Non-Hodgkin’s lymphoma in pediatric patients with chromosomal breakage syndromes (AT and NBS): Experience from the BFM trials

K. Seidemann, G. Henze, J. D. Beck, A. Sauerbrey, J. Kühler, G. Mann & A. Reiter
University children’s hospitals of Hannover, Berlin, Erlangen, Jena, Warzburg, Germany; St. Anna children’s hospital, Vienna, Austria

Summary

Background: Lymphoma and leukemia are the commonest malignant diseases in patients with chromosomal breakage syndromes and immunodeficiency (Ataxia teleangiectasia (AT) and Nijmegen breakage syndrome (NBS)). With improved management of infections, malignant disease is more frequently diagnosed and has become one of the commonest causes of death in pediatric AT and NBS.

Patients and methods: In three consecutive multicenter therapy trials for pediatric non-Hodgkin’s lymphoma (NHL) (NHL-BFM), 1569 patients with newly diagnosed NHL have been registered between 1986 and 1997. Nine patients with AT (n = 5) and NBS (n = 4) were identified and analysed.

Results: Median age of patients with AT and NBS at diagnosis of NHL was nine years. NHL-entities differed from non-AT/NBS-patients: diffuse large B-cell lymphomas, n = 7 (78%); ALCL, n = 1; lymphoblastic T-cell lymphoma, n = 1. Cervical nodes, paranasal sinuses and epipharynx were the sites most frequently involved. Stages were: I and II in three patients, III in five and IV in one patient. All patients received polychemotherapy according to tumor-entity and stage, none received radiation. Dose reductions according to individual tolerance concerned mainly ethotrexate, alkylating agents and epipodophyllotoxines. One patient died of toxic complications, two patients relapsed and died, one patient suffered from second malignancy. Five of nine patients are in I. CCR after a median follow-up of five years.

Conclusions: Patients with AT and NBS suffer from rare entities of pediatric NHL. Curative treatment is possible and should be attempted. Intensity of therapy should be adjusted to individual risk factors and tolerance. Alkylating agents, epipodophyllotoxines should be omitted, dose of MTX should be limited to 1 g/m². Further cooperative trials using standardized approaches are required.

Key words: AT, ataxia teleangiectasia, Nijmegen-Breakage Syndrome (NBS), non-Hodgkin's lymphoma (NHL)

Introduction

Ataxia teleangiectasia (AT) and Nijmegen-breakage syndrome (NBS) are autosomal recessive disorders that are characterized by defective DNA-repair and chromosomal instability [1–4]. Although both syndromes share these characteristics, they vary considerably in other clinical hallmarks: whereas patients with NBS are characterized by small stature, often severe microcephaly, bird-like facial appearance and progressive decrease of intellectual function of variable degree, patients with AT show normal intellectual development but suffer from progressive ataxia, teleangiectasias and elevated levels of alpha-fetoprotein [1, 3, 5, 6]. However, in both, AT and NBS, immune function is disturbed with combined primary immunodeficiency involving T- and B-cell function. Patients with AT and NBS suffer from frequent infections, mostly involving the paranasal sinuses and the lower respiratory tract. Infectious complications are still the commonest cause of death in patients with AT and NBS [1–4]. The genetic defect in both syndromes affects proteins (ATM on chromosome 11q22-23 [7] and Nibrin on chromosome 8q21 [8]) that are involved in cell cycle regulation, p53-induced apoptosis and cell cycle arrest in case of DNA-damage [9, 10]. As a consequence, defective expression of these cell cycle regulators leads to radio-resistant DNA-synthesis, increased chromosomal instability and multiple chromosomal aberrations frequently involving lymphocytes and genes of the immunoglobuline superfamily; many of these aberrations are potentially clonogenic [9, 11–13]. These genetic characteristics explain the extraordinary predisposition of AT- and NBS-patients for malignant disease, especially malignant lymphomas and leukemias [14–16]. In several large studies the relative risk of patients with AT and NBS to suffer from malignant disease has been estimated as high as 61, for lymphoid malignancies even 252 [15, 17–20].

