

Frontiers in HematOncology

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Welcome From the Editors

It is our pleasure to welcome you to the inaugural issue of **Frontiers in HematOncology**. This new international publication will seek to provide timely, compact reports of cutting-edge clinical and scientific developments in hematologic oncology. This and forthcoming issues will feature original articles and challenging new case studies by leading specialists from around the world, combined with news highlights from major scientific meetings such as those of the American Society of Hematology (ASH), the American Society of Clinical Oncology (ASCO), and the European Haematology Association (EHA).

This first issue features an incisive article by John M. Bennett on the new WHO classification system for acute myeloid leukemias and the myelodysplastic syndromes, together with a diagnostic study by John I. Olichney illustrating a rare pattern of immunoglobulin organ deposition. Also included are extensive news reports from the Orlando, Florida, ASH meeting and summary highlights from the recent literature. It is hoped that the ASH news coverage will provide a meaningful service for many who were prevented from attending this conference in the aftermath of September 11.

Your comments on this issue, as well as your recommendations and contributions for forthcoming issues, will be most welcome. Please write to the Editors at **Frontiers in HematOncology**, 1500 Broadway, New York, NY 10036, USA, or fax us at +212-704-0120. ■

WHO Classification of the Acute Myeloid Leukemias and Myelodysplastic Syndromes

BY JOHN M. BENNETT, MD

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For more than 20 years, the French-American-British (FAB) classification system for acute myeloid leukemias (AMLs) and the myelodysplastic syndromes (MDSs) has served as the reference standard throughout the world. This system has now been revised in the wake of newly developed World Health Organization (WHO) classifications for leukemias and lymphomas.¹ The WHO classifications represent the culmination of a 3-year effort by working committees worldwide under the auspices of the European Association of Hematopathologists and the Society for Hematopathology.²⁻⁴

General recommendations for the diagnosis of AML and MDS are the same in the WHO system as in the FAB system. Requirements call for a bone marrow aspirate and

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biopsy, standard Romanowsky stains and cytochemistry (peroxidase, esterases), and flow cytometry for immunotyping.¹ Assessments of cytogenetics and molecular genetics are also strongly encouraged as additional, if not integral, components of the diagnostic process for many of these disorders.

MDS Classification

The WHO classification for MDS is based on the previous FAB system, albeit with several major changes. Refractory anemia (RA) and refractory anemia with ringed sideroblasts (RARS) and minimal dysplasia have been redefined as <10% dysplastic granulocytes and <10% megakaryocytes.¹ A separate category has been created for refractory cytopenias with <5% blasts and multilineage dysplasia (defined as >10% dysplastic progeny of each cell line). Refractory anemia with excess blasts (RAEB) is now divided into RAEB-I (5% to 10% blasts) and RAEB-II (11% to 20% blasts). The division of the large group of RAEB into these 2 entities recognizes the fact that the medullary blast count is the most important prognostic factor and that a threshold of 10% is of prognostic importance.⁵

Chronic myelomonocytic leukemia (CMML) has been moved into a separate category (“Myelodysplastic and Myeloproliferative Disorders”). Included are CMML, atypical chronic myelogenous leukemia (CML), and juvenile CMML, as all 3 disorders share dysplastic features and are associated with proliferation.⁶ The 5q- (or 5q31) deletion syndrome is identified as a separate entity when the blast percentage is

TABLE 1. CLASSIFICATIONS OF MDS

Category	Peripheral Blood	Bone Marrow
1a. RA without dysplasia	Blasts <1%; monocytes <1000/mm ³	Blasts <5%; ringed sideroblasts <15%
1b. RA with dysplasia	Same + dysgranulocytes and/or giant platelets	Same + dysgranulocytes and/or dysmegakaryocytes
2a. RARS without dysplasia	Blasts <1%; monocytes <1000/mm ³	Blasts <5%; ≥15% ringed sideroblasts
2b. RARS with dysplasia	Same + dysgranulocytes and/or giant platelets	Same + dysgranulocytes and/or dysmegakaryocytes
3a. RAEB-I	Blasts 1%-4%; monocytes <1000/mm ³	Blasts 5%-10%
3b. RAEB-II	Blasts 5%-19%; monocytes <1000/mm ³	Blasts 11%-19%

MDS = myelodysplastic syndrome; RA = refractory anemia; RARS = refractory anemia with ringed sideroblasts; RAEB = refractory anemia with excess blasts. Reprinted with permission from Bennett.⁶

<5%. **Table 1** summarizes peripheral blood and bone marrow criteria that can be used to allocate a patient to a specific category of MDS.⁶

A somewhat controversial aspect of the WHO system is a reduction in the blast count required for definition of AML — from 30% to 20% in either the peripheral blood or the bone marrow aspirate.¹ This change eliminates the FAB category of refractory anemia with excess blasts in transformation (RAEBt), which was formerly regarded as the transition zone between MDS and AML. Clinical trials have shown that patients with MDS and 20% to 30% blasts have responses identical to those with AML (>30% blasts).⁶ The

majority of patients with RAEBt have short durations of survival (<6 months), and some may benefit from therapies designed for AML when clinically indicated. Consequently, all patients with >20% blasts are now categorized pathologically as having AML rather than MDS.

The WHO classification system is not intended to replace the International Prognostic Scoring System (IPSS) for MDS, but rather to be used in conjunction with this tool. In addition to the FAB subtypes, the IPSS takes into consideration other prognostic factors, including cytogenetics, the degree of cytopenia, and the percentage of marrow blasts.⁷ The IPSS categorizes patients as being at low, intermediate-I,

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This publication may contain some discussion of off-label medication uses. Dosages, indications, and methods for drug use and procedures referred to in this newsletter reflect data presented at the annual meeting of the American Society of Hematology or drawn from the clinical experience of the authors. Physicians should consult complete prescribing information before administering any of the drugs discussed herein and should follow their clinical judgment in weighing the benefits of treatment against the risks.

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TABLE 2. INTERNATIONAL PROGNOSTIC SCORING SYSTEM FOR MDS⁷

Risk Subgroup	Score	Median Survival (yr)	Median 25% AML Risk (yr)*
Low	0	5.7	9.4
Intermediate-1	0.5-1.0	3.5	3.3
Intermediate-2	1.5-2.0	1.2	1.1
High	≥2.5	0.4	0.2

*Risk that 25% of patients will undergo evolution to AML.

MDS = myelodysplastic syndrome; AML = acute myeloid leukemia.

intermediate-II, or high risk with regard to median survival and the risk of evolution to AML (Table 2).

AML Classifications

The FAB subtypes in AML (M0-M7) are retained in the WHO classification system, with the addition of a pure erythroid form of erythroleukemia (M6b). A separate category for AML with reciprocal cytogenetic abnormalities, including t(8;21), inv/del 16, t(15;17), and various translocations involving the 11q23 breakpoint, is specified without concern for the exact percentage of marrow blasts. Moreover, AML with multilineage morphologic dysplasia (≥50% of each cell line) is to be identified with or without a history of prior MDS. Characteristic

chromosomal abnormalities include 5q-, 7-, 7q-, +8, +9, +11, +13, 17p-, 20q, +21.6, and complex karyotype (>3 abnormalities). The molecular signatures of all AML subtypes should be specified when known. An additional category, “AML: Therapy Related,” has now been created for leukemias secondary to known exposures (such as radiation, alkylating agents, and topoisomerase-II-binding drugs).

Two recent studies have evaluated the impact of applying the new WHO classification system.

In 2000, Germing and colleagues published the results of a retrospective analysis aimed at validating the WHO classifications with regard to their prognostic relevance in a series of 1600 patients with

primary MDS and long-term follow-up.⁵ The investigators also sought to correlate the classifications with cytogenetic and hematologic features. Only 1% of cases were considered unclassifiable. The results confirmed a significant prognostic difference between RAEB-I and RAEB-II, as well as between RA and multilineage dysplasia. Compared with RAEB-I and RAEB-II, the 5q- abnormality was associated with a considerably better prognosis (median survival, 18, 10, and 116 months, respectively), but only in patients who had a medullary blast count of <5%. Other significant prognostic factors included age, blast count, karyotype, hemoglobin, and platelet count.

