Title of the Study	**Quality assurance on diagnosis and therapy of secondary immunodeficiencies (SID) in patients with chronic lymphocytic leukemia (CLL) or multiple myeloma (MM) in Germany (QS-SID)**
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Quality assurance on diagnosis and therapy of secondary immunodeficiencies (SID) in patients with chronic lymphocytic leukemia (CLL) or multiple myeloma (MM)

SYNOPSIS

Scientific project lead	Prof. Dr. Hartmut Link (AGSMO / AIO AG Supportivtherapie)
Title of the study	Quality assurance on diagnosis and therapy of secondary immunodeficiencies (SID) in patients with chronic lymphocytic leukemia (CLL) or multiple myeloma (MM).
Background	SIDs and resulting infection complications are a concomitant phenomenon of cancer patients, particular common in patients with CLL or MM. Especially hypogammaglobulinaemia is associated with the underlying disease as well as the anti-neoplastic therapy (CD19, CD20, CD52 antibodies, kinase and mTOR inhibitors, chemotherapy and immunotherapeutic agents) and its co-medication. Therefore, the European Conference on Infections in Leukemia (ECIL) recently published a position paper on infections associated with different immunotherapeutic and molecular targeted agents. [1] Since infections are an important cause of morbidity and mortality, the adequate diagnostic and therapy of SIDs regarding individual risk factors are essential to ensure quality of treatment. Guidelines [GL] on CLL[2], MM[3], the DGHO GL on therapy-induced secondary immunodeficiencies[4] as well as the German Bundesärztekammer (BÄK)[5] recommend an immunoglobulin-replacement therapy (IgRT) in patients with clinically relevant susceptibility to infections. Clinical relevance is defined as ≥ 3 bacterial infections within one year or a sepsis.
Primary objective	The aim of the study is to examine the monitoring of immunoglobulin levels (IgG, IgA, IgM; timing/interval/modus) and the therapy of hypogammaglobulinaemia in clinical routine in patients with systemic therapy of CLL or MM in Germany. To this end, a nationwide representative survey is to be conducted to observe the current practice of infections prophylaxis in hospitals and office-based physicians.
Secondary objective	Explorative analysis of correlations between type of antineoplastic therapy (CD229/CD20/CD52 antibodies, kinase and mTOR inhibitors, chemotherapy, immunotherapy), stage of disease and additional risk factors (age, comorbidities, neutrophil and lymphocyte counts) and the occurrence of hypogammaglobulinaemia, the number and severity of infections and mortality.
Hypotheses	The recommendations on immunoglobulin replacement therapy (IgRT) of the BÄK and national guidelines for CLL and MM therapy are implemented insufficiently in clinical routine. Guideline adherent prophylaxis and therapy is associated with fewer and less serious infections.
Intervention(s)	no interventions

Target criteria / Endpoints	Infections prior, during and after antineoplastic therapy (up to one year after begin of therapy) Immunoglobulin level (IgG, IgA, IgM) prior, during and after anti-neoplastic therapy IgRT in accordance to the recommendations of BÄK and guidelines Infection free survival according to IgG Substitution
Study design	Retrospective, representative registry. <u>Treatment structure analysis and recruitment (phase 1):</u> In a first step, data on care facilities, that treat patients with CLL or MM in Germany is obtained. In phase 1 all centers in Germany that potentially treat patients with the CLL or MM are contacted and data of its facility care level and its number of treated patients is recorded using a one-sided pen-to-paper form. In addition, the willingness of care facilities to become involved in patients' documentation is elicited (phase 2). <u>Patient documentation (phase 2)</u> To achieve a reliable, representative sample of patients treated in Germany, the distribution of cases to be documented is specified in the individual indications amongst the facilities involved. This is done using the facilities' data on patient numbers and treatment structure obtained in phase I: The participating centers are assigned to clusters based on key distinguishing features (facility type, care level and number of patients treated). This sample is modulated according to the previous treatment structure analysis. By taking this approach, the actual percentages of the various care facilities in an indication area can be reflected proportionally in the patient documentation sample. In phase 2 a multiple-page electronic case record form (eCRF) is completed in order to collect the original patient and treatment data, which are relevant to the purpose of the study. All data is gathered retrospectively and anonymously using the patient files. Patient and disease related variables (age, general condition according to the Eastern Cooperative Oncology Group (ECOG), relevant comorbidity, staging and relevant mutations), systemic antineoplastic treatment (chemotherapy, antibodies, kinase-inhibitors, relevant co-medication etc.) are recorded. Also, data on diagnosis of Ig-levels (IgG, IgA, IgM), therapy of secondary immunodeficiencies as well as the number and severity of occurred infections and their treatment is collected. Clusters for classification of infections will be developed (e.g. life-threatening, need for hospitalization). In order to ensure data quality, the scientific project lead will provide training for two employees of the commissioned institute on matters regarding the content of the study. This knowledge will be incorporated into the programming of the user interface and the patient databases so that the program will check for completeness and, as far as possible, plausibility, on the basis of defined requirements and constraints. These checks accompany the process of entering data into the eCRF and allow for validating data instantly. If inconsistencies, mistakes or omissions are

<table>
<tr><td></td><td>detected, data will be validated by an integrated query management system.

