Libertas Academica
FREEDOM TO RESEARCH

Open Access: Full open access to this and thousands of other papers at http://www.la-press.com.

Lymphoma and Chronic Lymphocytic Leukemias

New Therapies in T-cell Lymphoma

G.P. Collins, D. Bruce and T.A. Eyre

Department of Clinical Haematology, Oxford Cancer and Haematology Centre, Oxford University Hospitals NHS Trust, UK.

ABSTRACT: T-cell lymphomas represent 10–12% of all patients with non-Hodgkin lymphoma (NHL) in the Western world. When cutaneous T-cell lymphoma (CTCL) is excluded, peripheral T-cell lymphoma—not otherwise specified (PTCL-NOS), anaplastic large-cell lymphoma (ALCL), and angioimmunoblastic T-cell lymphoma (AITL) represent the overwhelming majority of patients in this population. These diseases remain a great challenge to treat. They are characterized by an aggressive presentation, extranodal disease, paraneoplastic phenomena, and resistance to standard chemotherapeutics. With the rapid development of new molecular gene profiling techniques, it is highly likely that these diseases will be subclassified by molecular abnormalities in the future. An evolving understanding of the tumor molecular pathogenesis will undoubtedly lead to further novel targeted therapies. Immunoconjugates, such as brentuximab vedotin (BV), have provided outstanding responses in relapsed, refractory CD30-positive ALCL. Histone deacetylase (HDAC) inhibitors have shown activity in PTCL and are potentially synergistic with proteasome inhibitors. Denileukin diftitox is an interesting recombinant DNA fusion protein linking fragments of the diphtheria toxin to interleukin-2 (IL-2) that is tested in clinical trials. Crizotinib, a highly specific anaplastic lymphoma kinase (ALK) inhibitor, has shown great promise in small number of patients with ALK-positive ALCL; the future of patients with this disorder looks very promising. Biomarker-driven chemotherapeutics is becoming a critical part of the state-of-the-art treatment in early- and late-phase clinical trials. It is crucial that future trials include sensible biomarker-based designs when future treatments are used in these challenging disorders.

KEYWORDS: T cell lymphoma, angioimmunoplastic lymphoma, anaplastic large cell lymphoma, brentuximab, crizotinib

CITATION: Collins et al. New Therapies in T-cell Lymphoma. *Lymphoma and Chronic Lymphocytic Leukemias* 2014:4 1–8 doi:10.4137/LCLL.S13716.

RECEIVED: February 25, 2014. **RESUBMITTED:** June 2, 2014. **ACCEPTED FOR PUBLICATION:** June 3, 2014.

ACADEMIC EDITOR: Mitchell Smith, Editor in Chief

TYPE: Review

FUNDING: Authors disclose no funding sources.

COMPETING INTERESTS: GPC has received honoraria for advisory work and as a speaker, from Takeda Pharmaceuticals, and research grants from Celgene and Onyx. Other authors disclose no potential conflicts of interest.

CORRESPONDENCE: graham.collins@ouh.nhs.uk

This paper was subject to independent, expert peer review by a minimum of two blind peer reviewers. All editorial decisions were made by the independent academic editor. All authors have provided signed confirmation of their compliance with ethical and legal obligations including (but not limited to) use of any copyrighted material, compliance with ICMJE authorship and competing interests disclosure guidelines and, where applicable, compliance with legal and ethical guidelines on human and animal research participants. Provenance: the authors were invited to submit this paper.

Introduction

Peripheral T-cell lymphomas (PTCLs) are a rare group of clonal, mature post-thymic T-cell lymphoproliferative disorders that arise predominantly in lymphoid tissue. They represent a particular treatment challenge as they are frequently poorly responsive to treatment and prone to relapse with a five year overall survival (OS) of only 30%. Novel therapies for PTCL are being investigated in an effort to improve their frequently dismal prognosis. PTCL represents 10–12% of all non-Hodgkin lymphomas (NHLs) in Europe, America, and Australasia. Generally, T-cell lymphomas are more common in the Far East where they account for up to 20% of NHLs.[1] In Europe, the three most common subtypes of PTCL are peripheral T-cell lymphoma—not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL), and anaplastic large-cell lymphoma (ALCL). Together, these make up approximately 80% of all T-cell lymphoma diagnoses.[2]

T-cell lymphoma subtypes have distinct clinical and pathological characteristics. These divisions have been helped by advances in molecular diagnostics, and refinement of the WHO classification has further improved diagnostic accuracy. Diagnosis remains a challenging field, and the International T-cell Lymphoma Project (ITLP) review of more than 1300 cases published in 2008 using centralized expert review found misclassification occurring in more than 10% of the cases.[2]

PTCLs frequently present with extranodal disease, advanced stage compared to B-cell lymphoid malignancies, paraneoplastic phenomena, and are more resistant to standard chemotherapy.[2] A large retrospective series has highlighted the poor prognoses of patients with PTCL. Typically, PTCL and AITL have a five-year failure free survival of 20% and OS of 30%.[2] This International T-cell Lymphoma (ITCL) project also displayed the relatively limited efficacy of anthracycline-based treatment. Given the historical disappointing results, novel treatments are desperately needed. Improved understanding of the different subtypes of T-cell lymphoma is helping to lay the foundations for novel therapies and improve survival.

Prognostic Scoring Systems

A variety of prognostic scoring systems have been developed for T-cell lymphomas. The International Prognostic Index (IPI) has been used for B-cell and T-cell lymphoid malignancies, but it is deemed less useful in non-anaplastic T-cell malignancies as cases tend to cluster in intermediate or high-risk groups.[3] Moreover, it is unhelpful in extranodal NK/T-cell lymphoma and enteropathic-associated T-cell lymphoma (EATL) as a low IPI in these conditions does not reflect their poor prognosis. New scoring systems have been developed in an effort to try to improve prognostication. An Italian review generated a scoring system based on age (>60 years), performance status, serum lactate dehydrogenase level, and bone marrow involvement.[4] This has been refined by the same group by the replacement of bone marrow involvement with proliferation index using Ki67 immunostaining.[5] Another scoring system created by the ITLP uses age, performance status, and platelet count as its main variables.

