



[haematologica reports]
2006;2(13):42-45

New drugs for peripheral T-cell lymphomas

B.D. CHESON

Georgetown University
Hospital Washington, D.C.,
USA

Over the past few years, considerable progress has been made in the treatment of patients with non-Hodgkin's lymphomas (NHL), primarily those with B-cell malignancies. Unfortunately, however, the outcome of patients with peripheral T-cell lymphomas remains disappointing. Although responses can be achieved with intensive combination chemotherapy regimens, relapse is common and few successful salvage therapies are available. Thus, new active agents are needed to improve the survival of these patients. A number of drugs have been identified with activity in T-cell lymphomas, including nucleoside analogs such as fludarabine, cladribine, pentostatin, and, most recently nelarabine and forodesine;¹⁻⁵ the histone deacetylase inhibitors depsipeptide and SAHA;⁶⁻⁸ novel new antifolates; denileukin diftitox,⁹ alemtuzumab,¹⁰ other monoclonal antibodies, such as those directed against CD30^{11,12} and others. In addition to these agents, a number of other old and new drugs with activity in B-cell lymphoma remain to be tested in this difficult patient population (Table 1).

Bendamustine

Bendamustine is a bifunctional compound that incorporates both a nitrogen mustard and purine analog moieties. The drug was first synthesized in the 1960's and subsequently, clinical activity was observed against a variety of solid tumors and hematologic malignancies. Several studies from East Germany and, more recently, the United States have demonstrated relatively consistent response rates of 70-80% in patients with CLL as well as follicular and low grade NHL, and 40% in relapsed and refractory aggressive NHL.¹³⁻²⁰ The combination of bendamustine with rituximab has resulted

in an overall response rate of 90% with 60% complete remissions in a variety of histologies of B-cell lymphomas.¹⁹ The drug is well tolerated with the major toxicities including myelosuppression, nausea and vomiting, and fatigue. There are as yet no data on the use of bendamustine in T-cell lymphomas and this agent is clearly worth pursuing.

Gallium nitrate

Gallium nitrate (Genta, Inc., Berkeley Heights, NJ, USA) is the nitrate salt of the *near metal* group IIIa element, gallium. This group of elements has preclinical antitumor activity and thus, was entered into the NCI anti-tumor screen where preclinical activity was identified. Responses in patients with a variety of tumors were observed in phase I trials, and further phase II testing identified meaningful activity in lymphomas as a single agent and in combinations with a variety of other drugs.²¹⁻²³ An unexpected benefit in those studies was the observation that gallium was a potent agent in the treatment of tumor-associated hypercalcemia, leading to its approval by the FDA for that indication. Moreover, its lack of myelosuppression made gallium an attractive agent to combine with other drugs. Unfortunately, optic neuritis, albeit generally reversible, has tempered enthusiasm for this agent. Nevertheless, since anecdotal reports suggest that gallium has activity against T-cell lymphomas,²⁴ further studies should be considered.

Bortezomib

Bortezomib (Millennium, Boston, MA, USA), the first proteasome inhibitor to enter clinical trials, was initially approved by the U.S. Food and Drug Administration for the treatment

Table 1. Potential new targeted therapies for PTCL.

Class	Representative Agents
HDAC inhibitors	SAHA, depsipeptide
Proteasome inhibitors	Bortezomib
Apoptosis targeting agents	Oblimersen, GX15070, AT-101, APO2L/TRAIL, ABT-737, anti-TRAIL
IMiDs	Thalidomide, lenalidomide
mTOR inhibitors	Temsirolimus
Monoclonal antibodies	Alemtuzumab, SGN-30
immunotoxins	Denileukin difitox

of relapsed and refractory multiple myeloma.²⁵ Subsequent studies in patients with a variety of histologies of non-Hodgkin's lymphoma showed variable results. Perhaps the most promising data have been in patients with relapsed and refractory mantle cell lymphoma where response rates of 30-50% have been reported in single institution and multicenter trials.²⁶⁻²⁸ Activity has also been reported in follicular NHL; however, few responses have been observed in diffuse large B-cell lymphoma or small lymphocytic lymphoma, and the drug appears to be inactive in Hodgkin's lymphoma.²⁹ Clinical trials are currently exploring the activity of bortezomib in patients with peripheral T-cell NHL.

