Anonymous events

Guide to the completion of the EBMT data collection form: Anonymous_events_v1.0

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EBMT Registry

EBMT Clinical Research & Registry Department

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Diagnosis

1. Year of diagnosis

Report the year of the first diagnosis of the disease.

2. Diagnosis classification

Select the diagnosis classification that is appropriate and check the box next to it.

- **Acute leukaemia**: Acute leukaemia is a malignant disease that originates either in a lymphopoietic stem cell (Precursor lymphoid neoplasms (PLN), previously ALL) or in a hematopoietic stem cell or progenitor cell (acute myeloid leukaemia, AML)
- **Autoimmune disorder**: Autoimmune disorders (ADs) represent a heterogeneous group of diseases that affect approximately 5–10% of the population in industrialised countries with increasing incidence. Although the clinical phenotypes of ADs vary widely depending on the type of tissue and immunologic components involved, their common characteristic is a break of self-tolerance with chronic inflammation of target organs or multiple organ systems. It is widely accepted that autoimmunity develops in a genetically predisposed population, where a combination of certain epigenetic factors and environmental triggers may result in the activation of normally quiescent autoreactive cells that escape self-regulation.
- **Bone marrow failure:** Bone marrow failure syndromes are disorders of the hematopoietic stem cells leading to cytopenia that can involve one or more cell lineages. They can be acquired (non-constitutional) or genetic (constitutional).
- **Chronic leukaemia:** Chronic leukaemia is a malignant disease that originates from either the bone marrow, lymphocytes or prolymphocytes. It can be divided into chronic myeloid or chronic lymphocytic leukaemia. For the purposes of reporting anonymous events, prolymphocytic leukaemia can be reported as ‘other’.
- **Haemoglobinopathies** are a heterogeneous group of inherited diseases characterised by alteration of haemoglobin production. Adult haemoglobin is composed of 2α and 2ß chains (tetramer 22).
  Main haemoglobinopathies treated with stem cell transplantation are:
  - Beta thalassemia
  - Sickle cell disease
  - Compounded heterozygosity.

- **Inborn errors** (inherited disorders) are a group of congenital diseases caused in whole or in part by a change in the DNA sequence away from the normal sequence. Inborn errors can be caused by a mutation in one gene (monogenic disorder), by mutations in multiple genes (oligogenic disorder), or by structural or numerical aberrations of chromosomes.
- **Lymphomas** are malignant neoplasms of the lymphatic system, which includes lymph nodes, spleen, thymus, Waldeyer's ring, appendix, and Peyer's patches. Lymphomas are divided into two subgroups: Hodgkin lymphoma (HL) and Non-Hodgkin lymphomas (NHL).
- **Myelodysplastic syndrome** (MDS) is a heterogeneous group of clonal haematopoietic stem cell disorders characterised by ineffective, dysplastic haematopoiesis, peripheral cytopenia and a variable rate of progression to acute myelogenous leukaemia (AML).
- **Myelodysplastic syndrome/myeloproliferative neoplasm** (MDS/MPN) are a group of chronic clonal myeloid malignancies in which there are features of both MDS and MPN at the time of presentation. This category was originally composed of the following major myeloid disorders: chronic myelomonocytic leukaemia (CMML), juvenile myelomonocytic leukemia (JMML), MPNMDS with ring sideroblasts and atypical chronic myeloid leukemia (aCML). Myeloid disease that shows features of both MDS and MPN but does not meet the criteria for any of the major MDS/MPN entities is designated as myelodysplastic/myeloproliferative neoplasm, unclassifiable (MDS/MPN-U). All MDS/MPN subclassifications are negative for BCR::ABL1 fusions, or rearrangements involving PDGFRA, PDGFRB, FGFR1 and PCM1-JAK2 and have
- **MPN:** Myeloproliferative neoplasms (MPNs) include a group of haematological disorders originating from a pluripotent stem cell of haematopoiesis that typically present with a hypercellular bone marrow with fibrosis, hepatomegaly, splenomegaly, and increased blood cell counts (cytopenias are possible). With advanced disease the cellularity may decrease, fibrosis becomes predominant, blood counts may be low and the patient may be transfusion dependent. The transformation from one entity to another is not uncommon, as is the case with the transition from polycythaemia or thrombocythemia to myelofibrosis. Moreover, all these conditions have an inherent tendency to progress to acute leukaemia. In addition, myeloproliferative neoplasms have specific mutations: to distinguish these forms from CML, all forms should be BCR::ABL1 negative. More than 90% of polycythaemia vera patients and about 50% of primary myelofibrosis and essential or primary thrombocythemia patients carry the JAK2 V617F mutation. FIP1L1-PDGFRA mutation can be found in hyper eosinophilic syndrome, whereas c-kit mutation is found in systemic mastocytosis in around 85% of cases.
- **Plasma cell disorder (incl. MM):** Plasma cell disorders are related to an overproduction of plasma cells in the body and subsequently a possible overproduction of