Comparative studies have showed that all the three specific T-cell prognostic scoring systems are useful in the prognostication of PTCL with no system having a definite advantage.[6,7]

Diagnosis and Classification of PTCL

The common subtypes of PTCL are explored in more detail below.

Angioimmunoblastic lymphoma. AITL was first recognized as a distinct clinicopathological entity in the 1970s.[8] The malignant clone is a follicular T-helper cell which secretes cytokines that drive vascular growth and CD21-positive dendritic cell proliferation, which form a meshwork. The cytokines are also responsible for germinal B-cell proliferation that subsequently secretes excess immunoglobulin. These activated B-cells may become immunoblastic and, in the presence of Epstein–Barr virus (EBV) reactivation, can result in a secondary high-grade B-cell lymphoma. AITL has a distinct set of features and is the T-cell lymphoma most associated with autoimmune phenomena such as hemolytic anemia, rheumatoid factor antibodies, and circulating immune complexes. Skin rashes, hypergammaglobulinemia, arthralgia, advanced stage at diagnosis, and prominent B-symptoms are all features of AITL.[9]

PTCL-NOS. PTCL-NOS is a pathological diagnosis of exclusion. It almost certainly represents a collection of diseases. It seems likely that molecular advances such as gene expression profiling will further help characterize these diseases.[10,11] PTCL-NOS tumors frequently show expression of platelet-derived growth factor-alpha receptor and have characteristics of activated peripheral T-cell lymphocytes.[12] The malignant clone expresses pan T-cell markers, and the T-cell receptor is clonally rearranged in most cases. PTCL-NOS has a male predisposition and the average age of a patient is 60 years. B-symptoms are prominent, stage 3 or 4 disease is common and presentation can be with rash, nodal, or extranodal disease.

Anaplastic large-cell lymphoma. ALCL, which was first described in 1985,[13] can be classified into two prognostic groups on the basis of anaplastic lymphoma kinase (ALK) status. ALK-positive ALCL tends to present in children and young adults, with a median presentation of 30 years and a male predisposition. It accounts for 30% of all childhood lymphomas. ALK-negative ALCL, by contrast, is seen in patients who are older with a median age of approximately 60 years.[14] ALK positivity can be demonstrated in 50–85% of all ALCL, depending on inclusion or exclusion of the pediatric population in studies. Morphologically, the cells are large with horseshoe or kidney bean nuclei. Characteristically, the cells express CD30 and epithelial membrane antigen (EMA), whereas the T-cell markers are normally underexpressed. ALK-positive ALCL is associated with a characteristic cytogenetic abnormality, t(2:5) in 85% of patients. This translocation leads to an expression of a novel nucleophosmin (NPM)–ALK fusion protein. There are a series of different ALK translocations that make up the remaining 15%. The ALK status of ALCL is a critical prognostic factor with a five-year OS of 70% for ALK-positive ALCL compared to 49% for ALK-negative ALCL.[15,16]

New Therapies

For historical reasons, CHOP-based chemotherapy has largely been the standard of care with disappointing results. Because of these poor outcomes, a plethora of new agents have been developed for use in PTCL.

Histone Deacetylase Inhibitors

Acetylation of histone proteins is one of the processes by which transcription of DNA is regulated.[17] Acetylated histones are associated with areas of open chromatin, which are relatively accessible for transcription factor binding and resulting gene expression. Deacetylated histones are associated with a repressive environment for gene expression. Deregulation of the so-called epigenetic code has long been recognized in cancer cells and so is a target for therapeutic intervention.[18] HDACs are a group of enzymes responsible for the acetylation of histone

and non-histone proteins. There are four families of HDACs and HDAC inhibitors have varying inhibitory activity against each family which may be important in their relative efficacy against a variety of tumor types.[19]

Vorinostat, panobinostat, and romidepsin have all been demonstrated to have activity in cutaneous T-cell lymphoma (CTCL) and both vorinostat and romidepsin are now licensed for this disease in a relapsed/refractory setting.[20–22] For PTCL, romidepsin has the most mature clinical data. A phase II trial including patients with both CTCL and PTCL showed an overall response rate among 47 PTCL patients of 38% and a median duration of response of 8.9 months.[23] Common toxicities were nausea, fatigue, and transient thrombocytopenia and neutropenia. Initial concern focused on possible cardiac toxicity seen in animal models. Intensive cardiac monitoring in the early clinical studies, however, demonstrated only transient ECG abnormalities and no treatment related arrhythmias. It is, however, recommended to keep potassium and magnesium levels well within the normal range during treatment.[24] A subsequent larger phase II study enrolled 130 patients with PTCL treated with single agent romidepsin until progression or toxicity necessitated withdrawal.[25] The drug was given on days 1, 8, and 15 of a 28 day cycle and the associated overall response rate was 25% with a complete remission rate of 15%. Interestingly, the duration of remission was a very impressive 17 months suggesting that a subset of patients have particular susceptible disease to HDAC inhibitor therapy. Based on these data, the drug has been licensed by the Food and Drugs Agency (FDA) but not by the European Medicines Agency (EMA). An important aim of further work will be to identify biomarkers, which can inform treating clinicians of who are most likely to respond to these agents.

Proteasome Inhibitors

Bortezomib is the first in class proteasome inhibitor which is used widely in the treatment of myeloma and mantle cell lymphoma.[26] A small phase II study with 15 patients in CTCL showed a promising 67% response rate.[27] Interestingly, two patients in this study had PTCL with one showing a response. New proteasome inhibitors are currently being developed and carfilzomib has been licensed by the FDA for multiply relapsed myeloma. In contrast to bortezomib, it is an irreversible proteasome inhibitor and does not appear to cause clinically significant peripheral neuropathy.[28] Other agents include oral formulation such as MLN9708 which is undergoing trials currently in various hematological malignancies. One way in which proteasome inhibitors are thought to work is via accumulation of ubiquitinylated protein aggregates which leads to proteotoxic stress and cell apoptosis.[29] This can be abrogated by HDAC6 mediated targeting of these proteins to aggresomes with resulting degradation through activation of autophagy. There is therefore a considerable rationale in combining an HDAC inhibitor with a proteasome inhibitor[30,31] and trials in PTCL are ongoing.

