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Overview

Cutaneous Lymphomas

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Abstract

Primary cutaneous lymphomas are the second most common form of extra-nodal lymphomas. They have special characteristics compared with other lymphomas. They are most frequently of T-cell origin and they generally have a much more indolent course than lymphomas of similar histology in other locations. Mycosis fungoides is the most common type of cutaneous lymphoma. Primary cutaneous lymphomas remain confined to the skin for a long time. Skin-directed therapies are the main treatments; systemic treatments are not very effective for the skin lesions. Skin-directed therapies used for the early and thin lesions are topical corticosteroids, phototherapy and topical retinoids and, for the more widespread or thick lesions, topical nitrogen mustard and radiation. Radiation therapy is highly effective and is indicated in virtually all cases of localised disease. Radiation therapy may be given to the whole skin surface, so-called total skin electron beam therapy. However, if the disease spreads to other organs, systemic treatments are indicated, often combined with skin-directed therapies. Conventional cytotoxic therapy is less effective in cutaneous lymphomas. The commonly used therapies, such as interferon, enhanced anti-tumour immunity and the recent advances in immune therapies may improve our treatments for cutaneous lymphomas.

Key words: Cutaneous lymphomas; diagnosis; prognosis; skin-directed therapy; systemic therapy; therapy

Statement of Search Strategies Used and Sources of Information

This overview was based on Medline searches including (in various combinations) the terms 'lymphoma', 'skin', 'cutaneous', 'extra-nodal', 'treatment', 'radiotherapy', 'chemotherapy', 'skin-directed therapy'. Searches were made with and without the term 'randomised trial'.

Introduction

Lymphoid neoplasms represent a complex group of diseases, which in the most recent World Health Organization classification encompasses over 100 distinct disease entities, defined by histopathological morphology, immunophenotype, genetic and clinical features [1]. They may arise both within and outside the lymphatic system. Lymphomas that present primarily with lesions wholly or predominantly confined outside lymph node areas, with or without involvement of adjacent or draining lymph nodes, are defined as primary extra-nodal lymphomas. They must be distinguished from disseminated lymphomas with extra-nodal spread, which are not considered primary extra-nodal lymphomas and often have a different clinical behaviour and require different treatments.

About one-third of non-Hodgkin lymphomas present as extra-nodal lymphomas [2]. The most common site is the gastrointestinal tract; the second most common is the skin. The estimated annual incidence of primary cutaneous lymphomas (PCL) is 1/100 000 in Western countries. PCL differ significantly from nodal lymphomas and from primary extra-nodal lymphomas in other locations. They tend to remain localised to the skin for a long time and they have a much more indolent course and a much better prognosis than lymphomas of similar histological subtype in other locations. In recent lymphoma classifications, PCL are therefore classified as separate entities [1], the most common (covered in this review) are listed in Table 1. The histopathological

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subtypes occur in a distinct pattern in PCL. In non-Hodgkin lymphomas in general, most lymphomas in adults are B-cell lymphomas (85%), whereas T-cell lymphomas constitute 75–80% of PCL. There are distinct geographical variations in the occurrence of the different subtypes. In the West, most cutaneous T-cell lymphomas (CTCL) are mycosis fungoides, whereas in Southeast Asia other types of CTCL predominate [3,4]. In the West, primary cutaneous B-cell lymphomas (CBCL) constitute around 20% of all PCL, whereas they are much less common in Asia.

PCL are rare diseases and should be treated by a multidisciplinary team of dermatologists, oncologists, haematologists and pathologists with experience in these diseases, in particular with respect to the very indolent behaviour of most of the subtypes. Overtreatment is a real risk for many patients with PCL.

Diagnosis

Cutaneous lymphoma is a heterogeneous group of lymphomas. The medical history together with a complete clinical examination and histopathology often supported by immunophenotypical and molecular data are important for the correct diagnosis. Histology can be carried out on complete excision of the tumour for single tumours or on incisional or punch biopsies. Especially for mycosis fungoides the diagnosis may be challenged and delayed for years, despite clinical suspicion, and several biopsies may be necessary [5]. Clonality of either the T-cell receptor (T-cells) or immunoglobulin heavy-chain (J_H) (B-cells) may support the diagnosis; however, clonal cells may also be found in benign reactive inflammatory skin diseases [6,7].