So far, little is known about therapeutic options and prognosis in patients with AT and NBS treated for NHL. Since both syndromes are rare (prevalence approximately 1:200,000 [21]), single centers will not be able to gain sufficient experience in the management of patients with AT or NBS and non-Hodgkin's lymphoma (NHL). However, multicenter therapy trials such as trial NHL-BFM for the treatment of pediatric NHL offer the unique opportunity to gather clinical experience in larger series of patients. The presented study analyzes clinical charac-
teristics, therapeutic aspects, response to therapy, and outcome in patients with AT or NBS uniformly treated for NHL.

Patients and methods

From April 1986 to October 1997, 1569 patients up to 18 years of age with newly diagnosed NHL or B-ALL were registered in the NHL-BFM study center. Among these 1569 patients, 9 patients were suffering from AT or NBS. These patients were analyzed regarding clinico-pathological features, treatment modalities and outcome. Informed consent for collection and evaluation of clinical data was given by all patients’ parents prior to admission to the BFM-trials.

Diagnosis

Diagnosis of NHL was based on cytological, histological and immunological/cytogenetic examination of tumor, bone marrow aspirates and/or cytospin-preparations from malignant effusions. Histological classification was performed according to the Updated Kiel Classification [22] and the Revised European–American Lymphoma Classification (R.E.A.L.) for non-Hodgkin’s lymphomas [23], cytological classification according to the French–American–British (FAB) Classification [24]. Immunological classification of lymphoma cells was performed using immunohistochemistry on conventional paraffin sections and/or immunophenotyping of cell suspensions from bone marrow, malignant effusions or fresh tissue as described previously [25].

Staging

Staging followed the criteria of the St. Jude staging system [26] and was performed according to findings on physical examination, peripheral blood- and bone marrow-smears, CSF-analysis, ultrasonography, and other imaging techniques such as MRI.

Therapy and response criteria

Patients suffering from lymphoblastic T-cell lymphoma received ALL-type therapy consisting of induction, consolidation, re-induction, and maintenance therapy as previously described [25]. Patients with B-cell lymphoma or anaplastic large-cell lymphoma of either immunophenotype received four to six courses of polychemotherapy as described elsewhere [25].

Intensity and duration of therapy was stratified according to stage at diagnosis and to initial tumor mass, determined by serum-concentration of lactate dehydrogenase (LDH). In patients with AT or NBS, the study-center recommended to start therapy with reduced intensity, depending on the physical state of the patient, history of previous infections and other ID-related complications (Figure 1). Therapy was intensified during following courses according to tolerance of the first course.

Response to therapy was evaluated at the beginning of each therapy course using the same investigations as used for initial staging, including imaging and clinicopathological studies. Events were defined as initial tumor failure, relapse, death of any cause on treatment and thereafter, and second malignancy.

Evaluation of clinical data

Participating hospitals submitted material and results of imaging studies, relevant for diagnosis and evaluation of therapy response, to the study-center for further analysis. Events and therapy complications were communicated to the study center through standardized follow-up questionnaires, informal letters and submission of essential parts of the patients’ charts. Administered chemotherapy and therapy-related toxicity were documented on standardized charts and submitted to the study-center.

Results

Patient characteristics

Of nine patients with chromosomal breakage syndromes and NHL, five patients were suffering from AT and four from NBS. Four were male and five were female. Median age at diagnosis of NHL was nine years in patients with AT and NBS and did not differ from other pediatric patients with NHL (median 9.3 years). However, the youngest patient was only 0.5 years at diagnosis of NHL, and AT was diagnosed after diagnosis of NHL. Unusually young age and severe therapy-related toxicity lead to further evaluation of immunodeficiency in this patient. In all other patients, underlying primary immunodeficiency had been diagnosed at least one year prior to the diagnosis of NHL. In two patients, however, NBS as cause of underlying immunodeficiency was only diagnosed during thorough immunological evaluation after diagnosis of NHL.
or soft tissues of the neck (lymph nodes, tonsils, hypopharynx) were involved. Other involved sites were mediastinal large B-cell lymphoma with sclerosis.