Pralatrexate

Pralatrexate is an anti-metabolite related to methotrexate but with increased affinity for the reduced folate carrier and an increased rate of polyglutamation.[32] Initial studies used an unusual schedule of a weekly infusion for six weeks of a seven-week cycle. The maximum tolerated dose was 30 mg/m^2 and the dose limiting toxicity was mucositis which was ameliorated with the administration of folate and B12 supplementation.[33] A subsequent phase II study (the PROPEL study) recruited 111 patients and treated patients with relapsed/refractory T-cell lymphoma until progression or excess toxicity. There was a 29% overall response rate and an 11% complete response rate with a 10 month median duration of response.[34] Further studies are investigating pralatrexate use as a maintenance treatment and also in combination with other drugs as first line treatment.

Immunomodulatory Agents

Lenalidomide is an oral immunomodulatory agent with a number of pharmacological effects including cytotoxicity, anti-angiogenic effects, and enhanced T- and NK-cell function through promotion of immunological synapse formation.[35–37] Earlier experience of using this agent in PTCL suggested that it may be particularly useful in AITL with case reports highlighting some impressive responses.[38,39] A larger phase II trial of 54 patients assessed lenalidomide in relapsed/refractory PTCL (the EXPECT trial). The overall response rate was 22% but this rose to 31% in the 26 AITL patients, with 15% achieving CR or CRu. It is unclear how tolerable lenalidomide will be in combination with other agents. Indeed, a recent study using lenalidomide in combination with vorinostat and dexamethasone reported an unacceptable rate of toxicity with little evidence of enhanced efficacy.[40]

Small Molecules

Crizotinib. As described, ALK-positive ALCL is characterized by the expression of the abnormal fusion gene *NPM1–ALK* in the majority of cases and other ALK-translocations in a minority. By a variety of mechanisms, ALK can therefore be typically overexpressed within malignant ALCL cell nuclei. Crizotinib is an exciting orally bioavailable, ATP competitive, selective inhibitor of the tyrosine kinase domain within the ALK protein. Its activity has predominantly been described in non-small cell lung cancer with ALK expression (due to *EML4–ALK* fusion gene), for which it has received FDA approval.[41]

A recent letter in the New England Journal of Medicine[42] described excellent and relatively durable responses in two cases of ALK positive relapsed, refractory ALCL. Both patients entered complete remission (at 28 days and 12 days, respectively) and remained in remission (at six and five months follow up, respectively). Early-phase trial data have demonstrated safety and efficacy of crizotinib in nine pediatric patients[43] and a recent abstract[44] at the American Society of

Hematology in December 2013 described its use in a phase 1 study of 14 ALK-positive ALCL and 1 ALK positive diffuse large B-cell lymphoma (DLBCL). The overall response rate was an impressive 60% in these patients, all of whom had relapsed disease. There were toxicities described with its use. Perhaps most notably, 4 of the 15 patients developed grade 4 adverse events (abdominal pain, increased creatinine phosphokinase, lymphopenia, and multi-organ failure). Grades 1 and 2 diarrhea and visual disturbance (flashing lights, blurred vision, and floaters) were also relatively common. This oral agent has clear efficacy in ALK-positive ALCL and further trials will be needed to establish its role in the first line setting.

There is some evidence that point mutations within the ALK domain[45,46] can lead to resistance to crizotinib. Although these data are derived from ALK-positive Non-small cell lung cancer (NSCLC), they are highly likely to be relevant to ALK-positive ALCL. Second-generation ALK inhibitors, such as aminopyridine-8e, are in pre-clinical studies, and have greater potency and ability to overcome crizotinib-resistance across a panel of ALK mutant cell lines.[46]

Denileukin diftitox. Denileukin diftitox is a recombinant DNA fusion protein linking fragments of the diphtheria toxin to interleukin-2 (IL-2). The IL-2 receptor (also known as CD25) is commonly expressed on T-cells, and its binding to the IL2-R results in endocytosis of the toxin and subsequent cell apoptosis. The 'CONCEPT' phase II study[47] investigated denileukin diftitox combined with CHOP-21 by treating 49 patients with PTCL first line with six to eight cycles. The overall response rate was 47% in PTCL-NOS ($n = 19$), 80% in AITL ($n = 10$), and 87% in ALCL ($n = 8$). The median OS was not reached by the end of the trial follow up, with the OS 63.3% at that time. The treatment was generally well tolerated. Interestingly, responses were seen irrespective of CD25 status. A larger, phase III randomized multicenter study comparing CHOP with Denileukin diftitox plus CHOP is required to confirm its value in the first line setting. Unfortunately, denileukin diftitox has not been available since 2011 and there is no estimated date for its availability, which limits its clinical utility at present.

Monoclonal Antibodies

Brentuximab vedotin. Brentuximab vedotin (BV) is an exciting new antibody-drug conjugate that has been through phase I and II trials in CD30-positive lymphoma. BV delivers a potent anti-microtubule agent monomethylauristatin E (MMAE) to CD30-positive malignant cells via a linker molecule attached to the CD30 monoclonal antibody (see Fig. 1). BV is administered as a three-weekly short intravenous infusion. It has a relatively non-toxic profile with its main side effects being neutropenia and peripheral neuropathy.

