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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  $33.7 \times 10^{9}$ /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 x 10<sup>9</sup>/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<sup>9</sup>/L with leukemic blasts and promyelocytes constituting 28.0 x 10<sup>9</sup>/L, neutropenia 0.3 x 10<sup>9</sup>/L, mild normocytic anemia with Hb 112 g/L and severe thrombocytopenia 14 x 10<sup>9</sup>/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.

DateClinical statusHaWBCPlateleteNeutr.NotesThrrapy for AMLProcedures9.410%L10%L10%L10%L10%L10%L20.0.11GP annual check1374.32.132.0Normal FBCNore20.10.11GP annual check1373.374.42.0Normal FBCNore6.12.11Dg,AML,HC1083.424.5-HC 1.0 g.p. avening7.12.11Dg,AML,HC1083.291.0IHC 1.0 g.p. avening7.12.11LDAC1083.221.4-HC + DAC 20m g.e BD10.12.11LDAC1881.12-IHC + DAC 20m g.e BD11.12.11ILDAC8.11.181.1IHBIHB12.12.11ILDAC8.01.90.1IHC + DAC 20 m g.e BD15.12.11ILDAC8.11.181.1mo blastsILDAC 20 m g.e BD16.12.11Ambulatory FU8.51.60.1mo blastsILDAC 2								
Procedures       gl       10 <sup>1</sup> 10 <sup>1</sup> /L       10 <sup>1</sup> /L       10 <sup>1</sup> /L       10 <sup>1</sup> /L         Image: Section of the section of	Date	Clinical status	Hb	WBC	Platelets	Neutr.	Notes	Therapy for AML
Description       Description       Description       Description       Description       Description         20.10.11       GPanual check       17       3.3       1.4       0.3       blasts 28.0       Nome         51.211       GAH admission       112       3.37       1.4       0.3       blasts 28.0       None         51.211       Dg, AML, HC       100       34.2       4.55        HC 1.10 g.p. x2         71.211       LDAC       102       2.27       1.4        HC + excing LLAC 20 mg se BD         11.12.11       LDAC       63       198       1.2         HC + LAC 20 mg se BD         11.12.11       LDAC       65       8.0       199       0.1            11.12.11        45       8.0       199       0.1             11.12.11        42.0       3.4       0.1       no blasts       dto          11.12.11       Ambulatory F-U       85       1.6       0.1 <td></td> <td>Procedures</td> <td>g/L</td> <td>10<sup>9</sup>/L</td> <td>10<sup>9</sup>/L</td> <td>10<sup>9</sup>/L</td> <td>10<sup>9</sup>/L</td> <td></td>		Procedures	g/L	10 <sup>9</sup> /L	10 <sup>9</sup> /L	10 <sup>9</sup> /L	10 <sup>9</sup> /L	
20.0.11       GP anual check       137       4.3       213       2.0       Nomal FBC       Nome         5.12.11       Og AH admission       112       337       114       0.3       bilasts 2.0       Nome         6.12.11       Og AH admission       112       337       114       0.3       bilasts 2.0       Nome         6.12.11       Og AML, HC       109       3.42       455								
Image: Section of the secti	20.10.11	GP annual check	137	4.3	213	2.0	Normal FBC	None
512.11       QAH admission       112       3.37       14       0.3       blasts 28.0       Note         61.211       Dg, AHL, HC       109       342       450								
612.11Dg. AML, HC19934.245I.M.I.M.HC1.0 g.o. x27.12.11LDAC108329199I.M.MC1.0 g.o. x210.2.11LDAC108227144I.M.MC4-upAc2 Drags cBD11.12.110.18119.8120I.M.MC4-upAc2 Drags cBD11.2.111.M.8319.8120I.M.MC4-upAc2 Drags cBD13.2.110.18530190.1Mtb.Mtb.13.2.111.M.851201.M.DatasisILDAC2 Drags cBD15.1.2111.M.802.8120I.M.DatasisILDAC2 Drags cBD15.1.2110.AH discharge941.81.41.0I.M.Mtb.17.1.2110.AH discharge941.81.60.1I.DAC 20 mg cBD17.1.2110.AH discharge941.81.60.1I.DAC 20 mg cBD21.1.2110.AH discharge941.81.60.1I.DAC 20 mg cBD21.1.2110.AH discharge941.81.60.1I.DAC 20 mg cBD21.1.21Ambulatory F-U851.81.60.1I.DAC 20 mg cBD21.1.21Ambulatory F-U851.81.60.1I.DAC 20 mg cBD21.1.21Ambulatory F-U871.4510.3I.DAC21.1.21Ambulatory F-U871.4510.3I.DAC 20 mg cBD21.1.21Ambulatory F-U<	5.12.11	QAH admission	112	33.7	14	0.3	blasts 28.0	None
