Review and Research on Cancer Treatment
Volume 7, Issue 1 (2021)

Changes in skin physiology in patients during cancer treatment

Klaudia Mazurek[1], Ewa Pierzchała[1], Magdalena Skrzypiec[2], Alicja Bielecka[2]

[1] Department of Aesthetic Medicine, Faculty of Pharmaceutical Sciences in Sosnowiec, Medical University of Silesia, Katowice, Poland

[2] graduate of cosmetology (first degree), Faculty of Pharmaceutical Sciences in Sosnowiec, Medical University of Silesia, Katowice, Poland

***Corresponding author: Klaudia Mazurek, Ph.D.**

Department of Aesthetic Medicine, Faculty of Pharmaceutical Sciences in Sosnowiec, Medical University of Silesia, ul. Kasztanowa 3, 41-200 Sosnowiec,

email: kmazurek@sum.edu.pl

ABSTRACT

Invasive cancers pose a major challenge for the public health sector around the world. The Key methods of treatment, which currently include surgery, chemotherapy and radiotherapy, always negatively affect the patient's skin to a greater or lesser extent, disrupting its proper metabolism. For the most part, these changes are temporary and reversible, but the lack of knowledge about the side effects of therapy can be extremely surprising for the patient and is associated with severe stress.

The aim of this work is to present skin physiology in oncologically treated patients, with a particular emphasis on the characteristics of radiation-induced reactions and dermatitis resulting from chemotherapy.

Chemotherapeutic drugs are based on toxic compounds, the purpose of which is to inhibit the rapid proli-feration of cancerous cells. Unfortunately, their action is not selective and, at the same time, other normal cells with intensive cell division are also damaged, including cells of the bone marrow, gastrointestinal tract, as well as cells of the epidermis and skin appendages, i.e. hair and nails.

In radiotherapy of cancerous lesions, the purpose of the emitted ionizing radiation is to act as precisely as possible on the area affected by the growth process. The skin, therefore, is an organ damaged every time, regardless of the location of the cancerous tumour or the administered method of radiotherapy. Depending on onset of a radiation-induced reaction, local skin lesions may be divided into early (acute) and late. Radiation-induced dermatitis is a common problem – it affects 80-95% of patients treated with radiotherapy.

The characteristics of skin disorders as a consequence of oncological therapy, still remains a niche topic. Therefore, the organization of current information on the topic became the authors' motivation to write the article.

INTRODUCTION

Invasive cancers pose a major challenge for the public health sector around the world.

For example, it is estimated that every day in the United States, the number of new, registered cases may be close to 4800 (Siegiel, 2019). Cancer formation is the endpoint of a multistep process called carcinogenesis. As a result of a mutation, a dysregulated, uncontrolled cellular proliferation occurs, the final effect of which is the formation of a tumour (Presta, 2020).

The worrying, growing number of diagnosed cancer diseases is the result of multiple factors, which include a decrease in physical activity, obesity, smoking, alcohol intake, chronic exposure to selected chemical agents or a change in typical reproductive patterns. The issue of increased life expectancy for both women and men is also crucial (Torre, 2015). It is extremely difficult today to completely eliminate all potential carcinogenic factors. Invasive cancers are currently one of the leading causes of death in the human population (Wang, 2018).

In the case of suspicion of cancer, it is very important to have a quick and thorough diagnosis, enabling the assessment of the stage of the disease, and thus the application of appropriate therapy. Hormone and biological therapies are used to treat oncological patients, but surgical procedures, chemotherapy and radiotherapy remain the key treatments, applied as standalone or combined methods (Wang, 2018).

Once diagnosed with cancer, it is very important for the patient to obtain full information regarding the proposed treatment methods and any consequences associated with them. Skin is a large human organ, the physiology of which undergoes significant changes as a result of oncological treatment. The skin, especially in the face and neck area, is an element conditioning the aesthetics of appearance. Unfortunately, any form of treatment has a negative

effect on both the epidermis and the dermis. For the most part, these changes are temporary and reversible, but the lack of knowledge about the side effects of therapy can be extremely surprising for the patient and is associated with severe stress. The quality of life for oncological patients, defined as the perception of a patient's own physical, mental and social health, becomes significantly reduced (Mokhatri-Hesari, 2020). This is due to the deterioration of the general condition, and is also associated with a change in appearance, which is often very drastic. Therefore, making the patients aware that most of the side effects disappear after the therapy, gives strength to the patients and thus motivates them to fight the disease.