immunoglobulins. For the purpose of reporting anonymous events, the only distinction that is made is between multiple myeloma and the other plasma cell disorders.

- **Solid Tumour:** Solid Tumours are a group of malignancies presenting with masses internal or external to organs such as breast, ovarian or lung carcinoma. Although lymphomas may present with solid masses internally or externally, they are categorised under a different section because lymphomas are related to the lymphatic system and investigated under the lymphoma working party. The diagnosis form is meant for the indication of treatments.
- **Other**

3. Subclassification

3.1. Acute Leukaemia

Select the main class that is appropriate for acute leukaemia and check the box next to it.

There are distinguished 3 main classes of acute leukaemia, which are

Acute myeloid leukaemia (AML) is characterised by disordered differentiation and proliferation of hematopoietic stem cells or progenitor cells into myeloblasts in acute myeloid leukaemia.

Precursor lymphoid neoplasms (PLN, previously ALL) is characterised by disordered differentiation and proliferation of lymphopoietic cells into lymphoblasts in precursor lymphoid neoplasms.

Other: If the classification of Chronic leukaemia is not listed, check the box “Other”.

3.2. Bone marrow failure

Select the classification that is appropriate for Bone marrow faliure and check the box next to it.

Aplastic anaemia (AA) is a bone marrow failure syndrome characterised by bicytopenia (decrease in two of three cell lines: erythrocytes, leukocytes, or platelets) or pancytopenia (decrease in all blood cell lines) in the peripheral blood and an aplastic (absence of cellular proliferation) or hypoplastic/hypocellular (insufficient cell proliferation) bone marrow in the absence of major dysplastic features or neoplastic (malignant) cells and in the absence of chemotherapy- or radiation therapy-induced damage, or increased reticulin. Aplastic anaemia is classified by its severity as moderate, severe, and very severe aplastic anaemia based on peripheral blood counts and is this case, **Severe Aplastic anaemia** is as described in table 1. Therefore, it is important to get information on blood counts at the first immunosuppressive treatment episode.

Aplastic anaemia grade	Description
Severe	BM cellularity < 30% (or < 50% if < 30% of BM are hematopoietic cells) And 2 out of 3 criteria ○ Neutrophils < 0.5 x 109/L ○ Platelets < 20 x 109/L ○ Reticulocytes < 60 x 109/L

Table 1, description of Severe aplastic anaemia.

If the diagnosis was not severe aplastic anaemia, select **"Other".** No further specification is required for reporting anonymous events.

3.3. Chronic leukaemia

Select the classification that is appropriate for chronic leukaemia and check the box next to it.

Chronic myeloid leukaemia (CML) is also known as chronic myelogenous leukaemia. It's a type of cancer that starts in certain blood-forming cells of the bone marrow. In CML, a genetic change takes place in an early (immature) version of myeloid cells: the cells that make red blood cells, platelets, and most types of white blood cells (except lymphocytes). This change is related to a translocation between chromosome 9 and 22, t(9;22) which forms an abnormal gene called BCR-ABL and, which turns the cell into a CML cell. The leukaemia cells grow and divide, building up in the bone marrow and spilling over into the blood. In time, the cells can also settle in other parts of the body, including the spleen. CML is a fairly slow growing leukaemia, but it can change into a fast-growing acute leukaemia that's hard to treat. CML occurs mostly in adults, but very rarely it occurs in children, too. It belongs to the myeloproliferative neoplasms, and present initially as an indolent or chronic phase (CP), easily controlled with treatment. The natural history continues with a bi- or triphasic stage, becoming more aggressive through accelerated phase (AP) and then blast crisis (BC) or directly from CP to BC.