mTOR inhibitors

Temsirolimus (CCI-779), an analog of rapamycin (sirolimus, Rapamune®, Wyeth-Ayerst, Princeton, NJ, USA), is another agent of interest in lymphoma. Rapamycin is a potent immunosuppressive agent used in stem cell and organ transplantation, and which induces apoptosis of lymphocytes *in vitro*.³⁰ Rapamycin analog (CCI-779, temsirolimus) was selected for testing in clinical trials because of a more favorable toxicity profile. This drug acts through the PI3-K/AKT pathway by inhibiting the mammalian target of rapamycin (mTOR), downregulating translation of specific mRNAs required for cell cycle progression from G1 to S phase.³¹ Preclinically, mTOR inhibitors potently suppress growth and proliferation of lymphocytes and tumor cell lines. Temsirolimus has been shown to induce a response rate of about 38%, in patients with relapsed and refractory mantle cell lymphoma, but with considerable myelotoxicity at the originally studied dose of 250 mg a week.³² Ongoing trials are being conducted in patients with relapsed or refractory mantle cell lymphoma. In a recently reported trial using 25 mg, the response rates were comparable to the higher dose.³³ A multicenter study

is currently seeking to identify more tolerable doses by comparing 175 mg weekly for 3 weeks followed by either 25 mg or 75 mg weekly for up to 2 years, with a third study arm of physician's choice.

Proapoptotic agents

One of the most interesting classes of new drugs includes the small molecules that influence the apoptotic pathways. The intrinsic pathway of apoptosis is mitochondrial based and reflects balances among bcl-2 and other family members, such as BAX, while the extrinsic pathway is activated through the death receptor domains.³⁴ Bcl-2 is an anti-apoptotic protein critical to the intrinsic pathway of apoptosis. This gene is overexpressed in a number of tumors, notably NHL. An important feature of overexpression of bcl-2 and other family members, including Bcl-XL is that they confer resistance to a wide variety of chemotherapy and biological agents.

The most widely studied of the proapoptotic agents has been oblimersen sodium (Genasense, Genta, Inc., Berkeley Heights, NJ, USA). This 16-MER is directed at the open reading frame of bcl-2 mRNA. The agent induces apoptosis of CLL and lymphoma cells *in vitro* and demonstrates synergistic activity with drugs such as fludarabine, cyclophosphamide, and rituximab. Modest activity has been demonstrated in phase I and II trials in patients with CLL, including the development of tumor lysis syndrome.³⁵ However, the greatest promise of this drug will be in combination with other agents. In a randomized phase III trial in patients with malignant melanoma, oblimersen plus dacarbazine was associated with greater clinical benefit than dacarbazine alone.³⁶ In a recent study in which patients with relapsed or refractory CLL were treated with cyclophosphamide and fludarabine with or without oblimersen, the major response rate and duration of response were superior in the oblimersen arm with only a modest increase in adverse events, particularly thrombocytopenia.³⁵ Activity as a single agent and in combination with chemotherapy has been reported in patients with mantle cell lymphoma.³⁷ Future studies should explore this agent in patients with T-cell malignancies.

Gossypium is a genus of approximately 40 species of shrubs belonging to the *Malvaceae* family of plants. Several of these species have been used in the textile industry to produce cotton fibers. Extracts from the seeds of *Gossypium sp.* have been used for centuries for their purported medicinal value, such as in the treatment of male

infertility. Gossypol is a racemic mixture of two stereochemical isomers. Preclinical studies subsequently demonstrated activity against a variety of human tumors. However, early clinical trials with an oral preparation were associated with minimal activity. Nevertheless, further study identified that R-(-)-gossypol had the greater antitumor activity, functioning like a BH3 only binding molecule, inhibiting the effects of Bcl-2 and Bcl-XL. This isomer came to be known as AT-101 (R-(-) 2, 2'-bis (1, 6, 7-trihydroxy-3-methyl-5-isopropyl-8-aldehydo-naphthalene) acetic acid) (Ascenta Therapeutics, San Diego, CA, USA). Following demonstration of activity against lymphoma cell lines, this isomer has now entered clinical trials. Of interest is the apparent synergy with other agents including cyclophosphamide and rituximab. A phase I study of AT-101 in treatment naïve CLL is ongoing;³⁸ the drug has not been associated with any dose-limiting toxicities to date but has shown evidence of clinical activity. Combinations with other agents are in development.

