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Herzlich Willkommen in der Fachklinik Hornheide

Gorlin-Goltz-Syndrom (GGS)

Basalzellnävus-Syndrom (BCNS)

- Seltene Erbkrankheit (Häufigkeit 1 : 56.000)
- Ursache: Mutationen der Sonic Hedgehog-Genkaskade, insbesondere des PTCH 1-Gens auf Chromosom 9
- Wirkung: Steuerung des Zellwachstums
- Vererbungsrate: 50%, bislang 100 Fälle bekannt
  - Die meisten Ärzte kennen das GGS nicht und somit auch nicht die Kriterien dieser Krankheit
- Diagnose gesichert, wenn 2 der Hauptkriterien oder 1 Hauptkriterium in Verbindung mit 2 Nebenkriterien nachweisbar

Hauptkriterium

- Mehr als 2 Basaliome oder 1 Basaliom vor dem 20. Lebensjahr
- Kieferzysten
- Mehr als drei Dellen an der Hand- oder Fußinnenfläche
- Verkalkung an den Hirnhäuten
- Rippenanomalien
- Ein Verwandter 1. Grades mit dem Syndrom

Nebenkriterien

- Ungewöhnlich großer Kopfumfang
- Lippen, Kiefer-, Gaumenspalte oder andere Auffälligkeiten des Gesichtsschädels (z.B. Stirnhöcker)
- Knochenanomalien (z.B. Wirbelkörper)
- Fibrome an den Eierstöcken
- Hirntumor (Medulloblastom)

Diagnostik

- Zur Sicherung knöcherner Anomalien: Röntgendiagnostik notwendig (z.B. Kieferpanoramaaufnahme)
- Nach Möglichkeit sollten Patienten mit GGS allerdings möglichst wenig mit ionisierender Strahlung untersucht werden, Alternative: Sonographie (Ultraschall), MRT-Untersuchung
- Das Basaliom entwickelt sich über Monate bis Jahre und geht in langen Verläufen in ulzerierende Läsionen über, die auch tiefe Gewebsstrukturen zerstören können

Therapie

- Operative Therapie mit histologischer Kontrolle der vollständigen Resektion im Gesunden = Therapie der ersten Wahl
  - Operation mit systematischer Randschnittkontrolle (mikroskopisch kontrollierte Chirurgie)
  - Operation mit tumoradaptiertem Sicherheitsabstand und konventioneller Histologie
  - Bei oberflächlichen Basaliomen auch Horizontalexzision („Shave-Exzision“) mit konventioneller Histologie

Therapie

- Bei nicht im Gesunden resezierbaren Tumoren oder bei inoperablen Patienten soll ein interdisziplinäres Behandlungskonzept erstellt werden
  - In der Regel eine Strahlentherapie
  - Bei therapierefraktären Basaliomen oder solchen, bei denen eine Strahlentherapie nicht indiziert ist, Therapie mit einem Hedgehog-Inhibitor (Vismodegib, Sonidegib)
- Patienten mit GGS sollen nicht mit ionisierender Strahlung behandelt werden

Therapie

- Alternativen: Lokal destruierende Therapieverfahren
  - Elektrodesikkation
  - Kürettage
  - Kryochirurgie
  - Lasertherapie
  - Photodynamische Therapie
  - Lokale medikamentöse Therapie mit Imiquimod oder 5-Fluorouracil
- Insbesondere bei
  - Multiplen, oberflächlichen Basaliomen
  - Inoperablen Patienten

› Clin Cancer Res. 2024 Apr 4. doi: 10.1158/1078-0432.CCR-23-4033. Online ahead of print.

Update on cancer predisposition syndromes and surveillance guidelines for childhood brain tumors

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PMID: 38573059 DOI: 10.1158/1078-0432.CCR-23-4033

Abstract

Tumors of the central nervous system (CNS) comprise the second most common group of neoplasms in childhood. The incidence of germline predisposition among children with brain tumors continues to grow as our knowledge on disease aetiology increases. Some children with brain tumors may present with non-malignant phenotypic features of specific syndromes (e.g. nevoid basal cell carcinoma syndrome, neurofibromatosis type 1 and type 2, DICER1 syndrome, and constitutional mismatch repair deficiency), while others may present with a strong family history of cancer (e.g. Li-Fraumeni syndrome), or with a rare tumor commonly found in the context of germline predisposition (e.g. rhabdoid tumor predisposition syndrome). Approximately 50% of patients with a brain tumor may be the first in a family identified to have a predisposition. The past decade has witnessed a rapid expansion in our molecular understanding of CNS tumors. A significant proportion of CNS tumors are now well characterized and known to harbor specific genetic changes that can be found in the germline. Additional novel predisposition syndromes are also being described. Identification of these germline syndromes in individual patients has not only enabled cascade testing of family members and early tumor surveillance but increasingly has also impacted cancer management in those patients. Therefore, the AACR Cancer Predisposition Working Group chose to highlight these advances in CNS tumor predisposition and summarize and/or generate surveillance recommendations for established and more recently emerging pediatric brain tumor predisposition syndromes.

› Chin J Dent Res. 2024 Mar 28;27(1):83-88. doi: 10.3290/j.cjdr.b5128601.

Novel PTCH1 Mutation Causes Gorlin–Goltz Syndrome

Hai Tang Yue, Hai Yan Cao, Miao He

PMID: 38546523 DOI: 10.3290/j.cjdr.b5128601

Free article

Abstract

Objective: To analyse the aetiology and pathogenesis of Gorlin-Goltz syndrome (GS; also known as nevoid basal cell carcinoma syndrome [NBCCS] or basal cell nevus syndrome [BCNS]) in a Chinese family.

