Protocol Synopsis

Study Title

A prospective, multicenter European Registry for newly diagnosed patients with Myelodysplastic Syndromes of IPSS low and intermediate-1 subtypes.

Short Title

European MDS Registry

Study Objectives

To describe the demographics and the disease-management of IPSS low and intermediate-1 MDS patients who are newly diagnosed and classified according to the WHO criteria.

To collect and to present data on clinical characteristics, disease-management and relevant outcomes.

Methodology

Data on patients with low or intermediate-1 risk MDS will be collected prospectively at diagnosis and at 6-months intervals after diagnosis. The data will be gathered by seventeen existing national MDS Registries that are represented within the LeukemiaNet MDS Working Party and will be combined in one central European Database. Data analyses will be conducted by the Data Management Centre after every 400 patients included in the European Registry and at the end of the follow-up period.

Number of Patients & Centres

Over 150 hematology centres in seventeen different countries (Austria, Croatia, Czech Republic, Denmark, France, Germany, Greece, Israel, Italy, the Netherlands, Poland, Portugal, Republic of Serbia, Romania, Spain, Sweden, and United Kingdom) will participate in this Registry. The recruitment target is a minimum of 2000 cases.

Population

The study population will consist of newly diagnosed patients with IPSS low- or intermediate-1 risk myelodysplastic syndrome.

Study Duration

The enrolment time will continue until January 1st 2017. The follow-up period will be 5 years.

1. Introduction

Myelodysplastic syndromes (MDS) are a heterogeneous group of hematopoietic stem cell disorders(1). They are characterized by dysplasia in the myeloid, megakaryocytic and/or erythroid lineages. The abnormal cells belong to a malignant clone, which represses the remaining normal cells in the bone marrow. Patients suffer from peripheral blood cytopenias (anemia, leukopenia and/or thrombocytopenia). The natural course of MDS ranges from an indolent disease that may span years, to a more acute manifestation with severe bone marrow failure resulting in life-threatening complications. About 30% of the patients show progression towards acute myeloid leukemia (AML), but most patients eventually die from complications of bone marrow failure.

Incidence of MDS

The overall incidence of MDS is estimated to be 3-4 per 100 000 per year. Approximately 70% patients will be defined as low-risk disease. These numbers are often based on local studies. It is generally assumed that the incidence is underestimated due to the complexity of diagnosing MDS. The more indolent forms of MDS, when the number of blasts in the bone marrow or blood is not or only slightly increased, are especially difficult to diagnose. In clinical practice today, cytomorphologic evaluation of the peripheral blood and bone marrow still is the basis of MDS diagnostics. The clonal hematopoietic cells show dysplastic features. However, there are a number of other conditions, such as infections or medication that can result in transient cytopenias and dysplastic cells, without clonal aberrations. In approximately 50% of patients chromosomal abnormalities are found using conventional cytogenetics, which can facilitate the diagnosis of MDS.

Classification of MDS

Classification systems have been developed to serve as a guide for the diagnosis, estimation of prognosis and management of patients with this disease. However, newly acquired knowledge about the pathogenesis of MDS and the development of novel forms of therapy require that classification systems are continuously open to changes.

The World Health Organization (WHO)(2) has provided a system that classifies patients according to the number of cell lineages affected, the number of blasts in peripheral blood and bone marrow, the presence of ringed sideroblasts and the result of cytogenetic analysis. Patients with RA (-RS), RCMD (-RS), or a solitary deletion of the long arm of chromosome 5, have a relatively good prognosis regarding survival and risk of developing AML. Prognosis is worse in the RAEB-1 subgroup. Patients with RAEB-2 in general have the highest risk of progression to AML and the lowest overall survival.

The International Prognostic Scoring System (IPSS) was developed for assessment of prognosis(3). The IPSS system comprises three parameters, bone marrow blast percentage, karyotype and number of cytopenias. Patients with a low or intermediate-1 score are more likely to have an indolent disease course (often defined as “low-risk). Patients in the intermediate-2 or high risk group are more likely to suffer from aggressive disease with a higher frequency of transformation to AML. The IPSS has been revised recently(4). Patients are subdivided in 5 prognostic groups based on a more precise cytogeneic risk calculation, and more detailed subdivision of the cytopenias and percentage of marrow blasts. We decided to maintain the low and intermediate-1 risk groups of original IPSS classification as the inclusion criterion for the Registry in view of the homogeneity of the Registry.

In the near future, it is expected that genetic markers will be increasingly incorporated in the classification of MDS(5).

