

LETTER TO THE EDITOR

Coexistence of primary myelofibrosis and chronic lymphocytic leukaemia: treatment of two different diseases with one agent

Blood Cancer Journal (2011) 1, e20; doi:10.1038/bcj.2011.18;
published online 27 May 2011

Coincidence of primary myelofibrosis (PMF) and chronic lymphocytic leukaemia (CLL) in one patient is a rare phenomenon. To date, eight cases have been described in the literature. A 61-year-old woman presented with transfusion-dependent anaemia in February 2008. Peripheral blood count showed a normochromic, normocytic anaemia with a haemoglobin level of 6.0 g/dl, and the white blood cell count and platelets were within the normal range. Differential blood count revealed leukerythroblastosis, anisocytosis and poikilocytosis, indicating the presence of myelofibrosis. In addition, atypical lymphocytes and some Gumprecht's shadows were present. Immunophenotyping confirmed the presence of a CD5, CD19 and CD45 positive clone. Bone marrow histology showed a hypercellular marrow with atypical megakaryopoiesis and a WHO grade 2 fibrosis (Figure 1), as well as a small lymphocytic infiltrate with the CLL phenotype, accounting for 5% of the marrow volume (Figure 2). This was consistent with coexistence of PMF and CLL. Cytogenetic analysis showed a normal karyotype and molecular analysis revealed no JAK2 mutation. Ultrasound showed splenomegaly of 17 cm at initial presentation.

At the time of diagnosis, CLL was classified as Binet A. Anaemia was considered to be secondary to myelofibrosis. Treatment was started with lenalidomide 5 mg/d for 21 days of a 28-day-cycle, because preliminary data showed promising results for lenalidomide in patients with PMF and CLL. After 2 months of therapy, no severe side effects were observed. The dose of lenalidomide was then increased to 10 mg/d for 21 days of a 28-day-cycle.

At 6 months of therapy, haemoglobin levels increased to 8.5 g/dl and the patient became transfusion independent. Spleen size decreased to 15 cm after 3 months of therapy. Differential blood count was normal at 9 months of treatment. Since February 2010, lymphocyte counts are within normal range.

After a follow-up period of 35 months, the patient remained transfusion-independent, with a haemoglobin level of 11.8 g/dl. White blood cell counts and thrombocytes are within normal range. Leukerythroblastosis, anisocytosis, poikilocytosis and lymphocytosis did resolve as well, and splenomegaly had decreased to 13 cm. Bone marrow histology showed no substantial change; fibrosis was still classified as WHO grade 2, the marrow was still hypercellular. A lymphocytic infiltration could not be demonstrated at that time. The patient is completely asymptomatic with an Eastern Cooperative Oncology Group performance status of 0.

PMF has an overall median survival of 69 months (range 2–11 years).¹ Risk factors are age > 65 years, haemoglobin < 10 g/dl, WBC > 25 G/l and circulating blasts > 1%. Beside these risk factors, prognosis of patients with PMF is strongly dependent on the presence of cytogenetic abnormalities, transfusion dependency and the presence of comorbidities. The only curative treatment option for patients with PMF is allogeneic stem cell

transplantation.² For symptomatic splenomegaly, radiation and splenectomy may be considered. Drugs used for the treatment of anaemia include androgens, danazol, corticosteroids, erythropoietin-stimulating agents and hydroxyurea.² Asymptomatic patients without severe anaemia or marked splenomegaly are usually under close observation. Recently, immunomodulating drugs were used in patients with myelofibrosis. Lenalidomide was shown to be effective as single agent in two phase II trials, with an overall response rate of 24% for anaemia, 33% for splenomegaly and 50% for thrombocytopenia.³ In two other trials, the combination of lenalidomide with prednisone led to ambiguous results. The study conducted by Quintas-Cardama *et al.*⁴ showed promising results with benefits for anaemia and splenomegaly. Reduction of fibrosis could be demonstrated. Mesa *et al.*⁵ demonstrated modest activity with a similar regimen, but no resolution of fibrosis was demonstrated.

Lenalidomide was also shown to be effective in CLL patients with relapsed/refractory disease, as well as in chemotherapy naïve patients. A phase II study conducted by the Roswell Park Cancer Institute showed an overall response rate and complete response rate of 47 and 9%, respectively, in relapsed CLL patients, including patients with high risk cytogenetics.⁶ Previously untreated patients achieved overall response rates between 47 and 65%.⁷ Severe tumour lysis and tumour flare reactions have been described in patients treated with 25 mg/d of lenalidomide.

