Translocation (12;22) with TEL-MN1 (ETV6-MN1) fusion transcript: a recurrent but rare genetic abnormality in acute myeloid leukaemia: case report and review of the literature.

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INITIAL PRESENTATION

- Female, 51 years old
- Bone marrow examination: 28% myeloid blasts
- Karyotype: XX, 46, del(20)(q11.2), t(12;22)(p13;q12)
- Molecular analysis: *TEL-MN1* fusion [encoded by der(12)], *WT1* overexpression, no mutations detected by NGS

DIAGNOSIS

- Acute myeloid leukaemia, not otherwise specified, with maturation.
- ELN 2017 intermediate-risk AML.

TREATMENT

- Intensive chemotherapy:
- 1st induction cycle ('7+3'): no morphological remission
- 2nd induction cycle (cytarabine 2g/m² 2dd d1-3 + idarubicin 12 mg/m² 1dd d3-5): complete morphological, flowcytometric and cytogenetical remission (CR). *TEL-MN1* qualitative nested RT-PCR still detectable.
- 1 consolidation cycle with cytarabine 2g/m² 2dd d1-3-5: CR, with molecular MRD.
- Int-risk AML, with clear molecular MRD indicated for an allogeneic stem cell transplantation (alloSCT).
- Feb 2017: AlloSCT after reduced intensity conditioning (Flu-Bu-ATG) with unmanipulated stem cells from a MUD. Immunosuppressive therapy with tacrolimus + mycophenolate mofetil.

EVOLUTION

- Engraftment on day 17.
- Day 100 evaluation: morphological, flowcytometric and cytogenetic CR, but still persistent detection of *TEL-MN1*. Blood and bone marrow chimerism > 95%. **CD3 declined** to 89%.
- Accelerated tapering of tacrolimus, which was stopped at day ...
- This lead to mild graft-versus-host disease (GVHD) of liver and gastro-intestinal tract (unfortunately not biopsy-proven). After re-starting tacrolimus and associating local corticosteroid therapy, symptoms regressed.
- 6 months post-alloSCT: complete donor CD3 chimerism was reached, and ***TEL-MN1* PCR became negative**.
- 10 months post-alloSCT: patient remains in good clinical condition and sustained molecular remission 9 months post-alloSCT.

TEL-MN1 and leukemogenesis

- Translocation between TEL gene (or ETV6) and MN1 is recurrent, but rare in myeloid malignancies.
- The TEL gene (locus 12p13) belongs to the ETS family of transcription factors. (1).
- The MN1 gene on chromosome 22q12 is a transcriptional coactivator. It is overexpressed in subsets of AML and high MN1 expression level is a poor prognostic factor for outcome in AML with normal karyotype. (2)
- Potential target genes of the chimeric MN1/TEL protein are still unknown. As such, the exact mechanism of this translocation in AML pathogenesis is not yet elucidated.

Cases in literature

- Only **12** other patients with myeloid malignancies and t(12;22)(p13;q12)/MN1-ETV6 have been described in the literature. (3-8)
- Eight of them had AML, 2 MDS, 1 CMML and 1 aCML-accelerate phase.
- In 7/12 patients, additional chromosomal aberrations have been identified, such as monosomy Y, monosomy 7, trisomy 8, trisomy 9, trisomy 21, del (5)(q13q33), and del (20)(q11q13). (3)
- 8/12 were known to have received chemotherapy, but overall response was **poor**: 0/6 patients with available information reached complete remission after the first cycle. Three of them had primary refractory disease. Two patients have undergone allogeneic stem cell transplantation (1 after chemotherapy, 1 after hypomethylating agent). (3)
- Only one patient (CMML who received decitabine, followed by alloSCT) is known to have achieved long-term survival (alive at 15 months) (3)

Prognosis

- Based on case reports: poor prognosis, average survival **5 months** (3)
- Best treatment strategy is unclear
- Patients probably benefit from **allogeneic SCT**.
- Three out of 6 patients were refractory to chemotherapy, 1 long-term survival after decitabine and allo-SCT: suggestion that **hypomethylating** agent could be preferred above chemotherapy
- Currently no firm recommendations possible.

Discussion

The reported **poor prognosis and the persistent molecular MRD** in bone marrow lead us to decide for allogeneic stem cell transplantation. The appearance of mild GVHD probably induced a **graft-versus-leukaemia** effect, leading to **complete molecular remission** 6 months after allo-SCT. Our patient is the **first** AML case reported with **long-term survival** after intensive chemotherapy and allogeneic stem cell transplantation, with clear evidence of a graft-versus-leukemia effect.

Conclusion

Translocation (12;22) is a rare genetic abnormality in AML, often but not always resulting in the TEL-MN1 or MN1-TEL transfection transcript, involved in leukaemogenesis and associated with an apparent poor prognosis. Hypomethylating agents might be the preferred induction regimen. These patients probably benefit from an alloSCT.

Referenties:

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