Novel Therapies for T-cell Lymphomas

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Introduction

Advanced stages of mycosis fungoides (MF) and Sézary syndrome (SS) are often refractory to treatment and have an unfavorable prognosis. It is not clear what mechanisms are adopted by the malignant T-lymphocytes to proliferate and to escape immune surveillance. Immune dysregulation is demonstrated by the constitutive phosphorylation of STAT-3 protein in neoplastic T-cells [1, 2]. These cells may express the IL-2 alpha receptor (CD25) which is a target for biologic therapy with denileukin diftitox. Naturally occurring regulatory T-cells (Tregs) also express the CD25 molecule. They suppress the activity of other immune cells, thus maintaining immunological tolerance. Features of Tregs appear to play a role in the immunosuppression of advanced stages, but their role in CTCL is still controversial [3, 4]. Strategies for driving immune responses to lymphoma have been investigated, including the use of immunomodulatory drugs (IMiDs), which target immune cells rather than the malignant lymphocytes [5]. Mutations affecting the *p16*, *FAS*, and *JUNB* genes and alterations of death receptor signaling have been identified in patients with MF/SS [6–9]. The clonal expansion of the malignant T-cells is proposed to be at least in part due to defective regulation of apoptosis. Some of the investigational therapies used in cutaneous T-cell lymphoma (CTCL) such as enzastaurin are able to induce apoptosis via activation of the AKT and caspase-9-dependent pathway [10]. Other important novel agents include the Bcl-2-antagonists; a novel antifolate, pralatrexate, and the proteasome inhibitor bortezomib. The mechanisms of action of the novel agents are reviewed as well as available clinical data.

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Bortezomib

The ubiquitin–proteasome pathway plays a critical role in the degradation of proteins involved in cell cycle, survival, and apoptosis. It modulates cell cycle proteins such as the cyclins, cyclin-dependent kinases, and their inhibitors p21 and p27, but is also central to the regulation of transcription, through its control of NF-κB levels. The proteasome pathway is activated in malignant cells and inhibition of this activity is thought to induce antitumor effects. Bortezomib, first approved by the US Food and Drug Administration (FDA) for the treatment of

F. Foss (ed.), *T-Cell Lymphomas*, Contemporary Hematology,
DOI 10.1007/978-1-62703-170-7_17, © Springer Science+Business Media New York 2013

relapsed and refractory multiple myeloma (MM), was the first proteasome inhibitor to enter clinical trials for MM and is now being widely tested in clinical trials for other malignancies [11–14]. The best evidence of single-agent activity is in patients with mantle cell lymphoma (MCL) in which response rates (RR) of 30–40% were seen [12]. Responses have been infrequent in patients with other refractory B-cell non-Hodgkin lymphomas (NHLs) [14].

Recently, the mechanism by which bortezomib leads to tumor cell apoptosis in T-cell lymphoma was investigated using CTCL and adult T-cell leukemia/lymphoma cell lines [15]. Bortezomib treatment was found to induce mitochondrial membrane injury mediated by Noxa, an apoptosis-inducible BH3-only protein, which interacts with and inactivates Mcl-1, an antiapoptotic Bcl-2 family protein, and triggers mitochondrial membrane permeabilization leading to apoptosis. Clinical trials were exploring the activity of bortezomib in patients with CTCL and peripheral T-cell lymphoma (PTCL). A phase I trial of cyclophosphamide, hydroxydaunorubicin, oncovin, prednisone, and bortezomib in 13 previously untreated patients with PTCL or aggressive NK/T-cell lymphoma showed overall RR and CR of 61.5% (eight patients). Three patients relapsed at 3, 4, and 12 months [16]. NF-κB is constitutively activated in CTCL, which may be crucial for its resistance to apoptosis [17]. Bortezomib at nanomolar concentrations inhibited constitutive activation of NF-κB and induced apoptosis in CTCL cell lines and provided a rationale for its clinical use in CTCL [18]. A phase II study of bortezomib in patients with relapsed or refractory CTCL and PTCL with isolated skin involvement showed promising activity with an overall RR of 67%, with six (17%) complete (CR) and six (50%) partial remissions (PR) among the 12 patients enrolled lasting 7 to 12+ months [19]. The most significant toxicity was sensory neuropathy in 50% of patients followed by neutropenia and thrombocytopenia in 17% of patients.

Two recent laboratory studies have shown that bortezomib and the histone deacetylase inhibitor SAHA synergistically induces apoptosis in T-cell leukemia/lymphoma cells [20, 21]. Moreover, bortezomib inhibits tumor growth in a murine xenograft model [21]. Future clinical applications of combined bortezomib/SAHA regimen in T-cell lymphomas are warranted.

