



Buddhist community building, Bakong, Cambodia. Photograph courtesy of J. Bryan Murphy, MD, Clearwater, Florida.

The development of a targeted treatment approach has increased therapeutic options for patients with hematologic malignancies.

Targeted Therapy for Hematologic Malignancies

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Background: *The introduction of monoclonal antibodies, either as native molecules or conjugated to radioisotopes or other toxins, has led to new therapeutic options for patients with hematologic malignancies. In addition, the use of small molecules against specific cell surface receptors, enzymes, and proteins has become an important strategy in the treatment of such disorders.*

Methods: *The author reviewed the published clinical trials of monoclonal antibody and other targeted therapies in hematologic malignancies.*

Results: *Results from several trials demonstrate a therapeutic benefit for the use of monoclonal antibodies (either native or conjugated) and other targeted therapies, used alone or in combination with standard cytotoxic chemotherapy.*

Conclusions: *Targeted therapy of hematologic malignancies seems to be an effective and less toxic approach to the treatment of such disorders. Nevertheless, additional studies are needed to determine where and when such management fits into a therapeutic regimen for any given disorder, whether upfront or as salvage therapy, alone or in combination with chemotherapy (concurrent or sequential).*

Introduction

The treatment of hematologic malignancies has been a forerunner to the medical management of neoplastic disorders in general. Hence, it is not surprising that even in the area of targeted therapy — immunotherapy or otherwise — the treatment of these malignancies remains in the forefront of ongoing research. Though all cancer treatments (including perhaps surgery, radiation, and cytotoxic chemotherapy) could be considered as therapy targeted against cancer, the term *targeted therapy* is more narrowly defined as the use of directed immunotherapy or molecularly directed therapy. Such targeted therapy approaches have been developed to reduce the nonspecific toxicity of cytotoxic chemotherapy and also to improve the efficacy of treatment.

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Abbreviations used in this paper: CR = complete response, NHL = non-Hodgkin's lymphoma.

This paper addresses the use of targeted therapy as it pertains to hematologic malignancies by reviewing individual disease entities in which these agents are used. Also, agents that are currently approved by the Food and Drug Administration (FDA) and those that appear promising are discussed. As some of these agents are utilized in more than one disease entity, they have been discussed only under the disease of greatest indication or maximum use.

Acute Myeloid Leukemia

The intervention of targeted therapy in acute myeloid leukemia (AML) is perhaps most notable in the treatment of acute promyelocytic leukemia (APL). The role of all-*trans*-retinoic acid (ATRA) in APL in causing differentiation of cells with t(15;17) has led to long-term disease-free survival and/or cure in 70% to 80% of cases.^{1,2} ATRA works by terminal differentiation of APL blasts. Its effectiveness is determined by the expression of the PML/RAR- α fusion transcript, with sensitivity to it being dependent on the exact breakpoint in the PML gene on chromosome 15.³ The main complication associated with its use is the retinoic acid syndrome, characterized by a capillary leak syndrome with fever, respiratory and perhaps cardiac failure, and renal dysfunction. This syndrome, which is seen in up to 25% of patients, especially those with a high white blood cell count, can be treated or prevented with corticosteroids or chemotherapy. ATRA, used concurrently with an anthracycline for induction and consolidation and followed by maintenance in combination with low-dose chemotherapy, is currently the standard treatment of APL.⁴ Trials in the United States and Europe are assessing the role of single-agent ATRA as maintenance therapy. Drawing from the success of arsenic trioxide in patients with relapsed APL, investigators have shown evidence of efficacy in combining ATRA with this agent for upfront therapy.^{5,6} Likewise, in an attempt to avoid conventional chemotherapy, a combination of ATRA with gemtuzumab ozogamicin for induction has also been used, with good response.⁷

