Pharmacodynamic Evaluation: Dermatology

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Contents

Psoriasis ................................................................. 2
Pathophysiology ......................................................... 2
Clinical Features ....................................................... 2
Diagnostics ............................................................... 2
Treatment ................................................................. 3
Therapeutic Management ............................................ 4
Feature Treatments .................................................... 4

Atopic Dermatitis .................................................... 4
Pathophysiology ....................................................... 4
Clinical Features ..................................................... 5
Diagnostics ............................................................. 5
Treatment ............................................................... 6
Therapeutic Management .......................................... 8
Future Treatments .................................................... 9

Neoplasms of the Skin ................................................ 9
Nonmelanoma Skin Cancer: Basal Cell Carcinoma and Squamous Cell Carcinoma . . 9
Malignant Melanoma .................................................. 13

References and Further Reading .................................... 16

Abstract

Psoriasis, atopic dermatitis, and skin cancer are the three main dermatological, highly prevalent diseases for which new effective systemic therapies have been developed. For the immune-mediated inflammatory skin diseases, several biologic agents are now available for the chronic plaque psoriasis. These agents target one specific proinflammatory cytokine (TNF-alpha, interleukin (IL)-17, and (IL)-23) or its receptor. The IL-4 receptor blocking dupilumab is the first biologic agent which can be used for the chronic inflammatory skin disease, atopic dermatitis. By interfering in the Hedgehog signaling pathway, vismodegib proves to be effective in metastasized or extensive basal cell carcinoma (BCC) where a surgical procedure is no longer feasible. Immuno-therapy with checkpoint inhibitors is a major breakthrough in melanoma and is rewarded with the Nobel Prize in Physiology and
medicine, 2018. All these new systemic therapies are valuable additions to the already existing armamentarium of the dermatologist.

Psoriasis

Pathophysiology

Psoriasis is a chronic immune-mediated inflammatory skin disease. Predisposition is polygenic and the disease is triggered by trauma, infection, or medication such as beta-blocking agents. Both innate as adaptive immunity are involved in the pathogenesis of psoriasis (Nestle et al. 2009). Dendritic cells, T cells, neutrophils, keratinocytes, and cytokines released by immune cells (especially TNF-alpha, interleukin (IL)-17, and (IL)-23) contribute to the initiation of the disease (Fig. 1).

Clinical Features

Psoriasis has various distinct clinical variants. The major categories include chronic plaque psoriasis, which is the most common, guttate psoriasis, inverse psoriasis, scalp psoriasis, nail psoriasis, pustular psoriasis, and erythrodermic psoriasis (Boehncke and Schön 2015). The typical psoriatic skin lesions are symmetrical, well-demarcated erythematous plaques with silvery scales. Trauma of the skin may provoke new psoriasis lesions. This is called Koebner phenomenon. An associated disorder is psoriatic arthritis in which psoriasis is related to with spondyloarthropathy and/or peripheral arthritis (Fig. 2).

Diagnostics

In clinical practice, diagnosis can be made by proper anamnesis and physical examination.
However, in some cases, it is necessary to do a skin biopsy to confirm the diagnosis. Histopathologic findings in psoriatic skin are confluent parakeratosis with some neutrophils, regular acanthosis, epidermal hypogranulosis, dermal inflammatory infiltrate, and tortuous dilated dermal capillaries.

**Treatment**

A broad spectrum of topical and systemic treatment options are available for psoriasis and are discussed below.

**Topical Corticosteroids and Vitamin D Analogs**

The first choice treatment are topical corticosteroids frequently in combination with a vitamin D analog, such as calcipotriol (Mason et al. 2013). Topical corticosteroids exert anti-inflammatory, antiproliferative, and immunosuppressive effects. Based on vasoconstrictive assays, they are categorized in low, medium, high, or very high potent groups. Vitamin D analog binds to its receptor, which inhibits keratinocyte proliferation and enhances keratinocyte differentiation. Vitamin D has also specific immunomodulatory effects.

**Ultraviolet Phototherapy**

Moderate to severe psoriasis can be treated with ultraviolet B (UVB), narrowband UVB (nUVB), and photo chemotherapy with ultraviolet A (UVA) following topical or systemic pretreatment with psoralen. All these treatments are antiproliferative and anti-inflammatory by apoptosis of activated inflammatory cells (Weichenthal et al. 2005).

**Systemic Medication**

Systemic medication is used for moderate to severe psoriasis with large affected body skin surface, but also for nail psoriasis. Regular blood tests should be performed with all systemic medications.