Methods: Whole-exome sequencing (WES) was performed on genomic DNA samples from the subjects in a family, followed by the investigation of pathogenesis via bioinformatic approaches and conformational analysis.

Results: A novel heterozygous non-frameshift deletion patched 1 (PTCH1) [NM_000264: c.3512_3526del (p.1171_1176del)] was identified by WES and further validated by Sanger sequencing. Bioinformatic and conformational analysis showed that the mutation caused altered PTCH1 protein structure, which may be related to functional abnormalities.

Conclusion: This study expands the mutation spectrum of PTCH1 in GS and facilitates the early diagnosis and screening of GS. PTCH1 [c.3512_3526del (p.1171_1176del)] may cause structural abnormalities and functional disabilities, leading to GS in families.

GS has been reported to be related with mutations in patched 1 (*PTCH1*), suppressor of fused (*SUFU*) and *PTCH2*.[4] Among them, *PTCH1*, which is located on chromosome 9q22.3, is the major pathogenic gene involved in GS. It consists of 24 exons encoding PTCH1 protein with 1447 amino acids. PTCH1 is a 12-pass transmembrane protein that negatively regulates the Hedgehog (HH) signalling pathway.[5] In the unliganded state, PTCH1 maintains Smoothened (SMO) in an unphosphorylated state, contributing to its endocytosis and degradation. Upon binding of HH ligands, the repression of PTCH1 on SMO is relieved, leaving SMO hyperphosphorylated, capable of activating glioma-associated oncogene homologue 1 transcription factors from SUFU (encoded by *SUFU*) inhibition to translocate into the nucleus and stimulate the targeted gene expression.[6,7] The HH signalling pathway is fundamental to proliferation and differentiation during embryonic patterning and development and homeostasis. Dysregulation of this pathway leads to a wide variety of developmental deficiencies, including holoprosencephaly, brachydactyly, non-syndromic colobomatous microphthalmia and solitary median maxillary central incisor syndrome.[8-12] It has also been involved in tumours, including BCCs, medulloblastoma, rhabdomyosarcoma, glioblastoma and breast, ovarian, prostate, colon, stomach, pancreas and lung cancers, making it a potential target for therapy.[13,14]

To date, over 600 *PTCH1* mutations have been identified in patients with GS, most of which are nonsense, small indels and missense, according to the Human Gene Mutation Database (https://www.hgmd.cf.ac.uk/ac/index.php).

In the present study, a novel heterozygous non-frameshift deletion *PTCH1* [NM_000264: c.3512_3526del (p.1171_1176del)] was analysed in a 13-year-old proband and his mother with GS. The clinicopathologic characteristics of the patients and the pathogenic mechanism of the mutant were further explored.

Case Reports > Front Med (Lausanne). 2024 Mar 4:11:1327505. doi: 10.3389/fmed.2024.1327505. eCollection 2024.

Case report: A novel PTCH1 frameshift mutation leading to nevoid basal cell carcinoma syndrome

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PMID: 38500952 PMCID: PMC10946671 DOI: 10.3389/fmed.2024.1327505

Abstract

A patient presenting with several basal cell carcinomas, pigmented nevi, and developmental defects was diagnosed with nevoid basal cell carcinoma syndrome. Gene panel sequencing and Sanger sequencing were used to identify a novel heterozygous frameshift mutation, c.1312dupA:p.Ser438Lysfs, in exon 9 of PTCH1. I-Tasser and PyMol analyses indicated that the mutated protein patched homolog 1 (PTCH1) lacked 12 transmembrane domains and the intracellular and extracellular rings of ECD2 compared with the wild-type protein, resulting in a remarkably different structure from that of the wild-type protein. This case extends our knowledge of the mutation spectrum of NBCCS.

Case Reports > Cureus. 2024 Mar 6;16(3):e55677. doi: 10.7759/cureus.55677.
eCollection 2024 Mar.

Genetic Complexity in Recurrent Basal Cell Carcinoma: A MUTYH Variant Case Report

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Affiliations + expand

PMID: 38586659 PMCID: PMC10997523 DOI: 10.7759/cureus.55677

Abstract

The MYUTH gene plays a critical role in preserving the integrity of the human genome, with mutations being identified in several different cancer diagnoses. It serves its purpose by encoding a DNA glycosylase enzyme responsible for preventing oxidative damage through the excision of adenine that is incorrectly paired with guanine or cytosine. Mutations of the MUTYH gene have been most frequently associated with MUTYH-associated polyposis (MAP) and colorectal cancer. Biallelic mutations of the MUTYH gene are implicated in MAP, and carriers of this mutation have an increased lifetime risk of developing colorectal cancer of 43% to 100%, depending on the appropriate screening and surveillance steps taken. This case describes a patient with recurrent basal cell carcinomas (BCC) and subsequent genetic testing that revealed a pathogenic monoallelic mutation of the MUTYH gene, as well as the interventions that were subsequently performed. It highlights a potentially new patient population that would benefit from early screening to assess the risk of developing colorectal cancers as well as BCC.

› Clin Exp Dermatol. 2024 Apr 9:llae126. doi: 10.1093/ced/llae126. Online ahead of print.

