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Successful treatment of relapsed/refractory anaplastic large cell lymphoma in adolescent patient: a case report

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Summary

The present case report demonstrates current opportunities for the treatment of relapsed/refractory anaplastic large cell lymphoma, ALK-positive (R-R ALCL) in children and adolescents. This type of lymphoma lends sufficient chance of cure even in R-R cases, due to effective targeted therapy and high efficiency of allogeneic hematopoetic stem cell transplantation, thus demonstrating curative potential in the patients with active disease prior to transplantation.

Keywords

Anaplastic large cell lymphoma, ALK+, relapsed/refractory, targeted therapy, hematopoetic stem cell transplantation.

Introduction

Lymphoma is the third most common cancer in children. Opposite to adult tumors, pediatric non-Hodgkin lymphomas (NHL) tend to proceed in aggressive manner [1]. Pediatricians usually face only distinct types of NHL, i.e., anaplastic large cell lymphoma, ALK+ (ALCL) which occurs in 10-12% of the cases, lymphoblastic lymphoma (LL), in 20-25%; diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (10-15%), and Burkitt lymphoma affecting 50-60% of the patients [2]. Other types of NHL are uncommon in children. In developed countries, the relapsed or refractory (R-R) NHL occur in 10-25%, being more common in low-income and middle-income countries [3]. The choice of intensive first-line therapy is one of the reasons for high level of chemoresistance in case of relapse [4]. Mistiming, unreasonable dose reduction and excessive surgical activity may also affect prognosis [5]. Targeted therapy and immunotherapy increase chance of cure in cases of R-R NHL. However, hematopoietic stem cell transplantation (HSCT) still remains a cornerstone in its treatment [6]. There is no doubt that autologous hematopoietic stem cell transplantation (auto-HSCT) is a gold standard for the remission consolidation in R-R NHL, except of LL and, probably, ALCL where allogeneic HSCT (allo-HSCT) is more effective. This fact reflects weak or absent graft-versus-tumor effect (GVT) in B-NHL, and presence of GVT in LL and ALCL. These data were supported in randomized clinical trials in adult cohorts [7, 8]. The randomized trials in children were not yet performed due to ethical reasons and limited number of patients. Anyway, effectiveness of HSCT was demonstrated in many non-randomized studies in children [9, 10]. In general, HSCT doesn't solve the problem of R-R NHL but it may increase chances for cure approximately to 40-50% in the entire group. At the same time, allo-HSCT is associated with increased overall survival (OS) rates to 83% and should be regarded as very effective approach in the first

ALCL relapse. Moreover, ALCL patients can be rescued with allo-HSCT even in progression observed pre-transplant, and in cases of relapse after auto-HSCT [11]. ALCL is a unique clinical entity that has a more favorable outcome in the cases with R-R course compared to other NHL subtypes. Presence of several effective targeted therapies (brentuximab vedotin, ALK-inhibitors) and high efficiency of allo-HSCT results in high rates of survival in children with R-R ALCL, ALK+.

Present case report demonstrates an adolescent patient with R-R ALCL successfully treated with several lines of chemo-immunotherapy and two HSCTs.

Case description

The patient is a 12-year-old girl from Donetsk. First symptoms of the disease consisted of abdominal pains and nausea since July 2018, later followed by fatigue, cough, dyspnea, and weight loss. Abdominal ultrasound demonstrated tumor in mesogastric region (140×60×47 mm). By computed tomography (CT), pleural effusion was revealed (right, 1140 mL; left, 360 mL). The tumor biopsy (August 17, 2018) showed initial morphology of leiomyosarcoma. First-line chemotherapy (2.10.18-1.11.18) consisted of I2VAd (ifosfamide 3000 mg/m^2 №2, doxorubicin 40 mg/m^2 №2 and vincristine 1.5 mg/m^2 №3), followed by I^{2}VA (ifosfamide 3000 mg/m^2 №2, vincristine 1.5 mg/m^2 №2, actinomycin D). Reduction of tumor volume was registered according to ultrasonography.

Later revision of histology and immunohistochemistry revealed ALCL, ALK+, and appropriate therapy was initiated according to NHL-BFM-like protocol (3 courses of A, and 3 courses of B, with 3 g/m^2 of methotrexate in each block) continued from November 2018 to April 2019. Complete remission was achieved at the end of treatment.

The ALCL, ALK+ was confirmed histologically, upon H&E staining (Fig. 1). Large polymorphic cells showed ovoid, polygonal and round pattern, with eosinophylic or translucent cytoplasm. Cell nuclei are irregular and ovoid, with lumpy chromatin. Apoptotic and mitotic activity were high. Immunohistochemistry demonstrated positive reaction with ALK (Fig. 2A), CD30 (Fig. 2B), GrB antibodies in intraplasmatic cytotoxic granules. Reactive microenvironment was presented by CD3+ lymphocytes. Ki-67 proliferation marker was seen in 50% of tumor cells.