7.12.11   100   104   29   101   101   HC 10 g p.o.x 2     9.12.11   LDAC   108   32.9   19   10   HC + UAC 20 mg sc BD     10.12.11   93   19.8   12   10   HC + LDAC 20 mg sc BD     11.12.11   91   19.8   12   10   dtto     11.2.11   81   11.8   34   0.1   Mc + LDAC 20 mg sc BD     15.12.11   90   2.6   12   Mc + IDAC 20 mg sc BD     15.12.11   90   2.6   12   Mc + IDAC 20 mg sc BD     15.12.11   90   2.6   12   Mc + IDAC 20 mg sc BD     15.12.11   90   2.6   14   17   IDAC 30 mg sc BD     15.12.11   OAH discharge   94   19   9   0.1   IDAC 30 mg sc BD     15.12.11   Ambulatory F-U   85   1.6   1.6   0.1   IDAC 30 mg sc BD     11.12   Ambulatory F-U   84   1.4   1.4   0.0   IDAC 30 mg sc BD     11.11   Ambulatory F-U   87   1.4   51   0.3   IDAC 30 mg sc BD     11.1.12   Ambulatory F-U   87   1.4   1.4   0.0   IDAC 40 mg sc BD     11.1.12   Ambulatory F-U	6.12.11	Dg. AML, HC	109	34.2	45			HC 1.0 g p.o. evening
9.12.11       LDAC       108       32.9       19       I.       I.       HC+ evening LDAC 20 mg sc PD         11.12.11       92       2.7       144       I.       HC+ LDAC 20 mg sc PD         11.12.11       93       198       12       I.       HC+ LDAC 20 mg sc PD         12.12.11       81       118       344       0.1       Interpreter       Mtto         13.12.11       85       8.0       199       0.1       Batts HC       Mtto         15.12.11       90       2.6       12       Interpreter       Mtto       Mtto         17.12.11       OAH discharge       94       1.9       9       0.1       ILDAC last dose moring         21.12.11       Ambulatory F-U       85       1.6       1.6       OL       ILDAC last dose moring         21.12.11       Ambulatory F-U       87       1.4       51       0.3       ILDAC last dose moring         21.12.11       Ambulatory F-U       87       1.4       51       0.3       ILDAC last dose moring         21.12.12       Ambulatory F-U       87       1.4       51       0.3       ILDAC last	7.12.11		105	30.4	29			HC 1.0 g p.o. x 2
10.12.1114.14<	9.12.11	LDAC	108	32.9	19			HC+ evening LDAC 20 mg sc
11.12.1114.149.319.81214.89.440.110.140.140.140.1413.12.1110.18.68.69.90.10.10.10<	10.12.11		92	22.7	14			HC + LDAC 20 mg sc BD
12.12.1114.1414.1834.40.114.4dtodto13.12.1114.115.210.111.417.70.1blasts +LDAC 20m g a B16.12.1114.117.00.1blasts +LDAC 20m g a B17.416.12.1114.117.82.03.40.1no blastsdtto17.12.1114.417.82.03.40.1no blastsdtto17.12.110.4H discharge9.41.99.90.11.0LDAC last dose morning17.12.110.4H discharge9.41.99.90.11.0LDAC last dose morning17.12.110.4H discharge9.41.99.90.11.0LDAC last dose morning17.12.110.4H discharge9.41.99.90.11.0LDAC last dose morning17.12.11Ambulatory F-U8.51.60.11.01.01.018.12.1Ambulatory F-U8.61.60.11.02.42.419.117.41.36.50.2Last RBC transfusions3.232.12FBC: CR9.43.83.41.51.63.41.029.1219.141.113.83.441.51.21.0AC, hext evek intraval29.1219.141.113.83.441.51.21.14 <sup>a</sup> LDAC, next evek intraval29.1219.141.121.23.43.51.51.21.0AC	11.12.11		93	19.8	12			dtto
