Patients with indolent lymphomas are at high risk of infections - Experience from a German outpatient clinic

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Abstract

Background: Patients with indolent B-cell non-Hodgkin lymphomas (B-NHL) have an increased risk of infection which is caused by pathomechanisms of the diseases itself but also as a result of anti-tumor therapy. Especially the effects of anti-CD20 antibodies are well understood as these lead to decreased antibody production.

Most analyses regarding this issue were performed in studies with multiple myeloma and chronic lymphocytic leukemia patients. As these studies not always represent the general population we collected real life data from 227 patients with indolent lymphomas undergoing therapy or who were regularly monitored in a watch and wait approach over the time of one year. As control we collected data from an age and sex matched control group of 145 persons.

Results: Patients with B-NHLs had an increased rate of infection that was detectable in all subgroups. Consistent with this finding B-NHL patients received more antibiotic treatment and were more often hospitalized than patients from the control group. Lymphoma patients without immunodeficiency had a significantly lower infection rate than patients with immunodeficiency but it was still significantly higher compared to the control group. Patients with symptomatic immunodeficiency were mostly treated with regular immunoglobulin infusions and infection rates were comparable to those of patients with asymptomatic immunodeficiency.

Conclusions: Our data suggest an approach with regular immune monitoring of all indolent lymphoma patients in order to identify patients with increased risk of infections. It also raises the question if patients with immunodeficiency should be treated more often with regular immunoglobulin infusion, but so far more studies are necessary to answer this question.

Background

Patients with hematological diseases have an increased risk of infections (1, 2). This susceptibility to infection is caused by malignant infiltration in hematopoietic and especially lymphopoietic tissue, thereby suppressing immune cell development and antibody production (3–8). In addition, patients suffering from these diseases are often treated with cytotoxic chemotherapy which often leads to depletion or prolonged suppression of hematopoiesis with various degrees of lymphopenia and neutropenia (5).

In recent years the development and use of monoclonal antibodies has improved the outcome of B-cell lymphomas (9). Over the years many different antibodies against various B-cell or Plasma cell targets like CD20, CD19, CD22 or CD38 have been developed. Especially the widespread use of B-cell directed monoclonal antibodies against CD20 has improved progression-free (PFS) and overall survival (OS) over the last years in B-cell lymphomas (10).

Depending on their targets, monoclonal antibodies deplete B-, T-, or Plasma Cells which can cause reduced immunoglobulin production and/or inhibited immune-cell-function (3, 11). One of the most used

and studied monoclonal antibodies is the anti-CD20 antibody rituximab which is able to induce a secondary immunodeficiency syndrome with hypogammaglobulinemia and resulting increased infection rate (12–14).

Over the years a continuous flow of new antitumor agents ranging from inhibitors of Bruton's tyrosine kinase affecting B-cell signaling to bispecific T-cell engager (BiTE) antibodies targeting CD19 have been developed (3, 15, 16). These therapies are very effective in tumor treatment but can also cause severe side effects with increased incidences of immunodeficiency syndromes and infections (17).

As more and more patients are treated with these new therapies the number of patients with clinically significant immunodeficiency syndromes increases. Prophylactic infection management becomes therefore more and more important. In multiple myeloma and chronic lymphocytic leukemia, in which infections are a major cause of death, disease and therapy related immunodeficiencies have been studied for a long time (1, 2). As a consequence, over the years immune surveillance and prophylactic treatment strategies were developed and are now widely used. Part of these strategies are regular patient contacts as well as the measurement of antibody and immune cell levels (T- and B-cell fractions) (18). Guided by the obtained results different prophylactic strategies can be employed including vaccination and prophylactic antibiotic treatment. In the case of clinically significant secondary immunodeficiency which is defined by low immunoglobulin levels and an increased rate of infections, patients are usually treated with vaccination and prophylactic antibiotics as a first step measure (19, 20). If these measures fail, regular immunoglobulin replacement is an effective therapy (21–23).

In patients with chronic lymphocytic leukemia and multiple myeloma it has been shown in various analyses that regular immunoglobulin infusions significantly decrease the rate of infections (24–26). As a result, prophylactic immunoglobulin infusions have become a well established and widely used treatment strategy for hematological patients with secondary immunodeficiency which is also recommended by European guidelines (EMA/CHMP/BPWP/94038/2007 Rev. 5, Committee for Medicinal Products for Human Use (CHMP)). Of note, this kind of therapy can now be administered either intravenously or subcutaneously.

