REVIEW ARTICLE

Basal Cell Carcinoma—Treatments for the Commonest Skin Cancer

Carola Berking, Axel Hauschild, Oliver Kölbl, Gerson Mast, Ralf Gutzmer

SUMMARY

Background: With an incidence of 70 to over 800 new cases per 100 000 persons per year, basal cell carcinoma (BCC) is a very common disease, accounting for about 80% of all cases of non-melanoma skin cancer. It very rarely metastasizes. A variety of treatments are available for the different subtypes and stages of BCC.

Methods: This review is based on pertinent literature retrieved by a selective search in the Medline database, as well as the American Cancer Society guidelines on BCC and the German guidelines on BCC and skin cancer prevention.

Results: The gold standard of treatment is surgical excision with histological control of excision margins, which has a 5-year recurrence rate of less than 3% on the face. For superficial BCC, approved medications such as imiquimod (total remission rate, 82–90%) and topical 5-fluorouracil (80%) are available, as is photodynamic therapy (71–87%). Other ablative methods (laser, cryosurgery) are applicable in some cases. Radiotherapy is an alternative treatment for invasive, inoperable BCC, with 5-year tumor control rates of 89–96%. Recently, drugs that inhibit an intracellular signaling pathway have become available for the treatment of locally advanced or metastatic BCC. Phase I and II clinical trials revealed that vismodegib was associated with objective response rates of 30–55% and tumor control rates of 80–90%. This drug was approved on the basis of a non-randomized trial with no control arm. It has side effects ranging from muscle cramps (71%) and hair loss (65%) to taste disturbances (55%) and birth defects.

Conclusion: The established, standard treatments are generally highly effective. Vismodegib is a newly approved treatment option for locally advanced BCC that is not amenable to either surgery or radiotherapy.

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Basal cell carcinoma (BCC) is the most common cancer in individuals with fair skin type and steadily increasing in incidence (1–3). Especially within the framework of skin cancer screening, a variety of specialists are increasingly confronted with BCC, which accounts for 80% of non-melanoma skin cancer. BCC is often misdiagnosed because of its pale color and lack of symptoms; it develops slowly over months to years. Metastasis is extremely rare with an estimated incidence of 0.0028–0.55% (4). Nonetheless the invasive growth pattern can destroy cartilage and bone and reach vital structures (major vessels or CNS) with a fatal course. Thus early recognition is especially important (5). Standard therapy is complete surgical removal. Radiation therapy is an option for inoperable tumors or those where the post-operative defect would be cosmetically disfiguring or functionally disabling. In recent years new therapeutic approaches have been developed both for locally advanced or metastatic disease (systemic medications) as well as for superficial BCC (topical medications) (6, 7). These therapeutic options should be considered in the multidisciplinary management of patients with sporadic or hereditary BCC.

Epidemiology, risk factors and subtypes

With around 2 million new tumors annually, BCC is the most common non-benign tumor in individuals with fair skin type (5, 7). It accounts for 80% of non-melanoma skin cancer and is increasingly seen in younger patients (<40 years) although the average age at first diagnosis is 60 years (3, 8). A recently published metaanalysis (1) showed regional differences in annual incidence rates/100 000 population: 115 BCC in Great Britain; 70–80 BCC in Germany, Switzerland and Italy; 170 BCC in the USA; and >800 BCC in Australia. In the past 30 years the incidence has at a minimum increased 2–3 fold (2, 3). The site of predilection is the chronically sun-exposed skin of the head and neck region, but multicentric-superficial BCC frequently are found on the trunk. In addition to skin type and exposure to UV irradiation, other risk factors include immunosuppression, exposure to arsenic, scars and hereditary disorders such as nevoid basal cell carcinoma syndrome (Gorlin–Goltz syndrome) and xeroderma pigmentosum (6, 9) (Tables 1 and 2).