- **Methotrexate** – Methotrexate is a folic antagonist closely related with the substance aminopterin (Menter et al. 2009). It inhibits keratinocyte proliferation and has immunosuppressive effect of activated T cells in psoriatic plaques. Maximum improvement can be seen after 8–10 weeks.

- **Ciclosporin** – Ciclosporin is a calcineurin inhibitor, which prevents T cells from releasing proinflammatory effector cytokines like IL-2. The maximum treatment duration is 1 year due to potential nephrotoxic effects.

- **Acitretin** – Synthetic derivatives of vitamin A normalize keratinocyte proliferation and differentiation, but it has also distinct inhibitory effects on Th-17 cells.

- **Fumarates** – Dimethylfumarate and the biologically active subunit monomethylfumarate
act anti-inflammatory and immunosuppressive by inhibiting proliferation of dendritic and T cells and the release of cytokines like TNF alpha and IL-8. Clinical effects can be seen after 6–8 weeks.

- **Apremilast** – A small molecule inhibitor of the intracellular enzyme phosphodiesterase 4 has anti-inflammatory effects. This oral medication has also a profound antipruritic effect in psoriasis.

- **Biologic agents** – Biologic agents are the latest addition in the treatment of psoriasis and are more expensive compared to other systemic medication (Menter et al. 2008). The mode of action differs per biologic agent, but all biologic agents induce an anti-inflammatory response. Infliximab, adalimumab, etanercept, and certolizumab are TNF-alpha inhibitors. Certolizumab is of special interest due to its pegylated form. This biologic agent can be safely prescribed in pregnant and lactating female psoriasis patients. Secukinumab and ixekizumab are anti-IL-17A monoclonal antibodies and brodalumab blocks the IL-17 receptor. Ustekinumab is a human monoclonal antibody that targets IL-12 and IL-23, while guselkumab is a specific IL-23 antagonist (Fig. 3).

### Therapeutic Management

Treatment evaluation can be done by physical examination. To evaluate objectively, physicians use PASI: Psoriasis Area and Severity Index (Schmitt et al. 2005). Points are given for severity of erythema, induration, and scaling respectively on the head, upper limbs, trunk, and lower limbs. A high score means severe psoriasis.

### Feature Treatments

Research suggests new treatment options for psoriasis, such as other small molecules that target the intracellular signaling. This includes JAK (Janus kinase) inhibitors: tofacitinib and baricitinib (Ports et al. 2013).

### Atopic Dermatitis

#### Pathophysiology

Atopic dermatitis is a chronic pruritic inflammatory skin disease that occurs mostly in young children that can persist in adulthood. Atopic syndrome stands for a group of IgE-related diseases:

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Fig. 3  Immunopathogenesis of psoriasis and the mode of action of the biologic agents
atopic dermatitis, allergic rhinoconjunctivitis, and asthma. The pathogenesis of atopic dermatitis is multifactorial and involves genetic predisposition, immune dysregulation, and environmental irritation (Weidinger et al. 2018). This leads to defects of the skin barrier and major skin inflammation.

**Genetics**

The most important part of the barrier function of the skin is located in the stratum corneum, the outer layer of the epidermis. It prohibits environmental irritants from entering the skin and prevents excessive water loss. Filaggrin is a protein produced by differentiating keratinocytes in the epidermis and is encoded by the FLG gene on the 1q21 epidermal differentiation complex. Filaggrin is needed for correct formation of corneocytes and therefore responsible for an intact barrier function of the skin. A loss-of-function mutation of the filaggrin (FLG) gene leads to skin barrier abnormalities and is a major risk factor for atopic dermatitis (Thyssen and Kezic 2014). Another risk factor is a positive family history of parents with an atopic disease. One atopic parent gives a two- to threefold increased risk of atopic dermatitis. Two atopic parents increase the risk even three- to fivefold.

**Immune Dysregulation**

The innate immune system in atopic dermatitis is altered and leads to a different skin microbiome and more severe inflammations. Patients with atopic dermatitis have more often colonization and infections with *Staphylococcus aureus*.

The adaptive immune system in atopic dermatitis is also altered by increased expressions of Th2, Th22, and Th17 cytokines leading to immune dysregulation (Boguniewicz and Leung 2011) (Fig. 4).

**Environmental Irritation**

Irritation factors for the skin vary from excessive contact with water, temperature changes, low humidity, bacterial or viral infection, scratching, and stress (Weidinger et al. 2018). Topical treatment and emollients are needed to prevent these factors from penetrating the skin and causing flares.

