Published in final edited form as:

Hematology Am Soc Hematol Educ Program. 2010 ; 2010: 265–270. doi:10.1182/asheducation-2010.1.265.

Signal Transduction Inhibitor Therapy for Lymphoma

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Abstract

Current research in lymphoma is focused on two areas of lymphoma biology—the signal transduction pathways used to maintain the growth of malignant lymphocytes and the role of the tumor microenvironment in lymphoma growth and survival. This review focuses on three signaling pathways: the phosphatidylinositol 3-kinase/mammalian target of rapamycin (PI3K/mTOR) pathway, the B-cell receptor/spleen tyrosine kinase (BCR/Syk) pathway, and the protein kinase C-beta (PKC- β) pathway, known to be important to lymphoma cells. The mTOR inhibitors temsirolimus and everolimus have demonstrated antitumor activity in all types of lymphoma, the Syk inhibitor fostamatinib has activity in diffuse large B-cell lymphoma and chronic lymphocytic leukemia, and the PKC- β inhibitor enzastaurin is being used as consolidation therapy after remission in diffuse large B-cell lymphoma. This review discusses the biology behind the development of each new agent and the results of initial clinical trials. The goal is to provide the hematologist/oncologist background information on these new agents and understand their current and potential role in the management of patients.

Introduction

Chemotherapy has been the mainstay for the treatment of non-Hodgkin's lymphoma (NHL) since the development of nitrogen mustard in the 1940s. In 1999, the approval of rituximab launched the era of immunotherapy with monoclonal antibodies. In 2002, the first radioimmunotherapy was approved. Rituximab and radioimmunotherapy revolutionized the treatment of B-cell NHL, and are now in common use for all phases of NHL. They have improved the response rates and overall survival of these diseases through single-agent activity, in combination with chemotherapy, and through their use as consolidation and maintenance therapies after initial treatment. The treatment of NHL has now reached a new plateau and there remains ample room for improvement. Recent research in lymphoma has focused on two areas of lymphoma biology—the signal transduction pathways used to maintain the growth of NHL and the role of the tumor microenvironment in lymphoma growth and survival. This review will focus on three signaling pathways known to be important to lymphoma. We review the biology behind the development of each new agent and the results of initial clinical trials. The goal is to provide the hematologist/oncologist with background information on these new agents and an understanding of their current and potential roles in the management of patients.

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Disclosures

Conflict-of-interest disclosure: TEW has been an uncompensated advisory committee member for Novartis and Celgene (with compensation to the Mayo Clinic) and has from both entities received research funding and patent royalties. Off-label drug use: Temsirolimus and everolimus are both FDA approved for renal cell cancer in the United States but are not approved currently for mantle cell lymphoma. Revlimid is approved for myeloma but not lymphoma.

Mammalian Target of Rapamycin Inhibitors

The phosphatidylinositol 3-kinase (PI3K)/acutely transforming retrovirus (Akt)/mammalian target of rapamycin (mTOR) signal pathway is used by malignant cells to promote growth and survival.¹⁻³ The PI3K pathway has been demonstrated to be constitutively activated in the majority of B-cell lymphomas, as manifested by phosphorylation of S6K and 4E-BP1.⁴⁻⁶ The mTOR kinase, a key member of the pathway, is now known to exist in two different complexes referred to as mTORC1 and mTORC2.⁷ Both complexes contain the catalytic subunit mTOR. mTORC1 components are Raptor (regulatory-associated protein of mTOR) and mLST8 (mammalian lethal with Sec13 protein 8). mTORC1 positively regulates cell growth and proliferation and has been characterized as rapamycin sensitive. mTORC2 includes Rictor (rapamycin-insensitive companion of mTOR) and mSIN1 (mammalian stress-activated protein kinase interacting protein) and is the rapamycin-insensitive part of the pathway serving to regulate Akt signaling. Unraveling the relative importance of mTORC1 and mTORC2 in cancer cells is not only interesting but has relevance for drug development using mTOR-targeted agents.

