American Journal of Hematology 81:470–477 (2006)

LETTERS AND CORRESPONDENCE

Letters and correspondence submitted for possible publication must be identified as such. Text length must not exceed 500 words and five bibliographic references. A single concise figure or table may be included if it is essential to support the communication. Letters not typed double-spaced will not be considered for publication. Letters not meeting these specifications will not be returned to authors. Letters to the Editor *are utilized to communicate a single novel observation or finding.* Correspondence *is to be used to supplement or constructively comment on the contents of a publication in the journal and cannot exceed the restrictions for* Letters to the Editor. *The Editor reserves the right to shorten text, delete objectional comments, and make other changes to comply with the style of the journal. Permission for publication must be appended as a postscript. Submissions must be sent to Jay Umbreit, MD, PhD, Editor of* Brief Reports/Letters to Editors, American Journal of Hematology, *Winship Cancer Institute, Emory University, 1365-B Clifton Road, Suite B4100, Atlanta, GA 30322 to permit rapid consideration for publication.*

Induction Chemotherapy and Post-Remission Imatinib Therapy for de Novo *BCR-ABL*-Positive AML

To the Editor: Translocation t(9;22)(q34;q11) is found in 1–2% of newly diagnosed patients with de novo AML. The prognosis of Ph^+ AML is very poor with a median survival time of only 7 months. We present two patients with de novo Ph^+ AML who received induction chemotherapy and post-remission imatinib therapy.

A 73-year-old man was admitted in November 2003 with fatigue and palpitation. Physical examination showed only pallor. The Hb was 83 g/L, platelets 145×10^9/L, and WBC 1.4×10^9/L, 0.12×10^9/L blast cells. FACS analysis of marrow mononuclear cells showed 22% blast cells positive for HLA-DR, CD34, CD117, CD13, CD33, MPO, and CD38 and partially CD11b. Karyotype analysis of bone marrow cells with GTG banding showed 46,XY,t(9;22)(q34;q11) in 20 analyzed metaphases. Interphase FISH with probe specific for t(9;22)(q34;q11) showed only one fusion signal in 174 out of 200 cells. The patient received induction treatment with amsacrine, cytarabine, and etoposide. Bone marrow on day +28 showed remission with 1% blast cells and imatinib was instituted in a dose of 600 mg/day. Quantitative RT-PCR for *BCR-ABL* (major) was performed repeatedly (Fig. 1). The patient is still taking imatinib at 400 mg/day, 19 months after diagnosis, and he is in complete molecular remission.

A 63-year-old male patient was admitted in May 2004 with lymphadenopathy and splenomegaly. Blood counts showed Hb 71 g/L, WBC 115.9×10^9/L, platelets 58×10^9/L. The differential count showed blast cells 82.3×10^9/L, band forms 1.2×10^9/L, neutrophils 4.6×10^9/L, eosinophils 1.2×10^9/L, monocytes 6.9×10^9/L, lymphocytes 18.5×10^9/L. Bone marrow aspiration showed 40–45% blast cells in two populations of similar size. One line expressed predominantly myeloid markers; HLA-DR, CD34, CD13, CD117, and TdT. Another population expressed HLA-DR, CD34, CD19, CD22, CD79, TdT, and CD13. The karyotype was 46,XY,der(9)t(9;22)(q34;q11),del(10)(q23), der(22)(9;10;22) in 20 analyzed cells. FISH analysis confirmed the presence of t(9;22) in 194/200 interphase nuclei. RT-PCR was positive for minor *BCR-ABL* rearrangement. The patient received induction therapy with daunorubicin, cytarabine, and betamethasone. A bone marrow aspirate on day +20 showed remission with 4% blast cells, and imatinib 400 mg/day was started. Four months after diagnosis, cytogenetic analysis showed Philadelphia chromosome in 3 out of 20 metaphases and FISH analysis showed fusion signals in 27/400 peripheral blood cells. The patient is in continuous remission 1 year after commencing imatinib therapy, and he is still taking 400 mg/day.

In the literature, we have found three patients treated with imatinib for Ph-positive AML [1–3]. One of the patients was induced into remission with chemotherapy similarly to our patients [3]. The first of our patients obtained complete molecular remission during imatinib therapy. In the second case, the number of copies decreased during imatinib therapy but reached a plateau. Both patients are enjoying a good quality of life more than 1 year after diagnosis. The strategy of standard chemotherapy induction followed by consolidation/maintenance with continuous imatinib treatment has been successful in our two Ph-positive AML patients and could be explored in a future trial.

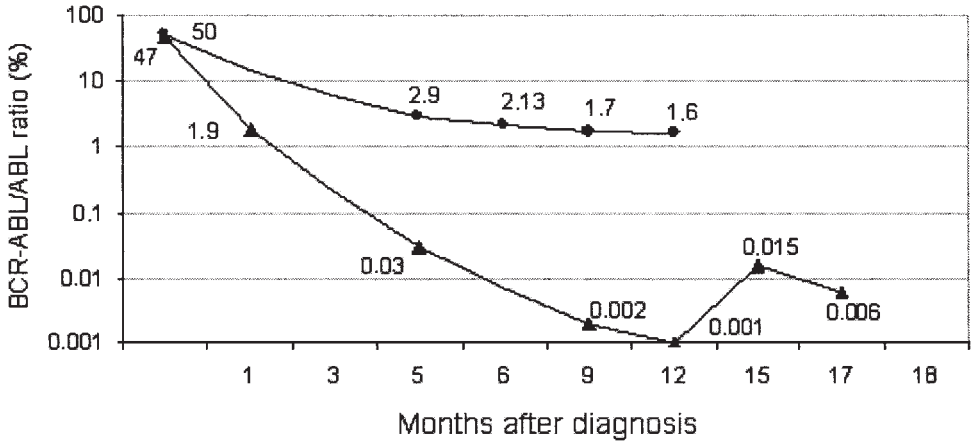


Fig. 1. Quantitative RT-PCR for BCR-ASL rearrangement in two patients with Ph^+ AML treated with imatinib.

