New therapeutic approaches in cutaneous T-cell lymphomas

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SUMMARY

Cutaneous T-cell lymphoma is a heterogeneous group of T-cell neoplasms presenting in the skin, mycosis fungoides being the most common subtype and Sézary syndrome the leukemic form. Treatment is dependant on stage and responses to previous therapy. Treatments are divided into 'skin-directed therapies', which are first-line for early stage diseases, and 'systemic therapies' reserved for advanced stages or refractory cutaneous T-cell lymphoma. There are currently no curative therapies for cutaneous T-cell lymphoma and consecutive treatments have to be given in function of the progression of the disease. There is an urgent need for new therapies to treat symptoms, particularly pruritus and pain, and to prolong survival. This paper summarises new drugs available for cutaneous T-cell lymphoma and their mode of action. Most new drugs for cutaneous T-cell lymphoma have response rates between 30% and 50% with response durations being less than a year. New studies looking at combination or maintenance therapies may improve quality of life and disease outcome.

(BELG J HEMATOL 2017;8(3):102-6)

INTRODUCTION

There are no curative treatments for cutaneous T-cell lymphomas (CTCL) with the exception of allogeneic bone marrow transplantation (BMT) in selected patients.[1] Patients are currently treated with consecutive therapies until loss of response. As survival in CTCL may be long, patients may suffer many years with pruritus and have to cope with skin lesions resulting in poor quality of life (QOL).[2]

Primary cutaneous lymphomas are classified according to the World Health Organization (WHO) - European Organisation for Research and Treatment of Cancer (EORTC) and subdivided into indolent or aggressive-subtypes.[3] Mycosis fungoides (MF) is the most common form and typically presents with indolent early stage disease. Early stage MF is usually manifested with cutaneous patches and plaques (stage disease IA-IIA) and may progress to develop skin tumours, erythroderma, nodal or visceral involvement (advanced stage disease IIB-IVB).[4] Around 25% of patients will present with these advanced stages. In early stages, survival may be as long as 25 years, whereas those with advanced disease have a poor prognosis and median survival of one to four years.[5] Sézary syndrome (SS) is the leukemic form of CTCL with extreme pruritus, erythroderma, lymphadenopathy and circulating Sézary cells (>5%). Treatment of MF/SS is stage dependant.

Another category of CTCL is the CD30 positive CTCL which include primary cutaneous large cell anaplastic lymphoma (cut-ALCL) and lymphomatoid papulosis (LyP). Cut-ALCL typically presents with rapidly enlarging skin nodules and plaques with central necrosis, typically in adolescence or young adulthood. The histology shows nodular or diffuse infiltrates characterised by cohesive sheets of large CD30+ cells (Lorenzo, Cerroni, Skin lymphoma, 4th edition, Blackwell). Although cutaneous relapses are frequent, prognosis is good and systemic spread only rarely occurs, the 5-year survival rate being more than 90%.[3] Lymphomatoid papulosis is the self-resolving form of primary CTCL which typically occurs in early adulthood and presents with recurrent

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Conflict of interest: The authors have nothing to disclose and indicate no potential conflict of interest.

Keywords: anaplastic large cell lymphoma, cutaneous T-cell lymphoma, mycosis fungoides, Sézary syndrome, targeted therapy.

nodules and papules, typically less than 1 cm in diameter, at distant sites which become necrotic and resolve with a residual atrophic scar.

MYCOSIS FUNGOIDES AND SÉZARY SYNDROME

CURRENT MANAGEMENT

There are no clear guidelines for treatment of MF/SS but published recommendations are now available.[6-8] Treatment depends on stage of disease, age, comorbidities and responsiveness to previous therapy.

Early stage disease should be treated with 'skin directed therapy', which includes topical steroids, psoralens and ultraviolet A (PUVA), narrowband ultraviolet B (UVB), topical retinoids (bexarotene) and topical cytostatic agents, such as mechlorethamine or carmustine (BCNU). Unfortunately, topical mechlorethamine (Valchlor) and topical bexarotene are not licensed in Europe. Other interesting therapeutic options based on individual case reports include photodynamic therapy (Acta Derm Venereol 2012;92:264-68, Actas Dermosifiliogr 2010; 101785:91) and imiquimod 5% cream (J Am Acad Dermatol 2005;52:275-80).

Systemic therapy includes interferon alpha, retinoids (bexarotene), histone deacetylase inhibitors (HDAC-I), extracorporeal photopheresis (ECP), monoclonal antibody therapy (alemtuzumab), single agent chemotherapy (doxorubicin, methotrexate, gemcitabine) and multi agent chemotherapy as a last resort. For patients with advanced disease who achieve a remission, allogeneic stem cell transplantation may offer prolonged survival.[9] Sixty European patients with advanced MF/SS undergoing allogeneic BMT had an overall 5-year survival of 46% and progression free survival of 32%.[10] At present, the optimal conditioning regime remains to be established. Skin directed therapy may be used in combination with systemic agents for progressive disease, particularly combination of PUVA with systemic retinoids or interferon alpha.