SEARCH STRATEGY AND SELECTION CRITERIA

The aim of this work is to present skin physiology in oncologically treated patients, with a particular emphasis on the characteristics of radiation-induced reactions and dermatitis resulting from chemotherapy.

The epidermis, dermis, as well as skin appendages undergo significant changes, but the characteristics of skin disorders as a consequence of oncological therapy, still remains a niche topic. Therefore, the organization of current information on the topic became the authors' motivation to write the article.

The study refers to international institutions dealing with the issue of cancer (the International Agency for Research on Cancer – IARC, the World Health Organization – WHO, the European Cancer Organisation) and uses recognized medical databases to verify the latest publications (PubMed, Cochrane Database of Systematic Reviews, Google Scholar). All databases were searched using a combination of keywords: quality of life oncology, cancer statistics, cancer therapy, the hand-foot syndrome, toxic erythema chemotherapy, toxic side effect chemotherapy skin, chemotherapeutic hair, nail disorders chemotherapeutic, radiotherapy, ionizing radiation, and radiation induced dermatitis.

Eligibility criteria for inclusion were review articles and original articles on invasive cancers and oncological therapy-induced dermatitis. The work is based on the latest and most relevant data.

REVIEW

CHEMOTHERAPY

Chemotherapy (CHT) acts as the leading method of the systemic treatment of malignant tumours, which means that it affects the patient's entire body. It is effective both in the case of a focal lesion and in the diagnosis of metastases, since the drugs applied are able to reach every organ of the body via the bloodstream. Chemotherapeutic drugs are based on toxic compounds, the purpose of which is to inhibit the rapid proliferation of cancerous cells. Unfortunately, their action is not selective and, at the same time, other normal cells with intensive cell division are also damaged, including cells of the bone marrow, gastrointestinal tract, as well as cells of the epidermis and skin appendages, i.e. hair and nails (Pérez-Herrero, 2015).

Since the application of the first drugs approved by the Food and Drug Administration (FDA) for the treatment of solid tumours and haematological cancers (such as methotrexate, nitrogen mustards, antifolate drugs) in the 1940s and 1950s, chemotherapy has significantly evolved. The treatment is becoming more and more effective, but despite medical advances, side effects accompanying the treatment, like deviations in blood counts, vomiting, changes in the condition and appearance of the skin, hair, eyelash, eyebrow loss or significant fragility of nails are still a big problem for patients (Pérez-Herrero, 2015; Chabner, 2005).

Antineoplastic drugs are a wide group of substances with anticancer activity. The mechanism of their action consists in blocking the cell cycle and triggering programmed cell death – apoptosis in order to eliminate cancer cells. Generally, a multidrug chemotherapy is used. Only in justified cases, it is possible to use a single drug. For effective therapy, antineoplastic agents of different classes are combined to enhance the cytostatic effect. Chemotherapy can be applied to patients both before (neoadjuvant CHT) and after surgery (adjuvant CHT). It is often given in combination with radiotherapy. Antineoplastic drugs can be divided into two groups, i.e. the cell cycle phase specific (cell cycle phase dependent) and the cell cycle phase non-specific (or cell cycle phase independent). The cell cycle phase specific drugs have an impact on cells that are in a specific phase of the cell cycle. They can act on cells in phase S –

methotrexate, 5-fluorouracil or cells in phase M – vinblastine, vincristine. In addition, there are antineoplastics acting on cells in the G1 phase – corticosteroids, or the G2 phase – bleomycin. On the other hand, drugs referred to as cell cycle phase independent, have an impact on dividing cells, regardless of the phase of the cycle. This group of drugs includes alkylating drugs and antibiotics with anticancer activity. Chemotherapy is most effective in the treatment of early-stage cancer (Pérez-Herrero, 2015; Hanahan, 2011; Ingham, 2017; Mutsuga, 2002).

EFFECTS OF CHEMOTHERAPY AND SYSTEMIC TREATMENT ON SKIN PHYSIOLOGY

Antineoplastic drugs significantly contribute to the impairment of the condition and appearance of the skin and its appendages. The severity and course of side effects of chemotherapy depend on the type, dosage and combination of drugs administered, as well as the individual reaction of the patient's body. Although complications in most cases do not pose a threat to life, they notably worsen its quality and limit the patients' daily activities.