**Clinical Features**

Main characteristics of atopic dermatitis are pruritus and dry skin. Physical examination show morphological differences between acute and chronic atopic dermatitis lesions. In the acute phase, the lesions are erythematous squamous papules and plaques with exudate and vesicles. When this persists, it passes into the chronic form with xerosis and erythematous squamous plaques with lichenification (Rudikoff and Lebwohl 1998).

The form and localization of skin lesions differ per age.

Young children with atopic dermatitis, before the age of two, show the acute form of skin lesions on the cheeks and extensor sites of the body. Napkin area is usually spared. Older children and adolescents, until the age of 18, show more frequently the chronic form of skin lesions on flexor sites of the body, such as antecubital and popliteal fossae, and the neck. Lichenification is more present due to intensive scratching. In adulthood, the chronic form is also seen on flexure sites and to a lesser extent on the hands, neck, and face.

Besides the main characteristics described above, there are several clinical findings that are seen as minor criteria for atopic dermatitis. These are the following: keratotic pilaris, pityriasis alba, periorbital darkening, Dennie-Morgan infraorbital folds, and Hertoghe’s sign (hair loss of lateral eyebrows).

Atopic dermatitis can be complicated with a secondary impetiginization, usually with *Staphylococcus aureus*. If so, yellow crusts and exudate are seen at the affected skin lesions (Rudikoff and Lebwohl 1998). Another infectious complication may occur with the herpes simplex virus. This is known as eczema herpeticum and needs intravenous treatment with antiviral agents, because of high morbidity (Leung 2013).

**Diagnostics**

Atopic dermatitis is a clinical diagnosis based on major and minor disease symptoms, family history, and physical examination. A skin biopsy
may help for histological confirmation of the diagnosis. Histological findings are hyperkeratosis, epidermal edema (spongiosis) with acanthosis, and lymphohistiocytic dermal infiltration (Weidinger et al. 2018).

An elevated total IgE in blood may support the diagnosis (Fig. 5).

**Treatment**

Various treatments are available for atopic dermatitis. Often are education, use of emollients, and topical corticosteroid therapy sufficient. In severe disease, ultraviolet phototherapy or systemic medication can be given.

**Education and Use of Emollients**

First step in treatment of atopic dermatitis is education about pathophysiology of atopic dermatitis, good skin care, and avoidance of skin irritants (Tollefson and Bruckner 2014). It is better to avoid excessive water contact because it causes dehydration of the skin. Triggers of skin irritation need to be avoided. Frequent application of skin emollients, two to three times a day, helps recover the stratum corneum lipids. Anti-itch treatment with (sedating) antihistamines can be prescribed to stop scratching and can restore insomnia.
Topical Corticosteroids and Calcineurin Inhibitors

The mainstay in treatment of atopic dermatitis is topical corticosteroids (Eichenfield et al. 2014). Mild atopic dermatitis reacts well to low potent corticosteroids, such as hydrocortisone 1%. Patients with moderate disease need medium to high potent corticosteroids, such as betamethasone dipropionate 0.05%. Mechanism of action is antipruritic, vasoconstrictive, and anti-inflammatory. It suppresses the release and activity of various proinflammatory mediators, such as kinines, histamine, and prostaglandins.

Topical calcineurin inhibitors, tacrolimus and pimecrolimus, are good alternatives for topical corticosteroids. Mechanism of action is binding to FKBP-12, an intracellular protein, and other complexes with calcineurin dependent proteins (Eichenfield et al. 2014). This leads to inhibition of calcineurin phosphatase activity and thereby reduction of T-lymphocytes activation. It can be used in the face, neck, and skinfolds. Most common side effects are temporal sensations of burning, redness, and itch.
Ultraviolet Phototherapy

Ultraviolet phototherapy is indicated in moderate atopic dermatitis when topical therapy fails. Narrowband ultraviolet B (UVB) with a spectrum of 311–313 nm is preferred. This treatment is only suitable for adults and not for children. The mechanism of action is anti-inflammatory (Weichenthal et al. 2005).

Systemic Medication

Systemic medication is indicated in moderate to severe atopic dermatitis. First choice of systemic medication is cyclosporine due to fast relieve of symptoms. Systemic medication used in atopic dermatitis is described below (Ring et al. 2012).

- **Ciclosporin** – Ciclosporin is a lipophilic cyclic peptide of 11 amino acids that binds to cyclophilins. This drug-receptor complex binds and inhibits calcineurin, causing a reduced release of cytokines IL-2, TNF-alpha, and IL-3. It suppresses T-cell proliferation. The maximum treatment duration is 1 year due to nephrotoxic effects.

