NEW SYSTEMIC TREATMENT OPTIONS FOR ADVANCED BASAL CELL CARCINOMA

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Abstract

Basal cell carcinoma is a very common skin malignancy that is usually able to be cured by simple local treatment (surgical excision, radiotherapy or cryotherapy). However, patients sometimes present with or develop locally advanced or metastatic basal cell carcinoma, requiring other therapeutic options to be considered. Aberrantly active hedgehog pathway signalling underlies both sporadic basal cell carcinoma and the basal cell naevus syndrome. Recently developed small molecule inhibitors of SMO, a transmembrane protein downstream of hedgehog and PTCH1 (which is mutated in basal cell naevus syndrome) have demonstrated remarkable clinical activity in locally advanced and metastatic basal cell carcinoma. Common side-effects of altered taste, hair loss and muscle cramps appear related to inhibition of physiological hedgehog pathway activity and necessitate discontinuation of systemic treatment in some patients. Inhibitors of hedgehog pathway signalling provide a new treatment option for patients with locally advanced or multiple basal cell carcinomas who otherwise require extensive or repeated surgery, and for patients with metastatic basal cell carcinoma for whom no active systemic treatments have previously been available.

Basal cell carcinoma (BCC) is probably the most commonly occurring malignancy in developed nations, however its true incidence can only be inferred from community surveys as it is not recorded by most cancer registries.[1] The predominant cause of BCC is ultraviolet radiation from sun exposure, although the pattern rather than the total cumulative amount of exposure appears to determine risk. Immune suppression increases the risk of developing BCC and associations have also been seen with exposure to arsenic and ionising radiation. The rare DNA repair deficiency disorder, xeroderma pigmentosum, is characterised by a high incidence of squamous cell carcinoma, however BCC is also increased in incidence, implicating a role for DNA repair integrity. The malignant cells resemble undifferentiated basal cells of the epidermis and its appendages. This stem cell-like nature is thought to be responsible for the multiple morphological types of BCC that are recognised (for review see Kasper et al 2012 and Rubin 2005).[2,3]

