the total average cost is $75,000.[9] This represents a cost increase of 150-fold over the current modalities. The sales projections in Europe are predicted to reach $401 million by 2015, and peak at $533 million in 2022.[9]

Differentiate Disease Characteristics and Diagnostic Markers to Better Identify Patients With Advanced Basal Cell Carcinoma With the Presence of Basal Nevus Syndrome

While the majority of BCC cases are found early and effectively cured by surgery and other treatment modalities, the minority that present late can progress to life-threatening, unresectable, advanced BCC, either in the form of locally advanced BCC or metastatic BCC tumors.[2,8] Late presentations and progression to advanced disease can occur due to a variety of factors. The patient may not have sought out timely treatment due to denial or neglect, or perhaps due to lack of finances or access to health care.[5] Psychiatric comorbidities can also play a role in the progression of BCC to advanced disease.[5] The point at which BCC becomes "advanced" or "inoperable" is somewhat subjective, as some physicians may be more willing than others to attempt surgical treatment, based on experience and expertise. Additionally, surgery may be precluded as a treatment modality secondary to patient age or comorbidities. In these situations, a multidisciplinary team comprised of experts in dermatologic surgery, surgical oncology, head and neck oncologic surgery, radiology, medical oncology, and radiation oncology should be considered.[10]

The instances when advanced BCC tumors develop despite aggressive treatment are known as "high risk BCC." These lesions are characterized by several markers hypothesized to be related to a more aggressive BCC tumor phenotype.[5] Characteristics include long duration, location on central face or ears, diameter greater than 2 cm in size, aggressive histologic subtype, perivascular or perineural spread, a history of radiation exposure, incomplete treatment, or previous treatment failure.[5,11,12] Other reasons, however, for this high risk phenotype are not fully understood at this time.[8]

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While large BCCs are difficult to manage, the size itself does not necessarily deem a BCC "inoperable" or metastatic. In fact, certain BCCs that appear "typical" may very well be recurrences requiring multiple procedures, which, in turn, become inoperable or metastatic. In the past, radiation was the only alternative for these patients. However, there are certain skin conditions in which radiation is contraindicated, such as basal cell nevus syndrome (BCNS) or xeroderma pigmentosum.[8]

Basal cell nevus syndrome is an autosomal dominant disorder characterized by multiple basal cell carcinomas with onset occurring between puberty and 35 years of age.[13] The current prevalence is estimated to be 1/57,000 to 1/256,000.[13] Males and females are equally affected, and the syndrome has been found across multiple ethnicities and geographic locations.[13] The classical clinical triad of BCNS is multiple BCCs, jaw keratocysts, and bifid ribs. Additional clinical features may include craniofacial defects such as macrocephaly, frontal bossing, and coarse facial features, facial milia, downward sloping shoulders, palmar-planar pits, ectopic intracranial calcifications, and central nervous system defects.[12,13] As the syndrome may manifest in a variety of ways, the diagnosis of BCNS is fulfilled with 2 major criteria and 1 minor criterion, or 1 major criterion and 3 minor criteria.

Basal cell nevus syndrome is caused by mutations in the sonic hedgehog (SHh) pathway, with the most common mutation located in the patched homologue 1 (PTCH1) gene, a tumor suppressor gene mapped to chromosome 9q22.3.[13] The SHh pathway, while essential during embryogenesis for cell proliferation and growth, typically becomes inactive during adulthood.[10] Patched homologue 1 is a SHh receptor on the cell membrane that suppresses the activation of another transmembrane protein, smoothened (SMO), a SHh pathway activator.[13] When the

secreted SHh protein binds to its receptor, PTCH1, it activates SMO. Once activated, SMO promotes downstream transcription of target genes and activates other transcription factors in the glioma-associated oncogene (GLI) family, including GLI1 which is specifically involved in cellular proliferation and growth.[8,12] Glioma-associated oncogene 1 serves as a transcription factor for itself, as well as inducing PTCH1 transcription, creating a negative feedback loop.[13] In an individual with BCNS, however, PTCH1 genes are mutated and inappropriately inactivated, leading to unregulated simulation of the SHh pathway because the PTCH1 protein cannot effectively inhibit SMO. Constitutive activation of SHh causes abnormal cell growth and carcinogenesis, leading to multiple BCCs.[13] In cases of sporadic BCC, not only have loss-of-function mutations in PTCH1 been implicated in 30% to 40% of cases, but also gain-of-function mutations activating SMO are also a possible mechanism as SMO is mutated in about 10% of sporadic BCC cases.[5,11]

Because radiation is contraindicated in BCNS and other genetic syndromes that predispose one to skin cancer, few treatment options remain for these patients. Topical therapy, such as 5-floro-uracil and imiquimod, photodynamic therapy, and cryotherapy, may be used, but they are less effective than the conventional treatments of surgery and radiation.[9] Prior therapies have included chemotherapy (ie, cisplatin-based chemotherapy) as well as molecular targeted therapies (ie, cetuximab).

One of the most recent additions to the armamentarium of therapies for patients with BCNS has been vismodegib (Erivedge®; Genentech). Vismodegib was approved by the United States Food and Drug Administration in January 2012 as the first oral medication for adults with metastatic or locally advanced BCC that has recurred after surgery or for patients who are not candidates for surgery or radiation.[9] This medication is particularly promising as a prophylactic agent because the number of BCCs among patients with BCNS is high, ranging from hundreds to thousands in a single patient.[14] Tang et al studied the use of vismodegib in patients with BCNS and found that the drug significantly reduced existing BCC tumor burden as well as blocked the growth of new BCCs.[14] However, adverse events (AEs), such as dysgeusia, hair loss, muscle cramps, and weight loss, led to discontinuation of over half the patients enrolled in the study.[14] In addition to these AEs, there are recent reports in the literature of patients on vismodegib experiencing secondary (acquired) resistance to treatment, even in patients with BCNS.[15] Chang et al studied 28 patients with advanced BCC on continuous vismodegib therapy and found that 21% developed at least one tumor regrowth.[16] While the molecular mechanism for this acquired resistance is still unclear, it is important to closely monitor patients on vismodegib as this may be an increasing phenomenon that is only beginning to be described.[16] Additionally, there have been reports in the literature of the development of rapid new onset keratoacanthomas (KAs) and squamous cell carcinomas (SCCs) associated with vismodegib treatment.[17] While KAs and SCCs have previously not been associated with SMO inhibitors, such cases warrant further investigation, especially since hereditary disorders such as BCNS would require long-term therapy. As promising as vismodegib may be, systemic therapy for advanced BCC is not curative, requires long-term treatment, and should not take the place of curative procedures such as surgery.[10]

DISCLOSURES

John A. Carucci MD PhD has served as an advisory board participant and clinical investigator for Genentech, Novartis, and Pfizer. Arielle W. Haves BA and Panta Rouhani Schaffer MD PhD MPH have no conflicts of interest to disclose.

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