- **Systemic corticosteroids** – Short period of prednisone is given in moderate to severe atopic dermatitis when ciclosporin is contraindicated. Prednisone is converted in the liver to an active metabolite, prednisolone. It acts as a glucocorticosteroid, which has immunosuppressive action due to reduction in activity of lymphocytes and suppression of the adrenal function.

- **Methotrexate** – Methotrexate is used as a long-term treatment in patients with severe atopic dermatitis. Remission induction is seen several weeks after start. Folic acid is daily given to prevent methotrexate toxicities. Methotrexate is a folate antimetabolite that interferes with DNA synthesis and repair. Rapidly proliferating tissue is most receptive for methotrexate.

- **Dupilumab** – Dupilumab is most recently accepted as a treatment for moderate atopic dermatitis (Beck et al. 2014). It is a human monoclonal IgG4 antibody and works immunosuppressive by blocking IL-4R alpha subunits, which leads to inhibition of IL-4 and IL-13. Administration is by subcutaneous injections once every 2 weeks.

Antibacterial and Antiviral Treatment

Atopic dermatitis patients with mild bacterial superinfection, usually with *Staphylococcus aureus*, can be treated with topical mupirocin 2% cream twice daily for 2 weeks. Severe infections are treated with oral antibiotics (Ring et al. 2012). Viral superinfections with herpes simplex need to be treated with an oral antiviral therapy; valaciclovir. Intravenous antiviral treatment during hospital admission is indicated for severe life-threatening cases of eczema herpeticum.

Therapeutic Management

Efficacy of treatment is clinically observed by the treating physician. Objective tools can be used for treatment evaluation, such as EASI, SCORing, and POEM.

The Eczema Area and Severity Index (EASI) is used to measure extend and severity of atopic dermatitis (Hanifin et al. 2001). The score can be calculated by recording the severity of redness, thickness of the skin, scratching, and lichenification at four different body areas. This results in a score 0, for no active lesions, till 72, for very severe atopic dermatitis.

Another tool to measure the extent and severity of atopic dermatitis is the SCORAD (SCORing Atopic Dermatitis) (SCORAD 1993). First, the percentage of affected skin is measured. Next, one region is assessed as none 0, mild 1, moderate 2, or severe 3 for redness, swelling, oozing/crusting, scratch marks, lichenification, and dryness. Subjective symptoms, itching and sleeplessness, are scored 0 for not present to 10 for worst as possible.

Patient-oriented eczema measure (POEM) is a questionnaire filled in by patients or caregivers that result in an anamnestic severity index for atopic dermatitis (Charman et al. 2004).
Future Treatments

Studies of new treatments for atopic dermatitis show promising results for JAK inhibitors and monoclonal anti-IL 31, 13, and 22 antibodies. Tofacitinib is a small-molecule Janus kinase (JAK) inhibitor which inhibits cytokine signaling of interleukin (IL)-4, IL-5, and IL-13 in a 2% ointment topical treatment (Bissonnette et al. 2016). Nemolizumab, lebrikizumab, and fezakinumab are monoclonal antibodies that bind to, respectively, IL-31 receptor A, IL-13, and IL-22 (Ruzicka et al. 2017; Simpson et al. 2018; Guttman-Yassky 2018). Working mechanism is by interfering with the cytokine-mediated immune response and inflammation in affected skin.

Neoplasms of the Skin

Nonmelanoma Skin Cancer: Basal Cell Carcinoma and Squamous Cell Carcinoma

Pathophysiology

Basal Cell Carcinoma

Basal cell carcinoma (BCC) is the most common type of skin cancer and consists of 80% of all skin cancers. It originates from the basaloid cells in the epidermis and grows very slowly. Without treatment it grows invasive and causes tissue destruction. BCC is usually diagnosed in early stages and metastasize rarely.

The most important risk factor for BCC is intense intermittent ultraviolet radiation (UV) in sunlight/sunburn (Gallagher et al. 1995). Extensively, sun light exposure, before the age of 18 years old, has a direct relation with risk of BCC. The use of tanning beds also elevates the risk for BCC (Ferrucci et al. 2012). Related risk factors are fair skin with freckling’s and light colored eyes and older age. Prevention of sunburn with sun protection cream under the age of 18 decreases the risk of nonmelanoma skin cancer dramatically.

Other risk factors are a past of radiation therapy, long-term use of immunosuppressants in organ transplant patients, and genetics. Patients with family members with BCC have an increased risk of developing BCC during life.