Staging

Adequate staging examinations should be carried out in all patients with PCL to exclude the presence of extracutaneous disease. This includes a complete physical examination, complete blood cell counts, routine serum biochemistry, including lactate dehydrogenase (LDH), and imaging studies, either computed tomography or fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) scans. PCL are not universally FDG-avid [8] and FDG-PET scans are not routinely recommended. However, it is mostly in the cutaneous sites that the FDG uptake is variable, whereas subcutaneous involvement or involvement of other organs is usually seen on PET scans. Hence, an FDG-PET/CT scan is recommended in most cases. A bone marrow examination should be carried out in lymphomas with an intermediate or aggressive clinical behaviour, but is not mandatory in the indolent types. Flow cytometry is recommended for patients suspected of having Sézary syndrome.

Staging of lymphomas is generally carried out according to the Ann Arbor classification, which was originally created for the staging of Hodgkin lymphoma [9–11]. However, this staging system is not well suited for extra-nodal lymphomas. For mycosis fungoides/Sézary syndrome a dedicated TNMB classification is used (see Table 2), which translates into a clinical staging system (see Table 3) [12]. This staging system has not so far been incorporated into the official TNM classification.

Table 1
The most common primary cutaneous lymphomas (PCL)

Cutaneous T-cell lymphomas (CTCL)
Mycosis fungoides
Sézary syndrome
Primary cutaneous CD30-positive lymphoproliferative disorders
• Primary cutaneous anaplastic large cell lymphoma (C-ALCL)
• Lymphomatoid papulosis
Cutaneous B-cell lymphomas (CBCL)
Primary cutaneous marginal zone lymphoma (PCMZL)
Primary cutaneous follicle centre lymphoma (PCFCL)
Primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT)

Most Common Disease Entities

Primary Cutaneous T-cell Lymphomas

Mycosis Fungoides and Variants

Mycosis fungoides is the most common type of cutaneous lymphoma [13]. The incidence is about $6–7/10^6$

Table 2
TNMB classification of mycosis fungoides and Sézary syndrome

T (skin)	
T_1	Limited patch/plaque (involving <10% of total skin surface)
T_2	Generalised patch/plaque (involving ≥10% of total skin surface)
T_3	Tumour(s)
T_4	Erythroderma
N (lymph node)	
N_0	No clinically abnormal peripheral lymph nodes
N_1	Clinically abnormal peripheral lymph nodes; histologically uninvolved
N_2	Clinically abnormal peripheral lymph nodes; histologically involved (nodal architecture uneffaced)
N_3	Clinically abnormal peripheral lymph nodes; histologically involved (nodal architecture (partially) effaced)
N_x	Clinically abnormal peripheral lymph nodes; no histological confirmation
M (viscera)	
M_0	No visceral involvement
M_1	Visceral involvement
B (blood)	
B_0	No circulating atypical (Sézary) cells (or <5% of lymphocytes)
B_1	Low blood tumour burden (≥5% of lymphocytes are Sézary cells, but not B_2)
B_2	High blood tumour burden (≥1000/μl Sézary cells and positive clone)

Table 3
Clinical staging system for mycosis fungoides and Sézary syndrome

Clinical stage				
IA	T_1	N_0	M_0	$B_{0–1}$
IB	T_2	N_0	M_0	$B_{0–1}$
IIA	$T_{1–2}$	$N_{1–2}$	M_0	$B_{0–1}$
IIB	T_3	$N_{0–2}$	M_0	$B_{0–1}$
III	T_4	$N_{0–2}$	M_0	$B_{0–1}$
IVA_1	$T_{1–4}$	$N_{0–2}$	M_0	B_2
IVA_2	$T_{1–4}$	N_3	M_0	$B_{0–2}$
IVB	$T_{1–4}$	$N_{0–3}$	M_1	$B_{0–2}$

[14,15]. The disease is more common in adults, but may also be seen in children. Mycosis fungoides is divided into the patch, plaque and tumour stages. The patch stage is often large, erythematous lesions with fine scaling (see Figure 1A), the plaque stage consists of more infiltrated lesions (see Figure 1B) and in the tumour stage, patches, plaques and tumours are present (see Figure 1C). The tumours may be numerous and ulceration is not uncommon. In all stages itching is an important symptom. Mycosis fungoides is a low-grade malignancy and progression from the patch stage to the tumour stage usually takes from years to decades [13] and only 15–20% of patients die of mycosis fungoides [16]. Several rare types exist, including mycosis fungoides with follicular mucinosis, erythrodermic mycosis fungoides and granulomatous mycosis fungoides. Treatment in the early stages is skin-directed; only in the more advanced stages are interferon-α (IFN-α), retinoids and chemotherapy used.