The first agent to be used clinically, and therefore is considered the parent drug of the class of mTOR inhibitors, is rapamycin (sirolimus).⁸ Rapamycin is a macrolide antibiotic and was approved as an oral immunosuppressant to prevent acute rejection in 1999.^{9,10} It binds to the immunophilin FK506-binding protein 12 (FKBP12), with the resulting complex directly inhibiting mTOR. This inactivation of mTOR results in G1 cell-cycle arrest or apoptosis. Rapamycin is available orally and is approved by the Food and Drug Administration (FDA) for the prevention of renal transplant rejection. It is now known that rapamycin targets mTORC1. Two rapamycin analogs, temsirolimus and everolimus, have been extensively tested and are now approved by the FDA for renal cell carcinoma.^{11,12} Rapamycin and temsirolimus have demonstrated antitumor activity in vitro against a variety of lymphoma cell lines and primary samples from patients.^{4,6} mTORC1 inhibitors are primarily antiproliferative and cannot be considered cytotoxic agents for lymphoma.⁶ The cell-cycle protein cyclin D1 is downstream of mTORC1, and the overexpression of cyclin D1 as a hallmark of mantle-cell NHL (MCL) provided the rationale to first test mTORC1 inhibitors in this type of NHL. In a sense, limiting the trial to MCL ensured that all patients selected for the trial overexpressed a member of the targeted signaling pathway. In the first trial for patients with relapsed MCL, single-agent temsirolimus was delivered intravenously every week at a dose of 250 mg to 34 patients, and the overall response rate (ORR) was 38% (13/34).¹³ The patients in this trial were elderly (mean age, 70 years), advanced stage (91% stage 4), heavily pretreated (median of three and a range of one to 11 prior therapies), and 54% were refractory to the last treatment. All but one of the responses was a partial response, and the median time to progression in all patients was 6.5 months; the duration of response for the 13 responders was 6.9 months (95% confidence interval [CI] 5.2–12.4 months). The primary toxicity was myelosuppression, with 71% (25/35) having grade 3 and 11% (4/35) having grade 4 toxicity. The most significant myelosuppression was thrombocytopenia that typically was of short duration.¹³ Due to the thrombocytopenia, the study was repeated with additional patients receiving a lower dose of 25 mg temsirolimus intravenously every week. Despite this substantially lower dose (10% of the previous study), the ORR was maintained at 41% (11 of 27 patients) with a lower incidence of thrombocytopenia. Again, nearly all (10 of 11) of the 11 responses were partial responses. The median time to progression in all patients was 6 months, and the mean duration of response of the 11 responders was 6 months. The dose of 25 mg weekly was recommended for additional studies.

The substantial response rate in MCL in these two initial studies led to a randomized phase III study reported by Hess et al.¹⁴ This trial enrolled 162 patients with relapsed or refractory

MCL. Patients were randomized to receive one of two temsirolimus regimens: 175 mg weekly for 3 weeks (loading), followed by either 75 mg (175/75 mg) or 25 mg (175/25 mg) weekly or the investigators' choice of therapy from a menu of approved single agents. This study found an ORR of 22% with temsirolimus compared with 2% with the investigators' choice of single agents. Patients in the investigators' choice group received agents such as gemcitabine, fludarabine, and a variety of other single agents. The median progression-free survival, which was the end point in this study, was longer in the temsirolimus-treated groups. The median progression-free survival time was 4.8, 3.4, and 1.9 months for the temsirolimus 175/75, 175/25, and investigators' choice groups, respectively. Those with the higher dose of temsirolimus had a longer progression-free survival than those treated with the investigators' choice therapy. This study found a lower response rate than the other two temsirolimus studies; however, it demonstrates the need for novel agents, as demonstrated by the dismal response with ordinary chemotherapy in the investigators' choice group.

The North Central Cancer Treatment Group (NCCTG) has completed a trial (N038H) of temsirolimus 25 mg weekly in combination with rituximab that has been reported in abstract form.¹⁵ The goal of the trial was to enroll patients with either rituximab-sensitive or rituximab-refractory MCL to learn whether combining rituximab and temsirolimus could improve the response rate over temsirolimus alone. Seventy-one patients with a median age of 67 years were enrolled. The ORR was 48% (34 of 71), with 20% (14 of 71) complete responses, and 28% (20 of 71) partial responses. The median duration of response was 9.5 months. The median duration of response in the rituximab-sensitive patients was 9.5 months, whereas it was 7.2 months in the rituximab-refractory patients. This study substantiates the activity of temsirolimus-based therapy and reports some of the highest ORRs and durations of response observed with mTOR inhibitors. In summary, temsirolimus has modest single-agent activity in relapsed MCL and is a new therapeutic choice for these patients. The myelosuppression can be problematic, especially in heavily pretreated patients, but is typically manageable with dose reduction or increased dosing intervals. These four studies have laid the foundation for using temsirolimus earlier in the treatment course for patients with MCL. The NCCTG is currently performing a trial (N078D) for new, untreated MCL patients that combines temsirolimus with rituximab and cladribine for patients who are not transplant eligible. This trial is in phase I and is accruing patients.

