Case Presentation

Prolonged Survival of a 79-Year Old Man with Acute Myeloid Leukemia M2, Normal Karyotype, NPM1 and FLT3-ITD Mutations, WBC $33.7 \times 10^9$/L, and Involving only Granulocyte-Macrophage Line on 53 Cycles of Low-Dose Cytarabine

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Abstract

The prognosis of older patients with de novo Acute Myeloid Leukemia (AML) is usually dismal. Palliative therapy with LDAC is one of the treatment options with a median survival of less than one year. Several reported older cases with AML with a survival of 25-51 months on therapy with LDAC lack details of the AML type, clinical characteristics, and treatment. This case report describes a 79-year-old man with AML M2, normal karyotype, leukocytosis $33.7 \times 10^9$/L, and involving only Granulocyte-Macrophage Line (GM-AML) who survived 84 months on 53 repeated cycles of LDAC, the longest described survival on LDAC. His leukemic cells exhibited Nucleophosmin 1 (NPM1) mutation and Fms-Like Tyrosine-kinase 3 gene (FLT3) Internal Tandem Duplication (ITD) with a high FLT3-ITD to FLT3 WT allelic ratio, typical immunophenotype, morphology and no dysplastic features. We propose that older patients with de novo GM-AML with these characteristics may benefit from prolonged LDAC therapy.

Keywords: Acute myeloid leukemia; Cytarabine; Hematopoietic myelodysplasia; NPM1; FLT3

Introduction

The prognosis of older patients with de novo Acute Myeloid Leukemia (AML) is poor. Palliative therapy using Low-Dose Cytarabine (LDAC) is one of the standard treatment options [1]. B.D. Cheson et al. (1986) reviewed studies on LDAC treatment in 237 patients with de novo AML of whom 77 (34%) achieved Complete Remission (CR) with a median duration of 9.5 months, the longest CR duration was 28 months and survival 30 months [2]. The UK MRC AML 14 Trial reported 102 elderly patients with AML treated with LDAC cycles which achieved CR in 18% with one exceptionally long CR duration of 51 months [3]. No diagnostic or clinical data of cases with their longest survival were described in these studies [2,3].

Here we report a case of de novo AML M2 [4] who had the first reported survival of greater than 5 years on repeated LDAC cycles. A detailed description of his AML characteristics and his therapy with LDAC cycles timing is presented which may be useful for selection of this successful and well-tolerated treatment in similar cases.

Case Presentation

A 79-year-old gentleman with a three weeks history of tiredness, weakness, night sweats and a recent episode of spontaneous epistaxis was admitted to Queen Alexandra Hospital (QAH) on December 5, 2011. His past medical history included right leg deep venous thrombosis with pulmonary embolism (1982), hypertension (1989), bilateral total knee replacement (2001/2). A routine blood count seven weeks prior had been normal (Table 1).

Laboratory tests demonstrated total leucocytosis $33.7 \times 10^9$/L with leukemic blasts and promyelocytes constituting $28.0 \times 10^9$/L, neutrophina $0.3 \times 10^9$/L, mild normocytic anemia with Hb 112 g/L and severe thrombocytopenia $14 \times 10^9$/L (Table 1). Blood chemistry showed raised serum bilirubin 27 μmol/L, urate 0.48 mmol/L, LDH 571 IU/L and CRP 14 mg/L. High plasma D-Dimer $> 6.00 \mu$g/mL and lower fibrinogen 1.2 g/L were found.