Chronic lymphocytic leukaemias (CLL) are malignancies of the mature lymphocyte. The normal lymphocytes can be divided into two main groups: B lymphocytes and T lymphocytes. B lymphocytes make antibodies (immunoglobulins) and T lymphocytes are cells that can kill foreign cells (e.g. virus infected cells or allogeneic transplants). The large majority of patients with, chronic lymphocytic leukaemias have a B-cell type. The T-cell types of chronic lymphocytic leukaemias are rare. General characteristics of this group of diseases are lymphocytosis (> 5 x 109 /L) and enlarged lymph nodes and spleen.

Other: If the classification of Chronic leukaemia is not listed, check the box "Other". Prolymphocytic leukaemia can be reported as other too.

3.4. Haemoglobinopathy

Select the classification that is appropriate for Haemoglobinopathy and check the box next to it.

Thalassemia: Lack of production of ß chains characterises ß-thalassemia (here and after referred to as Beta thalassemia), lack of production of ὰ chains characterises ὰ-thalassemia (which is a homozygous condition not compatible with life, Hemoglobin Bart's)

Sickle cell disease: Sickle Cell Disease is a homozygous congenital disease where a single point mutation characterised by the production of an altered ß-chain.

Other: if the patient was neither treated for thalassemia nor for sickle cell disease, select **"Other"**.

3.5. Inborn errors

Select the sub-classification that is appropriate for the Inborn Error and check the box next to it.

Inborn errors of immunity (IEI): a group of inherited disorders caused by mutations in single or multiple genes that result in the specific impairment of normal immune development and function. The clinical presentation of IEI is variable and includes severe or unusual infections, autoimmune diseases, autoinflammation, and malignancies.

Inborn errors of metabolism: a group of inherited disorders caused by mutations in genes coding for proteins that function in metabolism.

Other inborn errors: a group of inherited disorders that do not fall into any of the abovementioned categories. All inborn errors that are not an IEI or an error of the metabolism can be reported here.

3.6. Lymphoma

Select the classification that is appropriate for Lymphoma and check the box next to it.

Hodgkin lymphoma has a monoclonal origin with B-lymphocytes being involved in most cases. At an early stage, only lymph nodes are affected, at an advanced stage, it is a systemic disease that might as well affect extra lymphatic organs (bone marrow, liver). Ratio male:female is 3 to 2. In Europe and the USA, there are two age peaks: one around 30 and one above 60 years old. It is assumed that there is a connection in some cases between EBV infection and the pathogenesis of Hodgkin lymphoma. Typical symptoms are: swelling of lymph nodes without pain (60% cervical, 30% mediastinal, 20% axillar, 15% both abdominal or inguinal) - few patients describe painful lymph nodes after consumption of alcohol; fever, night sweats, weight loss, and

hepatosplenomegaly. The laboratory results often show elevated ESR and LDH values, anaemia, and typical lymphocytopenia.

Non-Hodgkin lymphomas have the tendency to grow discontinuously in the lymphatic system and they can involve the extra lymphatic system more often than HL. Thus, the gastrointestinal tract, the liver, the bone marrow, and the peripheral blood are affected much more often than in Hodgkin's disease. Ratio male:female = 1.5:1. About 2/3 of the patients with NHL are between 50 and 80 years old. Patients with AIDS have a 1000 times higher incidence of NHL. Typical symptoms are: swelling of lymph nodes, fever, night sweats, weight loss, and skin affection. The bone marrow is affected in 50% of cases, thus, the laboratory results often show anaemia, thrombocytopenia, and leukocytopenia. If the patient was treated for a non-Hodking lymphoma, indicate if this was a **DLBCL, other B-cell** or **T-cell lymphoma.**

Other: If the classification of lymphoma is not listed, check the box "Other".