The available data of infection prevalence and severity in patients with hematological diseases were mostly generated in clinical trials whose studied population usually don't represent the average population. This bias can be explained by variably strict study exclusion criteria and by focusing on patient populations that require treatment for their underlying hematological diseases. In addition many studies mostly include younger patients which may underestimate the risk of infections in older patients, if the obtained data are used to generalize the risk of infection.

Another data resource to better understand the risk of infections in older patients with hematological diseases represent data from healthcare provider. However, these data are usually limited by the fact that patients not always consult their physician in cases of infection and therefore possibly underestimate the risk of infection. In addition, these data are usually not very detailed and only allow a broad analysis. In

conclusion, more data analyzing the risk of infection for patients with hematological diseases, especially for older patients, are necessary to better understand the risk in these patients.

In order to obtain a more comprehensive picture, we collected real life data from patients with indolent lymphomas undergoing therapy or who were regularly monitored in a watch and wait approach in a German hematology/oncology outpatient center. Patients and the age and sex matched control group were regularly interviewed for the presence of infections, its treatment and if medical assistance was required. All the relevant data regarding therapy and medical history were collected prospectively and analyzed statistically.

Methods

Study design

We conducted a monocenter longitudinal prospective study using a participant-reported telephone survey. Infections were evaluated every four weeks in the course of one year for patients and a control group. Patients' treatment data were assessed additionally. The design was hypothesis-generating.

Setting and participants

All patients of an oncology group practice who suffered from indolent NHL were written to on behalf of the treating physicians. They were informed in detail about the project and had the opportunity to ask their doctors questions. Reminders were not sent nor were the patients contacted in another way. Written informed consent was obtained from the patients by sending the consent form to the center in a prepaid envelope.

Additionally, the patients' treatment data were linked to the interview data. Three subgroups were formed within the patient group: 'no immunodeficiency, no IgG substitution', 'non-symptomatic immunodeficiency, no IgG substitution' and 'symptomatic immunodeficiency, IgG substitution'.

Patients with IgG levels below 6g/l or IgG subclass deficiency were categorized as immunodeficient. The diagnosis of IgG subclass deficiency was made by the treating physician. Immunodeficient patients were further categorized in symptomatic, if they had suffered from two infections that required antibiotic treatment in the previous year.

Furthermore, a control group (CG) with a comparable distribution in terms of age and sex and not suffering from hematological or immunosuppressive diseases (e.g. diabetes mellitus, HIV infection / AIDS, cirrhosis of the liver) was questioned. This group was similarly contacted by telephone every four weeks over the course of one year (up to 12 times).

Patients and CG assessed their infections in the past four weeks retrospectively with the help of a short questionnaire. The survey was carried out between July 2017 and July 2018 and administered in German.

Variables

The frequency of infections and of infections requiring antibiotics was our primary outcome. Secondary outcomes were duration and treatment of infections, hospitalizations and sick leaves. The questionnaire was short and non-validated. It was comparable to a patient diary with the focus on infections. Age and sex as potential confounding variables were analyzed for differences.

Sample size

544 patients were eligible due to their diagnosis. An assumed response rate of at least 30% would have resulted in about 160 valid interviews. From a pragmatic point of view we decided to conduct the study without a priori calculation of sample size and to contact all patients and accordingly about 150 participants in the CG. A post hoc power analysis with regard to the primary outcome has been done with the help of G*Power version 3.1.9.2 (27).

Statistical methods

Data was analyzed with the Statistical Package for the Social Sciences (SPSS) 19. Frequencies, percentages, medians, means and standard deviations were calculated to describe the data. Data were analyzed for patients and CG as well as subgroups. All tests of statistical significance were two-sided, statistical significance was defined as a p value of .05 or less. The Bonferroni method was applied to correct for multiple testing. Descriptive statistics included demographics, treatment data and the results of the questionnaires. No participant was excluded from the analysis due to incomplete data. Statistical significance was checked using one-way analyses of variance (ANOVA) with pairwise treatments of missing values and Tukey post hoc tests, if applicable. Since simulation studies have shown that the one-way ANOVA is relatively robust against violations of the normal distribution assumption (28, 29) it was used even when this assumption was violated. In this case, the results were verified using the non-parametric Kruskal-Wallis test additionally. If several requirements for parametric test procedures were not met (normal distribution, homogeneity of variances, outliers), nonparametric tests such as Kruskal-Wallis test or Mann-Whitney-U test were used. The homogeneity of variances was checked with the Levene test.