Patient-Led Skin Cancer Teledermatology without Dermoscopy during the Covid pandemic: Important lessons for the development of future patient-facing teledermatology & AI-assisted self-diagnosis

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PMID: 38589979 DOI: 10.1093/ced/llae126

Abstract

MySkinSelfie was a mobile phone application for skin self-monitoring enabling secure sharing of patient-captured images with healthcare providers. This retrospective study assessed MySkinSelfie's role in remote skin cancer assessment at two centres for urgent (melanoma & squamous cell carcinoma) and non-urgent skin cancer referrals, investigating the feasibility of using patient-taken images without dermoscopy for remote diagnosis. Total number of lesions utilising MySkinSelfie was 814 with mean age of 63. Remote consultations reduced face-to-face appointments by 90% for basal cell carcinoma and 63% for two-week-wait referrals. Diagnostic concordance (consultant vs histological diagnosis) rates of 72% and 83% were observed for basal cell carcinoma (n=107) and urgent skin cancers (n=704), respectively. Challenges included image quality, workflow integration and lack of dermoscopy. Higher sensitivities have been observed in recent Artificial Intelligence (AI) algorithms employing dermoscopy. While patient-taken images proved useful during the pandemic, further research is needed to explore the feasibility of widespread patient-led dermoscopy to enable direct patient-to-AI diagnostic assessment.

Res Sq [Preprint]. 2024 Mar 6:rs.3.rs-4005623. doi: 10.21203/rs.3.rs-4005623/v1.

A Prospective Cohort Study Exploring the Joint Influence of Sunlight Exposure and Tanning Bed Use on Basal Cell Carcinoma, Squamous Cell Carcinoma, and Melanoma Risk

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PMID: 38496529 PMCID: PMC10942498 DOI: 10.21203/rs.3.rs-4005623/v1

Abstract

Exposure to solar ultraviolet (UV) radiation and use of UV-emitting tanning devices are known risk factors for skin cancer. Few studies have explored the interaction between these risk factors, namely how the risk of skin cancer increases among those who both have been exposed to high levels of natural sunlight and regularly use tanning beds. Nurses' Health Study II followed 116,430 women, aged 25-42, from 1991 to 2011. Cumulative average UV exposure was based on participants' residences at follow-up periods. History of severe sunburn during ages 15-20 was used as a proxy for early-life sunlight exposure. Tanning bed use in early life data was collected. Participants reported melanoma, basal cell carcinoma (BCC), and squamous cell carcinoma (SCC) diagnoses. We built multivariable Cox regression models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for risk of skin cancer associated with joint effects of sunlight exposure and tanning bed use. Participants with high sunlight exposure and tanning bed use during high school/college had an increased risk of BCC (HR=1.53, CI 1.37-1.71, P interaction =0.01; vs. low UV exposure and no tanning bed use). Participants with a history of severe sunburns and tanning bed use during high school/college were at increased risk of BCC (HR=1.62, CI 1.47-1.79, P interaction =0.02; vs. no sunburns and no tanning bed use). No significant interactions were found between sunlight exposure and tanning bed use on SCC and melanoma risk. We found significant interactions between sunlight exposure and tanning bed use on the risk of BCC.

› Front Med (Lausanne). 2024 Mar 14:11:1381492. doi: 10.3389/fmed.2024.1381492. eCollection 2024.

Basal cell carcinoma–a clinical indicator of immunosuppression

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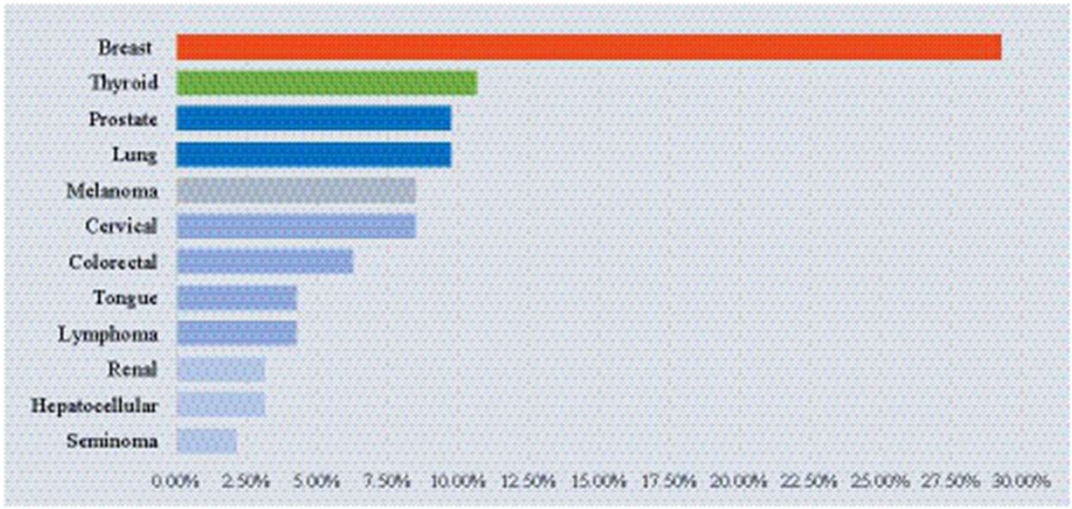
PMID: 38549869 PMCID: PMC10977600 DOI: 10.3389/fmed.2024.1381492

