Novel therapies for Hodgkin lymphoma

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Abstract: In recent years, improved understanding of the biology of Hodgkin lymphoma (HL) has uncovered many potential targets for the treatment of this disease. Clarification of the B-cell origin of the Hodgkin Reed Sternberg (HRS) cell and of the complex interactions between the HRS cell and the HL microenvironment have provided new insights into the pathophysiology of HL and identified extracellular and intracellular molecules which are essential for HRS survival. New agents directed at these molecules are now in early phase clinical trials.

Keywords: Hodgkin lymphoma, targeted therapy, new agents

Ther Adv Hematol

[2010] 1(1) 23–29

DOI: 10.1177/

2040620710387980

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Introduction

The probability of cure for patients with newly diagnosed Hodgkin lymphoma (HL) is high. Most recent studies of combined modality or chemotherapy-only approaches to the treatment of early stage disease report long-term disease-free survival rates in excess of 90% [Noordijk *et al.* 2006; Meyer *et al.* 2005; Engert *et al.* 2003]. For patients presenting with advanced stage disease, corresponding disease-free and overall survival rates over 85% have been reported for dose-intensive chemotherapy strategies [Engert *et al.* 2009]. Even in patients with relapsed disease, the use of high-dose therapy and autologous stem cell transplantation (ASCT) results in long-term disease-free survival in around 50–60% of patients [Moskowitz *et al.* 2001]. Recent data suggests that the survival after transplant in the ‘modern’ chemotherapy era may be higher.

Despite these advances, challenges remain in the treatment of HL. Although the use of anthracycline-based chemotherapy regimens has reduced the potential for secondary acute myeloid leukemia/myelodysplastic syndrome and for impaired reproductive function, these complications have not been eliminated. There is an increasing trend towards the avoidance of radiation therapy for patients with HL based on risk stratification using established prognostic factors, and on the increasing use of functional imaging techniques such as fluorodeoxyglucose positron emission tomography (FDG/PET) to evaluate residual

masses after chemotherapy [Gallamini *et al.* 2006], but the potential for secondary malignancies and cardiovascular disease for patients receiving radiation therapy still exists. For the minority of older patients with HL, current treatment regimens are associated with marked short-term toxicity and poor survival. The outlook for patients who experience relapse of their disease after high-dose therapy and ASCT is poor. Although the use of allogeneic transplantation in this setting has been reported to result in long-term survival, most patients are not eligible for this approach, which is associated with high toxicity and treatment-related mortality.

In recent years, improved understanding of the biology of HL has uncovered many potential targets for treatment of this disease. Clarification of the B-cell origin of the Hodgkin Reed Sternberg (HRS) cell and of the complex interactions between the HRS cell and the HL microenvironment have provided new insights into the pathophysiology of HL and identified extracellular and intracellular molecules which are essential for HRS survival [Re *et al.* 2005]. New agents directed at these molecules are now in early phase clinical trials.

Biology of Hodgkin lymphoma

The WHO Classification of lymphoid neoplasms [Swerdlow *et al.* 2008] recognizes two major subtypes of HL which differ in their morphology, immunophenotype, expression of B-cell genes, cellular background and clinical behavior.

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Classical Hodgkin lymphoma

Classical HL (cHL) is most commonly a B-cell derived neoplasm comprising mononuclear Hodgkin cells and multinuclear HRS cells within a microenvironment containing variable proportions of small lymphocytes, eosinophils, plasma cells, neutrophils, fibroblasts, histiocytes and collagen. The Hodgkin and HRS cells typically comprise between 0.1% and 10% of the total cellular infiltrate and the morphology of these cells along with the cellular composition of the surrounding cells allows classification into the four subtypes of cHL, designated as lymphocyte rich cHL, nodular sclerosis, mixed cellularity and lymphocyte depleted.

Almost all HRS cells are positive for CD30, expressed on the cell membrane as well as within the Golgi. CD30 is a member of the tumor necrosis factor (TNF) receptor family of prosurvival receptors which activate signaling pathways including PI3-kinase/Akt/mTOR, ERK/MAPK and NF- κ B [Clodi and Younes, 1997]. CD15 is also commonly expressed on HRS cells in a similar distribution to CD30, although its expression may be limited to the Golgi area. These cells also express other B-cell markers including the B-cell-specific activator protein PAX5/BSAP and the plasma cell transcription factor IRF4/MUM-1.

