**CLINICAL VIGNETTE**

# Use of Lenalidomide in Acute Myeloid Leukemia with Trisomy 13 A Case Report and Review of Literature

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## *Introduction*

Acquired trisomy 13 has been reported in patients with acute myeloid leukemia (AML) as early as in 1979.[1] As a sole abnormality, trisomy 13 are found in myelofibrosis, myelodysplastic syndrome (MDS), AML, acute lymphoblastic leukemia, and acute undifferentiated leukemia.[2-6] As more cases of trisomy 13 are reported, it became apparent that trisomy 13 is more commonly seen in minimally differentiated acute myeloid leukemia[7-12] and is associated with poor prognosis.[10,12-14] Trisomy 13 AML is strongly associated with RUNX1 mutations and increased FLT3 expression.[15-17] Fehniger et al reported 2 elderly AML patients with trisomy 13 as sole abnormality responded to high dose lenalidomide, compared to only 2 of 18 (11%) non-trisomy 13 AML patients have responded to lenalidomide.[18]

We report a case of acute myeloid leukemia with trisomy/ tetrasomy 13 without RUNX1 or FLT3 mutations that failed to respond to lenalidomide.

## *Case History*

An 86-year-old male presented with general malaise and WBC 48,600/µL, hemoglobin 5.4g/dL, platelets 14,000/µL. Bone marrow examination showed markedly hypercellular marrow with 96% myeloblasts consistent with acute myeloid leukemia with minimal differentiation. Flourescence in situ hybridization analysis showed no deletion of chromosome 5, 7, no evidence of rearrangement of MLL or CBFB genes and no BCR/ABL1, PML/RARA, or RUNX1T1/RUNX1 translocations. Conventional chromosome study showed 47,XY,+13 [3]/ 48, idem,+13[17]. Molecular studies showed no evidence of FLT3 Internal tandem duplication (ITD) or TKD mutation, no NPM1 mutation or CEBPA mutation.

He was initially treated with azacitadine for two cycles with no clinical improvement. He remained transfusion-dependent. He had to drive his son with schizophrenia to a shelter workshop every day and take care of his wife with severe dementia. The patient did not want further chemotherapy that made him fatigue easily. A recent study showed complete remission of AML with trisomy 13 treated with lenalidomide,[18] and he was started on oral lenalidomide 25 mg daily for 3 weeks, rest one week, every 4 weeks' cycle. He received two cycles of lenalidomide. Unfortunately, he remained transfusion-dependent and stopped all medications. He succumbed to refractory AML two months after lenalidomide was started.

## *Discussion*

Elderly patients with AML have poor prognosis because of poor tolerance to induction chemotherapy and co-morbid conditions. Hypomethylating agents, such as azacitadine, with lesser side effects are considered standard therapy for elderly AML per NCCN guidelines. Lenalidomide has various potential mechanisms of action including cytotoxic effects, immunomodulation of T and NK cells, alteration of tumor micro-environment and cytokine production and antiangiogenesis.[19]

Lenalidomide has been studied in treating MDS and AML. List el al published a pivotal trial of lenalidomide in 148 patients of low or intermediate risk MDS with chromosomal abnormalities containing 5q and two-thirds achieved transfusion independence. Among 85 patients with cytogenetic data, 62 (73%) showed cytogenetic improvement and 38 (60%) achieved complete cytogenetic remission. Lenalidomide is now FDA approved to treat MDS with 5q- abnormality.[20] However, the response of AML with 5q- is not as promising; only 14% achieving partial or complete response.[21]

Blum et al reported a dose escalating study of lenalidomide in patients with relapsed or refractory AML starting at 25 mg/day, day 1-21 of a 28-day cycle. Maximum tolerated dose was 50 mg daily with dose limiting fatigue. Overall complete remission rate was 16%.[22] Another phase II study of daily high dose (50mg) lenalidomide elderly patients over age 60 with newly diagnosed AML achieved a complete remission rate of 30%. The response did not appear to correlate to the chromosomal abnormalities.[23]

One may consider adding lenalidomide to azacitidine. However, recent studies showed disappointing results. Sekeres et al published a randomized phase II/III trial of azacitidine monotherapy or azacitadine combined with lenalidomide or vorinostat in patients with higher-risk MDS. There was no benefit of either combination compared to azacitadine monotherapy.[24] For elderly patients with newly diagnosed AML, Medeiros et al compared the efficacy of high-dose lenalidomide, sequential azacitidine and lenalidomide and azacitidine; the one-year survival was 21%, 44% and 52% respectively favoring conventional azacitadine.[25]

In our 86-year-old patient with main complaint being fatigue, lenalidomide was started at a standard dosage of 25mg daily, day 1-21 of a 28-day cycle [26] with an intention to dose escalate

if patient tolerates the treatment. Although initial case report suggested that lenalidomide has promising activity in AML with trisomy 13,[18] our patient did not respond to lenalidomide. We speculate that the lack of response may be partly due to drug non-compliance or suboptimal dose of 25 mg instead of 50 mg used in the phase II study. Alternatively, it may be partly due to the different molecular characteristic of our case. Trisomy 13 AML is strongly associated with RUNX1 mutations and increased FLT3 expression [15-17] suggesting a potential target for lenalidomide. When Fehniger et al initially reported the two cases of trisomy 13 AML responding to lenalidomide, one case was tested positive for FLT3-ITD mutation.[18] Our patient has neither RUNX1 translocation nor FLT3 mutation, which may be the molecular target for lenalidomide to be effective in MDS/ AML.

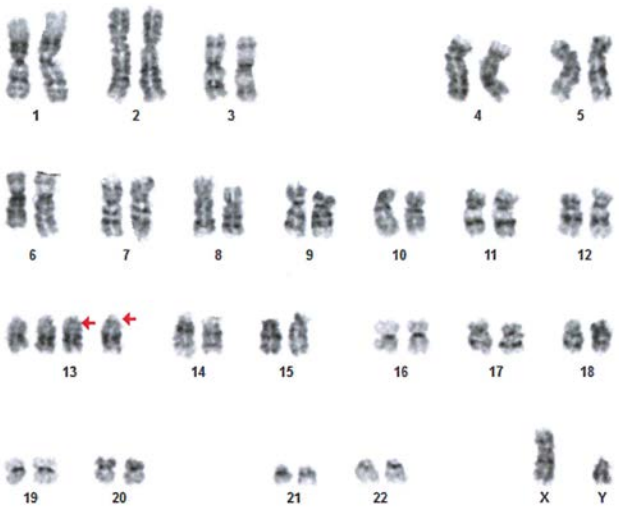


**Figure 1:** Bone marrow karyotype showing trisomy/tetrasomy 13.

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