Phase III trials are currently underway in first line treatment for Hodgkin lymphoma (ECHELON-1 trial) following

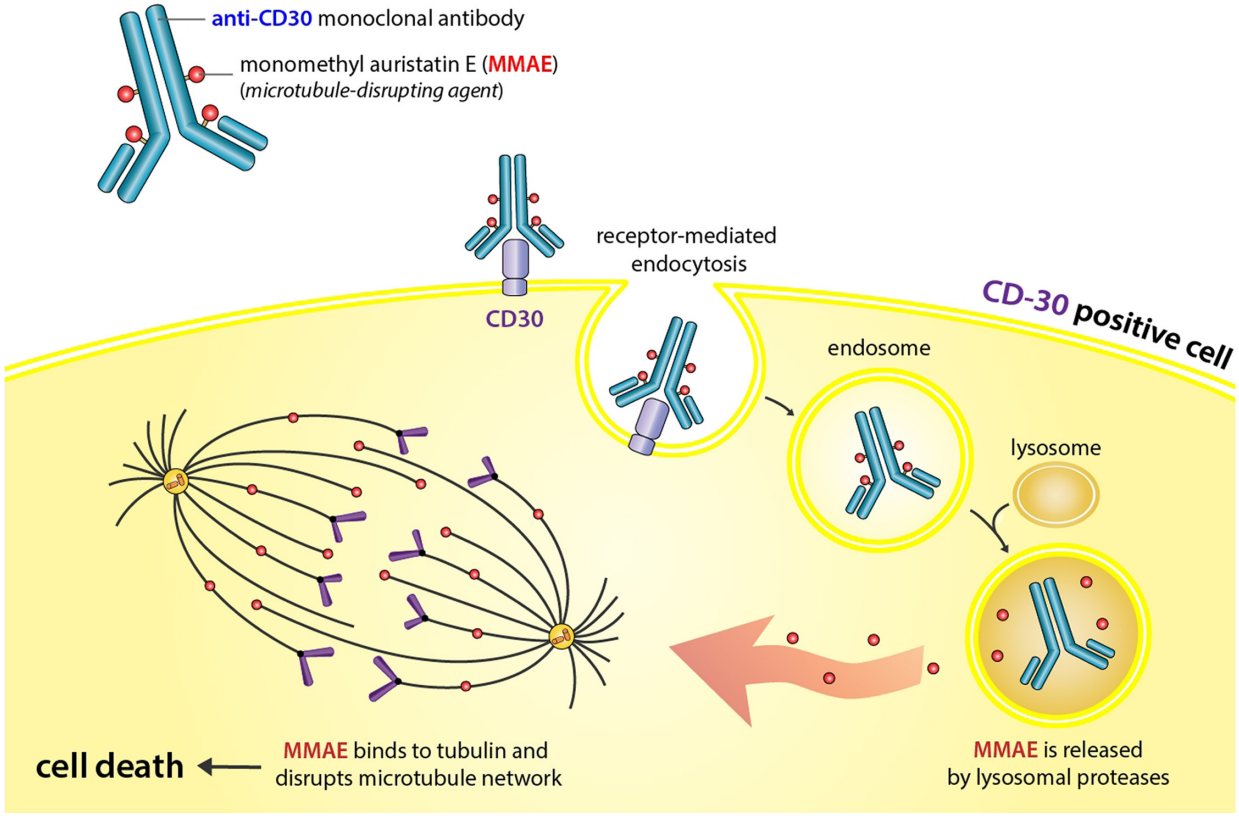

Figure 1. The mechanism of action of brentuximab vedotin.

impressive early phase response rates in the relapsed, refractory setting post-autologous stem cell transplant.[48] ALCL is characterized by its uniform CD30 expression and the early phase data in this specific T-cell subtype are also impressive. Following two phase 1 studies,[49,50] Pro et al[51] published the results of a phase II multicenter trial of 58 patients with relapsed or refractory systemic ALCL. The overall response rate was an impressive 86% with complete responses seen in 57% of patients. The median durations of overall response and complete response were 12.6 and 13.2 months, respectively. No clear plateau was seen on the disease-free survival curves in this cohort. BV may enable further consolidation therapy such as allogeneic or autologous transplantation when used in this setting. Randomized studies require careful design to establish the role of BV and crizotinib in the first line setting alongside CHOP-like regimens, which is the current standard in ALCL.

Moreover, greater than 40% of all PTCLs express CD30 on the cell surface, which increases the possible utility of BV. Interestingly, CD30 expression levels do not seem to directly correlate with response rates and therefore weakly expressing tumor can also respond to BV.[52]

Zanolimumab. Zanolimumab is a fully humanized CD4 specific monoclonal IgG1 antibody which has been previously used as an immunosuppressive treatment for rheumatoid arthritis and psoriasis with minimal success. More recently, it has been used in PTCL with some modest activity. Zanolimumab induces antibody-dependent cell cytotoxicity (ADCC), direct apoptosis of CD3/CD4-positive cells, and disrupts CD4-major histocompatability complex (MHC) class II interaction. A phase II, single-arm multicenter study[53] was performed in 21 patients with relapsed or refractory CD4-positive PTCL (AITL $n = 9$, PTCL-NOS $n = 7$, ALCL $n = 4$, and EATL $n = 1$). Treatment was given as weekly intravenous infusions of 980 mg for 12 weeks. Overall response rate was only 24%, with two in complete response unconfirmed (CRu). The monoclonal antibody was safe as a single agent in this setting, but there is no data on efficacy and safety in first line in combination with standard chemotherapy. The potential for profound immunosuppression when added to combination chemotherapy is a concern.

Mogamulizumab. CCR4 is a chemokine receptor which is highly expressed in most cases of adult T cell leukaemia/lymphoma (ATLL) and certain other PTCL histologies.[54] A defucosylated anti-CCR4 antibody has been generated which has shown enhanced activity in cell lines and animal models, compared with the fucosylated form.[55,56] A phase 1 study[57] in patients with relapsed PTCL (largely ATLL) showed encouraging results in terms of both activity and tolerability and a subsequent phase II study reported a 50% overall response rate in relapsed ATLL with resulting median progression free survival (PFS) of 5.2 months and OS of 13.7 months.[58] The main toxicities were infusion reactions seen in 89% of patients although these were mostly grade 2 and manageable. Studies looking at activity in non-ATLL subtypes are on going.

Alemtuzumab. CD52 is not only expressed on PTCL cells, but also expressed widely on other cell types, such as monocytes and B-cells. The GITIL study[59] was a small phase II study combining alemtuzumab and CHOP-28 in 18 patients. The complete response rate was an impressive 71% across patients with EATL, PTCL-NOS, AITL, and ALCL (ALK negative). This study reported moderate toxicity, but enthusiasm was tempered by the results of an Asian phase II study of CHOP-21 in combination with alemtuzumab. The trial was stopped early because of toxicity.[60] The HOVON group also performed a phase II study of CHOP-14 and alemtuzumab. The impressive overall response rate of 90% was tempered by the finding of three cases of late EBV-driven B-cell lymphomas out of the 20 patient cohorts. Serious infections were also seen.[61] A current European study (ACT I/II) is comparing CHOP-14 with and without alemtuzumab and will hopefully answer an open question about the use of alemtuzumab in PTCL in the first line setting. The initial dose in these studies resulted in excess toxicity but a subsequent dose reduction was well tolerated. Alemtuzumab has been withdrawn from the market by the EMA, and subsequently approved for a multiple sclerosis indication in Europe. It is currently unclear how this will affect drug availability now and in the future for PTCL patients.