Pralatrexate

The reduced folate carrier-type 1 (RFC-1), an oncofetoprotein predominantly expressed in the membranes of fetal and tumor cells, mediates cellular uptake of folates and antifolate drugs. Alterations of the RFC-1 protein have been associated with resistance to methotrexate (MTX). Pralatrexate [PDX (RS)-10-propargyl-10-deaza-aminopterin] is a 10-deaza-aminopterin-analog of MTX, and is a novel targeted antifolate that has shown higher affinity to the RFC-1, increased accumulation and polyglutamylation in tumor cells compared to MTX [22–24]. In prior studies, pralatrexate exhibited enhanced efficacy over MTX in human solid tumor xenografts [25].

Pralatrexate has marked activity in patients with relapsed and/or chemotherapy-resistant T-cell lymphoma that has led to FDA approval for its use as a single agent for the treatment of patients with relapsed or refractory PTCL [26]. In an early phase study of pralatrexate with various B-and T-cell NHL, all four patients with refractory aggressive T-cell lymphoma achieved CR [27]. More recently, a phase I/II study of two different doses and schedules of pralatrexate in patients with relapsed/refractory NHL or Hodgkin disease (HD) showed an overall RR of 55% in T-cell NHL on the phase I study weekly schedule and 50% on the phase II study including 44% and 19% CR/unconfirmed complete remission (CRu), respectively, while only minimal responses in B-cell NHL (10% RR) were seen. The dose-limiting toxicity for pralatrexate in the phase I with a treatment schedule of 135–150 mg/m^2 every other week used for non-small-cell lung cancer has been stomatitis. Symptoms have been ameliorated by a reduced weekly schedule of 30 mg/m^2 for 6 of 7 weeks with folate and B12 supplementation. Risk factors contributing to pralatrexate-related mucositis are homocysteine levels greater than or equal to

10 μmol/L and methylmalonic acid levels greater than or equal to 200 nmol/L. On the basis of the activity in T-cell NHL a pivotal phase II, non-randomized, open-label, international study (PROPEL) in patients with relapsed/refractory PTCL has been completed using the same weekly schedule showed a lower overall RR of 29% with CR in 10% of patients [28]. Most patients were heavily pretreated with a median of three prior treatments and had advanced disease. The most common grades 3 and 4 toxicities were mucositis and thrombocytopenia.

A phase I trial in patients with relapsed CTCL showed impressive activity of pralatrexate with responses seen in 11 of 18 patients (two CR and nine PR) [29]. Patients with MF, SS, and C-ALCL were included. Dose-limiting toxicity was mucositis. The optimal dose and schedule that provided activity with tolerability for CTCL was determined to be pralatrexate 15 mg/m^2 weekly on 3 of 4 weeks. A phase II study is ongoing. An interesting case of pralatrexate-induced tumor cell apoptosis within epidermal Pautrier microabscesses presenting as innumerable skin erosions in a patient with advanced adult T-cell lymphoma/leukemia was recently published [30]. Histologic examination revealed that epidermal Pautrier microabscesses showed extensive cellular debris, with normal-appearing adjacent keratinocytes. The erosions healed within a few days and a complete resolution of disease was observed while continued on pralatrexate. Pralatrexate was also given at weekly doses in a patient with relapsed CD4+ CD56+ hematodermic/plasmacytoid dendritic cell tumor presenting with skin lesions only that resulted in a remarkable clinical response with regression of cutaneous tumors after two treatments [31]. Response lasted for about 4 months.

Preclinical data reported synergy for the combination with gemcitabine. A recent phase I study of pralatrexate with gemcitabine in patients with lymphoproliferative malignancies have been reported [32]. Thirty-four patients: 13 with B-cell lymphoma, 11 with T/NK-cell lymphoma, 7 with HD, and 3 with "other" lymphoma were included. Three treatment schedules were applied ranging from once weekly sequential-day dosing (pralatrexate 10–15 mg/m^2 and gemcitabine 300–400 mg/m^2), sequential-day dosing every 2 weeks, to same day dosing every 2 weeks. Preliminary results showed activity in 21% (7/34) of patients with acceptable toxicities with every 2 week dosing. Dose limiting toxicities were grade 3 to 4 hematologic toxicities.