Using both clinical and histological criteria, one can distinguish between the most common subtype, nodular BCC, which accounts for 50% of lesions and the

Clinic and Policlinic for Dermatology and Allergology, Ludwig Maximilian University of Munich (LMU): Prof. Dr. med. Berking

Department of Dermatology, Allergology and Venerology, University Medical Center Schleswig-Holstein, Kiel: Prof. Dr. med. Hauschild

Department of Radiotherapy, University Medical Center Regensburg, Germany: Prof. Dr. med. Kölbl

Department of Oral and Maxillofacial Radiology, Clinic for Oral and Craniomaxillofacial Surgery, Ludwig-Maximilians University of Munich (LMU): Dr. med. Dr. med. dent. Mast

Department of Dermatology and Allergology, Hannover Skin Cancer Center, Hannover Medical School: Prof. Dr. med. Gutzmer

TABLE 1

Risk factors for developing BCC (10–12)

Risk factor	Risk
Fair skin (skin types I and II)	OR 5.1 (95% CI: 1.4–11.3) in comparison to skin type IV
Intermittent UV exposure (sun burns)	OR 1.4 (see Table 2)
Personal history of BCC	3-year risk 44% (33–70%)
Prior treatment with ionizing radiation	RR 2.3 (95% CI: 1.7–3.1)
Genetic syndromes such as nevoid BCC syndrome; xeroderma pigmentosum	Development of multiple BCC in childhood possible
Chronic arsenic exposure	N.A.
Immunosuppression	N.A.

BCC, basal cell carcinoma; OR, odds ratio; CI, confidence interval; RR, relative risk; N.A., not available

TABLE 2

Relative risk* (with 95% CI) for the development of BCC with various types of sun exposure (13)

Type of sun exposure	RR for BCC
Total (cumulative)	0.98 (0.68–1.41)
Occupational	1.19 (1.07–1.32)
Non-occupational or intermittent	1.38 (1.24–1.54)
Sunburn at any age	1.40 (1.29–1.51)

* in comparison to control groups with lowest possible exposure. 95% CI, 95% confidence interval; BCC, basal cell carcinoma; RR, relative risk

infiltrative subtypes (sclerodermiform BCC and micro-nodular BCC) and the multicentric-superficial subtype, each of which makes up around 25% of tumors (6). Additional rare variants include pigmented BCC (1%) and the aggressive ulcerative and destructive forms (ulcus terebrans, ulcus rodens). Depending on the pattern of growth and location, there are a variety of therapeutic options which will be presented (Table 3).

The goal of this paper is to review the current therapeutic options for BCC. A selective literature search in the PubMed database was performed, with last search in January 2014, using the key words „basal cell carcinoma“ and „randomized controlled trial“, as well as „epidemiology“, „hedgehog inhibitor“, „review“, „photodynamic therapy“, „imiquimod“, „5-fluorouracil“, and „radiation therapy“. In addition we considered the current German S2 guideline on BCC and the S3 guideline on skin cancer prevention (5, 7)

Surgical treatment

The treatment of choice is complete excision of the BCC. Especially on the face in the problem zones of the

eyes, lips, and nose, microscopically-controlled surgery (MCS, micrographic surgery, Mohs surgery) with systematic 3-D evaluation of excision margins has become established (7). By carefully marking the excision margins, tumor extension to the border can be precisely identified microscopically and only involved areas re-excised, sparing normal skin. MCS has led to a reduction of the recurrence rate for primary tumors from 3–4.1% to 2–2.5% and for recurrent tumors from 3–12.1% to 0–2.4% (14, 15). Alternatively the excision can be performed using tumor-adjusted safety margins and conventional histological evaluation. Since the infiltrative subtypes are more likely to recur, a wider excision margin (0.3–1 cm) is recommended. Multicentric-superficial BCC on the trunk and extremities can in exceptional cases be treated by horizontal excision (shave excision) with conventional histology.

Even though there are no randomized controlled trials comparing surgical excision to non-operative approaches, excision is recommended as the therapy of choice in the guidelines. In addition to the low recurrence rate, excision is an efficient approach and allows for histological control of tumor margins. In addition, the therapy is independent of patient compliance. Disadvantages are the usual operative risks, aesthetically or functionally disturbing scars and pigment changes, as well as possible delays in wound healing. Both hypo- and hyperpigmentation can result.

Radiation therapy

Radiation therapy is an option when a tumor is inoperable because of its size or location, or when the patient is not eligible for surgery because of other medical problems, or if the patient declines surgery. Another indication is incomplete surgical excision of a BCC (R1, R2) when re-excision is not possible.

