EHA-PTHiT Hematology Mini Tutorial

Self-assessment Case 2 – Session Title […]

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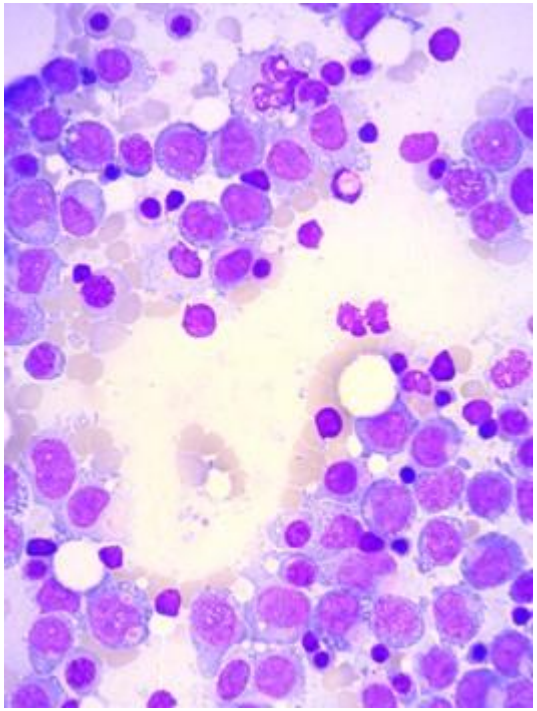
Introduction

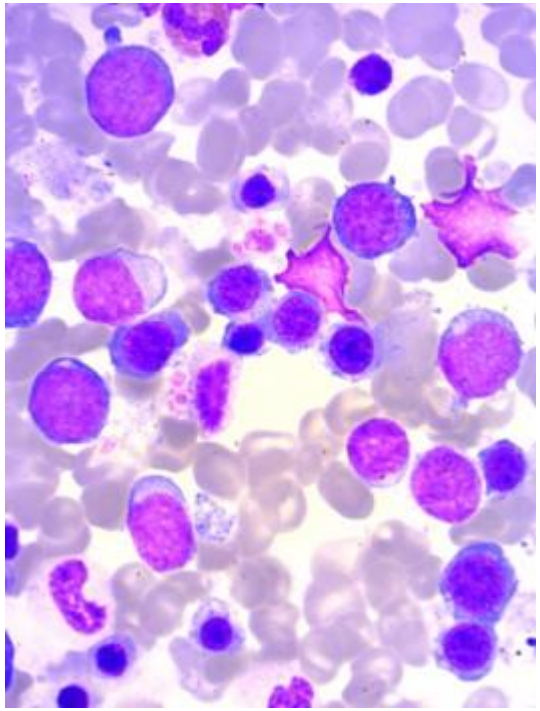
- A 63-year-old woman reported to the emergency department due to dyspnoea at rest
- Medical history
  - Breast cancer (2009) – treated with surgery, chemotherapy (Tx) (anthracycline – 90% of maximal dose was used) and radiotherapy (Rx)
  - Lung cancer (2017) – surgery (right lung lobectomy)

Blood test	
WBC	**91.29** × 10^9/l
Neutrophils (ANC)	0.63× 0^9/l
Hb	76 g/l
RBC	2.12× 10^{12}/l
MCV	100.4 fl
Platelets	**124** × 10^9/l
PB film	**Blasts 88%**

Introduction

- Bone marrow aspirate
  - Blasts - 88.4 %
  - Dysplasia in erythroid line (20% of erythroid cells)
- Immunophenoptyping:
  - SSCmedCD45dim/CD13+/CD33+/CD34+/CD117+/HLA-DR-/CD38+/CD31+/CD64-/CD11b-/CD11c-/CD56-.

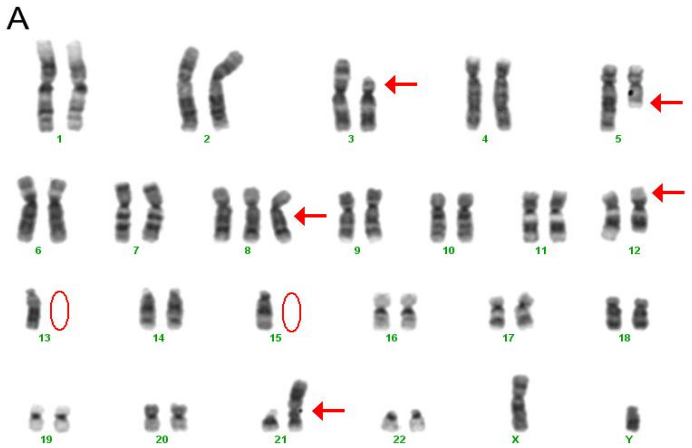




Courtesy of Marta Robak

Introduction

- **Cytogenetics**
  - complex karyotype
- **Molecular genetics**
  - *NPM1* (-)
  - *FLT3*-internal tandem duplication (ITD) (-)
  - *FLT3-TKD (-)*
  - *CEBPA* (-)
  - *DNMT3A* ()
  - *RUNX1* (-)



