Topical Treatment of Actinic Keratosis - New Ways of Treatment
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Actinic Keratosis (AK) is a squamous cell carcinoma of the epidermis in situ. There are a number of treatment options currently available but not all are appropriate for all patients or all lesions. AK lesions can be treated individually or, if the lesions are numerous in an area of sun-damaged skin the whole area should be treated to remove subclinical lesions as well as those clinically visible (field-directed therapy). Polyphenon® E is a defined extract from green tea leaves, containing a mixture of green tea catechins. Developed for the topical treatment of HPV related skin tumors with Genital Warts as first indication. We did the first promising phase II study on actinic keratoses. Inhibitors of cyclo-oxygenase 2 (COX-2) inhibit prostaglandin E2 (PGE2) that is known to suppress the production of immune-regulatory lymphocytes, T-and B-cell proliferations and the cytotoxic activity of natural killer cells. Cox-1/2 inhibitors like the combination between diclofenac and hyaluronic acid work against AKs through inhibition of angiogenesis or through induction of apoptosis. Recent Phase III clinical studies have highlighted that the immune response modifier (IRM) imiquimod is effective in clearing both clinical and subclinical AK lesions. In addition, initial results from three recently completed studies of imiquimod: (1) a comparative study, (2) open label study with 829 patients and (3) a study in organ transplant recipients provides promising outcomes.

Graft Versus Host Disease and Extracorporeal Photopheresis, Reflection on the Mechanism of Action
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Chronic graft versus host disease (cGVHD) affects 50% of long-term marrow transplant survivors and remains a cause of major long-term morbidity in these patients despite aggressive therapy. Extracorporeal photopheresis (ECP), considered as an effective treatment for patients with erythrodemic cutaneous T-cell lymphoma, recently has been successfully used in the treatment of GVHD. It consists on infusion of UVA irradiated autologous peripheral blood mononuclear cells collected by apheresis and incubated with 8-methoxypsoralen. We report our experience in 12 patients with chronic GVHD following non-myeloablative stem cell transplantation for acute myeloid leukemia (n = 3), chronic myeloid leukemia (n = 2), non-Hodgkin lymphoma (n = 2), acute lymphoblastic leukemia (n = 2), multiple myeloma (n = 1), chronic lymphocytic leukemia (n = 2) and one case of metastatic ovarian cancer. Besides peripheral blood mononuclear cell spontaneous apoptosis, coexpression of CD4-CD25 molecules and cytokine production before and after ECP treatment was evaluated. In all treated patients, but in two, we observed after therapy a partial or complete response of cutaneous, oral/facial and liver involvement. In all these cases it was possible to reduce or discontinue immunosuppressive therapy. As regards programmed cell death, both annexin V staining and measurement of DNA fragments showed that lymphocytes and partially monocytes (about 50%) from the PUVA treated bulky coat bag undergo enhanced spontaneous apoptosis in comparison with the other samples. Moreover overexpression of CD4 + CD25 + molecules was observed after ECP in 10 out of 12 treated patients after one year of treatment. In conclusion, ECP is effective as either single or concomitant therapy in patients with chronic GVHD without relevant side effects. Moreover in our study we demonstrated that lymphocytes from the PUVA-treated bag undergo enhanced apoptosis in vitro. This accelerated cell death together with overexpression of CD4-CD25 molecules may play a key role in the not yet completely understood mechanism of action of ECP.