Treatment of MDS

As MDS is a heterogeneous disease, so is its treatment. Management decisions are partly based on the WHO classification and IPSS score. Allogeneic stem cell transplantation remains the only potentially curative treatment. Due to the lack of suitable donors, the intensity of this treatment and the fact that most patients are over the age of 60, stem cell transplantation is only available to a limited number of patients. The care of patients with MDS has improved during the past decades. For example, the implementation of growth factors and immunomodulating agents has improved the management of patients with IPSS low and intermediate-1 risk MDS. Also, drugs are being developed to prevent and to treat the complications of MDS, such as infections or transfusion-induced iron overload. A number of new drugs are under investigation. Although cooperation between centres has led to the development of national and international guidelines on the treatment of MDS, there is a large variation in clinical management. Published data on the management of MDS are mainly based on local experience(6).

MDS Registry

The current registry is designed to collect information about a large cohort of newly diagnosed MDS patients with low-risk disease defined as IPSS low or intermediate-1 categories. In a number of countries, MDS Registration projects are ongoing. These registries aim at improving the knowledge of the local incidence and management of these patients. In this project, data will be collected using registries in several European countries as the platform for registration. This will create an international registry to study the demographics and disease-management of patients with MDS.

2. Study objectives

Primary objective

The primary objective of this study is to describe the demographics and the disease-management of newly diagnosed MDS patients within IPSS low and intermediate-1 categories.

Secondary objectives

The secondary objectives are:

1. To investigate any correlation between:
   - Clinical characteristics (including WHO classification and known prognostic factors) at inclusion
   - Secondary iron overload due to transfusions
   - Treatments received

   and
   - Overall survival (censored at 5 years)
   - Time to Leukemia Progression (TLP)
   - Karnofsky Performance Status, EQ-5D

2. To collect safety data on treatment with iron chelators, when applicable, including:
   - Renal safety (serum creatinine, creatinine clearance and urine protein)
   - Liver safety (serum liver transaminases)

3. Study Design

The registry is designed to collect information about a large cohort of newly diagnosed MDS patients. Patients will be prospectively assessed in the context of existing registries(1) represented within the LeukemiaNet MDS Work Package. Patients will be observed until death, or for a maximum of 60 months (5 years).

- *Enrolment*: each centre should register all consecutive eligible patients who present during the enrolment period, or until the achievement of the study recruitment target. Patients with IPSS low or intermediate-1 MDS can be included up to 100 days after diagnosis.

- *Follow-up:* follow-up visits will be scheduled according to the standard practice of the centre and to the treating physician's best judgment. Clinical data will be collected if available. It is assumed that at least an assessment every six months (in the context of regular follow-up visits) will be performed. Laboratory evaluations for disease or iron chelation treatment monitoring may be performed more often; values available at follow-up visits will be recorded.

In this study, no clinical, instrumental or laboratory assessments will be performed other than those required for disease management according to local best practice, or required to monitor iron chelation treatment as per the approved Summary of Product characteristics. The only exceptions will be the Patient Reported Outcomes (PRO) questionnaires and blood sample collection for biological correlative studies. In selected countries and centers, ancillary quality of life, cardiac function and pharmacoeconomics sub-projects will be launched to collect information about the quality of life of patients and costs implications of the therapeutic strategies (separate protocols).

Study Population

The European Registry will be limited to patients with low or intermediate-1 risk MDS. These represent a group that is generally considered to have a more indolent disease course. Most patients with IPSS low or intermediate-1 risk receive supportive or non-intensive treatment. The main aims of the treatment are to reduce morbidity and mortality and to provide an acceptable quality of life. Management of anemia includes administration of red cell transfusions and iron chelation therapy to prevent or to treat transfusion-induced hemosiderosis. Also, treatment with growth factors, immunomodulators, demethylating agents or immunosuppression can increase hemoglobin levels in a subset of patients. Prevention of the complications of thrombocytopenia is important, as is the prevention and treatment of infections with antibiotics. A number of drugs that may improve the care for these patients are under investigation.

A minimum of 2000 patients will be enrolled in this study. The aim is to yield approximately 500 to 1000 subjects at the end of 5 years of observation. All patients will have been diagnosed with myelodysplastic syndrome within 100 days of enrolment. This sample size is intended to be a broad representation of the European MDS patients and sufficiently large for meaningful analysis of MDS subgroups.

Inclusion Criteria

Patients must meet all of the following criteria to be included in the European MDS Registry:

- Male or female.
- Age > 18 years.
- Newly diagnosed patient (within 100 days from the date of the diagnostic bone marrow aspirate).
- MDS classified according to WHO criteria (2001).
- IPSS Risk group Low or Intermediate-1.
- Able and willing to provide the written informed consent.

Exclusion Criteria

- Age <18 years
- Patient unwilling or unable to give consent
- intermediate-2 or high risk MDS
- secondary/therapy-related MDS.

Withdrawal from the Study

Patients will be withdrawn from the study in case of:

- Progression to leukemia.
- Necessity to treat the patient with intensive chemotherapy or hematopoietic stem cell transplantation.
- Treatment with a drug that changes the natural history of the disease or prevents follow-up.
- Withdrawal of consent without a reason required.

