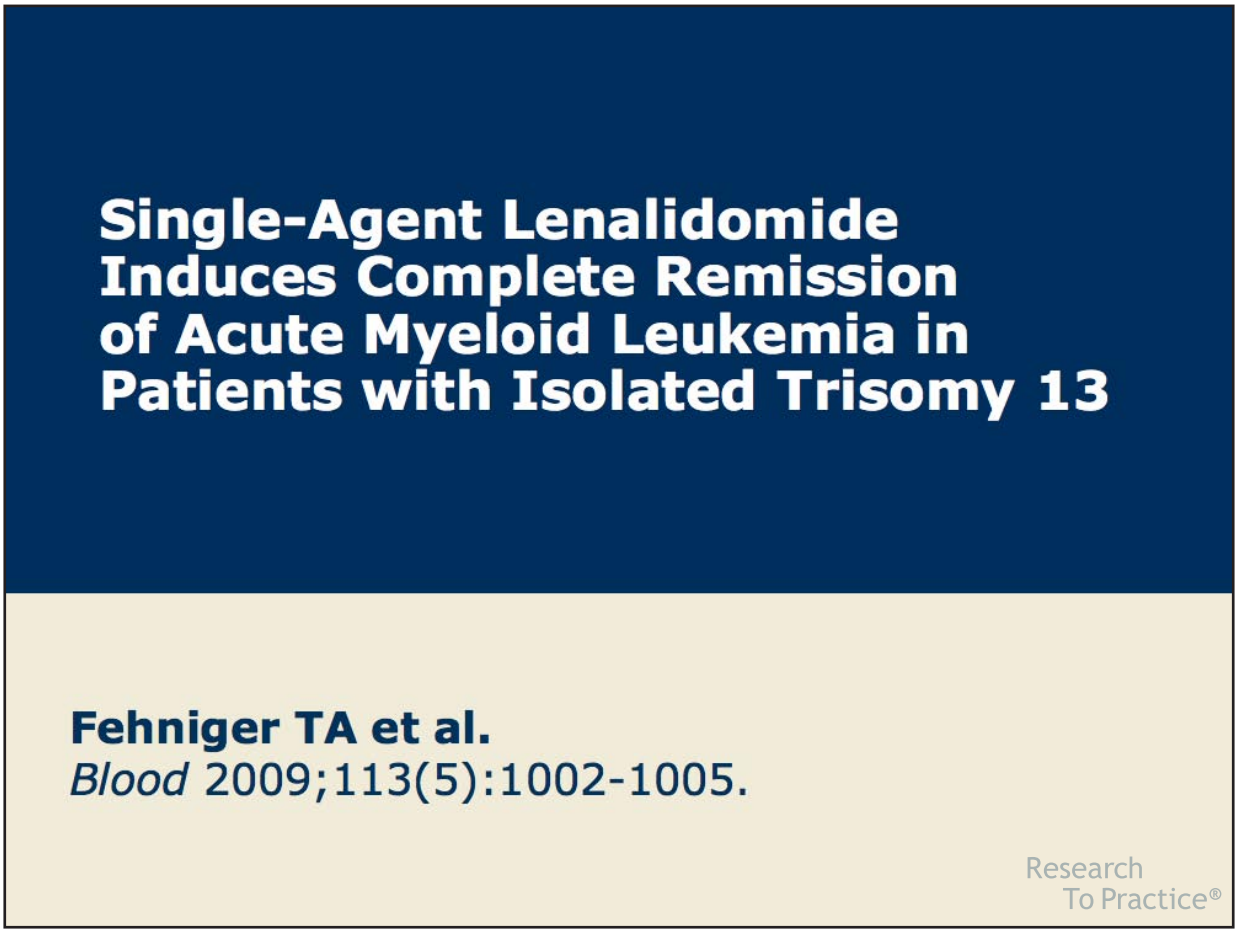
Lenalidomide Activity in AML with Trisomy 13

Presentation discussed in this issue:

Fehniger TA et al. **Single-agent lenalidomide induces complete remission of acute myeloid leukemia in patients with isolated trisomy 13.** *Blood* 2009;113(5):1002-5.
Abstract

Slides from a journal article



Introduction

- Most patients with AML are elderly (≥ 60 years), and the prognosis is poor
  - Cytogenetic abnormalities remain one of the most important prognostic factors.
  - AML with trisomy 13 is rare (3% of all cases) and associated with very poor prognosis (*Blood* 2006;108:63; *Blood* 1990;76:1614)
- Lenalidomide is active in del (5q) MDS, and is administered at low dose (10mg/day) due to myelosuppression at higher doses
- Two independent trials (NCT00466895; NCT00546897) explored higher doses of lenalidomide in older patients with AML and activity is reported in two patients harboring trisomy 13 as the sole cytogenetic abnormality

