Therapeutic principles in primary cutaneous T-cell lymphomas

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A B S T R A C T

Cutaneous T-cell lymphomas (CTCL) are the second most common group of extranodal non-Hodgkin lymphomas. Standard therapeutic approaches are well established and are summarized by the National Comprehensive Cancer Network in the clinical practice guidelines in Oncology (NCCN Guidelines®; available from: www.nccn.org). Although effective, currently available drug therapies only temporarily control disease and the only option for curing CTCL is allogeneic stem cell transplant. In recent years, there has been an incredible effort made to improve the understanding and treatment of CTCL. Several novel therapies show great potential, most promising being antibody drug conjugates targeting surface markers such as CD30 (e.g. brentuximab) or CCR4 (e.g. mogamulizumab) in some CTCL subtypes, and novel chemotherapeutic agents (e.g. pralatrexate) and small molecule compounds (e.g. panobinostat). Although progress has been made in the treatment of CTCL, and new, innovative and promising therapies are being developed, there is still an urgent need to identify and test additional attractive targets in well-designed clinical trials.

Learning goals

At the conclusion of this activity, participants should know that:
- standard therapeutic approaches for cutaneous T-cell lymphoma are summarized by the National Comprehensive Cancer Network in the clinical practice guidelines in oncology (NCCN Guidelines®; www.nccn.org);
- currently available therapies aim to control disease, while stem cell transplant remains the only curative option;
- novel molecules, targeting cell surface markers such as CD30 (e.g. brentuximab) or CCR4 (e.g. mogamulizumab) may have great potential in the disease management of CTCL.

Introduction

While there is no unified international algorithm for the treatment of cutaneous T-cell lymphoma (CTCL), there are several therapeutic options to treat CTCL, with increasing interest in and development of targeted therapies.[1,2]

Standard therapeutic approaches are summarized by the National Comprehensive Cancer Network in the clinical practice guidelines in oncology (NCCN Guidelines®; www.nccn.org) (Table 1).

Skin-directed therapies

Since mycosis fungoides (MF), the most common form of CTCL in all age groups, presents frequently with patch and plaque stage disease, skin-directed therapies are considered first line.

Skin-directed therapies for limited/localized skin involvement

Skin-directed therapies for limited/localized skin involvement in CTCL include topical steroids, topical retinoids (bexarotene,

Table 1. Standard therapeutic alternatives for cutaneous T-cell lymphoma (CTCL). Please see also the clinical practice guidelines in Oncology summarized by the National Comprehensive Cancer Network in (NCCN Guidelines®; available from: www.nccn.org).

Skin-directed therapies
Topical steroids
Topical retinoids: bexarotene and tazarotene
Topical immunomodulators: imiquimod and resiquimod
Topical chemotherapy: mechlorethamine (nitrogen mustard) and carmustine
Phototherapy: NB-UVB and psoralen+UVA)
Local radiotherapy
Total skin electron beam therapy (TSEBT)
Systemic therapies
Retinoids: bexarotene, all-trans retinoic acid, isotretinoin and acitretin
Interferons (IFN-α, IFN-γ)
Histone deacetylase inhibitors (HDAC-linhibitors): vorinostat and romidepsin
Extracorporeal photopheresis (ECP)
(Liposomal) doxorubicin
Gemcitabine
Antifolate: methotrexate and pralatrexate
New targeted therapies
Alemtuzumab
Brentuximab
Mogamulizumab

tazarotene), topical imiquimod, topical chemotherapy [mechlorethamine (nitrogen mustard) carmustine], phototherapy (NB-UVB for patch/thin plaques, and psoralen+UVA for thicker plaques), local radiotherapy (8-36Gy).

Skin-directed therapies for generalized skin involvement

Skin-directed therapies for generalized skin involvement in CTCL include topical steroids, topical chemotherapy [mechlorethamine (nitrogen mustard) carmustine], phototherapy (NB-UVB for patch/thin plaques, and psoralen+UVA for thicker plaques), and total skin electron beam therapy (TSEBT).

