EUROPEAN JOURNAL OF CANCER 43 (2007) 2321–2329

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Review

Maintenance therapy in cutaneous T-cell lymphoma: Who, when, what? ☆

R. Dummer[a,*], C. Assaf[b], M. Bagot[c], R. Gniadecki[d], A. Hauschild[e], R. Knobler[f], A. Ranki[g], R. Stadler[h], S. Whittaker[i]

[a]Department of Dermatology, University Hospital of Zurich, Gloriastrasse 31, CH-8091 Zürich, Switzerland
[b]Department of Dermatology and Allergy, Skin Cancer Center Charité, Charité-Universitätsmedizin Berlin, Schumannstrasse 20/21, 10117 Berlin, Germany
[c]Department of Dermatology, AP-HP, Hôpital Henri Mondor, INSERM, U 659, University Paris 12, Créteil F-94010, France
[d]Department of Dermatology, University of Copenhagen, Bispebjerg Hospital, Bispebjerg bakke 23, DK-2400 Copenhagen, Denmark
[e]Department of Dermatology, University of Schleswig-Holstein, Schittenhelmstrasse 7, 24105 Kiel, Germany
[f]Department of Dermatology, Division of Special and Environmental Dermatology, Medical University of Vienna, Wahringergürtel 18-20, A-1090 Vienna, Austria
[g]Skin and Allergy Hospital, Helsinki University Hospital, PO Box 160, 00029 HUS, Helsinki, Finland
[h]Department of Dermatology, Medical Centre Minden, Portastrasse 7–9, 32423 Minden, Germany
[i]St. John's Institute of Dermatology, Guys and St. Thomas' Hospital, Lambeth Palace Road, London SE1 7EH, UK

ARTICLE INFO

Article history:
Received 29 May 2007
Received in revised form 26 June 2007
Accepted 27 June 2007
Available online 17 August 2007

Keywords:
T-cell lymphoma, cutaneous
Combined modality therapy
Remission induction
Minimal residual disease
Mycosis fungoides
Progression-free survival
Quality of life
Sézary syndrome
Treatment efficacy

ABSTRACT

The aim of current therapy for cutaneous T-cell lymphoma (CTCL) is to induce clinically meaningful remission, provide symptom relief, improve patient quality of life (QoL) and prolong disease-free and overall survival. A key research question is whether such remissions or minimal disease status can be maintained in the long term. There have been few formal studies of maintenance therapy in CTCL. Some skin-directed therapies such as total-skin electron-beam therapy and high-dose psoralen plus ultraviolet A may not be considered suitable, because of the risk of long-term cumulative toxicities. Other therapies such as nitrogen mustard, interferon (IFN)-α and bexarotene have demonstrated positive effects in prolonging remissions in small numbers of patients. Large longitudinal studies are required to investigate the efficacy of maintenance treatments in CTCL and their impact on patients' QoL and overall survival. Of the systemic therapies currently approved for the treatment of CTCL, bexarotene and IFN-α are obvious candidates for testing, because they can be self-administered by the patient and provide good long-term tolerability.

☆ A meeting of the authors was sponsored by Cephalon Europe; however, the company did not participate in the preparation of the manuscript or influence its content.

* *Corresponding author:* Tel.: +41 44 255 2507; fax: +41 44 255 8988.
E-mail address: Reinhard.Dummer@usz.ch (R. Dummer).

0959-8049/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ejca.2007.06.015

1. Introduction

Primary cutaneous T-cell lymphomas (CTCLs) are indolent, non-Hodgkin's T-cell lymphomas that initially present with skin lesions and rarely affect other organs except in very advanced stages. The most common form, mycosis fungoides (MF), is characterised by the presence of a clonal T-cell population in the cutaneous microenvironment. In the less common Sézary syndrome (SS), the dominant T-cell population also circulates in peripheral blood. In the early stages, MF presents as scaly patches or plaques, which resemble the clinical manifestations of eczema or psoriasis and are often associated with pruritus. At later stages, patients may experience the growth of nodular lesions and large tumours, also with pruritus, which may ulcerate and result in chronic septicaemia, thrombosis and pain. In addition, sleep disturbances and eye irritation due to specific T-cell infiltrates may occur. Thus, CTCL commonly has an indolent course but can become highly symptomatic, cosmetically disfiguring, and associated with profound impact on patients' quality of life (QoL).

In MF, patient prognosis and duration of survival are primarily affected by the disease stage. At the earliest disease stage, patient survival is similar to that of age-matched healthy controls, whereas later disease stages are associated with progressively shorter median durations of survival.[1] Treatment is also dictated by the disease stage. Skin-directed therapies are generally the first-line treatment option for early disease stages, whereas systemic therapies, particularly biological response modifiers such as the rexinoid bexarotene, the fusion protein denileukin diftitox and interferon (IFN)-α are used at later disease stages or as a second-line therapy once patients have relapsed during topical therapy.[1] Conventional systemic chemotherapies are also reserved for advanced stages of MF and SS.

CTCL is responsive to current treatment modalities but generally resistant to cure. The aim of the therapy is therefore to induce clinically meaningful remission (reduction or clearance of skin lesions, most relevantly the clearing of tumours, and reduction of pruritus), thereby providing symptom relief, improving patient QoL and prolonging disease-free and overall survival. The recent consensus recommendations for the treatment of MF/SS of the European Organisation for Research and Treatment of Cancer (EORTC),[1] interdisciplinary recommendations of the German Cancer Society[2] and guidelines from the joint British Association of Dermatologists and UK Cutaneous Lymphoma Group[3] provide valuable guidance on the appropriate treatment choices for different disease stages.