The S2-K guidelines recommend high-energy radiation therapy (electron or photon beam); primary tumors are treated with daily doses of 2–3 Gy and a total dose of 60–70 Gy. After R1 resection, 50–60 Gy are recommended and after R2 resection, 60–70 Gy (7).

If orthovoltage (soft) X-rays are used, then higher single doses (for example, 5 Gy) are administered but with a lower total dose. By using modern radiation therapy techniques (intensity-modulated radiation therapy, tomotherapy), today one can treat large tumors or those in unfavorable locations such as the periorbital region (16, 17).

Large retrospective series show, depending on the size of the tumor, 5-year control rates of 96.1% (T1), 95.6% (T2) and 88.6% (T3) (18). Although the previously common local late reactions, such as chronic radiation dermatitis, are no longer relevant with modern techniques (19), in young patients one must be alert to the theoretical possibility of the induction of secondary malignancies. Radiation therapy is contraindicated in nevoid BCC syndrome and xeroderma pigmentosum.

TABLE 3

Therapeutic options for basal cell carcinoma

Subtype	Therapy	Comments
Solid/sclerodermiform	Surgery	Complete excision with 0.3–1 cm safety margin; on face, microscopically-controlled surgery
Superficial-multicentric	Surgery	Excision as above; possibly horizontal excision
	Cryosurgery	Liquid nitrogen; either direct contact or spray
	Laser surgery	Ablative lasers (CO ₂ , Erbium:YAG)
	5-Fluorouracil	5% cream twice daily for 3–12 weeks
	Imiquimod	5% cream 5 times weekly for 6 weeks
	Photodynamic therapy	MAL-PDT, 2 cycles 1–4 weeks apart
Locally advanced, surgery not suitable or contraindicated	Radiation therapy	High-energy therapy (single dose 2–3 Gy with total dose of 60–70 Gy)
	Hedgehog pathway inhibitors, systemic oral	Vismodegib 150 mg daily LE225 (not approved) 200–800 mg daily

Liquid nitrogen cryotherapy and ablative laser therapy

Small and superficial BCC are occasionally still treated with liquid nitrogen (–196°C) either with direct contact or using a spray. Cure rates in two randomized controlled trials were 85–95% (20, 21). In daily clinical practice cryotherapy is not a standardized procedure so there is considerable individual variation. In general, freezing times of 10–20 seconds are employed.

Side effects develop in 20–50% of patients and include pain, erythema, blisters and crusts. The wounds may heal with hypopigmentation or scarring, which along with the lack of histological control, are further disadvantages of the procedure (20).

The problems are similar with ablative laser therapy which is usually performed with the CO₂ or Erbium:YAG laser.

Topical medical therapy

There are a variety of agents available to topically treat superficial BCC.

The immunomodulatory agent imiquimod binds to toll-like receptor 7 and induces the release of pro-inflammatory cytokines including IFN- α , TNF- α and IL-12. Imiquimod is approved as a 5% cream for treatment of small (<7.25 cm²) superficial BCC and is applied nightly five times a week for six weeks. The histologically controlled complete cure rate in the randomized controlled registration trial was around 80% (22).

Topical photodynamic therapy (PDT) with 5-amino levulinic acid or with its methyl ester (MAL, 160mg/g cream) plus red light is another therapy option for BCC (Figure 1). The MAL cream is applied to the tumor and covered with an occlusive dressing for three hours. During this time, the tumor cells form increasing

Figure 1: Superficial-multicentric basal cell carcinoma in the axilla, a) before and b) after photodynamic therapy

amounts of a photosensitizer, protoporphyrin IX, which is stimulated by irradiation with red light to form reactive oxygen species which are in turn cytotoxic. PDT for BCC should be repeated after 1–4 weeks. PDT achieved complete remission in 92% of superficial BCC in a randomized controlled trial (23).

The cytostatic agent 5-fluorouracil is available as a 5% prescription cream which is designed to be applied twice daily for 3–12 weeks until erosions develop. Even though the preparation has been on the market for many years, there are no prospective randomized trials addressing cure and recurrence rates.

