Myelodysplastic Syndrome (MDS) – Brief information

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1. General information on the disease

Myelodysplatic syndrome (briefly MDS) involves a group of diseases with impaired *bone marrow* function and subsequently insufficient production of red blood cells.

All blood cells in the blood – these include red blood cells (*erythrocytes*), white blood cells (*leukocytes*) and platelets (*thrombocytes*) – arise from the blood forming cells in the bone marrow, the so-called *blood stem cells*. Before the blood stem cells in the bone marrow become functioning blood cells, they must undergo multiple differentiating and dividing processes. Specialists call this *haematopoiesis*.

In patients with MDS, these processes in the bone marrow are impaired. The cells maturate defectively, they also look different under the *microscope* when compared to healthy cells (*dysplasia*). These defective cells often die already in the bone marrow, and thus, not enough blood cells enter the blood stream. As a consequence, there are not enough red and white blood cells in the blood, which in turn leads to various health problems, such as *anaemia*, *infection*s or increased risk of bleeding.

The impaired maturation of the blood stem cells also results in a continuous increase of immature blood cells (so-called *blasts*) in the bone marrow. Because of their immaturity, they are unable to fulfill their assigned functions. In some MDS patients, the amount of blasts in the bone marrow increases to a degree that does not allow to differentiate MDS from a *leukaemia* any more. Hence, MDS was formerly also known as “pre-leukaemia”.

2. Incidence

While myelodysplastic syndromes (MDS) are the most frequent malignant diseases of the *bone marrow* in older people, it is very rare in childhood and adolescence. MDS accounts for about 8 % of all blood cancer diseases in children and adolescents under 18 years of age and for about 2.5 % of all cancers in this age group.

According to the German Childhood Cancer Registry, about 54 children and adolescents aged between 0 and 17 years are newly diagnosed with MDS in Germany every year. The young patients’ average age at diagnosis is approximately nine years. Boys are slightly more affected than girls (sex ratio: 1,2 : 1).

3. Types of myelodysplastic syndrome (MDS)

Depending on the way a myelodysplastic syndrome (MDS) has developed and based on microscopical features of blood and bone marrow, there are different types of MDS, which will be introduced in the following paragraphs.

3.1. Primary and secondary MDS

Myelodysplastic syndrome (MDS) often develops without an obvious reason. It's known as "primary" MDS. About 75 % of children with MDS are in this group. t is assumed, however, that „primary" childhood MDS may also involve *genetic* alterations that have not been identified yet (*see chapter „Causes"*).

In some patients, development of MDS may be associated with certain triggers; those cases are called "secondary" MDS. For example, some patients develop MDS after a preceding *radiation therapy* or *chemotherapy* done for treatment of another, often malignant disease. Others have been suffering of an underlying congenital disease before the diagnosis of MDS. These include, for example, *Fanconi anaemia*, *dyskeratosis congenita*, *Shwachman-Diamond syndrome*, *Diamond-Blackfan anaemia* (DBA) or a severe congenital *neutropenia*, all of which involve a dysfunction of the bone marrow. Also, severe *aplastic anaemia* (SAA) may precede the diagnosis of MDS.

3.2. Subtypes of primary childhood MDS as per WHO classification

According to the classification of the World Health Organization (see *WHO classification*), primary childhood MDS is subdivided into two subtypes. This differentiation is mainly based on the blast counts in blood and *bone marrow*.

3.2.1. Refractory cytopenia of childhood (RCC)

The blast count in patients with „*refractory cytopenia* of childhood" (RCC) is usually below 2 % in the peripheral blood and below 5 % in the bone marrow and thereby not much higher than in healthy children. However, the bone marrow in children with RCC is frequently very low on cells, which means that the numbers of all the cells usually found in the bone marrow (red and white blood cells, platelets) are reduced. Therefore, another congenital bone marrow disease (bone marrow failure) or *aplastic anaemia* always need to be considered as a *differential diagnosis*, because these conditions typically present with low bone marrow cell counts as well.

3.2.2. Myelodysplastic syndrome with excess blasts (MDS-EB)

In MDS patients, blast counts [see *blasts*] may markedly exceed 2 % or 5 %, respectively. This type is known as MDS-EB, meaning MDS with blast excess. However, bone marrow blast counts should not exceed 29 %, because then it would be called a *leukaemia*. Since other factors are also being considered when differentiating between MDS and leukaemia, such as the rate of blast increase, distinction (differential diagnosis) between MDS and leukaemia can sometimes be challenging. In

borderline scenarios, such as dealing with blast counts between 20 and 30 %, it is recommended to repeat *diagnostics* by *bone marrow puncture* after a couple of weeks to confirm diagnosis.