Gemtuzumab ozogamicin (GO; Mylotarg) is an antibody conjugated with calicheamicin (a potent plant cytotoxic antibiotic that leads to inhibition of DNA synthesis and apoptosis⁸) directed against the surface marker CD33 expressed by 90% of myeloid leukemic blasts. In combined phase II studies of 142 patients with CD33+ AML in first relapse, treatment with GO was associated with an overall response (OR) rate of 30%.⁹ The incidence of typical side effects of conventional chemotherapy, such as myelosuppression, was less with GO, although tumor lysis and the adult respiratory distress syndrome have been encountered in patients with a white blood cell count of less than 30,000/mL.^{9,10} GO was approved by the Food and Drug Administration in May 2000 for patients with AML who are 60 years of age or more in first relapse and not candidates for chemotherapy.^{9,10} The use of GO, either

alone or in combination, has been associated with the development of potentially fatal hepatic venoocclusive disease in both frontline and relapsed settings.^{11,12} The feasibility of combining GO with induction and consolidation therapy for newly diagnosed patients is being studied.¹³

A myriad of chromosomal translocations and mutations contributing to the development of AML act as potential targets for directed therapy. Mutations leading to up-regulation of kinases, more specifically tyrosine kinases, in AML blasts¹⁴ are likely targets. Since these mutations result in unchecked proliferation of such cells, their inhibition by small molecules could lead to interference with the necessary signaling mechanisms that allow their survival. Of the known tyrosine kinase mutations in AML, the most commonly encountered are *c-kit* and *flt3*. Two small molecules, SU5416 and SU6668, predominantly inhibit the former.^{15,16} There has been some response to SU5416 in refractory AML; in a phase 2 study of 42 patients, complete and partial responses were seen in 1 and 7 patients, respectively.¹⁷ *Flt3* mutations appear to be independent poor prognosticators in AML.¹⁸ Phase I and II clinical trials have shown that inhibitors of *flt3* (CEP-701, PKC412, SU5416, SU5614, SU11248)^{19,23} have been well tolerated and have shown evidence of activity.

Ras proteins are membrane-associated G proteins that are activated downstream of protein tyrosine kinases under the influence of the enzyme farnesyltransferase. Inhibition of farnesyltransferase with tipifarnib (R115777) has shown activity in relapsed/refractory AML.²⁴ This agent is currently being studied as first-line therapy and as maintenance in the elderly patient population.

Acute Lymphoblastic Leukemia

The treatment of adult acute lymphoblastic leukemia (ALL) has improved over the years with the use of intensive chemotherapy, stem cell transplantation, and more refined supportive care. Further improvement perhaps calls for a different approach from conventional chemotherapy, such as molecular targeting with kinase inhibitors (imatinib mesylate) and/or antibody therapy. Transient responses have been noted with imatinib (discussed below) in Philadelphia chromosome-positive (Ph+) ALL. Improved response rates have been reported with imatinib mesylate when combined with upfront chemotherapy.²⁵ Studies are currently evaluating this strategy in this subset of patients who otherwise tend to have a poorer prognosis. The presence of CD20 on precursor B-cell and mature B-cell ALL, as well as in Burkitt's lymphoma, would dictate the likelihood of response to rituximab (an anti-CD20 monoclonal antibody, discussed in the non-Hodgkin's lymphoma section). A CR rate of 89% with no additional toxicity was reported in Burkitt's and Burkitt's-like leukemia or lymphoma when rituximab was used in combination with hyperfractionated cyclophos-

phamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD).²⁶ It could also perhaps serve as an adjunct to induce molecular remissions following conventional treatment.²⁷ Antibodies targeting other surface antigens, including CD19, CD22, CD25, and CD52, both as single agents or in combination with chemotherapy, in preclinical and clinical settings (upfront, or relapsed/refractory), have produced varying response.²⁸⁻³²

Chronic Myeloid Leukemia

Chronic myelogenous leukemia (CML) is characterized by a genetic abnormality, the Ph chromosome, resulting from the reciprocal translocation between the long arms of chromosomes 9 and 22, t(9;22)(q34;q11).³³ The resultant fusion protein, BCR-ABL, is a constitutively active tyrosine kinase that is responsible for the development of CML.