Antineoplastic drugs cause dilution of the epidermis, including the stratum corneum, which affects the weakening of the barrier functions of the skin. Damage to the hydrolipid film, which is the natural protective barrier of the skin, is visible. As a result, transepidermal water loss (TEWL) increases. The skin becomes dehydrated, and thus dry, red and scaly. These symptoms are usually accompanied by persistent itching. Damage to the protective barrier makes the skin susceptible to bacterial, viral and fungal infections. The risk of infection is intensified by the fact that the patient's immune system during chemotherapy is weakened.

Metabolites of the drugs taken are partially released through the sweat glands, therefore the areas rich in eccrine glands are particularly vulnerable to side effects (Yosipovitch, 2019; Jennings, 2020; Owczarek, 2017).

In patients treated with chemotherapy, the hand-foot syndrome – HFS, otherwise known as hand-foot skin reaction (HFSR), palmoplantar dysesthesia, or acral erythema is very often observed. HFS is one of the most frequently diagnosed dermatological complications in the course of oncology treatment. Symptoms can occur from 24 hours up to 10 months from the beginning of therapy, which correlates with the type of medication administered. It is characterized by the formation of erythematous lesions on inner surfaces of the hands and soles of the feet. Usually, the first symptoms are a feeling of warmth in the skin and erythematous lesions. Gradually, there is tingling, anesthetizing, paraesthesia and associated problems with holding objects and even walking. These symptoms may be due to neuropathy of fine nerve fibres. In the course of HFS, swelling and blisters on erythematous medium may occur. On the skin, foci of hyperkeratosis are formed together with strong exfoliation, even bleeding. Skin lesions may be accompanied by pain that limits the performance of instrumental activities. The drugs most commonly causing HFS include 5-fluorouracil – 5-FU, pegylated liposomal doxorubicin (PLD), docetaxel, capecitabine. The pathogenesis of HFS is not fully discovered. However, it is believed that the high concentration of eccrine glands in the hands and feet causes high exposure of the skin to chemotherapeutic agents in these areas, due to the release of drug metabolites through the sweat glands (Chidharla, 2021; Kwakman, 2020). The following table (Table 1) shows the severity of HFS symptoms according to the National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE).

Table 1. Symptom severity classification in the hand-foot syndrome according to the NCI-CTCAE (Chidharla, 2021)

HFS advancement level according to the NCI-CTCAE v. 4.0	characteristics of lesions
grade 1	minimal skin changes or dermatitis (e.g. erythema or oedema) without pain
grade 2	skin changes (e.g. peeling, blisters, bleeding, or hyperkeratosis) with pain leading to limitation of instrumental activities of daily living (ADL)
grade 3	severe skin changes (e.g. peeling, blisters, bleeding, oedema, or hyperkeratosis) with pain, limiting basic self-care ADL

In a group of patients treated with inhibitors of epidermal growth factor receptor inhibitor (EGFRI) and mitogen-activated protein (MAP) kinase kinase inhibitor (MEKI), acneiform rash is the most commonly diagnosed. These changes usually develop within 2-4 weeks of treatment. The clinical picture consists of papules and pustules, which may be accompanied by itching and even pain. Sometimes spontaneous bleeding from the lesions occurs, which significantly worsens the quality of patients' lives. The acneiform rash is located mainly on the face, especially in the middle part, in the behind-the-ear area, on the neck and in the upper part of the chest, i.e. in the areas rich in sebaceous glands, which is why it is referred to as "acneiform". The EGFR inhibitors disrupt the natural balance between proliferation and differentiation of keratinocytes. An inflammatory reaction develops. The incision of hair follicles by T lymphocytes is observed. Sometimes the histological image reveals damage to the hair apparatus, the influx of neutrophils and even abnormal structure of sweat glands (Lacouture, 2018; Lacouture, 2006; Wu, 2011; Kowalska, 2016).

Hair follicles are one of the main structures that are damaged during treatment with antineoplastic drugs. Anticancer drugs damage cells of the hair matrix, which are characterized by high proliferation recorded in the anagen phase. Hair follicles are extremely sensitive to the toxic effects of drugs (Trüeb, 2010). After 2-4 weeks of treatment, the separation of the hair fibre from the hair bulb begins. Initially, soreness of the scalp may be felt. The process of hair loss depends significantly on the type of drugs administered. For example, the use of anti-microtubule agents in the treatment causes baldness in 80% of patients, while topoisomerase inhibitors lead to alopecia in 60-100% of patients (Rossi, 2017).