Abstract

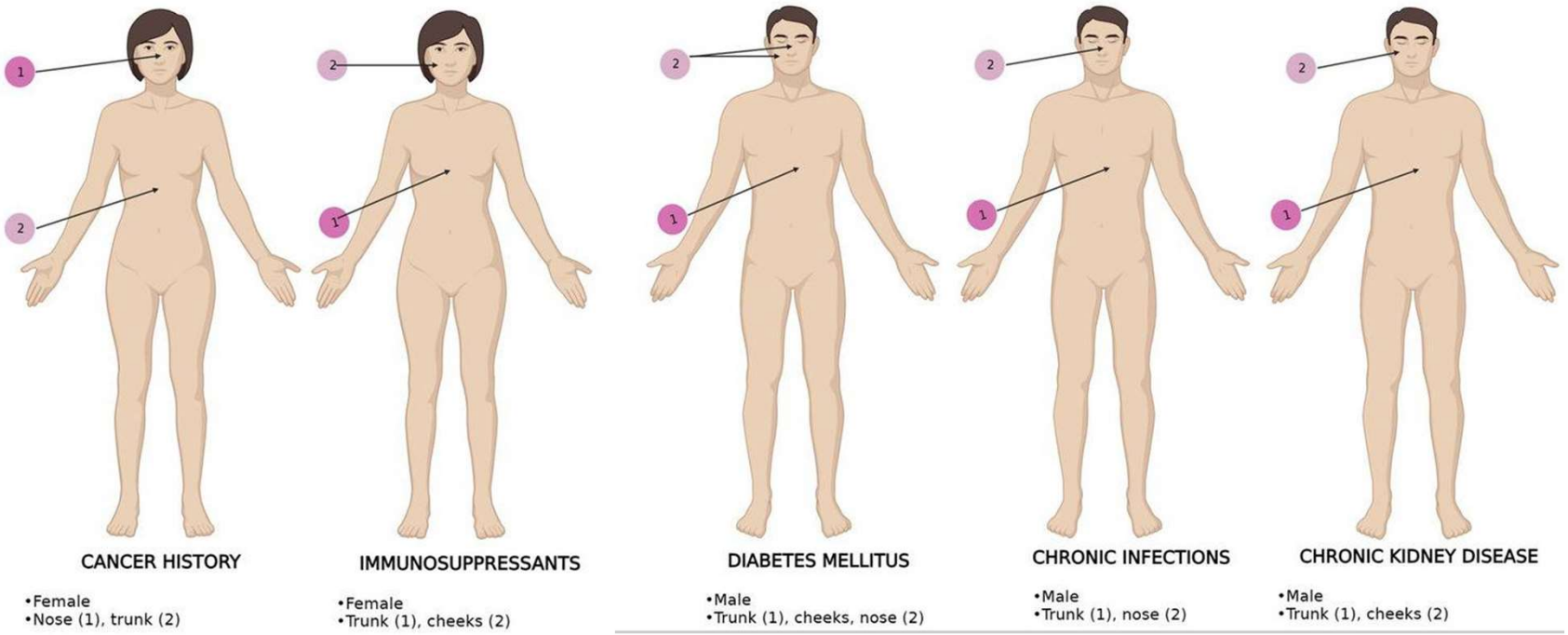
Background: Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are skin-derived carcinomas. The literature strongly connects SCC with acquired immunosuppression. Current data regarding BCC's association with immunosuppressive comorbidities are vague. The primary objective of this study was to establish the correlations between BCC and immunosuppressive comorbidities of patients. Materials and methods: We conducted a retrospective cohort study on 275 patients with a histopathological proven diagnosis of BCC from October 2019 to October 2023. Demographic data, BCC characteristics, and patients' comorbidities were analyzed. Comorbidities were classified as non-immunosuppressant and immunosuppressant (primary and secondary immunodeficiencies).

Results: We recorded 292 BCCs from 275 patients (142 females, 133 males), with equally distributed skin phototypes. 66.44% of the BCCs were detected in patients with various comorbidities ($p < 0.001$), of which 81.44% had immunosuppressive comorbidities ($p < 0.001$). All the immunosuppressive comorbidities were secondary and included diabetes mellitus (47.55%), history of solid or hematogenous cancer in the last 5 years (26.57%), chronic kidney disease (8.39%), chronic infections (9.09%), and antirheumatic immunosuppressive therapies (8.39%) ($p < 0.001$). BCC patients with immunosuppressive comorbidities did not develop larger BCCs ($p = 0.2577$) or more aggressive subtypes ($p = 0.4269$) and BCC did not arise earlier in their life ($p < 0.001$). BCC on the nasal pyramid was frequent in cancer history patients ($p = 0.008$). The ulcerated form of BCC is more confined to patients with chronic kidney disease ($p = 0.006$). Multiple BCCs are more frequent in patients with secondary immunodeficiencies ($p = 0.027$).

Conclusion: BCC represents a clinical indicator of secondary immunodeficiency. Further research should establish if cancer screening campaigns may be beneficial in BCC patients.



Distribution of cancer history among BCC patients. Breast, thyroid, prostate, and lung cancer represented the most encountered malignancies.



BCC anatomical distribution upon gender and comorbidities in IPs. The most frequent (1) and second most frequent (2) localizations are displayed. BCC localizations are represented for each comorbidity. The most representative gender is shown for each comorbidity.

Review > Cancer Lett. 2024 May 1:589:216821. doi: 10.1016/j.canlet.2024.216821.
Epub 2024 Mar 21.

Treatments on the horizon for locally advanced basal cell carcinoma

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PMID: 38521198 DOI: 10.1016/j.canlet.2024.216821

Abstract

Basal cell carcinoma (BCC) is one of the most common human cancers. Most cases of BCC are amenable to surgical and topical treatments with excellent prognosis if diagnosed timely and managed appropriately. However, in a small percentage of cases, it could be locally advanced BBC (laBCC) and not amenable to surgery or radiation, including recurrent, large tumors or tumors that invade deeper tissue. Hedgehog inhibitors (vismodegib and sonidegib) are approved as the first-line treatment of laBCC. PD-1 inhibitor immunotherapy (cemiplimab) is indicated for cases that progressed on or could not tolerate hedgehog inhibitors or when hedgehog inhibitors are contraindicated. Given the modest response and bothersome side effects of some of the agents above, there are reports of novel treatments, and clinical trials are currently evaluating multiple agents.