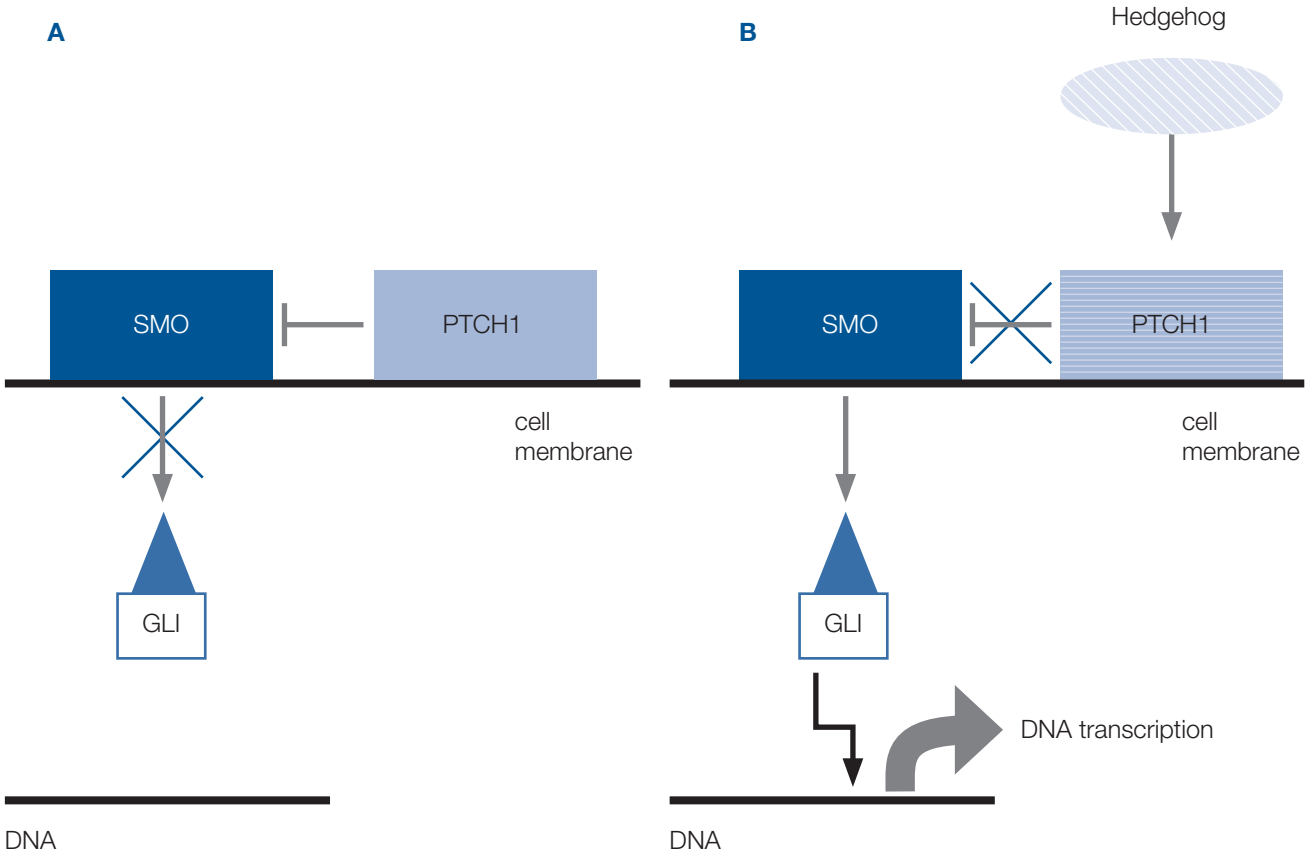
The overwhelming majority of BCCs are cured by local treatment such as surgical excision, radiotherapy or cryotherapy. A small proportion of BCCs are more aggressive and exhibit multiple recurrences to the extent that further local surgery or radiotherapy are not possible, or require substantial surgical procedures with sometimes complex reconstruction. Some patients have co-morbidities that preclude surgery with curative intent. Other patients with BCC present with neglected, locally-advanced lesions, again requiring quite substantial surgical procedures to effect cure. The metastatic potential of BCC is generally low, but occasional spread does occur, particularly to local lymph nodes and distantly to the lungs, liver and bone. Distant spread is currently incurable.

A number of pathological classifications for BCC have been proposed, reflecting an ongoing search for consensus in classification and prognosis. Certain histological variants are associated with a worse prognosis, including micronodular, morpheaform, infiltrative and basosquamous subtypes. Superficial and nodular subtypes generally have a less aggressive course.[4]

The molecular biology of BCC was substantially revealed by study of the rare entity of Gorlin's syndrome, also known as basal cell naevus syndrome.[5] This rare (incidence 1 in 19,000 to 1 in 57,000) autosomal dominant disease is characterised by jaw cysts, prominent jaw, wide set eyes, pitted depressions on the hands and feet and multiple, early onset BCCs, numbering many hundreds per patient over time. This can result in considerable scarring from repeated and extensive surgery. Affected individuals are also at increased risk of medulloblastoma, a tumour arising in the posterior cranial fossa in childhood and young adulthood, as well as rhabdomyosarcoma. Basal cell naevus syndrome patients inherit a germ-line mutation in one copy of the PTCH1 gene and BCCs occur when the remaining allele is inactivated.[6]

The molecular pathway is shown schematically in figure 1. Hedgehog family proteins are secreted glycoproteins. PTCH1 is a cytoplasmic protein that interacts with another cytoplasmic protein, SMO, a constitutive inhibitor of the transcription factor Gli, which controls expression of genes involved in cell survival, proliferation and apoptosis. Hedgehog signalling is a developmentally active transcriptional program regulating normal polarisation, among other functions. It is required to develop a normal midline zone of the foetal face and its absence leads to merging of the lateral facial structures resulting in a Cyclops appearance. Hedgehog signalling is also important for normal cell growth and differentiation. Abnormal hedgehog signalling is also prominent in medulloblastoma and rhabdomyosarcoma, and has been reported in tamoxifen-