In both adults and children, patch disease shows good response to narrow-band UVB (NB-UVB, 311-nm), whereas plaque disease often requires the use of psoralen+UVA (PUVA), though relapse can occur within a few months to two years after treatment in both treatment groups and often occurs earlier in those treated with NB-UVB.[3-5] Given the relapse rate in patients treated with NB-UVB, bath psoralen plus UVA shows promise with a 62% complete response rate while curtailing the risk of systemic side-effects and decreasing the restrictions on post-treatment sun exposure.[6]

More recently, the use of 308-nm excimer laser to treat early stage (IA-IIA) disease was examined in a small group of 6 patients with less than 10% body surface area involvement refractory to topical therapy. Complete response was seen in 50% of patients.[7] This modality may be useful in targeting treatment to anatomically difficult intertriginous regions while reducing phototoxicities.[7] Brachytherapy is another safe and effective therapeutic approach for difficult regions, such as the delicate facial skin. We recently conducted a clinical trial aimed at examining the overall clinical response to low-dose:high-dose rate brachytherapy in MF. In 10 patients and 23 facial MF lesions treated with brachytherapy, a complete response occurred in 6 patients (13 lesions) and a partial response in 4 patients (10 lesions).[8] CTCL is amenable to conventional localized radiation therapy and total skin electron beam therapy (TSEBT). In a study looking at treatment of solitary MF (<5% body surface area), complete response at 4-48 months was recorded in 4 patients treated with localized radiotherapy, highlighting both the good prognosis of low-grade disease and the curative effect of localized radiotherapy.[9] TSEBT can irradiate the entire skin to treat large surface areas and dermo-epidermal regions with limited effect on deeper dermal and subcutaneous structures.[10] Moreover, the depth of penetration can be titrated according to the electron energy used.[10] With a total dose of 30-36 Gy, TSEBT has been effective in treating T2-T4 disease.[11,12] In a retrospective Dutch study looking at TSEBT and its efficacy in 35 patients from 2001 to 2008, complete response was seen in 66.7% of those with T2 disease and 78.9% in those with T3 disease, with disease progression at median of nine months of 22.2% and 35.7%, respectively.[11] Though only 2 patients with erythroderma (T4) were treated in the Dutch study, complete response was seen in both patients with no disease progression during the study period.[11] Interestingly, it has been shown that if TSEBT treated-T3 disease is stratified by body surface area involvement, overall survival and disease-free survival are significantly higher in patients with less than 10% involvement.[12] Side-effects of TSEBT include erythema, ulceration, pruritus, xerosis, and dyspigmentation.[11]

Systemic therapies

Refractory disease and advanced-staged disease often require systemic therapy. Systemic therapies include a number of newly emerging treatments with increasing effectiveness in stabilizing disease.

Systemic therapies: category A

Retinoids (bexarotene, all-trans retinoic acid, isotretinoin, acitretin): these have been shown to play a role in the regulation of cell differentiation, proliferation and apoptosis.[13] Bexarotene is an orally administered selective retinoid X receptor agonist, approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) since 1999 for the treatment of advanced CTCL. In a large multinational phase II/III study including patients with CTCL in advanced stages (IIB-IVB), clinical complete and partial responses were reported in approximately 50% of the patients enrolled. The rate of relapse after response was 36% and the projected median duration of response was 299 days.[14] Bexaroten is well tolerated; however, hypertriglyceridemia (associated rarely with pancreatitis) and hypothyroidism are common adverse events. A dosing schedule and monitoring protocol have recently been published in the UK consensus statement on safe clinical prescription of bexarotene.[15]

Interferons (IFN-α, IFN-γ): interferons are signaling proteins with broad biological action. For the treatment of CTCL, IFN-α is generally administered subcutaneously from 3x3 Mio IU per week with gradual escalation to a maximum reported tolerated dose of IFN-α2a of 18 Mio IU every day. For most patients, 3x9 Mio IU per week is the highest tolerated dosage long term; after obtaining evidence that high-dose IFN treatment is no more beneficial than low-dose IFN treatment in CTCL, doses higher than 3x9Mio IU per week are seldom applied.[16]