Basal cell carcinoma (BCC) is one of the most common cancers in human beings [1]. BCC's global incidence is increasing worldwide with a lifetime risk of 20–30% [2]. An estimated 3.6 million cases of basal cell carcinoma were diagnosed in the United States in 2021 [3]. Clinically, BCC often presents as a non-healing, enlarging lesion that may occasionally bleed [2]. Associated symptoms might include pain or pruritus [2]. BCC has multiple histologic variants, including superficial, nodular, infundibulocystic, morpheaform, infiltrative, micronodular, fibroepithelial, and basosquamous subtypes [2]. Among the variants, nodular BCC accounts for 50–80% and is primarily located on the head and neck [2]. Risk factors for the development of basal cell carcinoma include fair skin, history of previous BCC, ultraviolet radiation exposure, advanced age, immunosuppression, and genetic syndromes that predispose to BCC (for, e.g., Rombo syndrome, Xeroderma pigmentosum, Bazex-Dupré-Christol syndrome, Gorlin syndrome) [4].

The treatment of BCC depends on stratification, either as low-risk or high-risk, depending on factors including clinical size, anatomic site and histological subtype of the tumor, demarcation, history of recurrence, and patient factors [5]. Low-risk BCCs are amenable to treatment with excision followed by postoperative margin evaluation or electrodesiccation and curettage. Other treatment options for select subtypes of basal cell carcinoma include cryotherapy, topical treatments, intralesional therapies, lasers, and radiation [5,6]. High-risk BCC, including recurrent BCC, is best treated by Mohs micrographic surgery [5,7]. Appropriate use criteria for Mohs micrographic surgery have been developed based on patient factors and tumor features to triage patients for whom the procedure would be indicated [8].

Most basal cell carcinomas have a good prognosis with the standard treatment options described above. However, some patients can present with severe or advanced disease ranging in incidence from 0.8 to 2% [9,10]. This subset of advanced cases includes locally advanced BCC (laBCC) and metastatic BCC (mBCC), which can be challenging to manage.

Several multidisciplinary groups have proposed definitions for laBCC based on host factors, tumor characteristics, and amenability to surgical treatment [[11], [12], [13]]. In synopsis, the groups defined laBCC as aggressive, large-size, or recurrent tumors or those tumors that penetrate deeper tissue [[11], [12], [13]]. LaBCC may not be amenable to radiotherapy, and surgical management might cause severe disfigurement, loss of function, and high morbidity [11,14,15]. For practical purposes, the National Comprehensive Cancer Network (NCCN) define laBCCs as “those that have primary or recurrent extensive disease where surgery and/or radiotherapy are unlikely to result in a cure” [5].

LaBCC is a relatively rare form of BCC. In a large cohort of commercially insured patients in the United States, laBCC was observed in about 0.8% of the study population with a statistically significant preponderance for males ($p=0.021$) [16]. The overactivation of the Sonic Hedgehog (Hh) pathway (discussed below) is a main driver in the pathogenesis of a majority of sporadic BCCs including laBCC [17]. Clinically, laBCC can present as an erythematous or flesh-colored papule or plaque with telangiectatic blood vessels but could be ulcerated, larger or, fixed to the underlying skin signifying deeper invasion.

Given the complexities and intricacies of managing patients with laBCC, optimal care is best delivered in a multidisciplinary setting. In recent years, there have been multiple new treatments developed for locally advanced BCC, including hedgehog inhibitors (Hh) inhibitors and PD-l inhibitor immunotherapy (Cemiplimab). Hh inhibitors are the first-line treatment per the NCCN but can have bothersome side effects, leading to treatment discontinuation [18]. Resistance could also complicate treatment with hedgehog inhibitors [15]. Cemiplimab immunotherapy is currently indicated for laBCC, which has either failed or progressed with hedgehog inhibitors and is showing promising results [19]. The above agents have modest clinical efficacy and good safety record. Still, their use can be limited by intolerable side effects and tumor resistance, fueling the investigation of better treatment options. The objective of this review is to highlight several novel or combination therapies that have been reported in the literature and investigational treatments in the pipeline for laBCC.

Hedgehog inhibitors

The Hh pathway is a transduction signaling cascade regulating a myriad of cellular functions, including cellular proliferation, differentiation, and tissue polarity in the embryo [20]. The pathway is strictly regulated, and aberrant activation of the pathway is a hallmark of many human cancers, including basal cell carcinomas [20].

In the activated state, the Hh ligand binds to and inhibits the Patched 1 (PTCH) receptor, an inhibitor of the G-protein-coupled smoothed (SMO) transmembrane…

Combination therapies

As discussed above, primary or secondary resistance can complicate treating laBCC with currently approved Hh inhibitors. Combining different treatments with synergistic mechanisms might mitigate the non-response related to resistance.

