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Preexisting conditions in pediatric ALL patients: Spectrum, frequency and clinical impact

P. Schütte [a, *], A. Möricke [b], M. Zimmermann [a], K. Bleckmann [b], B. Reismüller [c], A. Attarbaschi [c], G. Mann [c], N. Bodmer [d], F. Niggli [d], M. Schrappe [b], M. Stanulla [a], C.P. Kratz [a]

[a] Department of Pediatric Hematology and Oncology, Hanover Medical School, Germany
[b] Department of Pediatrics, ALL BFM trial center, University Medical Center Schleswig-Holstein, Campus Kiel, Germany
[c] Department of Pediatric Hematology and Oncology, St. Anna Children's Hospital, Medical University of Vienna, Austria
[d] Department of Oncology, University Children's Hospital, Zurich, Switzerland

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ABSTRACT

Introduction: The etiology of acute lymphoblastic leukemia remains undisclosed in the majority of cases. A number of rare syndromic conditions are known to predispose to different forms of childhood cancer including ALL.
The present study characterized the spectrum and clinical impact of preexisting diseases in a cohort of ALL patients from Germany, Austria and Switzerland with a focus on genetic diseases predisposing to cancer development.
Methods: Retrospective database and study chart review included all patients from Germany, Austria and Switzerland (n = 4939) enrolled into multicenter clinical trial AIEOP-BFM ALL 2000 between July 1999 and June 2009. Patients enrolled into study AIEOP-BFM ALL 2009 – which was initiated subsequent to AIEP-BFM ALL 2000 – who were reported with a cancer prone syndrome or chromosomal abnormality were additionally included in this study to increase conclusiveness of observations.
Results: A total of 233 patients with at least one reported condition could be identified. The following conditions were reported in more than one patient: Gilbert's disease (n = 13), neurofibromatosis type I (n = 8), ataxia telangiectasia (n = 8), thalassemia (n = 7), Nijmegen Breakage syndrome (n = 6), cystic fibrosis (n = 4), glucose-6-phosphate dehydrogenase deficiency (n = 4), Noonan syndrome (n = 2), Klinefelter syndrome (n = 2), alpha-1-antitrypsin deficiency (n = 2), primary ciliary dyskinesia (n = 2). Especially those syndromes with a known cancer predisposition (NF type I, Ataxia telangiectasia, Nijmegen Breakage syndrome etc.) were associated with certain general and ALL-related characteristics, high therapy-related toxicity and reduced survival.
Conclusion: The spectrum of underlying diseases within ALL patients is dispersed. A small number of ALL patients are reported with cancer predisposition syndromes at initial diagnosis which are associated with high rates of therapy-related toxicity and a markedly reduced chance of survival. The true prevalence of these conditions within the ALL population remains unknown due to inapparent clinical presentation. A targeted clinical and/or genetic examination for certain diagnoses like NF type I, Ataxia telangiectasia or Nijmegen Breakage syndrome could identify patients who benefit from adjustment of antileukemic therapy or intensification of supportive care.

1. Introduction

The etiology of acute lymphoblastic leukemia (ALL) in children and adolescents remains largely unknown in most individual cases. Of interest, recent findings have identified common germline genetic variants that confer susceptibility to develop ALL (Walsh et al., 2014; Shah et al., 2013; Noetzli et al., 2015). Besides these common variants being implicated in the pathogenesis of ALL, a number of rare syndromic conditions have been described to predispose to

* Corresponding author.
E-mail address: schuette.peter@mh-hannover.de (P. Schütte).

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different forms of childhood cancer including ALL (Seif, 2011; Stieglitz and Loh, 2013).

To improve our understanding of the extent of rare syndromic conditions in pediatric ALL, the present study characterized the spectrum and clinical impact of preexisting diseases in a cohort of ALL patients from Germany, Austria and Switzerland. Particular attention was given to hereditary genetic constellations, especially cancer predisposition syndromes.

2. Methods

2.1. Patients and data analysis

Retrospective database and study chart review included all patients from Germany, Austria and Switzerland (n = 4939) enrolled into multicenter clinical trial AIEOP-BFM ALL 2000 between July 1999 and June 2009.

Database and study chart data were surveyed for patients who were reported with preexisting conditions at the time of ALL diagnosis. Confirmation of chart information was obtained by reviewing the respective study files for precise medical reports and/or results of molecular genetic testing.

Patients with Down's syndrome and ALL form an independent entity and were, therefore, excluded from this study (n = 125).

All patients treated for childhood ALL according to the ALL BFM 2000 protocol who were not reported with a preexisting disease served as control population for comparison purposes (n = 4594).