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16.12.11   90   2.6   12   10   no blasts   dtto     17.12.11   0AH discharge   94   1.9   9   0.1   no blasts   dtto     19.12.11   0AH discharge   94   1.9   9   0.1   no blasts   dtto     21.12.11   Ambulatory F-U   85   1.6   0.1   0.1   LDAC last dose morning     21.12.11   Ambulatory F-U   85   1.6   0.1   0.1   1.0   1.0     21.12.11   Ambulatory F-U   87   1.4   51   0.3   0.1   1.0     6.1.12   Ambulatory F-U   87   1.4   51   0.3   1.0   1.0     6.1.12   Ambulatory F-U   87   1.4   51   0.3   1.0   1.0     32.12   FBC : CR   90   3.8   324   1.6   retics 162   3"LDAC, 4week interval     292.12   FBC : CR   91   3.8   348   1.5   1.0   4"LDAC     283.12   Inter fascilits   111   3.8   341   1.5   1.0   14"LDAC, insterval interval     241.212   Plantar fascilits   122   3.5   2.30   1.1   1.0   1.0     104.13   <	15.12.11		101	4.1	17	0.1	blasts +	LDAC 20 mg sc BD
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19.12.11QAH discharge941.990.11.10LDAC last dose morning21.12.11Ambulatory F-U841.66.60.1	17.12.11		78	2.0	34	0.1	no blasts	dtto
21.1.2.11       Ambulatory F-U       85       1.6       16       0.1       Image: Constraint of the con	19.12.11	QAH discharge	94	1.9	9	0.1		LDAC last dose morning
28.12.11       Ambulatory F-U       84       1.4       1.4       0.0       Incomposition         6.1.2       Ambulatory F-U       87       1.4       51       0.3       C $2^{ac}$ orgole LDAC         11.1.12       Ambulatory F-U       87       1.4       51       0.3       C       Last RBC transfusions         3.2.12       FBC : CR       90       3.8       324       1.6       retics 162       3"LDAC, 4 week interval         29.2.12       FBC : CR       94       3.8       409       1.7       C       4"DAC, 4 week interval         28.3.12       111       3.8       348       1.5       G       5"LDAC         24.10.12       Plentar fascitits       112       3.4       391       1.3       12"LDAC, insole, physiotherapy         24.12.12       Plentar fascitits       112       3.4       391       1.3       12"LDAC, insole, physiotherapy         24.12.12       Plentar fascitits       112       3.4       291       5.5       14"LDAC, insole, physiotherapy         24.12.12       Intervest fascitits       112       3.4       291       5.5       14"LDAC, insole	21.12.11	Ambulatory F-U	85	1.6	16	0.1		
Image: Market Mathematican Stratet Mathmater Mathematican Stratet Mathematican Stratet Math	28.12.11	Ambulatory F-U	84	1.4	14	0.0		
6.1.12     Ambulatory F-U     87     1.4     51     0.3     0.2     2" 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     3" LDAC, 4 week interval       29.2.12     94     3.8     409     1.7     3" LDAC, 4 week interval       28.3.12     111     3.8     348     1.5     3" LDAC, 4 week interval       24.10.12     Plantar fascittis     112     3.4     391     1.3     12" LDAC, insole, physiotherapy       24.12.12     Plantar fascittis     112     3.4     391     1.3     12" LDAC, insole, physiotherapy       24.12.12     Plantar fascittis     112     3.4     391     1.3     12" LDAC, insole, physiotherapy       24.12.12     Plantar fascittis     112     3.4     391     5.5     16" LDAC     14" LDAC, next 5 week int.       30.1.13     IAT     130     8.5     239     5.5     16" LDAC     15" LDAC, next 6 week int.       22.5.13     IAT     12" PLAC     7.9     225     5.6     17" LDA								
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       94       111       3.8       348       1.5       5th LDAC         24.10.12       Plantar fascititis       112       3.4       391       1.3       12th LDAC, insole, physiotherapy         24.12.12       Plantar fascititis       112       3.4       391       1.3       12th LDAC, insole, physiotherapy         24.12.12       Plantar fascititis       112       3.4       391       1.3       12th LDAC, insole, physiotherapy         24.12.12       Plantar fascititis       112       3.4       391       1.3       12th LDAC, insole, physiotherapy         24.12.12       Plantar fascititis       12th       6.9       5.5       16th Plant       13th Plant         30.113       12th Plant       132       8.9       200       7.1       26th Plant       12th Plant         164.14       133	6.1.12	Ambulatory F-U	87	1.4	51	0.3		2 <sup>nd</sup> cycle LDAC
