EHA-PTHiT Hematology Mini Tutorial

Self-assessment Case 1 – Session Title […]

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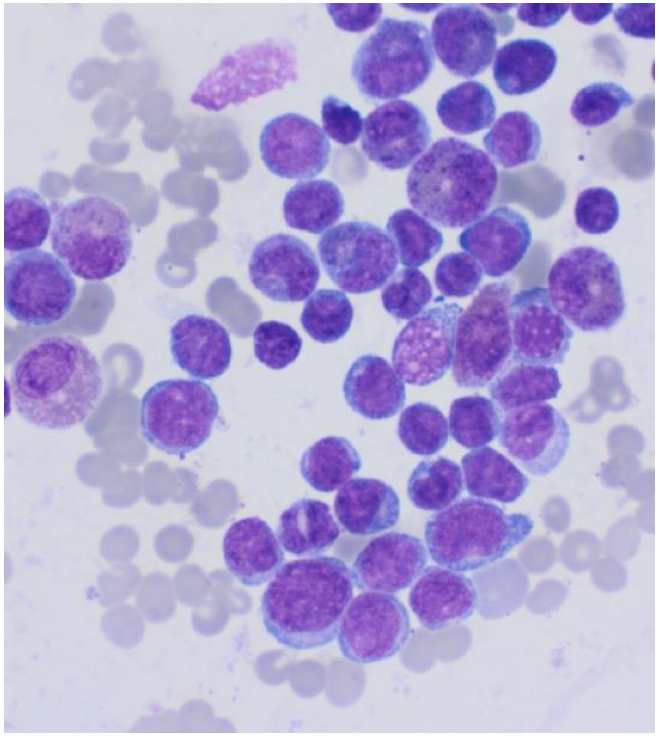
Introduction

- A 27-year-old man reported to the emergency department due to dyspnoea at rest
- Medical history
  - Progressive weakness for 1 month
  - Upper respiratory tract infection 4 days ago (treated with amoxicillin)
- Physical examination:
  - Palatine tonsils enlarged, gingival hyperplasia,
  - Bilateral cervical lymphadenopathy,

Blood test	
WBC	**174.84** × 10^9/l
Neutrophils (ANC)	11.76 × 0^9/l
Hb	54 g/l
RBC	2.98 × 10^{12}/l
MCV	92 fl
Platelets	**32** × 10^9/l
PB film	**Blasts 76%**

Introduction

- Bone marrow aspirate:
  - Hypercellular
  - Blasts - 60.5%
  - Eosinophilia -15.5%
  - Dysplasia in myeloid line -10%

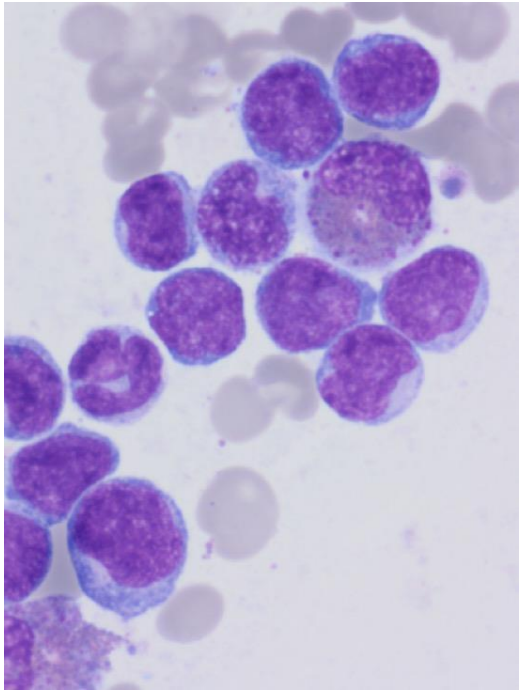


Courtesy of Marta Robak

Introduction

- Bone marrow aspirate immunophenotyping
- Immunophenotype:
  - SSClow/CD45weak/CD13+/CD33+/CD34+/CD117+/CD38+/CD31+/CD123+/CD64+/-