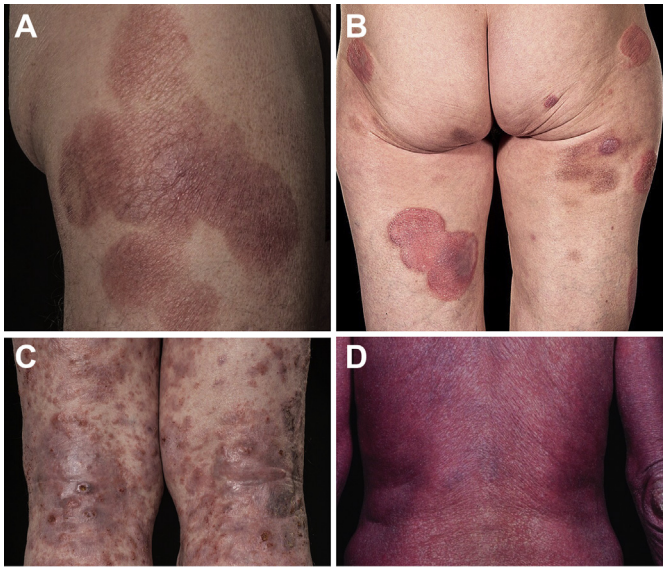

Fig 1. Mycosis fungoides and Sézary syndrome. (A) Mycosis fungoides with patches (upper left); (B) mycosis fungoides with plaques (upper right); (C) mycosis fungoides with tumours (lower left); (D) Sézary syndrome with erythroderma (lower right).

Sézary Syndrome

Sézary syndrome is typically seen in elderly adults and consists of erythroderma, generalised lymphadenopathy and circulating Sézary cells [13,17] (see Figure 1D). Patients suffer from severe pruritus and often have hyperkeratosis in hands and soles in combination with alopecia. Being a leukaemia, Sézary syndrome is treated with photopheresis or psoralen plus ultraviolet A (PUVA) in combination with IFN-α or retinoids and chemotherapy.

Primary Cutaneous CD30-positive Lymphoproliferative Disorders

This group contains a spectrum of diseases from lymphomatoid papulosis to cutaneous anaplastic large cell lymphoma (C-ALCL). All types have a good prognosis, with 10-year survival between 90 and 100% [13,18]. Lymphomatoid papulosis is defined as chronic, recurrent papules and small nodules with ulceration that heal spontaneously and histology as CTCL (see Figure 2A). Treatment is topical steroids, PUVA or low-dose methotrexate [7,8]. Patients with C-ALCL usually have one or a few tumours that may ulcerate (see Figure 2B). Treatment is surgical (single lesion) or radiotherapy and brentuximab vedotin for widespread disease [19].

Primary Cutaneous B-cell Lymphomas

Three main types of CBCL are described: primary cutaneous marginal zone lymphoma (PCMZL), primary cutaneous follicle centre lymphoma (PCFCL) and primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT).

PCMZL and PCFCL have an excellent prognosis, with 10-year survival of more than 90% [13,20,21]. PCMZL is seen as red–brown tumours in young adults, mainly on the upper extremities or trunk (see Figure 3A). PCFCL is mainly seen in adults as blue–red tumours in the scalp (see

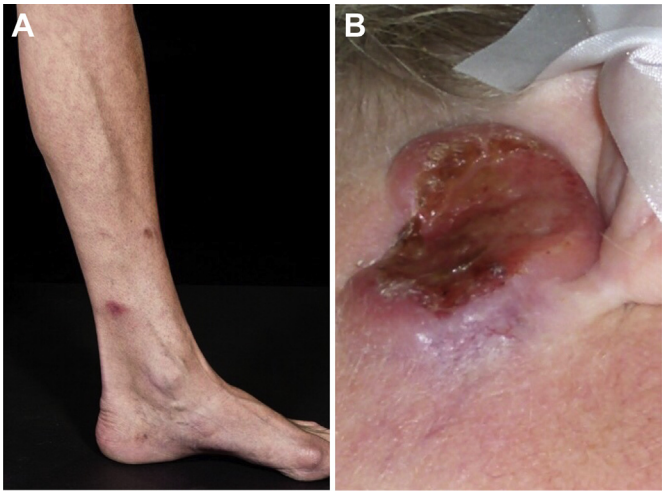

Fig 2. Primary cutaneous CD30-positive lymphoproliferative disorders. (A) Lymphomatoid papulosis (left); (B) primary cutaneous anaplastic large cell lymphoma (right).