T-lymphoblastic lymphoma. Six of eight mature B-cell lymphomas were diffuse large B-cell lymphomas, one was a mediastinal large B-cell lymphoma with sclerosis and one an anaplastic large-cell lymphoma of B-lineage.

In eight of nine patients with AT or NBS, the tumor was of mature B-cell origin; only one patient suffered from T-lymphoblastic lymphoma. Six of eight mature B-cell lymphomas were diffuse large B-cell lymphomas, one was a mediastinal large B-cell lymphoma with sclerosis and one an anaplastic large-cell lymphoma of B-lineage (Table 1).

Three patients were diagnosed as stage I or II, five patients were stage III and one stage IV (bone-marrow infiltration). Serum-LDH was below 500 U/l in eight of nine patients; only the patients with stage IV disease had high serum-LDH levels (1600 U/l).

In eight of nine patients, the paranasal sinuses and/or soft tissues of the neck (lymph nodes, tonsils, hypopharynx) were involved. Other involved sites were mediastinum (n = 3), spleen (n = 2), lung (n = 1), and bone (n = 1).

Disease characteristics

In eight of nine patients with AT or NBS, the tumor was of mature B-cell origin; only one patient suffered from T-lymphoblastic lymphoma. Six of eight mature B-cell lymphomas were diffuse large B-cell lymphomas, one was a mediastinal large B-cell lymphoma with sclerosis and one an anaplastic large-cell lymphoma of B-lineage (Table 1).

In eight of nine patients, the paranasal sinuses and/or soft tissues of the neck (lymph nodes, tonsils, hypopharynx) were involved. Other involved sites were mediastinum (n = 3), spleen (n = 2), lung (n = 1), and bone (n = 1).

Therapy, toxicity and outcome

All patients received essential parts of BFM-type chemotherapy. Dose reductions mainly concerned the following cytostatic agents (see also Figure 1): MTX was reduced to 50%–20% (i.e., 1 g/m² instead of 5 g/m²), alkylating drugs and epipodophyllotoxines (ifosfamide and VP16) were omitted or reduced to 50%–20%. Radiotherapy was not part of the protocol therapy and was not administered to any patients with AT or NBS.

The individually administered therapy and modifications made are given in Table 1. In four patients, dosages of chemotherapeutic agents were reduced in all courses (less than 50% dose reduction in two patients, more than 50% dose reduction in the other two patients). In one of these patients (non-B therapy), therapy had to be stopped completely due to severe toxicity. Four patients received therapy with reduced dosages in only part of the courses and received full-dose therapy during the second half of chemotherapy. Only one patient received full-dose therapy from the beginning of therapy; this patient died of sepsis after the first course.

Following the regimen of increasing dosages acór...
Table 2  Therapy related toxicity in patients with AT and NBS.

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Patients (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None (i.e., no delay, no complication)</td>
<td>3</td>
</tr>
<tr>
<td>Septic episodes after &lt; 50% of courses</td>
<td>2</td>
</tr>
<tr>
<td>Septic episodes after &gt; 50% of courses</td>
<td>3</td>
</tr>
<tr>
<td>Toxic death</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 3  Events in patients with AT and NBS, status after median follow-up of five years (range 1–10 years)

<table>
<thead>
<tr>
<th>Event/status</th>
<th>Patients (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapy-related death</td>
<td>1</td>
</tr>
<tr>
<td>Relapse/progress</td>
<td>2</td>
</tr>
<tr>
<td>Second malignancy</td>
<td>1</td>
</tr>
<tr>
<td>First CCR</td>
<td>5</td>
</tr>
</tbody>
</table>

ing to individual tolerance during the course of therapy, three patients did not suffer from severe complications and did not experience delay in therapy. Two patients suffered from septic episodes in less, three patients in more than 50% of therapy courses.