Data protection and ethical approval

Data were captured pseudonymized. Written informed consent was obtained before the first interview from the patients, the CG verbally agreed to be interviewed by telephone. The study had been approved by the ethics committee of Rhineland-Palatinate, Germany.

Results

From July 2017 to July 2018 227 patients with lymphoproliferative diseases as well as 145 individuals of a matched control group were contacted monthly and interviewed for the presence of infections. Inclusion and exclusion criteria are described in detail in the supplementary material. The median age of

patients with lymphoma was 68.8 years and 67.2 years for the control group ($p = .164$). Both groups were well balanced for sex and age (Table 1).

Table 1
Demographics

		Patients		Control Group	
		number	mean	number	mean
age		n = 227	68.8 years	n = 145	67.2 years
		number	%	number	%
age groups	69 years or younger	n = 118	52.0%	n = 74	51.0%
	70 years or older	n = 109	48.0%	n = 71	49.0%
sex	female	n = 81	35.7%	n = 51	35.2%
	male	n = 146	64.3%	n = 94	64.8%
hematological diagnosis	CLL	n = 76	33.5%		
	follicular lymphoma	n = 50	22.0%		
	multiple myeloma	n = 50	22.0%		
	Waldenström's disease	n = 20	8.8%		
	hairy cell leukemia	n = 16	7.0%		
	mantle cell lymphoma	n = 5	2.2%		
	marginal zone lymphoma	n = 5	2.2%		
	lymphoplasmocytic lymphoma	n = 3	1.3%		
	small cell B-cell lymphoma	n = 1	0.4%		
	multiple myeloma and CLL	n = 1	0.4%		
systemic therapy	no systemic therapy	n = 50	22.0%		
	no systemic therapy during observation	n = 116	51.1%		
	systemic therapy during observation	n = 61	26.9%		
IgG replacement	no IgG replacement	n = 171	75.3%		
	no IgG replacement during observation	n = 14	6.2%		
	IgG replacement during observation	n = 42	18.5%		

		Patients		Control Group	
		number	mean	number	mean
patient groups	no immunodeficiency.	n = 105	46.3%		
	no IgG replacement				
	non-symptomatic immunodeficiency.	n = 60	26.4%		
	no IgG replacement				
	symptomatic immunodeficiency.	n = 51	22.5%		
	IgG replacement				
	symptomatic immunodeficiency.	n = 6	2.6%		
	no IgG replacement				
death during observation	deceased	n = 4	1.8%		
	not deceased	n = 223	98.2%		
cause of death	comorbidity	n = 2	50.0%		
	lymphoma	n = 1	25.0%		
	other	n = 1	25.0%		

Table 1: Demographics

Patients in the lymphoma group suffered from various B-cell non-Hodgkin lymphomas (B-NHL). Chronic lymphocytic leukemia was the most common B-NHL representing 33.5% followed by follicular lymphoma (22.0%), multiple myeloma (22.0%) Waldenström macroglobulinemia (8.8%) and hairy cell leukemia (7%). The patient cohort also included rare B-NHL subtypes. For detailed information see Table 1. 26.9% of lymphoma patients received systemic anti-tumor therapy for their disease during the time of study, 51% received therapy at any time prior to the study and 22% hadn't been treated by the time of analysis. Based on the measured IgG blood-levels and clinical symptoms, patients were categorized as immunodeficient with the subgroups of symptomatic and asymptomatic patients. 46.3% of patients (n = 105) were categorized as patients without immunodeficiency. For detailed definitions of immunodeficiency see the methods section.

Most symptomatic patients received regular IgG substitution. In detail, 25.1% of patients (n = 57) had a symptomatic IgG deficiency and 89.6% of these received regular therapeutic Immunoglobulin Infusions either before (n = 9) or during (n = 42) the time of observation (n = 51). Interestingly, about 2.6% of

patients (n = 6) didn't receive regular immunoglobulin infusions although categorized as symptomatic. 60 of 227 lymphoma patients (26.4%) were categorized as immunodeficient due to decreased immunoglobulin blood-levels but received no specific treatment as they had no increased infection rate. 5 patients (2.2%) received IgG replacement although they showed no (symptomatic) immunodeficiency according to our definition. For detailed patient information see Table 1.

In our study we used the age-adapted Charlson comorbidity index (aaCCI) to characterize the comorbidities of patients in order to predict the risk of death due to comorbidities. The aaCCI is widely used and includes 19 health conditions that are associated to an increased mortality. Each comorbidity is based on its severity rated with 1–6 points. Additional points (0–7) are added age dependent. In our study the median aaCCI was 5 (range 2–11) (Fig. 1).