However, multiple questions about the treatment of CTCL remain, and need to be addressed through clinical trials. There are several treatment approaches that efficiently induce tumour regression, qualifying as partial or, less frequently, complete remissions.[4–8] One key question is how remissions could be made more durable, thus halting disease progression, improving patients' QoL and hopefully prolonging disease-free and overall survival.

Regardless of the therapy being used in CTCL, the median duration of response is generally relatively short and declines as the severity of the disease increases. Response duration after CHOP polychemotherapy for advanced CTCL was only 5.7 months,[8] and after 2-chlorodeoxyadenosine was a median of 4.5 months in patients with complete remission and 2 months among those with partial remissions.[5] Each relapse or progression requires further treatment, often with a different therapy or combination of therapies and, as the majority of patients with CTCL will gradually develop more advanced disease, there is a movement towards potentially more toxic, aggressive therapies. In this context, there is a need to investigate how an initial remission or minimal stable disease can be maintained in the long term using a well-tolerated therapy without significant cumulative toxicities.

2. Maintenance treatment of indolent B-cell lymphomas

Recently, the use of rituximab has improved the treatment of other indolent non-Hodgkin's lymphomas (NHL). Initial studies demonstrated that polychemotherapy in combination with rituximab increased the complete remission rate in nodal B-cell NHL.[9] Subsequent studies investigated whether these remissions could be prolonged using maintenance therapy. Patients with nodal follicular B-cell lymphoma who had stable disease or a complete response (CR) or partial response (PR) after standard 'induction' therapy with CHOP and rituximab, 375 mg/m^2 once weekly, were randomised to receive a prolonged schedule of treatment every 2 months with the drug at the same dose, or no further treatment. Patients receiving the prolonged-treatment schedule showed a longer duration of remission and longer event-free survival than those who discontinued treatment after induction.[10] A comparison of regular maintenance therapy versus re-treatment at relapse in patients with indolent NHL found that, while there was no difference between the two treatment groups in overall 3-year actuarial survival, maintenance treatment produced a greater response rate and longer progression-free survival than re-treatment.[11] Likewise, in patients with large B-cell lymphoma, there was no difference in overall survival after induction therapy alone versus induction followed by maintenance therapy with rituximab. The latter group did, however, show an increase in failure-free survival (defined as the time from randomisation to relapse, non-protocol treatment or death) compared with induction therapy alone.[12]

The clinical importance to patients and healthcare providers of this therapeutic profile of prolongation of remissions without a clear overall survival benefit depends on the disease being treated, and on patients' attitudes to their disease and to maintenance therapy. For asymptomatic NHL, relapses may have a minimal direct effect on patients' QoL. Nevertheless, the diagnosis of cancer itself places a substantial burden on patients,[13] which is heightened by the occurrence of relapses.[14] In the case of asymptomatic lymphoma, some patients prefer to take a maintenance therapy as this reassures them that active steps are being taken to control their disease and retain their current health status, whereas others would prefer not to take regular therapy as this is seen as a reminder of their disease.[15] Advanced CTCL patients are confronted with visible manifestations on a daily basis, with pruritus and ulcerations that affect their daily life. For this patient population, preservation

of complete remission, with or without minimal residual disease, has obvious advantages.

3. What is 'maintenance' in the context of CTCL?

In the use of rituximab, as described above in nodal B-cell lymphoma, maintenance therapy was designed to preserve or improve the current disease status of patients who had experienced a CR, PR or stable disease during induction therapy. In these studies, disease response was defined clinically, although the presence of B-lymphocytes showing the characteristic t(14; 18) chromosome translocation was used successfully as a surrogate measure for tumour burden in one study.[10]

In CTCL, disease response is defined clinically, with confirmation by histology (including eventual blood and bone marrow samples) and computed tomography, and the clinical manifestations of the disease directly affect patient QoL. The health distress associated with CTCL was demonstrated clearly by the results of the 2005 National Cutaneous Lymphoma Foundation Survey, which showed the profound impact of the disease on the functioning, emotional and social well-being of patients.[16] Therefore, the goal of maintenance therapy in CTCL may not only be to preserve the current disease status of patients with a CR, PR or stable disease during induction therapy but also, realistically, to maintain a minimal residual disease state, reduce relapses or prolong disease-free intervals, thereby preserving patient QoL (Fig. 1). In patients in whom there is a clinical CR, molecular techniques to investigate persistence of the dominant T-cell clone may help to identify those with a high risk of relapse, who therefore have an urgent need of maintenance therapy. However, we do not know which compartment, whether skin, blood or even lymph node, is the most appropriate for this molecular screening.[17–19]

4. Efficacy of maintenance therapy in CTCL

There have been few formal studies of maintenance therapy in CTCL and there is little evidence currently available to guide practice. Table 1 provides information on the maintenance studies in CTCL that are discussed in the text below. Most of these are retrospective analyses as data from randomised clinical trials in this area are limited. Treatment decisions about whether or not a patient receives maintenance therapy are based largely on the judgement of the practising physician, who must balance the benefits and side effects of a given therapy. There is a need to define which therapies are appropriate to be used in this context and in which patients, bearing in mind that such long-term treatment should be well tolerated without cumulative toxicities.

