Zentrum für Kinder- und Jugendmedizin

Pädiatrische Hämatologie und Onkologie

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Zeichen:

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A3070222.002
Nadja Novakovic geb. 03.02.2005, PIZ 30702220,
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N./ Fam. Nadja Novakovic, Vukasoviceva 2 F/22, SRB-11000 Belgrade
N./ Prof. Niemeyer, EWOG-MDS/SAA Studienzentrale

Dear colleagues,

we report on the above mentioned patient who presented to our clinic on January 9, 2014 and January 10, 2014.

Diagnosis: **Suspected Myelodysplastic Syndrome,**
Refractory Cytopenia of Childhood
Normal Karyotpye

History: Nadja became symptomatic in June 2013 with bruises. Her blood count revealed a thrombocytopenia of 69 000/µl and an anemia with hemoglobin of 9,9 g/dl. A bone marrow aspirate and a trephine biopsy showed hypocellular bone marrow and lack of megakaryocytes. Hemoglobin F was 0.5 %, folate and vitamin B12 levels were normal. Virus diagnostics were negative for EBV, Hepatitis B, Parvovirus. Diagnostics for paroxysmal nocturnal hemglobinuria was negative. An analysis of the chromosome stability had been performed but results were ambiguous. Peripheral blood cytogenetics had been normal. Lymphocyte phenotyping revealed a slightly reduced number of NK cells but was otherwise normal.

A control bone marrow aspirate and biopsy in November 2013 were sent to the EWOG-MDS study and were highly suspicious for refractory cytopenia.

So far, Nadja had received 3 red cell concentrates (the last was given on January 3rd, 2014) and 9 platelet concentrates (the last on January 3rd, 2014). Mucosal bleeding occurred only with dental transition, when she was given tranexamic acid as well.

HLA typing of the family was performed and no HLA-compatible donor was found.

The mother´s pregnancy with Nadja had started as a twin pregnancy, only one fetus survived; the mother had been treated with progesterone. The girl was born spontaneously with a birth weight

of 3 100 g and a length of 52 cm, Apgar-Score 10.
Nadja had been breastfed for 18 months, feeding continued to be normal. She had been vaccinated according to her country´s recommendations including BCG. Apart from uncomplicated febrile infections of the upper respiratory tract she had always been well, milestones of psychosocial development were reached normally. She is now visiting the 3rd grade of primary school, has very good marks and likes to draw.

She is the first child of her non consanguineous family, her 3 year old sister is healthy. Her mother´s father had suffered from malignant melanoma.

Her parents both work as managers.

Physical examination: 8 11/12 year old girl in good general status with hypertrichosis. Some pretibial petechiae. Mucous membranes without bleeding symptoms, no fungal infection. Cervical lymphnodes of 1 cm on both sides, no other lymph node enlargement. Cardiopulmonary and abdominal findings normal, no splenomegaly. Tanner stage B1-2, P1. Neurologic examination normal.
Somatogramm: Length 143 cm, weight 42,1 kg.

Diagnostics:
Blood count of January 9th, 2014: Leukocytes 4,2 G/l; Platelets 36 G/l; Red cells 3,39 T/l; Hemoglobin 10,8 g/dl; Hematokrit 31 %; MCV 91 fl; MCH 32 pg; MCHC 35 g/dl; Retikulocytes 12 Promille; Bands 2 %; Neutrophils 38 %; Eosinophils 1 %; Basophils 0 %; Monocytes 4 %; Lymphocytes 54 %;
Hb F of January 9th, 2014: (HPLC) 2,5 %;

Clinical Chemistry of January 9th, 2014: Sodium 140 mmol/l; Potassium 3,9 mmol/l; Calcium 2,36 mmol/l; Chloride 105 mmol/l; Magnesium 0,78 mmol/L; Phosphate 1,5 mmol/L; Nitrogen 25 mg/dl; Kreatinine 0,37 mg/dl; Uric acid 3,5 mg/dl; Glucose 91 mg/dl; LDH 255 U/l; GOT (AST) 32 U/l; GPT (ALT) 43 U/l; Alk. Phosphatase 245 U/l; Gamma-GT 20 U/l; total Bilirubin 0,5 mg/dl; Cholin-Esterase 10033 U/l; total protein 7,3 g/dl; Immunglobuline G 1463 mg/dl.