The other mTORC1 inhibitor that has undergone extensive testing in lymphoma is everolimus. Treatment of MCL lines with everolimus inhibits phosphorylation of mTOR substrates and induces G1 arrest at nanomolar concentrations.¹⁶ Everolimus can also sensitize MCL cell lines to a variety of cytotoxic agents, including doxorubicin and bortezomib. Similar results have been observed in diffuse large B-cell lymphoma (DLBCL) cell lines.¹⁷ Hodgkin's lymphoma cell lines also show activation of the PI3K pathway.^{5,18} This preclinical data provided the rationale to perform a phase I trial of everolimus in hematological malignancies testing 5 mg and 10 mg given orally every day.¹⁹ This trial enrolled 27, patients including four with relapsed NHL (all MCL). There were no responses in the MCL patients, and 10 mg everolimus daily was recommended for further study.

A large phase II study of single-agent everolimus enrolled patients with a variety of types of lymphoma. All patients were initiated on everolimus 10 mg/d. Patients were eligible for the trial if they had failed standard therapy, had measurable disease, a platelet count of $75,000 \times 10^6/L$ or above, an absolute neutrophil count of $1000 \times 10^6/L$ or above, and a performance status of 2 or under. This study has confirmed the safety of the 10 mg dose, which also demonstrated substantial antitumor activity.²⁰⁻²² Johnston et al.²⁰ reported an ORR of 47% (95% CI 24%–71%) in patients with relapsed Hodgkin's lymphoma. In this study, the patients were young (median 37 years; range, 27–68 years), heavily pretreated (median six prior therapies; range, three to 14), and 84% had undergone prior autologous stem cell

transplant. Patients received a median of seven cycles of everolimus therapy; eight patients achieved a partial response and one a complete response. The median time to progression was 7.2 months. Four responders remained progression free at 12 months. This exciting result in relapsed Hodgkin's lymphoma needs confirmation in a larger study. It appears to offer a new area of therapeutic options for this group of patients.

Zent et al.²¹ treated 22 patients with chronic lymphocytic leukemia/ small lymphocytic lymphoma (CLL/SLL) with everolimus and demonstrated an 18% (4 of 19) ORR (all partial responses). An intriguing finding in this study was the observation of an increase in absolute lymphocyte count in the blood, which was associated with a decrease in lymphadenopathy in eight (36%) patients. Absolute lymphocyte count increased a median of 4.8-fold (range, 1.9–25.1-fold), concomitant with the clinically measurable lymphadenopathy decreasing a median of 75.5% (range, 38%–93%) compared with pretreatment measurements. This observation may have clinical application. For example, malignant cells in circulation are generally more sensitive to antibody therapy than those in the tumor compartment or those bound to stroma. The Mayo Clinic CLL/SLL group has initiated a study of everolimus combined with Campath anti-CD52 monoclonal antibody for patients with bulky adenopathy.

Everolimus has also been studied in patients with relapsed Waldenstrom's macroglobulinemia.²² Eligible patients had measurable disease as defined by immunoglobulin M monoclonal protein of 1000 mg/dL or above with 10% or more marrow involvement or nodal masses of 2 cm or above. Fifty patients were enrolled, and the ORR was 42% (all partial responses). An additional 28% had a minor response, for a total ORR of 70%. The median duration of response and median progression-free survival have not been reached; however, the estimated progression-free survival at 6 and 12 months is 75% (95% CI 64%–89%) and 62% (95% CI 48%–80%), respectively. The primary toxicity was hematologic with dose reductions in 52% of patients. Pulmonary toxicity occurred in 10% of patients.

mTORC1 inhibitors also have activity in relapsed, aggressive NHL.²³ As reported in that abstract, 47 patients with relapsed DLBCL were treated with single-agent everolimus with an ORR of 30% (95% CI 17%–45%); 19 patients with MCL had an ORR of 32% (95% CI 13%–57%), 16 patients with follicular NHL had an ORR of 50% (95% CI 25%–75%), and the ORR in eight patients with relapsed T-cell NHL was 63% (95% CI 24%–91%). Smith et al.²⁴ have reported that intravenous temsirolimus 25 mg weekly had an ORR of 35% (26 of 74) in patients with relapsed non-MCL-type NHL.