Vladimir Lazarevic[1]
Irina Golovleva[2]
Ida Nygren[1]
Anders Wahlin[2]

[1]Department of Hematology, University Hospital of Northern Sweden, Umeå, Sweden
[2]Medical and Clinical Genetics/Medical Biosciences, University Hospital of Northern Sweden, Umeå, Sweden
Published online in Wiley InterScience (www.interscience.wiley.com).
DOI: 10.1002/ajh.20578

References

1. Ito K, Tominaga K, Suzuki T, Jinna I, Bessho M. Successful treatment with imatinib mesylate in a case of minor BCR-ABL-positive acute myelogenous leukemia. Int J Hematol 2005;81:242–245.
2. Viniou NA, Vassilakopoulos TP, Giakoumi X, Mantzouranis M, Pangalis GA. Ida-FLAG plus imatinib mesylate-induced molecular remission in a patient with chemoresistant $Ph1^+$ acute myeloid leukemia. Eur J Haematol 2004;72:58–60.
3. Jentsch-Ullrich K, Pelz AF, Braun H, et al. Complete molecular remission in a patient with Philadelphia-chromosome-positive acute myeloid leukemia after conventional therapy and imatinib. Haematologica 2004;89(5):ECR15.

Folic Acid Deficiency: Main Etiological Factor of Megaloblastic Anemia in Kazakhstan?

To the Editor: Megaloblastic anemia (MA) is the common final expression of a variety of conditions, including nutritional deficiency, drug toxicity, inborn errors of metabolism, and other abnormalities. In clinical practice, 95% of cases are caused by deficiencies of vitamin B_{12} (VB12, cobalamin), folic acid, or both [1]. Although it is estimated that dietary VB12 deficiency occurs less frequently than folate deficiency does [2], detailed reports on folate and/or VB12 deficiency in patients with MA are quite rare. Nevertheless, from the clinical point of view, MA due to folate deficiency tends to receive less attention. Accurate identification of the etiology of MA is important for appropriate treatment and management of MA patients.

In the Republic of Kazakhstan, located in central Asia, 60% of the population is Kazakh and 40% is Russian or of other ethnicities. Because the roots of the Kazakh culture are nomadic, the traditional diet consists mainly of meat, such as mutton and beef, and vegetable intake tends to be deficient. As this eating pattern may contribute to the occurrence of MA, we screened levels of VB12 and FA in Kazakh patients with MA in order to clarify the causal relationship between their eating pattern and the etiology of MA.

We screened 20 Kazakh adults with MA, age range 40–87 years, who received preliminary diagnoses of MA on the basis of peripheral blood manifestations, such as significant macrocytosis (increase in mean cell volume and mean cell hemoglobin), marked anisocytosis, and poikilocytosis. After obtaining informed consent, we collected the serum from each patient to measure FA and VB12 using the chemiluminescent immunoassay radioimmunoassay (CLIA) method. Normal ranges of FA and VB12 were 3.6–12.9 ng/mL and 233–914 pg/mL, respectively.

Eleven of 20 patients (55%) showed isolated FA deficiency, 5 (25%) showed isolated VB12 deficiency, and 4 (20%) showed combined deficiency of FA and VB12; these findings indicate that 75% of MA is associated with FA deficiency, whereas 45% of MA is associated with VB12 deficiency.

It has been reported that FA deficiency is a relatively rare cause of MA in Scandinavia but common in North America [3]. Although the sample number in our study is quite limited, our preliminary results suggest that FA deficiency may be more important than VB12 deficiency in the causation of MA in Kazakhstan. The traditional dietary habits of the Kazakh people may be associated with the high prevalence of FA deficiency in patients with MA. Therefore, special efforts to ensure regular and adequate intake of FA are needed for the prevention of MA in this population as well as for the appropriate treatment of patients.

Recently, it has been emphasized that FA deficiency may be the main determinant of hyperhomocysteinemia, a novel and independent risk factor for birth defects such as spina bifida and Down syndrome, as well as atherosclerosis and the resulting cardiovascular diseases [4,5]. Further studies, including evaluation of the normal population, will be needed for the improvement of health status in Kazakhstan.

Ainur Akilzhanova[1]
Noboru Takamura[2]
Kiyoshi Aoyagi[2]
Ludmila Karazhanova[1]
Shunichi Yamashita[3,4]

[1]Department of Therapy No. 2, Semipalatinsk State Medical Academy, Semipalatinsk, Republic of Kazakhstan
[2]Department of Public Health, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan
[3]Department of Molecular Medicine, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan
[4]Department of Protection of the Human Environment, World Health Organization, Geneva, Switzerland
Published online in Wiley InterScience (www.interscience.wiley.com).
DOI: 10.1002/ajh.20576

References

1. Sullivan LW. The differential diagnosis and management of the patients with megaloblastic anemia. Am J Med 1970;48:609–617.
2. Herbert V. Vitamin B_{12}. In: Olesen RE, Broquist HP, Chichester CO, et al., editors. Nutrition Reviews' present knowledge in nutrition, 5th edition. Washington, D.C.: The Nutrition Foundation; 1984. p 347–364.
3. Grasbeck R. Biochemistry and clinical chemistry of vitamin B_{12} transport and the related diseases. Clin Biochem 1984;17:99–107.
4. Verhoef P, Kok FJ, Kruyssen DACM, et al. Plasma total homocysteine, B vitamins and risk of coronary atherosclerosis. Arterioscler Thromb Vasc Biol 1997;17:989–995.
5. Graham IM, Daly LE, Refsum HM, et al. Plasma homocysteine as a risk factor for vascular disease. The European Concerted Action Project. JAMA 1997;277:1775–1781.