Vismodegib has been used concurrently with radiation in laBCC of the head and neck. In a report by Schulze et al., three patients with recurrent laBCC of the head and neck were treated with vismodegib 150mg daily in combination with fractionated radiation (total…

Investigational and experimental therapies

Several completed and ongoing clinical trials and experimental treatments for laBCC, some of which have provisional or published results are available. A phase 1 study of taladigeb (competitive SMO antagonist in SMO mutants) in laBCC and mBCC showed a complete or partial response in about 46.8% of patients at 10.2 months [48]. A phase 1 study of LEQ506 (SMO antagonist) showed the safety of the agent for three weeks in advanced tumors, including laBCC, but no efficacy data were available…

Conclusion

Locally advanced BCC (laBCC) is usually not amenable to standard treatments and might require discussion and management planning in a multidisciplinary setting. Currently approved treatments for laBCC include Hh inhibitors as first-line (Vismodegib and Sonidegib) and immunotherapy (Cemiplimab) as second-line in those patients intolerant to or had failed Hh inhibitors or as first-line in those who are not eligible to Hh inhibitors. Hh inhibitor treatment might be complicated, with significant…

Clin Exp Dermatol. 2024 Mar 18:llae099. doi: 10.1093/ced/llae099. Online ahead of print.

Metastatic basal cell carcinoma with neuroendocrine differentiation. Complete response to cemiplimab

Ignasi Marti-Marti [1], Susana Puig [1 2 3], Raquel Albero-González [4], Emili Masferrer [5], Pablo Iglesias [1], Javiera Pérez-Anker [1], Laura Serra-García [1], Xavier Tarroch [6], Neus Curcó [5], Agustí Toll [1]

Affiliations + expand

PMID: 38494790 DOI: 10.1093/ced/llae099

Case Reports > JAAD Case Rep. 2024 Mar 1:46:67-69. doi: 10.1016/j.jdcr.2024.02.011. eCollection 2024 Apr.

Complete response of metastatic cutaneous squamous cell carcinoma and multiple locally advanced basal cell carcinomas with concomitant pembrolizumab and sonidegib therapy

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Affiliations + expand

PMID: 38577496 PMCID: PMC10992265 DOI: 10.1016/j.jdcr.2024.02.011

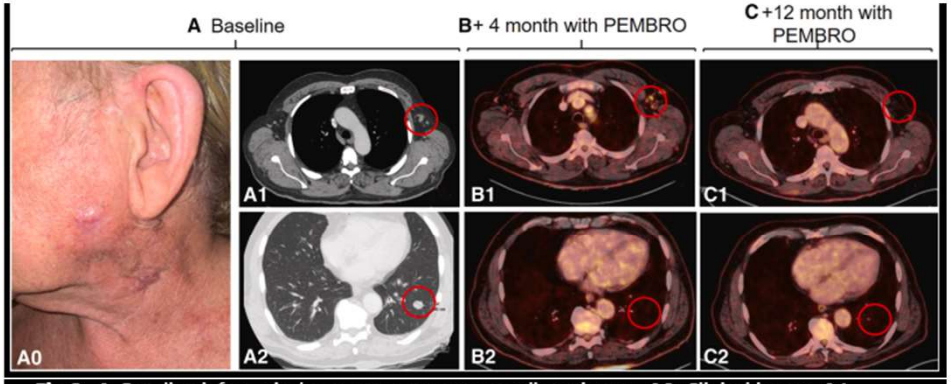

Fig 2 **A**, Baseline left cervical cutaneous squamous cell carcinoma. **A0,** Clinical image; **A1,** axillary lymph nodes by CT; **A2,** pulmonary metastases by CT. **B,** Dissociate response after 4 months of pembrolizumab treatment. **B1,** Lymph node pseudoprogression in PET/CT; **B2,** complete response of the lung metastases by PET/CT. **C,** Complete response after 12 months with pembrolizumab treatment. **C1,** Complete response of axillary lymph nodes by PET/CT; **C2,** complete maintained response of the lung metastases by PET/CT. *PET*, Positron emission tomography; *CT*, computed tomography.