4.1. *Skin-directed therapies, phototherapy and radiotherapy*

In the early stages of MF (stages IA, IB and IIA), the disease is highly responsive to therapies such as psoralen plus ultraviolet A (PUVA), total-skin electron-beam (TSEB) therapy and topical chemotherapies.[1,20,21] However, most patients receiving these treatments will eventually show disease relapse and require re-treatment. For example, among patients mostly with

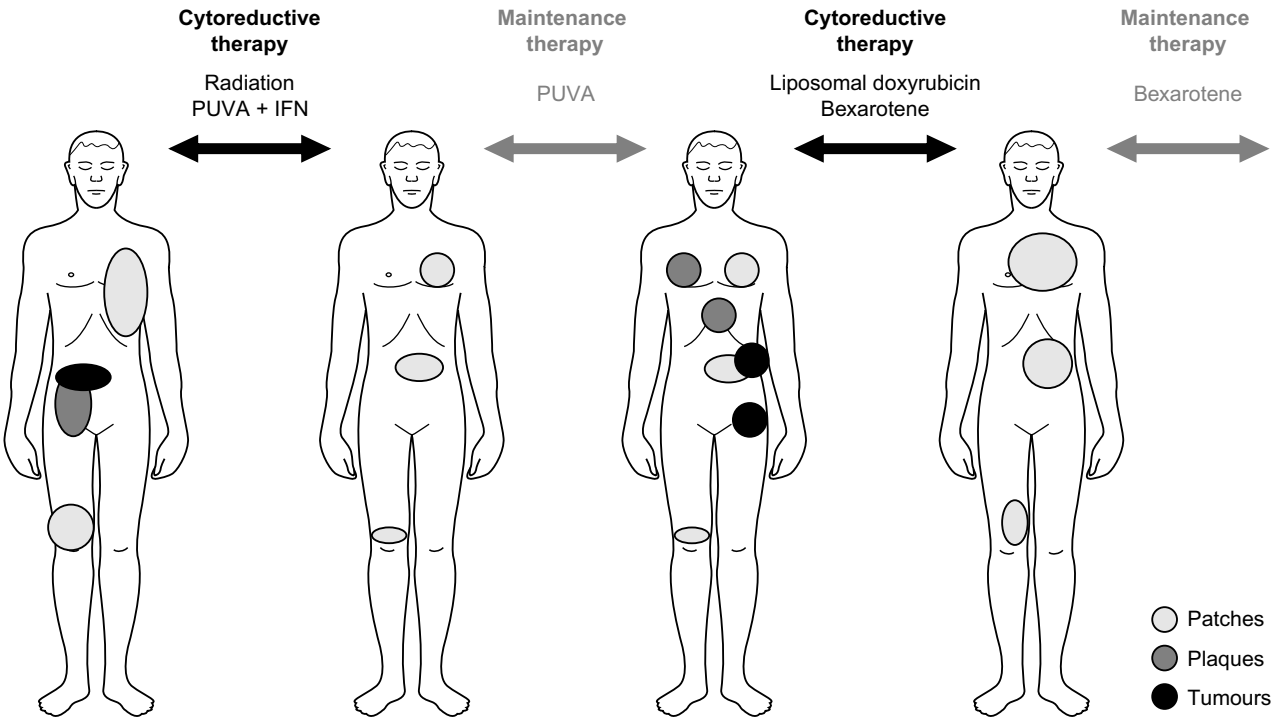

Fig. 1 – Example of the use of cytoreductive induction therapy, alternating with maintenance therapy, to maintain disease status in a patient with mycosis fungoides.

Table 1 – Studies of maintenance therapy in cutaneous T-cell lymphoma

Maintenance treatment	Disease stage	Study design	Patients treated (*n*)	Duration of treatment	Outcome	Reference
Topical NM	I–II	Single-centre, retrospective analysis	81 with CR to initial NM therapy	3 groups with medians of 0, 6 and 20 months	• Better maintenance of CR with longer duration of therapy • No difference in relapse rate when therapy discontinued	Kim et al.[24]
Topical NM	II–III	Single-centre, retrospective analysis	23 with CR to TSEB	Various	• Improved freedom from relapse compared with TSEB alone	Chinn et al.[25]
PUVA	I–II	Single-centre, retrospective analysis	14 treated initially with TSEB	Median of 62 months	• Significant improvement in DFS versus non-PUVA group	Quiros et al.[27]
NB UVB	IA–IIA	Single-centre, retrospective analysis	10 with CR to initial NB UVB therapy	Median of 18 months	• No patients relapsed during maintenance • Mean RFS was 26 ± 9.9 months	Boztepe et al.[33]
NB/BB UVB	IA, IB	Single-centre, retrospective analysis	70 with CR to initial NB or BB UVB	14 weeks (NB) 11.6 weeks (BB)	• No significant difference in relapse rate between those who did and did not have maintenance therapy	Pavlotsky et al.[34]
IFN-α2b + PUVA	I–II	Prospective, multicentre, Phase II, single-arm	25	12 months	• Probability of freedom from treatment failure was 82% after 12 months of maintenance therapy and 62% at 24 months	Rupoli et al.[35]
IFN-α2b	IA–IVA	Single-centre, retrospective analysis	19 treated with TSEB 2 weeks after start of IFN-α	12 months	• Addition of IFN-α to TSEB did not increase CR rate or DFS compared with TSEB alone	Roberge et al.[37]
Etretinate	Biopsy-proven MF	Prospective, single-arm, pilot study	23 treated initially with TSEB	Average of 6.7 months	• RFS with etretinate + TSEB was similar to concurrent and historical control subjects	Jones et al.[38]
IFN-α followed by NM	I–IV MF & SS	Prospective, single-centre	28 treated initially with combined modality therapy[a]	IFN-α for 1 year NM for 2 years	• Median FFS was 6 months • Response was more prolonged in early-stage disease than in advanced-stage disease	Duvic et al.[39]
IFN-α followed by NM	I–IV	Single-centre, retrospective analysis	56 with CR after initial combined modality therapy[a]	IFN-α for 1 year NM for 3 years	• Median DFS of 62 months for those with stage I–IIA disease and 7 months for stage IIB–IV disease	Duvic et al.[40]
Low-dose bexarotene	I–IVB	Prospective, single-centre	4	2 years	• CR maintained	Talpur et al.[41]