The distribution of the Charlson Comorbidity Index of all 227 patients is shown. The median score was 5 (range 2–11). The aaCCI was used to give an overview of the general health status of all patients as it can be used to predict the one year mortality.

Patients suffering from B-NHL had statistically significant more infections per month compared to patients from the control group (0.36 vs 0.22, $p < 0.01$). This increased infection rate was a consistent finding and could be shown for male and females as well as for different age groups. Figures 2a and 2b depict the mean infection numbers for subgroups.

Aggregated data over 12 months show a significantly increased infection rate of patients compared to the control group. This statistically significant difference was observed in all analyzed age subgroups as well as in women and men. Patients on treatment or after treatment had, although not statistically significant, higher infection rates.

As expected patients suffering from immunodeficiency defined by decreased IgG levels had more infections per month than patients without documented immunodeficiency. However, although the subgroup of patients without immunodeficiency suffered from less infections than patients with immunodeficiency, its infection rate was still much higher than the infection rate of the control group. This finding points out that B-NHL patients have an increased risk of infection even when IgG levels are normal.

All analyzed lymphoma subgroups suffered from higher infection rates compared to the control group, including lymphoma patients without measurable immunodeficiency.

Patients with symptomatic or asymptomatic immunodeficiency had comparable infection rates suggesting a therapeutic effect of regular Immunoglobulin infusions. Of note, patients categorized as having an asymptomatic immunodeficiency and were therefore not treated with regular immunoglobulin infusions suffered from an increased infection rate questions their categorization as asymptomatic. Figure 3a depicts the frequency of antibiotic treatment in participants suffering from infections.

A higher rate of antibiotic treatment was observed in all analyzed patient subgroups compared to control groups. Only patients with reported infections were included in this analysis.

Consistent with these findings patients with B-NHL required statistically significant more antibiotic treatment than members of the control group (mean antibiotic treatment displayed as days/month: 3.55 vs 2.07; $p = 0.01$). This effect was again observed in all subgroups. Interestingly, patients who received anti-tumor treatment during the observation period had the highest rate of antibiotic treatment.

Although not significant, patients with documented immunodeficiency (symptomatic or asymptomatic) required more antibiotic treatment than B-NHL patients without immunodeficiency. However, although no immunodeficiency was detectable these patients still required more antibiotic treatment than the control group. Figure 3b depicts the mean duration of antibiotic treatment for all participants.

Mean antibiotic treatment days per month and participant. All analyzed lymphoma subgroups required significantly longer antibiotic treatment in comparison to the control group. Treatment times are displayed as days per month. Participants who did not receive antibiotics were considered with 0 days.

As hospitalization is a good marker for severe infections we also compared days in hospital/month for B-NHL patients and our control group. As expected and in line with the previous findings we also found a much higher hospitalization rate for B-NHL patients than in the matched control group. This effect was again detectable in all subgroups. Figure 4a depicts the frequency of hospitalizations in participants suffering from infections.

All patient subgroups had a higher rate of hospitalization compared to control group during the time of observation. Only patients with reported infections were included in this analysis.

Patients without reported immunodeficiency had the lowest incidence of infections which again, was much higher than for patients of the control group. As shown before patients with detectable immunodeficiency had the highest risk of infection irrespective of the classification as symptomatic or asymptomatic. Figure 4b depicts the mean duration of hospitalizations for all participants.

Mean hospitalization times displayed as days per month and participant. All analyzed lymphoma patient subgroups required significantly longer in-patient treatment in comparison to the control group. Hospitalization time is displayed as days per month. Participants who did not need hospitalization were considered with 0 days.

Discussion

In our prospective study we can show an increased infection rate of patients suffering from B-NHLs in comparison to an age and sex matched control group. Many studies, mostly conducted with Multiple Myeloma and CLL patients, have already reported this increased risk of infection (2, 8). Several mechanisms are responsible for this increased susceptibility to infection in lymphomas. One of the main reasons is a frequently observed decreased level of immunoglobulins which can be caused by the

disease itself with suppression of immune cell development as well as reduced antibody production (3, 5). In addition the administered anti-tumor therapy also frequently leads to depletion or prolonged suppression of hematopoiesis with various degrees of lymphopenia and neutropenia (5). In this context the development and use of CD20 antibodies play an important role as these state of the art therapies in B-NHL treatment efficiently deplete antibody producing CD20-positive B-cells (12, 13).