In a 2013 multicenter single-blinded, controlled randomized comparative trial involving 601 patients, the complete cure rate for imiquimod was 83%; for

Hedgehog signal pathway. While the hedgehog signal pathway is important in embryogenesis, it is usually inactivated in adult cells. The figure shows mutations (red border) which can lead to the activation of the hedgehog pathway in a basal cell carcinoma and inhibitors (gray border) which can block the pathway. PTCH, patched; SMO, smoothened; SHH, sonic hedgehog; SUFU, suppressor of fused; Gli, Gli transcription factors (modified from [27])

FIGURE 2

5-fluorouracil, 80%; and for MAL-PDT, 73% (24). In a systematic review of clinical studies treating superficial BCC, the average cure rate for imiquimod was 86% (95% confidence interval 82–90%) and for PDT, 79% (71–87%), while there was too little study data to determine the rate for 5-fluorouracil (21). Advantages of topical cream therapy and PDT are scar-free healing and the possibility to treat wider areas. Disadvantages of 5-fluorouracil and imiquimod are the sometimes severe inflammatory and erosive reactions (although these are desirable for destruction of tumors) which develop at individually variable time intervals (several days to several weeks) and the dependence on good patient compliance. Disadvantages of PDT are the pain during the irradiation and the local inflammatory reaction (erythema, erosions, pustules, and crusts) which lasts for 1–2 weeks.

Disadvantages of topical therapy and PDT are the lack of histological control and the relatively limited depth of action, raising the spectre of residual or recurrent disease at the base of the treatment site which is clinically difficult to identify and considering the above-listed cure rates should not be underestimated.

Systemic medical therapy

Hedgehog pathway inhibitors

Activating mutations in the hedgehog pathway play a key role in the pathogenesis of BCC (*Figure 2*) (25–29). Topical application of the hedgehog pathway inhibitors cyclopamine and LDE225/sonidegib reduced the size of BCC in humans (30, 31). The first agent to be used successfully systemically was the hedgehog pathway inhibitor vismodegib (32). Numerous systemic hedgehog pathway inhibitors are in various stages of

clinical testing including LDE225/sonidegib (33), Cur61414, IPI-926, BMS-833923, TAK-441 and itraconazole (34).

Clinical studies with vismodegib

The efficacy of vismodegib was first shown in a Phase I dose-finding study treating patients with locally advanced or metastatic BCC who were not candidates for surgery or radiation therapy (32). Oral vismodegib produced objective reduction in tumor size in 18 of 33 patients (55%) with complete remissions in two cases.

In a subsequent Phase II study, ERIVANCE BCC (Efficacy and safety of vismodegib in advanced basal cell carcinoma), the response rate to vismodegib 150 mg daily was confirmed. In 63 patients with locally advanced BCC, the objective response rate was 43% (13 complete and 14 partial remissions); in an additional 38%, the disease was stabilized (tumor growth $\leq 30\%$) (35). In 33 patients with metastatic BCC, the objective response rate was 30% and stabilization rate was 64%. The median progression-free survival in both groups was 9.5 months. Aleksandar Sekulic, M.D., Ph.D., the global director of the ERIVANCE registration trial, provided an 18-month update at the American Society of Clinical Oncology (ASCO) meeting in June 2013. Patients with locally advanced BCC had been treated for a median of 12.7 months, while those with metastatic BCC had been treated for 13.3 months. The median duration of response to therapy was 20.3 months for locally advanced BCC and 14.7 for metastatic BCC, with an overall median of 16.8 months. Reasons for stopping therapy included disease progression (16% for locally advanced BCC; 53% for metastatic BCC), adverse effects (29%; 15%) and patient's request (41%; 15%).

Figure 3: Sporadic solitary locally advanced basal cell carcinoma on the scalp of an 89-year-old woman a) before and b) after 10 weeks of therapy with the hedgehog signal pathway inhibitor vismodegib. Multiple BCC on back of a 62-year-old man with nevoid BCC syndrome c) before and d) after 8 months of therapy with the hedgehog signal pathway inhibitor LDE225. His seborrheic keratoses did not change during therapy.