3.7. Plasma cell disorder (incl. MM)

Select the classification that is appropriate for Plasma cell disorder (incl. MM) and check the box next to it.

Multiple myeloma (MM; synonyms: 'Myeloma', 'myelomatosis') is a malignant lymphoproliferative disorder arising

from a clonal plasma cell population. The malignant cells usually produce a monoclonal immunoglobulin readily identifiable in either the plasma (M-component) or the urine (Bence Jones' protein or urinary light chains). The most common clinical presentation in MM is skeletal damage with lytic bone lesions and generalised osteopenia. Other features include anaemia, hypogammaglobulinemia, renal failure and hypercalcaemia. Indicate the subtype of multiple myeloma by checking the corresponding checkbox or select 'Unknown' if this information is not available.

Other: If the classification of plasma cell disorder is not multiple myeloma, select "Other".

3.8. Solid Tumours

Select the classification that is appropriate for the solid tumour at the time of diagnosis and check the box next to it. If the diagnosis subtype is not listed, check the box "Other".

Neuroblastoma is as a malignancy originating from the neural crest within the peripheral nervous system. This tumor holds the distinction of being both the most prevalent and lethal neoplasm affecting pediatric patients.

Soft tissue/Ewing sarcoma: is a tumour that originates in the bones or soft tissues that are around the bones and usually occurs in adolescents.

Germ cell tumour: is a tumour that starts in cells from the reproductive system called germ cells. Germ cell tumours can be malignant or benign.

Other: If the solid tumour was not one of the tumours mentioned above, select “Other”.

Treatment

4. Year of treatment

Report the year treatment took place.

5. Chronological number of this treatment

Indicate the chronological number of the current treatment among other treatments (HCT, CT, IST) received by the patient throughout their lifetime, regardless of whether the previous treatments have been performed in your centre or other centres.

6. Age category at treatment

Select the appropriate age category, **Adult** (18 years and older) or **Paediatric** (aged below 18 years), for this treatment.

7. Type of treatment

Select the treatment that is appropriate

- **HCT:** An HCT is defined as the transfer of stem cells, defined as progenitor cells with repopulating capacity and the potential to sustain long-term hematopoiesis, within one

person or from one person to another, in a dose that is sufficient to restitute hematopoiesis in all lineages.

- Type
  - **Autologous HCT** is a treatment where patients receive their own stem cells to replace diseased or damaged bone marrow.
  - **Allogeneic HCT** (Allo-HCT) uses hematopoietic stem cells collected from another related or unrelated individual. Allo-HCT is increasingly used to treat a variety of hematologic neoplasms and non-malignant marrow disorders (acquired and inherited), including inborn errors of metabolism.
  - Cell source
    - Select all sources of stem cells that were used for this autologous HCT. It can be: **bone marrow**, **peripheral blood**, or **cord blood**.
- **CT**: cell therapies are defined as medicines for human use that are based on genes, tissues or cells. This definition covers CAR-Ts as well as other CTs such as tumour infiltrating lymphocytes or mesenchymal cells.
- Source of cells
  - Autologous: mark if the cells were collected from the same patient.
  - Allogeneic: mark if the cells were collected from another person (donor).

- **IST**: An immunosuppressive treatment (IST) episode is defined as any treatment combination containing one of the following components:
  - Alemtuzumab
  - Androgens: Danazol, Etiocholanolone, Fluoxymesterone, Nandrolone, Norethandrolone, Oxandrolone, Oxymetholone, Testosterone
  - ATG
  - Corticosteroids: Beclometasone, Budesonide, Dexamethasone, Methylprednisolone, Prednisolone
  - Cyclophosphamide
  - Cyclosporin
  - Growth factors: Filgrastim, Lenograstim, Pegfilgrastim
  - Mycophenolate mofetil
  - Rituximab