The activity of protein tyrosine kinases is tightly regulated since they function as mediators of cell growth, differentiation, and death. Protein tyrosine kinases are grouped based on structural similarities and cellular function as receptor and nonreceptor tyrosine kinases. Receptor tyrosine kinases have an extracellular and a cytoplasmic portion. Nonreceptor tyrosine kinases lack receptor-like features, but they mediate critical cell signals of many cell surface receptors and also interact with other proteins, lipids, and DNA. Protein tyrosine kinases catalyze the transfer of phosphate from adenosine triphosphate (ATP) to the hydroxyl group of a tyrosine residue in the protein substrate.³⁴

Imatinib mesylate (STI571; Gleevec) competitively inhibits the ATP binding site on ABL, platelet-derived growth factor (PDGF), stem cell factor (SCF) and *c-kit* tyrosine kinases, and it inhibits PDGF- and SCF-mediated cellular events. Imatinib is considered to be one of the first clinically useful molecules in a new class of cancer agents called signal transduction inhibitors, and it inhibits the BCR-ABL tyrosine protein kinase found in CML.

Druker et al³⁵ reported complete hematologic response rates of more than 95% and major cytogenetic

responses in 40% to 50% with imatinib in patients with chronic-phase CML resistant to interferon alpha (IFN- α). Imatinib was approved by the FDA in May 2001 for the treatment of CML when IFN- α therapy has failed. Side effects include nausea, diarrhea, headache, skin rash, fluid retention, and myelosuppression. Compared to alternative therapies or to historical controls, imatinib appears to prolong event-free and overall survival in all phases of CML (chronic, accelerated, and blast).³⁶⁻⁴⁰ Although imatinib has been reported to provide a response rate of more than 50% in the myeloid blast crisis of CML,⁴¹ this response is rarely durable.

While current data on cytogenetic responses as a surrogate for survival suggest that imatinib prolongs survival, long-term follow-up of patients treated with this drug is needed to establish its effectiveness. It has been demonstrated that a 3-log reduction in BCR-ABL/ABL ratio detected via real-time quantitative polymerase chain reaction (RT-PCR) confers a superior progression-free survival, an indication perhaps of the importance of an adequate molecular response for a survival benefit.⁴² Strategies to improve molecular remission, such as with high-dose therapy, are being studied.^{43,44} High-dose imatinib (800 mg per day) as first-line therapy resulted in higher rates of both cytogenetic and molecular remission.⁴⁴

Resistance to imatinib and subsequent disease relapse appear to be associated with a failure to maintain effective inhibition of BCR-ABL activity. However, although rare in the chronic phase, resistance and relapse eventually occur in the advanced phases of the disease. Resistance has been reported due to *BCR-ABL* gene amplification⁴⁵ or point mutations in the *abl* kinase domain leading to specific amino acid substitutions⁴⁶ or via mutations outside the kinase domain.⁴⁷ Second-generation targeted therapies (such as BMS-354825) that retain inhibition against imatinib-resistant mutants are currently being developed.⁴⁸ Inhibition of wild-type and mutant BCR-ABL by an ATP-based protein kinase inhibitor and pyridopyrimidine-type small molecule kinase inhibitors has been reported^{49,50} and will likely pave the way for introduction of therapies directed against CML resistant to imatinib. Activation of

Table 1. — Summary of Selected Studies of Imatinib Mesylate in Chronic, Accelerated, or Blast Phases of Chronic Myelogenous Leukemia (CML)

Study	CML Phase	Complete Cytogenetic Response (%)	Survival
Kantarjian ³⁶ (phase 2, interferon refractory)	Chronic	41	NR
Marin ³⁷ (phase 2, interferon refractory)	Chronic	NR	Probability of survival at 8 years 78.4% (historical control 22.6%)*
O'Brien ⁴⁰ (phase 3, randomized, first-line)	Chronic	76.2	NR
Talpaz ³⁸	Accelerated	19 (600 mg/d) 11 (400 mg/d)	12-month progression-free and overall survival for 600 mg/d vs 400 mg/d: 67% vs 44% and 78% vs 65%, respectively
Wadhwa ³⁹	Blast	NR	6 of 21 patients went into chronic phase; median duration of remission of chronic phase 205 days

* Statistically significant improvement in survival in those achieving cytogenetic response. NR = not reported.