Histone deacetylase inhibitors (HDAC-Iinhibitors): vorinostat and romidepsin, two histone deacetylase inhibitors (HDIs) that are FDA-approved for the treatment of CTCL have shown efficacy in treating relapsing CTCL and in providing extended response times. Studies to understand the response mechanisms have shown that HDIs induce cell cycle arrest and promote apoptosis, though resistance by suppression of pro-apoptotic proteins has been shown *in vitro*.[17] Overall response rate for both agents is approximately 33%-34% with a durable response of 12-15 months at best.[18,19] The most common side-effects are weight loss, weakness, hematologic abnormalities, namely anemia and thrombocytopenia, nausea/vomiting, and increased risk of infections.[19,20]

Extracorporeal photopheresis (ECP): this exposes UVA to blood in the presence of 8-methoxypsoralen, a potent photosensitizer. Overall response rate was 63% in erythrodermic patients, showing minimal toxicities.[21] Data on the efficacy of ECP in SS patients show a similar overall response rate with improvement in both skin and blood disease, though it is unclear whether survival is necessarily prolonged.[22,23] To date, there have been no randomized studies comparing ECP with standard systemic therapies.

Systemic therapies (adapted from Category B and C of the NCCN guidelines®)

(Liposomal) doxorubicin: this is the most prevalently used anthracycline in the treatment of refractory and advanced-stage CTCL.[24] In one prospective French trial, the pegylated liposomal formulation, known to have reduced cardiotoxicity, was administered to 25 patients with stage II-IV disease previously treated with at least two lines of treatment. Overall response rate was reported to be 56%, with SS patients having a 60% response rate.[24] Common adverse effects include weakness, nausea, vomiting, anemia and neutropenia, and palmoplantar erythrodysesthesia.[24]

Gemcitabine: this is a nucleoside analog with antitumor cytotoxic activity, widely used in advanced stage CTCL, although the data on its efficacy are limited. A recent retrospective observational analysis of clinical data from 25 CTCL patients showed an overall response to gemcitabine of 48% with 20% complete response. At 15 years of retrospective observation, the estimated disease-free survival was 40% (median reached at 2.9 years). The patients in this study had had at least one therapy (range 1-8) prior to gemcitabine. At least three cycles of gemcitabine were administered as a monotherapy.[25]

Antifolates

Low-dose methotrexate (β100 mg/m^2/week) is widely used for the treatment of both MF and SS alone or in combination with other agents.[26] Pralatrexate belongs to the same pharmacological group of antifolate antineoplastic agents, and has recently received FDA and EMA approval for the treatment of peripheral T-cell lymphoma. Pralatrexate inhibits the dihydrofolate reductase with greater anti-tumor effect than methotrexate due to increased internalization by tumor cells.[20] The overall response rate in one study assessing dose de-escalation while treating both advanced MF and SS was 41%, with higher doses reported to lead to an overall survival of 51%.[20] In patients who had progression of disease on methotrexate, a response rate of 46% was seen, suggesting that another mechanism of action may allow pralatrexate to exert its effect.[20] Common adverse events included mucositis, fatigue, nausea, fevers, anorexia, edema, and anemia, which were balanced with efficacy at a dose of 15 mg/m^2.[20]

Hepatoxicity may occur and is usually mild (grade 1 or 2), while severe (grade 3 or 4) hepatoxicity is rarely encountered.

New targeted therapies

Recent success in targeted cancer therapies has reinvigorated the hypothesis that monoclonal antibodies against cell surface molecules have the potential to eliminate malignant cells in CTCL and induce durable remission of the disease. In general, malignant T cells in leukemic CTCL are characterized by loss of cell surface markers, most commonly CD26 and CD7, and also loss or, more often, dim expression of T-lymphocyte lineage markers, such as CD4 and CD3. Overexpression of several markers, such as CLA, CCR4 or CD30 is of potential therapeutic interest in CTCL, but unfortunately, convincing data for a unique and specific cell surface marker consistently up-regulated on malignant but not benign T cells has yet to be described.[28] The lack of such a targetable marker in CTCL, but also in primary systemic T-cell leukemia and lymphomas, led to the development of some therapeutic strategies based on targeting all T cells (both malignant and benign) or with an even less specific approach, targeting multiple blood cell lineages, e.g. in the case of systemic anti-CD52 treatment.[29]