Patients enrolled into study AIEOP-BFM ALL 2009 – which was initiated subsequent to AIEP-BFM ALL 2000 – who were reported with a cancer prone syndrome or chromosomal abnormality were additionally included in this study to increase conclusiveness of observations.

For details of patient selection see supplementary figure S1.

Available information was analyzed for general features and leukemia-specific characteristics.

These included sex, age, immunophenotype, initial white blood cell (WBC) count, central nervous system (CNS) involvement and somatic genetic aberrations.

The individual course of therapy was evaluated using information on response to the prednisone prephase, achievement of complete remission (CR), risk stratification according to AIEOP-BFM ALL 2000 standards (standard risk – SR, medium risk – MR, high risk – HR), dose reductions, need for stem cell transplantation (SCT), development of serious adverse events (SAE), development of secondary malignant neoplasms (SMN), event free survival (EFS) and overall survival (OS).

To define frequencies of underlying conditions within the general ALL population cases from AIEOP-BFM ALL 2009 had to be excluded since the control population comprised patients from the AIEOP-BFM ALL 2000 cohort only.

Data management and analysis were carried out with IBM SPSS Statistics 22 software.

Due to limited patient numbers associations between diagnoses and documented features could not be tested for statistical significance. Thus, results of the present analysis are descriptive only.

3. Results

3.1. Spectrum and frequency of preexisting conditions

Our survey of data sources identified 220 of 4939 patients (4.45%) from AIEOP-BFM ALL 2000 who were reported with a preexisting condition to the trial study center.

In addition 13 patients from trial AIEOP-BFM ALL 2009 were included in this study who were reported with cancer predisposition syndromes or constitutional chromosomal aberrations between July 2009 and March 2014.

Nine patients were reported with two different conditions, thus, leading to a total of 242 independent diagnoses in a total of 233 patients.

As expected the spectrum of different conditions was rather dispersed (see Table 1). However, diagnoses could be divided into the following groups:

- Cancer predisposition syndromes (n = 29)
- Genetic diseases with no known predisposition to the development of cancer (n = 44)
- Autosomal and allosomal aberrations (n = 12)
- Unspecified/unidentified syndromic conditions (n = 19)
- Organ malformations (n = 64)
- Malignancies – not in the context of a known cancer prone syndrome (n = 3)
- Conditions of no monogenetic or known multifactorial etiology (n = 55)
- Acquired/temporary or questionable conditions (n = 16)

3.2. Cancer predisposition syndromes

There were 29 patients reported with genetic conditions that predispose to the development of different types of cancer during childhood and adolescence.

These conditions included neurofibromatosis type 1 (NF1, n = 8), ataxia telangiectasia (AT, n = 8), Nijmegen Breakage Syndrome (NBS, n = 6), Noonan syndrome (n = 2), LEOPARD syndrome, Lynch syndrome, Rothmund Thomson syndrome, Fanconi anemia, and Li Fraumeni syndrome (one case each).

The frequencies of NF1, AT and NBS within the AIEOP-BFM ALL 2000 patient cohort were 0.12%, 0.14 and 0.08 respectively. In the general population these conditions are detected at much lower rates (Lammert et al., 2005; Swift, 1985; Chrzanowska et al., 2012) supporting the predisposing effect of NF1, AT and NBS on the development of childhood ALL which has been described previously for all three conditions (Stiller et al., 1994, Taylor et al., 1996, Gładkowska-Dura et al., 2008).

General features and characteristics of ALL patients diagnosed with NF1, AT or NBS in comparison to the AIEOP-BFM ALL 2000 control cohort are shown in Table 2.

NF1 was reported in eight patients resulting in a frequency of about 0.12% of AIEOP-BFM ALL 2000 patients. NF1 patients were mostly male (6/8). Distribution of age at diagnosis, immunophenotype, WBC count at diagnosis, prednisone response, achievement of CR, risk stratification or specific genetic aberrations did not differ greatly from control patients. EFS was only 50% (median follow up 5.8 years) although this was partly due to one NF1 patient developing astrocytoma as an SMN after treatment for ALL. There were no fatal SAE during first-line treatment. Three patients suffered a relapse, two of which died (see Table 3).

AT was reported in eight patients with a frequency of 0.14%. There was a marked male preponderance (6/8, 75.0%). AT was associated with the development of precursor T cell-rather than precursor B cell ALL (6/8, 75.0%) which is consistent with previous findings (Ziino et al., 2006, Bienemann et al., 2011).

Accordingly initial WBC count at diagnosis was higher than in control patients (median 18,550/µl vs. 11,400/µl). Treatment response was largely favorable with only one patient stratified into the high-risk group. However EFS was only 37.5% and OS 25% (median follow up 3.5 years).

This was due to six out of eight AT patients developing at least one SAE during or following first-line ALL therapy (see Table 4). In