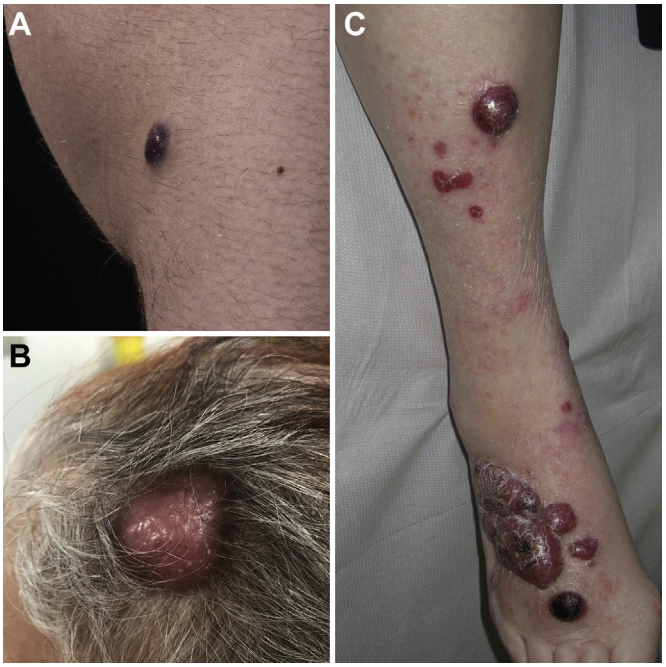

Fig 3. Primary cutaneous B-cell lymphomas. (A) Primary cutaneous marginal zone lymphoma (upper left); (B) primary cutaneous follicle centre lymphoma (lower left); (C) primary cutaneous diffuse large B-cell lymphoma, leg type (right).

Figure 3B). Patients may have a few or multiple tumours. Single tumours may be treated with local radiotherapy or excision; in the case of multiple tumours, treatment is with radiotherapy or anti-CD20 [22,23].

PCDLBCL-LT is typically seen in elderly patients, especially women. The patient presents with red–brown tumours on the lower leg, ulcerations are typically seen, and both legs may be affected (see Figure 3C). It has an unfavourable prognosis, with 5-year overall survival of around 50%. Systemic treatment with rituximab, cyclophosphamide, adriamycin, vincristine and prednisone (R-CHOP) is recommended; if the disease is localised, radiotherapy is also recommended. However, most patients are elderly, and many do not tolerate multi-agent chemotherapy. Rituximab as a single drug, followed by local radiotherapy if indicated, may achieve remission. Remissions have also been achieved with Bruton's tyrosine kinase inhibitors, which block the NF-κB pathway, which seems to be often constitutively activated in this disease entity [24]. In a subgroup of patients this disease seems, however, to take a more indolent course, and can be managed with local radiotherapy, which is repeated when the patient has a recurrence, often with intervals of 6–12 months.

General Treatment Principles

Most PCL have an indolent clinical course and remain localised in the skin for a very long time. Skin-directed therapies are the most active agents for cutaneous disease. Systemic cytotoxic therapy, which is very active in non-cutaneous lymphomas, has only a short-lived effect in the skin, but is active against involved lymph nodes or visceral involvement.

Skin-directed Therapies

Skin-directed therapies are first-line treatment for the early stages of PCL, including early stage mycosis fungoides. The aim of skin-directed therapy is to control the skin lesions and to minimise morbidity. In the more advanced stages of cutaneous lymphomas and in cases of treatment failure with topical therapies, skin-directed therapies are often used as adjuvant therapy to radiation or systemic therapies. The following therapies are the key choices of skin-directed therapy.