GX15-070 (Gemin X Biotechnologies, Inc., Montreal, Canada) is a synthetic small molecule pan-Bcl-2 family inhibitor, capable of inducing apoptosis in a variety of preclinical models. It has demonstrated a broad spectrum of cytotoxicity in cell lines *in vitro* and *in vivo*. In a recent phase I trial in patients with relapsed or refractory CLL, there was a suggestion of activity with a partial response in one patient, and hematologic improvement in several others.³⁹ A correlation between dose and induction of apoptosis was demonstrated. Future studies are aimed at optimizing the dose and schedule.

Anti-TRAIL (Tumor necrosis related apoptosis inducing ligand) (Genentech Biooncology, San Francisco, CA, USA) is a member of the TNF gene superfamily and is able to induce apoptosis through activation of two cell surface death receptors, DR4 and DR5. This apoptosis is independent of p53.⁴⁰ It also cooperates with chemotherapy, radiation therapy, and rituximab in animal models. It is well tolerated in primate models and, therefore, is now entering clinical trials in NHL.

Immunomodulatory agents

Thalidomide and lenalidomide (revlimid) (Celgene Corporation, Summit, NJ, USA) are the two most widely studied of this class of drugs. Thalidomide has impressive activity in patients with multiple myeloma. However, in a recent study conducted by the Cancer and Leukemia

Group B (CALGB) in patients with relapsed and refractory, follicular and low-grade B-NHL, limited activity was noted with a response rate of 8%.⁴¹ In contrast, a response rate of 60% has been reported in patients with CLL who received revlimid.⁴² Further study in patients with other histologies, including T-NHL is warranted.

Conclusions

The peripheral T-NHL remain a therapeutic challenge and new approaches are urgently needed. Other than patients with CD30+ anaplastic large cell NHL, various combinations of conventional agents have not improved on survival. Thus, there are several areas of drug development that require attention. First, since patients usually relapse after initial induction chemotherapy, new agents must be studied in previously treated patients. However, the lack of single agent activity should not deter further exploration if there is sufficient preclinical rationale to suggest the possibility of enhanced activity in combinations with other agents. However, the more important goal is how best to incorporate new and active agents into front-line regimens. What is of critical importance is the need for further study of the biology and immunology of this diverse group of lymphomas. The development of novel regimens based on scientific rationale is the approach most likely to lead to improved survival of patients with T-NHL.

References

1. Mercieca J, Matutes E, Dearden C, et al. The role of pentostatin in the treatment of T-cell malignancies: analysis of response rate in 145 patients according to disease subtype. *J Clin Oncol* 1994;12:2588-1593.
2. Kong LR, Samuelson E, Rosen ST, et al. 2-chlorodeoxyadenosine in cutaneous T-cell lymphoproliferative disorders. *Leuk Lymphoma* 1997;26:89-97.
3. Kuzel TM, Hurria A, Samuelson E, et al. Phase II trial of 2-chlorodeoxyadenosine for the treatment of cutaneous T-cell lymphoma. *Blood* 1996;87:906-11.
4. Gandhi V, Kilpatrick JM, Plunkett W, et al. A proof-of-principle pharmacokinetic, pharmacodynamic, and clinical study with purine nucleoside phosphorylase inhibitor immucillin-H (BCX-1777, forodesine). *Blood* 2005;106:4253-60.
5. Berg SL, Ernst TJ, Keating MJ, et al. Phase II study of nelarabine (compound 506U78) in children and young adults with refractory T-cell malignancies: a report from the Children's Oncology Group. *J Clin Oncol* 2005;23:3376-82.
6. Piekarczyk RL, Robey R, Sandor V, et al. Inhibitor of histone deacetylation, depsipeptide (FR901228), in the treatment of peripheral and cutaneous T-cell lymphoma: a case report. *Blood* 2001;98:2865-8.
7. Heaney M, O'Connor OA, Richon V, et al. Clinical experience with the histone deacetylase (HDAC) inhibitor suberoylanilide hydroxamic acid (SAHA) in heavily pretreated patients with hematological malignancies. *Proc ASCO* 2003;22:577 (abstr 2321).
8. Olsen E, Kim YH, Kuzel T, et al. Vorinostat (suberoylanilide