A more recent study compared the application of FAB and WHO classifications in 432 unselected patients with MDS from a single center.⁸ Although the findings failed to support the applicability of some components of the new WHO classifications, this conclusion was most likely the result of several methodological flaws in the study.

Conclusions

The introduction of the new WHO classification system is a significant and timely step toward improving the identification and treatment of AML and MDS, which continue to increase in prevalence. US data from the year 2000 indicate that AML is the most common type of acute leukemia (Table 3). If one adds the 20% to 30% of patients with very-high-risk MDS who are now to be treated as though they had acute leukemia, AML/MDS becomes the most common form managed with intensive chemotherapy, with or without autologous or allogeneic bone marrow transplantation. Clearly, this is an extremely important group of disorders.

The WHO classifications preserve the long-established FAB system while incorporating revisions based on newer information. For AML, unfavorable and favorable cytogenetic groups (regardless of blast percentage) are recognized. For MDS the 5q- syndrome is preserved, but other changes are incorporated: RARS and RA are subdivided, RAEB is subdivided, CMML is listed under MDS/MDP, and RAEBt is eliminated.

TABLE 3. INCIDENCE OF LEUKEMIA IN THE UNITED STATES, 2000

Type	Children	Adults	Total
AML	1020	9300	10,320
ALL	2900	1300	4200
CML	120	4380	4500
CLL	0	10,800	10,800
MDS	1000	12,000	13,000
Total	5040	37,780	42,820

AML = acute myeloid leukemia; ALL = acute lymphoid leukemia; CML = chronic myelocytic leukemia; CLL = chronic lymphocytic leukemia; MDS = myelodysplastic syndrome.

J.M. Bennett, written communication, February 2002.

By incorporating recent cytogenetic, molecular, immunologic, and morphologic/cytochemical criteria, the revised WHO classifications represent the most current approach to the identification of specific disease entities. Broader use of this system will undoubtedly give rise to critiques that will necessitate revisions in the future. As the system evolves, however, it should become an even more valuable tool in the future. ■

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A Rare Case of Monoclonal Immunoglobulin Deposition Disease

BY JOHN I. OLICHNEY, MD

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This patient adds an unusual disease category to the differential diagnosis of jaundice and hepatomegaly. His case illustrates a rare pattern of immunoglobulin organ deposition and points up the importance of obtaining tissue to reveal immunoglobulin disease, even in the absence of discernible paraprotein in the serum or urine. Of particular interest are the absence of clinical renal involvement and the patient's excellent response to VAD and thalidomide.

Presentation

A 45-year-old man presented in September 1999 with painless jaundice. This followed an episode of vomiting that had lasted several days when he was at a summer camp. He had lost 5 pounds but had no fever or diarrhea.

On exam, he was clearly jaundiced and had a massively enlarged liver (12 cm below the costal margin). His alkaline phosphatase was 680 U/L, total bilirubin 10.8 mg/dL, ALT 18 U/L, AST 46 U/L, and GGT 1550 U/L. Abdominal CT revealed hepatomegaly and retroperitoneal adenopathy, but the gallium scan was normal. His spleen was not enlarged. His serum immunofixation was negative for paraproteins, but IgG, IgM, and IgA levels were all slightly low (799, 17.3, and 47.2 mg/dL, respectively). A skeletal survey was negative for lytic lesions. Beta₂-microglobulin was normal (2.6 µg/mL), and serum viral hepatitis antibodies were negative. Urine immunofixation was normal. The serum electrophoresis showed only a small peak in the beta region. His total protein was 7.5 g/dL, and albumin was 4.0 g/dL (normal). CBC, BUN, and creatinine were normal.

A liver biopsy revealed an infiltrative protein that was Congo red negative but positive for IgG kappa gammaglobulin. A

bone marrow revealed amorphous amyloid-like deposits that were "felt-like" fibrils but noncongoophilic. Electron microscopy revealed these fibrils to be thinner in diameter (60 angstroms) than typical amyloid fibrils (100 angstroms). A moderate plasmacytosis (10% to 25%) was seen in the marrow without sheets or clusters of atypical plasma cells. The diagnosis of monoclonal immunoglobulin deposition disease (MIDD) was made.

Clinically, the patient's course waxed and waned with fluctuating levels of jaundice over the next 8 months. His bilirubin dropped to 2.5 mg/dL without treatment, and although he maintained his weight and appetite, his liver remained enlarged. Repeated serum and urine immunofixations were negative for paraprotein. A cryoglobulin test was negative.

Subsequently, he developed massive leg edema, gained 40 pounds, and was bedridden with severe cellulitis of the lower extremities. His echocardiogram was normal, and he had no signs or symptoms of congestive heart failure. Treatment with dexamethasone pulse doses was initiated. He received 2 pulse cycles of 35 days each, but his disease progressed, prompting a change to vincristine, doxorubicin, and dexamethasone (VAD) therapy.

He received 3 cycles of VAD over the next 10 weeks. Although his edema and hepatomegaly responded completely, he developed severe osteoporosis, with low back pain as well as profound proximal

muscle weakness. VAD was stopped, and pamidronate, calcium, and alendronate were instituted. He was also placed on thalidomide maintenance. His improvement continued over the next 6 months.

Currently, he is free of clinical disease and tolerates thalidomide 200 mg daily. He has no back pain and is fully ambulatory 14 months after stopping VAD.

Discussion

MIDD is a relatively new category of diseases. It encompasses a group of diseases including amyloidosis (AL and AH, ie, amyloid light and heavy chains), adult Fanconi syndrome (AFS), myeloma cast nephropathy (MCN), light-chain deposition disease (LCDD), heavy-chain deposition disease (HCDD), and whole immunoglobulin deposition disease (L/H CDD). Some authors prefer to restrict the term MIDD to light/heavy-chain deposition in order to differentiate between AL and AFS.¹ Although there may be more involvement of the kidneys, heart, and liver in MIDD than in AL, there are no distinctive clinical features between amyloidosis and L/H CDD. Thus, the diagnosis depends on the immunochemical and electron microscopic and chemical differences between deposits of amyloid vs immunoglobulins. In essence, congophilia, a dominance of lambda light chains, and the felt-like fibrillar nature of the protein under electron microscopy are characteristic of amyloid deposits.

Subgrouping the V region of light chains has shed more light on the clinical differences in this group of diseases. For example, there is a relatively exclusive relationship of amyloid to the V lambda 6 subgroup of light chains. It is theorized that variance in amino acid substitution in these light chains configurationally modifies them, thus contributing to their toxicity by forming insoluble complexes² or dimerizing.³

In this patient, however, nonamyloid fibrillary deposits were found. These have been described before by Korbet et al in the kidney.⁴ The kidney is the organ most commonly involved in MIDD, usually presenting as nephrotic syndrome, proteinuria, or azotemia. More sophisticated tests may be necessary (demonstration of the nonfibrillar P glycoprotein component and gly-

cosaminoglycans [GAGs] seen in amyloid deposits) to definitively differentiate amyloid from nonamyloid immunoglobulins in rare cases.

This patient represents a rare subtype of MIDD, where IgG kappa deposits infiltrated the liver and bone marrow and probably the interstitial tissue of the lower extremities. However, the IgG kappa was not seen in immunofixation tests of the blood or urine. There were no light chains found in the urine, cryoglobulins were absent, and there was no evidence of kidney involvement or lytic bone disease in spite of a moderate marrow plasmacytosis. The only hint of a paraprotein was a mild peak migrating in the beta region on the serum electrophoresis. This may have represented a nonimmunoglobulin protein or molecularly modified forms of IgG kappa not recognized by immunofixation test anti-globulin antibodies.