BB UVB, broadband UVB; CR, complete response; DFS, disease-free survival; FFS, failure-free survival; IFN, interferon; MF, mycosis fungoides; NB UVB, narrowband UVB; NM, nitrogen mustard; PUVA, psoralen plus UVA; RFS, relapse-free survival; SS, Sézary syndrome; TSEB, total skin electron beam; UVA, ultraviolet A; UVB, ultraviolet B.

a Combined modality therapy consisted of IFN-α, isotretinoin and TSEB.

stage I CTCL, Herrmann and colleagues found the median duration of response after PUVA to be 43 months.[22] With TSEB, the 5-year relapse-free survival among 241 patients with CTCL was 56% in those with stage IA, 25% with stage IB, 13% with stage IIA and only 2% with stage IIB.[23] Among those with a CR to topical nitrogen mustard, Kim and colleagues reported a median time to relapse of 12 months (range 1–60 months) in stages IA and IB.[24]

The effects of topical nitrogen mustard as an initial and maintenance therapy were reviewed by the Stanford group.[24] Among patients with a CR to nitrogen mustard this response was better maintained with longer duration of maintenance therapy, although there was no effect on the length of overall or disease-specific survival (deaths attributable to MF). Furthermore, the disease relapsed at the same rate once maintenance therapy was discontinued. The Stanford group therefore recommends that nitrogen mustard therapy is discontinued temporarily following a CR, in order to minimise cost and patient inconvenience and avoid long-term toxicity. The topical therapy may then be re-started, as a maintenance or a salvage therapy once the disease relapses.[24] Adjuvant treatment with topical nitrogen mustard in patients with T2 and T3 MF who had achieved a CR to TSEB has also been shown to result in a longer freedom from relapse compared with patients who received no further treatment, but with no improvement in overall survival.[25]

Long-term treatment with PUVA at its normal dose is hampered because of the risk of non-melanoma skin cancer following such long-term exposure[3] and, over a longer time frame, the risk of melanoma is also increased.[26] Patients with early-stage MF who received a PUVA maintenance regimen after initial TSEB treatment showed an improvement in 5-year disease-free survival compared with those given TSEB alone or TSEB followed by other forms of adjuvant therapy. However, many secondary cutaneous malignancies (malignant melanoma, basal cell carcinoma and squamous cell carcinoma) were seen among those treated with adjuvant PUVA.[27] Nevertheless, as every therapeutic effort should be made to prevent progression of CTCL stage IB into the tumour stage of the disease, low-dose PUVA therapy could be worthy of consideration, despite the long-term toxicity. Maintenance therapy with low-dose PUVA in combination with IFN-α has also been studied and will be discussed below in the section on systemic therapies.

In contrast to UVA, UVB and narrowband UVB phototherapy does not require psoralen ingestion.[28] There have been reports of successful management of early-stage MF with narrowband UVB,[29–32] although the disease may relapse following discontinuation,[29,31] leading to the suggestion that the use of maintenance therapy would be a logical approach.[33] A small study in early-stage MF showed that, after an initial CR to narrowband UVB, maintenance therapy at gradually decreasing frequency was effective in providing freedom from relapse.[33] From the limited data available, it appeared that a longer duration of maintenance treatment was associated with longer relapse-free intervals.[33] Contrasting data were reported from a large retrospective analysis of patients who had received either narrowband or broadband UVB for the treatment of early MF, which found no difference in the rates of relapse between patients who did and did not receive maintenance therapy.[34] The authors therefore concluded that, as for nitrogen mustard therapy, treatment with UVB can be stopped completely following induction of a first CR. When patients relapse, re-treatment with UVB is effective in producing a second CR, and maintenance therapy may be considered at this stage.[34]

The length of maintenance therapy (18 months versus 3 months), and its frequency (starting at three times weekly compared with twice weekly), are key differences in the methodologies of the two studies described above.[33,34] The results may indicate that maintenance therapy with UVB could be optimised by relatively high-frequency, long-duration therapy, although this approach would be highly inconvenient for patients. Furthermore, as the studies with UVB that are currently available are mostly retrospective and uncontrolled, this question requires further investigation in large, long-term, well-designed trials.

4.2. *Systemic therapies*

Patients with refractory early-stage MF or more severe disease (stages IIB or III) are likely to receive systemic therapies, either alone or in combination with skin-directed therapies.[1] A few studies have investigated the use of these therapies for the long-term management of MF.

Combination therapy with IFN-α2b and PUVA was studied in patients with stages I–II disease, most of whom had received some prior therapies for MF.[35] Those who achieved a CR or PR after initial therapy with IFN-α2b and PUVA were given maintenance therapy. This consisted of IFN-α2b combined with PUVA at gradually reduced doses for an overall period of 12 months, by which time patients were on IFN-α2b given twice weekly, and PUVA once a month. The authors concluded that this treatment combination can produce long-lasting clinical responses in patients with MF, but stressed the importance of a long duration of maintenance and the need to decrease the dosage of IFN-α and PUVA very slowly in order to prevent recurrence.[35] Treatment was generally well tolerated, although side effects necessitated the interruption of therapy in two patients, withdrawal of PUVA in one patient and withdrawal of both treatments in one patient. A more recent study has confirmed the benefits of combination therapy with IFN-α and PUVA in achieving high remission rates and prolonging progression-free survival.[36] In this prospective study, patients with CTCL stages I and II were randomised to receive PUVA alone or IFN-α2a plus PUVA at gradually decreasing frequency. Among those in the combination arm, 79% of patients showed a complete remission with a median progression-free time of 113 weeks, compared with 72% and 53 weeks, respectively, in the PUVA arm.[36]