Figure 1: *Panel A illustrates the quiescent state of the hedgehog pathway. PTCH1 inhibits SMO resulting in inhibition of Gli activation. In the presence of sonic hedgehog binding to PTCH1 inhibition of SMO is relieved and activation of Gli and DNA transcription occurs. In basal cell carcinoma, PTCH1 is inactivated by mutation and SMO is constitutively active.*



resistant breast cancer,[7] and oropharyngeal squamous cell carcinoma.[8] Abnormal activation of the hedgehog signalling pathway can arise due to overexpression of hedgehog proteins, or from mutation in the PTCH1 or SMO proteins, resulting in the loss of inhibition of Gli activation.[9,10]

Inhibitors of the hedgehog pathway also have an interesting historical background. Certain farms in Idaho in the 1950s reported the birth of lambs having a Cyclops appearance with a single midline eye and other cranial defects. The cause was found to be ingestion by pregnant ewes of a local plant the corn lily *(Veratrum californicum).* The mutagen isolated from the corn lily was termed cyclopamine and was subsequently found to be an inhibitor of hedgehog signaling.[11]

The hedgehog gene itself was first identified by Christiane Nusslin-Volhard and reported in 1980.[12] In studies in the fruit fly *Drosophila melanogasta,* embryos with a mutant phenotype displaying loss of hedgehog gene function were covered with denticles, resembling a hedgehog – hence the name. Three homologous hedgehog genes were subsequently shown to exist in mammals; desert hedgehog and Indian hedgehog were named after species of hedgehogs, while sonic hedgehog was named after the video game character Sonic the Hedgehog!

Recent clinical trials

Vismodegib (GDC-0449) is a low molecular weight inhibitor of the hedgehog signalling pathway, binding and inhibiting SMO, thus acting downstream of the mutated PTCH1 protein. Vismodegib has been one of the first agents tested in patients and a positive phase 1 study,[13] led to it being trialled in a group of patients with Gorlin's syndrome and also in a cohort of patients with locally advanced or metastatic BCC. These two important clinical trials have demonstrated the impressive activity of this SMO inhibitor; the results are summarised in table 1 and described below.

Sekulic et al (2012) conducted an international, multicentre phase II study with daily oral vismodegib 150mg given to 33 patients with metastatic BCC and 63 patients with locally advanced BCC.[14] The primary response was independently assessed. The trial design did not include a control arm on the basis that no effective systemic therapy existed, the historical observation that spontaneous remissions did not occur, and the relatively small potential patient population. A response rate of 30% was seen in the metastatic cases and 43% (with 21% having complete responses) in the locally advanced group. The median duration of response was 7.6 months in both cohorts. Serious adverse events were seen in 25% of patients, including seven deaths (one

Table 1: *A summary of the main results from two recently published trials of the SMO inhibitor Vismodegib in patients with metastatic and locally advanced BCC (Sekulic et al 2012) or Basal Cell Nevus Syndrome (Tang et al 2012). Note the negative biopsy rate includes patients assessed as either confirmed response, stable or progressive disease, and was performed at one site within the original lesion on 34 patients from the locally advanced cohort. Key: CR, complete response.*

Cohort	Number	Response rate	Reduction in new lesions	Median duration of response	Serious adverse event rate	Discontinuation rate due to patient choice, adverse event	Negative Biopsy rate
Metastatic BCC Sekulic et al 2012	33	30%	N/A	7.6 months	25%	6%, 12%	-
Locally Advanced BCC Sekulic et al 2012	63	43% overall 21% CR	N/A	7.6 months	25%	25%, 12%	54%
Basal Cell Nevus Syndrome Tang et al 2012	41 (26 on active drug, 15 on placebo)	Mean reduction of BCC 65% v 11%, no progressors seen on vismodegib	2 v 29	8 months	40%	N/A, 54%	54% at three months

each due to meningeal disease, myocardial infarction, ischaemic stroke, hypovolemic shock and three of unknown cause), however the relationship between these deaths on study and vismodegib is unknown. Across both cohorts, 12% of patients in total stopped the drug due to adverse events. Biopsy within the original area of tumour revealed absence of histological evidence of BCC in 56% of 34 locally advanced patients with clinical complete or partial responses, or apparent progressive disease.

