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Original Research Article

Clinical features and treatment outcomes of peripheral T-cell lymphoma in children. A current data report from Polish Pediatric Leukemia/Lymphoma Study Group (PPLLSG)

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ABSTRACT

Purpose: Peripheral T-cell lymphomas (PTCL) are lymphoproliferative disorders derived from post-thymic cells, that occur extremely rarely in children. The optimal treatment of pediatric PTCL remains still unclear.

Patients and methods: Ten children with PTCL from 3 up to 18 years of age registered by the Polish Pediatric Leukemia/Lymphoma Study Group (PPLLSG) were retrospectively analyzed. All patients were treated with different regimens including protocols: for lymphoblastic lymphoma in 7 cases, for anaplastic large cell lymphoma in 1, CHOP in 1. Five of the 10 patients with PTCL were classified as stage II; 4 as stage III and 1 as stage IV due to extralymphatic organs (bone marrow) involvement. Four histological subtypes of PTCL were recognized: extranodal NK/T-cell lymphoma, nasal type (ENTNT), peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), subcutaneous panniculitis-like T-cell lymphoma (SPL), Sezary syndrome (SS). After first-line therapy 9 patients initially achieved complete remission, 4 relapsed, 5 died. One patient achieved remission spontaneously. Three children (1 with stage IV and 2 in relapse) underwent high-dose chemotherapy with allogeneic bone marrow stem cell transplantation and all of them are alive and in CR.

Results: The cumulative probability of 5-year overall survival (OS) for our whole group was 63.9% (95%CI: 35.2–88.2%) with a median follow-up time of 48.4 months (range 24–90+ months). The 5-year event free survival (EFS) was 81%. PTCLs are a heterogeneous and rare group of childhood NHLs.

Conclusions: According to our experience the standard chemotherapy for precursor lymphomas seems to be a beneficial treatment option for children with PTCL. Allogeneic stem cell transplantation may improve the outcome in selected patients.

1. Introduction

Peripheral T-cell lymphoma (PTCL) is an extremely rare lymphoproliferative disorder in children. According to the WHO classification of hematopoetic and lymphoid neoplasms this subset of lymphomas is heterogeneous and originates from mature, post-thymic T or NK cells [1], while most T-cell lymphomas in this age group stem from immature T-cells [2,3].

PTCLs that occur in adults, except for ALK-positive anaplastic large cell lymphomas (ALCLs), are usually highly aggressive with an unfavorable outcome [4,5]. The number of pediatric PTCL patients is too small for drawing definitive conclusions when it

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comes to treatment recommendations, but some authors have reported a much better response to chemotherapy in children in comparison to adults [6–8].

We report herein the retrospective analysis of ten patients with PTCL from the Polish Pediatric Leukemia/Lymphoma Study Group (PPLLSG) over a 25 year period excluding ALCL ALK+, characterized by different biological properties [9] and different clinical course. Blastic plasmacytoid dendritic cell neoplasm subtypes were excluded because of changes in classification in 2008.

2. Material and methods

2.1. Patients

We collected 10 patients with different types of PTCL, which constitutes 1.3% of 772 new cases of non-Hodgkin lymphomas registered by the PPLLSG from 1986 to 2013 (PPLLSG PTCL group). Every patient had documented histological and immunohistochemical diagnosis of PTCL. The clinical evaluation of the patients included: patient history, physical examination, CT scans, ultrasonography, bone marrow biopsy, blood cell count, and standard biochemical tests with serum lactate dehydrogenase measurement. The median age was 13 years (range from 3 to 18 years). The male to female ratio was 1:1. The clinical characteristics, treatment and outcome of the patients from the PPLLSG PTCL group are presented in Table 1. Four histological subtypes of PTCL were recognized: extranodal NK/T-cell lymphoma, nasal type (ENTNT), peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), subcutaneous panniculitis-like T-cell lymphoma (SPL), and Sezary syndrome (SS) (Table 3). The patients with ALCL were ruled out of this study. The clinical staging of the disease was performed according to the Murphy staging system [9].

The most common histological subtype of PTCL in our group was ENTNT – four patients. B-symptoms (fever >38 °C, drenching sweats and weight loss >10% of normal body weight over a period of 6 months) were observed in half of them. The majority of the patients (3/4) were diagnosed with localized disease (II stage). Clinical manifestation in this subtype included: cutaneous and subcutaneous lesions (three patients), lymphadenopathy (two patients), and lungs involvement (one patient). In this group of the patients different chemotherapy regiments were introduced (ALCL-like, CHOP with Bexarotene, and two for LBL), which resulted in unsuccessful descent: only one girl survived, she received 2 cycles of SMILE in the recurrence.