Classification of primary childhood MDS: World Health Organization (WHO), 2016

MDS Subtype	Blood	Bone marrow
Refractory cytopenia of childhood (RCC)	less than 2 % blasts	less than 5 % blasts
Myelodysplastic syndrome with blast excess (MDS-EB)	2 – 29 % blasts	5 – 29 % blasts

4. Causes

The exact causes for myelodysplastic syndrome (MDS) mostly remain unclear; however, like other types of cancer, the disease is neither contagious nor can it be transferred to other humans. In most cases, MDS develops in previously healthy children without an apparent reason (so-called primary MDS). It is assumed, however, that the affected have a certain predisposition for development of an MDS or a *leukaemia*, respectively.

Cause of the predisposition are altered *gene*s (*mutation*s) that are also present in sperm or egg cells (hence in the *germline*) and can therefore be inherited. In this case, the mutation is present in all body cells of the patient, too. The affected children have inherited this germline mutation from either one or both parents, or the gene alteration has developed *de novo* (sponateously) in the fertilized egg cell.

It has been known for many years that gene alterations that are capable of causing impaired haematopoiesis in the bone marrow (such as *Fanconi anaemia*, severe congenital *neutropenia*, *dyskeratosis congenita* or *Diamond-Blackfan anaemia*) are also associated with a predisposition for MDS. Over the past years, additional inheritable diseases that play a role have been identified. These include the so-called *GATA2* deficiency or the *SAMD9/SAMD9L syndrome*. Since these congenital diseases are usually associated with an increased cancer risk, they are also known as *cancer predisposition syndrome*s.

MDS develops differently in older persons. Most adults do not present with congenital impairments, but with gene alterations acquired over decades, which can transform a cell slowly into an MDS or leukaemia cell. Some patients have received *chemotherapy* or *radiation therapy* (radiotherapy) for another malignancy prior to the diagnosis of MDS. In those cases. MDS thus represents the secondary disease (secondary MDS), which has at least partially been induced by the treatment of the primary malignancy.

5. Symptoms

Symptoms in a patient with myelodysplatic syndrome (MDS) are mainly determined by the severity of the lack of functioning blood cells, meaning the degree of *cytopenia*. Depending on which blood cells are affected, the following types of cytopenia and associated *symptom*s can occur:

5.1. Anaemia: lack of red blood cells

The job of the red blood cells (*erythrocytes*) is to transport the oxygen, which is inhaled by the lungs, to the different organs and tissues of the body. Lack of red blood cells (*anaemia*) leads to pallor, fatigue, weakness and headache.

5.2. Immune deficiency: lack of white blood cells (leukopenia, neutropenia)

White blood cells (*leukocytes*) are responsible for the defense of pathogens and hence for the prevention of *infection*s. There are different types of leucocytes, for example *lymphocytes* and *granulocytes*, which have different functions in *immune defence*. In case of lack of functioning white blood cells, so-called *leukopenia*, the body is at risk of infection. Frequently, patients with MDS in particular present with reduced granulocyte count (so-called *granulocytopenia* or neutropenia). Since these are responsible for fighting *bacteria* and fungi, MDS patients often have bacterial or fungal infections associated with fever.

5.3. Bleeding tendency: lack of platelets (thrombocytopenia)

Platelets (*thrombocytes*) play an important role in clotting. If their count is reduced (so-called *thrombocytopenia*), the risk of both spontaneous and injury-induced bleeds increases. These may, for example, present as small red spots on the skin or mucous membranes (*petechiae*), bruises (haematoma) and/or nose-/gum bleeds, but sometimes also as severe bleedings in inner organs or the brain. The risk of severe bleeds increases with the degree of thrombocytopenia.

MDS patients with blast excess (MDS-EB, *see chapter „Types of MDS“*) sometimes present with side effects that are difficult to treat, such as inflammation of small blood vessels or the so-called Sweet syndrome, which is characterized by fever and red nodules on the skin.