Despite these reductions in dosage of crucial drugs, five of nine patients are in first complete remission after a median observation time of five years (range 1–10 years). One patient died of therapy related toxicity (sepsis, see above); one patient relapsed and died; one patient suffered from progress during chemotherapy and died; one patient (T-lymphoblastic NHL and non-B therapy) suffered from second malignancy (low-grade T-NHL) shortly after initial chemotherapy and died.

Conclusions

Of 1569 pediatric patients with newly diagnosed NHL, 0.06% of patients were suffering from AT or NBS. However, the prevalence of AT and NBS among pediatric patients with NHL might be higher, because patients with chromosomal breakage syndromes may not be considered eligible for therapy and are therefore not registered in therapy trials. On the other hand, diagnosis of NHL might precede diagnosis of chromosomal breakage syndrome and may be present even before any other clinical evidence of disturbed immune function. This may especially occur in patients with AT, in whom the characteristic symptom – ataxia – does usually not become apparent before the age of three to six years [1, 2]. It is thus crucial to suspect underlying immunodeficiency or chromosomal breakage syndrome in all patients who present with NHL at unusually young age or who suffer from unusually severe toxicity during chemotherapy.

Previous studies analyzing the association of malignant disease and NHL concentrated on epidemiologic data, showing the high incidence of lymphoid malignancies in patients with AT and NBS [14–17]. However, due to the rarity of the disease, data on therapy and optimal clinical management of these patients are still lacking. With increasing survival rates and improved management of infectious complications in patients with AT and NBS, diagnosis and management of malignant disease in these patients will be a matter of increasing interest in the future challenging different medical specialties involved in the care of patients with AT and NBS. Experiences from trials NHL-BFM show that treatment for NHL in the presence of chromosomal breakage syndromes is possible and should be attempted whenever possible and favoured by patients and families. Data from the BFM-trials show that five of nine patients are alive after a median observation time of five years – previous studies report of survival rates of only 35% or less [14, 17].

The most critical aspect in the chemotherapy of NHL in AT or NBS is certainly the risk of toxic complications. The approach used in trial NHL-BFM 90 – consisting of at least 50% dose reduction during the first one to two courses of chemotherapy and then increasing dosages according to individual tolerance – was shown to be effective in limiting toxic complications. Only one patient died of therapy-related toxicity, and this was the only patient in whom dosages were not reduced.

Interestingly, most patients reached remission and remained in CCR despite significant reduction of therapy intensity. This observation raises the question whether malignancies in patients with AT and NBS are more chemosensitive and require less intensive therapy. This question is of special interest, since patients with AT and NBS may be at risk to develop second malignancies after chemotherapy. Any therapy for malignant disease in AT and NBS should therefore aim at limiting possible toxic long-term effects. Alternative treatment strategies, such as treatment with monoclonal antibodies in selected patients may further limit toxicity of therapy in patients with AT and NBS.

As long as standardized alternative therapy strategies are lacking for patients with chromosomal breakage syndromes and NHL, experiences from the BFM-trials may lead to the following recommendations: Therapy should be started with reduced dosages; dose intensity should be increased according to individual tolerance and toxicity. Dose of MTX (danger of severe orointestinal mucositis as source of systemic infection) should be limited to 1 g/m²; alkylating drugs should be omitted or used with special caution (risk of second malignancies). Meticulous supportive care, including prophylactic antibiotic treatment and/or substitution of immunoglobulins, should be part of any chemotherapy in patients with chromosomal breakage syndromes.

Acknowledgements

The authors would like to thank all investigators and staff involved for their continuous cooperation with the
BFM-study center. Our special thanks go to E. Odenwald and E. Yakisan for their expert work in cytomorphology, and to Ulrike Meyer for excellent data management.

Therapy trials NHL-BFM were generously supported by the 'Deutsche Krebshilfe'.

References