NEW DRUGS

No new therapies have been approved by the European Medical Association (EMA) for CTCL since oral bexarotene in 1999 (Targretin capsules®). A number of drugs have received U.S. Food and Drug Administration (FDA) approval including bexarotene 1% gel (Targretin gel®) and mechlorethamine gel 0.02% (Valchlor®) for early stage disease. Denileukin diftitox, a CD25 directed cytotoxin (Ontak®), and two histone deacetylase inhibitors (HDAC-I) vorinostat (SAHA, Zolinza®) and romidepsin (depsipeptide, Istodax®) were recently approved by the FDA for advanced refractory CTCL. However, a recent international publication including >1,200 patients with advanced MF/SS failed to find survival benefit despite new therapies.[5] This suggests these newer treatments may improve QOL, but not survival.

ANTI-FOLATE ANTAGONIST

Pralatrexate is a synthetic folate analogue and is emerging as a new oral therapeutic agent for CTCL. Phase II trials demonstrated 25% response by independent central review and 58% by investigator assessment, with discrepancy due to the pictorial analysis of skin lesions. The median progression-free survival was only two months. Thirty-one patients with CTCL (relapsed/refractory MF, SS and primary cutaneous anaplastic large-cell lymphoma) established the optimal schedule as 15 mg/m^2 weekly for three out of four weeks with a response rate of 45%. Adverse effects typically include a mucositis.[11-13] This drug is currently not available in Belgium.

HISTONE DEACETYLASE INHIBITORS (HDAC-INH)

Activity of genes such as tumour suppressor genes may be restored by increasing histone acetylation, allowing growth inhibition and apoptosis. Two HDAC-Inh, vorinostat (oral suberoylanilide hydroxamic acid) and romidepsin (intravenous depsipeptide), have been approved by the FDA for the treatment of CTCL. The response rates reach 30-40% and they improve the intractable itching.

Vorinostat, is an oral pan HDAC-Inh which is not licensed in Europe. Side effects are fatigue, anorexia, diarrhoea and myelosuppression. The recommended dose is 400 mg orally once daily. The multicentre phase IIB trial showed an overall response rate of 30%, with only complete response. The median time for response was 56 days and late responders (6$^+$ months) were also reported.[14] Vorinostat is currently being explored in combination with other agents such as bortezomib, lenalidomide and chemotherapy.

Romidepsin is an intravenous HDAC-Inh, approved by the FDA for the treatment of CTCL patients who failed one prior systemic therapy. It is not yet licenced in Europe. It is administered as a 4-hour IV infusion at the dose of 14 mg/m^2 on days 1, 8, and 15 of a 28-day schedule. Results were similar with response rates of 34-39%. The study also showed an improvement in pruritus which didn't always correspond with a clinical response. The response duration was 11-15 months.[15,16]

Overall romidepsin was well tolerated. Nausea, anorexia, and vomiting were commonly reported. Thrombocytopenia and neutropenia were the most common grade 3 or 4 toxicities. Early concern of QT prolongation was found not to be significant. This drug is currently tested in peripheral T-cell lymphoma in Belgium.

MONOCLONAL ANTIBODIES

SGN-35 (brentuximab vedotin) is an antibody-drug conjugate composed of an anti-CD30 monoclonal antibody conjugated to the synthetic microtubule-disrupting agent (monomethyl auristatin E). After binding CD30 surface antigen, the conjugate is rapidly internalised inside the cell where it binds to tubulin and initiates cell cycle arrest. Impressive results in refractory Hodgkin lymphoma and ALCL with response rates >75% led to accelerated approval of brentuximab for the treatment of both relapsed and refractory Hodgkin lymphoma and ALCL. Fifty percent of CTCL express the CD30 antigen. The recent phase II trial showed an overall response rate of 73% and complete response rate of 35%. One hundred percent of OR was observed in $CD30^+$ LP and CALCL. In patients with MF/Sézary syndrome, OR was 54%. Time to response was twelve weeks (3-39), and duration of response was 32 (3-93) weeks. The dose is 1.8 mg/kg every three weeks. Dose reductions to 1.2 mg/kg may be applied for peripheral neuropathy which occurs in 65% of patients. Other side effects include neutropenia and nausea.[17] A medical need program is now open in Belgium.

Mogamulizumab (KW-0761) is a humanised anti-CCR4 monoclonal antibody, but unlike brentuximab, it is not internalised and does not exhibit complement-dependent cytotoxic activity or directly induces apoptosis. A recently published phase I/II study evaluated the efficacy of mogamulizumab in 41 MF/SS patients. The maximum tolerated dose was not reached in phase I. In phase II, patients were treated with 1.0 mg/kg mogamulizumab every two weeks until disease progression. The most common adverse effects were nausea, headache, and infusion-related reaction (grade I-II). The overall response rate was 37% and higher in SS (47%) than MF patients.[18] International phase III clinical trials are eagerly awaited.

