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ORIGINAL ARTICLE

Gene mutations in a patient with chronic myelomonocytic leukemia and changes upon progression to acute myeloid leukemia and during treatment*

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Abstract

Objective Chronic myelomonocytic leukemia (CMML) has been categorized as an uncommon hematological malignancy with overlapping features of myelodysplastic syndromes (MDS) and myeloproliferative neoplasms that have an inherent risk of progressing to acute myeloid leukemia (AML).

Methods This study presents a case of confirmed CMML combined with M protein, in which the molecular changes upon progression to AML and under decitabine (DAC) plus bortezomib therapy were reported by tracking variant allele frequency (VAF) of mutations in a series of bone marrow samples.

Results First, variable sensitivity of clones was observed during DAC treatment, and incomplete mutation clearance may be associated with low overall response rate and unsustained response. Secondly, DAC cannot prevent the new genetic alterations and accumulation of genetic progression on treatment, leading to acute transformation. Finally, autoimmunity was found to have acted as an important pathogenetic factor, increasing the additive mutations that further drive the clonal evolution in CMML.

Conclusion Overall, changes in mutations and clonal architecture during CMML progression or treatment are predictive of an early evaluation of therapeutic strategies in CMML.

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Key words: chronic myelomonocytic leukemia; acute myeloid leukemia; mutation; decitabine; bortezomib; platelets; SETD2; LILRB4

Chronic myelomonocytic leukemia (CMML) is a clonal hematopoietic neoplasm that shares clinical and morphologic features with myelodysplastic syndromes (MDS) and myeloproliferative neoplasms. A number of molecular abnormalities are most frequently exhibited in patients with CMML, including TET2 (60%), SRSF2 (50%), ASXL1 (40%), and RAS (30%) mutations [1], which are variably distributed, yielding an enormous number of combinations that might be important during tumorigenesis and for the outcomes. CMML has been currently postulated to arise as a result of the acquisition of an initial driver mutation, and subclones emerge from an ancestral clone due to the sequential gain of mutations, leading to a proliferative oligoclonality and disease progression. Hypomethylating agents (HMAs), including decitabine (DAC), are approved for the treatment of CMML. However, only approximately 50% of patients show hematological improvement and short response duration. Mutations in genes, including TET2 or DNMT3A, have been previously reported as predictors of responses to HMAs, and the specific molecular signatures predict primary DAC resistance in CMML [2–3].

We described a clinical case of CMML, associated with presence of IgG-κ type M proteins that progressed to AML in a short period of time. The patient received DAC (20 mg/m^2, d1-3) every 2 months, and achieved marrow complete response after one cycle of therapy. However, the patient became more thrombocytopenic and required

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Table 1 Changes of baseline characteristics during the whole duration of illness

Therapy	Plasma cell (%)	Blasts (%)	MK	PLT 10^9/L	κ	Serum Ig (mg/dl)			CD56 (%)
						IgG	IgA	IgM	
Pre		9.5	603	119	(+)	3060	304	806	5.5
D1-Pre	1.0	2	587	67	NA	2590	280	985	NA
D2-Pre	1.0	1.5	351	23	NA	2470	268	1030	4
D3-Pre	1.0	4	35	28	NA	2090	241	933	NA
B-Pre	1.0	0.5	624	60	(+)	1920	220	1060	3
D4-Pre	1.5	9.5	519	53	(–)	1840	200	1000	2
R-Pre	0.5	45	NA	195	(–)	1870	296	572	2

D-Pre: before DAC treatment; B-Pre: before bortezomib treatment; R-Pre: before ruxolitinib treatment; PLT: Platelet, MK: megakaryocytopoiesis, κ: Kappa light chain, NA: No test results

more platelet transfusions after 3 cycles of therapy. As a result, he was administered bortezomib (1.6 mg/m^2, d1/d8) and dexamethasone (20 mg/d, d1–4/8) regimen, and the platelet counts increased above 60 × 10^9/L without follow-up transfusions. Unfortunately, the CMML progressed to AML 11 months after. Shortly thereafter, he developed hyperleukocytosis and died. Table 1 illustrates the baseline characteristics of the patient's illness history.

To better understand the cytogenetic changes, a whole-exome (WES) approach was used to screen for mutations. Before DAC therapy, somatic variants in TET2, SRSF2, and ASXL1 genes had been identified. After three cycles of DAC therapy, WES analysis showed that TET2 p.P29R and SRSF2 p.P95H mutation VAFs were decreased, while TET2 p.I1873T and TET2 p.F1309fs remained unchanged. At the time of progression, FLT3 p.T2727M and ASXL1 p.G642fs VAFs increased to 62% and 40%, respectively (Fig. 1). This observation further suggested that the falling clones were susceptible to DAC, whereas stable or ascending clones were not, even a relative growth advantage [4–5]. Collectively, a large degree of variability in the response to DAC in patients with CMML was presented due to variable sensitivity of clones and incomplete mutation clearance.

DAC did not reduce the mutated allele burden. During DAC treatment, somatic mutations were successively acquired, and these mutations in each chromosome were listed in Fig. 2a. New gene mutations encoding a signaling protein (CSF3R, KRAS, SPEN, and MECOM) were identified. Additionally, these additional mutations were accompanied by expansion of the existing mutations involved in signaling pathway (FLT3 p.T227M, SETD2 p.M761I, KIAA1429 p.I826T, and MAP3K14 p.R99C) (Fig. 2b). Whether the acquisition of mutations was induced by DAC during the course of treatment or was part of the natural disease course remains unclear.