6. Diagnosis

If the doctor, based on the young patient’s history (*anamnesis*) and *physical examination*, suspects a blood disease, he or she will first initiate a comprehensive blood test. If the results, due to certain *blood count* changes, promote the diagnosis of a blood disease such as myelodysblastic syndrome (MDS), a sample of the bone marrow (bone marrow biopsy) is required for confirmation. For bone marrow tests and other diagnostic procedures, the doctor will refer the patient to a children's hospital with a paediatric oncology program (paediatric oncology unit).

6.1. Analysis of blood and bone marrow

Since the *symptom*s in MDS patients are not specific for MDS and can also present in other blood diseases such as *leukaemia*s, diagnosis can only be confirmed by comprehensive analysis of the blood and the *bone marrow*.

Bone marrow obtained from the pelvic bone is required for establishing the final diagnosis of MDS. For this, *bone marrow puncture* and *bone marrow punch biopsy* are necessary. Both methods add to one another and are done during the same procedure. For bone marrow aspiration, a special

syringe is used to aspirate a small amount of bone marrow. A bone marrow biopsy is performed by using a larger syringe to take larger samples of marrow (about 1 mm in diameter). *Further information on bone marrow puncture and punch biopsy can be found here.*

After obtaining the sample, the blood forming bone marrow cells are examined under the *microscope* by a specialist for blood and malignant diseases. In MDS, cells may look different in various ways (dysplasia), which are crucial for diagnosis. In MDS with blast excess (MDS-EB), bone marrow blast counts are increased (*see chapter "Types of MDS"*). The sample obtained by bone marrow aspiration is also used for *chromosomal* analysis (*cytogenetics*, *see below*). If MDS is the suspected diagnosis, bone marrow puncture and punch biopsy should be repeated after about 14 days in order to securely confirm the diagnosis.

6.2. Examination of the chromosomes (cytogenetics)

Chromosomal changes in the *bone marrow* and blood cells are found in more than half of the children with MDS with excess blasts (MDS-EB) and in about 30 % of patients with refractory cytopenia (RCC). Identification of these changes helps with establishing the diagnosis of MDS. The most common and typical chromosomal aberration in children with MDS is the loss of *chromosome* 7 (so-called *monosomy 7*). In these cases, cells only have one chromosome 7 instead of two.

6.3. Molecular genetic testing

Some children and adolescents with MDS present with a *genetic* predisposition for the disease, meaning that they have a *germline mutation* (*see chapter "Causes"*). For the analysis of these genetic alterations, cells other than blood and/or bone marrow, such as hair follicle cells (germline material), require *molecular genetic* analysis as well. In case of identification of a germline mutation in a patient, a potentially matching family donor for *stem cell transplantation* (SCT) also needs to be tested for this mutation. Only a family member without this mutation should consider to serve as a donor.

Psychosocial Care

A child's cancer is a stressful situation for the whole family. The psychosocial team of the clinic or later the aftercare facility provides advice and support to patients and their relatives from diagnosis to completion of treatment as well as during aftercare. Don't hesitate to take advantage of this offer. It is an integral part of the treatment concept of all paediatric oncology centres in many countries. Here you will find comprehensive information on this.

7. Treatment

Treatment of patients with myelodysplastic syndrome (MDS) depends on the form of the disease, meaning, on whether it is a primary or secondary MDS or, in the first case, whether it is refractory cytopenia of childhood (RCC) or an MDS with excess blasts (MDS-EB), respectively (*see chapter „Types of MDS*"). Treatment basically consists of the following options:

- Transplantation of blood-forming stem cells from a donor (*allogeneic stem cell transplantation*, SCT) following a conditioning therapy (*high-dose chemotherapy*)

- *immunosuppressive* therapy (IST)
- other kinds of drug-based therapies: *chemotherapy*, agent azacitidin
- supportive treatments: *blood transfusion*s, antibiotic therapy [see *antibiotics*]

The following paragraphs will introduce treatment of patients with different types of MDS.

7.1. Refractory childhood cytopenia (RCC)

Patients with refractory childhood cytopenia (RCC) receive – depending on presence or absence of *chromosomal* aberrations, extent of lack of blood cells (*cytopenia*) and on cell content (cellularity) in the *bone marrow* – different therapies.