There were two patients diagnosed with SPL in our group. One of the patients presented with B-symptoms. Both of them had skin and subcutaneous lesions, one additionally peripheral lymphadenopathy, the second one extralymphatic organs involvement. They presented with either II or III stage of the disease. In the boy with neoplasm in the skin and lymph nodes in II stage spontaneous remission was observed. The girl who presented with skin and extralymphatic organs lesions (III stage) received treatment for lymphoblastic lymphoma and remains in CR1.

PTCL-NOS was diagnosed in three of our patients; most of them had B-symptoms and were diagnosed with III stage. All of the patients with PTCL-NOS had lymphadenopathy, none had skin or subcutaneous lesions, and one of them had spleen and liver lesions. They were all treated according to protocols for lymphoblastic lymphomas. The chemotherapy was successful in one patient (alive in CR1), the second one (with initial lymphadenopathy) developed recurrence in lymph nodes and is alive in CR2 (treated according to protocol ALL-REZ BFM 2002), the third one developed secondary neoplasm (acute myeloid leukemia) and died of its progression.

In our group there was one boy with Sezary syndrome in fourth stage (skin lesions, lymphadenopathy, and bone marrow involvement), without general symptoms. He remains in CR1 after chemotherapy for lymphoblastic lymphomas with immunotherapy (antiCD52).

Sometimes the symptoms were not characteristic, thus making the diagnosis difficult. This is demonstrated by two patients (#7, #9) with PTCL-NOS from the north of Poland initially presented with isolated fever, and it was not until 3–6 weeks later that other symptoms, such as lymph nodes enlargement, appeared. This disease history is typical for lymphoproliferations with cytotoxic lymphocytes T with large areas of necrosis and secondary haemaphagocytosis. This lymphoproliferative disease is based mainly on viral infections (Parvo, Epstein–Barr viruses) and is connected with rather poor prognosis [10–13]. These two patients, however, remain in complete remission. One boy developed relapse, underwent megachemotherapy with allo-BMT and remains disease-free for 90 months (#7). One girl remains in complete remission for 24 months (#9).

There is a known relationship between EBV infection and development of non-Hodgkin lymphoma. In six of all our patients the past infection of EBV virus (LMP1 and EBER antigen) was proven. In four of these six children the presence of EBV genome in neoplastic cells was detected.

2.2. Histology and immunochemistry

The diagnosis of lymphoma was based on histological and immunohistochemical examination of tumor tissue deriving from pathologic lymph nodes or extranodal sites, fixed in formalin, processed using routine techniques and embedded in paraffin. All cases were centrally verified according to the WHO classification.

2.3. Chemotherapy

Seven children received schedules known to be effective for lymphoblastic lymphoma (LBL) (BFM-86, BFM-90, EURO-LB-02/BFM-90 based schedule) [14]. One patient underwent BFM based protocol for ALCL (#1) [15] and another was treated according to CHOP (triweekly) (#2), which is used for mature B-cell lymphomas [16,17]. One child with SPL (#4) achieved complete remission spontaneously without treatment. The chemotherapy in the patient with Sezary syndrome (#8) was intensified by monoclonal antibody therapy with anti-CD52, and in patient with ENTNT (#2) with retinoids. High-dose chemotherapy with allogenic bone marrow stem cell transplantation (alloBMT) was used in advanced stages and relapses.

2.4. Outcome

Treatment outcomes were determined by overall survival (OS). Events were defined as death from any cause, tumor progression or relapse. Progression was considered to be an increase of tumor mass during treatment and before achieving a complete remission. Relapse was defined as a recurrence of resolved tumor proven by biopsy. Overall survival was measured from the date of diagnosis to the date of death from any cause or the last contact.

Ten children achieved CR. Four patients relapsed: 1 in bone marrow (#1), the second one in lymph nodes (#7), the third one in her lower lip, soft palate, tonsils and cervical lymph node on the left (#10), and the fourth boy developed relapse in primary site (#2). One of them survived after second line chemotherapy and alloBMT (#7). Five children died: one due to relapse in the bone marrow (#1), second one in progression of the original lesions (#2), third one with Down's syndrome due to disease progression and chemotherapy toxicity (#3), fourth child developed the fatal secondary malignancy (#6) (acute myeloid leukemia), which occurred 3.5 years after completing the PTCL treatment, and the fifth one died in an accident in CR (#4). Three patients received