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Successful allogeneic stem cell transplantation of a patient with Werner syndrome and acute myeloid leukemia

Letter to the Editor

Werner syndrome (WS, OMIM #277700) is an adult-onset syndrome of accelerated aging caused by homozygous or compound heterozygous mutations in the *WRN* gene located on chromosome 8p12. The encoded WRN protein is multifunctional, comprising an exonuclease, a RecQ helicase and a nuclear localization signal domain [1]. Pathogenic variants of *WRN* detected in WS lead to a loss of function of RecQ helicase resulting in impaired DNA replication, chromosomal instability and premature telomere shortening. Cardinal signs of WS typically manifest in early adolescence and include growth retardation, cataracts, skin alterations, and progeroid changes of hair [1,2]. Patients with WS have an increased risk of age-related disorders such as atherosclerotic cardiovascular diseases, osteoporosis, type 2 diabetes mellitus and solid cancers as well as hematological malignancies [3]. The most common tumors in WS are thyroid follicular carcinoma, malignant melanoma, meningioma, soft tissue sarcomas, leukemia, myelodysplasia (MDS) and primary bone tumors [1,3]. The age-adjusted risk for these malignancies is increased by 2–60 times compared to the normal population and median age of appearance is 44,5 years, beginning at the age of 20 years [3]. Cancer and atherosclerotic cardiovascular diseases reduce the median age of death for patients with WS to 54 years [3]. In WS patients, 9,3 % of neoplasms are hematologic neoplasms [3] and there is little information available on the best treatment of these patients. Many affected patients received best supportive care only and a minority were treated with chemotherapy all deceasing shortly after diagnosis [4].

We present an 18-year-old female patient with acute myeloid leukemia (AML) and WS who was successfully treated by chemotherapy and allogeneic hematopoietic cell transplantation (alloHCT) in 2015. She was referred to our department for pancytopenia and we detected 5% blasts in peripheral blood. No previous history of pathological blood cell counts was reported. Clinically, the patient was conspicuous with syndromic features including short stature, loss of subcutaneous fat, absence of breast development, thin limbs, a beaked nose, truncal obesity, and light hair (Fig. 1A). She was the third child of a consanguineous couple, her younger sister showed an overlapping phenotype with the same syndromic features as well as mild learning disability and signs of liver cirrhosis. Both brothers of the patient were healthy.

Bone marrow cytology revealed 27 % myeloid blasts confirming the diagnosis of AML. Karyotyping and FISH showed a complex aberrant karyotype including TP53 deletion, monosomy 7, 5q deletion and an ETV6 deletion indicating AML with MDS related changes. Based on the clinical appearance of the patient, various tests to detect the precise underlying syndrome were initiated. Following informed consent, she was included in the «Aachen Telomeropathy Registry» (approved by the ethical committee of the University Hospital RWTH Aachen, EK225/14). Telomere length measurement by Flow-FISH showed telomeres in the lower range of normal [5–7]. Additional testing for Fanconi anemia showed normal chromosomal breakage. Whole exome sequencing was finalized closely after alloHCT and revealed a homozygous frameshift mutation (NM_000553.4:c.2278del; p.(His760Thrfs*17)) in the *WRN* gene leading to the diagnosis of WS (Fig. 1B). This mutation results in a premature stop codon causing loss of function of the RecQ helicase that has not been previously described [1,8].

The patient received induction chemotherapy with cytarabine and daunorubicin (3 + 7) and had blast persistence in the bone marrow at day 28 with partial recovery of platelets and neutrophils. Following salvage chemotherapy with a FLAG-Ida regimen, a morphologic leukemia-free state (MLFS) in the bone marrow was found at day 28, but without any recovery of normal hematopoiesis (Fig. 2). In contrast to previously reported patients, we did not observe severe non-hematological toxicities caused by chemotherapy [4].

The patient had an indication for alloHCT due to the cytogenetic risk profile and the AML MRC. Prompt alloHCT was carried out in view of the MLFS and lack of excessive non-hematological toxicity, despite the absence of normal hematopoiesis recovery after salvage treatment and missing results from the diagnostic work up of the syndromic features. The younger brother, without any clinical stigmata of WS and with a normal blood cell count, was found to be HLA-identical and was chosen as the stem cell donor. The donor was subsequently confirmed to not be affected by WS on a molecular level.

The conditioning regimen comprised melphalan (150 mg/m^2, day -2) and fludarabine (150 mg/m^2, days -6 to -2) and was well tolerated by the patient. AlloHCT was performed using 7.67*10^6 CD34+ cells/kg obtained by G-CSF stimulated peripheral blood stem cell apheresis. Graft versus host disease (GvHD) prophylaxis consisted of methotrexate on day 1, 3 and 6 and cyclosporine A. Methotrexate on day 11 was not given due to grade III mucositis.