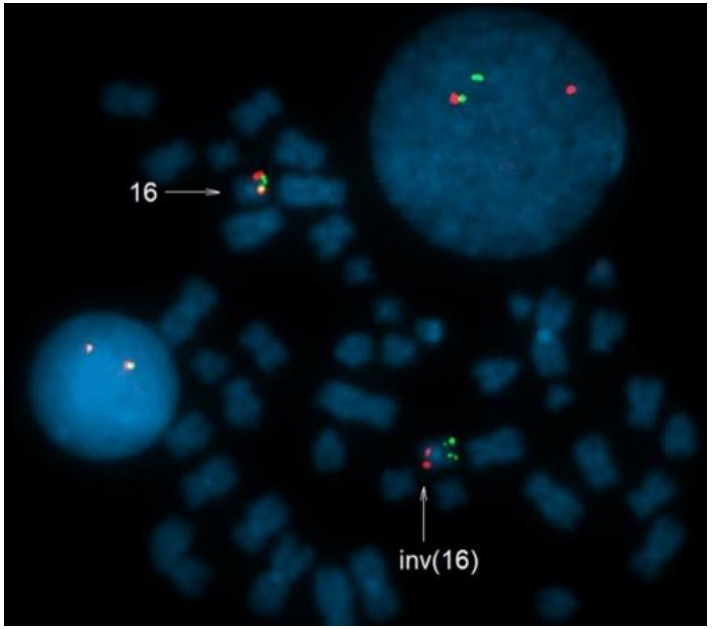
SCC = Side scatter



Courtesy of Marta Robak

Introduction

- **Cytogenetics**
- 46,XY,inv(16)(p13q22)[15]/46,XY[1]
- **Molecular genetics**
  - *NPM1* (-),
  - *FLT3*-internal tandem dulication (ITD) (-)
  - *FLT3-TKD* (+)
  - *CEBPA* (-)
  - *RUNX1-RUNX1T1* (*AML1-ETO*) (-)
  - *CBFB-MYH11* (+)
  - *KMT2A* (*MLL*) partial tandem duplication (PTD) (-)



Courtesy of Ewa Wawrzyniak

Q1) What diagnosis should be made to this patient, according to WHO 2016 classification?

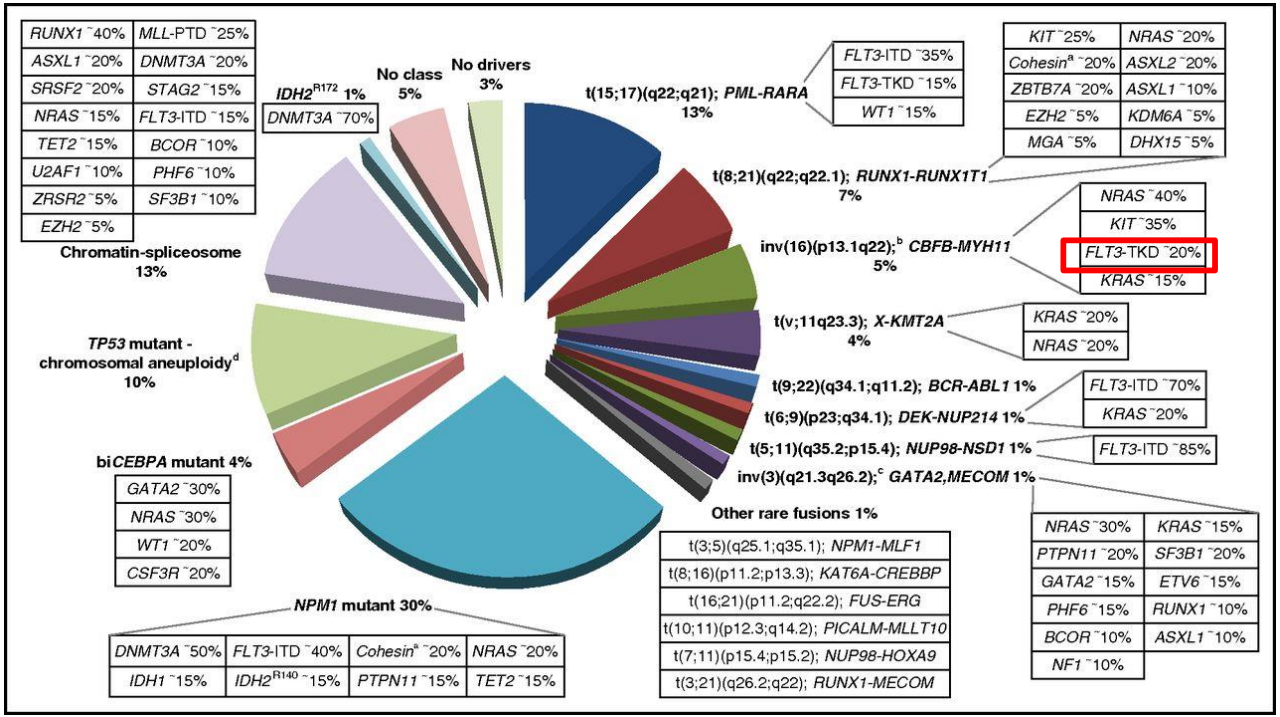
1. MDS with excess blasts-2 (MDS-EB-2)
2. AML with myelodysplasia-related changes
3. AML with recurrent genetic abnormalities
4. AML not otherwise classified
5. Therapy-related AML