RCC patients presenting with only one chromosome 7 (*monosomy 7*), as diagnosed by chromosomal analysis, usually experience a less favourable course of the disease with a risk of blast increase within one to two years. Hence, these patients should receive *allogeneic stem cell transplantation* (SCT) as soon as possible. For this form of treatment, patients first receive high doses of *cytostatics* (*high-dose chemotherapy*) as the so-called *conditioning* regimen, in order to eliminate all (healthy and sick) bone marrow cells. After that, the recipient receives healthy *blood stem cells* obtained from the bone marrow or peripheral blood of a donor.

Patients with RCC without chromosomal aberrations may experience stable disease for years. If they don't require any *blood transfusion*s and present with sufficient *granulocytes* (white blood cells that defend *bacteria* and fungi), they won't be treated at first and just observed, with the course of the disease being monitored via regular (blood) tests (so-called watch-and-wait strategy). If the results of the blood tests do deteriorate over time, treatment, usually stem cell transplantation, may be indicated after all.

Patients with normal chromosomal findings who require blood transfusions shortly after diagnosis or who present with very low granulocyte counts will receive stem cell transplantation as soon as possible. Healthy siblings or a matching unrelated donor are chosen for stem cell donation. In case of no matching sibling, *immunosuppressive* therapy (IST) is the gold standard for patients with *hypocellular bone marrow*. This immunosuppressive therapy is similar to treatment of *aplastic anaemia* (severe aplastic anaemia, SAA) and can take many months or years.

With immunosuppressive therapy (IST), sufficient increase of blood cell counts can be achieved in about half of the patients, so that blood transfusions are not required any longer. It is also possible that *cytopenia* recurs after an initially successful IST (so-called *recurrence*). In case of recurrent disease or non-responding to IST, stem cell transplantation from an appropriately matching non-related donor is recommended.

7.2. MDS with excess of blasts (MDS-EB)

MDS patients with excess of blasts (MDS-EB), considered as an advanced stage of the disease, have a high risk of developing a *leukaemia* later. Hence, early *stem cell transplantation* is the therapy of choice for MDS-EB. Healthy siblings or a matching unrelated donor are options for stem cell

donation. In case of very high blast counts [see *blasts*], pretreatment with *chemotherapy* (azacitidin treatment) for blast reduction may be indicated prior to conditioning (high-dose therapy) and stem cell transplantation.

7.3. Secondary MDS

Patients with a secondary myelodysplastic syndrome (MDS) are usually treated like patients with primary MDS with excess blasts (MDS-EB) (*see previous chapter*). Hence, these patients should receive stem cells from a matching donor shortly after diagnosis.

7.4. Supportive therapy during treatment

In all patients with myelodysplastic syndrome (MDS), supportive treatment measures (*supportive therapy*) are appropriate and required. These supportive measures help to reduce *symptom*s caused by the disease and to manage or prevent treatment-induced side-effects.

Most patients present with *anaemia* and/or lack of platelets (*thrombocytopenia*) at diagnosis, which are associated with health problems (*see chapter „Symptoms“*). These problems can be treated by *blood transfusion*s (transfusion of red blood cells or platelets, respectively). However, repetitive transfusions of red blood cells are associated with high loads of iron, which, over time, can deposit in organs (in particular liver and heart) and harm them (so-called *iron overload*, haemochromatosis). Therefore, patients with iron overload require iron deprivation treatment.

Patients‘ *immune defence* mechanisms are weakened by the MDS itself and also by its therapy, such as *stem cell transplantation* or *immunosuppressive* therapy. Hence, they need to be protected from infections as best as possible and, in case of infection, treated as soon as possible. Infections in immunosuppressed children should always be considered as life-threatening.

Fever is usually the first symptom of an infection. Parents or relatives with a fever should, therefore, immediately contact the caregiver team (even at night), so that the children can receive broad spectrum *antibiotics* as soon as possible. In patients with *neutropenia* (lack of granulocytes), preventive treatment with antibiotics and antimycotics (agents against fungi) is indicated.

8. Prognosis

Myelodysplastic syndrome (MDS) can have different courses. Some diseases remain stable over a long period of time, while others progress rapidly. A patient’s *prognosis* is dependent on the subtype of the disease (*see chapter „Types of MDS“*) and on the presence of *genetic* alterations in the *bone marrow* cells.