The primary side effects of mTOR inhibitors are myelosuppression (particularly thrombocytopenia), mouth ulcers, rash, fatigue, and, uncommonly, interstitial lung disease. These side effects are generally manageable, but often result in dose reductions to maintain the patient on treatment. These dose reductions can result in reduced antitumor activity. The pulmonary toxicity has been observed with both temsirolimus and everolimus and is considered to be a side effect of this class of agents. Infection or tumor invasion of the lung must also be considered in the differential diagnosis. It is usually manifest by "ground glass" bilateral lung infiltrates that are often initially asymptomatic and detected only on computed tomography scans being done to monitor the lymphoma. If they are symptomatic, then the mTOR inhibitor is stopped. A short course of corticosteroids is sometimes necessary. Once the toxicity has cleared, the drug can often be restarted at a lower dose without recurrence of the toxicity.

The mTOR inhibitors temsirolimus and everolimus clearly have single-agent activity in NHL, CLL/SLL, Hodgkin's lymphoma, and Waldenstrom's macroglobulinemia. The

activity is modest and the drugs are generally well tolerated. These agents are now being tested in larger single-agent studies as consolidation after induction therapy for DLBCL, as treatment for new untreated Waldenstrom's macroglobulinemia, relapsed Hodgkin's lymphoma, and in combination with chemoimmunotherapy for untreated MCL. One mechanism of resistance to mTORC1 inhibitors is that mTORC2 is unaffected. This results in reflex up-regulation of the mTORC2 target Akt.⁶ Strategies to block this up-regulation with histone deacetylase inhibitors or with novel agents that simultaneously block mTORC1 and mTORC2 are in progress.

In addition to mTOR, there are other relevant targets in the PI3K pathway that have relevance to lymphoma biology and treatment. CAL-101 (Calistoga Pharmaceuticals, Seattle, WA, USA) is an inhibitor of PI3K p110 δ that is being tested in hematologic malignancies. The rationale for targeting p110 δ is that it is expressed in over 90% of lymphoma cell lines and in many primary lymphoma samples, resulting in constitutive Akt phosphorylation.²⁵ Flinn et al.²⁶ reported on 43 patients treated in a phase I trial using CAL-101 and found an ORR of 56% (10 of 18) with reasonable toxicity.

Akt is an important kinase downstream of PI3K. Perifosine is an oral alkylphospholipid (Keryx Biopharmaceuticals, New York, NY, USA) that targets Akt.^{27,28} The agent has been tested in Waldenstrom's macroglobulinemia at a dose of 150 mg/d and demonstrated an ORR of 25% (11% partial response; 24% minor response), with mild to moderate gastrointestinal toxicity being the main side effect. It will be interesting to learn the full reports of these trials of CAL-101, perifosine, and other new agents undergoing study that are focused on similar targets.

Inhibitors of the B-Cell Receptor Signaling Pathway

B-cell receptor (BCR) cross-linking leads to activation of protein tyrosine kinases: the SRC family kinases Lyn, the spleen tyrosine kinase (Syk), and the TEC family kinase Bruton's tyrosine kinase (BTK). The recognition of antigen by the BCR results in B-cell proliferation and differentiation into antibody-secreting plasma cells. BCR signaling has been shown to be important for the growth of B-cell NHL.²⁹ Recent investigations have focused on developing inhibitors to the Syk and BTK components of the signaling pathway. It was noted that Syk activation functions to amplify the BCR signal and connects the BCR with important major pathways such as PI3K/Akt.³⁰ Syk activation is countered or balanced by inactivation by protein tyrosine phosphatases such as PTP receptor-type O truncated (PTPROt).³¹ In vitro studies have demonstrated that overexpression of PTP induces apoptosis and inhibits DLBCL cell proliferation.