Other New Therapeutics of Interest

Asparaginase use in extranodal NK/T-cell lymphoma. Extranodal NK/T-cell lymphoma characteristically presents with a necrotic, paranasal, and destructive mass. It has a clear association with EBV and is typically seen in patients of South-East Asian origin. The tumor is particularly radiosensitive, with reasonable cure rates seen in localized disease.[2] Historically, patients with disseminated disease had a dreadful prognosis. Extranasal disease is associated with disseminated intravascular coagulation, multi-organ failure, and a five-year OS of only 9%.[2] A high level of p53 deletion and overexpression of P-glycoprotein within the malignant cells are thought to contribute to resistance to standard chemotherapy. P-glycoprotein acts as an efflux pump within the malignant cells and an overexpression leads to an excessive efflux of chemotherapy and subsequent resistance.[62,63]

Asparaginase depletes extracellular asparagine and glutamine, and therefore starves malignant cells of these necessary amino acids, inducing apoptosis. Traditionally used during induction in acute lymphoblastic leukemia, its use in extranodal NK/T-cell lymphoma has evolved. Recent French and Japanese phase II trials have shown that asparaginase-based regimens can improve the previous dismal prognosis of disseminated extranodal NK/T-cell lymphoma. A Japanese group performed the largest phase II study[64] to date using the "SMILE" (steroids, methotrexate, ifosfamide, L-asparaginase, and etoposide) regimen in 38 newly diagnosed stage IV, relapsed, or refractory patients. The two planned cycles were completed by 74%, which resulted in an overall response rate

of 79% and a complete response rate of 45%. The one year OS was 55%, with the suggestion of a plateau on the survival curve after three years follow up. The regimen is particularly myelotoxic (92% grade IV neutropenia and 61% grade III and IV infection) and granulocyte colony stimulating factor (G-CSF) support is a necessity. Given the prognosis in this subset of patients, most treating physicians would still consider this regimen as a bridge to allogeneic or autologous stem cell transplantation.[65]

The GELA/GOELAMS group[66] has published good results in a smaller trial with a less toxic regimen. The asparaginase, methotrexate, and dexamethasone (AspaMetDex) regimen was used in 19 relapsed or refractory patients with a complete response rate of 61% and a one year OS of 45%.

Standard treatment of early stage disease until recently has been combined modality therapy with 50 Gy localized radiotherapy and anthracycline-based chemotherapy. Recent phase II data have challenged this approach. The L-asparaginase, vincristine, and prednisolone (LVP) regimen for six cycles with radiotherapy dovetailed between cycle two and three displayed an overall response rate of 89%, complete response rate of 81%, and an impressive two-year OS of 88.5% and progressive free survival of 80.6%.[67] Similar impressive phase II data was displayed using gemcitabine, L-asparaginase, and oxaliplatin (GELOX) followed by involved-field radiotherapy (56 Gy) for patients with stage IE/IIE Extranodal NK/T-cell lymphoma.[68] The overall response rate was 96% and complete response rate was 74%, and two-year OS and progressive free survival were both 86% in the 27 patients treated. None of these data are randomized but still seem likely to represent a step forward in the management of both localized and disseminated NK/T-cell lymphoma. Ideally, randomized studies are required to understand how L-asparaginase can be best incorporated into treatment regimens.

Biomarker-directed Therapy

A biomarker can be defined as a substance which indicates the presence of a disease state and/or the prognosis of a condition. Importantly, the presence or absence of some biomarkers may also help define groups of patients more or less likely to respond to treatment. In a heterogeneous disease process, such as PTCL, which generally has a poor outcome, defining groups of patients more or less likely to respond to different treatments can serve to target such treatments more effectively, thereby maximizing outcomes. In PTCL, the obvious biomarker with relevance to therapy is CD30. CD30 is a transmembrane glycoprotein of the tumor necrosis factor receptor family. It is involved in cell signaling via activation of the NF-κB and mitogen-activated protein kinase (MAPK) pathways leading to modulation of cell growth, proliferation, and differentiation.[69] The expression of CD30 in normal tissue is restricted to activated T- and B-immunoblasts whereas strong and homogenous expression is characteristic of ALCL (ALK positive or negative).[70] CD30 may also be expressed by almost every other subtype of PTCL although at more variable and lower levels.[71] As discussed above, the anti-CD30 immunoconjugate BV has shown impressive activity in relapsed/refractory ALCL. Its role is being evaluated in other CD30-expressing PTCL subtypes and correlation of activity with CD30 expression will be interesting.

Another interesting approach for predictive biomarker discovery is illustrated by a study performed by Fotheringham et al.[72] They took U2OS cells and transfected them with a small hairpin RNA library in order to perform a genome wide loss of function screen. Untransfected cells exposed to an HDAC inhibitor died by apoptosis. However, when transfected cells were exposed, some colonies survived drug treatment, were isolated, and analyzed to determine which genes had been knocked down. HR23B was discovered as a gene conferring sensitivity to HDAC inhibitors. Functional assays revealed that the HR23B protein to be involved in the shuttling of ubiquitinated proteins to the proteasome for destruction. In those cells expressing HR23B, HDAC inhibitor treatment led to further upregulation of expression and a saturation phenomenon. A subsequent study assessed the expression of HR23B in CTCL samples from patients subsequently treated with HDAC inhibitors. Eleven of the 16 patients with high expression achieved stable disease or a partial remission. In those weakly expressing the protein, 2/5 responded.[73] Numbers are clearly small in this analysis, but further work to evaluate the role of HR23B as a sensitivity determinant for HDAC inhibitor therapy are warranted.