Immunophenotyping was performed on a Beckman Coulter 3L 10 Color Navios Flow Cytometer revealing a population of myeloid...
| Date       | Clinical status | Hb  | WBC  | Platelets | Neutr. | Notes                  | Therapy for AML          |
|------------|-----------------|-----|------|-----------|--------|------------------------|---------------------------|
| 20.10.11   | GP annual check | 137 | 4.3  | 213       | 2.0    | Normal FBC             | None                      |
| 5.12.11    | QAH admission   | 112 | 33.7 | 14        | 0.3    | blasts 28.0            | None                      |
| 6.12.11    | Dg. AML, HC     | 109 | 34.2 | 45        |        |                        | HC 1.0 g p.o. evening     |
| 7.12.11    | LDAC            | 105 | 30.4 | 29        |        |                        | HC 1.0 g p.o. x 2         |
| 9.12.11    |                 | 108 | 32.9 | 19        |        |                        | HC+ evening LDAC 20 mg sc  |
| 10.12.11   |                 | 92  | 22.7 | 14        |        |                        | HC + LDAC 20 mg sc BD     |
| 11.12.11   |                 | 93  | 19.8 | 12        |        |                        | dtto                      |
| 12.12.11   |                 | 81  | 11.8 | 34        | 0.1    |                        | dtto                      |
| 13.12.11   |                 | 85  | 8.0  | 19        | 0.1    |                        | dtto, HC last dose morning|
| 15.12.11   |                 | 101 | 4.1  | 17        | 0.1    |                        | blasts + LDAC 20 mg sc BD |
| 16.12.11   |                 | 90  | 2.6  | 12        |        |                        | dtto                      |
| 17.12.11   |                 | 78  | 2.0  | 34        | 0.1    |                        | dtto                      |
| 19.12.11   | QAH discharge   | 94  | 1.9  | 9         | 0.1    |                        | LDAC last dose morning    |
| 21.12.11   | Ambulatory F-U  | 85  | 1.6  | 16        | 0.1    |                        |                           |
| 28.12.11   | Ambulatory F-U  | 84  | 1.4  | 14        | 0.0    |                        |                           |
| 6.1.12     | Ambulatory F-U  | 87  | 1.4  | 51        | 0.3    |                        | 2nd cycle LDAC            |
| 11.1.12    |                 | 74  | 1.3  | 65        | 0.2    |                        | Last RBC transfusions     |
| 3.2.12     | FBC : CR        | 90  | 3.8  | 324       | 1.6    | retics 162             | 3rd LDAC, 4 week interval |
| 29.2.12    |                 | 94  | 3.8  | 409       | 1.7    |                        | 4th LDAC                  |
| 28.3.12    |                 | 111 | 3.8  | 348       | 1.5    |                        | 5th LDAC                  |
| 24.10.12   | Plantar fascitis| 112 | 3.4  | 391       | 1.3    |                        | 12th LDAC, insole, physiotherapy|
| 24.12.12   |                 | 118 | 4.7  | 292       | 2.3    |                        | 14th LDAC, next 5 week int.|
| 30.1.13    |                 | 130 | 8.5  | 239       | 5.5    |                        | 15th LDAC                 |
| 10.4.13    |                 | 122 | 7.9  | 225       | 5.6    |                        | 17th LDAC, next 6 week int.|
| 22.5.13    |                 | 122 | 8.5  | 216       | 6.3    |                        | 18th LDAC                 |
| 23.9.13    |                 | 127 | 9.2  | 172       | 6.9    |                        | 21st LDAC                 |
| 16.4.14    |                 | 133 | 8.9  | 200       | 7.1    |                        | 26th LDAC, next 7 week int.|
| 4.6.14     |                 | 134 | 7.9  | 225       | 5.9    |                        | 27th LDAC                 |
| 5.1.15     | Atrial fibrillation| 134 | 8.0  | 246       | 6.0    |                        | 31st LDAC, bisoprolol+rivaroxaban|
| 2.3.15     | Fall, bilat. rib fract. | 116 | 6.6  | 316       | 4.8    |                        | 32nd LDAC, DC cardiovers. 24/3|
| 20.4.15    |                 | 123 | 8.7  | 223       | 6.6    |                        | 33rd LDAC                 |
| 2.11.15    |                 | 126 | 7.8  | 229       | 6.0    |                        | 37th LDAC, next 8 week int.|
| 28.12.15   |                 | 130 | 7.9  | 244       | 5.5    |                        | 38th LDAC                 |
| 1.12.16    |                 | 128 | 8.5  | 227       | 6.1    |                        | 44th LDAC                 |
| 24.5.17    |                 | 127 | 7.4  | 211       | 5.3    |                        | 47th LDAC                 |
| 19.7.17    |                 | 127 | 6.6  | 200       | 4.5    |                        | 48th LDAC, next 2 months  |
blasts comprising approximately 80% of CD45+ve peripheral blood leucocytes expressing cytoplasmic myeloperoxidase and lysozyme (weak), CD13+, CD33+, CD56+, but negative for CD34, HLA-DR, CD117, CD11b, CD34, CD15, CD41, CD61, CD235a, and T and B lymphocyte associated markers.