8.1. Prognosis of patients with refractory childhood cytopenia (RCC)

Patients with *refractory* childhood *cytopenia* (RCC) are – based on the presence or absence of certain risk factors – assigned to different treatment groups, thereby receiving different therapies

(observation, *stem cell transplantation* or *immunosuppressive* therapy, *see chapter "Treatment"*). Overall, these patients have a favourable prognosis with a probability of survival of 80 – 90 %, regardless of the treatment group. This also applies to RCC patients with *monosomy 7*, who have received *allogeneic stem cell transplantation* early due to the high risk of advanced MDS or leukaemia (progressive disease). The prognosis with such a treatment is as favourable as that of other RCC patients.

In RCC, the risk of relapse (*recurrence*) after stem cell transplantation is very low. However, every stem cell transplantation is an intensive therapy, involving substitution of the ill bone marrow by a healthy bone marrow of a donor following *high-dose chemotherapy*. Hence, these patients should make at least yearly follow-up appointments in order to have long-term sequelae diagnosed and treated in a timely manner.

Patients who have been successfully treated with immunosuppressive therapy (IST) or who are being observed without treatment, also require regular bloodwork as well as a *bone marrow punch biopsy* and *cytogenetic* testing once a year in order to diagnose recurrent or progressive disease as early as possible.

8.2. Prognosis of patients with advanced MDS (MDS-EB) or secondary MDS

Allogeneic stem cell transplant has proven to be a curative treatment option for children and adolescents with MDS with excess blasts (MDS-EB) or with secondary MDS. About 50 – 60 % of patients can be cured by this therapy. Patients with severe *chromosomal* aberrations, such as three or more chromosomal changes (so-called complex karyotype), have a rather unfavourable prognosis.

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Glossary

allogeneic stem cell transplantation	transfer of stem cells from a donor to a recipient. The prerequisite for an allogeneic transplant is that the tissue characteristics of the donor and recipient are largely identical. The stem cells are obtained from the blood or bone marrow.
anaemia	„lack of blood“; reduction of the red blood pigment (haemoglobin) and/or the proportion of red blood cells (haematocrit) in the blood below the normal value typical for a given age. Signs of anaemia include palor, headache, dizziness, and fatigue.
anamnesis	medical interview, a patient’s history, development of signs of illness; the type, onset and course of the (current) symptoms as well as any risk factors (e.g. hereditary diseases) are evaluated during a medical interview.
antibiotics	natural metabolites of bacteria, fungi, algae, lichens and higher plants that have a (sometimes specific) growth-inhibiting or cell-killing effect against the smallest pathogens and other cells and are, therefore, used as drugs in the treatment of infectious diseases and/or cancer;
aplastic anaemia	failure of bone marrow function with severely impaired formation of certain white blood cells (granulocytes) as well as red blood cells and platelets; it is characterised by an increased tendency to bleed, increased risk of infections as well as developing anaemia. Aplastic anaemia can be congenital (e.g. Fanconi anemia) or acquired.
bacteria	tiny organisms consisting of a single cell without a nucleus that can cause numerous diseases (bacterial infections), but these can be treated successfully with antibiotics for the most part;
blasts	immature (here also degenerated) progenitor cells of white blood cells (leukocytes) or their subtypes (e.g. granulocytes, lymphocytes)
blood count	blood test to determine the qualitative and quantitative composition of the blood in a blood sample: the number of red and white blood cells as well as platelets, the haemoglobin content (Hb value) of the blood and the volume fraction of red blood cells in the entire blood volume (haematocrit) are assessed. The "complete blood count" also includes a so-called differential blood cell count, in which the white blood cells in particular are examined

	more precisely for their composition (percentages of the various subtypes) and their appearance.
blood stem cells	precursor cells of all blood cells, which give rise to red blood cells (erythrocytes), white blood cells (leukocytes), platelets (thrombocytes) and some other cells. This process is called blood formation. The various blood cells are formed in the bone marrow before they enter the blood stream.
blood transfusion	transfer of blood (whole blood) or blood components (e.g. red blood cells or platelets) from a donor to a recipient.
bone marrow	site of blood formation; spongy tissue with a strong blood supply that fills the cavities inside many bones (e.g., vertebrae, pelvic and thigh bones, ribs, sternum, shoulder blade, and collarbone); in the bone marrow, all forms of blood cells develop from blood progenitor cells (blood stem cells).
bone marrow punch biopsy	removal of bone marrow tissue for the purpose of examining the cells; with the help of a special hollow needle, a tissue cylinder about 2 cm long is punched out of the bone. The examination is always carried out under anesthesia. A bone marrow punch biopsy may be necessary in addition to or instead of a bone marrow puncture if the latter does not provide sufficient tissue for a reliable examination. Like the bone marrow puncture, it is usually performed from the posterior iliac crest bone. There, the bone marrow is only separated from the skin by a relatively thin layer of bone, so that the removal can take place without significant risk.
bone marrow puncture	removal of bone marrow tissue to examine the cells; during the puncture, a few milliliters of liquid bone marrow are drawn from the pelvic bone or sternum into a syringe with the help of a thin hollow needle. The puncture is performed under local anaesthesia in older children; a sedative may also be administered (sedation). For smaller children, a short period of anesthesia may be appropriate.
cancer predisposition syndrome	genetic disorders that can include malformations and intellectual disability in addition to an increased risk of tumors; according to current knowledge, about 10% of childhood and adolescent cancers develop due to a known hereditary change or cancer predisposition syndrome. Cancer predisposition syndromes include Louis Bar syndrome (= ataxia telangiectatica), Beckwith-Wiedemann syndrome, Down syndrome, Hippel-Lindau syndrome, Li-Fraumeni syndrome, MEN syndrome,