The patient's massive hepatomegaly and leg edema indicate specific target-organ preference of this specific antibody. The combination of absence of serum paraprotein and massive organ infiltration has been observed before and suggests a low rate of IgG kappa synthesis and/or secretion as well as specific tissue tropism. It is also possible that some conformational change in this IgG kappa, due to some blood cofactor, may have rendered it unrecognizable in the blood by the test antiglobulins.

The absence of clinical renal involvement is another interesting feature of this case. Typically, kappa light chains are the ones most commonly associated with renal involvement, although within the kappa group there are more and less nephrotoxic subtypes. The fact that this is an intact IgG kappa without demonstrable light chains probably protected the renal tubules. In addition, the tropism of this globulin in the

liver may have kept the blood level so low as to prevent glomerular damage from a buildup of glomerular IgG kappa.

Of interest is the lack of response to 2 pulsed courses of dexamethasone. When it became clear that the patient was deteriorating, the switch to VAD therapy was made and he responded quickly and completely. Although he developed symptomatic osteoporosis, this has responded well to IV pamidronate, calcium, and alendronate. He is on thalidomide 200 mg daily, is fully ambulatory, and remains in clinical remission.

In summary, this patient with a plasma cell disease illustrates the need to obtain tissue to reveal immunoglobulin disease even in the absence of discernible paraprotein in the serum or urine. In addition to demonstrating an unusual pattern of immunoglobulin organ deposition, this patient represents the addition of an unusual disease category to the differential diagnosis of jaundice and hepatomegaly. The absence of clinical renal involvement and his excellent response to VAD and thalidomide are particularly noteworthy. ■

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ASH News

The 43rd Annual Meeting of the American Society of Hematology (ASH) was held at Orlando, Florida, in December 2001. The following pages contain news coverage of selected highlights of scientific sessions from that meeting.

Epigenetic Silencing and Hypomethylating Agents in Myelodysplastic Syndromes

Jean-Pierre Issa, MD, of the M.D. Anderson Cancer Center in Houston, Tex, noted at the ASH meeting that molecular abnormalities in myelodysplastic syndromes (MDS) are both common and varied, “and almost every single one is associated with a bad prognosis.” Such abnormalities provide investigators with tools for disease classification and targets for therapeutic intervention. One of the most interesting forms of molecular pathology, as well as one of the more promising targets for new MDS therapy, is epigenetic silencing, Dr. Issa said.

Epigenetic silencing entails the transcriptional suppression of an intact gene, “the functional equivalent of a mutation. It is a cell that is throwing away a gene,” he explained. “Even though the DNA of that gene remains intact, the cell is no longer capable of utilizing it. The effect is permanent and cannot be reversed—except, potentially, with drugs.”

Mechanisms of Silence

The mechanism of silencing usually involves changes in chromatin structure, such as the insertion of methyl groups into specific DNA sites. DNA methylation and consequent silencing appear to be a highly conserved process that is found in many different types of cancer. In MDS, several genes with specific DNA methylation have been observed, but the most common and therapeutically relevant of these is *P15INK4B*. This gene expresses P15, a cell cycle regulatory protein that mediates growth suppression via TGF-beta, a prominent suppressor cytokine. One of the homologues of P15 is P16, a well-known suppressor protein active in solid tumors.

Recent studies have shown that the frequency of *P15INK4B* methylation increases with MDS stage, from relative rarity in refractory anemia (RA) to intermediate in refractory anemia with excess blasts (RAEB) to very common in acute myeloid leukemia (AML) that has emerged from MDS (Table)—although it is not demonstrated that this increase is a major cause of progression.

The tumors that are methylated at *P15INK4B* have no detectable expression of P15, which may enable them to evolve along a different pathway from those that have active P15, Dr. Issa said.

TABLE. FREQUENCY OF METHYLATION AT *P15INK4B* BY MDS CLASS

MDS Class	Methylation
RA/RARS	17%
CMML	17%
RAEB/RAEBt	48%
AML from MDS	89%

MDS = myelodysplastic syndrome; RA = refractory anemia; RARS = RA with ringed sideroblasts; CMML = chronic myelomonocytic leukemia; RAEB = RA with excess blasts; RAEBt = RAEB in transformation; AML = acute myeloid leukemia.

Potentially, however, DNA methylation and loss of P15 expression can be modulated by 2 nucleoside cytosine analogs—5-azacytidine and 5-aza-2'-deoxycytidine, or decitabine. “This represents a new therapeutic modality,” he added. The aim is not directly to kill the cells, but to induce in them a more favorable gene expression pattern—which would then theoretically result in their senescing or dying of apoptosis.

Clinical Studies With Hypomethylating Agents

In a subsequent talk, Hagop M. Kantarjian, MD, also of M.D. Anderson Cancer Center, summarized the clinical trial experience

with 5-azacytidine and decitabine. He noted that the efficacy of 5-azacytidine had been investigated for years by Silverman and colleagues, who in 1998 presented results of the pivotal Cancer and Leukemia Group B trial of 191 evaluable MDS patients (median age, 68 years) randomized to receive either the hypomethylating agent or standard supportive care.

In this trial, 5-azacytidine was associated with response rates that were significantly higher than those seen with supportive care (61% vs 5%). “Also, the median time to transformation was significantly longer, and the quality of life of these patients was significantly better,” said Dr. Kantarjian. “Therefore, we are hoping that this study will confirm 5-azacytidine as the first agent to be approved specifically for the treatment of MDS.”

A more recent series, reported by Jani and colleagues and published as a 2001 ASH abstract, indicated that outpatient treatment with 5-azacytidine (75 mg/m²/d subcutaneously for 7 days every 4 weeks) is feasible and could provide an effective and reasonably well tolerated option for patients with advanced MDS.

Decitabine was initially studied in Europe as a classical chemotherapy agent, but investigators found that at maximum doses (1 to 2 g/m²) it could be highly toxic. It was later studied at much lower doses (50 mg/m² tid for 3 days) in MDS patients by Wijermans and colleagues in The Netherlands, who in 1999 presented their findings from 125 patients (median age, 70 years). “The objective response rate was 49%, and the complete remission rate was 20%, with a median survival of 15 months,” Dr. Kantarjian said. “Benefit was also shown in the category of pathologic

improvement, which can be quite relevant to the quality of life and survival of these patients.”

A new analysis by Wijermans’ group, presented as a poster at ASH, found that initial demethylation of clonal cells and induction of P15 protein occurred after a single course of decitabine treatment. After 4 to 6 courses of decitabine, the “emergence of fully demethylated P15 alleles and reversion to normal karyotype [were] indicative of subsequent suppression of clonal cells,” the authors observed.

On the Horizon

Drs. Issa, Kantarjian, and colleagues at M.D. Anderson are currently studying very-low-dose, long-duration exposure to decitabine (5 mg/m² for 10 days) in an effort to identify the maximally effective regimen to reverse methylation without significant myelosuppression. They are also considering protocols in which decitabine dosing is determined by degree of methylation.

Another promising approach may consist of combination therapy with a hypomethylating agent and a histone deacetylase inhibitor, thereby attacking 2 of the mechanisms responsible for structural changes in epigenetic silencing. Two preliminary studies (by Miller et al and Camacho et al) were presented at ASH, supporting the feasibility of combining 5-azacytidine with sodium phenylbutyrate in the treatment of myelodysplasia. Preclinical data describing another similar combination of decitabine and depsipeptide, a more potent histone deacetylase inhibitor, were presented in a poster session. ■

Molecular and Chromosomal Mechanisms of Resistance to Imatinib

Phase I and II clinical trials of imatinib (STI-571, Gleevec™) have shown that this drug is an effective treatment for patients with chronic myelogenous leukemia (CML). Overall, the beneficial effects of imatinib on hematologic and cytogenetic response have been observed in patients with chronic-phase CML, as well as in patients with accelerated-phase and blast-crisis CML. Unfortunately, treatment responses are transitory in most advanced-stage patients and in a significant minority of chronic-phase patients. According to results from recent studies, gene mutations and amplification of the tyrosine kinase BCR-ABL may be partly responsible for the development of imatinib resistance in these patients.