Myelodysplastic Syndrome and Acute Myeloid Leukemia after Treatment with Fludarabine, Mitoxantrone, and Dexamethasone

To The Editor: We reported recently the occurrence of therapy-related myelodysplastic syndrome/acute myeloid leukemia (t-MDS/AML) in a patient after single-agent treatment with the purine analog fludarabine [1]. From 1996 to 2004, we treated 148 cases of indolent B- and T-cell lymphomas with fludarabine in combination with mitoxantrone and dexamethasone (FND) [2]. At a median follow-up of 42 months after FND treatment, 4 (2.7%) of these patients had developed MDS/AML (Table I).

There were two cases of acute promyelocytic leukemia (APL). When these two patients were compared with other reported cases of therapy-related APL (t-APL) [3], there were a number of important similarities. First, the latency of our cases at 22 and 26 months after FND was comparable with the median latency of 25–29 months reported for t-APL. In fact, the latency of t-APL is characteristically much shorter than other t-AML/MDS, which varied from 59 to 72 months [3]. Second, treatment with topoisomerase II inhibitors was distinctly frequent in previous studies of t-APL, with mitoxantrone identified as a particularly important risk factor [3]. Moreover, t-APL was unusually prevalent in breast cancer patients treated with mitoxantrone-containing chemotherapy, accounting for about 25% of all cases of t-MDS/AML in such patients. Finally, mitoxantrone-induced DNA cleavage by topoisomerase II has been shown recently to underlie the pathogenesis of t-APL [4]. Therefore, these observations suggest that mitoxantrone in the FND regimen might be the important cause of the t-APL in our cases.

American Journal of Hematology DOI 10.1002/ajh

TABLE I. Four cases of myelodysplastic syndrome/acute myeloid leukemia (MDS/AML) after FND treatment

		Lymphoma				MDS/AML							
		Type	Dx date	Initial Rx	Relapses (Rx)	Dx date	Latency	Marrow blasts	WHO	Cytogenetics	Lymphoma	Rx	Outcome
1	F/45	FL	Apr 03	FND × 6 anti-CD20	Nil	Jan 05	22 months	52%	APL	46,XX,t(15;17)(q22;q21)	CR PCR −ve	ATRA, 7+3	CR, 2 months
2	M/65	FL	Nov 85	Local RT	Nov 89 (CVP × 10) May 00 (FND × 6)	Jun 02	26 months	76%	APL	46,XX,t(15;17)(q22;q21)	CR PCR −ve	ATRA	Died, 2 months
3	M/53	FL	Jun 89	CHOP × 6	Oct 97 (FND × 6)	Feb 99	16 months	5%	RCMD	46,XY,del(7)(q22)	NR	Supportive	Defaulted
4	M/71	MCL	Mar 96	m-BACOD × 5 local RT	Nov 98 (FND × 3, anti-CD20)	Dec 00	24 months	6%	RAEB-1	46,XY,add(3)(q27), add(4)(q21),−5, t(13;22)(p11;q11), add(16)(p11),+mar	NR	Supportive	Died, 2 months

Note: Dx, diagnosis; Rx, therapy; latency, calculated from the commencement of FND to diagnosis of MDS/AML; WHO, diagnosis accordingly to World Health Organization classification scheme; M, male; F, female; FL, follicular lymphoma; MCL, mantle cell lymphoma; FND, fludarabine, mitoxantrone, dexamethasone; anti-CD20, rituximab; RT, radiotherapy; CHOP, cyclophosphamide, Adriamycin, vincristine, prednisolone; m-BACOD, methotrexate, bleomycin, Adriamycin, cyclophosphamide, vincristine, dexamethasone; APL, acute promyelocytic leukaemia; RCMD, refractory cytopenia with multilineage dysplasia; RAEB, refractory anemia with excess blasts; CR, complete remission; PCR, polymerase chain reaction for t(14;18) in the marrow; −ve, negative; NR, nonremission; ATRA, all *trans*-retinoic acid; 7+3, cytarabine (7 days) and daunorubicin (3 days).

For the other two patients presenting with MDS, deletion of the long arm of chromosome 7 (7q−) and complex karyotypic aberrations with monosomy 5 (−5) were found. Both cases had received prior treatment with alkylating agent-containing chemotherapy. However, McLaughlin et al. recently described the development of t-MDS/AML in six patients who had been treated with FND, which was combined with rituximab and interferon α [5]. In four patients, FND was the only chemotherapy given. The median time from FND treatment to the development of t-MDS/AML was 31 (15–57) months. All patients were characterized by complex karyotypic aberrations that included 5q−, monosomy 7 (−7), or 7q−. Therefore, data from McLaughlin et al. would suggest that FND alone might give rise of t-MDS/AML with −5/5q− and −7/7q−. Furthermore, it is intriguing to note that another purine analog, azathioprine, has been found to induce t-MDS/AML. After prolonged treatment, often as a single agent, azathioprine had been reported to lead to t-MDS/AML that was characterized by −7/7q− [1]. Moreover, in our previous case of fludarabine-induced t-MDS/AML [1], an unbalanced translocation der(1;7)(q10;p10) (which resulted effectively in monosomy 7q) was also observed. These results suggest that fludarabine may be important in the pathogenesis of t-MDS/AML with −5/5q− and −7/7q− after FND treatment.

Therefore, this series further supports that fludarabine, either as a single agent or in combination chemotherapy, might be potentially leukemogenic. Further studies are required to define the exact risks, as well as whether synergistic mutagenic interactions of fludarabine with other chemotherapeutic agents might happen.