Some antineoplastic drugs do not cause complete hair loss. Hair can only become thinner, dry, brittle, and less thick. Also, the dose of an antineoplastic drug has a significant effect on the severity and course of alopecia. Polychemotherapy is associated with higher incidences compared to monotherapy. With a low dose of chemotherapeutic agents, hair loss may be slower or less intense. The individual predisposition of the oncological patient is also an important factor. Alopecia may occur suddenly or hair may fall out gradually. Different shedding patterns are observed, both dystrophic anagen effluvium and telogen effluvium. It should be noted that hair loss affects not only the hairy scalp, but the whole body. There is a loss of eyelashes, eyebrows, facial hair, hair on the limbs, armpits and intimate areas. Hair begins to grow back a few months following the end of antineoplastic drug therapy, and full hair regrowth usually occurs up to a year after the end of treatment. The new hair may differ in colour, structure and thickness. It is usually darker and more curly than before (Trüeb, 2010; Heidary, 2008; Rossi, 2017).

The side effects of chemotherapy also appear in the nail area. Changes can take different forms. They concern the appearance of the nail plate, the slower growth or separating of the plate from the nail bed (onycholysis). Nails become tender and can hurt. They are prone to mechanical injuries. Onychomycosis or bacterial infections are more common, caused, for example, by Staphylococcus aureus, and leading to the development of abscesses under nails or in the nail area. Patients' nails tend to split. Discoloration may appear on their surface as a consequence of the deposition of drug metabolites in the plate or nail bed. Discolorations are usually black or blue in colour. In some patients, vertical or horizontal furrows are visible, arranged parallel to each other. Antineoplastic drugs also have a significant impact on slowing down the growth of the nail plate (Kowalska, 2016; Wasner, 2001; Roh, 2007).

RADIOTHERAPY

Radiotherapy (RTH) is an important aspect of invasive cancer treatment. It is based on the use of ionizing radiation to damage abnormal cells. The effect of ionizing radiation on a living organism may be direct and indirect. As a consequence of photon absorption, the centre is ionized and electrons detach, which damages the most sensitive elements of the cell (DNA, cell membranes). Such a mechanism of damage to living matter is referred to as direct mechanism. Definitely, more damage to cellular structures is induced by the activity of reactive oxygen species (ROS) formed as a result of the water radiolysis process, in the so-called indirect mechanism. Reactive oxygen species cause about 75% of radiation-induced damage (Mondini, 2020; Ryan, 2012; Mazurek, 2018).

Radiotherapy is generally used in order to fully cure a sick person (radical radiotherapy). How-

ever, in a situation of significant advancement of the disease, it is used to maximize the patient's life or improve their comfort. It is then referred to as palliative radiotherapy. RTH can be both neoadjuvant – preceding the main treatment, which is most often surgery, and adjuvant – supplementing the basic treatment. In many cases, it is also a complement to chemotherapy. This method of treatment is successfully used in the treatment of many invasive cancers, including the treatment of malignant head and neck cancers, breast cancer, malignant cancers of the reproductive system in women or prostate in men (Rai, 2015; Murthy, 2016).

THE EFFECT OF RADIOTHERAPY ON SKIN PHYSIOLOGY

In RTH of cancerous lesions, the purpose of the emitted ionizing radiation is to act as precisely as possible on the area affected by the growth process. In the therapeutic field, however, there is always a fraction of healthy tissues. Undesirable effects include radiation-induced reac-+tions, which are the response of the epidermis and dermis to ionizing radiation. The intensity of radiation-induced reactions depends on the patient's age, general health, possible concurrent diseases, the advancement stage of the disease, the histological image of the tumour, the dose fractionation scheme used or the use of simultaneous chemotherapy (Ryan, 2012; Mazurek, 2018).