Imatinib, a 2-phenylamino pyrimidine that selectively inhibits the BCR-ABL protein tyrosine kinase, was recently granted fast-track approval by the US Food and Drug Administration for the treatment of CML patients who have failed interferon therapy. It is the subject of several ongoing clinical investigations, including a phase II trial by Kantarjian et al that was recently published in *The New England Journal of Medicine* (see **Highlights From the**

Literature). In this study, patients with late chronic-phase CML who had failed interferon therapy were treated with 400 mg of imatinib daily. After a median follow-up of 18 months, 95% of patients had a complete hematologic response, 60% had a major cytogenetic response, and 41% had a complete cytogenetic response. However, disease progression occurred in nearly 10% of patients within 18 months.

Why Are Some Patients Resistant?

A series of recent studies have shed new light on the potential molecular and chromosomal mechanisms that might be responsible for imatinib resistance, Charles Sawyers, MD, of the University of California, Los Angeles, told an ASH session. One such study suggests that disease progression in patients who initially responded to imatinib may be associated with failure to maintain effective inhibition of BCR-ABL kinase activity. Gorre et al, the authors of this study, measured levels of Crkl (an adaptor protein that is phosphorylated by BCR-ABL in CML cells) in imatinib-treated

patients and found that Crkl phosphorylation fell during treatment response but increased during relapse, indicating that imatinib was no longer inhibiting BCR-ABL.

Dr. Sawyers noted that the results of this study could be explained by several pathologic mechanisms, including host-mediated changes (eg, imatinib is inactivated by serum proteins) and genetic changes in the cancer cell. The impact of the latter on imatinib response is the subject of intensive investigation by several research groups, including that of Andreas Hochhaus, MD, of the University of Heidelberg in Germany. Dr. Hochhaus reported at ASH that imatinib resistance may be caused by several different molecular and cytogenetic mechanisms, including *BCR-ABL* gene amplification, *BCR-ABL* mRNA expression, new cytogenetic aberrations leading to clonal evolution, and point mutations in the tyrosine kinase domain of BCR-ABL.

Molecular and Genetic Mechanisms

To assess the possible effects of molecular or genetic changes on imatinib resistance, Dr. Hochhaus and colleagues studied 50 CML patients who were resistant to imatinib at a dose of 400 to 800 mg/d po. This study found that more than 50% of the cases of imatinib resistance were associated with molecular or genetic mechanisms. Overall, the median levels of *BCR-ABL* transcripts expressed as a ratio of *BCR-ABL* to glucose-6-phosphate dehydrogenase (G6PD) were not significantly altered at the time of resistance, although 5 of 46 patients had a 10-fold increase in *BCR-ABL* levels. Additional chromosomal aberrations leading to clonal evolution were seen in 15 of 29 patients. Two out of 26 imatinib-resistant patients had multiple copies of *BCR-ABL* (measured by interphase fluorescence in situ hybridization), and 6 patients had 2 *BCR-ABL* genes that indicated the acquisition of a second Philadelphia chromosome.

Dr. Hochhaus and colleagues also found that 11 of 50 patients had heterogeneous point mutations of the ABL tyrosine kinase domain, including a threonine to isoleucine substitution at position 315 of ABL (point mutation T315I). According to Dr. Hochhaus, the location of this point mutation in the critical imatinib-binding pocket of BCR-ABL may account for its association with imatinib resistance. A molecular model of mutant BCR-ABL suggests that when isoleucine replaces threonine at position 315, this enzyme loses a critical hydrogen bond needed to bind imatinib. Moreover, the presence of isoleucine may also increase steric hindrance at the binding pocket, further reducing the ability of imatinib to inhibit the tyrosine kinase activity of BCR-ABL (see **Figure**).

According to Dr. Sawyers, while these studies have provided useful insights into imatinib resistance, many questions remain unanswered. For example, it is well known that blast crisis is characterized by a state of genetic instability that allows mutations to occur. Does this also hold true for chronic-phase CML? Another question of immediate importance is whether imatinib dosing schedules can be adjusted to reduce the likelihood of resistance. For example, if genetic mutations have conferred only partial

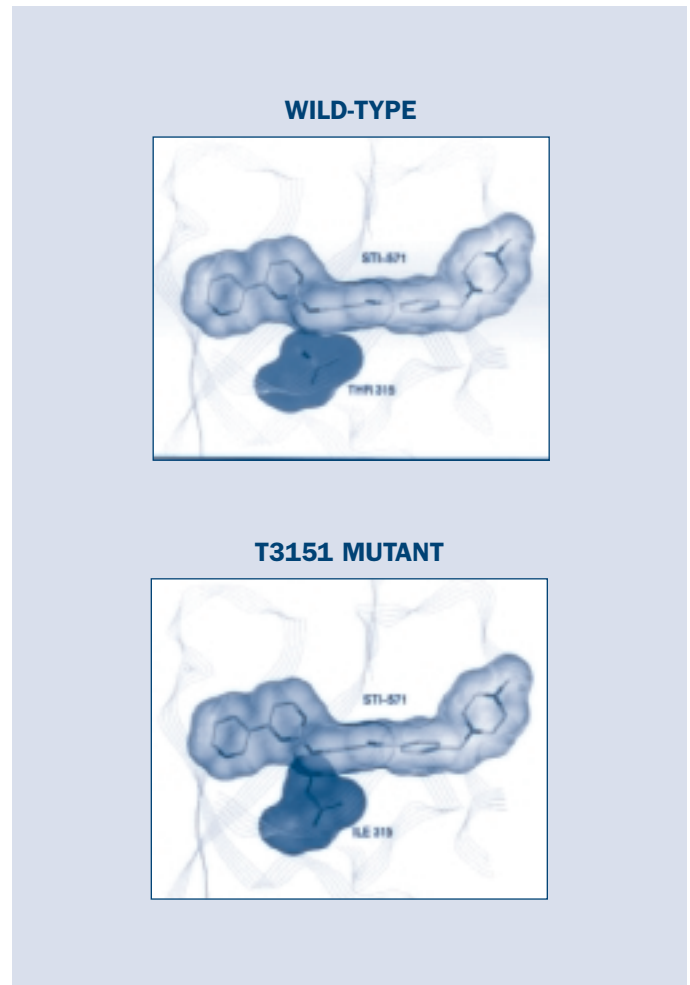


Figure. A molecular model of mutant BCR-ABL suggests that when isoleucine replaces threonine at position 315, this enzyme loses a critical hydrogen bond needed to bind imatinib. Moreover, the presence of isoleucine may also increase steric hindrance at the binding pocket, further reducing the ability of imatinib to inhibit the tyrosine kinase activity of BCR-ABL. Reprinted with permission from Gorre et al.

rather than complete resistance, an increase in imatinib doses might significantly improve drug efficacy. On the other hand, if resistance to imatinib is due to gene amplification, an increase in dosing may simply lead to an increase in gene amplification, in which case intermittent dosing might be required. “These questions are all food for thought as we move forward in the development of imatinib,” concluded Dr. Sawyers. ■

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New Approaches to Lymphoma Diagnosis

Recent advances in our understanding of the genetic mechanisms underlying B-cell differentiation and malignant transformation represent a major contribution to the diagnosis and treatment of lymphoma. According to Nancy Lee Harris, of the Massachusetts General Hospital in Boston, the rapidity of these genetic discoveries—in conjunction with the ongoing classification of lymphoid neoplasms into ever-more specific subtypes and disease entities—poses a unique challenge for clinicians, who are now faced with the daunting task of reconciling the new discoveries of geneticists and pathologists with traditional diagnostic and treatment strategies. It should come as no surprise, then, that many physicians fondly recall the “good old days” when there were only 4 categories of lymphoma to remember—lymphosarcoma, reticulum cell sarcoma, follicular lymphoma, and Hodgkin’s disease.