Src family kinases is seen in Ph+ myeloid cells,⁵¹ SKI-606, a 4-anilino-3-quinolinecarbonitrile dual inhibitor of Src and Abl kinases, is a potent antiproliferative agent against chronic myelogenous leukemia cells, both in culture and in nude mice.⁵² Pyridopyrimidines have been shown to have efficacy against both BCR-ABL and Src-family kinase in cells sensitive and resistant to imatinib.⁵³ In addition, the use of alternate targeted therapies, such as harnessing the in vitro synergism between bortezomib and the cyclin-dependent kinase inhibitor flavopiridol, warrant further study.⁵⁴

Table 1 summarizes selected studies of imatinib in chronic, accelerated, or blast phases of CML.

Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia (CLL) is a heterogeneous neoplastic disorder associated with the accumulation of nonproliferating mature lymphocytes uniquely expressing the surface markers CD5 and CD23.

Alemtuzumab (Campath-1H) is a humanized monoclonal antibody targeting CD52, an anchored glycoprotein expressed on the surface of normal B and T lymphocytes, leading to complement and antibody-dependent cell cytotoxicity.^{55,56} In previously untreated patients with B-cell CLL, alemtuzumab has demonstrated an OR rate of approximately 90% with a median survival of 9 to 12 months. In patients who relapsed after prior therapy with fludarabine, an OR rate of approximately 40% with a CR rate of 2% to 4% was noted. These responses often are limited to the peripheral blood, bone marrow, or spleen, with lower response in lymph nodes.⁵⁷ Nevertheless, alemtuzumab has been able to induce significant and durable responses in refractory nonbulky B-cell non-Hodgkin's lymphoma (NHL).⁵⁸ Cytokine-mediated infusion-related toxicities of rigors, fever, rash, urticaria, and hypotension are often encountered with its use.⁵⁹ In addition, normal B- and T-cell depletion can result in an immunosuppressed state, with an increased risk for opportunistic infections.⁶⁰ Alemtuzumab was approved by the FDA in May 2001 for treatment of B-cell CLL in patients previously treated with alkylating agents who have failed fludarabine therapy.

Approaches to ameliorate the drug's toxicity or improve efficacy have included subcutaneous dosing⁶¹ or combination with rituximab⁶² and chemotherapy,⁶³ respectively. Its role in the treatment of aggressive T-cell or NK-cell NHL⁶⁴ and as part of an allogeneic transplant regimen⁶⁵ has also been explored.

Other targeted therapies used in CLL have included rituximab and denileukin diftitox (discussed below). The former has been used in combination with chemotherapeutic drugs such as nucleoside analogs as well as a single agent, with good response.⁶⁶⁻⁶⁸

Advances in molecular technology could lead to better treatment selection based on specific targets. Molecu-

lar profiling using microarray analyses has confirmed that those with mutated immunoglobulin genes have a more indolent course than those with unmutated genes; the unmutated group has an increased expression of the tyrosine kinase ZAP70, which in turn could serve as a target for therapy.^{69,70}

Non-Hodgkin's Lymphoma

NHL is predominantly a disease of older adults, comprising an array of neoplastic disorders that are diverse both in their presentation and outcome. The introduction of rituximab in the therapeutic armamentarium of NHL in recent years has been the most visible "targeted therapy" for this lymphoma.

Rituximab

Rituximab (Rituxan) is a chimeric monoclonal immunoglobulin G1 (IgG1) antibody targeted against the cell surface receptor CD20 common in many B-cell NHL subtypes, leading to apoptosis, antibody-dependent cell cytotoxicity, and complement-mediated cytotoxicity.⁷¹ It was initially used in high-grade refractory or recurrent NHL and in relapsed indolent NHL, with improved disease-free survival.⁷²⁻⁷⁷ Since then, studies have been undertaken to investigate its role in lymphoid leukemias and highly aggressive lymphomas. It is also being studied with other anticancer antibodies, small molecule-targeted agents, antichemoresistance gene therapies, and biologic response modifiers.⁷³ Major toxicities include infusion-related chills (typically with the first treatment), fever, fatigue, nausea, and vomiting. Rituximab was approved by the FDA in November 1997 for relapsed or refractory B-cell NHL.