	neurofibromatosis and WAGR syndrome. The familial form of retinoblastoma is also part of it.
chemotherapy	here: use of drugs (chemotherapeutic agents, cytostatics) for the specific inhibition of tumor cells in the organism
chromosomal	referring to the chromosomes, carriers of the genetic material (see chromosomes)
chromosome	chromosomes are the carriers of the genetic material, i.e. the genetic information of a cell; chromosomes consist mainly of DNA and proteins and are components of the cell nucleus. The shape and number of chromosomes are species-specific. Humans have 46 chromosomes (23 pairs of chromosomes) per cell in the body.
conditioning	preparatory treatment of a patient before receiving a blood stem cell transplant; it serves to suppress the patients own immune system by more or less completely destroying the bone marrow cells and thus the patients own blood formation, so the donor's cells cannot be rejected by the patient's immune system. At the same time, space is created in the bone marrow for the new donated blood stem cells. The choice of the conditioning scheme usually depends on the type and stage of the disease as well as the type of donor available. After conditioning, the actual transplant takes place.
cytogenetic	the number and structure of the chromosomes contained in the nucleus
cytogenetics	a field of research that deals with the number and structure of chromosomes located in the nucleus; it involves the microscopic examination of cells, e.g. from blood, swabs or tissue samples.
cytopenia	a decrease in the number of cells in the blood; cytopenia can describe either a reduction in one, two or three hematopoietic cell lines (monocytopenia, bicytopenia, pancytopenia) or a reduction in a specific type of cell, such as red blood cells (erythrocytopenia), platelets (thrombocytopenia) or white blood cells (leukocytopenia or leukopenia).
cytostatics	drugs that inhibit cell growth; cytostatics can affect the metabolism of different types of cells, thereby destroying them and/or preventing them from multiplying. Cells that divide frequently are particularly affected.
diagnostics	methods / measures for the detection of a disease

Diamond-Blackfan anaemia	hereditary blood disorder characterised by impaired bone marrow function, growth disorders and malformations (the latter in approximately 40 % of patients); there is also an increased risk of developing acute myeloid leukaemia or myelodysplastic syndrome (MDS). The disease is caused by a disorder of the formation of red blood cells in the bone marrow (white blood cells and platelets are not affected), which is associated with chronic severe anaemia and must be treated for life. The disease usually occurs in early childhood.
differential diagnosis	any possible diagnosis to be considered in the case of a disease
dyskeratosis congenita	hereditary disorder that affects multiple organ systems; the syndrome is primarily characterised by abnormal pigmentation of the skin and mucous membranes, as well as growth disorders of fingernails and toenails. Causative treatment is often only possible through a stem cell transplant. Life-threatening symptoms of the disease include, for example, disorders of bone marrow function with suspension of normal blood formation (bone marrow suppression) and consequently a lack of red and white blood cells as well as platelets, myelodysplastic syndrome (MDS), or aplastic anaemia.
dysplasia	malformation or maldevelopment of a tissue with insufficient differentiation (maturation)
erythrocytes	red blood cells, the most abundant cells in the blood, they are mainly used to transport oxygen in the body; erythrocytes are formed in the bone marrow (erythropoiesis). The red blood pigment (haemoglobin) inside the erythrocytes is responsible for binding and transporting the oxygen absorbed in the lungs. If red blood cells are not present in sufficient quantities or, due to a lack of haemoglobin, are not functional, it is referred to as anaemia.
Fanconi anaemia	hereditary haematopoietic disorder; it is mainly characterized by a progressive dysfunction of the bone marrow, which leads to a reduced formation of blood cells (bone marrow insufficiency), as well as by chronic anaemia and a high risk of cancer (especially for acute myeloid leukaemia). Other concomitant symptoms include skeletal malformations (e.g. short stature, malformations of the thumbs and arms). Fanconi anemia is one of the cancer predisposition syndromes. At the cellular level, there is an increased chromosomal fragility; this leads to chromosomal changes and, as a result, to disorders of cell cycle control.