Bridging the Knowledge Gap

Fortunately, the gap between geneticists/pathologists—who speak in terms such as “antigen receptor gene rearrangements” and “subcutaneous panniculitis-like T-cell lymphoma”—and clinicians—who tend to focus on treatment strategies in relation to broad prognostic groupings, is by no means insurmountable. In fact, this gap has been bridged in the past, with remarkable results. For example, morphologic and immunohistochemical studies were originally used to discover a new type of lymphoma, mucosa-associated lymphoid tissue (MALT) lymphoma, while pathology studies revealed that this novel lymphoma was associated with *Helicobacter pylori* infection. It did not take long to establish that some cases of MALT lymphoma could be successfully treated with antibiotics against *H pylori*.

Presiding at an ASH session, Dr. Harris also noted that a comprehensive classification scheme produced by the International Lymphoma Study Group (ILSG), which outlined approximately 2 dozen types of B-cell and T-cell neoplasms and 5 forms of Hodgkin’s disease, was criticized at the time of its publication as lacking clinical relevance.

Classification System Validated

“One critic (Rosenberg) pointed out that if there were a complete understanding of lymphoid neoplasms, with tools and methods to precisely dissect each patient’s cell of origin, genetic abnormality, level of differentiation and proliferation, every patient’s lymphoma might be different, one from the other. It is doubtful that such complete knowledge would be helpful.” Within a few years, however, a study of 1403 patients with non-Hodgkin’s lymphoma (The Non-Hodgkin’s Lymphoma Classification Project, 1997) provided validation of the ILSG classification, demonstrating diagnostic accuracy of at least 85% for most of the major lymphoma types.

Lymphomas are genetic diseases characterized by both normal

and abnormal genetic alterations of B cells, Dr. Harris said. Normal genetic alterations include antigen receptor gene rearrangement, somatic mutations of the Ig variable region genes, receptor editing, Ig heavy-chain class switch, and differential expression of a variety of adhesion molecules and receptor proteins, while abnormal genetic alterations include translocations and other mutations that occur during normal B-cell differentiation. Importantly, most lymphoid neoplasms derive from B cells at various stages of differentiation and share many features of their normal B-cell counterparts.

As B cells differentiate, they pass through distinct stages, from stem cells through progenitor B cells to germinal center cells (centroblasts and centrocytes), and on to memory B cells and plasma cells. Each stage is characterized by a dramatic change in cell morphology, which can be used to classify and diagnose particular lymphoma subtypes, Dr. Harris noted. For example, plasma cells correspond to plasmacytoma/myeloma, while memory B cells correspond to marginal zone B-cell lymphoma and B-cell lymphoblastic lymphoma. In addition, lymphomas can be analyzed by looking at antigens associated with stages of normal differentiation, including CD5 for naïve B cells and CD10 and BCL6 for germinal center cells.

Searching for Genetic Abnormalities

Most lymphomas are associated with genetic abnormalities, although only a few of these abnormalities are disease specific, said Dr. Harris. For example, the t(8;14) translocations of Burkitt’s lymphoma and the t(14;18) translocations of follicular lymphoma are also present in large B-cell lymphoma. Nevertheless, genetic analysis is an important tool for classification and diagnosis of lymphoma, as can be seen in genetic studies that have identified the relation between t(11;14) and mantle cell lymphoma. This translocation, which results in overexpression of cyclin D1, is detectable by immunohistochemistry and is useful in distinguishing mantle cell lymphoma from other types of small B-cell lymphomas. Other genetic abnormalities that exhibit diagnostically useful protein expression include t(14;18), a translocation that can help clinicians distinguish between reactive hyperplasia and follicular lymphoma, and t(2;5), a translocation useful for both defining and diagnosing anaplastic large cell lymphoma (see **Table** on next page).

Measurement of protein expression is not the only way to identify genetic abnormalities—genetic techniques such as Southern and Northern blots, cytogenetics, and PCR analysis currently play a role in lymphoma diagnosis, while the use of DNA microarray analysis (gene chips) may become a routine diagnostic procedure in the coming years. It is also important to remember, added Dr. Harris, that morphology is an important manifestation of gene expression and can be used to define disease entities. According to Dr. Harris, most lymphomas can be

TABLE. GENETIC ABNORMALITIES IN LYMPHOID NEOPLASMS ASSOCIATED WITH DIAGNOSTICALLY USEFUL PROTEIN EXPRESSION

Translocation	Protein Expression	Distribution	Utility
t(14;18)	BCL2	Germinal centers (–), follicular lymphoma (+)	Reactive vs neoplastic follicles
t(11;14)	Cyclin D1	Mantle cell lymphoma (all), hairy cell leukemia (some), plasma cell myeloma (some)	Mantle cell lymphoma vs other lymphomas or reactive process
t(2;5)	ALK (anaplastic lymphoma kinase)	Anaplastic large cell lymphoma (most)	ALCL vs other lymphomas of ALCL
t(1;14) or t(11;18)	BCL10	MALT lymphomas unresponsive to <i>H pylori</i> eradication	Prognosis/response prediction of MALT lymphomas

Reprinted with permission from Harris NL et al. New approaches to lymphoma diagnosis. In: *Hematology 2001*. ASH Education Program Book; 194-220.

diagnosed through a combination of morphology and immunophenotyping. Morphology alone is extremely effective, but the addition of immunophenotyping increases overall diagnostic accuracy, particularly in mantle cell lymphoma, diffuse large B-cell lymphoma, and T-cell lymphomas of all types. For primary diagnosis and classification of lymphoma, genetic techniques are required in 10% of cases or less.

“What about the future? Believe it or not, we need to define more categories of disease,” Dr. Harris said. “Our cure rate with current therapies is not optimal; it’s only about 50% for large cell lymphoma and even less for other disease categories. We need to identify prognostic or predictive groups within known disease categories, and we need to identify new disease entities that are currently lumped within broad categories, such as diffuse large B-cell and peripheral T-cell lymphoma.” ■

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Multiple Myeloma Therapy: Targeting the Microenvironment

This is a “very exciting time” in multiple myeloma therapy—“perhaps as exciting as when melphalan and prednisone first came into existence nearly 50 years ago,” Kenneth C. Anderson, MD, of Harvard Medical School, Boston, Mass, told a session at the ASH annual meeting.

The cause of this excitement, he explained, is the emergence of a new crop of agents that target not only the myeloma cell itself but also the cell’s interactions with various immunologic and angiogenic factors in the bone marrow microenvironment.

The first and most widely studied of these agents is thalidomide, which was the subject of numerous abstracts presented at the ASH meeting. Important new data were also presented docu-

menting the clinical promise of the proteasome inhibitor PS-341 and the so-called IMiD, or immunomodulatory drug derivative, of thalidomide, CC-5013.

Thalidomide Dosing Debated

The immunomodulatory and antiangiogenic properties of thalidomide in multiple myeloma are well documented. At ASH, the quest for optimal dosing and combination strategies dominated the discussion of this agent.

The Total Therapy II trial, conducted by Bart Barlogie, MD, and colleagues at the University of Arkansas, Little Rock, included up-front administration of thalidomide at the standard dose of

400 mg/d in 1 arm of a study focusing on intensive, multiple regimens of chemotherapy prior to autologous blood marrow transplantation. After a mean follow-up of 18 months, Dr. Barlogie reported, the rates of complete remission (45%), event-free survival (73%), and overall survival (80%) in the first 231 Total Therapy II patients were superior to those of an equivalent number of patients from the previous Total Therapy I study, which featured less intensive chemotherapy without thalidomide.

Increased Risk for DVT?

However, the investigators observed a significant association between thalidomide treatment and deep vein thrombosis (DVT). Close analysis of DVT risk factors indicated that patients with a baseline coagulation abnormality, indicated by reduced response to activated protein C in the absence of factor V Leiden, were at increased risk for DVT during chemotherapy in general. The combination of thalidomide and doxorubicin, in particular, also increased the risk of DVT. According to Dr. Barlogie, the presence of doxorubicin was responsible for the DVT associated with thalidomide treatment, and when doxorubicin was removed, thalidomide did not cause DVT.