The role of rituximab in combination with systemic chemotherapy has been demonstrated in the spectrum of B-cell lymphoproliferative disorders, including CLL, and indolent and aggressive NHL.⁷⁸⁻⁸⁰ Cytokine-mediated^{81,82} and host effector-cell upregulation by target-specific agents (granulocyte colony-stimulating factor [G-CSF], granulocyte-macrophage colony-stimulating factor [GM-CSF]) has demonstrated increased antitumor activity of monoclonal antibodies.⁸³ Clinical trials combining rituximab with various cytokines, including interferon alpha, interleukins, and G-CSF in relapsed or refractory NHL, have reported OR rates of 45% to 70%, CR rates of 11% to 33%, and time to progression of 8 to 24 months.⁸⁴⁻⁸⁹

The use of rituximab as maintenance therapy following induction and also as in vivo purging prior to stem cell harvest are areas of research, mainly in low-grade follicular NHL.

Radioimmunotherapy

Radioimmunotherapy is another strategy to optimize the efficacy of anti-CD20 monoclonal antibody therapy by combining the antibody with a radioconjugate, yttrium-90

(⁹⁰Y) ibritumomab tiuxetan (Zevalin) or iodine-131 (¹³¹I) tositumomab (Bexxar).

By covalently linking ibritumomab to the metal chelator tiuxetan, stable binding of indium-111 (¹¹¹In) for radionucleotide tumor imaging and ⁹⁰Y ibritumomab tiuxetan for enhanced targeted cytotoxicity is possible with ⁹⁰Y ibritumomab tiuxetan.⁹⁰⁻⁹² In a randomized phase III trial in which patients with relapsed indolent or transformed follicular NHL received either ⁹⁰Y ibritumomab tiuxetan or rituximab, a statistically significant improvement in the OR rate of 80% vs 56% and in the CR of 30% vs 16%, respectively, was obtained.⁹⁰ Its toxicity is primarily hematologic, which is both transient and reversible. Its effect on survival is not known; however, the duration of response in this trial was approximately 2 months longer compared with rituximab therapy. ⁹⁰Y ibritumomab tiuxetan was the first radioconjugated antibody therapy approved by the FDA in February 2002 for the treatment of relapsed or refractory low-grade, follicular, or transformed NHL, including patients with rituximab-refractory NHL.

Tositumomab is a murine IgG_{2a} λ monoclonal anti-CD20 antibody. ¹³¹I-tositumomab is a radio-iodinated derivative of tositumomab that has been covalently linked to ¹³¹I. Administration of a dosimetric dose and determination of individual patient residence time (ie, a measure of how long the radionuclide is retained in the body) allow adjustment of the patient's therapeutic dose to maximize efficacy and minimize toxicity. A phase III trial of patients with relapsed, refractory, or transformed low-grade NHL reported an OR rate of 63%, a CR rate of 25%, and a median duration of response of 25 months.⁹³ Toxic-

ities associated with this regimen include myelosuppression, as well as the risk of secondary acute leukemia, myelodysplasia, and hypothyroidism. Tositumomab received FDA approval in June 2003 for the treatment of CD20+ follicular non-Hodgkin's lymphoma, with or without transformation, that was refractory to rituximab and had relapsed following chemotherapy.

Table 2 is a summary of selected studies of single-agent rituximab or radioimmunotherapy, and the combination of rituximab with chemotherapy.