A recent retrospective review of 50 patients with MF compared the outcome among those treated with TSEB alone with a cohort that had also received IFN-α, initiated 2 weeks prior to the start of TSEB and continued along with the radiation and then for the subsequent 12 months. The addition of IFN-α did not appear to increase the CR rate, disease-free survival or overall survival.[37] Similarly, the addition of oral etretinate to TSEB did not appear to confer an advantage in disease-free survival compared with TSEB alone.[38]

Table 2 – Examples of patients with cutaneous T-cell lymphoma (CTCL) who, in the experience of the authors, are at high risk of relapse following a complete or partial response, and who should therefore be considered for maintenance therapy

- Patients who present at an advanced CTCL stage (IIB or higher)
- Mycosis fungoides patients who suffer multiple tumours and demonstrate new tumour lesions within a few weeks. Relapses are generally seen within a few months of a partial or complete response after effective therapy
- Patients who have stage IB CTCL and either folliculotropic disease or thick plaques as well as large cell transformation
- Sézary syndrome patients with a significantly elevated CD4+:CD8+ ratio. Complete remissions are rare among this group and prolonged treatment is needed, usually with a continuation of their initial therapy, which frequently includes extracorporeal photopheresis

The effects of combined-modality therapy, including long-term maintenance treatment, were reported for patients with MF or SS, who were treated initially with IFN-α and isotretinoin followed by TSEB alone (for stages I–II disease) or preceded by chemotherapy (for stages III–IV disease).[39] They subsequently received maintenance therapy with IFN-α for 1 year and topical nitrogen mustard for 2 years. Duration of remission was short in most patients with advanced-stage disease (although two patients did remain in complete remission at more than 39 months), leading the authors to suggest that either consolidation chemotherapy or more intensive maintenance therapy should be tested in such patients. On the other hand, patients with early-stage disease showed a good and prolonged response to therapy, and had not reached a median duration of remission after 18 months' follow-up. Thus, for these patients, this sequential use of effective agents and prolonged maintenance therapy with a systemic and topical agent provided effective long-term control of clinical disease.[39] However, it is important to bear in mind that these studies with combined-modality therapy are uncontrolled, which weakens the data and does not allow robust conclusions.

A retrospective review also presented data on similar combined-modality therapy in 95 patients with MF.[40] After an induction therapy with IFN-α, isotretinoin and TSEB, those who achieved a CR received maintenance therapy with IFN-α for 1 year and topical nitrogen mustard for 2 years. Like the previous report, this analysis presents no separate assessment of the efficacy of maintenance therapy compared with cessation of therapy after induction, or of different durations of maintenance therapy. Nevertheless, this therapeutic regimen again produced long-lasting responses in large proportions of patients, particularly those with early-stage disease.[40]

The use of oral bexarotene as a maintenance therapy has been reported in six patients with CTCL who achieved either CR or 99% PR following initial treatment with this agent.[41] In two patients with CR, bexarotene was maintained at the full dose for 2 years then reduced to 2–4 tablets (150–300 mg) per day; two other patients who experienced dramatic partial remissions that lasted more than 3 years also received low-dose bexarotene maintenance therapy for 2 years without relapse of their disease. In these six patients, bexarotene was able to induce and maintain long-lasting responses.[41]

5. Can we identify patients with CTCL who are likely to relapse?

CTCL is a chronic disease with a prolonged course and, if maintenance treatment is used, some patients may receive therapy for long periods of time. In order to make a rational use of maintenance therapy, it would be desirable to apply it to those patients who are more likely to relapse following a CR. At present, they cannot readily be identified, although disease stage, degree of skin involvement and the kinetics of new lesions may be predictive. Table 2 lists examples of patient groups who, in the experience of the authors, are likely to relapse.

According to the EORTC consensus recommendations for the treatment of MF and SS, 'Expectant Policy' is a legitimate management option for patients with early-stage (IA) MF.[1] As these patients have a normal life expectancy, they can remain untreated, but should be carefully monitored for signs of disease relapse or progression. If it were possible to identify those patients at later stages of disease who are unlikely to relapse after first-line therapy, a similar policy of waiting and careful monitoring may be appropriate for this group too. In the future, we may have new biomarkers to identify such cases.

A possible means of monitoring the likelihood of relapse was identified for patients with stages IB–III CTCL treated with bexarotene.[42] Almost all patients had an elevated CD4+:CD8+ ratio and a low CD8+ count in peripheral blood at diagnosis. Following bexarotene therapy, responders showed higher CD8+ counts and lower CD4+:CD8+ ratios than non-responders. In addition, in most patients who relapsed, there was at least a 50% reduction in CD8+ count between 3 and 6.5 weeks before cutaneous relapse was observed. Thus, as the authors observed, if these results are confirmed in larger numbers of patients, monitoring sub-populations of T-cells in peripheral blood may provide a means of predicting patient response and relapse in MF.[42]

6. Discussion

There is a clear need for clinical studies in CTCL to investigate how an initial remission or minimal stable disease can be maintained in the long term, in the absence of a targeted therapy for the disease. As discussed above, such studies have been conducted with rituximab in NHL and chronic lymphocytic leukaemia, showing that this drug can prolong relapse-free intervals and may even have beneficial effects on patient survival.[9–11,43] Maintenance therapy for CTCL has, potentially, additional benefits, as the symptoms can be pronounced, have possible long-term sequelae and a profound effect on patients' QoL.[44]

The goals of induction treatment of CTCL are to clear lesions (remission), improve symptoms (palliation) and improve patient survival. Likewise, the goals of maintenance

therapy are to preserve and prolong remissions (whether complete or partial) and prolong survival (Fig. 1). Ideally, molecular or phenotypic biomarkers will help to identify those patients who are likely to relapse or progress, and research is ongoing in this area.[45–48] However, studies will then be required to formally validate the biomarkers and define the appropriate monitoring frequency and, ultimately, screening facilities will need to be made accessible to treating dermatologists or oncologists. This raises a dilemma about whether or not studies of maintenance therapy in CTCL should be delayed until such biomarkers are available and validated, although this does not seem to be a viable reason for delay.