Topical Steroids

Topical steroids are often used in the treatment of early stage mycosis fungoides. Their mechanisms of action as anti-inflammatory and immunosuppressive agents are well known. Despite topical corticosteroids being used as treatment for mycosis fungoides since the 1960s, documentation for the beneficial effects on mycosis fungoides and other PLCs is limited. A study published in 1998 by Zackheim *et al.* [25] is the largest prospective study of 79 patients with stage T1 or T2 mycosis fungoides; most patients were treated with group 3 or 4 topical steroids once or twice daily. Complete remission was achieved in 63% and partial remission in 31%, with a total response rate of 94% in the stage T1 group. Nearly the same results were seen for stage T2 and the response after local steroids was often long lasting.

Topical Nitrogen Mustard

Topical nitrogen mustard, also known as mechlorethamine, is an alkylating agent exerting its effects through the attachment of an alkyl group to DNA. Successful nitrogen mustard use was first described in the late 1940s [26]. In the USA it is considered to be a primary therapy for mycosis fungoides, but is rarely used for other PCLs. It can be administered as a gel or an ointment. Three relatively new large studies (one controlled and two retrospective) have shown good response rates between 50 and 80% [27–29]. The side-effects are mainly mild and skin related but may affect up to 50% of the patients primarily as dermatitis [27–29].

Topical Retinoids

Topical retinoids are vitamin A derivates. The Food and Drug Administration has approved the topical retinoid bexarotene 1% gel (Targretin®) for patients with mycosis fungoides stage IA and IB who have refractory or persistent disease after other treatments. The drug has not been approved in Europe. Bexarotene (1%) gel has been effectively used in patients where other topical therapies have failed. In a phase I and II, open-label, dose-escalation trial of

topical bexarotene gel, the overall response rate was 63%, with a complete response rate of 21% in early disease (stage IA and IB) [30]. The response rate was 75% if patients had not tried other topical therapies; the estimated median response duration was 23 months [30]. An open-label phase III trial showed comparable results [31]. Other topical retinoids, such as tazarotene, also seem to be useful in mycosis fungoides.

Phototherapy

Phototherapy is a frequently used therapy in managing patients with mycosis fungoides and lymphomatoid papulosis. Narrowband ultraviolet B (UVB) and PUVA photochemotherapy are traditional treatments. UVB therapy is recommended for patch or thin plaque mycosis fungoides and PUVA for thicker plaques [32]. Narrowband UVB has a spectrum centred at 311–312 nm and absorption primarily takes place in the epidermis; UVB exerts its effects on epidermal keratinocytes, Langerhans cells, as well as lymphocytes. There are several, but small, mainly retrospective studies on narrowband UVB treatment for patch and plaque mycosis fungoides with a good response [33–35].

PUVA, as treatment for mycosis fungoides, uses UVA as ultraviolet therapy in combination with psoralen, which makes the skin more sensitive to the ultraviolet light. Normally 8-methoxypsoralen is used as the photosensitising agent. It is taken up by epidermal cells and subsequently forms DNA adducts when photoactivated. Psoralen can be taken orally or applied directly to the skin, followed by UVA exposure. PUVA has been used as both concomitant therapy and monotherapy for early stages of mycosis fungoides; it was first reported as a treatment option for mycosis fungoides in 1976 [36]. Since then, the use of PUVA as a treatment for mycosis fungoides has been described many times, but most of the studies have only included small series of patients. The current literature on PUVA as monotherapy for mycosis fungoides is mainly retrospective studies with a complete response at 60% for early mycosis fungoides [32,37]. Adverse events of PUVA therapy include nausea from the ingestion of psoralen; PUVA-related side-effects include pruritus, erythema, photodermatitis and pigment changes. The disadvantages of phototherapy include travel time to the hospital and an increased risk of other skin cancers. PUVA treatment for a longer time with a high cumulative dose increases the risk of non-melanoma skin cancer, especially squamous cell carcinoma [38,39]. Overall, for widespread but thin disease, phototherapy has high complete remission rates but a variable response duration.

Radiation Therapy

Radiation remains the most active single modality in the treatment of most types of lymphoma. This is certainly true of PCL. Shortly after Wilhelm Röntgen discovered X-rays, the first cases of cutaneous lymphomas (mycosis fungoides) were treated with the new rays, which resulted in the healing of tumours, patches and plaques [40]. Local X-ray therapy remains a very effective local treatment for PCL. However, if it is administered over large areas, the dose to the underlying internal organs exceeds their tolerance. Electrons, by contrast, have a limited range of penetration and deposit their total energy within that range. The effect of electrons is therefore limited to superficial tissues, the depth depending on the energy of the electrons. They can therefore be used for the treatment of larger areas, and they are today preferred for the treatment of cutaneous lymphomas because of the sparing of deeper-lying tissues [41].