45,XY,der(3;13)(q10;q10)del(13)(q14),del(5)(q13q33),+8,der(12)(del)(12)(p13)t(12;12)(p13;q22),-15,der(21)t(13;21)(q14;p11)

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 reccurent genetic abnormalities
4. AML not otherwise classified
5. Therapy-related AML

Discussion

- The category of therapy-related AML includes patients with AML arising after prior exposure to cytotoxic therapy and/or radiotherapy for malignant or non-malignant disease.
- The more common subtype, seen in ~75% of patients, typically occurs 5 to 7 years after first exposure to alkylating agents or radiation, is often preceded by MDS, and is frequently accompanied by abnormalities affecting chromosomes 5 and/or 7, complex karyotype, and *TP53* mutation.
- In t-AML after treatment with topoisomerase II inhibitors the latency period is shorter (often only 1 to 3 years), antecedent MDS is rare, and balanced rearrangements involving (*MLL*) at 11q23, *RUNX1* or *PML/RARA* are common.

Arber DA et al. Blood. 2016;127:2391-405
Dohner H et al. Blood. 2017; 129: 424-447

Diagnosis summary

- 63-year-old woman
- t-AML
- Complex karyotype
- Poor-risk according to ELN2017
- ECOG-2
- HCT-CI-3 (cancer history)
- ECG – normal
- ECHO – ejection fraction 51%

Q2) Which first line treatment would be the most appropriate for this patient?

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

Discussion

- If tAML or MRC-AML is diagnosed in patients ≥60 years, treatment with CPX-351 is recommended
  - In a randomized phase 3 trial older ‘secondary-AML’ patients (including t-AML) treated with CPX-351 had significantly better overall survival, event-free survival and composite complete remission rates with lower 60-day mortality rate. Moreover, CPX-351-treated patients appear to experience superior survival following allogeneic transplant.

But….

Heuser M, et al. ESMO Guidelines Committee. Ann Oncol. 2020 Jun;31(6):697-712)
Lancet JE et al. Blood 128(22), 906 (2016)

Discussion

- The patient had already received 90% of maximal anthracycline dose
- CPX-351 treatment could increase the risk of severe cardiotoxicity
- Clinical trials with novel efficient drugs are available
- Treatment with venetoclax in combination with azacitidine (VEN-AZA) results with high response rate (CR+CRi - 66.4%)

Lancet JE et al. Blood 128(22), 906 (2016)
DiNardo CD, et al. N Engl J Med. 2020;383(7):617-29

Disscussion

	CPX-351 (n=153)	AZA+Ven (n=286)
CR + CRi (%)	**47.7**	**66.4**
CR (%)	37.3	38.7
CR in poor-risk karyotype (%)	**34.7**	**52.9**
D-30 mortality (%)	5.9	2
D-60 mortality (%)	13.7	8
Median duration of response (mos)	**6.93**	**17.5** (13.6, NR)
Median OS [95%CI]	9.56 [6.60–11.86]	14.7 [10.2–NR]

Lancet JE, et al. *J Clin Oncol.* 2018;36(26):2684–92;
DiNardo CD, et al. N Engl J Med. 2020;383(7):617-29

Treatment (1)

- Clinical trial
- Treatment with Azacitidine + Venetoclax + Cusatuzumab (anti-CD70 MoAb) - CVA

Q3) Which precautions should be taken in this patient during venetoclax-based therapy?

1. Prevention of tumor lysis syndrom (TLS)
2. Prophylaxis of allergic reactions with steroids and anti-histaminic drugs
3. Venetoclax dose reduction in case of concomitant antifungal prophylaxis with azoles
4. All above
5. Prevention of TLS and venetoclax dose reduction in case of concomitant antifungal prophylaxis with azoles

Q4) Which toxicity could you expect to be more pronounced with venetoclax-azacytidine treatment as compared to azacytidine monotherapy?