Lenalidomide

Lenalidomide is probably the most extensively studied compound of a new class of agents which are known as IMiDs [33]. It is a 4-amino-gultaramide derivative of thalidomide and was designed to enhance the immunological and anti-tumor properties of thalidomide with improved safety profile. It is a lead therapeutic in multiple myeloma and myelodysplastic syndromes associated with the deletion of 5q cytogenetic abnormality (del-5q MDS). Lenalidomide has been FDA approved for previously treated multiple myeloma in combination with dexamethasone and del-5q MDS [34].

The mechanisms of action remain uncertain, but appear to involve direct cytotoxic action in some cell types, the modulation of immunity via altered cytokine production and cellular changes both on the malignant cell and reactive T- and NK-cells, and the suppression of angiogenesis by downregulation of vascular endothelial growth factor (VEGF). In multiple myeloma, lenalidomide has been demonstrated to directly induce apoptosis via caspase-8 activation, to inhibit VEGF, and to reduce adhesion of myeloma cells to bone marrow stroma. In preclinical observations, lenalidomide inhibits or modulates various cytokines including tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, IL-6, and IL-12. Furthermore it has demonstrated its ability to increase T- and NK-cell stimulation, T-cell proliferation, and production of IL-2 and interferon-γ (IFN-γ) by T-cells, and to inhibit expression and function of Tregs [35, 36].

Lenalidomide has been shown activity against chronic lymphocytic leukemia (CLL), relapsed or refractory NHL, and various solid cancers in phase II studies. In general the activity seen in patients with recurrent and refractory lymphoma

has been moderate with RR between 22 and 50%. An overall RR of 35–50% with lenalidomide was reported in patients with CLL. Results from phase I/II trials in relapsed multiple myeloma show RR of 14–29% with lenalidomide alone.

Cytopenias are the primary adverse events associated with the administration of lenalidomide, particularly in subjects with compromised bone marrow. However, these are manageable with dose interruptions and reductions. Other side effects include malaise, fatigue, diarrhea, rash, and muscle cramps. An increased risk of thromboembolism has been noted when lenalidomide is combined with steroids. A "flare" phenomenon has been observed in CLL prior to disease response [37]. The recommended starting dose is 10 mg. Patients with multiple myeloma typically receive 25 mg daily for three weeks followed by a 1-week rest period.

There have been two recent reports of lenalidomide for the treatment in T-cell lymphoma. The immunomodulatory properties of lenalidomide such as T-cell co-stimulation with induction of Th1 cytokine production and cytotoxic activity along with antiangiogenic, anti-proliferative, and pro-apoptotic properties provided the rationale to use this agent in CTCL [38]. Preliminary results of 25 patients show that lenalidomide has clinical activity in patients with advanced CTCL with a toxicity profile similar to that previously reported. The first fifteen patients received 25 mg lenalidomide daily for 21 days of a 28-day cycle that was adjusted to an initial dose of 10 mg with dose escalation up to 25 mg. Seven patients have achieved a PR. Responding patients received a median of nine cycles of therapy; median time to best response was 6 months. Four of the responding patients developed new skin lesions. Eight patients had stable disease (SD) ≥ 4 months. A regrowth of disease-related hair loss was observed in some patients. The most common side effects were anemia, fatigue/malaise, skin burning, pruritus, diarrhea, and lower leg edema.

The mechanism of the observed antitumor effects remains unclear. An initial flare reaction manifested by a temporary increase in the size, number, and discomfort of skin lesions and/or tender swelling of lymph nodes and/or increase in Sézary cell count was noted in some patients during the first cycle of treatment and/or each cycle for the remainder of therapy with subsequent improvement of symptoms and/or disease. The cause of this phenomenon has not been studied in CTCL and could be related to the co-stimulatory or cytotoxic activity of lenalidomide and represent an immune response against the disease with enhanced $CD8^+$ T-cell and NK-cell cytotoxic activity, but may, in fact, represent a combination of cytotoxic and cytokine-mediated events. One could suggest that the flare reaction could actually predict the subsequent antitumor response in CTCL patients. Correlative biologic studies will include analysis of antiangiogenic and immunomodulatory activity on skin biopsies and peripheral blood samples.

Twenty-four patients with relapsed and refractory T-cell lymphomas other than MF were treated in a phase II trial with lenalidomide 25 mg daily on days 1 to 21 of each 28-day cycle with standardized dose reductions for toxicity [39]. Twenty-three patients were eligible for response with seven patients (30%) achieving PR. Responses were seen in patients with anaplastic large cell lymphoma (ALCL), angioimmunoblastic lymphoma, and PTCL, unspecified. Two patients had SD for ≥3 cycles. Median overall survival (OS) was 8 months. The most common grade 3 and 4 toxicities were thrombocytopenia, neutropenia, neutropenic fever, and pain. Although moderate responses are seen in patients with T-cell NHL, lenalidomide holds considerable promise for both combination and maintenance treatment given its oral availability.