32.12       FBC : CR       90       3.8       324       1.6       retics 162       3" LDAC, 4 week interval         29.2.12       94       3.8       409       1.7       4"       4" LDAC         28.3.12       111       3.8       348       1.5       5" LDAC, insole, physiotherapy         24.10.12       Plantar fasciitis       112       3.4       391       1.3       12" LDAC, insole, physiotherapy         24.12.12       Plantar fasciitis       118       4.7       292       2.3       14" LDAC, insole, physiotherapy         30.1.13       130       8.5       239       5.5       14" LDAC, insole, physiotherapy         104.13       140       130       8.5       239       5.5       14" LDAC, insole, physiotherapy         104.13       122       7.9       225       5.6       17" LDAC, next 6 week int.         225.13       122       8.5       216       6.3       16" DAC       18" LDAC         23.9.13       127       9.2       172       6.9       26" LDAC, next 7 week int.       16.4         4.6.14       133       8.9       200       7.1       26"	11.1.12		74	1.3	65	0.2		Last RBC transfusions
29.2.12       94       3.8       409       1.7       4 <sup>h</sup> LDAC         28.3.12       111       3.8       348       1.5       5 <sup>h</sup> LDAC         24.10.12       Plantar fasciitis       112       3.4       391       1.3       12 <sup>h</sup> LDAC, insole, physiotherapy         24.12.12       118       4.7       292       2.3       14 <sup>th</sup> LDAC, next 5 week int.         30.1.13       130       8.5       239       5.5       15 <sup>h</sup> LDAC         104.13       122       7.9       225       5.6       17 <sup>th</sup> LDAC, next 6 week int.         22.5.13       122       8.5       216       6.3       17 <sup>th</sup> LDAC, next 6 week int.         23.9.13       122       8.5       216       6.3       18 <sup>th</sup> LDAC         164.14       133       8.9       200       7.1       26 <sup>th</sup> LDAC, next 7 week int.         4.6.14       134       7.9       225       5.9       27 <sup>th</sup> LDAC         5.1.15       Atrial fibrillation       134       8.0       246       6.0       31 <sup>th</sup> LDAC, bisoprolei+rivaroxaban         2.3.15       Fall, bilat.rib fract.       116       6.6       316	3.2.12	FBC : CR	90	3.8	324	1.6	retics 162	3 <sup>rd</sup> LDAC, 4 week interval
28.3.12       111       3.8       348       1.5       5 <sup>th</sup> LDAC         24.10.12       Plantar fasciitis       112       3.4       391       1.3       12 <sup>th</sup> LDAC, insole, physiotherapy         24.12.12       118       4.7       292       2.3       14 <sup>th</sup> LDAC, insole, physiotherapy         30.1.13       130       8.5       239       5.5       15 <sup>th</sup> LDAC         10.4.13       122       7.9       225       5.6       17 <sup>th</sup> LDAC, next 6 week int.         22.5.13       122       8.5       216       6.3       121 <sup>th</sup> LDAC, next 6 week int.         23.9.13       122       8.5       216       6.3       21 <sup>th</sup> LDAC, next 7 week int.         164.14       133       8.9       200       7.1       26 <sup>th</sup> LDAC, next 7 week int.         4.6.14       134       7.9       225       5.9       27 <sup>th</sup> LDAC         5.1.15       Atrial fibrillation       134       8.0       246       6.0       31 <sup>th</sup> LDAC, Discription/trivaroxaban         2.3.15       Fall, biat. rib fract.       116       6.6       316       4.8       32 <sup>th</sup> LDAC, DC cardiovers. 24/3         2.4.15       <	29.2.12		94	3.8	409	1.7		4 <sup>th</sup> LDAC