The skin, therefore, is an organ damaged every time, regardless of the location of the cancerous tumour or the administered method of radiotherapy. Depending on onset of a radiation-induced reaction, local skin lesions may be divided into early (acute) and late. Early radiation-induced reactions of the skin develop during radiation therapy and up to 6 months after its completion, and are mostly temporary. They usually cover the area directly exposed to radiation. Initially, these are epidermal lesions, because the epidermis reacts faster. Subsequent fractions of radiation gradually damage the dermis as well. The first noticeable symptom is erythema of a transient nature, caused by an increased activity of pro-inflammatory cytokines, such as the interleukin-1 (Il-1) and Il-6, the tumour necrosis factor α (TNF-α) and the transforming growth factor β β (TGF-β). The erythema becomes pale pink to bright or smoky pink in colour. Overstimulation of pigment cells takes place as well. As a result of damage to the keratinocytes of the stratum basale, dry exfoliation of the epidermis is observed, and at a later stage, there is moist exfoliation, accompanied by serous exudate. As a result of the destruction of all cells of the stratum basale, the dermis becomes exposed. Skin irritation is characteristic of acute radiation-induced dermatitis, which is accompanied by a feeling of warmth and itching, sometimes there is also pain. The activity of sweat and sebaceous glands is noticeably reduced, which is manifested by dryness of the skin. Dystrophic alopecia is observed in radiated areas. Permanent hair loss is not to be excluded when high doses of ionizing radiation are applied (Ryan, 2012; Stone, 2003; Chan, 2014).

Late radiation-induced dermatitis develops from 6 months to several years after the completion of radiation treatment. Disorders in the functions of mature fibroblasts are observed. Fibroblasts are cells of the connective tissue and are responsible for the production of collagen and elastin. As a consequence of the ionizing radiation, a reduced number of fibroblasts is observed, which begin to produce a greater amount of collagen fibres, with irregular arrangements. The result of these changes are manifested in skin abnormalities such as loss of elasticity, the presence of skin fibrosis, increased hardness, as well as swelling. As a result of damage to the vascular endothelium, there is a permanent expansion of blood vessels – visible on the skin in the form of telangiectasia. Nerve fibres also become damaged, which translates into sensory disturbances. Atrophic changes may also develop, and in extreme cases, dermal necrosis. The sebaceous and sweat glands undergo atrophy. In the case of late radiation-induced reactions, the dose of absorbed radiation is of great importance. The higher the dose, the faster the reaction can be visible. It should be understood that the appearance of a late reaction is essentially irreversible. The most severe consequence of radiation therapy is the risk of induction of secondary cancers (Chan, 2014; de Andrade, 2012; Iacovelli, 2020).

Radiation-induced dermatitis affects 8-95% of patients treated with radiation therapy (Ryan, 2012; de Andrade 2012) with the head and neck region, the breasts and perineal area being particularly vulnerable to acute radiation-induced reactions. It is worth emphasizing that radiation therapy does not only affect the area subjected to radiation, but to some extent, it has

an impact on the whole body. In addition to discomfort of the skin or mucous membranes, the patients also report general symptoms such as malaise, drowsiness or weakness (Iacovelli, 2020).

In order to correctly assess the severity of the local radiation-induced dermatitis, specific scales are applied. One of the most commonly used is the RTOG/EORTC (Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer) scale. It allows for the assessment of early and late radiation-induced dermatitis in the degree of severity from 0 to 5. However, practice has shown that this scale has some limitations and also does not take into account the symptoms reported by patients (Mondini, 2020). Another scale, the Dische scale, focuses on damage to the mucous membranes and takes into account clinical disorders (pain, problems with swallowing) in addition to clinical symptoms (erythema, epitheliolysis, oedema). To assess late changes, the LENT-SOMA (Late Effect Normal Tissue Task Force – Subjective, Objective, Management, Analytic) scale is used. This scale determines the degree of skin fibrosis, the surface of telangiectasia and the severity of skin discoloration. In addition to the above, the NCI-CTCAE (National Cancer Institute – Common Terminology for Adverse Events) scale is also used. It is a 5-degree scale, the first degree of which means weak erythema or dry exfoliation, and the last means death. There is also the RISRAS (Radiation-Induced Skin Reaction Assessment Scale) that details and objectively assesses both dermic lesions and the subjective sensations of the patient, which are equally important (Stryczyńska, 2011; Raza, 2012; Kumaran, 2014).

DISCUSSION

Oncological therapy is directed towards rapidly dividing cancer cells, but there is always damage to normal cells, characterized by a high proliferative index. The skin is classified as an organ whose physiology changes significantly as a result of therapy, which is confirmed by researchers studying the impact of individual therapeutic methods used on the patient's skin in oncology (Choi, 2014; Macdonald, 2015; Anforth, 2015).