- hydroxamic acid, SAHA) is clinically active in advanced cutaneous T-cell lymphomas (CTCL): results of a phase IIb trial. *J Clin Oncol* 2006;24:422s (abstr 7500).
9. Talpur R, Apisarnthanarax N, Ward S, et al. Treatment of refractory peripheral T-cell lymphoma with denileukin diftitox (ONTAK). *Leuk Lymphoma* 2002;43:121-6.
 10. Enblad G, Hagberg H, Erlanson M, et al. A pilot study of alemtuzumab (anti-CD52 monoclonal antibody) therapy for patients with relapsed or chemotherapy-refractory peripheral T-cell lymphomas. *Blood* 2004;103:2920-4.
 11. Ansell S, Byrd J, Horwitz S, et al. Phase I/II study of a fully human anti-CD30 monoclonal antibody (MDX-060) in Hodgkin's disease (HD) and anaplastic large cell lymphoma (ALCL). *Blood* 2003;102:181a (abstr #632).
 12. Bartlett NL, Bernstein SH, Leonard JP, et al. Safety, antitumor activity and pharmacokinetics of six weekly doses of SGN-30 (anti-CD30 monoclonal antibody) in patients with refractory or recurrent CD30+ hematologic malignancies. *Blood* 2003;102:647a (abstr #2390).
 13. Schwänen C, Karakas T, Begmann L. Bendamustine in the treatment of low-grade non-Hodgkin's lymphomas. *Onkologie* 2000;23:318-24.
 14. Kath R, Blumenstengel K, Fricke HJ, et al. Bendamustine monotherapy in advanced and refractory chronic lymphocytic leukemia. *J Cancer Res Clin Oncol* 2001;127:48-54.
 15. Rummel MJ, Mitrou PS, Hoelzer D. Bendamustine in the treatment of non-Hodgkin's lymphoma: results and future perspectives. *Sem Oncol* 2002;29:27-32.
 16. Rummel MJ, Kim SZ, Chow KU, et al. Bendamustine and rituximab act synergistically in vitro and are effective in the treatment of relapsed or refractory indolent and mantle cell lymphomas. *Blood* 2003;102:104a (abstr 353).
 17. Bremer K. High rates of long-lasting remissions after 5-day bendamustine chemotherapy cycles in pre-treated low-grade non-Hodgkin's lymphomas. *J Cancer Res Clin Oncol* 2002;128:603-9.
 18. Weidmann E, Kim SZ, Rost A, et al. Bendamustine is effective in relapsed or refractory aggressive non-Hodgkin's lymphoma. *Ann Oncol* 2002;13:1285-9.
 19. Rummel MJ, Al-Batran S, Kim SZ, et al. Bendamustine plus rituximab is effective and has a favorable toxicity profile in the treatment of mantle cell and low-grade non-Hodgkin's lymphoma. *J Clin Oncol* 2005;23:3383-9.
 20. Friedberg JW, Cohen P, Cheson BD, et al. Bendamustine HCL (TREANDA) treatment results in high rates of objective response in patients with rituximab-refractory and alkylator-refractory indolent B-cell non-Hodgkin's lymphoma (NHL): Results from a phase II multicenter single-agent study. *Blood* 2005;106:70a (abstr 229).
 21. Warrell RP, Jr., Coonley CJ, Straus DJ, et al. Treatment of patients with advanced malignant lymphoma using gallium nitrate administration as a seven-day continuous infusion. *Cancer* 1983;51:1982-7.
 22. Keller J, Bartolucci A, Carpenter JT, Jr., et al. Phase II evaluation of bolus gallium nitrate in lymphoproliferative disorders: A Southeastern Cancer Study Group trial. *Cancer Treat Rep* 1986;70:1221-3.
 23. Weick JK, Stephens RL, Baker LH, et al. Gallium nitrate in malignant lymphoma: A Southwest Oncology Group study. *Cancer Treat Rep* 1983;7:823-5.
 24. Huang Z, Higgins B, Foss F. Activity of gallium nitrate in refractory T-cell lymphoma. *Clin Lymphoma* 2005;6:43-5.
 25. Richardson PG, Sonneveld P, Schuster MW, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. *New Engl J Med* 2005;352:2487-98.