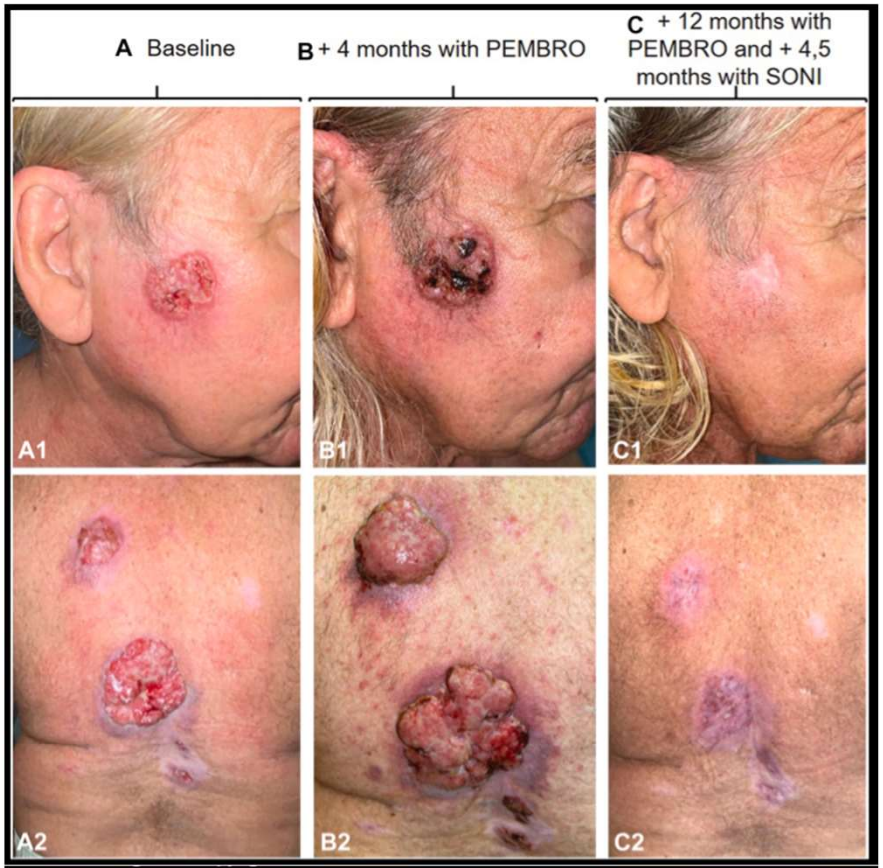

Fig 1 Locally advanced basal cell carcinoma (BCC) on (**A1**) cheek and (**A2**) back. **B,** BCCs pseudoprogression after 4 months of pembrolizumab. **C,** BCCs complete response after 4.5 months with sonidegib treatment and 12 months with pembrolizumab.

Randomized, Double-Blind Study of Sonidegib (LDE225) in Patients With Advanced Basal Cell Carcinoma

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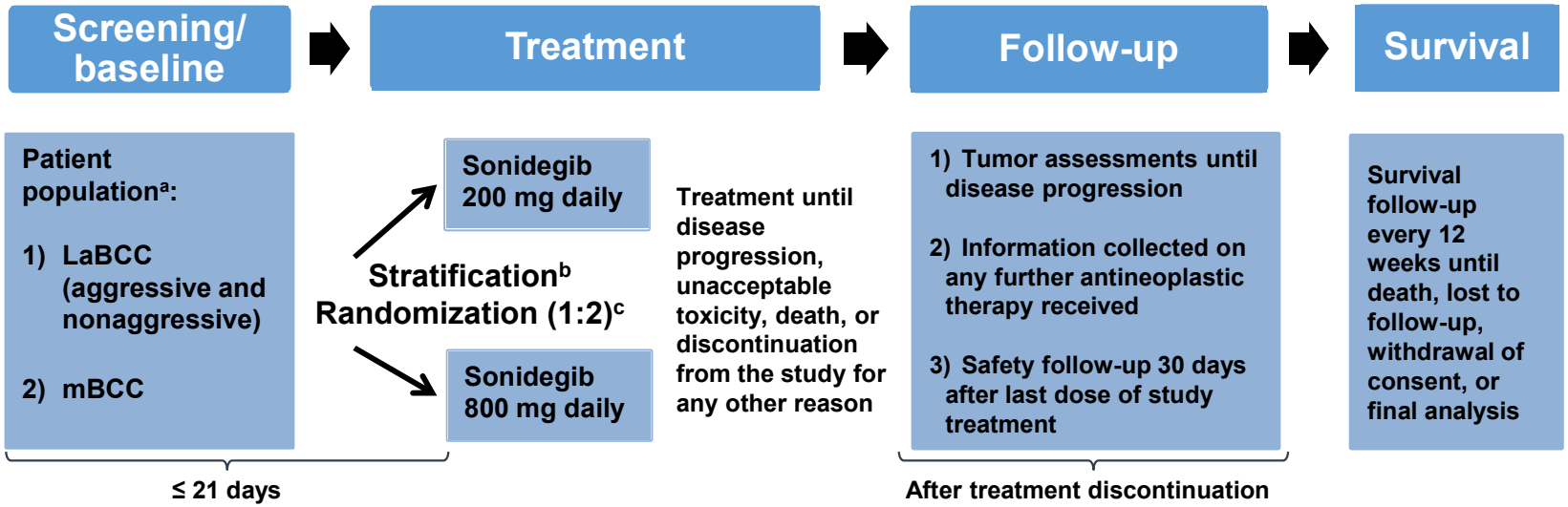
BOLT Study Design



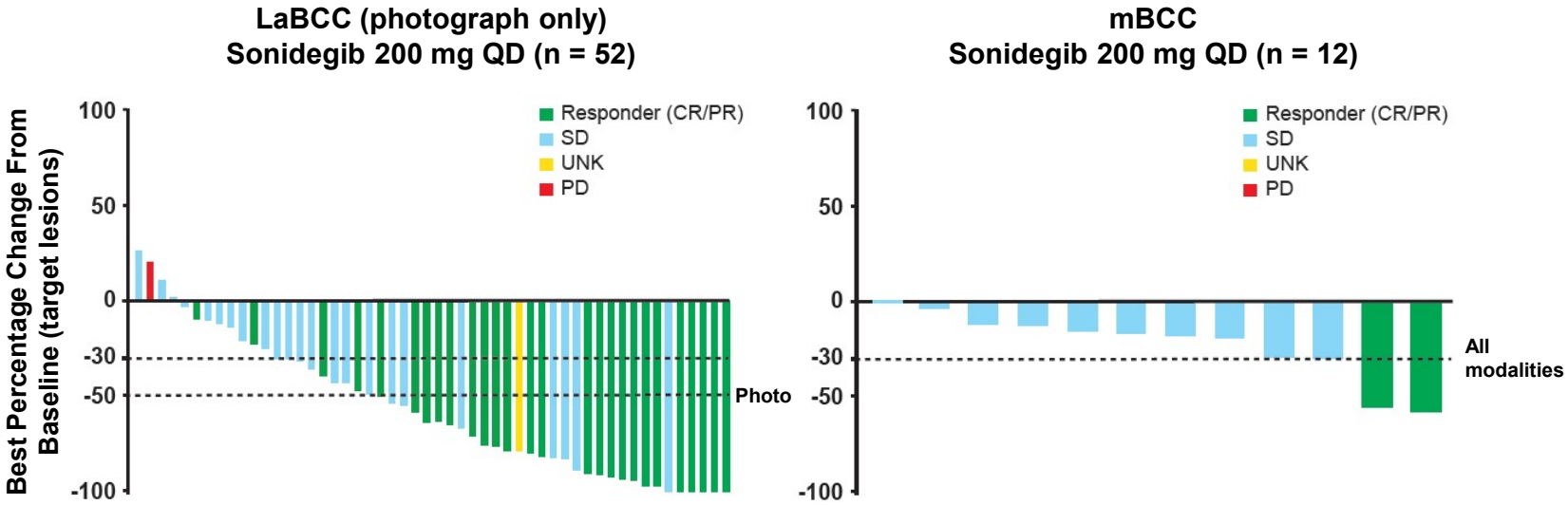
[a] Patients with prior treatment with sonidegib or other Hh pathway inhibitors were excluded.
[b] Stratification based on stage, disease histology for LaBCC patients (nonaggressive vs aggressive), and geographic region.
[c] Doses chosen based on data from the phase 1 study.[1] Sonidegib 200 mg once daily was the lowest dose level tested with evidence of antitumor activity; sonidegib 800 mg once daily was the highest well-tolerated, biologically active dose.