Denileukin Diftitox

Denileukin diftitox (Ontak) is a fusion protein that targets the diphtheria toxin to cells expressing the interleukin-2 receptor. When internalized into the cell, it inhibits protein synthesis. In a phase III clinical trial, pretreated patients with cutaneous T-cell lymphoma had an OR rate of 30%, with improvement in quality of life in responders and nonresponders.^{94,95} In addition, denileukin diftitox has been studied in relapsed refractory B- and T-cell NHL. It has been shown to have activity in fludarabine refractory B-cell CLL⁹⁶ and in steroid refractory acute graft-vs-host disease after allogeneic hematopoietic stem cell transplant.⁹⁷ The most common adverse reaction is a flu-like syndrome consisting of fever, chills, nausea, vomiting, myalgia, and arthralgia, occurring within several hours to days after its infusion. A hypersensitivity reaction consisting of hypotension, back pain, dyspnea, rash, chest pain, tachycardia, syncope, or anaphylaxis (vascular leak) is often seen within 24 hours of infusion, mostly on the first day of each infusion cycle.

Table 2. — Selected Studies of Single-Agent Rituximab or Radioimmunotherapy, and Combination of Rituximab With Chemotherapy in Indolent and Aggressive Non-Hodgkin's Lymphoma (NHL)

	Study	Disease	OR (%)	CR (%)	Survival
Indolent NHL	McLaughlin ⁷⁷	Relapsed	48		Projected TTP for responders: 13 months
	Czuczman ⁷⁸	Front line (with CHOP)	95	55	74% remained in remission during a median follow-up of 29+ months
	Witzig ⁹⁰	Relapsed, refractory, or transformed B-cell NHL (phase III randomization vs rituximab)	80	30	Duration of response: 2 months longer than rituximab arm
	Kaminski ⁹³	Relapsed, refractory, or transformed B-cell NHL	63	25	Median duration of response: 25 months
Aggressive NHL	Coiffier ⁷⁹	Relapsed, refractory, elderly untreated (>60 years of age)	31	9	Median TTP: >246 days for responding patients
	Vose ⁷⁶	Front line (with CHOP)	94	61	Median duration of response and TTP not reached after a median observation time of 26 months
	Coiffier ⁸⁰	First-line CHOP + rituximab First-line CHOP alone	83* 70*	76 63	Overall survival* at median follow-up of 2 years: 70% vs 57%

OR = overall response
CR = complete response
TTP = time to progression
CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone
* Includes complete response, unconfirmed complete response, partial response, and stable disease.

Other Targeted Therapies

Another common antigen expressed on B cells is the sialoglycoprotein CD22, which is rapidly internalized following antibody binding.⁹⁸ Epratuzumab is a humanized anti-CD22 molecule that works by signal activation and induction of antibody-dependent cell cytotoxicity.⁹⁹ This drug, either alone or in combination with rituximab, has been studied in phase I and II trials of recurrent indolent and aggressive NHL. In indolent NHL, epratuzumab was associated with an OR rate of 18% to 58%, a CR rate of 6% to 28%, and time to progression of more than 2 years.¹⁰⁰⁻¹⁰² In aggressive NHL, it was associated with an OR rate of 10%, with time to progression of more than 6 months.¹⁰¹

The HLA class II molecules have been another target for B-cell malignancies as they play a role in the control of cell cycling and proliferation, but have limited expression on normal cells.¹⁰³ Two such agents, anti Lym-1 and apolizumab (or Hu-1D10) have been studied in clinical trials, either as naked antibodies¹⁰⁴⁻¹⁰⁶ or as a radioimmunoconjugate (¹³¹I Lym-1),¹⁰⁷ with an OR rate of more than 50% in two of the trials.¹⁰⁵⁻¹⁰⁷

With the knowledge that approximately 80% of follicular NHL and 30% of diffuse large B-cell NHL are associated with the bcl-2 (14;18) translocation and overexpression of the Bcl-2 protein,¹⁰⁸ which tends to predict a poorer overall survival,^{109,110} strategies to target the anti-apoptotic effect of bcl-2 overexpression are being studied. These include attempts at using small molecular-based targeting of the Bcl-2 protein, antisense oligonucleotides specific to the bcl-2 mRNA (oblimersen sodium), which leads to protein down-regulation and tumor cell apoptosis,¹¹¹ as well as transcriptional silencing of the concerned gene. In addition to *in vitro* activity against different tumor cell types, Bcl-2 antisense oligonucleotide therapy has been found to have efficacy in various hematologic malignancies, both alone¹¹² and in combination.¹¹³

Multiple Myeloma

Multiple myeloma is a neoplastic disorder characterized by malignant plasma cells with low proliferative rates for which no one molecular abnormality has been found. In the context of targeted therapy, bortezomib (Velcade), a proteasome inhibitor, has been introduced for the treatment of relapsed/refractory disease.