Treatment of Merkel Cell Carcinoma
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Because of the relative rarity of the tumor, the treatment of Merkel cell carcinoma (MCC) is not a matter of evidence based medicine. Despite the absence of large series and randomized trials, the radiosensitiveness of the tumor and its chemosensibility are well established. In stage I (primary tumour), surgery with excision margins is performed. In clinical practice the margins depend on the size and the site of the tumor. A two centimeters margin is recommended for tumours larger than 1 cm. Mohs surgery allows to spare tissue and offers maximal security of complete resection for tumors with an asymmetrical growth pattern. Most authors recommend an additional 1 cm margin following the last positive section. Adjuvant radiotherapy of the tumour site reduces the rate of local recurrence, as demonstrated by retrospective series and by a meta-analysis of 11 series including 1024 cases. Because of the high rate of lymphatic metastases, an adjuvant therapy concerning regional lymph nodes is often proposed. It consists in elective lymphadenectomy (eventually followed by irradiation) or, more often, in irradiation of the regional lymphatic area (50 GY). In France, a randomized trial has been performed comparing surgery-radiotherapy of the primary tumor to surgery-radiotherapy associated with prophylactic irradiation of the regional nodes. The trial was stopped after inclusion of 82 patients because of insufficient recruitment. The intermediate analysis has demonstrated no regional recurrence in the irradiated group. Complete results will be presented later. Sentinel node biopsy is now proposed to determine microscopic node invasion. Positivity of the sentinel node constitutes a strong prognostic factor. Selective lymph node dissection is performed in case of positivity. The benefit of this attitude in comparison with prophylactic irradiation remains to be determined. In stage II (nodes clinically detectable) radical lymph node dissection and adjuvant irradiation are performed. In advanced cases, neoadjuvant chemotherapy is proposed. In stage III (dissemination), a good response rate is obtained with different protocols. Cyclophosphamide, Doxorubicine or Epirubicine, Vinristine, Etoposide, Cis-platinum are the drugs most frequently used, when possible in combination (CYC-ADR-VCR, VP16-CDDP). In a meta analysis of 204 patients, the mean response rate is 75,6% (4). Despite of chemosensitivity, median survival in stage III is only 9 months. In conclusion, treatment of MCC is principally based on the association of surgery and radiotherapy. The exact role of sentinel node procedure remains to be assessed.

Apoptosis and Skin Tumors
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Impaired ability to undergo programmed cell death in response to a wide range of stimuli confers to cancers a selective advantage for progression and metastasis as well as their strong resistance to therapy. UV radiation causes DNA damage, followed by translocation of p53 to the nucleus with subsequent DNA repair or apoptosis. Keratinocytes carrying p53 mutations may acquire resistance to apoptosis. Thus, resistance to cell death is a key event in photocarcinogenesis. Apoptosis-resistant keratinocytes undergo clonal expansion that eventually leads to the formation of actinic keratoses and squamous cell carcinomas. Melanoma cells are notoriously resistant to a variety of chemotherapeutic drugs by exploiting their strong anti-apoptotic machinery or the alteration of molecules involved in the regulation and execution of apoptosis. New strategies are in progress to bypass these cell death defects through the modulation of pro-and antiapoptotic factors. Preliminary work suggests that this strategy is very promising to find new ways of treating cancer and to improve the actual poor prognosis of patients at late stages of the disease.
Primary cutaneous lymphomas (PCL) in the majority of histologic variants have an indolent behavior and a good prognosis with a prolonged survival. In a very small subset of patients, PCL is aggressive at the onset and in patients who are resistant or have relapsed after repeated traditional topical or systemic therapies, an advanced disease is more frequently observed. In these patients the choice of the treatment is not easy due to biologic and clinical heterogeneity of the disease and to cumulative toxicity of previous therapies. The administration of the traditional systemic (although aggressive) treatments results in a better initial response rate without improving prognosis. Our experience confirms the efficacy and low toxicity of PLD as single agent in second-line therapy of cutaneous T-Cell lymphoma as demonstrated by Wollina U. et al. (Cancer 2003). We tested the safety and efficacy of PLD in the treatment of 19 consecutive patients with advanced PCL (17 T-cell, 2 B-cell lymphomas), in association with three drugs of proven effectiveness in nodal lymphoproliferative and other primary cutaneous neoplastic disorders, the CBVD therapy: PLD (Caelyx®) 12 mg/m², Bleomycin 10 mg/m², Vinblastine 6 mg/m², Dacarbazine 375 mg/m² at days 1 and 15, administered intravenously every 4 weeks for 6 cycles. The overall response rate was 84.21% (Complete Response 63.15%, Partial Response 21.05%, Progression of Disease 15.78%). The CBVD therapy was well tolerated, only two patients presented neutrophil count below 500/microliter, no patient had cardiac or mucosal toxicity, nor alopecia or palmoplantar erythrodysesthesia.