The interactions between the HRS cell and its surrounding cellular infiltrate, mediated through cytokines via cell surface receptors on the HRS cell appear to be central to its prosurvival anti-apoptotic phenotype. HRS cells have been shown to secrete a variety of cytokines and chemokines for T-helper 2 (Th2) cells including thymus and activation regulated chemokine (TARC) which attract CD4 positive cells [van den Berg *et al.* 1999]. Subpopulations of these CD4 positive cells secrete interleukin 10 (IL-10) and transforming growth factor β (TGF β), inhibiting cytotoxic T-cell function and protecting HRS cells from apoptosis [Marshall *et al.* 2004]. Th2 secreted cytokines such as IL-13 directly promote HRS survival since these cells express IL-13 receptors and signal through the STAT-6 pathway. Multiple other cytokines secreted by infiltrating cells appear to provide survival signals to the HRS cell including CD30, CD40 and NOTCH1, all of which act through TNF family receptors as described above [Rodig *et al.* 2005; Zheng *et al.* 2003].

Molecular studies have shown that 98% of HRS cells contain clonal re-arrangements of immunoglobulin genes with a high rate of somatic hypermutation confirming their origin from germinal center-derived B-cells. Despite this, HRS cells have lost many features of B-cell identity as a result of 'crippled' gene expression. They lack functional B-cell receptors and are resistant to the normal process of CD95 mediated apoptosis within the germinal center [Re *et al.* 2000]. This is thought to be related to the constitutive expression of inhibitory molecules such as cFLIP (C-FLICE inhibitory protein) [Dutton *et al.* 2004] and XIAP (X-linked inhibitor of apoptosis) [Kashkar *et al.* 2003]. High expression of these molecules is thought to overcome the proapoptotic signals received by the HRS cell through surface expression of TNF receptor family members including TRAIL-R1 (TNF-related apoptosis inducing ligand receptor 1), which normally activate apoptosis by the intrinsic and extrinsic pathways [Mathas *et al.* 2004]. Drugs directed at various components of these pathways may be able to affect the balance of anti- and proapoptotic signals within the HRS cell in favor of cell death.

Nodular lymphocyte predominant Hodgkin lymphoma

Nodular lymphocyte predominant (LP) HL is a monoclonal B-cell neoplasm characterized by large 'popcorn' or LP cells in a network of follicular dendritic cells which are infiltrated by non-malignant histiocytes and lymphocytes. The LP cells are positive for CD20, BCL6 and CD79a and also express high levels of other B-cell markers including OCT 2 and BOB1, with frequent strong staining for immunoglobulin heavy and/or light chains. LP cells have been shown to have clonally re-arranged immunoglobulin genes and are thought to originate from germinal center B-cells at the stage of centroblastic differentiation. They have a high rate of somatic hypermutation confirming their germinal center derivation, but in contrast to HRS cells retain their B-cell identity.

Targeting cell surface antigens and receptors in Hodgkin lymphoma*CD20-rituximab in Hodgkin lymphoma*

The use of rituximab in nodular LP HL has been reported in phase II and retrospective studies from several groups, based on the CD20 expression of LP cells in this entity [Schulz *et al.* 2008;

Eckstrand *et al.* 2003]. These studies have included patients with relapse or refractory disease, as well as some with previously untreated disease. Reported overall response rates have been between 85% and 100%, with complete response rates of around 50–90%. Median progression-free survival rates between 10 and 33 months were seen in these studies. Current studies in nodular LP HL are directed towards combination studies with rituximab and chemotherapy as well as the use of new-generation anti-CD20 monoclonal antibodies.

Recent studies have also addressed the potential use of rituximab in classical HL. Although the majority of HRS cells in classical HL do not express the CD20 antigen, it can be identified in 20–30% of cases. The rationale for the use of rituximab in this disease is partly based on CD20 expression in the HRS cell but also on the ability to target infiltrating B-cells within the HL microenvironment and thereby deprive the HRS cells of necessary survival signals. Two phase II studies have described response rates of approximately 20% in patients with relapsed or refractory classical HL [Schulz *et al.* 2008; Younes *et al.* 2003]. More recently, rituximab has been combined with standard chemotherapy using ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) for patients with previously untreated advanced cHL. In the initial report, a response rate of 100% was observed with an event-free survival of 83% at a median of 21 months follow up. When compared with historical controls receiving ABVD only, improved progression-free survival was observed in the group with poor risk disease according to the International Prognostic Score, although the significance of this observation is unclear and requires prospective confirmation [Younes *et al.* 2005].

CD30 as a therapeutic target in classical HL

The high expression of CD30 on HRS cells has been exploited by several groups as a target for therapy using monoclonal antibodies. Initial studies of unconjugated antibodies showed only limited activity in phase I and II studies. For example, a phase II study of SGN-30 (cAC10) a chimeric monoclonal anti-CD30 antibody, in 22 patients with relapsed/refractory HL produced disease stabilization in 11 of 38 evaluable patients [Forero-Torres *et al.* 2009]. All other patients had disease progression with no responses reported. A fully humanized

anti-CD30 monoclonal antibody 5F11 (MDX-060), which recognizes a different epitope from cAC10, has also been evaluated in a phase II setting with only four responses observed in 67 patients with HL [Ansell *et al.* 2007]. Results from this study were also confounded by the fact that some of the patients were also taking corticosteroids at the time their responses were evaluated.