Discussion

- The category of AML with recurrent genetic abnormalities includes patients with:
  - AML with t(8;21) *RUNX1-RUNX1T1*
  - **AML with (inv 16) or t(16;16) *CBFB-MYH11***
  - Acute promyelocytic leukaemia (APL) *PML-RARA*
  - AML with t(9;11) *KMT2A (MLL)-MLLT3*
  - AML with t(6;9) *DEK-NUP214*
  - AML with inv(3) or t(3;3) *GATA2, MECOM*
  - AML (megakaryoblastic) with *t(1;22) RBM15-MKL1*
  - AML with t(9;22) *BCR-ABL1* (provisional entity)
  - AML with mutation of *NPM1*
  - AML with mutation of *CEBPA (biallelic)*
  - AML with mutation of *RUNX1* (provisional entity)

Arber DA *et al*. Blood. 2016;127:2391-405

Discussion



Dohner H *et al*. Blood. 2017 Jan 26;129(4):424-447.

Q2) What risk group according European LeukemiaNet 2017 classification does this patient belong to?

1. Favourable
2. Intermediate-I
3. Intermediate-II
4. Intermediate
5. Poor

Discussion

Risk group	ELN 2017
Good	t(8;21)(q22;q22) *RUNX1-RUNX1T1* inv (16)(p13.1;q22) or t(16;16) (p13.1;q22) *CBFB-MYH11* NK+ *NPM1* mutated and *FLT3-ITD* (-) or *FLT3-ITD* (low) AR<0.5 NK+ *CEBPA* mutated (biallelic)
Intermediate	NK+ *NPM1* mutated and *FLT3-ITD* (high) AR≥0.5 NK+ *NPM1* wild type and *FLT3-ITD* (-) or *FLT3-ITD* (low) AR<0.5 t(9;11)(p22;q23) *KMT2A-MLLT3* Cytogenetic abnormalities other than in good and poor-risk
Poor	t(6;9)(p23;q34); *DEK-NUP214* t(v;11)(v;q23), rearrangment of *KMT2A* t(9;22) *BCR-ABL1* Inv(3)(q21;q26) or t(3;3)(q21;q26.2) Complex karyotype (>2 aberrations), Monosomal karyotype -5, del(5q); -7, -17, abnormal(17p) Mutations: *RUNX1; AXLSL, TP53* *NPM1* wild type *FLT3-ITD* (high) AR≥0.5

AR – allelic ratio;

Dohner H *et al.* Blood. 2017 Jan 26;129(4):424-447.

Discussion

- Outcome of patients with mutation of the *FLT3* tyrosine kinase domain (*FLT3-TKD*) in AML remains controversial. *(Sakaguchi M et al.Int J Hematol. 2019 Nov;110(5):566-574.)*
- *FLT3-TKD* mutation is not included in ELN2017 prognostic classification. *(Dohner H et al. Blood. 2017 Jan 26;129(4):424-447.)*
- Patients with both *FLT3-TKD* and *NPM1* mutations seem to show a favourable outcome. *(Perry M et al. Clinical Lymphoma, Myeloma & Leukemia, Vol. 18, No. 12, e545-50)*

Diagnosis summary

- 27-year-old man
- AML with recurrent genetic abnormalities
- Additional *FLT3-TKD* mutation
- Favourable-risk according to ELN2017
- ECOG-1
- HCT-CI-0
- Electrocardiogram (ECG) – normal
- ECHO – ejection fraction 57%

Q3) Which first line treatment would be the most appropriate for this patient?