In a concurrent study reported by Tang et al (2012), 41 patients with basal cell naevus syndrome were randomised in a double blind fashion to either vismodegib or placebo.[15] The primary endpoint was a reduction in the incidence of new surgically resectable BCCs (greater in diameter than 3mm on the nose or periorbital area, 5mm elsewhere on the face, or 9mm on the trunk or limbs) after three months of treatment. Reduction in the size of BCCs present at baseline was a secondary outcome. Patients were followed for a mean of eight months (range 1-15 months). A positive outcome in favour of vismodegib was seen, with the rate of new BCCs per patient per year being two versus 29 in the control group, this result being highly statistically significant. A significant decrease in existing lesions was also seen, with a mean reduction of 65% versus a reduction of 11% in the control group. Of note, some patients had complete resolution of all their BCCs and no patients had progression of BCC in the vismodegib arm.

Assessing response in locally advanced BCC is difficult and a composite method, including clinical annotation with photography as well as conventional CT, was used in the vismodegib trials. Independent review noted a lower rate of response than that assessed by investigators. Conversely, several patients with residual apparent lesions had histologically complete remission on biopsy. This highlights the issue of residual scarring or ulceration associated with healing, which are both seen clinically and which can confuse the assessed response. There is exploration of other modalities such as superficial soft tissue MRI in an attempt to distinguish residual BCC from treatment-related changes. Repeat biopsy with histological examination is likely to remain the definitive standard for assessing the response in residual lesions after treatment, although even this is subject to sampling error.

The side-effect profile included hair loss, loss of taste (dysguesia), muscle cramps and rhabdomyolysis, weight loss and fatigue. Some of these side-effects were predictable, as hedgehog signalling is required for normal maintenance of tongue papillae and hair follicles.[16,17] These side-effects appear to be class effects for a variety of inhibitors.

A number of systemic inhibitors of smoothened have been assessed in human clinical trials including GDC-0449 (Vismodegib), LDE-225, IPI-926, BMS-833923, TAK-441, and CUR61414. Vitamin D3 inhibits hedgehog signalling through smoothened and also has a pro-differentiation effect on keratinocytes independent of vitamin D receptor activation; a phase III clinical trial has been initiated. Another alternative pathway inhibitor currently being assessed in a clinical trial is tartrazine, which downregulates the RAR-β/RAR-γ pathway. Preclinical work has also focused on developing inhibitors of downstream targets such as Gli. This approach may overcome acquired resistance to SMO inhibitors, due to activating mutations in SMO occurring while on treatment with a SMO inhibitor (www.cancer.gov/clinicaltrials).

Perspective

Future issues include understanding the natural history of prolonged exposure to hedgehog inhibitors with regard to long-term side-effects and the duration of tumour control, as well as the nature and characterisation of tumour cells that develop resistance. An attractive approach will be to use an inhibitor prior to surgery to improve resectability and reduce the potential morbidity of surgery. An important uncertain issue in this setting will be whether all of the previously involved tissue needs to be resected, and careful biopsy mapping studies may assist in clarifying this. It is likely that tumour shrinkage by drug, then resection of residual disease followed by close surveillance and "cherry-picking" of any further recurrences, will be the least morbid approach. Direct injection or topical application of inhibitor may also be a technique to maintain efficacy, but reduce side-effects and avoid the need for long-term discontinuation. LDE225 has been administered topically in a small trial with evidence of BCC regression.[18] Whether there may be a role for hedgehog inhibitors as preventive agents in patients with Gorlin's syndrome also requires testing. The current advances show a remarkable ability to translate basic biological research into clinically meaningful treatments and provide a more acceptable therapeutic option for patients with locally advanced or multiple BCCs.

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