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REVIEW

Novel agents for B-cell non-Hodgkin lymphoma: Science and the promise

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SUMMARY

There has been tremendous insight gained in the last two decades from basic science research. New molecular targets in neoplastic cells are emerging and provide the rationale for clinical development of novel agents in non-Hodgkin lymphoma. These novel agents can be broadly categorized into two groups. The first is by immunotherapy which includes novel monoclonal antibodies and immunomodulating drugs, which takes advantage of or optimizes immune system function. The other group of drugs target small molecules that may play an important role in tumorigenesis. The mechanisms of anti-tumor activity include targeting apoptotic pathways, inhibition of proteasomes, mammalian target of rapamycin (mTOR), cyclin-dependent kinases and histone deacetylases. The purpose of this review is to focus on these novel agents and the various treatment approaches that are currently being evaluated in non-Hodgkin lymphoma.

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Introduction

The treatment of non-Hodgkin lymphoma (NHL) in the last two decades have heralded an era of increasing exploration of therapies derived from improved biologic understanding of tumors and tumor-host interactions. The focus of drug discovery has moved from identifying classical cytotoxic agents to molecules that target specific pathways involved in signal transduction, apoptosis, and differentiation, to name a few. These efforts have been greatly aided by insights into the structure of proteins and the ability to design specific inhibitors using small molecules or monoclonal antibodies.

Although the introduction of new treatment agents and regimens for NHL has resulted in improved complete response (CR) rates and survival in some settings, the lack of any significant improvement in overall survival in many of the subtypes indicates a clear need for further novel drugs and interventions.[1–3] These novel agents can be broadly categorized into two groups. The first is by immunotherapy which includes novel monoclonal antibodies (MAb) and immunomodulating drugs (IMiDs), which take advantage of the immune system and/or optimize tumor cell targeting. The other group of drugs target small molecules that may play an important role in tumorigenesis. The mechanisms of anti-tumor activity include targeting apoptotic pathways, inhibition of proteasomes, mTOR, cyclin-dependent kinases and histone deacetylases. Herein we discuss several of these promising agents and the research that has led several of them into the clinic.

Monoclonal antibody therapy

Until 1980, the molecular architecture of the B-cell surface was known to consist of membrane-bound Ig, complement component receptors, and Fc receptors; beyond that, the molecular constitution of the cell surface was completely uncharacterized. That all changed with the advent of monoclonal antibody (MAb) technology.[4] Over the past 25 years, slightly over ten B-cell-specific cell surface molecules have been identified by MAbs. It has been demonstrated that B-cell antigen expression is variable and differs at various stages of B-cell development. However, many of these B-cell antigens are often expressed on malignant B-cells. Most of these antigens are involved in B-cell growth, differentiation, proliferation, and activation or have unknown functions. Several proposed mechanisms by which MAbs appear to produce their cytotoxic effects have been described: (1) Antibody-dependent cellular cytotoxicity (ADCC) is induced through binding of the Fc portion of the antibody to Fc receptors on host effector cells, such as natural killer (NK) cells, granulocytes, and macrophages,[5–7] (2) Complement-dependent cytotoxicity (CDC) is induced by promoting complement fixation at the cell surface, leading to complement-dependent lysis of target cells,[8,9] and (3) direct cytotoxicity via induction of cellular apoptosis following binding of the target antigen by MAb.[10–13] Both ADCC and CDC depend on the interaction of the antibody with the host's intrinsic immune system, while direct cytotoxicity is independent of it.

Novel anti-CD20 monoclonal antibodies

The CD20 antigen is expressed exclusively on normal and malignant B-cells.[14] It has a stable expression and is tightly bound

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to the membrane with little modulation during maturation. It is neither secreted nor rapidly shed in circulation,[15,16] and it likely has an important role in B-cell activation and regulation of cell cycle.[17,18] All these features make CD20 an "ideal" anti-B-cell target. Rituximab was the first MAb to be approved by the Food and Drug Administration (FDA) in 1997 for treatment of relapsed or refractory CD20-positive follicular or indolent B-cell NHL. Rituximab is a chimeric human–mouse IgG1 kappa monoclonal antibody that binds to CD20, inducing cell death in both normal and neoplastic B-cells. It has since been used in combination with chemotherapy and is now considered the cornerstone of therapy in both indolent and aggressive B-cell lymphomas. Although rituximab is a valuable addition to the treatment for B-cell NHL, 50% of patients with relapsed or refractory CD20-positive follicular lymphomas do not respond to initial therapy with rituximab[19] and close to 60% of patients who were previously treated with rituximab no longer benefit with retreatment.[20] Rituximab resistance represents a significant barrier to immunotherapy of B-cell lymphomas.