1. Standard 3+7 (daunorubicin + cytarabine) induction
2. Standard 3+7 induction + gemtuzumab ozogamicin (GO)
3. Standard 3+7 induction + midostaurin
4. CPX-351 (liposomal formulation of daunorubicin and cytarabine)
5. FLAG-IDA (fludarabine, cytarabine, granulocyte colony-stimulating factor and idarubicin)

Discussion

- GO is approved for CD33-positive AML patients (defined by ≥30% blasts expressing CD33 in the pivotal trial) in combination with 7+3 induction chemotherapy. *(Castaigne S et al. Lancet 2012; 379: 1508-1516)*
- Based on a meta-analysis of 5 studies with GO, patients with *CBFB* rearranged AML (*RUNX1-RUNX1T1* or *CBFB-MYH11* positive AML) benefit most from the addition of GO. Addition of GO improved 6-year overall survival (OS) by 20.7% to an OS of 75.5% in this meta-analysis. *(Hills RK et al. Lancet Oncol*. 2014 August ; 15(9): 986–996.*)*

Treatment (1)

- Induction - DA (daunorubicin + cytarabine) + midostaurin
- First complete remission (CR1)

Q4) Which molecular marker is a recommended single marker for measurable residual disease (MRD) monitoring in AML

1. *FLT3-ITD* mutation
2. *WT1*
3. *FLT3-TKD* mutation
4. *CBF-MYH11*
5. *DNMT3A* mutation

Q5) Which method would you consider the most helpful for MRD monitoring in this patient?

1. 8-colour flow cytometry using leukaemia-associated immunophenotype (LAIPs)
2. Quantitative real time PCR (qPCR) - *CBFB-MYH11*
3. Next generation sequencing (NGS)
4. 10-colour flow cytometry using 'different from normal' method
5. 10-colour flow cytometry using both LAIPs and 'different from normal' method.

Discussion

- Patients with mutant *NPM1*, *RUNX1-RUNX1T1*, *CBFB-MYH11* or *PMR-RARA* should have molecular assessment of MRD
- In AML subtypes other than above, MRD should be assessed using multicolour flow cytometry (MFC)
- The detection of persistent *DNMT3A*, *TET2* and *ASXL1* mutations, which are often present in persons with age-related clonal haematopoiesis does not correlate with an increased relapse rate.

Schuurhuis GJ *et al*. Blood.2018;131:1275-1291.
Jongen-Lavrencic M *et al.* N Engl J Med. 2018;378:1189-1199.

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Q6) What would be the best further treatment option?

1. Two cycles of consolidation with CPX-351 and observation
2. Three cycles of consolidation with DNR+AraC+GO
3. Allogeneic stem cell transplantation from matched unrelated donor (MUD-allo-SCT) regardless of MRD level
4. Three cycles of consolidation with high-dose cytarabine +/- midostaurin and observation with MRD monitoring; MUD-allo-SCT should be considered only if MRD(+)
5. Three cycles of consolidation with high-dose cytarabine with subsequent azacitidine maintenance

- If CBF-AML patients are consolidated with chemotherapy three cycles with intermediate dose cytarabine (IDAC) without GO are recommended, as no benefit was seen for GO in consolidation and to reduce toxicity of the schedule in these favorable risk patients. (Burnett AK et al. J Clin Oncol 2011; 29: 369-377; Heuser M, et al. ESMO Guidelines Committee. Ann Oncol. 2020 Jun;31(6):697-712)

Treatment (2)

- Consolidation – high-dose cytarabine + midostaurin (3 cycles)
- Response after consolidation complete remission (CR), MRD negative (RQ-PCR)
- Regular MRD monitoring is planned
- Midostaurin maintenance is planned

References

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2. Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017; 129(4): 424-447.
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5. Castaigne S, Pautas C, Terre C et al. Effect of gemtuzumab ozogamicin on survival of adult patients with de-novo acute myeloid leukaemia (ALFA-0701): a randomised, open-label, phase 3 study. Lancet 2012; 379: 1508-1516

6.Hills RK, Castaigne S, Appelbaum FR et al. Addition of gemtuzumab ozogamicin to induction chemotherapy in adult patients with acute myeloid leukaemia: a meta-analysis of individual patient data from randomised controlled trials. Lancet Oncol 2014; 15: 986-996.

Discussion

7. Schuurhuis GJ, Heuser M, Freeman S et al. Minimal/measurable residual disease in AML: a consensus document from the European LeukemiaNet MRD Working Party. Blood.2018;131:1275-1291.

8. Jongen-Lavrencic M, Grob T, Hanekamp D, et al. Molecular Minimal Residual Disease in Acute Myeloid Leukemia. N Engl J Med. 2018;378:1189-1199.

9. Burnett AK, Hills RK, Milligan D et al. Identification of patients with acute myeloblastic leukemia who benefit from the addition of gemtuzumab ozogamicin: results of the MRC AML15 trial. J Clin Oncol 2011; 29: 369-377.

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