Wing-Yan Au[1]
Li-Chong Chan[2]
Raymond Liang[1]
Yok-Lam Kwong[1]

[1]Department of Medicine, University of Hong Kong, Queen Mary Hospital, Hong Kong
[2]Department of Pathology, University of Hong Kong, Queen Mary Hospital, Hong Kong
Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/ajh.20599

References

1. Lam CC, Ma ES, Kwong YL. Therapy-related acute myeloid leukemia after single-agent treatment with fludarabine for chronic lymphocytic leukemia. Am J Hematol 2005;79: 288–290.
2. Ma SY, Au WY, Chim CS, Lie AK, Lam CC, Tse E, Leung AY, Liang R, Kwong YL. Fludarabine, mitoxantrone and dexamethasone in the treatment of indolent B- and T-cell lymphoid malignancies in Chinese patients. Br J Haematol 2004;124:754–761.
3. Beaumont M, Sanz M, Carli PM, Maloisel F, Thomas X, Detourmignies L, Guerci A, Gratecos N, Rayon C, San Miguel J, Odriozola J, Cahn JY, Huguet F, Vekhof A, Stamatoulas A, Dombret H, Capote F, Esteve J, Stoppa AM, Fenaux P. Therapy-related acute promyelocytic leukemia. J Clin Oncol 2003;21:2123–2137.
4. Mistry AR, Felix CA, Whitmarsh RJ, Mason A, Reiter A, Cassinat B, Parry A, Walz C, Wiemels JL, Segal MR, Ades L, Blair IA, Osheroff N, Peniket AJ, Lafage-Pochitaloff M, Cross NC, Chomienne C, Solomon E, Fenaux P, Grimwade D. DNA topoisomerase II in therapy-related acute promyelocytic leukemia. N Engl J Med 2005;352:1529–1538.
5. McLaughlin P, Estey E, Glassman A, Romaguera J, Samaniego F, Ayala A, Hayes K, Maddox AM, Preti HA, Hagemeister FB. Myelodysplasia and acute myeloid leukemia following therapy for indolent lymphoma with fludarabine, mitoxantrone, and dexamethasone (FND) plus rituximab and interferon alpha. Blood 2005;105:4573–4575.

Another Case of Myelodysplasia with Monosomy 7 Following Fludarabine-Based Chemotherapy

To the Editor: The recent case report by Lam et al. [1] adds to the small but growing number of reports of secondary myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) following fludarabine therapy. We report a further case of MDS with monosomy 7 associated with fludarabine therapy. This female patient developed stage IIIA follicular non-Hodgkin's lymphoma (NHL) 9 years ago, at the age of 47. Staging bone marrow aspirate and trephine biopsy showed normal cellularity, with normal bone marrow cytogenetics. The patient achieved complete remission with six courses of oral idarubicin, dexamethasone, and chlorambucil. She had biopsy-proven first relapse of her follicular NHL in September 2003, with a 6-cm subcutaneous soft tissue mass over her frontal bone and right-side cervical lymphadenopathy. Complete blood count (CBC), as well as restaging bone marrow aspirate, trephine biopsy, and bone marrow cytogenetics, was normal. Following four courses of fludarabine, cyclophosphamide, and rituximab [2], she remains in second complete remission. However, she developed prolonged pancytopenia following completion of chemotherapy, requiring blood product support as well as regular recombinant human erythropoietin (Epo) and granulocyte-colony stimulating factor (G-CSF). In mid April 2004, hemoglobin (Hb) was 8.5 g/dl, white blood count (WBC) 1.52×10^9/L, neutrophil count 0.97×10^9/L, and platelet count 32×10^9/L. Repeat bone marrow aspirate and trephine biopsy at this time showed marked hypocellularity (fat:cell ratio 95:5) with serous atrophy, consistent with postchemotherapy hypoplasia. Bone marrow cytogenetics were normal. Over the following months, there was a gradual improvement in CBC and by February 2005, Hb was 13.4 g/dl, WBC 1.54×10^9/L, neutrophil count 1.01×10^9/L, and platelet count 94×10^9/L, with the patient requiring only once weekly G-CSF (30 million units) as blood count support. Since then, the severity of pancytopenia has gradually worsened and in early October 2005, Hb was 8.9 g/dl, WBC 1.02×10^9/L, neutrophil count 0.49×10^9/L, and platelets 25×10^9/L, despite blood count support with Epo and G-CSF. Repeat bone marrow aspirate and trephine biopsy showed a hypercellular sample (fat:cell ratio 20:80) with trilineage myelodysplasia but without increase in blasts. Bone marrow cytogenetics showed monosomy 7 and monosomy 21.

McLoughlin et al. recently reported 8 treatment-related cases of MDS, with chromosome 7 abnormalities in 6, in a cohort of 202 patients with indolent NHL, between 1 and 5 years after chemotherapy with fludarabine, mitoxantrone, and dexamethasone ± rituximab, followed by interferon α [3]. Patients with chronic lymphocytic leukemia and indolent NHL are likely to require a number of courses of combination chemotherapy over several years, including alkylators and purine analogues such as fludarabine. The price for more effective fludarabine-based chemotherapy to treat these conditions may be a growing number of cases of treatment-related MDS and AML, such as the patient we describe.

P.T. Murphy
S. Mitra
D. O'Donghaile

Department of Haematology, Beaumont Hospital, Dublin, Ireland
Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/ajh.20621

References

1. Lam CCK, Ma ESK, Kwong Y-L. Therapy-related acute myeloid leukemia after single-agent treatment with fludarabine for chronic lymphocytic leukemia. Am J Hematol 2005;79:288–290.
2. Keating MJ, O'Brien S, Albitar M, et al. Early results of a chemoimmunotherapy regimen of fludarabine, cyclophosphamide, and rituximab as initial therapy for chronic lymphocytic leukemia. J Clin Oncol 2005;23:4079–4088.
3. McLaughlin P, Estey E, Glassman A, et al. Myelodysplasia and acute myeloid leukemia following therapy for indolent lymphoma with fludarabine, mitoxantrone, and dexamethasone (FND) plus rituximab and interferon alpha. Blood 2005;105:4573–4575.

Could the C677T Mutation in the MTHFR Gene be another Genetic Cause of Arrhythmogenic Right Ventricular Dysplasia?

Arrhythmogenic right ventricular dysplasia (ARVD) is an inherited cardiomyopathy characterized by progressive fibrofatty replacement of myocardium [1,2].