Newer-generation anti-CD20 antibodies designed to improve on rituximab are currently in development. Several approaches are under evaluation. Modification strategies include humanization of the molecule to decrease infusion reactions and immunogenicity, enhancement of binding affinity, and modification of the Fc portion of the molecule to optimize effector functions, particularly ADCC. Humanized anti-CD20 MAbs are appealing because they avoid antimurine immunogenic response and perhaps have a better side-effect profile. There are three humanized anti-CD20 MAbs undergoing clinical evaluation. One of these is ofatumumab (HuMaxCD20), a fully human IgG1 kappa antibody that binds to a novel CD20 epitope localized in the second extra-cellular loop distinct from that recognized by rituximab.[21,22] Compared with rituximab, ofatumumab elicits stronger complement-dependent cytotoxicity (CDC) but induces less apoptosis.[23] Preclinical data demonstrates that ofatumumab inhibits the growth of engrafted B-cell tumors in SCID mice more efficiently than rituximab. Ofatumumab was also able to lyse rituximab-resistant Raji Burkitt cells in vitro.[23]

In a recent phase I/II study, 33 patients with relapsed or refractory CD20-positive chronic lymphocytic leukemia (CLL) were treated with four once-weekly infusions of ofatumumab; 67% of the patients were Binet stage B and median number of previous treatments was 3 (range, 1–9). Three cohorts of patients with the following dosing schedule were used: cohort A, one 100 mg infusion plus three 500 mg infusions (three patients); cohort B, one 300 mg infusion and three 1000 mg infusions (three patients); cohort C, one 500 mg infusion and three 2000 mg infusions (27 patients). All patients had significant reduction in leukemic cells as well as rapid and prolonged depletion of normal B lymphocytes. Their recovery to normal levels was not observed until 5–6 months after completion of therapy. Overall response rate (ORR) in all three cohorts was 44%, and was 50% in cohort C (13 of 26 assessable patients). However, all were partial responses (PR). The majority of related adverse events occurred after the first infusion and these decreased at subsequent administrations. The most common grade 3–4 toxicity reported was myelosuppression (12%), followed by infections (9%). None of the patients developed human anti-human antibodies.[24] This phase I/II study indicates that ofatumumab is an active and well tolerated agent in refractory/relapsed CLL in doses up to 2000 mg, with a relatively encouraging objective response. A phase I/II study of 40 patients with follicular lymphoma evaluated 4-weekly infusions of ofatumumab given at different doses (300–1000 mg). Out of 38 patients, 5 CR, 2 CR unconfirmed (CRu), and 9 PR were observed. Based on the median follow-up of 9.2 months, the median time to disease progression was 8.8 months and the median duration of response (DR) was 29.9 months.[25] In view of these results, two phase III clinical trials are currently underway. Ofatumumab is being evaluated as a single agent in patients with refractory CLL and in patients with follicular lymphoma that are refractory to rituximab. Also currently under way is a phase II trial of ofatumumab in combination CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone) in patients with previously untreated follicular lymphoma.

Veltuzumab (hA20) is another humanized anti-CD20 MAb being evaluated in clinical trials. This MAb is engineered with complementarity-determining regions (CDR) of murine origin and with 90% of the human framework regions identical to epratumumab, a humanized anti-CD22 IgG1 antibody.[26,27] The mechanism of cytotoxicity of Veltuzumab is similar to rituximab and also very similar to rituximab in terms of antigen binding and specificity binding avidity. A phase I/II dose escalation study in 82 patients with recurrent B-cell lymphomas demonstrated a 40% ORR, including 17 patients who achieved CR/CRu (21%). In patients with follicular lymphoma (FL) which comprises the largest subgroup in this study, the ORR was 44% (24 of 55 patients) and 27% CR/CRu (15 of 55 patients). The 15 patients with FL who achieved CR/CRu generally had durable responses with a median duration of response (DR) and progression free survival (PFS) of 19.7 and 24.2 months, respectively. The drug was generally well tolerated. All treatment related adverse effects were mild to moderate with the exception of one grade 3 hypoglobulinemia; otherwise, most were transient infusion-related symptoms occurring predominantly at first infusion.[28] Another approach being investigated is anti-CD20 MAbs with enhanced binding to FcγRIIIa. Three novel engineered anti-CD20 antibodies, AME-133v, rhuMAb v114, and GA-101, are currently in early phases of clinical development. They are associated with a higher antibody-dependent cytotoxicity as compared with rituximab, and increased direct apoptosis with GA-101 (Table 1).

Targeting non-CD20 antigens

Clinical success with anti-CD 20 MAbs has led to further investigation and discovery of other potential targets in B-cell NHL. Some examples include CD22, CD23, CD40, CD80[29–32] (Fig. 1, Table 2). These agents have shown promise in early clinical trials and might represent an additional strategy to overcoming rituximab resistance. In this review, only galiximab, a MAb targeting CD80, will be discussed. CD80, a member of the B7 ligand family (B7.1), is a membrane co-stimulatory molecule that is involved in T-cell regulation and in regulation of normal and malignant B-cells.[33,34] Preclinical studies demonstrated that cross-linking of CD80 on B-cells resulted in upregulation of proapoptotic proteins such as caspase-3, caspase-8, Fas, Fas ligand, Bak, and Bax and downregulation of anti-apoptotic proteins such as Bcl-X_L.[34] CD80 is a good target antigen because it is constitutively expressed in a variety of B-cell lymphoma cells, including follicular lymphoma and Hodgkin lymphoma.[35,36]

Galiximab is a primate–human chimeric anti-CD80 MAb with human IgG1 constant region and macaque variable region, which is structurally indistinguishable from human antibodies. Galiximab was evaluated in a phase I/II study of 38 patients with advanced-stage relapsed or refractory follicular lymphoma. Patients received four infusions of galiximab at doses of 125, 250, 375 or 500 mg/m^2, given once weekly for 4 weeks. The overall RR was 11%, with two patients achieving complete response (CR) and two reaching partial response (PR); 12 patients (34%) had stable disease (SD). Both patients with complete response were administered the dose of 375 mg/m^2. All enrolled patients were CD80 positive by flow cytometry, but those who responded did not necessarily have greater CD80 density than non-responders. The most common adverse effects reported were grade 1 and 2 fatigue, nausea and head-