The key methods of treatment, which currently include surgery, chemotherapy and radiotherapy, always negatively affect the patient's skin to a greater or lesser extent, disrupting its proper metabolism.

For many patients, a postoperative scar is a significant problem, but it should be high-lighted that any aesthetic procedures to reduce it can be carried out after a sufficiently long time following the procedure and after obtaining permission from the oncologist. Apart from the dermatitis that accompanies chemotherapy, one of the most difficult adverse events connected with treatment, especially for women, is alopecia. On average, 65% of patients who have received treatment (de Barros Silva, 2020) are affected by this problem. 47% of patients perceive alopecia as the most traumatic aspect of chemotherapy (Trüeb, 2010). There are cases when the decision to start treatment is delayed or even declined for fear of hair loss.

One of the ways to reduce chemotherapy-induced alopecia (CIA) is to use scalp cooling during chemotherapy by using special machines ("caps"), e.g. Paxman, Dignitana. In Brazil, three scalp cooling devices to be used during chemotherapy have received approval from the Brazilian Health Regulatory Agency (Agência Nacional de Vigilância Sanitária) (de Barros Silva, 2020). However, access to this method is not common. It also seems that the safety of using this method and the absolute elimination of the possible negative impact of cooling on the effectiveness of treatment requires further study.

Radiation therapy, in addition to its positive aspects, is also the cause of bothersome and unesthetic skin lesions in the form of radiation-induced dermatitis. Research in the field of psychodermatology indicates that appearance has an extremely important impact on self-acceptance, satisfaction and self-esteem, which take on particular importance in the case of cancer.

Although many argue that in the face of cancer the quality of life seems to be a secondary issue, it should be remembered that stress and depression lead to a worse prognosis, although this mechanism has not been fully explained (Lang-Rollin, 2018). Thus, a thorough conversation with the patient, discussing the negative consequences of therapy, largely manifested by the deterioration of the function and appearance of the skin and its appendages, are of colossal importance. Making the patient aware that, to a large extent, these are only temporary dysfunctions and will make the patient prepared for the

side effects of the treatment and certainly cope with them better. It should also be emphasized that currently, there are many pharmacological and cosmetology methods that largely alleviate the skin-related side effects of oncological therapy. The developing field of oncology aesthetics has a positive effect not only on the appearance of the patients, but it also improves their well-being, which gives them strength to conquer the disease.

SHORT CONCLUSIONS

1. Chemotherapy and radiotherapy negatively affect the appearance and functioning of the skin and its appendages. Complications of oncological treatment significantly worsen the quality of life of patients.
2. Cytostatic drugs weaken the barrier functions of the skin, contribute to an increasing of the transepidermal escape of water, and thus to skin dehydration. The skin becomes susceptible to bacterial, viral and fungal infections.
3. The hand-foot syndrome (HFS) is one of the most frequently diagnosed dermatological complications in the course of oncological treatment.
4. Radiation-induced dermatitis is a common problem – it affects 80-95% of patients treated with radiotherapy.
5. Taking into account the time criterion, there are early radiation-induced reactions, manifested by a change in the anatomy and physiology of the epidermis and late radiation-induced reactions, in the course of which significant deviations are also observed not only in the epidermis, but also in the dermis.
6. One of the most difficult experiences associated with oncological treatment is alopecia, which affects on average 65% of patients.
7. Proper skin care during and after oncological therapy can contribute to the reduction of side effects and accelerate skin healing and its return to normal condition.

References

Anforth R., Carlos G., Clements A., Kefford R., Fernandez-Pénas P. **Cutaneous adverse events in patients treated with BRAF inhibitor-based therapies for metastatic melanoma for longer than 52 weeks**. Br J Dermatol. 2015, 172(1): 239-243.

Chabner B.A., Roberts Jr. T.G. **Timeline: Chemotherapy and the war on cancer**. Nat Rev Cancer 2005; 5(1):65-72.

Chan R.J., Webster J., Chung B., Marquart L., Ahmed M., Garantziotis S. **Prevention and treatment of acute radiation-induced skin reactions: a systematic review and meta-analysis of randomized controlled trials**. BMC Cancer 2014; 14: 53.