Direct targeting of the T-helper cell linage marker CD4 with zanolimumab (anti-CD4 monoclonal antibody) or targeting the cell surface IL-2 receptor (CD25) that is found on some immune and cancer cells, had been approved for the clinical management of CTCL, but are not widely used (zanolimumab) or are no longer commercially available.[30,31]

Alemtuzumab: this is a humanized monoclonal antibody targeting a pan-lymphocyte antigen CD52 that is expressed on malignant and benign T cells, B cells, monocytes and dendritic cells. Alemtuzumab is currently approved for the treatment of B-cell chronic lymphocytic leukemia, and several studies have analyzed its efficacy in CTCL. In a recent open-label trial of alemtuzumab in 19 pre-treated patients with advanced erythrodermic CTCL (i.e. erythrodermic MF and SS) and median follow up of 24 months, the overall response rate was 84%, with 9 (47%) complete and 7 (37%) partial remissions.[32] Further data show that alemtuzumab seems to be beneficial especially in patients with SS, and less effective in MF, which may be explained by the different origin of the malignant cells: mycosis fungoides is a malignancy of the skin's resident T cells, whereas Sézary syndrome arises from recirculating central memory T cells.[33] This hypothesisis is supported by a study that shows partial response to alemtuzumab in all tested Sézary patients (n=18), and even complete remission for up to two years in 50% of them.[34] Interestingly, alemtuzumab was ineffective in MF, malignant MF T cells remaining sessile in the skin and not recirculating through the blood, where alemtuzumab was effective. The exact mode of action of alemtuzumab and its lack of activity against CD52-expressing tissue-resident T cells still needs to be clarified. The most commonly reported alemtuzumab regimen for CTCL is intravenous application of 30 mg three times per week.[29] The observed rate of adverse events was relatively low and consistent throughout the different studies, but some severe infective episodes have been reported, even in patients receiving anti-infective prophylaxis.[35] However, although effective in many cases, alemtuzumab is not a cure for SS. Some patients are refractory to treatment, and most importantly, some patients experience acute disease progression after initiation of alemtuzumab therapy.[36] Furthermore, TCR clonality analysis revealed minimal residual disease in 11 (68.75%) out of 16 CTCL patients with initial complete or partial response to alemtuzumab treatment.[32] The response duration differed broadly throughout the literature, with the longest reported remission being 32 months.[37] Before starting alemtuzumab treatment, and especially before re-treatment after relapse and initial good response, a flow cytometrical evaluation of CD52 expression is advisable. In some cases, CD52 is down-regulated after alemtuzumab therapy, and in rare cases, malignant cells may intrinsically fail to express CD52.[38]

Brentuximab: the CD30 antigen is a surface marker that belongs to the TNF receptor superfamily.[39] Its expression

was first documented on Reed-Sternberg cells in patients with Hodgkin lymphoma,[40] and later in systemic anaplastic large cell lymphoma (ALCL).[41] Its expression is not limited to neoplastic cells and can also be found under normal conditions, especially on some activated T cells in the thymus.[42,43] Targeting CD30 already proved to be highly promising in both Hodgkin lymphoma and systemic ALCL,[44] and brentuximab-vedotin (Adcetris), an antibody-drug conjugate of anti-CD30 monoclonal antibody and the proapoptotic anti-tubulin agent monomethyl auristatin, was approved as a second-line treatment in these two systemic malignancies.

In the CTCL spectrum, CD30 is a hallmark of the group of primary cutaneous CD30+ lympho-proliferative disorders, including primary cutaneous ALCL and lymphomatoid papulosis.[45] Most cases of MF are usually CD30 negative; however, various levels of CD30-positive large cells may occur during disease progression (i.e. large cell transformation) and are considered to be a bad prognostic marker.