Enzastaurin

Enzastaurin (LY317615), an acyclic bisindolylmaleimide, is a novel orally available protein kinase C (PKC) inhibitor. Tumor-induced angiogenesis requires the activation of PKC-β, a key modulator of the VEGF signaling pathway, and enzastaurin was originally evaluated in human tumor xenograft mice models for its antiangiogenic activity upon PKC-β inhibition [40]. However, in addition to its antiangiogenic effects,

enzastaurin, at concentrations reached in clinical trials, directly suppressed proliferation and induced apoptosis of tumor cells in culture and in human colon and glioblastoma xenografts through the inhibition of the PI3Kinase/AKT/glycogen synthase kinase-3 signaling pathway [41].

PKC consists of a family of at least 12 serine-threonine protein kinases, which are divided into the classical (α, βI, βII, γ), novel (δ, ε, η, θ), and atypical (ζ, λ/ι) subtypes based on their second messenger requirements [42]. PKC-μ/PKD and PKC-ν were recently added to the PKC superfamily based on homology within the catalytic domain [43].

PKC isoenzymes exhibit distinct tissue distribution and play a distinct role in various cellular events including cell survival, growth factor response, proliferation and tumorigenesis in solid tumors, and several hematologic malignancies. PKC-β is the major PKC isoform involved in B-cell receptor signaling. Specifically, PKC-β mediates growth and survival of diffuse large B-cell lymphoma (DLBCL), cell proliferation in CLL, as well as migration and cell growth in multiple myeloma and Waldenström macroglobulinemia [44–48]. Overexpression in treatment-refractory DLBCL is associated with shortened survival [45]. In contrast, enzastaurin had no effect on normal mononuclear cells or hematopoietic progenitor cells suggesting a favorable therapeutic index.

The conventional PKC (α, β , γ, ε, and ζ) isoforms are not necessary for proliferation as previously shown in cloned cell lines derived from the CTCL cell line HuT-78 [49]. Functionally, PKC-β is critical for IL-2 secretion in HuT-78 cells, and for promoting the epidermotropism of CTCL, but its role in T-cell malignancies has not been determined yet [50]. PKC-θ mediates pre-TCR signaling and contributes to Notch3-induced T-cell leukemia [51].

Enzastaurin competes with ATP for the nucleotide triphosphate-binding site of PKC, thereby blocking its activation, but the exact mechanism of action of enzastaurin malignancies is not well defined. It is not completely specific to PKC-β as it inhibits several PKC isoforms. A recent multicenter phase I study evaluated dose escalation and pharmacokinetics of oral enzastaurin in 47 adult patients with advanced cancer [52]. The 525 mg daily dose produced the targeted steady-state concentration of 1.4 μmol/L and was selected as the recommended dose for phase II studies. The most common toxicities were grade 1 chromaturia, fatigue, and gastrointestinal toxicities; no clinically significant grade 3 or 4 toxicities occurred. Three cases of significant QTc prolongation occurred.

Enzastaurin has been administered to more than 620 cancer patients as a single agent or in combination with other antitumor drugs in a variety of hematological and solid tumor malignancies. Enzastaurin has shown clinical activity in relapsed and/or refractory DLBCL, relapsed/refractory MCL and Waldenström macroglobulinemia [44, 45, 48]. Importantly, enzastaurin enhanced in vitro antitumor activity of rituximab, bortezomib, fludarabine, and dexamethasone that supports the therapeutic combination of these agents.

Recently, the significance of enzastaurin activity on two CTCL cell lines HuT-78 and HH was demonstrated [10]. Enzastaurin, at clinically relevant concentrations, caused growth inhibition of CTCL cell lines. Enzastaurin was reported to block AKT activity, affected both caspase-mediated apoptosis and cell cycle regulatory pathways, but may involve other biochemical mechanisms. The promising preclinical activity has prompted the initiation of a multicenter phase II trial in patients with advanced CTCL and enrollment is ongoing.