Chidharla A., Kanderi T., Kasi A. **Chemotherapy Acral Erythema. StatPearls [Internet].** Treasure Island (FL): StatPearls Publishing; 2021.

Choi J.N. **Dermatologic adverse events to chemotherapeutic agents. Part 2, BRAF inhibitors, MEK inhibitors and ipilimumab**. Semin Cutan Med Surg. 2014, 33(1): 40-48.

de Andrade M., Clapis M.J., do Nascimento T.G., Gozzo T. de O., de Almeida A.M. **Prevention of skin reactions due to teletherapy in women with breast cancer: a comprehensive review**. Rev Lat Am Enfermagem. 2012; 20(3): 604-611.

de Barros Silva G., Ciccolini K., Donati A., van den Hurk C. **Scalp cooling to prevent chemotherapy-induced alopecia**. An Bras Dermatol. 2020; 95(5):631-637.

Hanahan D., Weinberg R.A. **Hallmarks of cancer: the next generation**. Cell. 2011; 144(5):646-74.

Heidary N., Naik H., Burgin S. **Chemotherapeutic agents and the skin. An update**. J Am Acad Dermatol. 2008, 58(4): 545-570.

Iacovelli N.A., Torrente Y., Ciuffreda A., Guardamagna V.A., Gentili M., Giacomelli L. et al. **Topical treatment of radiation-induced dermatitis: current issues and potential solutions**. Drugs Context. 2020; 9:2020-4-7.

Ingham M., Schwartz G.K. **Cell-Cycle Therapeutics Come of Age**. J Clin Oncol. 2017; 35(25):2949-2959.

Jennings E., Huang S., Lee J.B., Cha J., Hsu S. **Toxic erythema of chemotherapy secondary to gemcitabine and paclitaxel**. Dermatol Online J. 2020; 26(9):13030/qt86m5f6hh.

Kowalska M., Kowalik A., Góźdź S. **Dermatologiczne objawy uboczne w przebiegu chemioterapii i celowanej terapii przeciwnowotworowej**. Przegl Dermatol. 2016, 103, 127-138.

Kumaran A., Guruvare S., Sharan K., Rai L., Hebbar S. **Chemoradiation related acute morbidity in carcinoma cervix and correlation with hematologic toxicity: a South Indian prospective study**. Asian Pac J Cancer Prev. 2014; 15(11):4483-6.

Kwakman J.J.M., Elshot Y.S., Punt C.J.A, Koopman M. **Management of cytotoxic chemotherapy-induced hand-foot syndrome**. Oncol Rev. 2020; 14(1):442.

Lacouture M., Sibaud V. **Toxic Side Effects of Targeted Therapies and Immunotherapies Affecting the Skin, Oral Mucosa, Hair, and Nails**. Am J Clin Dermatol. 2018; 19(1):31-39.

Lacouture M.E., Lai S.E. **The PRIDE (Papulopustules and/or paronychia, regulatory abnormalities of hair growth, itching and dryness due to epidermal growth factor receptor inhibitors) syndrome**. Br J Dermatol. 2006, 155(4): 852-854.

Lang-Rollin I., Berberich G. **Psycho-oncology**. Dialogues Clin Neurosci. 2018; 20(1):13-22.

Macdonald J.B., Macdonald B., Golitz L.E., LoRusso P., Seculic A. **Cutaneous adverse effects of targeted therapies. Part II: inhibitors of intracellular molecular signaling pathways**. J Am Acad Dermatol. 2015, 72(2): 221-236.

Mazurek K., Siemianowicz K., Likus W., Pierzchała E., Kwiatkowski R., Markowski J. **Collagen Type III Metabolism Evaluation in Patients with Malignant Head and Neck Cancer Treated with Radiotherapy**. Biomed Res Int. 2018; 2018:8702605.

Mokhatri-Hesari P., Montazeri A. **Health-related quality of life in breast cancer patients: review of reviews from 2008 to 2018**. Health Qual Life Outcomes. 2020; 18(1):338.

Mondini M., Levy A., Meziani L., Milliat F., Deutsch E. **Radiotherapy-immunotherapy combinations - perspectives and challenges**. Mol Oncol. 2020; 14(7):1529-1537.

Murthy V., Kumar D.P., Budrukkar A., Gupta T., Ghosh-Laskar S., Agarwal J. **Twice-weekly palliative radiotherapy for locally very advanced head and neck cancers**. Indian J Cancer 2016; 53(1): 138-141.