Radiation doses for localised skin elements vary according to histological type. For the very indolent primary CBCLs (PCMZL and PCFCL), the recommended curative radiation dose is 24–30 Gy. However, indolent B-cell lymphomas are exquisitely radiosensitive, and in the palliative setting 2 Gy × 2 is effective and very convenient [41,42]. For the more aggressive PCDLBCL-LT, systemic treatment is combined with local radiotherapy for localised disease to a dose of 36–40 Gy. However, many of these patients are elderly and do not tolerate systemic treatment; if no systemic treatment is given, the recommended dose is 40 Gy [41,43]. In mycosis fungoides, radiation therapy can be curative in patients with early localised disease; the recommended dose is 20–24 Gy [41]. For local palliation in patients with more widespread disease the recommended dose is 8–12 Gy; 8 Gy may be given in one fraction, but often patients will require re-irradiation and smaller fractions of 3–5 Gy may be preferred [41]. For primary C-ALCL, a dose of 24–30 Gy has been recommended [41], but recent data indicate that a dose of 20 Gy or even lower may be effective [44,45].

Techniques for yielding a uniform electron dose to the entire skin surface became available in the 1960s [46], and total skin electron beam therapy (TSEBT) remains a highly effective treatment for widespread disease in the skin [41]. Different techniques may be used to ensure total skin coverage [47]. These include large electron field techniques [48–50], rotational techniques [51–53] and techniques involving moving the patient or the beam during irradiation [54,55]. The most commonly used technique is the six-field large electron field technique developed at Stanford [50]. The six positions used for this technique are shown in Figure 4. Areas that do not receive the prescribed dose in the TSEBT positions, e.g. the scalp, perineum and soles, will have supplementary conventional electron beam therapy to these areas. Supplementary electron beam therapy may also be given to tumours in the skin that may be too thick to be treated adequately with the TSEBT. The eyes are shielded during radiation therapy (to protect the lenses, which are very radiosensitive; this is not needed if the patient has had a cataract operation) and supplementary kilovolt irradiation to the eyelids is necessary if there is evidence of disease in the face. The TSEBT techniques are challenging, around 25% of the body volume is irradiated to a dose that would be lethal if given to the whole body. Recommendations regarding the technique have been made by the European Organization for Research and Treatment of Cancer (EORTC) Cutaneous Lymphoma Group [56]. In particular, it is important to keep photon contamination very low to avoid

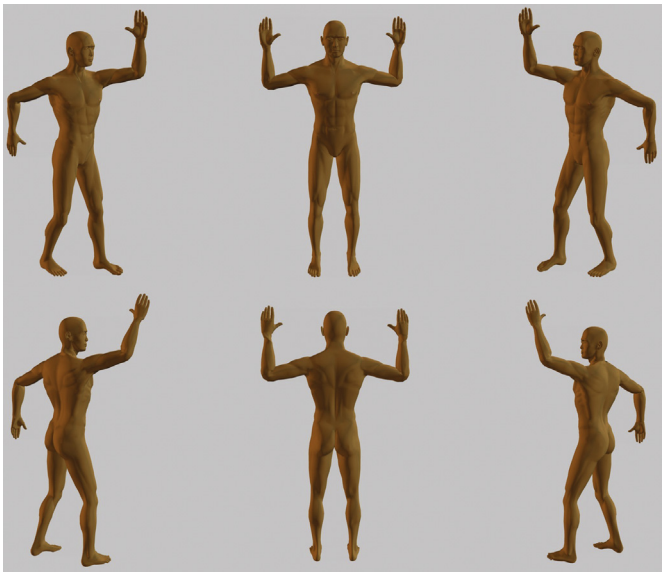

Fig 4. Patient positions for total skin electron beam therapy, six-field technique.

haematological sequelae. There should be no reduction in haemoglobin, leukocyte and thrombocyte count during or after TSEBT. Recently, different centres have tried to develop methods for total skin irradiation using photons and helical tomotherapy. However, too much dose reached the inner organs and, specifically, grade 4 haematological toxicity developed [57,58].