Zanolimumab (HuMax-CD4) is a humanised anti-CD4 monoclonal antibody specific for the CD4 receptor expressed on the majority of T-lymphocytes. Kim *et al.* reported on two phase II studies in 47 MF/SS patients with relapsed/refractory CTCL and found objective responses in 32% with a duration of response of 12-24 weeks.[19] A dose dependant response was noted with higher responders in the maximum dose group (56%) with median response duration of 81 weeks. Most common adverse reactions were skin reactions and infections. Further studies are awaited. This antibody is not available in Belgium.

Pembrolizumab is a monoclonal antibody which binds PD-1 receptor inhibiting its interaction with the PD ligands PD-L1 and PD-L2. The Programmed Death – 1 (PD-1) Pathway is an immune checkpoint which attenuates T-cell responses and may be harnessed by tumours to escape immune surveillance. A phase II trial in stage IB-IVB is ongoing. There is some activity in CTCL but as with other novel agents this remains around 30%.

Nivolumab is a PD-1 blocking agent. A recent study of 81 patients included thirteen patients with MF, two of which had a response. Most common toxicities include fatigue and skin rashes.20 These anti PD1-PDL1 are not available in this indication in Belgium.

PROTEASOME INHIBITOR

The proteasome inhibitor has also been shown to down regulate the transcription factor NF-kappa beta. A phase II trial of bortezomib (1.3 mg/m^2 on days 1, 4, 8, and 11 of a 21-day cycle) in fifteen patients with relapsed/refractory T-cell lymphoma reported a RR of 70% in MF patients including one CR. The most common adverse effects were neutropenia, thrombocytopenia, and neuropathy.[21]

ALKYLATING AGENTS

Temozolomide is an oral alkylating agent (75 mg/m^2 PO x 42 days followed by maintenance 150 mg/m^2 d1-5/28) with the ability to alkylate/methylate DNA. This has been reported in a phase II study of 26 patients with advanced MF/SS. The overall response rate was 27% with two complete responses.[22] Temozolomide is mostly used as a therapeutic agent in patients with glioblastoma and has shown to be active for MF with CNS involvement in a recent small cohort (four patients).[23] Side effects are haematological and liver toxicities.

IMMUNOMODULATORY AGENTS

Lenalidomide (Revlimid) is one of the novel oral immunomodulatory agents with anti-neoplastic properties licenced for the treatment of myeloma and 5q-myelodysplastic syndrome. It increases the Th1 response and enhances NK cell mediated killing. It is a synthetic compound derived by thalidomide and contraindicated in preg-

KEY MESSAGES FOR CLINICAL PRACTICE

1 **There are currently no curative therapies for cutaneous T-cell lymphoma, with the exception of allogeneic bone marrow transplantation, which is suitable in a selected number of patients.**

2 **Most monotherapies have response rates around 30-40%, with the exception of extracorporeal photopheresis and brentuximab, which have response rates >60% in selected cases.**

3 **Future studies should consider combinations of novel drugs which may act synergistically to improve objective and subjective responses in cutaneous T-cell lymphoma.**

nancy. Querfeld *et al*. conducted a phase II trial of lenalidomide in 32 patients with relapsed/refractory MF and SS patients. The overall response rate was 28% and the median response duration was ten months. The drug is given orally at 15-25 mg/q x 21 q 28 days. Grade 3 toxicities included fatigue, infections, and leucopaenia.[24]

CONCLUSION

A number of drugs have been FDA approved but are not available in Europe. Brentuximab Vedotin (Adcetris®) has shown to be active in CTCL with excellent response rates >50%, better than other drugs showing +/- 30% of OR. EMA approval is now eagerly awaited. There is a need for drugs to be used for maintenance therapy in patients with partial response in order to improve quantity of life.

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**This paper represents a large international study of more than 1200 advanced stage MF/SS and reports on survival in stages IIB-IVB. The study identifies 4 independent prognostic factors (stage IV, raised LDH, large cell transformation in skin and age at diagnosis >60 years) associated with a worse prognosis in MF/SS which when combined in a prognostic index model identify 3 risks groups with significantly different 5-year survival (low risk = 68%, intermediate risk = 44% and high risk 28%).*

***The results of this phase II study have shown excellent response rates. All patients with LCAL and LyP responded and 50% with MF/SS. A grade 1-2 peripheral neuropathy occurred in 65% and titrating the dose with response will be important to minimise this adverse affect.*

****This phase 1/2 study of mogamulizumab in MF/SS showed the drug is well tolerated with few severe adverse affects. The overall response rate was 37% with responses in 47% with Sézary syndrome and showed the drug to be highly affective in clearing peripheral blood with a response in 18/19 patients with blood involvement (95%).*