Coincidence of PMF and CLL is uncommon in one patient. Up to now, eight cases have been described in the literature.⁸ Median age of these patients (including our patient) was 66 years, with a male preponderance (m:f=2:1). PMF was the initial diagnosis in five patients and was followed by the manifestation of CLL, with a median time of 44 months. One patient had initially CLL, and PMF was diagnosed 31 months later. Two patients had a simultaneous diagnosis of PMF and CLL. Treatment of these patients was heterogeneous. Three out of eight patients did not receive any therapy. Two patients received chlorambucil with or without prednisone, and one patient was treated with steroids, vincristine and cyclophosphamide. Two patients received supportive therapy with blood transfusions only. All eight patients were published before lenalidomide was available. First reports of the efficacy of lenalidomide in PMF and CLL appeared in 2006.^{3,6} Our patient strictly refused allogeneic stem cell transplantation. On the basis of the literature, we commenced the patient on lenalidomide instead. The drug was administered within a named patient programme, offered by the manufacturing company.

Potential pathomechanisms for the coincidence of a myeloproliferative and a lymphoproliferative disease are being discussed in the literature, but remain unclear.⁸ Besides a random coincidence of two different diseases, a simultaneous proliferation of two cell lines triggered by a single cause could serve as an explanation. The proliferation of a lymphocytic and a myelogenous cell line derived from a common pluripotent stem cell is favoured as potential pathomechanism by the majority of authors. The presence of a cytogenetic or molecular

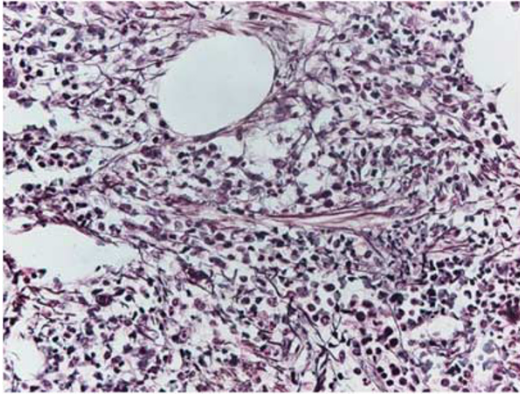


Figure 1 Bone marrow histology Gomori $\times 400$: fibrosis.

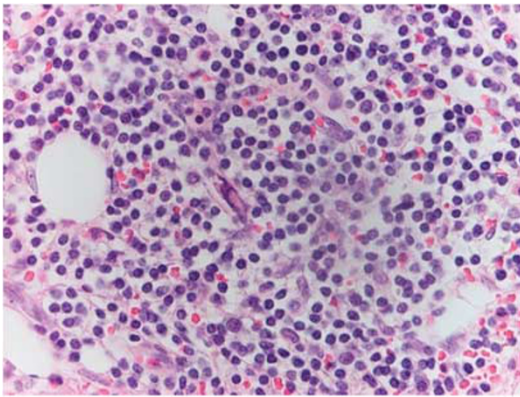


Figure 2 Bone marrow histology HE $\times 600$: lymphocytic infiltrate.

marker in both the lymphocytic and myelogenous cell line would support this hypothesis. Until now, a common marker for PMF and CLL has not been identified.

The patient in this case vignette was diagnosed with a myeloproliferative and a lymphoproliferative disease at the same time. PMF with leukerythroblastosis, splenomegaly and transfusion-dependent anaemia was clearly the dominant disease. CLL presented with lymphocytosis, a small bone marrow infiltrate, but no lymphadenopathy. First signs of a treatment effect were increasing haemoglobin levels and a decreasing spleen size at 3 months. In contrast, changes in lymphocytosis were noted after 24 months of therapy. These findings let us prefer the hypothesis that both diseases did emerge randomly in two different cell lines.

In summary, little is known about pathogenetic mechanism, treatment approaches and prognosis of patients presenting with

coexisting PMF and CLL. As publication of the first case in 1957, eight more cases have been reported in the literature. New agents like lenalidomide might be an option for some of those patients. Treatment with lenalidomide is successful in our patient; she is asymptomatic and does not need any transfusions or any other specific therapy since 2008.

Conflict of interest

The authors declare no conflict of interest.

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