Basal cell nevus syndrome or Gorlin syndrome is a rare autosomal dominant genetic disorder related with BCC (Gorlin and Goltz 1960). It is caused by a germline mutation of a human patches gene (PTCH). Multiple BCC are presented before the age of 35, mostly at the trunk. Other clinical features are dysmorphic facial characteristics, bifid ribs, palmar and plantar pitting, mandible bone cysts, calcification of flax cerebri, and medulloblastoma.

Squamous Cell Carcinoma

Squamous cell carcinoma (SCC) arises from keratinocytes in the epidermis. SCC represents 20% of all nonmelanoma skin cancers (Alam and Ratner 2001). Patient-specific characteristics and environmental factors contribute to the development of SCC. The incidence for SCC increases strongly with age. In addition, individuals with a light skin develop SCC much more often than people with dark type skin.

As for environmental factors, cumulative lifetime sun exposure is the most important cause of SCC. Other risk factors are radiotherapy, the use of chronic immunosuppressant for organ transplant patients, and positive family history of SCC (Alam and Ratner 2001). Chronic inflammation of the skin as in chronic ulcers or inflammatory dermatoses, such as lichen sclerosus et atrophicus, also increases the risk of SCC.

Clinical Features

Basal Cell Carcinoma

During physical examination, a distinction can be made between nodular and superficial BCC (Marzuka and Book 2015). Nodular BCC is pink or flesh-colored papules or plaques with a pearly reflection and telangiectasia. The border is usually elevated, which is described as rolled border. In more advanced stages, central ulceration is seen within the rolled border. Superficial BCC are most
commonly seen on the trunk. They present as red or pink macules with light scaling. When illuminated, they have a shiny appearance (Fig. 6).

**Squamous Cell Carcinoma**

Cutaneous SCC is most common at sun-exposed body sites. The head and neck represents about 55% of all SCC. Individuals with dark skin type usually develop SCC on body sites without sun exposure, such as perianal or chronic ulcers.

Most of the SCC (in situ) arises from actinic keratosis. Actinic keratosis is presented as scaly and red skin lesions at sun damaged skin, usually seen in older patients. Differentiation between actinic keratosis and SCC (in situ) can be difficult. Although SCC often arises from actinic keratosis, only 1% of all the lesions progresses into SCC (Criscione et al. 2009).

SCC in situ (Bowen’s disease) is a well-demarcated red or skin colored plaque with scaling (Alam and Ratner 2001). SCC in situ is most often asymptomatic. SCC in situ of the penis is called erythroplasia of Queyrat. This is presented as a well demarcated, velvety, and red papule or plaque (Fig. 7).

Invasive SCC has different clinical appearances depending on differentiation level (Alam and Ratner 2001). Well-differentiated SCC present as solid hyperkeratotic papules or plaques with or without ulceration. Poorly differentiated SCC is a more soft and granulomatous papule without hyperkeratosis. Sensation of pain can occur. Neurological problems at the lesion site, such as numbness, paraesthesias, or paralysis, indicate perineural invasion by the tumor, which is a poor prognostic factor.

When SCC metastasizes, this is most often seen in regional lymph nodes. In severe cases, metastasis can spread to lungs, liver, brain, skin, or bone. SCC on ears or mucocutaneous areas such as the lips tends to metastasize more often (Fig. 8).

**Diagnostics**

Diagnosis of BCC and SCC can be made based on physical examination. However, in most cases a skin biopsy is used for histological confirmation of the diagnosis. Histological findings of nodular BCC are large nests of atypical basaloid tumor cells with peripheral palisading in the dermis and slit-like stroma retractions (Crowson 2006). Superficial BCC are small clusters of atypical basaloid cells attached to the epidermal surface and show as well slit-like stroma retraction.

SCC in situ show keratinocytic dysplasia of the full thickness of the epidermis with no involvement of the dermis (Alam and Ratner 2001). The keratinocytes have intense mitotic activity, pleomorphism, and enlarged nuclei. Acanthosis, hyperkeratosis, and parakeratosis of the stratum corneum are often seen. The epidermis has a windblown look due to loss of maturity and polarity.

In contrast, actinic keratosis shows dysplastic keratinocytes only in parts of the epidermis.

In invasive SCC, the dysplastic keratinocytes are involved in the full epidermis and
penetrate the basement membrane into the dermis or further surrounded tissue. Well-differentiated SCC shows large atypical keratinocytes with abundant cytoplasm. Poorly differentiated SCC shows anaplastic keratinocytes without differentiation and with many mitoses. Invasive SCC has a few exclusive histopathological variants, such as spindle cell SCC, clear cell SCC, and desmoplastic SCC (Yanofsky et al. 2011).