1. Cardiotoxicity
2. Neurotoxicity
3. Myelosuppression
4. Gastrointestinal (GI) toxicity
5. Skin rash

Disscussion

- The most frequently reported hematologic adverse events of grade 3 or higher in the azacitidine–venetoclax and azacitidine-placebo groups include thrombocytopenia (in **45%** and 38%, respectively), neutropenia (in **42%** and 28%), febrile neutropenia (in **42%** and 19%), anemia (in **26%** and 20%), and leukopenia (in **21%** and 12%).

DiNardo CD, et al. N Engl J Med. 2020;383(7):617-29

Treatment (2)

- Cytoreductive treatment with hydroxyurea
- Clinical trial with Azacitidine + Venetoclax + Cusatuzumab (anti-CD70 MoAb)
- Day 19 - fever 38.9^{o}C
- CRP 228 mg/l
- procalcitonin 1.54ng/ml (normal <0.15 ng/mL)
- Wide-broad spectrum antibiotic I.V. (cefepime)

Blood test	
WBC	**0.43** × 10^9/l
Neutrophils (ANC)	0.05× 0^9/l
Hb	77 g/l
RBC	2.48× 10^{12}/l
MCV	90.7 fl
Platelets	**165** × 10^9/l
PB film	**Blasts 0%**

Q5) What would be the best further strategy

1. Continuation of venetoclax until D28 regardless of infection
2. Immediate bone marrow aspiration at day 21 and venetoclax continuation if measurable residual disease (MRD) present regardless of infection
3. Temporary discontinuation of venetoclax +/- G-SCF until infection is controlled
4. Permanent discontinuation of venetoclax and switch to another treatment
5. Continuation of venetoclax with G-CSF support regardless of infection

Treatment (3)

- Venetoclax temporary discontinuation
- After 3 days of antibiotics the patient became afebrile
- Blood cultures – Pseudomonas aeruginosa sp.
- Chest CT scan – normal
- CRP 147 mg/l

Day 21

Blood test	
WBC	**0.78** × 10^9/l
Neutrophils (ANC)	0.04× 0^9/l
Hb	7.5 g/l
RBC	2.42× 10^{12}/l
MCV	92.7 fl
Platelets	**947** × 10^9/l
PB film	**Blasts 0%**

Treatment (4)

- D28 – regeneration in PB
- Cycle 2 has been postponed
- Day 35 – full blood count recovery
- BM aspiration – CR
- CVA was continued
- ECOG-1 ↑

Blood test	
WBC	**3.96** × 10^9/l
Neutrophils (ANC)	2.54× 0^9/l
Hb	10.8 g/l
RBC	3.49× 10^{12}/l
MCV	92.7 fl
Platelets	**564** × 10^9/l
PB film	**Blasts 0%**

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Q6) What would be the best post-remission treatment option?

1. Continuation of Ven-Aza-Cusa till progression
2. Standard consolidation with high-dose cytarabine (HDAC)
3. Allogeneic stem cell transplantation from matched related or unrelated donor
4. Continuation of Ven-Aza-Cusa and allo-SCT only in case of relapse
5. Three cycles of consolidation with HDAC

Discussion

- In patients with ‘secondary’ AML (including t-AML) allogeneic stem cell transplantation is an independent prognostic factor associated with longer survival

Sengsayadeth S et al. Biol Blood Marrow Transplant. 2018;24:1406-1414.

Treatment (5)

- 5 cycles of CVA
- Lack of sibling donor
- Unrelated donor 9/10 has been found
- She was offered RIC-alloSCT

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References

1. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, Bloomfield CD, Cazzola M, Vardiman JW. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127:2391-405.
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.
3. Lancet JE, Uy GL, Cortes JE et al. Final results of a Phase III randomized trial of CPX-351 versus 7+3 in older patients with newly diagnosed high risk (secondary) AML. J. Clin. Oncol. 34(15 Suppl.), 7000 (2016)*

* This paper deals with t-AML, AML following MDS or CMML, and *de novo* AML with MDS-related cytogenetic abnormalities.

4. Heuser M, Ofran Y, Boissel N et al. ESMO Guidelines Committee. Acute myeloid leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2020 Jun;31(6):697-712.

5. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. N Engl J Med. 2020 Aug 13;383(7):617-629.

6. Sengsayadeth S, Labopin M, Boumendil A, et al Transplant Outcomes for Secondary Acute Myeloid Leukemia: Acute Leukemia Working Party of the European Society for Blood and Bone Marrow Transplantation Study. Biol Blood Marrow Transplant. 2018;24:1406-1414. *

*This paper deals with t-AML and AML with antecedent haematological neoplasm or bone marrow failure syndrome.