24.10.12       Plantar fasciitis       112       3.4       391       1.3       12" LDAC, insole, physiotherapy         24.12.12       118       4.7       292       2.3       14" LDAC, next 5 week int.         30.1.13       130       8.5       239       5.5       15" LDAC         104.13       122       7.9       225       5.6       17" LDAC, next 6 week int.         22.5.13       122       7.9       225       5.6       17" LDAC, next 6 week int.         23.9.13       122       8.5       216       6.3       12" LDAC         164.14       133       8.9       200       7.1       26" LDAC, next 7 week int.         46.14       133       8.9       200       7.1       26" LDAC, next 7 week int.         4.6.14       134       7.9       225       5.9       27" LDAC         5.1.15       Atrial fibrillation       134       8.0       246       6.0       31" LDAC, DC cardiovers.24/3         2.3.15       Fall, bilat.rib fract.       116       6.6       316       4.8       32" LDAC, DC cardiovers.24/3         2.4.15       123       8.7       223	28.3.12		111	3.8	348	1.5		5 <sup>th</sup> LDAC
24.12.12       118       4.7       292       2.3       14 <sup>h</sup> LDAC, next 5 week int.         30.1.13       130       8.5       239       5.5       15 <sup>h</sup> LDAC         10.4.13       122       7.9       225       5.6       17 <sup>h</sup> LDAC, next 6 week int.         22.5.13       122       7.9       225       5.6       17 <sup>h</sup> LDAC, next 6 week int.         23.9.13       127       9.2       172       6.9       21 <sup>at</sup> LDAC         164.14       133       8.9       200       7.1       26 <sup>h</sup> LDAC, next 7 week int.         46.14       133       8.9       200       7.1       26 <sup>h</sup> LDAC, next 7 week int.         5.1.15       Atrial fibrillation       134       7.9       225       5.9       27 <sup>h</sup> LDAC         5.1.15       Atrial fibrillation       134       8.0       246       6.0       31 <sup>at</sup> LDAC, DC cardiovers. 24/3         20.4.15       Fall, bilat. rib fract.       116       6.6       316       4.8       32 <sup>m</sup> LDAC, DC cardiovers. 24/3         20.4.15       Fall, bilat. rib fract.       126       7.8       229       6.0       37 <sup>m</sup> LDAC, next 8 week int.         211	24.10.12	Plantar fasciitis	112	3.4	391	1.3		12 <sup>th</sup> LDAC, insole, physiotherapy
30.1.13       130       8.5       239       5.5       15°       15°       15°         10.4.13       122       7.9       225       5.6       17° LDAC, next 6 week int.         22.5.13       122       8.5       216       6.3       117° LDAC, next 7 week int.         23.9.13       127       9.2       172       6.9       21° LDAC         16.4.14       133       8.9       200       7.1       26° LDAC, next 7 week int.         4.6.14       133       8.9       200       7.1       26° LDAC, next 7 week int.         4.6.14       134       7.9       225       5.9       27° LDAC         5.1.15       Atrial fibrillation       134       8.0       246       6.0       31° LDAC, DC cardiovers. 24/3         2.3.15       Fall, bilat. rib fract.       116       6.6       316       4.8       32° LDAC, DC cardiovers. 24/3         2.0.4.15       123       8.7       223       6.6       33° LDAC, next 8 week int.         2.11.15       126       7.8       229       6.0       37° LDAC, next 8 week int.         2.8.12.15       130       7.9       <	24.12.12		118	4.7	292	2.3		14 <sup>th</sup> LDAC, next 5 week int.