Bone Marrow (BM) smears and trephine were hypercellular (>85%) with 74.2% myeloblasts and 22.0% promyelocytes, neutrophilic granulocytes 1.0%, eosinophils 0.6%, erythroblasts 0.2%, lymphocytes 1.6%, osteoblasts 0.4%, single megakaryocyte, and > 5 osteoclasts per smear. Myeloblasts had a high N/C ratio with round, oval, cuplike and occasionally folded nucleus, with 1- 4 nucleoli, moderately basophilic cytoplasm with azurophilic granules in 15% or a vacuole/s in 7%. Intranuclear invaginations of cytoplasm (> 25% of nuclear diameter) were found as a giant pseudonucleolus in 8.5% blasts, cuplike nuclei in 3.0% or “fish mouth” nuclei in 7.5% of blasts, altogether in 19% of blasts [5,6]. A few myeloblasts contained 1- 4 Auer rods or one pseudo-Chediak-Higashi granule. A single megakaryocyte was found and low numbers of erythroblasts pointed to the absence of Erythroblastic and/or Megakaryocytic Dysplasia (EMD) and only granulocyte-macrophage line involvement in this AML M2 (GM-AML) [7-9].

BM cytogenetic examination showed a normal 46,XY[20] Karyotype (NK) and no evidence of a PML/RARA rearrangement by FISH using the Abbott PML/RARA dual fusion probe combination. RT-PCR analysis was also performed using the Hemavision screen kit, designed to detect 28 different fusion transcripts and associated breakpoints commonly seen in acute leukemia [10]; this showed no evidence of a cyogenetically cryptic fusion transcript. Molecular testing for mutations within exon 12 of Nucleophosmin 1 (NPM1) with Amplicon-based next generation sequencing technology detected the NPM1 c.860_863dupTCTG mutation, while fragment analysis detected an Fms-Like Tyrosine kinase-3 gene (FLT3) Internal Tandem Duplication (ITD) of 32 bp with a high FLT3-ITD to FLT3 WT allelic ratio (0.887).

The patient was afebrile with Performance Status 1 (PS 1). Cardiologic examination showed first degree A-V block. Therapy with Hydroxycarbamide (HC) 1 g p.o. twice daily for seven days was started on December 6, 2011. After confirmation of the diagnosis of AML M2, treatment with low-dose cytarabine 20 mg (9.5 mg/sqm) s.c. twice daily for 10 days (LDAC cycle) was initiated on December 9. He tolerated treatment well. Leukemic cells in his blood became undetectable by day 9, but he remained RBC and platelet transfusion dependent after his discharge day 11 of LDAC on December 19 (Table 1).

On January 6, 2012, he started the second LDAC cycle with co-amoxiclav added for a mild gastrointestinal infection. He tolerated this cycle well, administration of RBC transfusions was stopped before the third LDAC cycle on February 3, 2012. His clinical condition was good (recommencing golf) and his FBC (Table 1) fulfilled the criteria for CR [11] with reticulocytes 162.2 x 10^9/L. He refused BM examination.

He continued with ambulatory self-administration of LDAC cycles at home in 4-week intervals until December 2012 (14th cycle). LDAC cycles 15-17 (January - April 2013) were administered in 5-week intervals, cycles 18-26 (until April 2014) in 6-week intervals, cycles 27-37 in 7-week intervals (until November 2015) when this interval was prolonged to 8 weeks (Table 1). Health complications such as plantar fascitis, a fall with rib fractures, and atrial fibrillation treated with cardioversion were successfully managed (Table 1) and he remained an active carer of his wife. In March 2018 he attended the routine appointment for his 52nd cycle in a wheelchair, PS 3, suffering from left sciatica and back pain after a recent fall. Investigations demonstrated L3 vertebral body collapse and left L3 nerve root exit foraminal narrowing. He continued with his 52nd LDAC cycle.