Bone marrow aspirate of January 9th, 2014 (EWOG MDS/SAA study):

Blasts	0 %
Promyelocytes	0 %
Myelocytes	4 %
Metamyelocytes	4 %
Bands	4 %
Neutrophils	21 %
Eosinophils	4 %
Basophils	1 %
Monocytes	9 %
Lymphocytes	43 %
Erythrocyte Precursors	10 %

The peripheral blood smear displays an anisopoikilocytosis with macrocytes and polychromasia. ANC 1680/µl. Cell content in the aspirate and cellularity of the microbiopsies are reduced. No megakaryocytes. Erythro- and myelopoiesis are hypoplastic and mildly dysplastic. Scattered hemophagocytosis, no elevated blast count. The findings are compatible with refractory cytopenia without progress.

Bone marrow trephine of January 9th, 2014 (PD Dr. I. Baumann, EWOG-MDS/SAA reference pathologist): Biopsy with two subcortical marrow spaces with scattered normofrequent erythropoiesis shifted to the left, granulopoetic hypoplasia and lack of megakaryopoiesis. This corresponds to a myelodysplastic syndrome, stage refractory cytopenia. Immunhistochemically, no CD61-positive megakaryocytes were seen.

Bone marrow cytogenetics of January 9th, 2014 (Prof. Schlegelberger, EWOG-MDS/SAA reference geneticist): Normal karyotype, 46, XX, [15].

Evaluation: Blood smear, bone marrow and trephine biopsy are suspicious for a myelodysplastic syndrome, stage refractory cytopenia of childhood. The karytotype is unremarkable and the clinical course is characterized by transfusion dependency for red blood cells and platelets, but not by neutropenia. We strongly recommend the exclusion of Fanconi Anemia in all patients with hypocellular bone marrow disease. The respective diagnostic test has been performed in Serbia, but the results were inconclusive and we therefore recommend repeating the test in the Laboratory of Prof. Schindler in Würzburg. The parents have been informed and the diagnostic work up is ongoing.

For patients with refractory cytopenia the preferred curative treatment is allogeneic stem cell transplantation. However, Nadja does not have a matched sibling donor and therefore the feasibility of stem cell transplantation depends on the identification of a matched unrelated donor. We suggest performing the search for a matched unrelated donor via our institution. In order to perform a donor search we would need 20 ml EDTA blood of the patient (send to our institution at room temperature by a reliable courier service) for high resolution HLA-retyping, a written consent (form attached) and a pre-payment covering the estimated cost of the donor search (15.000 Euro).

Following the identification of a matched unrelated donor Nadja would be eligible for allogeneic stem cell transplantation with a reduced intensity regimen. This treatment resulted in an overall survival of 92 % for patients with refractory cytopenia in a prospective EWOG-MDS study. The main cause of treatment failure was primary graft failure in 5 out of 55 recipients of matched unrelated donors and secondary graft failure in 1 out of 55 recipients. There also was a significant incidence of viral infections probably related to the highly immunosuppressive regimen and of fungal infections in patients with preexisting neutropenia.

Alternatively, patients with refractory cytopenia may successfully be treated with immunosuppressive therapy with anti-thymocyte globulin and ciclosporin A. In this case we strongly recommend the use of horse anti-thymocyte globulin. Using this regimen, the cumulative incidence of relapse was 15 % at 4 years; the incidence of clonal evolution was 12 % at 4 years. About one third of the patients that have been treated with immunosuppressive therapy received second line allogeneic stem cell transplantation for treatment failure.

We offer to perform the search for an unrelated donor (see above) and allogeneic stem cell transplantation in our institution once the financial issues are settled.

Yours sincerely,

Prof. Dr. Charlotte Niemeyer
Medical director

Dr. Brigitte Strahm
Attending physician

Dr. Anke Peters
Pediatrician