Typical clinical manifestations include ventricular arrhythmias with left bundle branch block, occurring predominantly in young adults [1]. Although considerable progress has been made in understanding the pathogenesis of this autosomal dominant disease with the identification of various involved genetic loci, in many cases the molecular lesion is unknown [3]. I report here a case of a 16-year-old male who was referred to the Cardiology Division of Verona City Hospital with palpitations and anterior chest pain. Electrocardiography (ECG) showed severe ventricular arrhythmia (5400 ventricular extrasystoles/24 h on Holter monitoring). Two-dimensional echocardiography showed a reduced right ventricular ejection fraction (43%) with right ventricular dilatation and hypokinesia, while cardiac nuclear magnetic resonance imaging was diagnostic of ARVD (diffuse fibrofatty infiltration of the right ventricular myocardium with high signal intensity on T_1-weighted images). Among the various laboratory tests performed, the serum homocysteine level was high (30 μmol/L, normal values < 10 μmol/L). An analysis of the more common polymorphisms in the methylenetetrahydrofolate reductase (MTHFR) gene showed homozygosity for the C677T mutation. The same abnormalities (high serum homocysteine levels and homozygosity for the C677T mutation in the MTHFR gene) were present in his mother, who affirmed that she had not taken folate acid during her only pregnancy. The patient's relatives showed no ECG abnormalities and had no history of heart disease.

Inherited and nutritional disturbances in maternal folate metabolism have been associated with neural tube defects and congenital cardiac malformations in animals and humans [4,5]. Wenstrom and colleagues [5] hypothesized that this could be the effect of high levels of homocysteine in the amniotic fluid. Thus, an inherited abnormality of homocysteine metabolism could be the cause of the cardiac abnormalities observed in this young patient.

ARVD is known to have heterogeneous causes and this case could lead to the identification of a new subset of the condition with a different pathogenic mechanism and inheritance. It is certainly interesting that both the frequency of ARVD and the frequency of C677T mutations are high in northern Italy.

Massimo Franchini

Servizio di Immunoematologia e Trasfusione, Azienda Ospedaliera di Verona, Verona, Italy

Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/ajh.20588

References

1. Hulot JS, Jouven X, Empana JP, Frank R, Fontaine G. Natural history and risk stratification of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Circulation 2004; 110:1879–1884.
2. Naccarella F, Naccarelli G, Fattori R, et al. Arrythmogenic right ventricular dysplasia/cardiomyopathy: current opinions on diagnostic and therapeutic aspects. Curr Opin Cardiol 2001;16:8–16.
3. Ahmed F. The molecular genetics of arrythmogenic right ventricular dysplasia-cardiomyopathy. Clin Invest Med 2003;26:167–178.
4. Li D, Pickell L, Liu Y, Wu Q, Cohn JS, Rozen R. Maternal methylenetetrahydrofolate reductase deficiency and low dietary folate lead to adverse reproductive outcomes and congenital heart defects in mice. Am J Clin Nutr 2005;82:188–195.
5. Wenstrom KD, Johanning GL, Johnston KE, DuBard M. Association of the C677T methylenetetrahydrofolate reductase mutation and elevated homocysteine levels with congenital cardiac malformation. Am J Obstet Gynecol 2001;184:806–817.

Successful Treatment of Chronic Myeloid Leukemia with Imatinib Mesylate in a Patient with Chronic Renal Failure on Hemodialysis

To the Editor: Imatinib mesylate is a major breakthrough in the treatment of chronic myeloid leukemia (CML) with target specificity and acceptable toxicity [1]. Imatinib is mainly eliminated through the hepatobiliary system and the fecal to urinary excretion ratio is approximately 5:1 [2,3]. However, no clinical studies were conducted with imatinib in patients with impaired renal function and very limited data exist in such patients to guide the dosage [4]. Here, we report successful treatment of a CML patient on hemodialysis with standard dose imatinib.

A 54-year-old female who developed chronic renal failure (CRF) secondary to hypertensive nephropathy had been on hemodialysis three times a week for 13 years. In December 2004, the patient was found to have an elevated white blood cell count (30.4×10^3/μl with left shift and no blasts). The diagnosis of CML-chronic phase was made based on the presence of a hypercellular marrow with myeloid hyperplasia and bcr-abl transposition (p210) demonstrated with conventional cytogenetics, FISH, and quantitative RT-PCR techniques. She had low-risk disease according to the Sokal score. Due to the lack of any other significant long-term management strategy and after receiving the patient's consent, we decided to treat the patient with 400 mg imatinib po qd, given within 1 h after her hemodialysis sessions. The patient had history and physical examination weekly and her dry weight was measured before each hemodialysis session. CBC with peripheral smear and blood biochemistry were measured weekly for 1 month, biweekly for the following 2 months, and monthly thereafter. She had chest X-ray for cardiothoracic index measurements monthly for the first 3 months. The patient remained euvolemic with no evidence of peripheral or visceral edema necessitating excess ultrafiltration during hemodialysis sessions. She achieved hematologic remission at the end of the first month and both cytogenetic and molecular remissions demonstrated with conventional cytogenetics, FISH, and quantitaive PCR techniques at the end of 3 months. She remains in molecular remission at 9 months with no evidence of significant adverse effects.

Edema, muscle cramps, nausea, diarrhea, and cutanous reactions are the most common side effects of imatinib treatment [5]. Probable fluid overload and electrolyte disturbances due to gastrointestinal adverse effects were the primary concerns in our patient. However, she had no significant adverse effects of imatinib treatment during her follow-up and achieved a complete molecular remission within 3 months. Our experience is consistent with a recent case study demonstrating that pharmacokinetics of standard dose imatinib (400 mg/day) and its metabolite do not change in patients with end-stage renal disease on hemodialysis [4]. To our knowledge, this is the first report of successful treatment of a CML patient on hemodialysis with imatinib. We conclude that 400 mg/day imatinib mesylate can safely and successfully be administered to CML patients with CRF on hemodialysis with a close follow-up of potential adverse effects.