Source: Fehniger TA et al. *Blood* 2009;113(5):1002-5

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Case 1

- A 71-year-old man with no history of MDS presented with dyspnea and pancytopenia
- Bone marrow (BM) biopsy revealed undifferentiated AML with 90% myeloblasts expressing CD34, CD33, CD13 and CD117 with trisomy 13 in 5/20 metaphase cells as the sole chromosome abnormality by metaphase cytogenetics and FISH studies
- Therapy on clinical trial NCT00546897 consisted of lenalidomide, 50 mg/day for 14 days → 30 days off → lenalidomide, 50 mg/day for 21 days. Low-dose lenalidomide (10mg/day) was begun 30 days after completion of the 2nd high-dose cycle.

Source: Fehniger TA et al. *Blood* 2009;113(5):1002-5

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Case 1: Treatment Outcomes

Treatment	Outcomes
high-dose L, 50 mg/day, cycle 1 (days 1-14)	Day 14: Peripheral blood AML blasts cleared
off drug (days 15-44) high-dose L, 50 mg/day cycle 2 (days 45-65) off drug (days 66-95)	Day 30: 25% cellularity with 72% blasts on BM biopsy; *FLT3-ITD*-positive
	Day 66: Aplasia, <10% cellularity, blasts present on BM biopsy; transfusion dependent

L = lenalidomide

Source: Fehniger TA et al. *Blood* 2009;113(5):1002-5

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Case 1: Treatment Outcomes (Cont.)

Treatment	Outcomes
low-dose L, 10 mg/day (days 96-395)	Day 116: Blood cell counts normalized without transfusion or growth factors
	Day 124: 60% cellularity, <5% blasts on BM biopsy; no clonal abnormalities; *FLT3-ITD* negative. Two subsequent biopsies 6 and 14 weeks later confirmed this cytogenetic complete remission (CRc)
	Day 395: Relapse following low-dose lenalidomide for 10 months (CRc = 9 months)

L = lenalidomide

Source: Fehniger TA et al. *Blood* 2009;113(5):1002-5

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Case 2

- A 68-year-old man with relapsed AML presented with marked pancytopenia
- Initial diagnosis of AML was 3.5 years earlier, with normal karyotype, and was preceded by MDS. Remission was achieved upon his initial AML diagnosis with induction fludarabine/cytarabine/G-CSF (FLAG), which was the regimen chosen because of his underlying cardiomyopathy and other comorbidities, and this was followed by consolidation with one cycle of cytarabine (1.5 g/m^2 x 6 doses)
- At current relapse, BM biopsy showed 40% myeloblasts and FAB M2 AML; Metaphase cytogenetics revealed a clone with trisomy for chromosome 13
- Therapy on NCT00466895 study:Lenalidomide, 35 mg/day for 21 of repeated 28 day cycles

Source: Fehniger TA et al. *Blood* 2009;113(5):1002-5

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Case 2: Treatment Outcomes

Treatment	Outcomes
high-dose L, 35 mg/day (days 1-21) off drug (days 22-28)	Day 28: WBC=1200/µl, ANC=10/µl, RBC/platelet transfusion-dependent; 16% blasts on BM biopsy; 8/20 metaphase cells with persistent disease
high-dose L (days 29-31) off drug (days 32-78)	Day 32: lenalidomide held for fever, hypoxemia and pneumonia which resolved with medical treatment

L = lenalidomide

Source: Fehniger TA et al. *Blood* 2009;113(5):1002-5

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Case 2: Treatment Outcomes (Cont.)

Treatment	Outcomes
off drug (days 32-78) high-dose L, 35 mg/day (days 79-99) off drug (days 100-106) high-dose L, 35 mg/day (days 107-127)	Day 60: lenalidomide still held, blood counts recovered without G-CSF support; Day 78: CR on BM biopsy, normal male karyotype in 20/20 metaphase cells; FISH was negative. CRc was confirmed 5 weeks later on repeat BM biopsy.
low-dose L, 10 mg/day (x 21 days q28 days from day 128 until relapse)	Day 422: Relapse (CRc = 9 months)

L = lenalidomide

Source: Fehniger TA et al. *Blood* 2009;113(5):1002-5

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Discussion

- Lenalidomide has clinical activity in the poor-risk subset of AML with trisomy 13
- In two older patients with AML with isolated trisomy 13, sustained morphologic and cytogenetic remission were achieved with intermittent high-dose lenalidomide. In both patients, remission occurred after a prolonged delay (124 and 78 days, respectively) from initiation of this treatment.
- Further analysis of lenalidomide activity in additional patients with AML with trisomy 13 may lead to better understanding of myeloid leukemogenesis and aid in the development of new targeted therapeutic approaches for AML.

Source: Fehniger TA et al. *Blood* 2009;113(5):1002-5

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