The radiation dose with TSEBT used to be 30–36 Gy based on analyses showing higher complete response rates with higher total doses [59]. However, TSEBT is a palliative treatment and recurrences invariably occur. Lower doses of 10–12 Gy offer advantages of a shorter duration, fewer side-effects and the opportunity for retreatment, which may ultimately offer the patient better and longer overall palliation [60,61]. Most patients will experience relapse after TSEBT, and there is a limit as to how many times the treatment can be repeated, even when using the low-dose TSEBT. It is therefore important that the patient receives some form of maintenance treatment after TSEBT in order to have as long a remission as possible from each of the TSEBT treatments. Radiation is a very efficient method for enhancing the immunogenicity of tumours and trials are now ongoing combining TSEBT with immune treatments, e.g. checkpoint inhibitors.

Systemic Treatments

Methotrexate

Methotrexate is a well-known anti-metabolite inhibiting the dihydrofolate reductase enzyme. Methotrexate is used in a low dose of 10–50 mg once a week (starting at 10–15 mg) for mycosis fungoides and primary cutaneous CD30-positive lymphoproliferative disorders, especially lymphomatoid papulosis [19,62]. In the case of mycosis fungoides, methotrexate is often used in combination with skin-directed therapies. Side-effects are mucositis, myelosuppression, gastrointestinal symptoms, liver and pulmonary toxicity.

Retinoids

Several retinoids have been used for CTCL, including acitretin, and in 1999 a retinoid X receptor-selective retinoid was approved for CTCL [63–65]. Ninety-four patients with CTCL in advanced stages (IIB–IVB) were enrolled in the phase II–III study. The overall clinical response rate (complete response plus partial response) was 45% in the first group and 55% in the patients who received more than 300 mg/m^2/day [64]. Bexarotene showed a similar efficacy in patients with early stage CTCL [63]. It is recommended to start low at 150 mg/daily, and then increase up to 300 mg/m2, depending on side-effects. The most important side-effects are hypertriglyceridaemia, hypercholesterolaemia and central hypothyroidism.

Interferon-α

IFN-α has immunomodulatory activity and has been shown to have an effect in patients with CTCL, especially tumour mycosis fungoides and Sézary syndrome. IFN-α is given three times a week in doses of 3–10 million units. The overall response is 50–70%, with a complete response in 20–30% [66,67]. IFN-α can be used alone but is often used in combination with PUVA and also together with bexarotene and photopheresis [68,69]. Side-effects are dose-limiting 'flu-like symptoms and myelosuppression and liver toxicity.

Extracorporeal Photopheresis

Extracorporeal photopheresis (ECP) is a form of photochemotherapy, like PUVA, which was first described for CTCL in 1987 [70]. It is an apheresis procedure whereby a leukocyte-enriched fraction of blood in the presence of 8-methoxypsoralen is exposed to a UVA light source and then returned to patients. ECP induces an immune-mediated response to the malignant T-cell clone and the mechanism of action is believed to be the induction of apoptosis of malignant T-cells, the induction of immature dendritic cells and expansion of a population of cytotoxic T-cells against the malignant T-cell clone. There are different treatment regimens and no standard therapy. The European Dermatology Forum's guidelines from 2014 recommend the following for the treatment of mycosis fungoides/Sézary syndrome: one cycle every 2 weeks for the first 3 months, then once monthly or every 3 weeks [71]. ECP as monotherapy for erythrodermic mycosis fungoides or Sézary syndrome is based on retrospective data, as there is no controlled trial with ECP as monotherapy. Retrospective studies show an overall response rate with clearing in at least 50% [70–72]. ECP given as combination therapy, especially with IFN and bexarotene, leads to higher response rates [71].

Cytostatics

The standard drug combination for the treatment of non-Hodgkin lymphomas is cyclophosphamide, adriamycin, vincristine, and prednisone (CHOP). This regimen is, however, not as effective against skin involvement, and is also not well tolerated by these, often older, patients. As the treatment of widespread disease in the skin or disseminated disease is virtually always palliative, single drug treatment is often preferred. No single-agent or multi-agent regimen seems to yield significantly better results than the others [73].

Gemcitabine is a pyrimidine anti-metabolite. Given weekly for 3 weeks per 4-week cycle, it yields overall response rates of 48–70% in patients with advanced or refractory mycosis fungoides [74,75]. Toxicity is relatively mild, although pulmonary toxicity may be a problem.