gene	unit of genetic information in the genome of living organisms; a gene contains the genetic information – the blueprint – for a specific gene product (protein or RNA). In most organisms, the entirety of all genes, the genome, is present as a deoxyribonucleic acid chain (DNA), which forms the chromosomes in the cell nucleus. The information of a gene is mediated by a certain sequence of the nucleic acid building blocks adenine, guanine, cytosine and thymine.
genetic	concerning the (level of) inheritance or genes; inherited
germline	term for those cells that are in the service of the direct transmission of genetic material, i.e. from which germ cells (egg cells and sperms) arise in the course of individual development; the germline begins with the fertilized cell (zygote) and continues through the formation of primordial germ cells to the formation of the sex glands (gonads), which are responsible for reproduction and ultimately the germ cells.
granulocytes	subgroup of white blood cells (leukocytes); they are mainly responsible for defending against bacteria and other pathogens (such as viruses, parasites and fungi); granulocytes are also involved in allergic and inflammatory reactions, as well as pus formation. Granulocytes make up about 60 – 70% of the leukocytes in the blood. Due to their differently colourable granules and their different tasks, they are divided into three subtypes: neutrophils (90 %), eosinophils (2 – 4 %) and basophilic granulocytes (up to 1 %). The neutrophils (neutrophils for short) play the most important role in the defense against infections.
granulocytopenia	reduced number of (neutrophil) granulocytes in the blood; since granulocytes are important for the immune system, infections are easy to occur in patients with granulocytopenia (neutropenia). The most severe form of granulocytopenia is agranulocytosis, the (almost) complete lack of granulocytes in the blood. Granulocytopenia is the most common form of leukopenia (leukocytopenia).
haematopoiesis	formation of blood cells (blood cells and platelets) from haematopoietic stem cells (blood stem cells) in the bone marrow; blood cells have a limited lifespan, so they need to be renewed regularly.
high-dose chemotherapy	the use of a particularly high dose of cell growth-inhibiting drugs (cytostatics); in the case of cancer, it aims to destroy all malignant cells. Since the haematopoietic system in the bone marrow is

	also destroyed, the patients own or foreign blood stem cells must then be transferred (autologous or allogeneic stem cell transplantation).
hypocellular	reduced number of (blood-forming) haematopoietic cells in the bone marrow, which may affect one or more haematopoietic cell lines; this results in a reduced number of certain blood cells (erythrocytopenia, thrombocytopenia and/or leukocytopenia) or even all blood cells in the blood (pancytopenia).
immune defence	the bodys ability to fight off pathogens and other substances (antigens), which are identified as foreign by the organism‘s immune system, with the help of specific antibodies and certain defence cells (e.g. cytotoxic T lymphocytes)
immunosuppressive	suppressing the bodys immune defenses
infection	penetration of the smallest organisms (e.g. bacteria, viruses, fungi) into the body and subsequent multiplication within it. Depending on the characteristics of the microorganisms and the immune system of the infected person, various infectious diseases can occur after infections.
iron overload	iron levels in the blood and liver exceeding a certain level; these levels indicate that the bodys natural iron stores are full and that the body is depositing excess iron in organs such as the heart, liver, or endocrine glands. In the long run, however, it causes severe organ damage. Iron overload must, therefore, be treated consistently.
leukaemia	malignant disease of the blood forming (haematopoietic) system and the most common cancer in children and adolescents (about 33%); depending on the origin of the malignant cells, a distinction is made between lymphoblastic and myeloid leukaemias. Depending on the course of the disease (fast or slow), a distinction is made between acute and chronic leukaemias.
leukocytes	white blood cells; they serve as cells of the immune system, defending against pathogens and fighting infections. In addition, they remove the cell debris produced by the decay of body cells. Leukocytes include granulocytes (with 60 – 70 %), lymphocytes (20 – 30 %) and monocytes (2 – 6 %). Leukocytes are mainly produced in the bone marrow. This process is called leucopoiesis.
leukopenia	decreased white blood cells (leukocytes) in the blood to levels below the age-appropriate norm;