A low-dose approach to thalidomide therapy was championed by Brian G.M. Durie, MD, of Cedars-Sinai Comprehensive Cancer Center in Los Angeles, Calif. Dr. Durie's rationale was that initial studies in multiple myeloma patients indicated that thalidomide toxicity increases with dose escalation, whereas investigations in the laboratory and in other disease states suggest that "even tiny doses of thalidomide may produce benefit."

He presented long-term follow-up results from a phase II study of thalidomide 50 to 400 mg/d (median dose, 200 mg/d) in 36 patients with relapsing or progressive multiple myeloma after chemotherapy and transplantation. Complete remission (>75% regression in M-protein levels) was seen in 6 patients and partial remission (>50% regression) in 3; the overall response rate was 44%. Of the patients with >50% regression, all were still in remission at 6 months, 67% at 18 months, and 22% at 2 years.

Median Safe, Effective Dose

Low-dose thalidomide was generally well tolerated, but progressive peripheral neuropathy was a significant adverse event. In patients who were reduced to very low thalidomide doses or were relapsing on thalidomide alone, the addition of low-dose dexamethasone and biacin was effective in maintaining or recapturing remission.

"Thalidomide 200 mg/d is the median effective dose in multiple myeloma," Dr. Durie concluded, "although 50 mg/d may be sufficient, particularly in combination with other therapies."

Further support for low-dose thalidomide was provided by A.D. Wechalekar, MD, and colleagues at the University of Toronto, Ontario, Canada. They conducted a retrospective analysis of 37 patients with relapsed multiple myeloma who received thalidomide 200 mg/d with no dose escalation. Response rates were comparable to those previously reported with escalated doses

up to 800 mg/d, and the lower dose appeared to be better tolerated. "These results suggest that dose escalation beyond 200 mg/d should not be routinely employed in the absence of documented poor response to treatment," the authors noted.

On the other hand, Neben et al, of Heidelberg, Germany, have analyzed the efficacy of thalidomide in 83 refractory multiple myeloma patients and concluded that the benefit was dose dependent: "Cumulative thalidomide dosage is one of the major prognostic factors for overall survival, and a thalidomide dosage of 400 mg/d should be maintained as long as possible whenever the treatment is tolerated."

IMiDs: Building on Thalidomide

The thalidomide analogues known as immunomodulatory drugs (IMiDs) have also shown promise in the treatment of multiple myeloma. One member of the IMiD class, CC-5013, is currently under study in several groups of myeloma patients, including patients with relapsed and refractory multiple myeloma. According to Paul Richardson, MD, of the Dana-Farber Cancer Institute in Boston, Mass, the antimyeloma activity of CC-5013 appears to stem from multiple mechanisms of action, including effects on cell adhesion; induction of apoptosis or G1 growth arrest; inhibition of IL-6, TNF α , and IL-1 β production; upregulation of CD8 and T-cell activity; and antiangiogenesis activity.

Initial Safety Assessment

In one phase I study, Dr. Richardson and colleagues found that CC-5013 was well tolerated and exhibited significant antitumor activity in patients with relapsed and refractory multiple myeloma. The primary objective of this study was to assess the safety of CC-5013 at doses of 5 mg/d, 10 mg/d, 25 mg/d, and 50 mg/d given orally for up to 4 weeks. Assessments of patient response to CC-5013 were also conducted, and patients who tolerated the drug and did not show disease progression were allowed to continue therapy for up to 1 year. After a median duration of therapy of 4 months, no dose-limiting toxicity was seen in the initial 4-week stage of the study, although thrombocytopenia and neutropenia necessitating dose reduction were seen in the extension phase. Dr. Richardson stressed that no significant somnolence, constipation, or neuropathy was seen at any time. In terms of drug efficacy, 19 of 24 patients (79%) had stable disease or better as measured by paraprotein levels, while 63% of patients showed 25% or greater decreases in paraprotein levels.

A second phase I study, in 15 multiple myeloma patients who had relapsed after high-dose chemotherapy, further confirmed the safety profile and efficacy of CC-5013. Four escalating doses (5, 10, 25, and 50 mg/d) of CC-5013 were given to patients for 4 weeks. Patients who did not have disease progression or dose-limiting toxicity could receive further dose escalations in an extension study. Overall, 20% of study patients had a greater than 50% reduction in paraprotein levels after treatment with CC-5013. However, while neurologic toxicity was minimal, CC-5013 appeared to cause significant myelosuppression even in those

patients who had adequate platelet counts and bone marrow cellularity before the start of treatment.

Impact of Proteasome Inhibitors

According to Dr. Anderson, proteasome inhibitors also target both myeloma cells and their neighborhood microenvironment: “Proteasomes are intracellular enzymes whose job in life is to break down ubiquitinated proteins.” Dr. Anderson’s group has shown that the proteasome inhibitor PS-341 induces apoptosis of drug-resistant myeloma cell lines and patient cells and can overcome resistance to conventional therapy. PS-341 also inhibits the binding of myeloma cells to stromal cells, and inhibits the NF- κ B activation-dependent transcription and secretion of cytokines, such as interleukin-6, that are triggered in the neighborhood when a myeloma cell binds to bone marrow stroma. Moreover, like the IMiDs, PS-341 is an antiangiogenic compound.

Recent trial results suggest that the impact of PS-341 (also called LDP-341) on myeloma cells and the microenvironment can translate into therapeutic benefits for multiple myeloma patients. In one phase II study of 200 multiple myeloma patients, all of

whom had relapsed following a response to standard first-line treatment and were refractory to their most recent therapy (including thalidomide, steroids, and chemotherapy), PS-341 was shown to stabilize or reduce M protein levels in 85% of patients, according to Dr. Richardson. Although these results are still preliminary (only 54 of the 200 patients had been analyzed at the time of the report), data from an additional 22 patients appear to confirm the benefits of PS-341. Overall, PS-341 was well tolerated and had a manageable toxicity profile, said Dr. Richardson.

Another study of PS-341 has shown that this agent markedly enhances the sensitivity of multiple myeloma cells to chemotherapeutic agents and overcomes chemoresistance through inhibition of the NF- κ B pathway, reported Mark Ma, PhD, of Cedars-Sinai Medical Center in Los Angeles, Calif. According to Dr. Ma, a noncytotoxic dose of PS-341 was found to increase significantly the sensitivity of chemoresistant cell lines to chemotherapy agents, including melphalan, doxorubicin, and mitoxantrone—suggesting that the addition of PS-341 to multiple myeloma therapy could reduce the dosage requirements of chemotherapeutic agents. ■

Dual Stem Cell Graft Including a Nonmyeloablative Allogeneic Transplant in Multiple Myeloma

A new study conducted by David G. Maloney, MD, of Fred Hutchinson Cancer Research Center in Seattle, Wash—using nonmyeloablative allogeneic hematopoietic stem cell transplantation following a preliminary high-dose autologous graft—has shown a marked reduction in treatment-related mortality while maintaining high rates of complete remission in a small group of older myeloma patients.

Investigators were seeking to establish an effective therapy for patients with myeloma by combining the safety and cytoreductive capacity of high-dose melphalan and autologous hematopoietic stem cell transplantation with the curative potential of nonmyeloablative allogeneic transplantation from HLA-matched siblings, Dr. Maloney told an ASH session. “Our hypothesis was based on the observation that patients have a high relapse rate following the standard autologous transplant despite low mortality, whereas patients undergoing full allogeneic transplants have higher rates of remission but also higher transplant-related mortality.”

Thirty-two patients ranging in age from 39 to 71 years with a median of 52 years were included in the study. They had received prior chemotherapy but no transplantation for their myeloma. Disease status at the time of transplant was relapsed-to-refractory myeloma in roughly half the population and responsive disease in the other half; 36% had achieved partial remission and 15% complete remission.