Image: Market	30.1.13		130	8.5	239	5.5		15 <sup>th</sup> LDAC
10.4.13     122     7.9     225     5.6     17 <sup>h</sup> LDAC, next 6 week int.       22.5.13     122     8.5     216     6.3     18 <sup>h</sup> LDAC       23.9.13     127     9.2     172     6.9     21 <sup>st</sup> LDAC       16.4.14     133     8.9     200     7.1     26 <sup>h</sup> LDAC, next 7 week int.       4.6.14     133     8.9     200     7.1     26 <sup>h</sup> LDAC, next 7 week int.       4.6.14     134     7.9     225     5.9     27 <sup>h</sup> LDAC       5.1.15     Atrial fibrillation     134     8.0     246     6.0     31 <sup>st</sup> LDAC, DC cardiovers. 24/3       2.3.15     Fall, bilat. rib fract.     116     6.6     316     4.8     32 <sup>nd</sup> LDAC, DC cardiovers. 24/3       20.4.15     123     8.7     223     6.6     31 <sup>st</sup> LDAC, next 8 week int.       2.11.15     126     7.8     229     6.0     37 <sup>th</sup> LDAC, next 8 week int.       28.12.15     130     7.9     244     5.5     38 <sup>th</sup> LDAC       1.12.16     128     8.5     227     6.1     44 <sup>th</sup> LDAC       24.5.17     127     7.4     211     <								
22.5.13     122     8.5     216     6.3     18 <sup>h</sup> LDAC       23.9.13     127     9.2     172     6.9     21 <sup>st</sup> LDAC       16.4.14     133     8.9     200     7.1     26 <sup>th</sup> LDAC, next 7 week int.       4.6.14     134     7.9     225     5.9     27 <sup>th</sup> LDAC       5.1.15     Atrial fibrillation     134     8.0     246     6.0     31 <sup>st</sup> LDAC, bisoprolol+rivaroxaban       2.3.15     Fall, bilat. rib fract.     116     6.6     316     4.8     32 <sup>rd</sup> LDAC, DC cardiovers. 24/3       20.4.15     123     8.7     223     6.6     33 <sup>rd</sup> LDAC, next 8 week int.       2.11.15     126     7.8     229     6.0     37 <sup>th</sup> LDAC, next 8 week int.       28.12.15     130     7.9     244     5.5     38 <sup>th</sup> LDAC, next 8 week int.       28.12.15     130     7.9     244     5.5     38 <sup>th</sup> LDAC       1.12.16     128     8.5     227     6.1     44 <sup>th</sup> LDAC       24.5.17     127     7.4     211     5.3     47 <sup>th</sup> LDAC, next 2 months	10.4.13		122	7.9	225	5.6		17 <sup>th</sup> LDAC, next 6 week int.