Conclusions

Many challenges remain in the field of PTCL. Current treatment strategies are inadequate and survival at relapse is extremely poor, especially in the transplant ineligible group.[74] Although a plethora of new drugs have been trialed in the relapse setting, progressive free survival and OS remain disappointing. The use of intelligent combinations combined with a biomarker-driven approach is likely to be a fruitful avenue of further research. BV, targeting CD30 expression, has proven already to be a valuable therapy in selected patients. Crizotinib is also highly active, albeit in a small subset of ALK-expressing lymphomas. Crizotinib indeed illustrates the down-side of targeted therapy in PTCL. PTCL is rare, and there are 22 described entities, some being extremely rare. Some targeted treatments will be available for restricted subtypes in which the agent is active. This can make clinical trials harder to perform, and reduces the market available thus limiting pharmaceutical company engagement. Progress in this field will therefore rely on extensive international collaborative efforts.

Acknowledgments

Many thanks to Dr. Caroline Watson who provided expert assistance in the production of Figure 1. The British Journal of Hospital Medicine is acknowledged as the source of the image.

Author Contributions

GPC, DB and TAE contributed equally to the writing and editing of the manuscript. All authors reviewed and approved of the final manuscript.

REFERENCES

1. Anderson JR, Armitage JO, Weisenburger DD. Epidemiology of the non-Hodgkin's lymphomas: distributions of the major subtypes differ by geographic locations. Non-Hodgkin's Lymphoma Classification Project. *Ann Oncol*. 1998;9: 717–720.
2. Vose J, Armitage J, Weisenburger D, International T-Cell Lymphoma Project. (2008) International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. *J Clin Oncol*. 26:4124–4130.
3. Gisselbrecht C, Gaulard P, Lepage E, et al. Prognostic significance of T-cell phenotype in aggressive non-Hodgkin's lymphomas. Groupe d'Etudes des Lymphomes de l'Adulte (GELA). *Blood*. 1998;92:76–82.
4. Gallamini A, Stelitano C, Calvi R, et al. Peripheral T-cell lymphoma unspecified (PTCL-U): a new prognostic model from a retrospective multicentric clinical study. *Blood*. 2004;103:2474–2479.
5. Went P, Agostinelli C, Gallamini A, et al. Marker expression in peripheral T-cell lymphoma: a proposed clinical-pathologic prognostic score. *J Clin Oncol*. 2006;24:2472–2479.
6. Lee Y, Uhm JE, Lee HY, et al. Clinical features and prognostic factors of patients with "peripheral T cell lymphoma, unspecified". *Ann Hematol*. 2009;88:111–119.
7. Gutiérrez-García G, García-Herrera A, Cardesa T, et al. Comparison of four prognostic scores in peripheral T-cell lymphoma. *Ann Oncol*. 2011;22:397–404.
8. Frizzera G, Moran EM, Rappaport H. Angio-immunoblastic lymphadenopathy with dysproteinaemia. *Lancet*. 1974;1:1070–1073.
9. Federico M, Rudiger T, Bellei M, et al. Clinicopathologic characteristics of angioimmunoblastic T-cell lymphoma: analysis of the international peripheral T-cell lymphoma project. *J Clin Oncol*. 2013;31:240–246.
10. Piccaluga PP, Tabanelli V, Pileri SA. Molecular genetics of peripheral T-cell lymphomas. *Int J Hematol*. 2014;99:219–226.
11. Iqbal J, Weisenburger DD, Greiner TC, et al. Molecular signatures to improve diagnosis in peripheral T-cell lymphoma and prognostication in angioimmunoblastic T-cell lymphoma. *Blood*. 2010;115:1026–1036.
12. Piccaluga PP, Agostinelli C, Califano A, et al. Gene expression analysis of peripheral T cell lymphoma, unspecified, reveals distinct profiles and new potential therapeutic targets. *J Clin Invest*. 2007;117:823–834.
13. Stein H, Mason DY, Gerdes J, et al. The expression of the Hodgkin's disease associated antigen Ki-1 in reactive and neoplastic lymphoid tissue: evidence that Reed-Sternberg cells and histiocytic malignancies are derived from activated lymphoid cells. *Blood*. 1985;66:848–858.
14. Stein H, Foss HD, Dürkop H, et al. CD30(+) anaplastic large cell lymphoma: a review of its histopathologic, genetic, and clinical features. *Blood*. 2000;96: 3681–3695.
15. Savage KJ, Harris NL, Vose JM, et al. ALK⁻ anaplastic large-cell lymphoma is clinically and immunophenotypically different from both ALK+ ALCL and peripheral T-cell lymphoma, not otherwise specified: report from the International Peripheral T-Cell Lymphoma Project. *Blood*. 2008;111:5496–5504.
16. Eyre TA, Khan D, Hall GW, Collins GP. Anaplastic lymphoma kinase-positive anaplastic large cell lymphoma: current and future perspectives in adult and paediatric disease. *Eur J Haematol*. 2014 April 26. doi:10.1111/ejh.12360. [Epub ahead of print].
17. Thiagalingam S, Cheng KH, Lee HJ, Mineva N, Thiagalingam A, Ponte JF. Histone deacetylases: unique players in shaping the epigenetic histone code. *Ann N Y Acad Sci*. 2003;983:84–100.
18. Dawson MA, Kouzarides T. Cancer epigenetics: from mechanism to therapy. *Cell*. 2012;150:12–27.
19. New M, Olzscha H, La Thangue NB. HDAC inhibitor-based therapies: can we interpret the code? *Mol Oncol*. 2012;6:637–656.
20. Whittaker SJ, Demierre MF, Kim EJ, et al. Final results from a multicenter, international, pivotal study of romidepsin in refractory cutaneous T-cell lymphoma. *J Clin Oncol*. 2010;28:4485–4491.
21. Olsen EA, Kim YH, Kuzel TM, et al. Phase IIb multicenter trial of vorinostat in patients with persistent, progressive, or treatment refractory cutaneous T-cell lymphoma. *J Clin Oncol*. 2007;25:3109–3115.