Data on the effect of brentuximab (an antibody-drug conjugate of anti-CD30 monoclonal antibody and the proapoptotic anti-tubulin agent monomethylauristatin) in CD30 positive MF, primary cutaneous ALCL, and other rare CD30 positive cutaneous entities are currently being collected.[46-48] A phase III trial in CTCL is currently recruiting patients. Interim results of a phase II open label trial reported an overall response rate of 44% and mean duration of response of 12 weeks to brentuximab in 27 CD30+ MF patients (unpublished data, International Investigative Dermatology Meeting, 2013). Most recently, progressive multifocal leukoencephalopathy (PML) with lethal outcome has been reported in patients receiving brentuximab for: Hodgkin lymphoma (n=3), primary cutaneous ALCL (n=1), and transformed CD30+ MF (n=1). The 3 Hodgkin lymphoma patients and the MF patient developed progressive neurological deterioration and died soon after the development of the PML.[49]

Mogamulizumab: chemokine receptors are membrane proteins that specifically bind and respond to secreted small signaling molecules (chemokines). Expression of the chemokine receptor 4 (CCR4) is characteristic of, but not limited to, neoplastic cells in CTCL,[50] and is a further novel target for immunotherapy. Mogamulizumab is a monoclonal antibody against CCR4 that has been developed for the treatment of diverse hematologic malignancies and asthma.[51] Currently, clinical trials for patients with CTCL are ongoing. A phase I/II study on mogamulizumab in 38 pre-treated patients with CTCL showed overall response rates of 36.8%: 47.1% in SS and 28.6% in MF. Eighteen of 19 (94.7%) patients with B1 or more blood involvement had a response in blood, including 11 complete responses.[52] Nausea, chills, headache, and infusion-related reaction were the most frequently reported adverse events in this trial.[52]

Combination therapies

Many pre-clinical studies, as well as clinical trials, are currently investigating the role of different HDAC inhibitors as monotherapy or in combination in other hematologic malignancies and solid tumors. Of particular interest is the combination with demethylating agents such as decitabine and azacitidine (FDA-approved for the treatment of myelodysplastic syndrome) considering that they enhance each other's mechanism of action to relieve the transcriptional repression of particular tumor suppressor genes.[53] Few case reports of refractory CTCL patients demonstrated a better overall response, while the toxicity profile remained acceptable by combining HDAC inhibitors with interferon-γ as the latter induces cellular immunity.[54,55]

Further investigation is needed to characterize these combinations and their mechanisms of action. Meanwhile, one rationale to use combination therapies is the possibility of reducing the dose of each single agent to help tolerability. These combinations must be used with caution because not all available CTCL therapies can be used in combination as some agents can counteract major pathways involved and, as a consequence, can potentially do more harm than good.

Stem cell transplantation

In humans, the first report of hematopoietic stem cell transplantation (HSCT) as a treatment for hemato-oncological disorders appeared in 1957.[56] Since then, several milestones have been passed, such as the HLA skin-grafting experiment results or the use of calcineurin inhibitors to prevent graft-*versus*-host disease (GvHD). These have led to increased use of autologous and allogeneic stem cell transplantation and have improved outcome. Today, more than 30,000 autologous and 20,000 allogeneic SCT are performed every year in patients with leukemia or genetic hematologic diseases.[57]

As pointed out above, and despite a high number of immunomodulatory and chemotherapeutic approaches used in various protocols, no such regimen has been shown to increase overall survival in patients with CTCL.[58,59] In this context, HSCT was performed in a patient with MF for the first time in 1994,[60] based on the rationale that the allogeneic SCT-graft is: a) a tumor-cell free tissue; and b) has an adoptive immunotherapeutic potential. Since then, several case studies and retrospective analyses for autologous/allogeneic SCT have been published.[60-63] Even though high-dose radio-chemotherapy and autologous SCT induced complete response (CR) in the majority of patients, the responses were very short-lived, and thus autologous SCT cannot be recommended on the basis of these data.[64] On the other hand, CTCL patients showed decreased relapse rates after allogeneic SCT (38% after 1 year, 47% after 3 years post transplantation) and increased overall survival (66% after 1 year, 53% after 3 years post transplantation) when compared to published data of conventional (chemo)therapies.[65] The improved outcome may be due to the graft-*versus*-lymphoma (GvL) effect; however, the increased morbidity and mortality of active GvHD has to be kept in check with immunosuppressive drugs. In the future, the use of brentuximab in post-allotransplant recurrence of CD30+ transformed mycosis fungoides has to be tested, as the drug appears to have considerably high response rates in post-allotransplant Hodgkin lymphoma (overall and complete response rates 50%, and 38%, respectively, among 24 patients).[66] It remains to be seen to what extent brentuximab may decrease or increase the GvL effect of the allo-

transplant.