In our study we analyzed a representative large patient cohort with indolent B-NHL in comparison to an age and sex matched control group. In order to estimate the risk of comorbidities we calculated the age adjusted Charlson Comorbidity Index which showed an overall low value.

In our study patients were assessed based on their measurable immunoglobulin levels in which patients with IgG levels below 6 g/l or with IgG subclass deficiency were categorized as immunodeficient. Immunodeficient patients were further categorized in symptomatic, if they had suffered from two infections that required antibiotic treatment in the previous year. The remaining immunodeficient patients were categorized as asymptomatic. Interestingly, although categorized as asymptomatic, patients with decreased levels of IgG had an increased infection rate during the time of observation which was comparable to infection rates of patients that received regular IgG infusions for their symptomatic immunodeficiency.

Overall, patients with B-NHL suffered from more infections compared to the control group. As expected for B-NHL patients, those with immunodeficiency had an even higher risk of infection. Interestingly, patients with symptomatic immunodeficiency had comparable numbers of infections to patients with asymptomatic immunodeficiency. The most plausible explanation for this observation is that regular IgG infusions have a strong infection preventing effect suggesting that otherwise the rate of infection for this subgroup would be much higher. However, even regular IgG infusions cannot lower the risk of infection to the level of the control group which underlines the fact, that pathophysiological effects other than decreased immunoglobulin levels cause the observed clinical significant immunodeficiency.

Our data demonstrate that although scored asymptomatic, patients with measurable immunodeficiency do have an increased risk of infections. This also shows that the clinical assessment which decides about the treatment with regular immunoglobulin infusions does miss patients that are at increased risk of infections. These patients can be easily identified by routine laboratory parameters like the measurement of IgG levels. With this simple analysis it would be possible to identify all patients with increased risk of infection. It also raises the question if patients with immunodeficiency should be generally treated with regular immunoglobulin infusions, independent from the clinical assessment. Our data support this but there are still data missing and important points to consider. Over the last years the outcome of lymphoma patients has improved significantly by the development of new anti-tumor drugs. As a result patients live longer and more patients develop immunodeficiencies that require treatment. Regular immunoglobulin replacement is an expensive therapy regimen with considerably long infusion times that requires specialized outpatient clinics with well trained medical staff. Although in recent years subcutaneous immunoglobulin infusions are more and more used, the therapy regimens remain

expensive which is an important argument to restrict this therapy to symptomatic patients. However, the more widespread use of regular immunoglobulin infusions may reduce the overall infection rate of lymphoma patients which may lead to less antibiotic treatment and especially less hospitalization which would thereby prevent expensive therapies.

The main bias of our study is that it relies on patient self-assessments to analyze the number and treatment of infections. However, since we wanted to capture all infections, patients' assessments is the only possible data source.

So far the existing data are not sufficient to make a general recommendation to treat all indolent B-NHL patients with regular immunoglobulin infusions. It is therefore necessary to conduct larger prospective trials that should also analyze the effects on survival.

Conclusion

In conclusion we propose regular immune monitoring of all indolent lymphoma patients including the measurement of immunoglobulin levels, IgG subclasses and regular appointments for clinical assessment. With this approach patients at increased risk of infection can be identified early and lined up for prophylactic treatment.

Abbreviations

aaCCI

Age-adapted Charlson comorbidity index

ANOVA

Analyses of variance

B-NHL

B-cell non-Hodgkin lymphomas

BiTE

Bispecific T-cell engager

CG

Control group

CHMP

Committee for Medicinal Products for Human Use

OS

Overall survival

PFS

Progression-free survival

SPSS

Statistical Package for the Social Sciences

Declarations

Ethics and consent to participate

This study was approved by the ethics committee of Rhineland-Palatinate, Germany.

Written informed consent was obtained from all patients. All procedures performed in this study were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

All authors declare no competing interests.

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Authors' contributions

All authors read and approved the final manuscript. Conception and design: RW. Development of methodology: RW, SF. Acquisition of data: GC, JH, JT, CvR, RW. Analysis and interpretation of data: CL, RW, SF. Writing, review, and/or revision of manuscript: CL, RW, SF. Administrative, technical, or material support: SF.

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Figures

Figure 1

Age adjusted Charlson Comorbidity Index - aaCCI at the beginning of the observation.

Figure 2

a: Mean infection numbers during the course of 4 weeks.

b: Mean infection numbers during the course of 4 weeks.

Figure 3

a: Frequency of antibiotic treatment.

b: Time of antibiotic treatment.

Figure 4

a: Frequency of hospitalizations.

b: Time of hospitalization.