Besides diagnosis and tumor differentiation, the tumor depth and perineural invasion are also reviewed. This is necessary for proper tumor staging.

**Treatment**

Frequently used treatment of nonmelanoma skin cancer is surgical excision. Other treatment options are topical treatments, cryotherapy, photodynamic therapy, and radiation therapy, depending on the type and stage of skin cancer. The latest addition in therapeutic armamentarium is systemic therapy with vismodegib for the following treatments:

- **Surgical excision** – Surgical excision is one of the most effective treatment with low recurrence rates for both BCC and SCC. This is performed under local anesthesia. Histologic assessment is used to determine completeness of the procedure. Margins for BCC vary 3–5 mm of normal skin. For SCC, it varies from 4 mm for low risk to 1 cm for high risk tumors (Brodland and Zitelli 1992).
Besides conventional surgical excision, Mohs micrographic surgery can be used to obtain an even lower recurrence rate. Indications are high-risk nonmelanoma skin cancers at complex anatomic sites such as the nose, lips, eyelids, eyebrows, and ears (Van Loo et al. 2014). Mohs micrographic surgery is performed by a specialized dermatology surgeon. After excision of the tissue, the lesion is cut into horizontal sections which make it possible to evaluate the full peripheral and deep margins.

**Topical treatment** – Topical fluorouracil and imiquimod are topical treatment options which need to be applied 4–8 weeks at the tumor site (Love et al. 2009).

Topical fluorouracil (FU), usually 5% cream, is a treatment option for actinic keratosis, SCC in situ, and superficial BCC when surgical excision is not preferred. FU is a pyrimidine antimetabolite that interferes with DNA synthesis by inhibiting thymidylate synthesis. Blockage of DNA synthesis leads to prevention of cell proliferation and cell death. Success of treatment depends highly on adequate application, duration, and tumor selection.

Imiquimod 5% cream is used for actinic keratosis, anogenital warts, and superficial and nodular BCC at low-risk sites. It is a Toll-like receptor 7 agonist and immune cell modulator. It activates immune cells to produce cytokines that stimulate cell-mediated immunity and promotes apoptosis of malignant cells. Imiquimod is more effective in superficial BCC than topical fluorouracil. Oral immunosuppressive medication is a relative contraindication for the use of imiquimod.

**Cryosurgery** – In actinic keratosis, SCC in situ, small low-risk SCC, and superficial BCC, cryosurgery is an effective modality for treatment (Kuflik 2004). The tumor is one or two times frozen and thawed through application of liquid nitrogen. Malignant cell destruction is due to formation of intra- and extracellular ice crystals, vascular stasis, hypertonic damage, and breakdown of the phospholipid membrane. It is a fast, cost effective treatment and usually needs no anesthesia. Hypopigmentation and scarring are the most common lasting side effects.

**Photodynamic therapy** – Photodynamic therapy can be used in SCC in situ and superficial BCC (Morton et al. 2013). Mechanism of action is by topical applying a photosensitizing porphyrin, such as 5-aminolevulinic acid (ALA) or methyl aminolevulinate (MAL). Several hours after application, the tumor is exposed to a blue light (400–450 nm) or red light (630–635 nm). The photosensitizer absorbs the light and releases reactive oxygen. This leads to cell damage and cell death.

**Radiation therapy** – Patients with BCC and SCC who are not candidates for surgical excision or who have multiple recurrences can be treated with radiation therapy (Locke et al. 2001). Disadvantages are need of multiple treatments, lack of histological control, more expensive, and local and long-term side effects.

**Vismodegib** – Vismodegib is an orally available kinase inhibitor with specific activity against a key step in the Hedgehog signaling pathway. Hedgehog is a key regulator of embryonic development, cell growth, and differentiation. Clinical trials of vismodegib in patients with metastatic or locally advanced basal cell carcinoma reported at least partial responses in up to half of patients. Current indications include metastatic or locally advanced, recurrent, or unresectable basal cell carcinoma.

**Regional Lymph Nodes**

The extent of the disease in cutaneous SCC is evaluated through physical examination and ultrasound of locoregional lymph nodes. Patients with enlarged lymph nodes need to undergo biopsy via fine-needle aspiration or surgical excision. When metastasis in lymph nodes occurs, further research is indicated for staging and prognosis.