Evren Ozdemir
Yener Koc
Emin Kansu

Hacettepe University, Institute of Oncology, Section of Medical Oncology, Hematopoietic Stem Cell Transplantation Unit, Ankara, Turkey

Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/ajh.20620

References

1. Druker BJ, Talpaz M, Resta DJ, et al. Efficacy and safety of a specific inhibitor of the Bcr-Abl tyrosine kinase in chronic myeloid leukemia. N Engl J Med 2001;344:1031–1037.
2. Peng B, Hayes M, Resta D, et al. Pharmacokinetics and pharmacodynamics of imatinib in a phase I trial with chronic myeloid leukemia patients. J Clin Oncol 2004;22: 935–942.
3. Bauer S, Hagen V, Pielken HJ, et al. Imatinib mesylate therapy in patients with gastrointestinal stromal tumors and impaired liver function. Anticancer Drugs 2002;13:847–849.
4. Pappas P, Karavasilis V, Briasoulis E, et al. Pharmacokinetics of imatinib mesylate in end stage renal disease. A case study. Cancer Chemother Pharmacol 2005;56:358–360.
5. Kantarjian H, Sawyers C, Hochhaus A, et al. Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. N Engl J Med 2002;346:645–652.

Morphologic Heterogeneity of Acute Promyelocytic Leukemia: Therapy-Related Acute Promyelocytic Leukemia Presenting with FAB-M2 Morphology

To the Editor: Acute promyelocytic leukemia (APL) is characterized by *PML/RARα* (promyelocytic leukemia/retinoic acid receptor α) gene rearrangement. The diagnosis is usually made on the bases of its morphologic features, flow cytometry, and cytogenetics. APL patients are amenable to treatment with *all-trans*-retinoic acid (ATRA) making this the most curable form of acute myeloid leukemia (AML). Three morphologic forms (hypergranular, hypogranular, and hyperbasophilic) have been well described in the literature [1]. We report a patient with AML-M2 (French–American–British classification) morphology who was subsequently found to have a *PML/RARα* fusion gene.

A 67-year-old male treated with ^{125}I brachytherapy for prostate cancer 16 months earlier was hospitalized for diverticulitis. Laboratory studies showed WBC 9×10^9/L; hemoglobin 12.4 g/dL; and platelets 25×10^9/L. Blood smear revealed anisopoikilocytosis, 5% neutrophils, 3% bands, 30% lymphocytes, 20% monocytes, 2% metamyelocytes, 15% myelocytes, 15% promyelocytes, and 10% myeloblasts. Clotting profile was normal except for INR 1.6 and d-dimers > 8 μg/mL (normal < 0.5 μg/mL). Bone marrow biopsy was consistent with AML-M2 (cellularity 90%, M/E ratio 8:1, myeloblasts 31%, promyelocytes 15%, myelocytes 27%, metamyelocytes 6%, basophils 1%, lymphocytes 7%, monocytes 1%, plasma cells 1%, and erythroid cells 11%). Immunophenotype revealed positivity for CD45 (92.2%), CD38 (77.3%), CD13/33 (91.3%), myeloperoxidase (88.0%), and HLA-DR (85.%) but negative for CD34 (0.09%). Cytogenetic analysis yielded no dividing cells. He was treated with broad-spectrum antibiotics and was given induction chemotherapy with daunorubicin and cytarabine (3+7). He developed disseminated intravascular coagulation (DIC) in a few days requiring intensive care and transfusion support. Given this clinical picture and after being made aware of morphologic heterogeneity of APL from MEDLINE, fluorescence-in-situ-hybridization (FISH) and RT-PCR (reverse transcriptase polymerase chain reaction) studies for *PML/RARα* gene rearrangement were subsequently requested. FISH analysis was positive for *PML/RARα* fusion gene. It also showed trisomy 8 in 9.5% of the cells. Real-time RT-PCR detected long form of *PML/RARα* fusion gene. He was then started on ATRA at 45 mg/m^2 daily. Bone marrow biopsy a month later confirmed complete remission. At the time of writing, he has finished three cycles of consolidation chemotherapy and three cycles of maintenance chemotherapy and has remained in complete remission for 1 year.

Other APL morphologic variants, while rare, have also been reported [2–5]. A recent study looked at the role of molecular screening for the *PML/RARα* fusion gene in all AML patients. Of the 530 patients screened, only one individual was found to have the gene rearrangement. The authors concluded that routine molecular screening was not justified and should be reserved only for those cases displaying features that signal APL [5]. In our review of the literature of t(15:17) in AML subtypes other than FAB-M3 morphology, we found 17 reported cases, including our case (Table I). Our case and the literature review illustrate that there are occasions where the diagnosis of APL cannot be made by morphology and cytogenetics alone. Given the unique response to ATRA, we suggest that all efforts be made to rule out *PML/RARα* fusion gene in newly diagnosed AML with coagulopathy.

TABLE I. Summary of Patient Characteristics, Treatment, and Outcome in 17 Cases With APL and Morphologic Heterogeneity*

Reference	Age/sex	Morphology	DIC	Chemotherapy	ATRA use	Response	Outcome
Foley et al.	45/M	L2/M1 Undifferentiated	Yes	Induction and consolidation	Yes	CR PCR +	>12 m
Aventin et al.	22/F	M7	No	Induction, consolidation, intensification	Yes	CR PCR −	>12 m
Yu et al.	66/F	Acute eosinophilic leukemia	NA	Consolidation	Yes	CR PCR +	> 48 m
Parreira et al.	58/M	M4	NA	Yes	No	No	Died −30 days
Morgan et al.	18/F	M7	No	Induction and consolidation	No	CR, complete cytogenetic response	>6 m
Hast et al.	22/F	M4	Yes	Induction, consolidation, AutoBMT	No	CR	46+ m
Neame et al.	45/M	M2	Yes	NA	Yes	NA	NA
	53/F	M2	2 pts			Remission	>24 m
	54/M	M2			2/3 pts	NA	NA
	60/F	M1	1 - NA		No		NA
	73/F	M1	1 - Yes	NA	Yes	No	Died 3 days
Allford et al.	36/M	M2	NA		No	No	Died 2 days
Allford et al.	15/F	M1	No	Induction and consolidation	No	Relapsed	Died (duration of therapy unknown)
Head et al. (3 cases)	NA	M1	NA	NA	NA	NA	NA
	NA	M1	NA	NA	NA	NA	NA
	NA	M1	NA	NA	NA	NA	NA
This case	67/M	M2	Yes	Induction, consolidation maintenance	Yes	CR	>12 m

*Abbreviations: NA, not available; CR, complete remission; AutoBMT, autologous bone marrow transplantation; PCR, polymerase chain reaction; m, months; pt(s), patient(s).