The results of these Phase I and Phase II studies led to the approval of vismodegib by the Food and Drug Administration in the USA on 30 January 2012. The European Medicines Agency (EMA) on 12 July 2013 approved vismodegib throughout Europe for the treatment of patients with symptomatic metastatic or locally advanced BCC not suitable for surgery or radiation therapy. This approval was based on a non-randomized study without a control arm (35). On this basis, the German Federal Joint Committee (Gemeinsamer Bundesausschuss) determined on 6 February 2014 that there was no additional advantage for vismodegib over best supportive care for patients with symptomatic metastatic BCC. For patients with advanced local BCC not suitable for surgery or radiation therapy, there was only evidence for a minimal additional benefit (www.g-ba.de). The annual therapy costs for vismodegib in Germany as of February 2014 were 113 172.16 Euro, based on the retail pharmacy price.

In an additional Phase II study 41 patients with nevoid BCC syndrome were evaluated who had had at least 10 BCC up to two years before inclusion in the study (36). In comparison to a placebo group, those treated with vismodegib developed significantly fewer new BCC (2 versus 29 cases per group and year). The same was true for the size of pre-existing BCC (percentage change in sum of maximum diameters –65% versus –11%).

The safety of vismodegib was evaluated in around 1200 patients with advanced BCC in an international, open-label single-arm Phase II study STEVIE (SafeTy Events in Vismodegib). The third interval analysis of 300 patients confirmed the safety profile and the high tumor control rate (Grob JJ et al. JCO 2013, 31, suppl; abstr 9036).

Figure 3 shows examples of the therapeutic effect of hedgehog pathway inhibitor therapy in one patient with locally advanced BCC and another with multiple BCC.

Adverse effects of hedgehog pathway inhibitors

Hedgehog pathway inhibitors are markedly teratogenic and embryotoxic. Strict protocols must be followed to exclude pregnancy before starting therapy and to ensure reliable contraception during therapy.

The most common adverse effects of vismodegib include muscle cramps (71%), hair loss (65%), taste disturbances (55%) and weight loss (51%). Other undesired effects include fatigue (42%), nausea (33%), and diarrhea (27%) (35). Thus the patients must be adequately warned and counseled prior to starting therapy. In order to improve tolerability and patient acceptance, studies are in progress testing either regular interruptions in therapy (on-off schedule) or use as a neoadjuvant agent.

KEY MESSAGES

- Basal cell carcinoma is the most common cancer in individuals with fair skin type.
- Surgical excision is the gold standard treatment because the tumor grows slowly and only rarely metastasizes.
- Radiation therapy is an option for inoperable basal cell carcinomas.
- Superficial basal cell carcinomas can be treated with topical medical therapy or photodynamic therapy.
- Vismodegib is a newly licensed therapeutic option for patients with locally advanced or metastatic basal cell carcinomas.

Conflict of interest statement

Prof. Berking has received lecture and consultancy fees from Almirall Hermal, Biofrontera, Galderma, Leo Pharma, Novartis, and Roche Pharma. She has received reimbursement of travel, accommodation, and conference/continuing education registration costs from Roche Pharma, Galderma, and Novartis. She has participated in clinical studies sponsored by Biofrontera, Galderma, Leo Pharma, Novartis, and Roche Pharma.

Prof. Hauschild has received lecture and consultancy fees, as well as reimbursement of travel, accommodation, and conference/continuing education registration costs from Almirall Hermal, Biofrontera, Galderma, Leo Pharma, MEDA Pharma, Novartis, and Roche Pharma. He has participated in clinical studies sponsored by Biofrontera, Leo Pharma, Novartis, and Roche Pharma.

Prof. Köhl has received lecture fees and conference/continuing education reimbursement of registration costs from Roche Pharma.

Prof. Gutzmer has received consultancy fees from Almirall Hermal, Leo Pharma, Novartis, and Roche Pharma. He has received lecture fees, as well as reimbursement of travel, accommodation, and conference/continuing education registration costs from Almirall Hermal, Roche Pharma, and Novartis. He has received research support from Roche Pharma, Novartis and Pfizer.

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Corresponding author

Prof. Dr. med. Carola Berking
 Klinik und Poliklinik für Dermatologie und Allergologie
 Klinikum der Universität München (LMU)
 Frauenlobstr. 9–11
 80337 München, Germany
 Carola.Berking@med.lmu.de