During aplasia after transplantation, she suffered mild renal insufficiency, and fungal pneumonia that was treated by liposomal amphotericin B. Leukocytes above 1 G/l were observed on day 15 after transplantation, platelets above 50 G/l were measured on day 28 and the patient was independent of red cell transfusion after day 32. Bone marrow aspiration showed cytological remission and full donor chimerism at day 50. The patient did not present any signs of acute GvHD.

During 5-years of follow-up, the patient showed no clinically relevant GvHD, severe long term toxicity, relapse or development of secondary neoplasia. She developed a chronic moderate renal failure, slight bilateral subcapsular posterior cataracts and moderate osteoporosis. In 2018, three

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Fig. 1. (A) Clinical features with typical signs of Werner syndrome: Short stature, loss of subcutaneous fat, loss of hair, a beaked nose, thin limbs, flat feet, truncal obesity. Middle right picture is showing our patient with her younger sister also suffering from Werner syndrome.
(B) Location of frameshift mutation in the *WRN* gene of our patient.

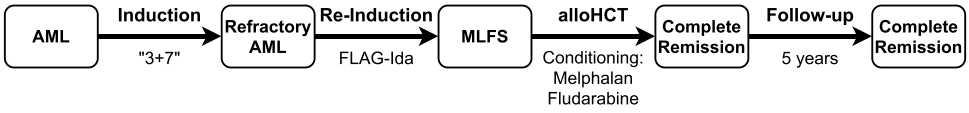

Fig. 2. Schematic of the patient's treatment process.

years after allogeneic transplantation, she developed pneumococcal pneumonia leading to sepsis and transient acute heart failure. She quickly recovered with antibiotics as well as a short treatment with catecholamines. She is currently in a good general state of health.

To the best of our knowledge, this is the first description of successful alloHCT in a young adult patient with WS-related AML, who is alive and in remission several years after transplantation. Hayashi et al. previously reported a patient with WS and high-risk MDS undergoing alloHCT [9]. The conditioning regimen consisted of fludarabine, busulfan and melphalan followed by cord blood transplantation. The patient died 15 months later of pneumonia, in remission of MDS.

Patients with classical WS carry biallelic loss-of-function mutations in *WRN*. Most of these pathogenic variants are nonsense-mutations, small insertions and deletions, or frameshift mutations which do not cluster to specific protein domains. The homozygous frameshift-mutation described here is in line with such a loss-of-function mechanism. The different clinical symptoms of the siblings, with one sister developing an early-onset malignant disease and the other sister mainly showing a hepatopathy, illustrates the variable outcome despite carrying the same *WRN* mutation.

Therapy of malignant diseases in patients with WS may be modified because cells have different sensitivities to several chemotherapeutic drugs

[10]. No correlation between the region and type of mutation in the *WRN* gene and response to chemotherapy has been described until now. WS cells have an increased sensitivity to DNA cross-linking agents such as melphalan, chlorambucil, mitomycin C, cisplatin and topoisomerase inhibitors such as camptothecin, amsacrine and etoposide [4,11,12]. However, there is no increased sensitivity to alkylating agents, UV, bleomycin and hydroxyurea [11]. Severe chemotherapy induced toxicity was described by Seiter et al. in a patient with WS and AML. The patient developed multiorgan failure three days after application of chemotherapy (cytarabine, mitoxantrone, etoposide) and died [4]. However, our patient did not show severe toxicity despite receiving melphalan. Presumably, a different conditioning therapy regimen without melphalan would have been chosen if the diagnosis of WS had been made before the start of conditioning for alloHCT. The favorable outcome of alloHCT in our patient most likely cannot be explained by the type of germline mutation in *WRN* but is probably related to graft versus leukemia effect. However, the AML cells responded to FLAG-Ida, providing evidence that despite the loss of *WRN* function and the complex karyotype, the malignant clone was still chemosensitive.

In conclusion, alloHCT was feasible in our patient with WS without severe chemotherapy or transplant induced toxicities. Despite the very poor cytogenetic risk profile of the AML, she has remained in complete remission to date, i.e. 5 years after transplantation. In general, early genetic counseling and work-up for cancer predisposition syndromes and hereditary bone marrow failure syndromes is important in young adults with concomitant hematological and non-hematological clinical stigmata to optimize therapy.

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Declaration of Competing Interest

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THB and FB have a research collaboration with RepeatDx, Vancouver, Canada. The remaining authors declare no publication-specific conflict of interest.

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