Taken together, although there have been no controlled prospective studies, allogeneic SCT may play a role in the management of advanced stage CTCL. Disease status, type of conditioning, and donor type are the main drivers of the outcome of allogeneic SCT. Importantly, clear criteria need to be defined to determine the optimal time point of allogeneic SCT in the course of the CTCL disease.

Therapeutic principles for rare CTCL

Primary cutaneous CD30+ T-cell lymphoproliferative disorders [e.g. anaplastic large cell lymphoma (ALCL), and lymphomatoid papulosis (LyP)] make up 20% of CTCL. Three percent of CTCL are comprised of other rare CTCL: subcutaneous panniculitis-like T-cell lymphoma (α/β subtype, [SPTCL]), primary cutaneous γ/δT-cell lymphoma (PCGD-TCL) extranodal NK/T-cell lymphoma, hydroa vacciniforme-like T-cell lymphoma, and the primary cutaneous peripheral T-cell lymphoma, not otherwise specified (PTCL-nos).

CD30$^+$ T-cell lymphoproliferative disorders

The expression of CD30 is a hallmark of the group of primary cutaneous CD30$^+$ lymphoproliferative disorders and therefore interesting as a therapeutic target.[4] Lymphomatoid papulosis (LyP), a common representative of the group, is a rare recurrent lymphoproliferative disorder of the skin. Standard therapy for LyP consists of corticosteroids, methotrexate and systemic photochemotherapy (PUVA).[68,69] LyP usually affects older adults (median age at onset: 45 years). However, in rare cases LyP may also occur in children.[70]

Successful treatment of LyP in children with PUVA-bath photochemotherapy has been described[71,72] However, in the majority of cases, LyP in children and young adults is difficult to treat, as most standard therapies are not applicable. High doses of systemic corticosteroids and methotrexate are contraindicated in children and systemic (oral) PUVA therapy is critical due to aggravated cutaneous photocarcinogenesis in these young patients. Compared with conventional oral PUVA therapy (the gold standard for LyP in most dermatological practices) PUVA-bath photochemotherapy offers numerous advantages, e.g. there are no systemic side-effects such as nausea, vomiting and cataractogenesis due to negligible serum levels of methoxsalen. Furthermore, PUVA-bath photochemotherapy does not induce photosensitivity in the face and hands, which is of special value in children who cannot be kept indoors all day.[73] Thirdly, studies by Hannuksela-Svahn *et al*. have shown that PUVA-bath photochemotherapy does not seem to increase the risk of skin cancer incidence compared to conventional PUVA therapy, which is significantly associated with cutaneous carcinogenesis.[74-76] However, as long-term risks of PUVA-bath photochemotherapy are still not completely known, and approximately 10% of patients with LyP develop malignant lymphomas, regular follow-up visits are needed for our young patients.[76]

Brentuximab-vedotin targets CD30 expression cells and its therapeutic efficacy has been recently investigated in a phase II trial for CD30$^+$ lymphoproliferative disorders.[46] Five out of 6 patients with LyP had a complete remission after treatment with brentuximab. One patient with ALCL included in the trial also responded well with a complete remission. The time from first treatment to response was approximately three weeks and duration of response was 20 weeks. These results are promising, but future trials with larger numbers of patients are needed.

Subcutaneous panniculitis-like T-cell lymphoma and others

The α/β subtype of the subcutaneous panniculitis-like T-cell lymphoma responds well to systemic corticosteroids with an excellent prognosis.[77,78] In contrast, primary cutaneous φ/δT-cell lymphoma (PCGD-TCL) subtype is associated with a high mortality and therapeutic options are limited. A doxorubicin-based multi-agent chemotherapy is usually applied in most centers. In addition, there have been case reports of successful treatment of PCGD-TCL lymphoma with romidepsin, bexarotene and allogeneic stem cell transplantation.[79,80]

Treatments for the other rare CTCL are mainly described as case reports in the literature, and further studies to better characterize and generalize these findings are urgently needed to identify new target molecules and beneficial therapeutic approaches.[81,82]

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