In any of these cases, only data on survival will be collected.

4. Visits and Assessments

The following data will be collected:

At inclusion

- Inclusion and Exclusion Criteria.
- Date of patient inclusion.
- Demographic information: sex, date of birth, ethnicity.
- Weight, height.
- Karnofsky Performance Status, EQ-5D.
- History of MDS: date of MDS diagnosis, WHO classification, IPSS and IPSS-R risk groups.
- Treatment for MDS :
  - Therapies for MDS.
  - Red cell transfusion: date of first transfusion, number of transfusions in the prior year, date of last transfusion and number of units transfused, pre-transfusion hemoglobin value.
  - If treatment with iron chelator is given: dose and schedule, start and stop date, and ferritin values with date if available.
- Concomitant diseases, including but not limited to cardiac insufficiency, ophthalmic conditions including lens opacities and cataract, hearing impairment, diabetes mellitus, endocrine dysfunctions, renal or liver disease.
- All concomitant medication.
- Laboratory values:
  - *Peripheral blood*: hemoglobin concentration, white cell count, neutrophil, lymphocyte, monocyte, eosinophil and basophil count, platelet count, MCV, reticulocytes, glucose, LDH, liver transaminases, ferritin, erythropoietin, transferrin saturation level, serum creatinine and calculated creatinine clearance
  - *Bone marrow*: date of bone marrow aspirate and/or biopsy, percentage of blasts, percentage of ring sideroblasts, cytogenetics (karyotype).
  - *Urine*: urinalysis for protein (by dipstick).
- Blood samples for biological correlative studies.

At each follow-up visit (every 6 months), including end of study:

- Date of visit.
- Weight
- Karnofsky Performance Status, EQ-5D
- Changes in concomitant conditions and medication since last visit.
- Number of transfusions since last visit, date of last transfusion and number of units, pre-transfusion Hb
- If treatment with iron chelators was started: dose and schedule, start date and pre-treatment and ferritin.
- Laboratory values:
  - *Peripheral blood*: hemoglobin concentration, white cell count, neutrophil, lymphocyte, monocyte, eosinophil and basophil count, platelet count, MCV, reticulocytes, glucose, LDH, liver transaminases, ferritin, erythropoietin, transferrin saturation level, serum creatinine and calculated creatinine clearance
  - *Bone marrow*: date of bone marrow aspirate and/or biopsy, percentage of blasts, percentage of ring sideroblasts, cytogenetics (karyotype).
  - *Urine*: urinalysis for protein (by dipstick).
- Patient outcome:
  - in case of MDS progression to a more advanced WHO subtype / AML: provide the date of progression.
  - in case of death: provide date and cause of death.
- Blood samples for biological correlative studies.

Laboratory Tests

Laboratory tests will be performed as judged appropriate by the treating physician. This study does not require additional laboratory tests to be performed. The laboratory test results of interest will be registered if available.

5. Upcoming changes in study protocol

Currently, the study protocol is being updated. The main changes include:

- Extension of the follow-up from 5 to 9 years.
- The addition of analyses of molecular characteristics in MDS. This requires collection of EDTA blood samples (or in some cases bone marrow smears) for DNA.
- Serum sampling for biological correlative studies will no longer required, however it will remain optional.

The protocol amendments will soon be submitted for National and Ethical approval. The new protocol will only apply after approval has been obtained.

6. References

(1) Aul C, Giagounidis A, Germing U. Epidemiological features of myelodysplastic syndromes: results from regional cancer surveys and hospital-based statistics. Int J Hematol 2001 Jun;73(4):405-10.

(2) Vardiman JW, Harris NL, Brunning RD. The World Health Organization (WHO) classification of the myeloid neoplasms. Blood 2002 Oct 1;100(7):2292-302.

(3) Greenberg P, Cox C, LeBeau MM, Fenaux P, Morel P, Sanz G, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood 1997 Mar 15;89(6):2079-88.

(4) Greenberg PL, Tuechler H, Schanz J, Sanz G, Garcia-Manero G, Sole F, et al. Revised international prognostic scoring system for myelodysplastic syndromes. Blood 2012 Sep 20;120(12):2454-65.

(5) Langemeijer SM, Kuiper RP, Berends M, Knops R, Aslanyan MG, Massop M, et al. Acquired mutations in TET2 are common in myelodysplastic syndromes. Nat Genet 2009 Jul;41(7):838-42.

(6) Bowen D, Culligan D, Jowitt S, Kelsey S, Mufti G, Oscier D, et al. Guidelines for the diagnosis and therapy of adult myelodysplastic syndromes. Br J Haematol 2003 Jan;120(2):187-200.