Expert Opinion

Rational combinations of enzastaurin with novel targeted agents for patients with B-cell non-Hodgkin's lymphoma

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Lymphoma

Non-Hodgkin's lymphoma (NHL) is the most common hematologic malignant neoplasm in adults [1]. Combination chemotherapy regimens have been the mainstay of treatment for NHL for several decades. In the 1990s, the introduction of rituximab marked the beginning of the era of immunotherapy with monoclonal antibodies and revolutionized the treatment of B-cell NHL (B-NHL). Chemotherapy combined with anti-CD20 monoclonal antibodies has improved survival in both indolent and aggressive B-NHL [2,3]; this combination has become the standard of care for these patients. However, a substantial subset of patients does not achieve a cure or long-term disease remission. In recent years, advances in the knowledge of NHL biology have improved our understanding of cell growth, proliferation and cell death in malignant cells. This has promoted the identification of new targeted treatments and new agents that have shown promising efficacy for future B-NHL therapies [4]. Protein kinase C beta (PKC-β), a serine/threonine kinase, is involved in several signal transduction pathways, from differentiation and cell growth to survival and cell migration. It has been shown that PKC-β is overexpressed in 20 – 25% of diffuse large B-cell lymphomas (DLBCLs) at diagnosis and 90% of DLBCLs at relapse [5,6]. Therefore, PKC represents a potential targeted therapy for lymphomas. Enzastaurin (LY317615.HCl), an acyclic bisindolylmaleimide, is one of several new molecules directed against PKC-β. Enzastaurin is an ATP-competitive selective inhibitor of PKC. Enzastaurin suppresses the phosphoinositide 3-kinase (PI3K)/acutely transforming retrovirus (AKT) pathway, which blocks the phosphorylation of glycogen synthase kinase 3 beta (GSK3-β), mammalian target of rapamycin (mTOR) and ribosomal protein S6 [7-9]. It also suppresses cyclin D1 synthesis [10], induces dephosphorylation of p90 and ribosomal S6 kinase (RSK), regulates the MAPK pathway [11] and seems to be involved in the interferon-regulated JAK/STAT pathways [12]. Furthermore, it affects BAD, a pro-apoptotic member of the Bcl-2 family proteins, which is particularly important in lymphoma [13].

Based on promising preclinical results [14] and the good tolerability profile [15], enzastaurin has been introduced in clinical trials as a treatment for patients. Enzastaurin has been used alone or in combination with other agents in more than 40 clinical trials (source: www.clinicaltrials.gov), and 9 of these focused on indolent or aggressive NHL. Patients with relapsed DLBCL have rarely shown responses to enzastaurin as a single agent, but a few patients have experienced long-term freedom from progression (FFP) [16]. Based on the good safety profile and the long-term FFP, a large randomized clinical trial was initiated. This ongoing trial has enrolled over 700 patients, and final data will be available in mid-2013. In clinical Phase II

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Table 1. Protein kinase targets and their inhibitor compounds.

Inhibitor compounds		Target	Ref.
Perifosine	→	AKT	Gills JJ, Curr Oncol Rep, 2009; Ghobrial IM, Clin Cancer Res, 2010
Sorafenib Tipifarnib	→	Ras/Raf	Witzig TE, Oncogene 2010; Rolland D, Cancer Chemother Pharmacol. 2008
BEZ 235	→	m-TOR-PI3K	Roccaro AM, Blood, 2010
Bortezomib	→	NF-Kb	Goy A, Ann Oncol 2009; Di Bella N, Blood, 2010
Carfilzomib			
IMIDs			
IMIDs	→	Mapk	Wiernik PH, J Clin Oncol, 2008; Witzig TE, Blood, 2009
ABT-263	→	Bcl-2, Bcl-x	Wilson WH, Blood, 2008; Goy A, Blood, 2007
Obatoclax			
CAL-101	→	PI3K	Lannutti BJ, Blood 2011
RAD001 Rapamycin,	→	m-TOR	Gobrial IM, J Clin Oncol, 2010; Smith SM, J Clin Oncol, 2008
Temsirolimus, Everolimus,			
Deforolimus			
PCI-32765	→	Btk	Advani R, J Clin Oncol, 2010
Fostamatinib disodium	→	Syk	Mocsai A, Nat Rev Immunol, 2010; Friedberg J, Blood, 2010
SB1518	→	JAK2/STAT	Yourne A, Blood, 2009
Vorinostat Romidepsin	→	HDAC	Goy A, Crit Rev Oncol Hematol, 2010
LBH589			
MGCD0103			

trials, enzastaurin showed promising results in patients with follicular lymphoma or Waldenstrom's macroglobulinemia [17,18]. For the latter diseases, enzastaurin treatment achieved more than 25% objective responses; by contrast, enzastaurin treatment for mantle cell lymphoma has produced no objective responses [19]. More details on preclinical and clinical data are discussed in this issue by Ysebaert and Morschhauser in a well-conceived, nicely written review [20].

Based on the identification of several new therapeutic agents that affect different regulatory pathways in lymphomas, the current challenge is to identify rational pharmacological combinations that can enhance the potency of single agents and improve patients' outcome. We can distinguish three categories of compounds for rational combinations: agents directed against cell surface receptors, agents that target intracellular pathways and, finally, agents that affect the microenvironment by altering the cytokine milieu (immunomodulatory agents). The three categories can be combined as follows: i) agents that target cell surface receptors plus signaling pathway inhibitors, ii) agents that target cell surface receptors plus immunomodulatory agents and iii) signaling pathway inhibitors plus immunomodulatory agents.

A good candidate for the first type of combination is the anti-CD20 monoclonal antibody, rituximab. Rituximab is given to nearly all patients with B-NHL, and it is associated with significant improvement in survival outcome. Several novel anti-CD20 antibodies with structural modifications are under investigation with the aim of improving efficacy [21,22]. Rituximab effects are mediated by the immune system and also by the apoptotic signaling pathway. A rational combination should target multiple targets, including cell surface receptors and intracellular pathways. Based on this rationale, rituximab was combined with proteasome inhibitors, and this combination has shown good preliminary results [23]. Another potentially effective combination would be anti-CD20 combined with enzastaurin. The second type of combination has been studied with the combination of anti-CD20 and immunomodulatory agents that were selected to enhance anti-CD20 activity [24]. The third type of combination has been studied, *in vitro* with the combination of lenalidomide, an immunomodulatory agent, and enzastaurin, which affects intracellular pathways that involve the induction of apoptosis [25]. A further approach might be to combine novel agents that target multiple cell pathways involved in cell survival, proliferation and apoptosis; for example, a combination of enzastaurin and proteasome inhibitors.

In conclusion, novel drug combinations with new monoclonal antibodies, agents that target the microenvironment, and new molecules that affect cell signal transduction represent promising, emerging therapeutic options for patients with NHL (**Table 1**). However, with the plethora of new agents that will become available in the near future, it is important to show a strong preclinical rationale before performing Phase I studies. In addition, in designing studies that utilize new compounds in combination with standard or novel agents, it is critical to show single-agent activity in patients who have relapsed and have a clear understanding of the safety profile.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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