Overall, results from first-generation anti-CD30 monoclonal antibodies have been disappointing. Possible reasons for this include the neutralization of antibody by circulating CD30, which has been documented in many patients with HL, low affinity of antigen binding or low affinity of the Fc component of the antibody for host effector cells. Attempts to overcome the limitations of these antibodies have included combinations with chemotherapy. For example, *in vitro* data have suggested that 5F11 and SGN-30 antibodies activate NF- κ B, leading to activation of cFLIP and protection of the HRS cell from apoptosis. The addition of bortezomib to 5F11 *in vitro* has been shown to overcome resistance to apoptosis and the two agents were shown to be synergistic in this situation, although this observation has not yet been exploited clinically [Böll *et al.* 2005].

Based on previous observations with rituximab in patients with non-Hodgkin lymphoma, which have shown that its efficacy is related to affinity of the Fc γ RIIIA receptor on effector cells second-generation anti-CD30 antibodies have been produced with higher affinity for this region. One such antibody, Xmab2513, has been the subject of a phase I study but only preliminary response data have been reported so far. Attempts have also been made to produce antibodies specific for transmembrane forms of CD30 but no clinical results have been reported for these antibodies.

Anti-CD30 immunoconjugates

The use of CD30–drug conjugates, exploiting the targeting ability of CD30 antibodies, have been reported from several studies. Early studies using immunotoxins had limited clinical activity, but promising data have recently been reported for SGN-35, a conjugate of the cAC10 (SGN30) monoclonal antibody with monomethyl auristatin (MMAE), an antimicrotubule agent. The initial phase I study of this agent included patients with HL and anaplastic large cell lymphoma, although 42 of the 45 patients included had HL

[Younes *et al.* 2008]. Complete or partial responses were observed in 37% of patients although it is noteworthy that 88% of patients had some reduction in tumor volume. A second phase I study using a 7-day as opposed to a 21-day schedule at a lower dose has proved less toxic, with responses observed in 7 of 17 evaluable patients. Formal phase II trials of this agent are now complete although results are not yet available. The potential for combining this agent with standard chemotherapy regimens for HL is also now under investigation.

Although many other antibody–drug conjugates have been evaluated *in vitro*, relatively few of these have entered clinical trials and most have had only limited activity. These have included an anti-CD30/deglycosylated ricin A immunoconjugate which had minor activity but significant toxicities, most notably vascular leak syndrome [Schnell *et al.* 2002].

Attempts to improve effector cell function have included the development of bispecific antibodies. One such antibody has combined anti-CD30 with anti-CD16, based on the hypothesis that this will activate natural killer (NK) cell function and lead to increased CD30 positive cell killing. Although responses were reported in a phase I study of this agent, the effectiveness was limited by a high rate of human antimouse antibody (HAMA) development and other allergic reactions which prevented subsequent use of the agent [Hartmann *et al.* 2001]. Comparable, disappointing results were reported for another similar bispecific antibody combining anti-CD30 and anti-CD64 (the FcγR1 receptor on activated neutrophils) which produced responses in 4 of 10 heavily pretreated HL patients, but these responses lasted for only a few weeks [Borchmann *et al.* 2002].

Additional studies with radioimmunoconjugates based on anti-CD30 monoclonal antibodies have also been reported although most have had response rates of 20–30% with short response durations.

TRAIL receptors as targets in cHL

In vitro studies using HL cell lines have demonstrated that APO2L/TRAIL protein and agonist antibodies against TRAIL-R1 and TRAIL-R2 receptors induce apoptosis and that this effect can be potentiated by proteasome and histone deacetylase inhibitors [Georgakis *et al.* 2005].

Based on these observations, a phase I study assessing these combinations is currently in progress.

Other surface targets

Several other molecules expressed on the surface of HRS cells have been targeted by novel agents currently under investigation in phase I or II trials. These include CD40, IL-13 and its receptor and CD80.