22. Duvic M, Dummer R, Becker JC, et al. Panobinostat activity in both bexarotene-exposed and -naïve patients with refractory cutaneous T-cell lymphoma: results of a phase II trial. *Eur J Cancer*. 2013;49:386–394.
23. Piekarz RL, Frye R, Prince HM, et al. Phase 2 trial of romidepsin in patients with peripheral T-cell lymphoma. *Blood*. 2011;117:5827–5834.
24. Piekarz RL, Frye AR, Wright JJ, et al. Cardiac studies in patients treated with depsipeptide, FK228, in a phase II trial for T-cell lymphoma. *Clin Cancer Res*. 2006;12:3762–3773.
25. Coiffier B, Pro B, Prince HM, et al. Results from a pivotal, open-label, phase II study of romidepsin in relapsed or refractory peripheral T-cell lymphoma after prior systemic therapy. *J Clin Oncol*. 2012;30:631–636.
26. Ludwig H, Khayat D, Giaccone G, Facon T. Proteasome inhibition and its clinical prospects in the treatment of hematologic and solid malignancies. *Cancer*. 2005;104:1794–1807.
27. Zinzani PL, Musuraca G, Tani M, et al. Phase II trial of proteasome inhibitor bortezomib in patients with relapsed or refractory cutaneous T-cell lymphoma. *J Clin Oncol*. 2007;25:4293–4297.
28. Jain S, Diefenbach C, Zain J, O'Connor OA. Emerging role of carfilzomib in treatment of relapsed and refractory lymphoid neoplasms and multiple myeloma. *Core Evid*. 2011;6:43–57.
29. Adams J. The proteasome: a suitable antineoplastic target. *Nat Rev Cancer*. 2004;4: 349–360.
30. Jagannath S, Dimopoulos MA, Lonial S. Combined proteasome and histone deacetylase inhibition: a promising synergy for patients with relapsed/refractory multiple myeloma. *Leuk Res*. 2010;34:1111–1118.
31. Dasmahapatra G, Lembersky D, Son MP, et al. Carfilzomib interacts synergistically with histone deacetylase inhibitors in mantle cell lymphoma cells in vitro and in vivo. *Mol Cancer Ther*. 2011;10:1686–1697.
32. Foss FM. Evaluation of the pharmacokinetics, preclinical and clinical efficacy of pralatrexate for the treatment of T-cell lymphoma. *Expert Opin Drug Metab Toxicol*. 2011;7:1141–1152.
33. O'Connor OA, Horwitz S, Hamlin P, et al. Phase II-I-II study of two different doses and schedules of pralatrexate, a high-affinity substrate for the reduced folate carrier, in patients with relapsed or refractory lymphoma reveals marked activity in T-cell malignancies. *J Clin Oncol*. 2009;27:4357–4364.
34. O'Connor OA, Pro B, Pinter-Brown L, et al. Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: results from the pivotal PROPEL study. *J Clin Oncol*. 2011;29:1182–1189.
35. Dredge K, Horsfall R, Robinson SP, et al. Orally administered lenalidomide (CC-5013) is anti-angiogenic in vivo and inhibits endothelial cell migration and Akt phosphorylation in vitro. *Microvasc Res*. 2005;69:56–63.
36. Zhu D, Corral LG, Fleming YW, Stein B. Immunomodulatory drugs Revlimid (lenalidomide) and CC-4047 induce apoptosis of both hematological and solid tumor cells through NK cell activation. *Cancer Immunol Immunother*. 2008;57:1849–1859.
37. Ramsay AG, Clear AJ, Kelly G, et al. Follicular lymphoma cells induce T-cell immunologic synapse dysfunction that can be repaired with lenalidomide: implications for the tumor microenvironment and immunotherapy. *Blood*. 2009;114: 4713–4720.
38. Fabbri A, Cencini E, Pietrini A, et al. Impressive activity of lenalidomide monotherapy in refractory angioimmunoblastic T-cell lymphoma: report of a case with long-term follow-up. *Hematol Oncol*. 2012;31:213–217.
39. Beckers MM, Huls G. Therapy refractory angioimmunoblastic T-cell lymphoma in complete remission with lenalidomide. *Eur J Haematol*. 2013;90:162–163.
40. Hopfinger G, Nösslinger T, Lang A, et al. Lenalidomide in combination with vorinostat and dexamethasone for the treatment of relapsed/refractory peripheral T cell lymphoma (PTCL): report of a phase I/II trial. *Ann Hematol*. 2014;93: 459–462.
41. Shaw AT, Kim DW, Nakagawa K, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. *N Engl J Med*. 2013;368:2385–2394.
42. Gambacorti-Passerini C, Messa C, Pogliani EM. Crizotinib in anaplastic large-cell lymphoma. *N Engl J Med*. 2011;364:775–776.
43. Mossé YP, Lim MS, Voss SD, et al. Safety and activity of crizotinib for paediatric patients with refractory solid tumours or anaplastic large-cell lymphoma: a Children's Oncology Group phase 1 consortium study. *Lancet Oncol*. 2013;14: 472–480.
44. Redaelli S, Farina F, Stasia A, et al. High response rates to crizotinib in advanced, chemoresistant ALK+ lymphoma patients. *Blood*. 2013:122(21 suppl).
45. Choi YL, Soda M, Yamashita Y, et al. EML4-ALK mutations in lung cancer that confer resistance to ALK inhibitors. *N Engl J Med*. 2010;18:1734–1739.
46. Huang Q, Johnson TW, Bailey S, et al. The design of potent and selective inhibitors to overcome clinical ALK mutations resistant to crizotinib. *J Med Chem*. 2014;57:1170–1187.
47. Foss FM, Sjak-Shie N, Goy A, et al. A multicenter phase II trial to determine the safety and efficacy of combination therapy with denileukin diftitox and cyclophosphamide, doxorubicin, vincristine and prednisone in untreated peripheral T-cell lymphoma: the CONCEPT study. *Leuk Lymphoma*. 2013;54: 1373–1379.
48. Younes A, Gopal AK, Smith SE, et al. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. *J Clin Oncol*. 2012;30:2183–2189.
49. Younes A, Bartlett NL, Leonard JP, et al. Brentuximab vedotin (SGN-35) for relapsed CD30-positive lymphomas. *N Engl J Med*. 2010;363:1812–1821.
50. Fanale MA, Forero-Torres A, Rosenblatt JD, et al. A phase I weekly dosing study of brentuximab vedotin in patients with relapsed/refractory CD30-positive hematologic malignancies. *Clin Cancer Res*. 2012;18:248–255.