Physicians questionnaire (phase 3)

In an additional step and alongside the patient documentation, the attending physicians in participating centers will be surveyed (phase 3) on their competency profile, their assessment of guideline quality and their approach to avoid infections of CLL and MM patients.</td></tr>
<tr><td>Population</td><td>Inclusion criteria: Patients with CLL or MM who started an anti-neoplastic systemic therapy between July 1st 2017 and June 30th 2018. The observation period for documented patients has to cover at least 12 months after beginning systemic therapy.

Exclusion criteria: Patient in terminal phase of the disease, life expectancy less than three months</td></tr>
<tr><td>Statistics</td><td>The primary analysis for all target criteria is performed in accordance with the intention-to-treat-principle (ITT). The descriptive statistics comprise absolute and relative frequencies for qualitative characteristics, e.g. Binet-classification. For continuous characteristics such as age, location parameter with respective measures of dispersion are calculated (mean with standard deviation, median with interquartile range as well as the minimum and maximum). The Kaplan-Meier method is used to estimate the time-related number of infections (differentiated by severity) and mortality; the log-rank test is used to check the equality of the distributions.
Two-sided 95% confidence intervals are given for the effect estimate. Subgroup analysis are planned for different type of antineoplastic therapy and patent related risk factors as well as site related characteristics (certified vs. non-certified, hospitals vs. office-based). In order to address the problem of inflation of type I errors (false-positive or α-errors) by multiple testing, the p-values of pairwise comparison were adjusted using the Bonferroni-Holm or Benjamini-Hochberg procedure to control the family-wise error rate (FWER) respectively the false discovery rate (FDR) (depending on issue).</td></tr>
<tr><td>Sample size calculation</td><td>To generate valid, reliable and representative data on infections, secondary immune deficiencies 1200 patients should be documented (550 CLL patients and 650 MM patients).

The sample size is calculated on the basis of the yearly incidence of the underlying disease (CLL and MM) and the rate of infections of patients with these indications under systemic therapy. The sample should represent 10% of yearly incidence to generate sufficient data on the diagnosis and therapy of infections and secondary immunodeficiencies.
<table>
<tr><th>disease</th><th>yearly incidence in Germany [6]</th><th>sample size</th><th>rate of SID[7-11]</th></tr>
<tr><td>Chronic lymphocytic leukemia (CLL)</td><td>~ 5.500</td><td>~ 550</td><td>20-85%</td></tr>
<tr><td>Multiple myeloma</td><td>~ 6.500</td><td>~ 650</td><td>25-60%</td></tr>
<tr><td>Total</td><td>~ 12.000</td><td>~ 1200</td><td></td></tr>
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<tr><td>Duration of study</td><td>2019/20</td></tr>
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Number of sites	About 100 centers, hospitals and office-based hematology practices
Ethics / Data protection	Data is collected retrospectively and completely anonymously from patent record. Data only includes the documentation of clinical routine; no additional study-related treatments or examinations are conducted. Only authorized personnel in the practices or hospitals, which are subject to an obligation to secrecy, will be able to view the original documents. Participation of the centers is therefore not dependent on obtaining informed consent from the patients. Data protection while entering data into the eCRF is guaranteed by the eCRF itself, which is compliant to the "standard requirements for GCP-compliant data management in multi-national clinical trials". Furthermore, data protection is guaranteed because all participating centers are given an individual access code to compose a personal combination of user name and password. SSL encryption prevents unauthorized access to the data as it is being entered.

STUDY MANAGEMENT

Institution	*Function*	*Contact*
AGSMO / AIO	Scientific project lead	**Prof. Dr. Hartmut Link** (Speaker of AG Supportive Therapy of AIO, AGSMO board member)
AIO-Studien-gGmbH	Legal sponsor	**Dr. Anette Hipper**
Institute MMF	Logistic, data collections, programming, analysis and statistics	**Markus Kerkmann** **Laura Holtmann**

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