Intracellular targets in HL

NF-κB

As described above, NF-κB is a key regulator of cell survival and apoptosis and an important target for therapy of several B-cell malignancies including multiple myeloma and mantle cell lymphoma. Many of the prosurvival, anti-apoptotic pathways in the HRS cell converge on NF-κB, which has been shown to be constitutively activated. As a result, inhibition of NF-κB with the proteasome inhibitor, bortezomib, has been investigated in patients with HL. Single-agent bortezomib has been evaluated in two phase I/II trials in HL, neither of which has demonstrated clinical activity despite encouraging preclinical data [Blum *et al.* 2007; Younes *et al.* 2006]. Bortezomib has been combined with chemotherapy in some patients with relapsed and refractory HL. Although impressive clinical responses have been reported from one of these studies in which bortezomib was combined with the ICE (ifosfamide, carboplatin, etoposide) regimen, the 75% response rate observed could have been attributable to the chemotherapy regimen alone; this will require further prospective evaluation [Fanale *et al.* 2008].

PI3K/Akt/mTOR

This pathway has been identified as a potential therapeutic target based on its frequent activation in HRS cells in primary culture and in cell lines. Activation probably occurs through multiple cell surface receptors including those for CD30 and CD40. The mTOR inhibitor everolimus has been shown to have single-agent activity in relapsed/refractory HL with responses observed in 7 of 15 patients in an ongoing phase II study [Johnston *et al.* 2007]. Current studies are exploiting the multiple pathways which converge on PI3/Akt/mTOR by investigating combinations of mTOR inhibitors with other agents including histone deacetylase (HDAC) inhibitors.

Histone deacetylase

In vitro studies have shown that HDAC inhibitors can induce apoptosis in HRS cell lines, possibly by inducing the expression of the B-cell genes which are underexpressed in HRS cells [Rosato *et al.* 2003]. Several HDAC inhibitors are currently in phase II trials. Preliminary clinical data are available from two phase II studies. In a phase II trial of an isotype-selective HDAC inhibitor, MGCD0103, Younes and colleagues report an overall response rate of 40% in 27 evaluable patients with relapsed or refractory HL, all of whom had previously been treated with high-dose therapy and autologous SCT [Younes *et al.* 2007]. A possible association between clinical response and reduction in serum levels of TARC was observed. A phase II trial of vorinostat in a similar patient population has reported a partial response rate of only 4%, although disease stabilization was noted in a further 16% of patients [Kirschbaum *et al.* 2007].

Other intracellular targets

Preclinical data have demonstrated the potential value of other intracellular molecules as targets for HL therapy including heat shock protein 90 (HSP 90), XIAP (for which small molecule and antisense inhibitors exist) cFLIP and various components of the JAK/STAT pathway. Clinical trials with appropriately targeted agents are in development.

Immunomodulatory agents

Preliminary results from phase II studies of lenalidomide have been reported. The mechanism of action of this class of drugs in HL is unclear, but probably includes antiangiogenic effects, NK- and T-cell activation and the direct induction of apoptosis in HL cells. Recently published results from one phase II study show responses in 6 of 12 heavily pretreated patients with HL [Böll *et al.* 2010]. The German Hodgkin Lymphoma Study Group has combined lenalidomide with conventional chemotherapy in its current study for elderly patients with HL.

Therapies directed at Epstein–Barr virus

Approximately 40% of cases of HL are associated with Epstein–Barr virus (EBV) infection, characterized by the expression of EBV nuclear antigen-1 (EBNA-1) and the transmembrane proteins latent membrane proteins 1 and 2 (LMP1 and LMP2). The expression of LMP1 and LMP2 has been shown to upregulate NF- κ B expression and is thought to be a potential mechanism for

oncogenesis by EBV in this disease. In view of this, treatments directed at EBV-encoded proteins have now entered early clinical trials. The most promising strategies have used cytotoxic T-lymphocytes (CTLs). Early studies used peripheral blood from patients with HL, from which EBV-specific CTL lines and B-lymphoblastoid cell lines were generated. The EBV-specific CTLs were then activated *in vitro* using lymphoblastoid cell lines as antigen-presenting cells, then expanded *in vitro* before being reinfused into HL patients. This approach was associated with decreased viral load of EBV and clinical responses in 3 of 11 patients [Bollard *et al.* 2004]. These early studies demonstrated that within the polyclonal autologous CTL lines were some cells specific for LMP2, which have the potential to generate a more potent antitumor effect than polyclonal CTLs. LMP 2a-specific CTLs have therefore been generated by exposing patient T-cells to autologous dendritic cells which overexpress LMP2a through an adenoviral vector. Objective responses were observed in five of six patients with relapsed/refractory HL treated in this way [Lucas *et al.* 2004]. Four of these patients achieved complete responses with a minimum duration of 9 months.

More recent studies have used additional modifications of this technique to reduce the risk of immune evasion by the tumor. These include genetic modification of EBV CTLs to express immunostimulatory cytokines such as TARC/CCL17, to promote resistance to TGF β and to express chimeric antitumor T-cell receptors [Di Stasi *et al.* 2009]. Clinical trials of this approach are in progress.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

None declared.

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