51. Pro B, Advani R, Brice P, et al. Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: results of a phase II study. *J Clin Oncol*. 2012;30:2190–2196.
52. Sabattini E, Pizzi M, Tabanelli V, et al. CD30 expression in peripheral T-cell lymphomas. *Haematologica*. 2013;98:e81–e82.
53. d'Amore F, Radford J, Relander T, et al. Phase II trial of zanolimumab (HuMax-CD4) in relapsed or refractory non-cutaneous peripheral T cell lymphoma. *Br J Haematol*. 2010;150:565–573.
54. Ishida T, Utsunomiya A, Iida S, et al. Clinical significance of CCR4 expression in adult T-cell leukemia/lymphoma: its close association with skin involvement and unfavorable outcome. *Clin Cancer Res*. 2003;9:3625–3634.
55. Ito A, Ishida T, Utsunomiya A, et al. Defucosylated anti-CCR4 monoclonal antibody exerts potent ADCC against primary ATLL cells mediated by autologous human immune cells in NOD/Shi-scid, IL-2R gamma(null) mice in vivo. *J Immunol*. 2009;183:4782–4791.
56. Ishii T, Ishida T, Utsunomiya A, et al. Defucosylated humanized anti-CCR4 monoclonal antibody KW-0761 as a novel immunotherapeutic agent for adult T-cell leukemia/lymphoma. *Clin Cancer Res*. 2010;16:1520–1531.
57. Yamamoto K, Utsunomiya A, Tobinai K, et al. Phase I study of KW-0761, a defucosylated humanized anti-CCR4 antibody, in relapsed patients with adult T-cell leukemia-lymphoma and peripheral T-cell lymphoma. *J Clin Oncol*. 2010; 28:1591–1598.
58. Ishida T, Joh T, Uike N, et al. Defucosylated anti-CCR4 monoclonal antibody (KW-0761) for relapsed adult T-cell leukemia-lymphoma: a multicenter phase II study. *J Clin Oncol*. 2012;30:837–842.
59. Gallamini A, Zaja F, Patti C, et al. Alemtuzumab (Campath-1H) and CHOP chemotherapy as first-line treatment of peripheral T-cell lymphoma: results of a GITIL (Gruppo Italiano Terapie Innovative nei Linfomi) prospective multicenter trial. *Blood*. 2007;110:2316–2323.
60. Kim JG, Sohn SK, Chae YS, et al. Alemtuzumab plus CHOP as front-line chemotherapy for patients with peripheral T-cell lymphomas: a phase II study. *Cancer Chemother Pharmacol*. 2007;60:129–134.
61. Kluin-Nelemans HC, Coenen JL, Boers JE, van Imhoff GW, Rosati S. EBV-positive immunodeficiency lymphoma after alemtuzumab-CHOP therapy for peripheral T-cell lymphoma. *Blood*. 2008;112:1039–1041.
62. Egashira M, Kawamata N, Sugimoto K, Kaneko T, Oshimi K. P-glycoprotein expression on normal and abnormally expanded natural killer cells and inhibition of P-glycoprotein function by cyclosporin A and its analogue. *Blood*. 1999;93: 599–606.
63. Drénou B, Lamy T, Amiot L, et al. CD3– CD56+ non-Hodgkin's lymphomas with an aggressive behavior related to multidrug resistance. *Blood*. 1997;89: 2966–2974.
64. Yamaguchi M, Kwong YL, Kim WS, et al. Phase II study of SMILE chemotherapy for newly diagnosed stage IV, relapsed, or refractory extranodal natural killer (NK)/T-cell lymphoma, nasal type: the NK-Cell Tumor Study Group study. *J Clin Oncol*. 2011;29:4410–4416.
65. Kwong YL. High-dose chemotherapy and hematopoietic SCT in the management of natural killer-cell malignancies. *Bone Marrow Transplant*. 2009;44: 709–714.
66. Jaccard A, Petit B, Girault S, et al. L-Asparaginase-based treatment of 15 western patients with extranodal NK/T-cell lymphoma and leukemia and a review of the literature. *Ann Oncol*. 2008;20:110–116.
67. Jiang M, Zhang H, Jiang Y, et al. Phase 2 trial of "sandwich" L-asparaginase, vincristine, and prednisone chemotherapy with radiotherapy in newly diagnosed, stage IE to IIE, nasal type, extranodal natural killer/T-cell lymphoma. *Cancer*. 2012;118:3294–3301.
68. Wang L, Wang ZH, Chen XQ. First-line combination of gemcitabine, oxaliplatin, and l-asparaginase (GELOX) followed by involved-field radiation therapy for patients with stage IE/IIE extranodal natural killer/T-cell lymphoma. *Cancer*. 2013;119:348–355.
69. Al-Shamkhani A. The role of CD30 in the pathogenesis of haematopoietic malignancies. *Curr Opin Pharmacol*. 2004;4:355–359.
70. Juco J, Holden JT, Mann KP, Kelley LG, Li S. Immunophenotypic analysis of anaplastic large cell lymphoma by flow cytometry. *Am J Clin Pathol*. 2003;119: 205–212.
71. de Leval L, Gaulard P. CD30+ lymphoproliferative disorders. *Haematologica*. 2010;95:1627–1630.
72. Fotheringham S, Epping MT, Stimson L, et al. Genome-wide loss-of-function screen reveals an important role for the proteasome in HDAC inhibitor-induced apoptosis. *Cancer Cell*. 2009;15:57–66.
73. Khan O, Fotheringham S, Wood V, et al. HR23B is a biomarker for tumor sensitivity to HDAC inhibitor-based therapy. *Proc Natl Acad Sci U S A*. 2010;107: 6532–6537.
74. Mak V, Hamm J, Chhanabhai M, et al. Survival of patients with peripheral T-cell lymphoma after first relapse or progression: spectrum of disease and rare long-term survivors. *J Clin Oncol*. 2013;31:1970–1976.