The BCR signal can be generated by a BCR ligand or, in the case of NHL, the signal can be chronically "on." This situation has been referred to as "tonic signaling."³² This tonic signaling is a characteristic of DLBCL, and there are now extensive efforts being made to target the molecules in this signaling cascade for therapeutic benefit. Interest in testing Syk inhibitors for B-cell NHL was enhanced by the findings from gene-expression profiling that demonstrated that some DLBCL have overexpression of the BCR, indicating a dependence on this signaling cascade.³³ Tumors also have increased expression of the components of the BCR signaling pathway, including Syk, and siRNA studies inhibiting the receptor have been effective in vitro.²⁹

One of the first and most mature agents in the pipeline to target Syk is the drug fostamatinib.³² Fostamatinib is the pro-drug of R406 and is an oral ATP-competitive Syk inhibitor with demonstrated antitumor activity both in vitro and in vivo. In preclinical studies, R406 inhibited the proliferation and induced apoptosis of DLBCL cell lines that exhibited tonic BCR signaling.³² DLBCL cell lines that expressed high levels of cell-surface

immunoglobulin were especially sensitive to R406. Using patient samples from five patients with DLBCL, three of five overexpressed phospho-Syk. R406 was also found to reduce inflammation in a mouse model and to be orally bioavailable in humans.³⁴

Friedberg et al.³⁵ performed a phase I/II trial of fostamatinib in patients with relapsed or refractory B-cell lymphoid malignancies. The first cohort of six patients received 200 mg twice daily, and seven patients in the second cohort received 250 mg twice daily. The disease types were: DLBCL (n = 3), MCL (n = 3), follicular lymphoma (n = 5), and CLL (n = 2). The dose of 200 mg twice daily was chosen for phase II testing. In phase II, 68 patients were treated: 23 with DLBCL, 21 with follicular lymphoma, and 24 with other lymphomas including 11 with CLL/SLL and 9 with MCL. Adverse events were generally mild and included myelosuppression, fatigue, and gastrointestinal upset (diarrhea). Although neutropenia was frequent, febrile neutropenia was uncommon. Hypertension occurred in 22% of patients, usually within the first month of therapy. This did not seem to correlate with prior history of hypertension. The ORR in relapsed DLBCL was 24% (4 of 17). In 6 additional patients with transformed DLBCL, 1 patient responded; therefore, the ORR for all DLBCL cases was 22% (5 of 23). The median progression-free survival was 2.7 months for the patients with DLBCL. The ORR was only 10% (2 of 21) in the follicular lymphoma group, with a median progression-free survival of 6.4 months. The ORR was 55% (6 of 11) in the patients with CLL/SLL, with a median progression-free survival of 6.4 months; the ORR was 11% (1 of 9) in MCL and 25% (1 of 4) in the other lymphomas.

Although Syk is generally thought to be a component of the BCR signaling pathway, Feldman et al.³⁶ demonstrated that Syk is also overexpressed in peripheral T-cell NHL. He studied 141 patients and found that malignant T cells expressed cytoplasmic Syk in 93% (133 of 141) of cases; normal T-cells in tonsils and nodes were Syk-negative. This research has led to an ongoing trial of fostamatinib in peripheral T-cell NHL.

Another approach to interrupting BCR signaling is with BTK inhibitors. BTK is a component of the BCR signaling pathway and is downstream of Syk. It is expressed in B cells, mast cells, and monocytes, and has an important function in B-cell activation. PCI-32765 (Pharmacyclics, Sunnyvale, CA, USA) is an oral BTK inhibitor that is in phase I for NHL and studies are ongoing.³⁷

In summary, fostamatinib and PCI-32765 are examples of the development of a signal transduction inhibitor based on enhanced understanding of the role of the relevant signaling pathway in NHL. These agents are now being tested in a wide variety of cancers, including B-cell and T-cell NHL, as well as in rheumatological diseases.