S. Sinha[1]
L. Aish[2]
T.H. Oo[1]

[1]Department of Hematology/Oncology, Caritas St. Elizabeth's Medical Center, Tufts University School of Medicine, Boston, Massachusetts
[2]Department of Pathology, Caritas St. Elizabeth's Medical Center, Tufts University School of Medicine, Boston, Massachusetts
Published as an abstract in the 2005 Proceedings of the American Society of Clinical Oncology (abstract 6741).
Published online in Wiley InterScience (www.interscience.wiley.com).
DOI: 10.1002/ajh.20577

References

1. Avvisati G, Lo Coco F, Mandelli F. Acute promyelocytic leukemia: clinical and morphologic features and prognostic factors. Semin Hematol 2001;38(1):4–12.
2. Sinha S, Aish L, Oo TH. Morphologic heterogeneity of acute promyelocytic leukemia. Proc Am Soc Clin Oncol 2005;23:618s.
3. Parreira L, Matutes E, Marcus RE, et al. Atypical promyelocytic leukemia (M3) with immature primary granules and t(15;17). Cancer Genet Cytogenet 1985;18(4):315–324.
4. Neame PB, Soamboonsrup P, Leber B, et al. Morphology of acute promyelocytic leukemia with cytogenetic or molecular evidence for the diagnosis: characterization of additional microgranular variants. Am J Hematol 1997;56(3):131–142.
5. Allford S, Grimwade D, Langabeer S, et al. Identification of the t(15;17) in AML FAB types other than M3: evaluation of the role of molecular screening for the PML/RARalpha rearrangement in newly diagnosed AML. The Medical Research Council (MRC) Adult Leukaemia Working Party. Br J Haematol 1999;105(1):198–207.

Acute Promyelocytic Leukemia with Secondary Myelofibrosis—Case Report and Review of the Literature

To the Editor: Bone marrow fibrosis is known to occur in acute myeloid leukemia although commonly with AML-M7 [1]. Myelofibrosis with acute promyelocytic leukemia (FAB-M3) is very rare. To date only three cases have been reported [2–4]. We report a case of APML with associated bone marrow fibrosis and include a review of the literature.

A 25-year-old male presented with excessive bleeding for 20 days following tooth extraction and sternal tenderness without any organomegaly. Investigation revealed hemoglobin 59 g/L, WBC count 5×10^9/L, and platelet count 10×10^9/L. Coagulation profile was suggestive of mild DIC.

The peripheral blood smear revealed 40% abnormal granular promyelocytes and 14% blasts. The promyelocytes and blasts were strongly positive for myeloperoxidase and Sudan Black B. The bone marrow trephine biopsy revealed sheets of immature cells along with broad bands of fibrosis (Fig. 1A). RT-PCR for the PML-RARα transcript on the peripheral blood was positive for the bcr3 isoform.

ATRA and daunorubicin were given as induction therapy. A repeat bone marrow biopsy performed on day 28 (the patient had normal blood counts) revealed extensive marrow fibrosis with only a few small clumps of cells, the morphology of which was not very clear (Fig. 1B). However, RT-PCR for the PML-RARα transcript was repeated on a peripheral blood sample using the same conditions and negative control and was found to be negative (molecular remission).

Consolidation therapy with two cycles of daunorubicin was given and currently the patient is on maintenance therapy and in hematologic and molecular remission.

This patient of AML-M3 showed myelofibrosis both at presentation before starting induction therapy and at the end of induction therapy (after 35 days) despite being in molecular remission.

Bone marrow fibrosis in AML-M3 has been very rarely reported. Mori et al. [2] described a case of APML in a 26-year-old male with diffuse marrow fibrosis at presentation. His marrow fibrosis disappeared after induction. Myelofibrosis was attributed to increased expression of TGF-β1.

Fukuno et al. [3] reported APML in an 18-year-old male with marked myelofibrosis. The promyelocyte morphology was atypical and there was expression of HLA-DR and CD-34. RT-PCR for PML-RARα was positive. Postremission bone marrow biopsy revealed diffuse moderate fibrosis. The patient underwent an auto PBSCT and did well till 21 months of follow-up. A bone marrow biopsy on day 45 post BMT showed the absence of myelofibrosis.

Aventin et al. [4] reported another case of APML with increased reticulin in the marrow, which had atypical morphology and positivity for CD 34 and HLA DR. Molecular remission was achieved after intensification therapy and remained so for a year of follow-up.