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, bisoproloi+rivaroxaban       2.3.15     Fall, bilat. rib fract.     116     6.6     316     4.8     32rd LDAC, DC cardiovers. 24/3       20.4.15     Fall, bilat. rib fract.     116     6.6     316     4.8     32rd LDAC, DC cardiovers. 24/3       20.4.15     123     8.7     223     6.6     33rd LDAC     33rd LDAC       211.15     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	22.5.13		122	8.5	216	6.3		18 <sup>th</sup> LDAC
16.4.14     133     8.9     200     7.1     26 <sup>h</sup> LDAC, next 7 week int.       4.6.14     134     7.9     225     5.9     27 <sup>th</sup> LDAC       5.1.15     Atrial fibrillation     134     8.0     246     6.0     31 <sup>st</sup> LDAC, bisoprolol+rivaroxaban       2.3.15     Fall, bilat. rib fract.     116     6.6     316     4.8     32 <sup>nd</sup> LDAC, DC cardiovers. 24/3       20.4.15     Fall, bilat. rib fract.     116     6.6     316     4.8     32 <sup>nd</sup> LDAC, next 7 week int.       20.4.15     Fall, bilat. rib fract.     116     6.6     316     4.8     32 <sup>nd</sup> LDAC, next 6 week int.       20.4.15     123     8.7     223     6.6     33 <sup>nd</sup> LDAC, next 8 week int.       2.11.15     126     7.8     229     6.0     37 <sup>th</sup> LDAC, next 8 week int.       28.12.15     130     7.9     244     5.5     38 <sup>th</sup> LDAC       1.12.16     128     8.5     227     6.1     44 <sup>th</sup> LDAC       24.5.17     127     7.4     211     5.3     47 <sup>th</sup> LDAC       19.7.17     127     6.6     200     4.5     48 <sup>th</sup> LDAC, next 2 months   <	23.9.13		127	9.2	172	6.9		21 <sup>st</sup> LDAC
4.6.14     134     7.9     225     5.9     27 <sup>h</sup> LDAC       5.1.15     Atrial fibrillation     134     8.0     246     6.0     31 <sup>st</sup> LDAC,bisoprolol+rivaroxaban       2.3.15     Fall, bilat. rib fract.     116     6.6     316     4.8     32 <sup>nd</sup> LDAC, DC cardiovers. 24/3       20.4.15     Fall, bilat. rib fract.     116     6.6     316     4.8     32 <sup>nd</sup> LDAC, DC cardiovers. 24/3       20.4.15     123     8.7     223     6.6     33 <sup>rd</sup> LDAC     33 <sup>rd</sup> LDAC       20.4.15     123     8.7     223     6.6     33 <sup>rd</sup> LDAC, DC cardiovers. 24/3       20.4.15     123     8.7     223     6.6     33 <sup>rd</sup> LDAC, DC cardiovers. 24/3       21.115     123     8.7     229     6.0     33 <sup>rd</sup> LDAC, next 8 week int.       28.12.15     130     7.9     244     5.5     38 <sup>th</sup> LDAC       1.12.16     128     8.5     227     6.1     44 <sup>th</sup> LDAC       24.5.17     127     7.4     211     5.3     47 <sup>th</sup> LDAC, next 2 months       19.7.17     127     6.6     200     4.5     48 <sup>th</sup> LDAC, next 2 months  <	16.4.14		133	8.9	200	7.1		26th LDAC, next 7 week int.
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       33 <sup>rd</sup> LDAC         20.4.15       123       8.7       223       6.6       33 <sup>rd</sup> LDAC, DC cardiovers. 24/3         20.4.15       120       123       8.7       223       6.6       33 <sup>rd</sup> LDAC         20.4.15       126       7.8       229       6.0       37 <sup>th</sup> LDAC, next 8 week int.         28.12.15       126       7.8       229       6.0       37 <sup>th</sup> LDAC, next 8 week int.         28.12.15       130       7.9       244       5.5       38 <sup>th</sup> LDAC         1.12.16       128       8.5       227       6.1       44 <sup>th</sup> LDAC         24.5.17       127       7.4       211       5.3       47 <sup>th</sup> LDAC, next 2 months         19.7.17       127       6.6       200       4.5       48 <sup>th</sup> LDAC, next 2 months	4.6.14		134	7.9	225	5.9		27 <sup>th</sup> LDAC