By May 2018 his clinical condition had deteriorated, his 53rd cycle was started but blasts <5% were found on blood film suspicious of AML relapse after 75 months in CR. He was now 86 years old with PS 3. He was reviewed 4 weeks later but he and his family refused bone marrow examination, refused further therapy with LDAC or azacitidine and opted for best supportive care. In August 2018 peripheral blood myeloblasts exhibited the same morphology and mutation profile including NPM1 duplication and FLT3-ITD and proved the relapse of AML (Table 1). He continued on best supportive care, with hydroxy carbamide added on November 8, and died from infectious complications of his AML progression on December 17, 2018.

Discussion

According to our best knowledge this case with AML and survival of 84 months and CR duration of 75 months is the first reported patient with survival of greater than 5 years on repeated LDAC cycles. The patient had an excellent quality of life and performance status, with self-administration of treatment at home, for almost all of his clinical course, except his initial admission and final months of
relapsed disease.

This case had rapidly developing de novo AML M2 with leukemic cells involving only GM-line (GM-AML) [7-9]. Patients with biological category of GM-AML of any age are known to achieve CR and prolonged survival after Standard Dose Induction Chemotherapy (SICT) in contrast to AML with Myelodysplasia related changes (AML-MRC) [1,4,7-9,12]. None of the 17 elderly cases with AML and cytogenetics associated with adverse prognosis reached CR post the same LDAC cycles in the UK MRC AML 14 Trial [3]. It seems probable that most of the 13 cases with AML and CR post LDAC cycles of 71 treated AML cases in this study were GM-AML.

Our institution continues LDAC maintenance in patients in remission when well tolerated, and we speculate that this may have contributed to the prolonged survival of this case. There were two cycles extended to nine, then ten week intervals from September 2017 due to clinic bookings, which might have caused or contributed to relapse.

Mutations of NPM1 and FLT3-ITD more precisely characterize this NK GM-AML case. Overall these genetic findings with a high FLT3-ITD to FLT3 WT allelic ratio are associated in NK AML cases <60/65 years with an intermediate prognosis [1] but not a favorable prognosis as found in this case. However, we cannot exclude that some other (unknown) factor(s) might have contributed to the good sensitivity of the patient’s leukemic cells to LDAC treatment.

Other treatment options for this case were SICT or high dose chemotherapy which are associated with much higher toxicity [1,7-9] or therapy with hypomethylating agents azacitidine or decitabine which are not recommended in patients with AML and WBC > 15 x 10^9/L [13,14].

The typical morphology of intranuclear invaginations of cytoplasm and immunophenotype of myeloblasts are associated with the combination of NPM1 and FLT3-ITD, mutations [5,6] and they may serve as a prompt to perform molecular testing of AML in elderly patients if this testing is not done routinely. We propose that elderly patients with de novo NK GM-AML with the same/similar characteristics may significantly benefit from long-term LDAC treatment although they are not cured and they should be reported. This case report will hopefully stimulate further research in similar patients with GM-AML and WBC > 15 x 10^9/L who may have a poor outcome after other treatment options or are not treated at all.

Statement of Ethics
The patient provided informed consent to therapy according to Declaration of Helsinki.

Disclosure Statement
The authors have no conflict of interest to declare; no funding source.

Author Contributions
HD and PL treated the patient, conceived the idea and wrote the first draft.

MG, RA, TC, GM, CJ and RC contributed to diagnosis and treatment of the patient.

LC and KB performed cytogenetic and genetic examinations.

SS performed immunophenotyping of leukemic cells.

All authors reviewed, corrected the manuscript and approved the final version.

The authors PL, HD, and MG equally contributed to this paper.

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