As survival times are long in patients with CTCL, particularly for those at an early disease stage, several years of follow-up and large numbers of patients would be required to assess the effects of maintenance treatment regimens on survival. Surrogate measures such as disease-free survival, progression-free survival or freedom from treatment failure have been used in various studies. Unfortunately, the different definitions of these parameters prohibit a direct comparison of retrospective studies.[40] Furthermore, changes in these parameters do not necessarily predict a change in overall survival rates.[11,12,15] In a symptomatic cancer such as CTCL, prolongation of remissions should allow patients to return to their normal activities and improve their QoL. Therefore, studies of maintenance therapies should, ideally, include patient-reported measures of QoL. Such measures should demonstrate not only the benefits of freedom from symptoms, but also the effects on patients of relative relief from the psychological burden of relapses. Measures of QoL have not been commonly used in studies of treatment in CTCL; however, two studies have reported such assessments. In patients with advanced, refractory CTCL, oral bexarotene produced improvements in QoL on a CTCL-specific QoL questionnaire.[49] Similarly, denileukin diftitox produced significant improvements in the QoL of patients with advanced, refractory CTCL, as assessed using the Functional Assessment of Cancer Therapy–General questionnaire.[50] Any measure of QoL used in studies of maintenance treatment should be designed to show differences between subgroups of patients (receiving different treatments, or responders and non-responders) and longitudinal changes over time.

Other important considerations in the assessment of maintenance treatments are their convenience, potential long-term risks, and the costs of treatments and any associated monitoring that may be required. The ideal treatment will be effective, convenient (portable, easy to store and for patients to administer themselves), cost-effective, have low long-term toxicity and a minimal requirement for monitoring. Several therapies which are widely used initial treatments for CTCL are therefore not appropriate choices for maintenance therapy because of the risk of long-term toxicity.

Of the therapies currently approved for the treatment of CTCL, bexarotene and IFN-α are obvious candidates for testing as maintenance therapy, because they can be self-administered by the patient (bexarotene taken orally, and IFN-α by subcutaneous or intramuscular injection). Vorinostat is an oral therapy that has recently been approved for use as a third-line therapy for CTCL, although the possibility of pulmonary embolism and deep vein thrombosis, and the need for frequent monitoring of blood counts and chemistry, may preclude its use as a maintenance therapy.[51] Oral forodesine is also in development for the treatment of CTCL, and is reported to have an encouraging safety profile.[52]

As discussed above, IFN-α has been shown to be effective alone or in combination with other therapies as a maintenance treatment in CTCL.[35–37,39,40] In addition, the efficacy of this drug as maintenance has been tested in other indolent lymphomas such as follicular lymphoma. A meta-analysis of studies of IFN-α in follicular lymphoma concluded that maintenance therapy with this drug, while not improving overall survival, was associated with prolongation of the duration of remissions.[53] However, the potential benefits of this agent as a maintenance therapy for CTCL must be balanced against the need for regular injections and the possible development of chronic side effects, including fatigue (which may be related to abnormal thyroid function), weight loss and depression.[54] Bexarotene is, as yet, relatively untested as a maintenance therapy, but has established efficacy and tolerability as an initial therapy for CTCL.[6,49] Bexarotene is taken orally and is thus convenient for the patient, it has minimal cumulative toxicity, and its common side effects of hyperlipidaemia and hypothyroidism can be managed with appropriate therapy, suggesting that it should be assessed as maintenance therapy.

7. Conclusions

Large longitudinal studies are required to assess the efficacy of maintenance treatments in patients with CTCL, concentrating on the skin-directed therapies and systemic biological response modifiers that are currently used as first- or second-line treatments. Ideally, these studies would include assessments of patient QoL, surrogate parameters for disease progression and overall progression-free survival. In addition, the costs of treatments, including their convenience for patients, long-term toxicity and requirement for monitoring, will need to be balanced against their efficacy and benefits on patients' QoL. However, because of the rarity of CTCL, it will be a challenge to conduct studies with sufficient power to show statistically significant differences between several treatment modalities on a range of outcome measures.

Conflict of interest statement

All the authors received an honorarium from Cephalon Europe for their advisory role in the development of this manuscript. R.D., C.A., M.B. and A.H. have spoken at sponsored satellite symposia and they and R.G. have acted as consultants for Cephalon.

Acknowledgements

A meeting of the authors was sponsored by Cephalon Europe; however, the company did not participate in the preparation

of the manuscript or influence its content. The authors thank Dr Ann McIlhinney for her help in writing the manuscript.