The patient in this study exhibited immune thrombocytopenia, reduced NK cell levels, and elevated

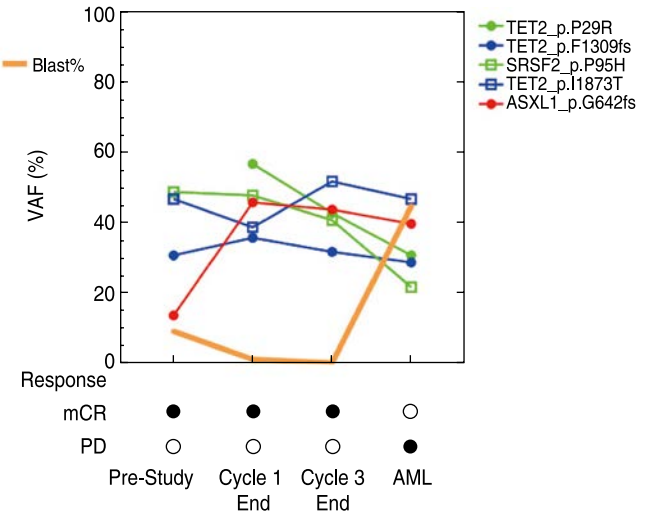

Fig. 1 Dynamic changes in mutation VAFs and incomplete mutation clearance during treatment. The blast % was indicated as a dark yellow line. The decreased, stable, and increased mutation VAF were shown as green, blue, and red lines, respectively

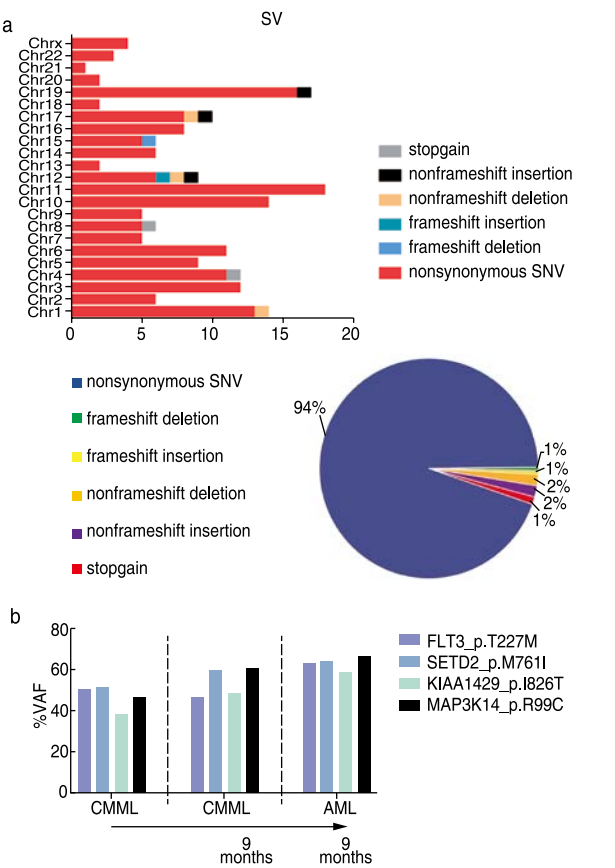

Fig. 2 Somatic variants in coding regions identified using the whole-exome sequencing. (a) The number and type of somatic mutations identified in each chromosome, showing a majority of nonsynonymous variants. Colors indicate the type of mutation; (b) Dynamic changes in mutation VAFs affecting signal transduction genes. Mutation VAF was sequenced before DAC therapy, after three cycles of DAC treatment, and during disease progression

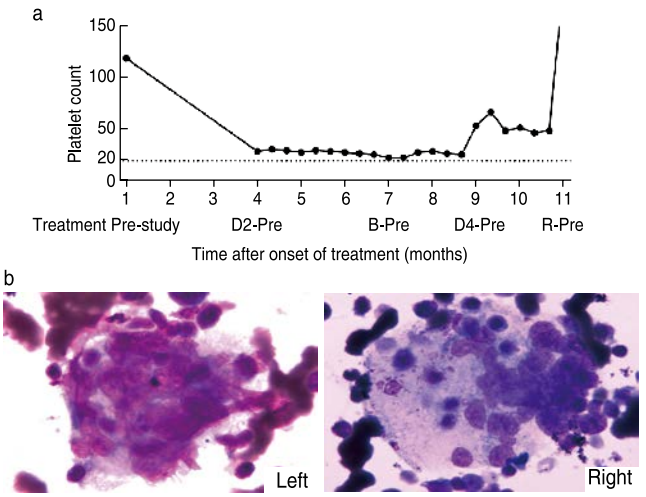

Fig. 3 Platelet response to decitabine/bortezomib therapy. (a) Time courses of platelet count during treatment; (b) Changes in megakaryocyte morphology before (left) and after (right) bortezomib treatment

M protein levels after three cycles of DAC therapy. At that time, new gene mutations involving immune conditions (LILRB4, MYBBP1A, NOTCH2, TNFAIP2, and MAGEC1) were detected. Autoimmune disease was suggested to be associated with increased risk of CMML progression, which is a threat to genomic stability.

These may be due to immune deregulation with aberrant immune responses and impaired tumor immune surveillance. Following the first cycle of bortezomib plus dexamethasone therapy, the patient achieved an excellent platelet response (Fig. 3). To our knowledge, this was the first reported case of CMML- and treatment-related thrombocytopenia s.fy.ated with bortezomib plus dexamethasone.

In conclusion, the findings in this study have clinical implications that may allow better evaluation of agents at earlier stages and guide strategies for subsequent treatment.

Ethics approval and consent to participate

Patient data were used after obtaining approval from the ethical committee of Ruijin Hospital.

Conflicts of interest

The authors declare no potential conflicts of interest.

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