Protein Kinase C Beta Inhibitors

Protein kinase C beta (PKC β) is another pivotal enzyme in the B-cell signaling pathway. In lymphocytes, PKC- β I and PKC- β II are the major isoforms of this enzyme, and they are commonly overexpressed by immunohistochemistry in samples of NHL.³⁸ PKC- β overexpression is an adverse prognostic factor in DLBCL as detected by either immunohistochemistry³⁹ or gene-expression profiling.⁴⁰ Another group has recently confirmed these findings, showing that patients with DLBCL and high expression of PKC- β II by immunohistochemistry had a poorer prognosis than those with low expression.⁴¹ In a further confirmation using an R-CHOP-treated patient group, these authors confirmed the same prognostic results with mRNA gene expression profiling.⁴¹ These studies have provided the rationale to develop inhibitors of the PKC- β pathway.

Enzastaurin is an oral serine/threonine inhibitor that suppresses cell signaling through the PKC- β /PI3K/Akt pathways. This results in apoptosis, a reduction of cellular proliferation,

and a suppression of tumor-induced angiogenesis. A phase I study was conducted by Carducci et al.,⁴² and in their results 525 mg daily was the recommended dose for future studies. Robertson et al.⁴³ performed a multicenter, phase II study of enzastaurin in 55 patients with relapsed or refractory DLBCL. Single-agent enzastaurin was taken orally once daily until disease progression or unacceptable toxicity. The original starting dose was 525 mg capsules, but was later changed to 500 mg tablets given within 30 min of eating a meal. The primary end point was freedom from progression for at least two cycles (2 months), and 22% of patients met this end point. There were three responders (all complete responses), and an additional four patients had long-term stable disease, with a freedom from progression of 20 to over 50 months after study entry. Eight patients remained free from progression for four cycles (15%). The agent was tolerated well, with the only grade 4 toxicity observed being hypomagnesemia.

Morschhauser et al. treated 60 patients with relapsed MCL with 500 mg of enzastaurin daily.⁴⁴ These patients had relapsed/refractory MCL with no more than four prior therapies. The most common side effect was fatigue. Although there were no documented anti-tumor responses, 37% (22 of 60) remained progression-free for at least three cycles, and six were progression-free for 6 months or more.

The preclinical work supporting the inhibition of PKC- β in NHL, the excellent tolerance of this oral agent, and the ability to induce disease stability has led to a large phase III study of enzastaurin versus placebo in patients with high-risk DLBCL who have entered remission after induction therapy. This trial is ongoing and will likely be the key trial with this agent in NHL.

Summary

Signal transduction inhibitor therapy represents an emerging therapeutic option for lymphomas of all types. The PI3K, BCR, and PKC signal pathways all are important pathways for the growth of malignant lymphoma cells. The agents discussed above have all moved from basic laboratory research on signal transduction to in vitro studies on malignant cell lines and primary samples, followed by phase I and II studies, and, in the case of mTOR inhibitors and enzastaurin, phase III clinical trials. The p110 δ , mTOR, BTK, and Syk inhibitors have all demonstrated single-agent anti-tumor activity in early trials, and the PKC- β inhibitors were able to induce long-term disease stability in relapsed DLBCL. With the plethora of signal pathways and the host of pharmaceutical agents becoming available in the near future, it is important to demonstrate the preclinical rationale to conduct the phase I studies. In addition, the observation of single-agent anti-tumor activity in humans with relapsed disease and an understanding of the toxicity profile are critical to designing studies in combination with standard agents or where the agent is used as consolidation or maintenance.

It is truly an exciting time for both investigators and patients. The ability to offer hope to a relapsed NHL or Hodgkin's lymphoma patient makes the current practice of hematology/oncology stimulating and rewarding. Despite the many new available agents and the need for new therapies, there remain substantial challenges. What level of anti-tumor activity and duration of response with a signal transduction inhibitor should be considered as "interesting" when the group being tested has been heavily pretreated? Should a drug that has a very low response rate but can induce prolonged stable disease move forward? When combinations are designed should they be tested "up front" or at relapse? Testing combinations in highly curable diseases such as de novo DLBCL and Hodgkin's lymphoma is especially challenging, because the cure rate is already high and there is little tolerance for

additional toxicity. We are confident that these challenges will be met and that these new treatments will affect the therapy of patients with NHL and Hodgkin's lymphoma.

Acknowledgments

Supported in part by CA97274 and CA127433 and the Henry J. Predolin Foundation.

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