REFERENCES

1. Trautinger F, Knobler R, Willemze R, et al. EORTC consensus recommendations for the treatment of mycosis fungoides/ Sézary syndrome. *Eur J Cancer* 2006;**42**:1014–30.
2. Dummer R, Stadler R, Sterry W. Kutane Lymphome. In: Garbe C, Albers P, Beckmann MW, et al., editors. *Kurzgefasste interdisziplinäre Leitlinien 2006*. Deutsche Krebsgesellschaft e.V. Münich, Zuckschwerdt Verlag; 2006, p. S.301–306.
3. Whittaker SJ, Marsden JR, Spittle M, Russell Jones R. Joint British Association of Dermatologists and UK Cutaneous Lymphoma Group guidelines for the management of primary cutaneous T-cell lymphomas. *Br J Dermatol* 2003;**149**:1095–107.
4. Wollina U, Dummer R, Brockmeyer NH, et al. Multicenter study of pegylated liposomal doxorubicin in patients with cutaneous T-cell lymphoma. *Cancer* 2003;**98**:993–1001.
5. Kuzel TM, Hurria A, Samuelson E, et al. Phase II trial of 2-chlorodeoxyadenosine for the treatment of cutaneous T-cell lymphoma. *Blood* 1996;**87**:906–11.
6. Duvic M, Martin AG, Kim Y, et al. Phase 2 and 3 clinical trial of oral bexarotene (Targretin capsules) for the treatment of refractory or persistent early-stage cutaneous T-cell lymphoma. *Arch Dermatol* 2001;**137**:581–93.
7. Olsen E, Duvic M, Frankel A, et al. Pivotal phase III trial of two dose levels of denileukin diftitox for the treatment of cutaneous T-cell lymphoma. *J Clin Oncol* 2001;**19**:376–88.
8. Fierro MT, Quaglino P, Savoia P, et al. Systemic polychemotherapy in the treatment of primary cutaneous lymphomas: a clinical follow-up study of 81 patients treated with COP or CHOP. *Leuk Lymphoma* 1998;**31**:583–8.
9. Cvetović RS, Perry CM. Rituximab. A review of its use in non-Hodgkin's lymphoma and chronic lymphocytic leukaemia. *Drugs* 2006;**66**:791–820.
10. Ghielmini M, Schmitz SF, Cogliatti SB, et al. Prolonged treatment with rituximab in patients with follicular lymphoma significantly increases event-free survival and response duration compared with the standard weekly × 4 schedule. *Blood* 2004;**103**:4416–23.
11. Hainsworth JD, Litchy S, Shaffer DW, et al. Maximizing therapeutic benefit of rituximab: maintenance therapy versus re-treatment at progression in patients with indolent non-Hodgkin's lymphoma – a randomized phase II trial of the Minnie Pearl Cancer Research Network. *J Clin Oncol* 2005;**23**:1088–95.
12. Habermann TM, Weller EA, Morrison VA, et al. Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. *J Clin Oncol* 2006;**24**:3121–7.
13. Derogatis LR, Morrow GR, Fetting J, et al. The prevalence of psychiatric disorders among cancer patients. *JAMA* 1983;**249**:751–7.
14. Northouse LL, Mood D, Kershaw T, et al. Quality of life of women with recurrent breast cancer and their family members. *J Clin Oncol* 2002;**20**:4050–64.
15. Ghielmini M. Patient benefits of maintenance immunotherapy. *Leuk Res* 2006;**30**(Suppl. 1):S22–6.
16. Demierre MF, Gan S, Jones J, Miller DR. Significant impact of cutaneous T-cell lymphoma on patients' quality of life: results of a 2005 National Cutaneous Lymphoma Foundation Survey. *Cancer* 2006;**107**:2504–11.
17. Assaf C, Hummel M, Zemlin M, et al. Transition of Sezary syndrome into mycosis fungoides after complete clinical and molecular remission under extracorporeal photophoresis. *J Clin Pathol* 2004;**57**:1325–8.
18. Assaf C, Hummel M, Steinhoff M, et al. Early TCR-beta and TCR-gamma PCR detection of T-cell clonality indicates minimal tumor disease in lymph nodes of cutaneous T-cell lymphoma: diagnostic and prognostic implications. *Blood* 2005;**105**:503–10.
19. Fraser-Andrews EA, Mitchell T, Ferreira S, et al. Molecular staging of lymph nodes from 60 patients with mycosis fungoides and Sezary syndrome: correlation with histopathology and outcome suggests prognostic relevance in mycosis fungoides. *Br J Dermatol* 2006;**155**:756–62.
20. Scarisbrick JJ. Staging and management of cutaneous T-cell lymphoma. *Clin Exp Dermatol* 2006;**31**:181–6.
21. McFarlane V, Friedmann PS, Illidge TM. What's new in the management of cutaneous T-cell lymphoma? *Clin Oncol (R Coll Radiol)* 2005;**17**:174–84.
22. Herrmann JJ, Roenigk Jr HH, Hurria A, et al. Treatment of mycosis fungoides with photochemotherapy (PUVA): long-term follow-up. *J Am Acad Dermatol* 1995;**33**:234–42.
23. Jones GW, Hoppe RT, Glatstein E. Electron beam treatment for cutaneous T-cell lymphoma. *Hematol Oncol Clin North Am* 1995;**9**:1057–76.
24. Kim YH, Martinez G, Varghese A, Hoppe RT. Topical nitrogen mustard in the management of mycosis fungoides: update of the Stanford experience. *Arch Dermatol* 2003;**139**:165–73.
25. Chinn DM, Chow S, Kim YH, Hoppe RT. Total skin electron beam therapy with or without adjuvant topical nitrogen mustard or nitrogen mustard alone as initial treatment of T2 and T3 mycosis fungoides. *Int J Radiat Oncol Biol Phys* 1999;**43**:951–8.
26. Stern RS. PUVA Follow up Study. The risk of melanoma in association with long-term exposure to PUVA. *J Am Acad Dermatol* 2001;**44**:755–61.
27. Quiros PA, Jones GW, Kacinski BM, et al. Total skin electron beam therapy followed by adjuvant psoralen/ultraviolet-A light in the management of patients with T1 and T2 cutaneous T-cell lymphoma (mycosis fungoides). *Int J Radiat Oncol Biol Phys* 1997;**38**:1027–35.
28. Smith BD, Wilson LD. Management of mycosis fungoides. Treatment: part 2. *Oncology* 2003;**17**:1419–28.
29. Hofer A, Cerroni L, Kerl H, Wolf P. Narrowband (311-nm) UV-B therapy for small plaque paraporiasis and early-stage mycosis fungoides. *Arch Dermatol* 1999;**135**:1377–80.
30. Clark C, Dawe RS, Evans AT, Lowe G, Ferguson J. Narrowband TL-01 phototherapy for patch-stage mycosis fungoides. *Arch Dermatol* 2000;**136**:748–52.
31. Gathers RC, Scherschum L, Malik F, Fivenson DP, Lim HW. Narrowband UVB phototherapy for early-stage mycosis fungoides. *J Am Acad Dermatol* 2002;**47**:191–7.
32. Diederen PVMM, van Weelden H, Sanders CJG, Toonstra J, van Vloten WA. Narrowband UVB and psoralen-UVA in the treatment of early-stage mycosis fungoides: a retrospective study. *J Am Acad Dermatol* 2003;**48**:215–9.
33. Boztepe G, Sahin S, Ayhan M, et al. Narrowband ultraviolet B phototherapy to clear and maintain clearance in patients with mycosis fungoides. *J Am Acad Dermatol* 2005;**53**:242–6.
34. Pavlotsky F, Barzilai A, Kasem R, et al. UVB in the management of early stage mycosis fungoides. *J Eur Acad Dermatol Venereol* 2006;**20**:565–72.
35. Rupoli S, Barulli S, Guiducci B, et al. Low dose interferon-alpha2b combined with PUVA is an effective treatment of early stage mycosis fungoides: results of a multicenter study. Cutaneous-T Cell Lymphoma Multicenter Study Group. *Haematologica* 1999;**84**:809–13.
36. Stadler R, Kremer A, Luger T, Sterry W. Prospective, randomized multicentre clinical trial on the use of interferon