1. Rodon J, et al. *Clin Cancer Res*. 2014;20:1900-1909.

- **Primary analysis:** data collected up to 6 months after the last patient randomization date
- **12-month analysis:** data collected up to 12 months after the last patient randomization date

Best Percentage Change in Target Lesions (Primary Analysis)

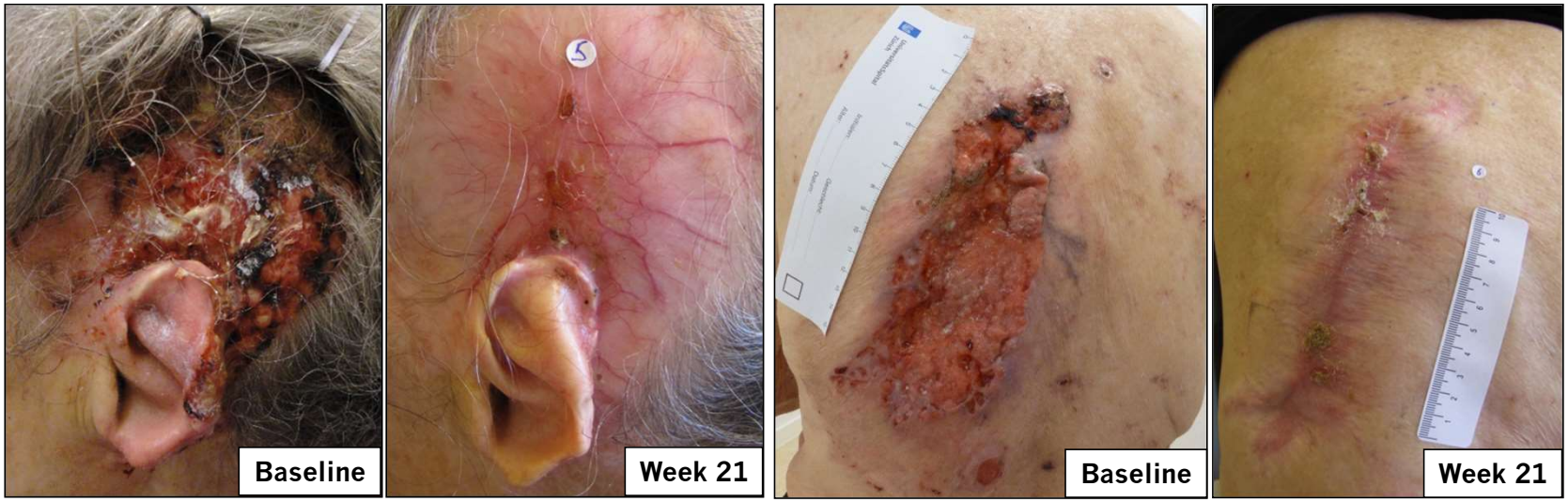
Central Review



Sonidegib Dose (daily)	200 mg		800 mg	
	LaBCC	mBCC	LaBCC	mBCC
Decrease in best percentage change from baseline, %	92	92	90	84
Increase or no change in best percentage change from baseline, %	8	8	10	16

CR, complete response; LaBCC, locally advanced BCC; mBCC, metastatic BCC; PD, progressive disease; PR, partial response; QD, once-daily; SD, stable disease; UNK, unknown.

Response in Patient Treated With Sonidegib 200 mg



Photographs provided by R. Dummer, Zürich, Switzerland.

- Patient with aggressive LaBCC treated with sonidegib 200 mg achieved an overall response of PR by central and investigator review

Conclusions

- The BOLT study met its primary endpoint (ORR) for both treatment arms
- With an additional 6-24 months of follow-up, sonidegib continued to exhibit sustained, clinically meaningful responses in patients with advanced BCC
- *GLI1* levels were reduced from baseline in patients with disease control
- Sonidegib has acceptable safety and tolerability; no new safety concerns emerged with longer follow-up
- Maintenance or improvement in quality of life was reported by most patients with advanced BCC treated with sonidegib
- Sonidegib is a promising treatment option for patients with advanced BCC; the 200-mg dose has been selected for future use based on its more favorable benefit-risk profile

Fragen und Diskussion

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