Mutsuga M., Kojima K., Yamashita M., Ohno T., Ogihara Y., Inoue M. **Inhibition of cell cycle progression through specific phase by pancratistatin derivatives**. Biol Pharm Bull. 2002; 25(2):223-8.

Owczarek W., Słowińska M., Lesiak A., Ciążyńska M., Maciąg A., Paluchowska E. et al. **The incidence and management of cutaneous adverse events of the epidermal growth factor receptor inhibitors**. Postepy Dermatol Alergol. 2017; 34(5):418-428.

Pérez-Herrero E., Fernández-Medarde A. **Advanced targeted therapies in cancer: Drug nanocarriers, the future of chemotherapy**. Eur J Pharm Biopharm. 2015; 93:52-79.

Presta I., Novellino F., Donato A., La Torre D., Palleria C., Russo E., Malara N. et al. **Ubc10 a Major Actor in Cancerogenesis and a Potential Tool for Diagnosis and Therapy**. Int J Mol Sci. 2020; 21(6):2041.

Rai N.P., Divakar D.D., Al Kheraif A.A., Ramakrishnaiah R., Mustafa S.M., Durgesh B.H. et al. **Outcome of palliative and radical radiotherapy in patients with oral squamous cell carcinoma – a retrospective study**. Asian Pac J Cancer Prev. 2015; 16(16): 6919-6922.

Raza S., Lymberis S.C., Ciervide R., Axelrod D., Fenton-Kerimian M., Magnolfi C. et. al. **Comparison of Acute and Late Toxicity of Two Regimens of 3- and 5-Week Concomitant Boost Prone IMRT to Standard 6-Week Breast Radiotherapy**. Front Oncol. 2012; 2:44.

Roh M.R., Cho J.Y., Lew W. Docetaxel-**induced onycholysis: the role of subungual hemorrhage and suppuration**. Yonsei Med J. 2007; 48(1):124-126.

Rossi A., Fortuna M.C., Caro G., Pranteda G., Garelli V., Pompili U. et al. **Chemotherapy-induced alopecia management: Clinical experience and practical advice**. J Cosmet Dermatol. 2017; 16(4):537-541.

Ryan J.L. **Ionizing radiation: the good, the bad, and the ugly**. J Invest Dermatol. 2012; 132: 985-993.

Siegel R.L., Miller K.D., Jemal A. **Cancer statistics**, 2019. CA Cancer J. Clin. 2019; 69(1): 7-34.

Stone H.B., Coleman C.N., Anscher M.S., Mc Bride W.H. **Effect of radiation on normal tissue: consequences and mechanisms**. Lancet Oncol 2003; 4(9): 529-536.

Stryczyńska G. **Assessment of the effectiveness and results of application research of soft cream AQUASTOP® RADIOTERAPIA (Ziołolek sp. z o. o.) in patients with dry and irritated skin, receiving radiotherapy**. Współcz Onkol. 2011; 15(1): 59-65.

Torre L.A., Bray F., Siegel R.L., Ferlay J., Lortet-Tieulent J., Jemal A. **Global cancer statistics**, 2012. CA Cancer J Clin. 2015; 65(2):87-108.

Trüeb R.M. **Chemotherapy-induced alopecia**. Curr Opin Support Palliat Care. 2010; 4(4):281-4.

Trüeb R.M. **Chemotherapy-induced hair loss**. Skin Therapy Lett. 2010; 15(7):5-7.

Wang J.J., Lei K.F., Han F. **Tumor microenvironment: recent advances in various cancer treatments**. Eur Rev Med Pharmacol Sci. 2018; 22(12):3855-3864.

Wasner G., Hilpert F., Baron R., Pfisterer J. **Clinical picture: nail changes secondary to docetaxel**. Lancet. 2001; 357(9260):910.

Wu P.A., Balagula Y., Lacouture M.E., Anadkat M.J. **Prophylaxis and treatment of dermatologic adverse events from epidermal growth factor receptor inhibitors**. Curr Opinion Oncol. 2011, 23(4): 343-351.

Yosipovitch G., Misery L., Proksch E., Metz M., Ständer S., Schmelz M. **Skin Barrier Damage and Itch: Review of Mechanisms, Topical Management and Future Directions**. Acta Derm Venereol. 2019; 99(13):1201-1209.