a 2a plus PUVA versus PUVA monotherapy in patients with cutaneous T-cell lymphoma, stages I and II. *J Clin Oncol* 2006;**24**(June 20 Suppl.):7541.
37. Roberge D, Muanza T, Blake G, Shustik C, Vuong T, Freeman CR. Does adjuvant alpha-interferon improve outcome when combined with total skin irradiation for mycosis fungoides? *Br J Dermatol* 2007;**156**:57–61.
38. Jones G, McClean J, Rosenthal D, Roberts J, Sauder DN. Combined treatment with oral etretinate and electron beam therapy in patients with cutaneous T-cell lymphoma (mycosis fungoides and Sezary syndrome). *J Am Acad Dermatol* 1992;**26**:960–7.
39. Duvic M, Lemak NA, Redman JR, et al. Combined modality therapy for cutaneous T-cell lymphoma. *J Am Acad Dermatol* 1996;**34**:1022–9.
40. Duvic M, Apisarnthanarax N, Cohen DS, et al. Analysis of long-term outcomes of combined modality therapy for cutaneous T-cell lymphoma. *J Am Acad Dermatol* 2003;**49**:35–49.
41. Talpur R, Ward S, Apisarnthanarax N, et al. Optimizing bexarotene therapy for cutaneous T-cell lymphoma. *J Am Acad Dermatol* 2002;**47**:672–84.
42. Porcu P, Baiocchi R, Buckner M, et al. Bexarotene-induced T-cell immunomodulation and response in CTCL. *Blood* 2004:104 [Abstract 744].
43. Berinstein NL. Principles of maintenance therapy. *Leuk Res* 2006;**30**(Suppl. 1):S3–S10.
44. Dummer R, Hess-Schmid M, Burg G. Cutaneous T-cell lymphomas: prognosis and quality-of-life issues. *Clin Lymphoma* 2000;**1**(Suppl. 1):S21–5.
45. Muche JM, Karenko L, Gellrich S, et al. Cellular coincidence of clonal T cell receptor rearrangements and complex clonal chromosomal aberrations – a hallmark of malignancy in cutaneous T cell lymphoma. *J Invest Dermatol* 2004;**122**: 574–8.
46. Karenko L, Sarna S, Kahkonen M, Ranki A. Chromosomal abnormalities in relation to clinical disease in patients with cutaneous T-cell lymphoma: a 5-year follow-up study. *Br J Dermatol* 2003;**148**:55–64.
47. Karenko L, Hahtola S, Paivinen S, et al. Primary cutaneous T-cell lymphomas show a deletion or translocation affecting NAV3, the human UNC-53 homologue. *Cancer Res* 2005;**65**:8101–10.
48. Hahtola S, Tuomela S, Elo L, et al. Th1 response and cytotoxicity genes are down-regulated in cutaneous T-cell lymphoma. *Clin Cancer Res* 2006;**12**:4812–21. 47.
49. Duvic M, Hymes K, Heald P, et al. Bexarotene is effective and safe for treatment of refractory advanced-stage cutaneous T-cell lymphoma: multinational phase II–III trial results. *J Clin Oncol* 2001;**19**:2456–71.
50. Duvic M, Kuzel TM, Olsen EA, et al. Quality-of-life improvements in cutaneous T-cell lymphoma patients treated with denileukin diftitox (ONTAK). *Clin Lymphoma* 2002;**2**:222–8.
51. Vorinostat (Zolinza) Prescribing Information, 2006. <http://www.fda.gov/cder/foi/label/2006/021991lbl.pdf>.
52. Duvic M, Foss FM, Olsen EA, et al. Intravenous forodesine (BCX-1777), a novel purine nucleoside phosphorylase (PNP) inhibitor, demonstrates clinical activity in patients with refractory cutaneous T-cell lymphoma. *Blood* 2004;**104** [Abstract 2491].
53. Rohatiner AZ, Gregory WM, Peterson B, et al. Meta-analysis to evaluate the role of interferon in follicular lymphoma. *J Clin Oncol* 2005;**23**:2215–23.
54. Bordern EC, Parkinson MD. Interferons. Effectiveness, toxicities and costs. *Ann Intern Med* 1996;**125**:614–5.