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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 × 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 x 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*

Abbreviations

AML: Acute Myeloid Leukemia; AML-MRC: AML with Myelodysplasia-Related Changes; EMD: Erythroblastic and/or Megakaryocytic Dysplasia; BM: Bone Marrow; FBC: Full Blood Cell count; *FLT3*-ITD: Fms-like Tyrosine kinase-3 gene (*FLT3*) Internal Tandem Duplication (ITD); *FLT3* WT: *FLT3* Wild Type; GM-AML: AML involving only cells of Granulocytic-Macrophage line; CR: Complete Remission; HC: Hydroxycarbamide; LDAC: Low-Dose Cytarabine; NK: normal karyotype; *NPM1*: Nucleophosmin 1 gene; *PML/RARA*: Fusion gene of Promyelocytic Leukemia gene/Retinoic Acid Receptor-Alpha gene; PS: Performance Status; RBC: Red Blood Cells; SICT: Standard-Dose Induction Chemotherapy; WBC: White Blood Cells

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 who 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 leukocytosis 33.7 x 10^9/L with leukemic blasts and promyelocytes constituting 28.0 x 10^9/L, neutropenia 0.3 x 10^9/L, mild normocytic anemia with Hb 112 g/L and severe thrombocytopenia 14 x 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 µg/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

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Table 1: Clinical status, blood counts and therapy.

Date	Clinical status	Hb	WBC	Platelets	Neutr.	Notes	Therapy for AML
	Procedures	g/L	10^9/L	10^9/L	10^9/L	10^9/L	
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		105	30.4	29			HC 1.0 g p.o. x 2
9.12.11	LDAC	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	no blasts	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 fasciitis	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

18.9.17		132	6.8	214	5.0		49th LDAC, next 9 weeks
20.11.17		125	6.6	246	4.5		50th LDAC, next 10 weeks
29.1.18	Fall, L3 fract. 2/18	129	5.5	209	3.8		51st LDAC, next 8 weeks
27.3.18	PS 3, poor mobility	121	5.2	238	3.3		52nd LDAC
18.5.18	Relapse	111	6.1	264	4.7	blasts<5%	53rd LDAC
15.6.18	Pt.decision BSC	86	0.6	138	0.1		Only best supportive care
3.7.18	Pt.confirmed BSC	98	3.1	224	1.7		MRI spine c/w BM leukem. infiltr.
7.8.18		110	10.3	201	2.7	blasts 5.4	
28.8.18	Proof of relapse	105	16.1	93	1.5	blasts 11.4	Identical *FTL3*-ITD, *NPM1* mutat.
5.12.18		77	36.7	6	0.0	blasts 35.6	Exitus on 17.12.2018

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, CD14, 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 cytogenetically 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 fasciitis, 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 hydroxycarbamide 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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