**Therapeutic Management**

Follow-up for BCC consists of physical examination by a dermatologist once every 6 months for
1 year and then annually. When no recurrence or new primary tumor occurs, follow-up will consist of self-examinations at home and visits as needed.

The follow-up interval for cutaneous SCC depends on the tumor stage and varies between 3 and 6 months for 2 years and afterwards yearly. Examination is targeting on recognition of recurrences, new primary skin cancers, and lymph node metastasis. Follow-up for SCC in situ is not necessary.

**Malignant Melanoma**

**Pathophysiology**
Malignant melanoma is the most aggressive type of skin cancer which derives from melanocytes in the skin (Rastrelli et al. 2014). Melanocytes are located in the basement layer of the epidermis. They transfer melanosomes to keratinocytes via dendritic processes. Nevi are proliferated nest of melanocytes with loss of dendritic processes. Almost all melanoma starts with a radial growth phase, which are restricted to the epidermis or hair follicle epithelium. These are the melanoma in situ. Next, the vertical growth phase starts and the melanoma grows invasively through the basement membrane into the dermis.

The most common subtypes of malignant melanoma are superficial spreading melanoma, lentigo malign melanoma, acral lentiginous melanoma, and nodular melanoma (Rastrelli et al. 2014). Rare variants of malignant melanoma are nevoid melanoma, desmoplastic melanoma, clear cell sarcoma, and solitary dermal melanoma. Superficial spreading melanoma are the most common and represents 75% of all melanoma.

Risk factors are environmental and genetic. Sunburn in childhood and sunbed usage under the age of 35 increases the risk of melanoma (Marks and Whiteman 1994). This is most important for fair skinned people with red or blond hair. A family history of one or more family members with malign melanoma also increases the risk of melanoma. Familial CDKN2A gene mutation gives an increased risk for malign melanoma and is associated with pancreatic cancer.

**Clinical Features**
Early detection of melanoma is important. Dermoscopy is used during physical examination to improve recognition of malignant melanocytic lesions. The first step is to determine if a lesion is melanocytic. If so, the following tools can be used for better and earlier detection.

The ABCDE acronym is developed for primary care givers and patients to differentiate nevi from malign melanoma (Abbasi et al. 2004). ABCDE stands for Asymmetry; Border irregularities; Color variation such as brown, black, red, gray, blue, or white; Diameter ≥6 mm; and Evolving (change of size, shape, color, or new lesion.)

Another tool is the “ugly duckling” sign (Gaudy-Marqueste et al. 2017). Patients with multiple nevi are screened for pigment lesions that are obviously different from other nevi. This is suspicious and needs further investigation, even when it does not fulfill the ABCDE criteria.

Patients with clinically suspected melanoma need to be quickly referred to a dermatologist (Fig. 9).

**Diagnosis**
Clinically suspected melanoma need to be histologically confirmed. Excisional biopsy with a margin of 2 mm normal skin and subcutaneous fat is needed (Marsden et al. 2010). The pathologist confirms the diagnosis and determines the Breslow depth, which is the strongest predictor of survival. Breslow tumor thickness is a measurement of micro staging of cutaneous melanoma from the top of the granular layer of the epidermis to the deepest part of the tumor in millimeters.

Melanoma have a combination of histopathological features which varies between melanoma subtypes. Atypical melanocytes and architectural disorder are main criteria for diagnosis. Atypical melanocytes are big cells with hyperchromatic, irregular, and/or polymorphic nuclei. Architectural disorder consists of asymmetry and/or nests of irregular melanocytes in parts of epidermis and dermis. Immunohistochemistry is used in difficult lesions. S-100, MART-1, and HMB-45 are markers that are often used.
After diagnosis, the tumor node metastasis (TNM) staging of the AJCC staging system is used for determination of prognosis group. This provides an accurate prognosis of life expectancy (Gershenwald et al. 2017) (Fig. 10).

Treatment

Primary Cutaneous Melanoma
After diagnostic excision, a wider excision of normal tissue is required to ensure complete removal of the primary tumor and micro metastases. The margin of normal tissue removal is based on the Breslow thickness. Melanomas ≤1 mm thick are resected with a 1 cm margin, and melanomas >1 mm are resected with a 2 cm margin. In situ melanomas are resected with a 0.5 cm margin (Marsden et al. 2010).

Primary melanomas of >0.8 mm thickness and <0.8 mm with ulceration are indicated for lymphatic mapping and sentinel lymph node biopsy.

Chemotherapy and adjuvant radiation therapy is not indicated for primary cutaneous melanomas without lymph node or distance metastasis (Marsden et al. 2010).