 26. O'Connor OA, Wright J, Moskowitz C, et al. Phase II clinical experience with the novel proteasome inhibitor bortezomib in patients with indolent non-Hodgkin's lymphoma and mantle cell lymphoma. *J Clin Oncol* 2005;23:676-84.
 27. Goy A, Younes A, McLaughlin P, et al. Phase II study of proteasome inhibitor bortezomib in relapsed or refractory B-cell non-Hodgkin's lymphoma. *J Clin Oncol* 2005;23:667-75.
 28. Goy A, Bernstein SH, Kahl BS, et al. Bortezomib in relapsed or refractory mantle cell lymphoma (MCL): results of the PINNACLE study. *J Clin Oncol* 24:425s (abstr 7513), 2006.
 29. Blum KA, Johnson JL, Niedzwiecki D, et al. A phase II study of bortezomib in relapsed Hodgkin's lymphoma: preliminary results of CALGB 50206. *J Clin Oncol* 2006;24:440s (abstr 7576).
 30. Muthukkumar S, Ramesh TM, Bondada S. Rapamycin, a potent immunosuppressive drug, causes programmed cell death in B lymphoma cells. *Transplantation* 1995;60:264-70.
 31. Schmelzle T, Hall MN. TOR, a central controller of cell growth. *Cell* 2000;103:253-62.
 32. Witzig T, Geyer S, Ghobrial I, et al. Final results of a phase II trial of single-agent temsirolimus (CCI-779) for relapsed mantle cell lymphoma. *Ann Oncol* 2005;16:19 (abstr 095).
 33. Ansell SM, Geyer SM, Kurtin PJ, et al. Anti-tumor activity of mTOR inhibitor temsirolimus for relapsed mantle cell lymphoma: A phase II trial in the North Central Cancer Treatment Group. *J Clin Oncol* 2006;24:430s (abstr 7532).
 34. Younes A, Kadin ME. Emerging applications of the tumor necrosis factor family of ligands and receptors in cancer therapy. *J Clin Oncol* 2003;21:3526-34.
 35. O'Brien SM, Cunningham CC, BGolenkov AK, et al. Phase I to II multicenter study of oblimersen sodium, a Bcl-2 antisense oligonucleotide, in patients with advanced chronic lymphocytic leukemia. *J Clin Oncol* 2005;23:7697-702.
 36. Kirkwood JM, Bedikian AY, Millward MJ, et al. Long-term survival results of a randomized multinational phase 3 trial of dacarbazine (DTIC) with or without Bcl-2 antisense (oblimersen sodium) in patients (pts) with advanced malignant melanoma (MM). *J Clin Oncol* 2005;23:711s (abstr 7506).
 37. Leonard J, Hainsworth J, Bernstein S, et al. Genasense (Oblimersen sodium, G3139) is active and well-tolerated both alone and with R-CHOP in mantle cell lymphoma. *Blood* 2003;102:abstr 490.
 38. James DF, Castro JE, Loria O, et al. AT-101, a small molecule Bcl-2 antagonist, in treatment naive CLL patients (pts) with high risk features: Preliminary results from an ongoing phase I trial. *J Clin Oncol* 2006;24:362s (abstr 6605).
 39. O'Brien S, Kipps T, Faderl S, et al. A phase I trial of the small molecule pan-Bcl-2 family inhibitor GX15-070 administered intravenously (IV) every 3 233ks to patients with previously treated chronic lymphocytic leukemia (CLL). *Blood* in press, 2005.
 40. Kelley SK, Ashkenazi A. Targeting death receptors in cancer with APO2L/TRAIL. *Curr Opin Pharmacol* 2004; 4:333-9.
 41. Grinblatt DL, Johnson J, Niedzwiecki D, et al. Phase II study of thalidomide in escalating doses for follicular (F-NHL) and small lymphocytic lymphoma (SLL). *Blood* 2004;104: 897-898a.
 42. Chanan-Khan AA, Miller KC, Dimiceli L, et al. Results of a phase II study of lenalidomide (L) (Revlimid) in patients with relapsed or refractory chronic lymphocytic leukemia (CLL). *Blood* 2005;106:abstr 448.