Apoptosis Antagonists

Defective regulation of apoptosis is a central feature of the pathology of several lymphoma types such as CTCL and ALCL. Apoptosis can be triggered by death receptors that belong to the tumor necrosis factor-receptor (TNF-R) family or by aberrations in expression of the B-cell lymphoma-2 (Bcl-2) family. Six death receptors (DR) are known including Fas (CD95, Apo-1), TRAIL-receptor 1 (DR4), TRAIL-R2 (Apo-2, DR5), TNF-R1, TRAMP (WSL-1, Apo-3, DR3), and

DR6. All contain a death domain protein that bridges the death receptors with downstream caspases. Their activation leads to apoptosis. Fas gene mutations leading to defective Fas/FasL signaling have been shown to result in autoimmune lymphoproliferative syndromes as a consequence of lymphocyte accumulation [53]. There are limited studies describing defects in proteins regulating apoptosis in CTCL, but loss of Fas and/or defects in Fas-mediated and TNF-R1-mediated apoptosis have been described in early and advanced stages of CTCL [8, 54–57].

Cellular caspase-8 (FLICE)-like inhibitory protein (cFLIP) was originally identified as an inhibitor of death-receptor signaling through competition with caspase-8 upon triggering Fas-mediated apoptosis. Resistance to Fas ligand (FasL) and TNF-related apoptosis-inducing ligand (TRAIL)-mediated apoptosis in malignant T-cells from patients with SS was associated with impaired death receptor and overexpression of cFLIP [58]. Overexpression of c-FLIP protects anaplastic lymphoma kinase (ALK)+ ALCL cells from death-receptor-induced apoptosis [59]. The overexpression of TRAIL in CTCL is not clear. TRAIL is a member of the TNF receptor/ligand family and a powerful inducer of apoptosis. It shares homology to other members of the TNF cytokine family, especially to FasL CD95L (FasL/APO-1L). TRAIL is known to effectively induce apoptosis in numerous tumor cell lines but not in the majority of normal cells. Currently, TRAIL-receptor-targeted therapies including the untagged recombinant Apo2L/TRAIL and agonistic antibodies to TRAIL-R1 and TRAIL-R2 are in clinical phase I and II studies in various tumors.

The intrinsic pathway of apoptosis is critically regulated by the Bcl-2 protein family. Few studies have analyzed the expression of the pro- and antiapoptotic Bcl-2 protein family proteins (Bax, Bak, Bcl-2, Bcl-x_L, Bcl-x, Mcl-1) in CTCL [60]. Overexpression of Bcl-2 and its family members confers resistance of lymphomas to various chemotherapies and biological agents. Investigational drugs targeting the antiapoptotic Bcl-2 protein family have preclinical activity as single agents and in combination with other antineoplastic agents. Cotreatment with the Bcl-2/Bcl-xL antagonist ABT-737 and panabinostat decreased resistance and synergistically induced apoptosis of human CTCL cell lines [61]. Clinical trials of several Bcl-2 antagonists (oblimersen sodium, AT-101, gossypol, obatoclax [GX15-070], ABT-737) in various solid and hematologic malignancies are ongoing.

Clinical phase III studies with oblimersen, a Bcl-2 antisense phosphorothioate oligonucleotide in patients with CLL have been completed. Despite modest single-agent activity in relapsed/refractory CLL, oblimersen combined with fludarabine offers responding patients (CR and PR) a significant survival benefit [62, 63]. The best-characterized target is the BH3 domain of the antiapoptotic Bcl-2, Bcl-XL, and Mcl-1 proteins, with several small molecule inhibitors being tested for their potential as enhancers of the cytotoxicty of conventional anti-lymphoma drugs. AT-101, an enantiomer of the natural compound gossypol, is a BH3-mimetic, which has shown promising results in CLL in vitro. Obatoclax (GX15-070) is a pan-BCL-2 inhibitor that has shown efficacy against various hematologic malignancies such as CLL, AML, MDS, and MM in early clinical studies [64]. It has also shown the potential to overcome Mcl-1-mediated resistance to bortezomib [65, 66]. The combination of obatoclax and bortezomib induced complete remission in some heavily pretreated chemo-refractory MCL patients [67]. One of the most common grade 3 adverse effects of these BH3-mimetics is thrombocytopenia due to the induction of apoptosis in platelets [68].

Conclusions

T-cell NHLs represent a spectrum of uncommon and heterogeneous malignancies with a wide range of genomic and cytogenetic aberrations that affect cell growth and regulation of apoptosis. It is important to identify the biology and immunology of these lymphomas to develop new and promising therapeutic targets.

Despite the lack of significant single-agent activity most of the novel therapeutics discussed

hold considerable promise for combination with other agents given their low toxicity profile and/or oral availability.

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