Patients underwent peripheral blood stem cell mobilization using high-dose cyclophosphamide before stem cell collection and

were conditioned with high-dose melphalan at 200 mg/m² before receiving the autologous transplant. Between 40 and 120 days later—after recovering from acute toxicities of the ablative transplant—they received a single fraction of 200 cGy total body irradiation and immunosuppression with 28 days of mycophenolate mofetil and at least 56 days of cyclosporine. Allografts from HLA-identical siblings were performed at a median of 62 days following the autologous transplants.

In the current study, the transplant-related mortality at day +100 was 5%. With a median follow-up of 423 days after the autologous transplant and 328 days after the allogeneic graft, the overall response rate was 84%, with 53% complete remissions, 31% partial remissions, and only 2 progressions (6%). The overall survival rate was 81%.

A Double-Edged Sword

The potentially curative graft-vs-myeloma effect offered by myeloablative allogeneic transplants presents a “double-edged sword,” Dr. Maloney said, since the benefit of this effect is associated with graft-vs-host disease (GVHD), the most serious complication of allografts. In a study population of 32 patients, 16 developed readily treatable stage II GVHD and only 1 a more serious grade III disease. Two developed fatal grade IV disease.

Tapering immunosuppression in these patients after the allograft can be “a bit of an art,” Dr. Maloney added. “We try to maintain immunosuppression when there is significant GVHD, tapering slowly when there is no real GVHD and the patient is in

remission or shows no evidence of myeloma, and tapering more quickly if there is progressive myeloma but no GVHD disease.”

For the Majority, an Outpatient Procedure

Median hospitalization periods were 1 week for the autologous procedure and 0 days for the nonmyeloablative allogeneic transplant—“which demonstrates that the majority of these patients can be treated as outpatients for the allograft, despite their generally advanced ages.”

The autologous transplants tended to produce neutropenia and thrombocytopenia that were severe at first but resolved gradually. There was severe neutropenia lasting a median of 6 days after the autologous procedure, but 0 days after the allogeneic transplant. Similarly, severe thrombocytopenia lasted a median of 1 day after the autograft but 0 days after the allograft, with platelet nadirs of less than 20,000 for the autograft compared with 94,000 for the allograft.

Dr. Maloney pointed out that “there are some caveats from this study. Longer follow-up is clearly necessary to see whether the disease response will be maintained, and GVHD remains a challenge. Strategies to develop a more specific graft-vs-myeloma effect are clearly warranted.”

He said he did not believe the tandem transplant technique would be limited to a minority of patients with myeloma owing to the lack of availability of HLA-identical siblings. “As data mature about the use of unrelated donor nonmyeloablative allografts, it appears it can be done with a similar degree of at least peritransplant-related mortality. We have not yet started a formal trial with this combination, but we have been approached by many patients who are interested in unrelated donor allografts.”

For the time being, however, such procedures should be limited to clinical trials, he emphasized. “Although this is being done as an outpatient procedure, there are significant issues of GVHD in complications.”

The Only Way to Cure Multiple Myeloma?

In a separate presentation, Jean-Luc Harousseau, MD, of University Hospital in Nantes, France, suggested that allogeneic bone marrow transplantation “could be the only way to cure multiple myeloma.” Analysis of the ABMT Registry has shown that long-term survival can be obtained with allogeneic transplants, especially in patients transplanted early, “and several groups have shown that molecular remissions are possible.”

Allograft results can be improved through better selection with earlier transplantation, use of unselected peripheral blood stem cells instead of marrow, use of a nonmyeloablative conditioning regimen, and manipulation of the graft-vs-myeloma effect, Dr. Harousseau said. ■

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HIGHLIGHTS FROM THE LITERATURE

Hematologic and Cytogenetic Responses to Imatinib Mesylate in CML

Kantarjian H, Sawyers C, Hochhaus A, et al. *N Engl J Med.* 2002;346(9):645-652

Rationale

The purpose of this study was to evaluate the use of imatinib mesylate (a selected inhibitor of BCR-ABL tyrosine kinase) in patients with late-phase chronic myelogenous leukemia (CML) in whom previous

therapy with interferon- α had failed. CML is caused by the BCR-ABL tyrosine kinase produced by the Philadelphia chromosome. While curable with allogeneic stem-cell transplantation, less than 30% of late-stage CML patients are able to locate suitable donors.

Methods

A phase II study evaluated 532 patients with late-stage CML in whom previous interferon- α therapy had failed. Each patient received 400 mg oral imatinib mesylate daily. Patients were monitored for

cytogenetic and hematologic responses, time to progression, survival, and toxic effects for 18 months, with ongoing evaluations being conducted every 6 months.

Main Results

Follow-up at 18 months revealed that CML had not progressed to accelerated or blast phases in an estimated 89% of patients and that 95% of patients were still alive. Drug-related toxic effects were infrequent (non-hematologic) or considered manageable (hematologic). Additional response rates are contained in the **Table** on page 14.

Conclusions

Imatinib mesylate induced high rates of cytogenetic and hematologic responses in patients with late, chronic-phase CML in whom previous treatment with interferon- α had failed. Because imatinib is well tolerated, it may be feasible to combine it with other agents to treat interferon-resistant CML in the late, chronic phase or to optimize the status of the disease before performing allogeneic stem cell transplantation. In this study, disease progression occurred in nearly 10% of patients within 18 months. Regimens that combine imatinib with other agents may improve results further, and ongoing clinical trials are testing the feasibility of these approaches. ■

TABLE. RESPONSE TO IMATINIB MESYLATE IN PATIENTS WITH CHRONIC MYELOGENOUS LEUKEMIA

Response	Number of Patients (%) [†]
Major cytogenetic response* (CR + PR)	272 (60)
Complete response (CR)	188 (41)
Partial response (PR)	84 (19)
Minor response	21 (5)
Minimal response	50 (11)
Complete hematologic response	430 (95)

*Level of cytogenetic response defined as percentage of Ph chromosome-positive cells in metaphase: CR, 0%; PR, 1%-35%; minor response, 36%-65%; minimal response, 65%-95%; no response, >95%.

[†]n = 454.

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Double-Delayed Intensification Improves Event-Free Survival for Children With Intermediate-Risk ALL: A Report From the Children's Cancer Group

Lange BJ, Bostrom BC, Cherlow JM, et al. *Blood*. 2002;99:825-833.

Rationale

Previous studies have demonstrated that the addition of a delayed-intensification (DI) phase following standard induction/consolidation therapy improves outcomes in patients with intermediate-risk acute lymphoblastic leukemia (ALL) younger than 10 years of age. Children with intermediate-risk ALL represent approximately two thirds of NCI-defined standard-risk patients.

The CCG-1891 study for this subset of patients has suggested that the addition of a second DI phase given 16 weeks after the first DI phase results in improved event-free survival (EFS). The present study compares the effectiveness of a single DI phase, a double-delayed intensification (DDI) phase, and a single DI phase in conjunction with

increased vincristine and prednisone pulses during maintenance (DIVPI) in intermediate-risk ALL patients (<10 years of age) in terms of EFS.

Methods

A total of 1204 intermediate-risk ALL patients (<10 years of age) were randomized into 3 treatment groups to receive standard induction/consolidation therapy followed by DI (n = 405), DDI (n = 402), or DIVPI (n = 397). Treatment outcomes were evaluated in terms of EFS (log-rank, Kaplan-Meier [KM], relative risk [RR]) and survival at 6 years. (Estimates of EFS and survival at 6 years are 79% \pm 1% and 89% \pm 1%, respectively.)

Main Results

EFS was improved with DDI, compared with DI (log-rank, $P = .04$; KM, $P = .04$; RR = 1.38) or DIVPI (log-rank, $P = .04$; KM, $P = .01$; RR = 1.39), with no significant differences in EFS between DI and DIVPI noted (log-rank, $P = .96$; KM, = .75). Estimates of survival at 6 years were 87%, 91%, and 90% (SD = 2%, $P = .17$), respectively. In addition, several significant univariate risk factors were identified, including poor day 7 marrow response,

black race, and age > 5 years.