2.3.15     Fall, bilat. rib fract.     116     6.6     316     4.8     32 <sup>nd</sup> LDAC, DC cardiovers. 24/3       20.4.15     123     8.7     223     6.6     33 <sup>rd</sup> LDAC       20.4.15     120     120     6.6     33 <sup>rd</sup> LDAC       2.11.15     126     7.8     229     6.0     37 <sup>th</sup> LDAC, next 8 week int.       28.12.15     130     7.9     244     5.5     38 <sup>th</sup> LDAC       1.12.16     128     8.5     227     6.1     44 <sup>th</sup> LDAC       24.5.17     127     7.4     211     5.3     47 <sup>th</sup> LDAC, next 2 months       19.7.17     127     6.6     200     4.5     48 <sup>th</sup> LDAC, next 2 months	5.1.15	Atrial fibrillation	134	8.0	246	6.0		31st LDAC, bisoprolol+rivaroxaban
20.4.15     123     8.7     223     6.6     33" LDAC       20.4.15     126     7.8     229     6.0     37" LDAC, next 8 week int.       2.11.15     126     7.8     229     6.0     37" LDAC, next 8 week int.       28.12.15     130     7.9     244     5.5     38" LDAC       1.12.16     128     8.5     227     6.1     44" LDAC       24.5.17     127     7.4     211     5.3     47" LDAC, next 2 months       19.7.17     127     6.6     200     4.5     48" LDAC, next 2 months	2.3.15	Fall, bilat. rib fract.	116	6.6	316	4.8		32 <sup>nd</sup> LDAC, DC cardiovers. 24/3
2.11.15       126       7.8       229       6.0       37 <sup>th</sup> LDAC, next 8 week int.         28.12.15       130       7.9       244       5.5       38 <sup>th</sup> LDAC         1.12.16       128       8.5       227       6.1       44 <sup>th</sup> LDAC         24.5.17       127       7.4       211       5.3       47 <sup>th</sup> LDAC, next 2 months	20.4.15		123	8.7	223	6.6		33 <sup>rd</sup> LDAC
2.11.15       126       7.8       229       6.0       37 <sup>th</sup> LDAC, next 8 week int.         28.12.15       130       7.9       244       5.5       38 <sup>th</sup> LDAC         1.12.16       128       8.5       227       6.1       44 <sup>th</sup> LDAC         24.5.17       127       7.4       211       5.3       47 <sup>th</sup> LDAC, next 2 months         19.7.17       127       6.6       200       4.5       48 <sup>th</sup> LDAC, next 2 months								
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	2.11.15		126	7.8	229	6.0		37 <sup>th</sup> LDAC, next 8 week int.
1.12.16       128       8.5       227       6.1       44 <sup>th</sup> LDAC         24.5.17       127       7.4       211       5.3       47 <sup>th</sup> LDAC         19.7.17       127       6.6       200       4.5       48 <sup>th</sup> LDAC, next 2 months	28.12.15		130	7.9	244	5.5		38 <sup>th</sup> LDAC
24.5.17       127       7.4       211       5.3       47 <sup>th</sup> LDAC         19.7.17       127       6.6       200       4.5       48 <sup>th</sup> LDAC, next 2 months	1.12.16		128	8.5	227	6.1		44 <sup>th</sup> LDAC
19.7.17       127       6.6       200       4.5       48 <sup>th</sup> LDAC, next 2 months	24.5.17		127	7.4	211	5.3		47 <sup>th</sup> LDAC
	19.7.17		127	6.6	200	4.5		48 <sup>th</sup> LDAC, next 2 months

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18.9.17		132	6.8	214	5.0		49 <sup>th</sup> LDAC, next 9 weeks
20.11.17		125	6.6	246	4.5		50 <sup>th</sup> LDAC, next 10 weeks
29.1.18	Fall, L3 fract. 2/18	129	5.5	209	3.8		51 <sup>st</sup> LDAC, next 8 weeks
27.3.18	PS 3, poor mobility	121	5.2	238	3.3		52 <sup>nd</sup> LDAC
18.5.18	Relapse	111	6.1	264	4.7	blasts<5%	53 <sup>rd</sup> 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 coamoxiclav 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 (14<sup>th</sup> 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 52<sup>nd</sup> 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 52<sup>nd</sup> LDAC cycle.

By May 2018 his clinical condition had deteriorated, his  $53^{rd}$  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

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### 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<sup>9</sup>/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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