lymphocytes	subgroup of white blood cells that are responsible for the bodys own defenses, especially the defense against viruses; there are B and T lymphocytes. They are formed in the bone marrow, but partly only mature to full functionality in the lymphatic tissue (e.g. lymph nodes, spleen, thymus gland). They eventually enter the blood via the lymphatic vessels, where they take over their respective tasks.
microscope	an instrument that allows you to magnify objects or certain structures of objects that are not visible to the human eye
molecular genetic	referring to structure, formation, development, function and interactions of cells and cell building blocks (e.g. nucleic acids, proteins) at the molecular level; the focus is on the analysis of the genetic information stored in the nucleic acids (DNA and RNA) and its processing in the context of protein synthesis as well as gene regulation.
monosomy 7	congenital condition associated with an increased risk of developing acute myeloid leukaemia (AML); the disease is caused by a genetic change (mutation) in which chromosome 7 is only present in a single rather than double version due to chromosome loss.
mutation	alteration of genetic material; it can arise without any identifiable external cause (so-called spontaneous mutation) or be caused by external influences (induced mutation). External influences include, for example, ionizing radiation or certain chemical substances (mutagens). If somatic cells are affected, it is referred to as a somatic mutation, and if germ cells are affected, it is referred to as a generative mutation. Somatic mutations are not heritable, while germ cell mutations can lead to hereditary damage. Depending on the extent of the change (single or multiple genes, larger chromosome segments or complete chromosomes), a distinction is made between point and block mutations as well as numerical and structural chromosomal aberrations.
neutropenia	reduction of neutrophils in the blood, increasing susceptibility to bacterial infections; the extreme form of neutropenia is agranulocytosis.
petechiae	smallest, punctual bleedings of the skin and/or mucous membranes

physical examination	an important part of diagnostic examinations; includes palpation and listening to certain body organs as well as testing reflexes to obtain indications of the nature or course of a disease.
prognosis	prediction of the course and outcome of a disease / prospect of recovery
recurrence	relapse, recurrence of a disease after recovery
refractory	not controllable, not excitable; a refractory disease cannot be successfully treated by otherwise effective therapies.
Shwachman-Diamond syndrome	very rare hereditary disorder characterised by impaired bone marrow and pancreatic function and growth disorders; there is an increased risk of developing leukaemia or myelodysplastic syndrome (MDS). Patients with Shwachman-Diamond syndrome (SDS) have defects in a gene whose exact function is still being researched. However, it is known that these mutations are inherited in an autosomal recessive manner and can affect several organ systems and body functions at the same time.
stem cell transplantation	transfer of haematopoietic stem cells after conditioning chemotherapy, radiation or immunosuppression of the recipient; the stem cells can be obtained either from the bone marrow or from the bloodstream. In the first case, the procedure of their transfer is called bone marrow transplantation, in the second case peripheral stem cell transplantation. Depending on the type of donor, a distinction is made between two forms of SCT: allogeneic SCT (stem cells from a foreign donor) and autologous SCT (own stem cells).
supportive therapy	supportive treatment measures to prevent, alleviate or treat disease and/or treatment-related side effects or complications; supportive therapy is designed to improve the patients quality of life.
symptom	sign of illness
syndrome	clinical presentation resulting from the coincidence of various characteristic signs (symptoms)
thrombocytes	blood cells that are responsible for haemostasis; they ensure that, in the event of an injury, the walls of the blood vessels are sealed within a very short time, thus stopping the bleeding.
thrombocytopenia	decreased platelets (thrombocytes) in the blood to levels below the age-appropriate norm (less than 150,000 platelets per microliter of blood); thrombocytopenia is associated with impaired

	haemostasis, which in turn may lead to increased bleeding tendencies (e.g. nose or gum bleeds, bleeding into the skin (petechiae, bruising) and/or prolonged bleeding time (e.g. after injury). A transfusion of platelets (platelet concentrate) may sometimes be necessary.
WHO classification	international guideline developed by the World Health Organization (WHO) for classification, diagnosis and differentiation/grading of (malignant) diseases