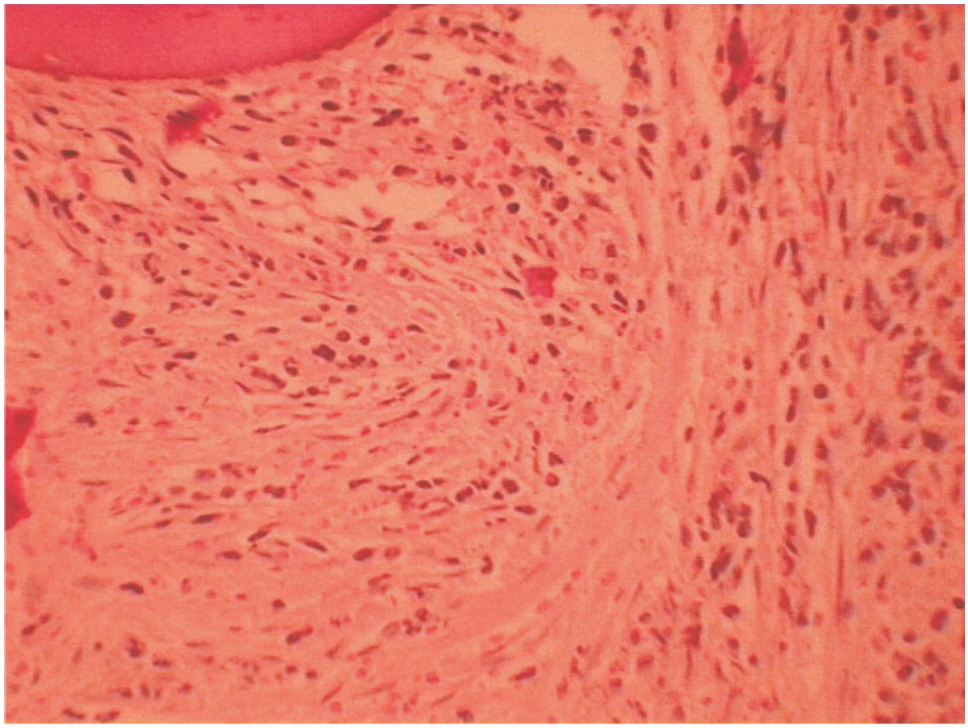
Thus, myelofibrosis may be present with AML-M3 and doesn't appear to be associated with any poor outcome. In fact, our case went into molecular remission at the end of induction. It is possible that bone marrow trephine biopsy, if done routinely in all patients of AML-M3, may reveal more patients with myelofibrosis. Also, longer follow-ups are needed in order to better define the association of myelofibrosis in AML-M3 and their outcome.

Pankhi Dutta
Syed Hasan
Jina Bhattacharyya
Rajat Kumar
Manoranjan Mahapatra
Renu Saxena
Seema Tyagi
Sudha Sazawal
Hara Prasad Pati

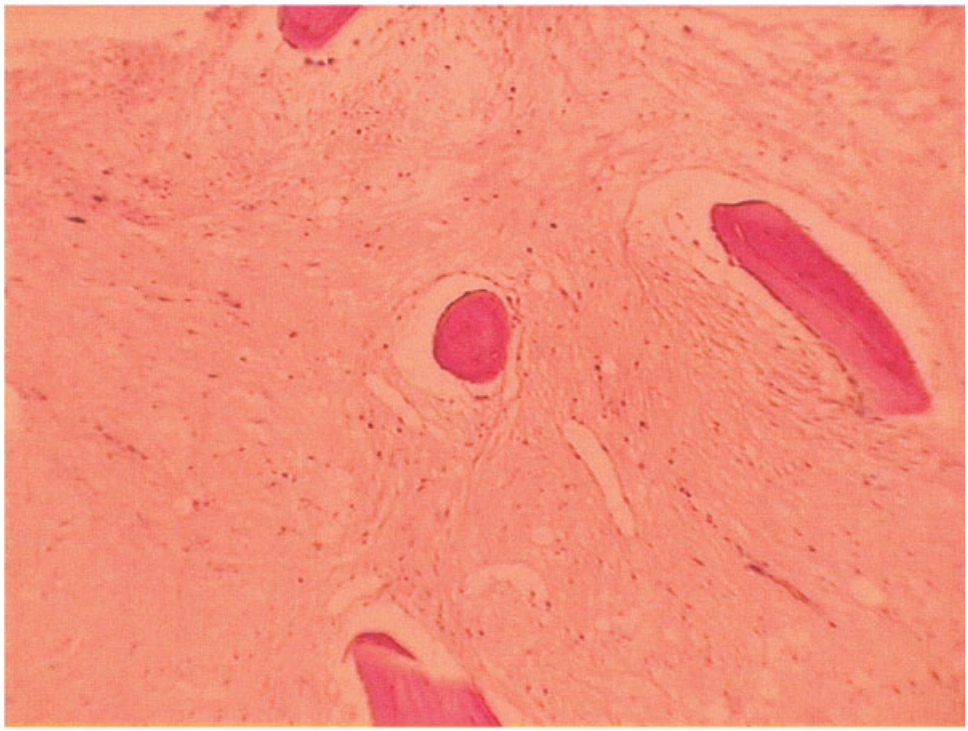
Department of Haematology, All India Institute of Medical Sciences, NewDelhi 110029, India
Published online in Wiley InterScience (www.interscience.wiley.com).
DOI: 10.1002/ajh.20607

References

1. Manoharan A, Horsley R, Pitney WR. The reticulin content of bone marrow in acute leukaemia in adults. Br J Haematol 1979;43:185–190.
2. Mori A, Wada H, Okada M, Takatsuka H, Tamura Amane, Fujimori Y, Okomata T, Takemoto Y, Kanamaru A, Kakashita E. :Acute promyelocytic leukaemia with marrow fibrosis at initial presentation: possible involvement of transforming growth factor β-1. Acta Haematol 2000;103:220–223.
3. Fukuno K, Tsurumi H, Yoshikawa T, Yamada T, Oyama M, Moriwaki H. A variant form of acute promyelocytic leukaemia with marked myelofibrosis. Int J Haematol 2001;74:322–326.
4. Aventin A, Mateu R, Martino R, Colomer D, Bordes R. A case of cryptic acute promyelocytic leukemia. Leukemia 1998;12:1490–1491.



A



B

Fig. 1. A. Bone marrow biopsy (×40) at diagnosis, showing leukemic cells with myelofibrosis. B. Bone marrow biopsy (×40), postinduction. Extensive fibrosis is shown. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]