Regional Lymph Nodes
Sentinel lymph node biopsy is recommended for patients without clinical signs of lymph node involvement and with an increased risk of metastasis. This include primary cutaneous melanomas of >0.8 mm or <0.8 mm with high risk features, such as ulceration. Patients with a positive sentinel lymph node without distant metastasis can be carefully observed with frequent nodal basin ultrasounds or complete lymph node dissection (Wong et al. 2012).

Patients with a clinically positive lymph node which is confirmed with fine needle aspiration cytology need to undergo complete lymph node dissection. Preoperative investigations for distant metastasis need to be performed for accurate staging (Rodrigues et al. 2000).

Adjuvant immunotherapy with anti-programmed cell death 1 (PD-1) agents or target therapy is recommended for patients with positive lymph nodes without distant metastasis and is discussed below.

Metastatic Melanoma
Since the use of new immunotherapy treatments and target therapies, the life expectancy of metastatic melanomas has been improved. Nowadays, chemotherapy and radiotherapy are only used for palliative purposes in a limited number of patients.

Prior to treatment, a full body investigation is performed with CT and/or MRI, and serum lactate dehydrogenase is tested for prognosis. Besides, tumor cells are screened for driver mutations at the V600 site in BRAF gene.

- Immunotherapy – Combining checkpoint inhibitors nivolumab (PD-1) and ipilimumab (CTLA-4) results in an enhanced T-cell function against melanoma cells and therefore
provides an antitumor response. Combination therapy provides better response rates and survival-free periods than single therapy (Larkin et al. 2015).

Nivolumab is a human IgG4 monoclonal antibody which inhibits programmed cell death-1 (PD-1) activity by binding to PD-1 receptor on T cells. PD-L1 and PD-L2 ligands are blocked from binding, causing reverse T-cell suppression, and induce antitumor responses. Pembrolizumab is a human monoclonal checkpoint inhibitor of PD-1 as well, but used in a lesser extent.

Ipilimumab is a recombinant human IgG1 monoclonal antibody that works by binding to cytotoxic T-cell associated antigen 4 (CTLA-4). CTL-4 inhibits T-cell activation. Blockage of CTLA-4 leads to T-cell activation and proliferation against melanoma cells.

- **Target therapy** – Patients with BRAF V600 mutation, about fifty percent of cutaneous melanomas, are candidates for target therapy against the mitogen-activated protein kinase (MAPK) pathway. This consists of BRAF-inhibitors (dabrafenib and vemurafenib) as monotherapy or combined with MEK-inhibitors (trametinib and cobimetinib).

  BRAF kinase inhibitors (dabrafenib and vemurafenib) inhibit the formation of activated BRAF proteins which are important for cell proliferation and differentiation in melanoma with the mutation. Therefore, BRAF kinase inhibitors
inhibitors cause tumor regression and or tumor growth inhibition (Chapman et al. 2011).

MEK-inhibitors (trametinib and cobimetinib) inhibit selectively mitogen-activated extracellular kinase (MEK) 1 and 2 activity. MEK 1 and 2 are part of the BRAF pathway. MEK-inhibitors provide an extra tumor growth inhibition when combined with BRAF kinase inhibitors (Flaherty et al. 2012).

- **Surgical metastasectomy** – Surgical resection provides a durable benefit when a small number of metastases occur, usually in the brain.

- **Radiation therapy** – Radiation therapy is used as palliative treatment mostly in brain metastases when surgical resection is not possible (Marsden et al. 2010).

- **Chemotherapy** – Chemotherapy does not contribute to overall survival in metastatic melanomas and is therefore not used as treatment (Marsden et al. 2010).

### Follow-Up

Follow-up for nonmetastatic melanoma consists of regular visits to detect local recurrences, regional metastasis, and second primary melanoma. Follow-up interval varies between 3 and 6 months, depending on the recurrence risk. Beside, patients need to be instructed about sun protection and self-examinations at home (Marsden et al. 2010).

Follow-up for metastatic melanoma with immunotherapy consists of CT of chest, abdomen, and pelvis every 3 months for the first 2 years. MRI of the brain is preformed every 6 months. After 2 years, the interval is 6 months to 1 year. Patients who receive BRAF inhibitors undergo CT and MRI scans every 3 months.

Patients with cutaneous melanoma who have two or more first degree family members with melanoma and/or family history of pancreatic cancer should consider genetic testing for genetic mutations, such as CDKN2A mutation.

### References and Further Reading