A variety of cancer cell types are more sensitive than normal cells to inhibition of the proteasome, an organelle responsible for the physiologic degradation and recycling of cellular proteins that regulate cell cycle progression.¹¹⁴⁻¹¹⁶ This function of the proteasome is achieved via proteolysis of I κ B, the endogenous inhibitor of nuclear factor kappa B (NF- κ B), which in turn leads to activation of NF- κ B and upregulation of transcription of proteins promoting cell survival and growth. Proteasome inhibition affects many cellular pathways, which has thus spawned

various inhibitors to it. Bortezomib, a boronic acid dipeptide, is a reversible proteasome inhibitor and is the only one studied in clinical trials.¹¹⁷ It works in multiple myeloma by leading to inhibition of different cellular processes, including growth, survival, and adhesion, while promoting apoptosis.¹¹⁷ In a phase II trial of 193 patients with relapsed and/or refractory disease, the rate of response to bortezomib was 35%, the median overall survival was 16 months, and the median duration of response was 12 months.¹¹⁸ Based on these results, the drug received FDA approval in May 2003 for the treatment of patients who had received at least two prior therapies and had demonstrated progression of disease on their last therapy. Adverse effects associated with its use include myelosuppression, fatigue, and peripheral neuropathy. Clinical trials will determine if bortezomib therapy offers clinical benefit to patients with multiple myeloma.

A comparative phase III trial of bortezomib to high-dose dexamethasone in patients with multiple myeloma who had progressed following previous treatment was stopped prematurely due to results of a prespecified interim analysis.¹¹⁹ A statistically significant difference in time to disease progression was seen in favor of patients who received bortezomib. This advantage led to a change of therapy to bortezomib in patients with disease progression on high-dose dexamethasone. In addition to a longer time to disease progression, bortezomib produced a statistically significant survival benefit, which was a secondary endpoint of the study.

Preclinical studies have shown that bortezomib is effective in different subtypes of NHL and is also able to increase the activity of other targeted therapies, such as rituximab and antisense oligonucleotides (against bcl-2).¹²⁰⁻¹²² Additionally, phase I and II studies have shown its efficacy in mantle cell lymphoma.¹²³⁻¹²⁵

The development of immunomodulatory drugs that are analogs of thalidomide has enabled an attempt to harvest modulation of immune responses to target tumors. These agents (CC5013 and CC4047) appear to work via inhibition of tumor necrosis factor alpha, vascular endothelial growth factor, NF κ B, and recruitment of natural killer cell cytotoxicity against multiple myeloma.^{126,127} Phase I and II studies of the CC5013 analog have demonstrated response rates of greater than 70% in relapsed/refractory multiple myeloma.^{128,129}

Conclusions

The use of these agents has emphasized the important role of the target in defining response. In part, this is because neoplastic cells have multiple, redundant pathways that could enhance their growth potential. Drugs targeting upstream molecular pathogenetic events are possibly more likely to be effective than those targeting late phenomena. Additionally, if we could identify the

genetically defined pathway on which a given neoplastic cell is dependent for its growth and survival, a targeted therapy could be devised to countermand this cell development. The application of DNA microarray technology to determine the genetic makeup of hematologic malignancies and to help identify specific risk categories for neoplastic disorders is a novel approach of further refining the selection of targets for directed therapy. This perhaps holds the greatest immediate promise for lymphomas. Coupled with the success of earlier cancer detection, this approach to the use of molecularly targeted therapies would no doubt be successful. The development of a targeted treatment approach has expanded the therapeutic options for patients with hematologic malignancies and has facilitated the translation of advances in cancer therapy from the laboratory to the bedside.

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