Treatment-related toxicities, attributable primarily to the myelosuppressive effects of daunorubicin, cytosine arabinoside, and cyclophosphamide, or the effects of L-asparaginase on coagulation, were more frequent for patients on DDI than on DI. These complications did not result in significantly increased treatment-related mortality or major late effects that might compromise the life or functioning of these patients.

Conclusions

Data from this study indicate that DDI improves EFS of patients younger than 10 years of age with intermediate ALL. Findings suggest that patients with a modest residual tumor burden are most likely to benefit from DDI. However, these results must be interpreted with caution, since they are based on subset analyses that were not part of the overall design of the study. Since half of all patients achieved a favorable day 7 response, these data also suggest that improved methods are needed to identify the subset of patients with a favorable day 7 M1 marrow response who will nevertheless experience events with current intensive therapies. ■

CHOP Chemotherapy Plus Rituximab Compared With CHOP Alone in Elderly Patients With Diffuse Large B-Cell Lymphoma

Coiffier B, Lepage E, Briere J, et al. *N Engl J Med*. 2002;346:235-242.

Rationale

A previous phase II study showed rituximab, a chimeric monoclonal antibody against the CD20 B-cell antigen, to be effective when given as a single agent in the treatment of relapsed or refractory indolent lymphomas and to have activity in relapsed or refractory diffuse large B-cell lymphoma. The purpose of this study was to evaluate the efficacy of adding rituximab to standard

treatment, consisting of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), in patients with diffuse large B-cell lymphoma.

Methods

This study recruited 399 patients with stage II to IV diffuse large B-cell lymphoma, Eastern Cooperative Oncology Group status of good to fair, and no previous evidence of indolent lymphoma or primary CNS location. These patients were treated with either standard-dose CHOP to 8 cycles or with the same chemotherapy plus a single infusion of rituximab 375 mg/m² on day 1 of each cycle. Histologic definition of diffuse large B-cell lymphoma was confirmed in 87% of patients in the combination group, and 60% of these had a high IPI score (≥ 2).

Main Results

When compared with standard CHOP therapy, CHOP plus rituximab significantly improved completion response (63% vs 76%, $P = .005$) and increased event-free and overall survival times (mean follow-up, 2 years) ($P = .007$ and $P < .001$, respectively). In addition, rituximab plus standard CHOP therapy resulted in a significantly reduced risk of treatment failure and death.

Conclusions

The addition of rituximab to CHOP therapy increases the complete-response rate and prolongs event-free and overall survival in elderly patients with diffuse large B-cell lymphoma, without a clinically significant increase in toxicity. ■

COMMENTARY

The CHOP-R Combination—an Advance in the Treatment of Elderly Lymphoma

By Gareth Morgan, MD

The cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) combination was developed early in the history of treating large cell lymphoma and has been associated with relatively good responses and survival figures. Attempts to improve these outcomes led to a number of more complicated and generally more dose-intensive regimens that, in initial pilot studies, seemed to offer improvements. However, when these regimens were formally evaluated in randomized comparisons with CHOP, they were seen to offer no advantage. Thus, CHOP was adopted as the gold standard treatment for large cell lymphoma.

While these alternative treatments were being explored, the International Prognostic Index (IPI) was developed to divide large cell lymphoma into a number of different prognostic categories, with higher scores indicating greater risk of death. These survival differences proved sufficiently large to warrant treating diseases of good vs poor prognosis with different approaches. Many studies in the poor-

prognosis group have involved autologous transplantation or high-dose sequential treatments as a way of increasing dose intensity. However, this dose-intensity increase has been achieved at the cost of increased toxicity for the patient.

The use of rituximab in combination with chemotherapy offers a way of increasing dose intensity without increasing toxicity, making the combination applicable for both standard- and poor-risk groups. Not only can this treatment induce antibody-dependent cell-mediated cytotoxicity (ADCC), but in addition, cell signalling via CD20 may sensitize the cell to the apoptotic effects of chemotherapy. This is exciting, because rituximab has an alternative mechanism of action and offers the potential for synergy with chemotherapy. There are therefore a number of clinical settings in which the combination of CHOP plus rituximab is being explored.

The first of these studies to be reported is the Groupe d'Études des Lymphomes Agressifs (GELA) trial. The data presented here on the basis of a median 18-month

follow-up support the benefit of combination treatment with better clinical outcomes without increased toxicity. The benefit of rituximab was shown to be independent of IPI status or age, and there was no evidence of an increase in adverse events in the combination arm.

On the basis of this study, we may conclude that the addition of rituximab to CHOP provides a new standard of care for the treatment of diffuse large B-cell lymphoma in patients between 60 and 80 years old. There are new studies investigating the potential role of this combination in other clinical settings—particularly in younger patients with diffuse large B-cell lymphoma, as maintenance after high-dose treatment, and in indolent lymphoma. On the basis of our previous experience with the treatment of diffuse large cell lymphoma, we should encourage entry into these studies so that an optimal role for this combination can be defined. It seems likely that the use of CHOP plus rituximab will continue to expand.

Prognostic Factors and Scoring Systems in CMML: A Retrospective Analysis of 213 Patients

Onida F, Kantarjian HM, Smith TL, et al. *Blood*. 2002;99:840-849.

Rationale

Chronic myelomonocytic leukemia (CMML) is characterized by increased monocytes in the bone marrow and peripheral blood and a variable degree of marrow dysplasia. The classification of CMML remains a subject of debate. Because it is frequently accompanied by dysplastic hematopoiesis, CMML was classified as a subcategory within myelodysplastic syndromes (MDSs) by the French-American-British Cooperative Leukemia Group (FAB) in 1982. However, CMML is more heterogeneous than other types of MDSs. Thus, while some patients present with only modest leukocytosis, others have high white blood cell (WBC) counts and organ involvement, eg, splenomegaly, serous effusions, and lymph node or skin infiltration. Accordingly, an arbitrarily chosen leukocyte count has been recently used to distinguish between a “dysplastic” type (MDS-CMML; WBC count $\leq 13 \times 10^9/L$) and a “prolifera-

tive” type (myeloproliferative disorder [MPD]-CMML; WBC count $> 13 \times 10^9/L$). A recent proposal by the World Health Organization’s classification committee included CMML in a new category of MDS/MPD disorders.

The purposes of this study were to evaluate the ability of published prognostic systems to stratify patients suffering from CMML according to risk and to design a new, simple, and clinically useful scoring system based on data from a large number of patients. In addition, prognostic variables and survival in CMML patients with “dysplastic” and “proliferative” disease were evaluated.

Methods

The investigators performed a retrospective analysis of 213 patients with CMML who were treated at M.D. Anderson Cancer Center from 1966 through March 1999. Their median survival was 12 months. In addition, a proposed prognostic model was compared with 6 previous prognostic tools for CMML.

Main Results

Univariate analysis identified the following characteristics associated with shorter survival: low hemoglobin level; low platelet count; high white blood cell, monocyte,

and lymphocyte counts; presence of circulating immature myeloid cells; high percentage of marrow blasts; low percentage of marrow erythroid cells; abnormal cytogenetics; and high levels of serum lactate dehydrogenase and β_2 -microglobulin.

Multivariate analysis revealed several independent factors associated with shorter survival: hemoglobin level below 120 g/L (12 g/dL); presence of circulating immature myeloid cells; absolute lymphocyte count above $2.5 \times 10^9/L$; and marrow blasts of 10% or more.

In addition, the study was unable to confer evidence that divisions of CMML by white blood cell counts into “dysplastic” and “proliferative” categories reflect clinical entities differing in the risk of acute leukemia development.

Conclusions

The proposed model predicted (on the basis of hemoglobin levels, lymphocyte counts, marrow blast cells, and circulating immature myeloid cells) 4 subgroups of patients with median survivals of 24, 15, 8, and 5 months for low, intermediate-1, intermediate-2, and high risk, respectively. These newly identified variables can provide physicians with a more accurate prognostic assessment tool for patients with CMML. ■

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