Pegylated liposomal doxorubicin has fewer side-effects than conventional doxorubicin, particularly cardiotoxicity, and has yielded response rates over 80% in patients with mycosis fungoides, but may be quite toxic [76–78]. Oral chlorambucil may control the lymphoma for some time with few side-effects.

Newer Drugs

Histone Deacetylase Inhibitors

Romidepsin and vorinostat inhibit deacetylation of the histones, which would otherwise prevent transcription of the cell's DNA. The overall response rate in primary CTCLs was 30–40% with a response duration of over 12 months [79–83]. Side-effects are mainly gastrointestinal.

Anti-metabolites

Pralatrexate is an anti-folate, which has shown an effect in both mycosis fungoides and transformed mycosis fungoides, with an overall response rate of 30–45% and a response duration of 27 weeks [84–86]. Side-effects are myelosuppression and mucositis.

Antibodies

Rituximab is a chimeric monoclonal antibody against CD20 that is found on the surface of all B-lymphocytes. It is active in primary CBCL. It is included in the treatment regimen for patients with PCDLBCL-LT [87–89]. For elderly patients with this disease who may not tolerate conventional cytotoxic therapy, rituximab as a single drug may induce remissions of an acceptable duration. It is also effective as a single drug for multifocal lesions of PCMZL or PCFCL, with overall response rates of 60–100% and a response duration of 2 years [90]. It has even been used as intralesional injections, yielding very high local response rates [91–94]. At recurrence the treatment may be repeated.

Brentuximab vedotin is a chimeric antibody against CD30 coupled with a cytostatic drug, monomethylauristatin E, an anti-microtubuli drug, which is only released when the drug has been transported into the cell. It is active in CD30-positive PCL, with high response rates in C-ALCL and CD30-positive cases of mycosis fungoides [95–97]. The response rate is higher in patients with high CD30 expression, but responses are also seen in patients with low CD30 levels.

Mogamulizumab is a humanised monoclonal antibody targeting the CC chemokine receptor 4 (CD194), which is expressed on Th2 T-lymphocytes. In a randomised trial it was superior to vorinostat, with an overall response rate of about 30%, with a median duration of 8 months [98]. The drug has recently been approved in the European Union for primary CTCL.

CTCL cells express CTLA-4, PD-1 and PD-L1 more often than the corresponding non-malignant cells, eliciting T-cell exhaustion. Antibodies that block these checkpoints can reverse T-cell exhaustion and could potentially be useful in the treatment of CTCL [99,100]. Pembrolizumab and nivolumab are both anti-PD-1 antibodies that cause checkpoint inhibition, and both have shown efficacy in CTCL. Preliminary results of a phase II study of pembrolizumab in mycosis fungoides and Sézary syndrome show an overall response rate of 38%, with a median response duration of 61 weeks. Atezolizumab is a human IgG1 monoclonal antibody that targets PD-L1. It is being tested in CTCL.

In PCDLBCL-LT, PD-L1 is variably expressed by the tumour cells, and very often by the numerous immune cells in the cellular background [101,102]; genomic analyses have shown translocations leading to overexpression of PD-L1 or PD-L2 in 50% [103]. Checkpoint inhibitors may therefore also turn out to be effective in this disease entity.

High-dose Chemotherapy with Autologous or Allogeneic Bone Marrow Transplant

Autologous stem cell transplantation has been tested in primary CTCL, but has not proved valuable, as responses have generally been short [104]. The results of allogeneic transplantation have been better, with evidence of an allogeneic graft versus lymphoma effect [105–108]. The long-term relapse-free survival is only about 30%, but may perhaps be improved with some form of maintenance treatment. Most of these allogeneic transplants have been non-myeloablative and the outcome is better when there is a lower tumour burden before transplant. It is therefore important for the patient to be in the best possible remission before the transplant; TSEBT is often needed to achieve remission in the skin.

Conclusion

Primary cutaneous lymphomas are a heterogeneous group of non-Hodgkin lymphomas with special characteristics, including, importantly, a much more indolent course than the corresponding histological types in other organs. Skin-directed therapies form the mainstay of treatment in most patients. For patients with advanced or refractory

disease, new drugs, mainly modulating the immune system, are becoming available.

Conflict of Interest

L. Specht is on the advisory board for Takeda; received honoraria from Merck Darmstadt, MSD and Takeda; and has a research agreement with Varian.

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