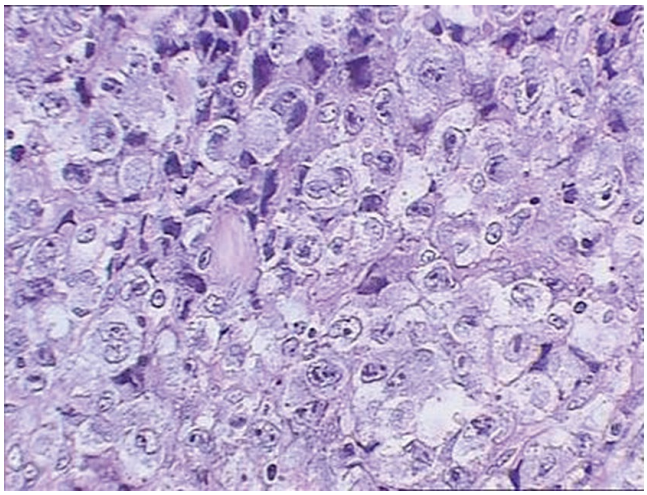
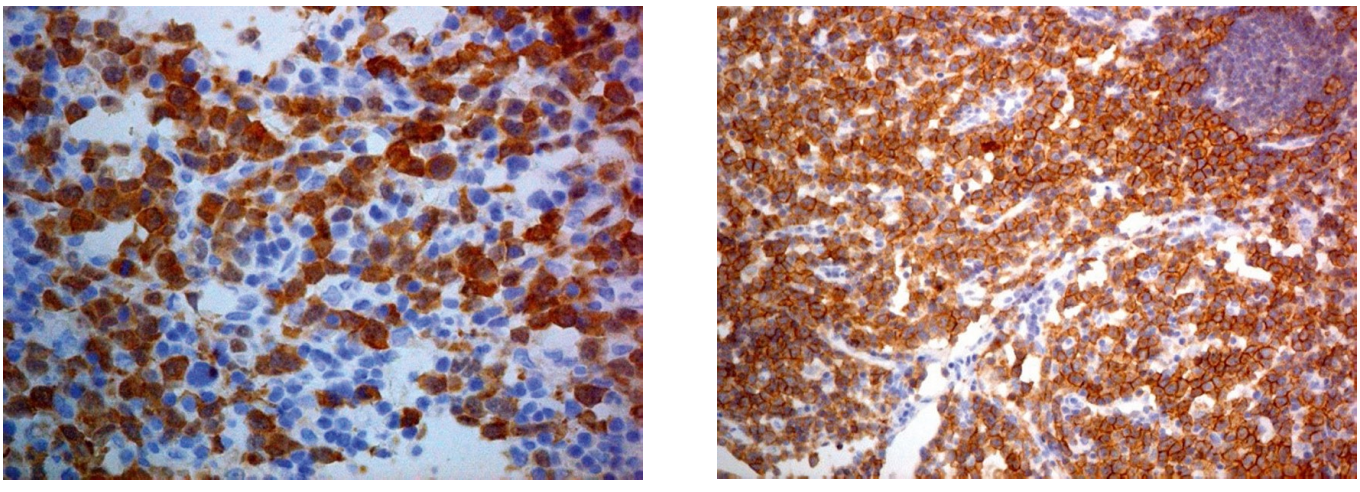


Figure 1. Anaplastic large cell lymphoma. Hematoxylin & eosin stain (x400)

On June 12, 2019 (two months after ending the therapy), the patient manifested with fatigue, pain in the right thigh, and fever. CT scans demonstrated a conglomerate of lymph nodes (8.5×5.2 cm) in the right iliac region with the involvement of *m.iliacus*. No tumor cells were found in bone marrow and cerebrospinal fluid. Serum lactatdehydrogenase level was 883.2 U/l. Clinical relapse was diagnosed after biopsy, and the patient was admitted to the N. N. Blokhin National Medical Research Center of Oncology (Moscow) for further treatment.

Second-line treatment consisted of vinblastine 6 mg/m^2 №2 and methotrexate 5000 g/m^2 №1 every 21-28 days (3 cycles, from 12.07.19 to 11.10.19). Partial response was diagnosed after second cycle, but progression occurred after third course, according to CT results (17.10.19), with enlarged lesion of iliac muscle up to 11×4.8×8.6 cm.



A **B**

Figure 2. Anaplastic large cell lymphoma. Immunohistochemical staining of tumor cells for ALK+ (A) and by CD30+ cells (B). The reaction product is brown

Third-line therapy consisted of brentuximab vedotin 1.8 mg/kg+ ICE №3 (05.11.19-28.01.2020): ifosfamide 1800 mg/m^2 №5, etoposide 100 mg/m^2 №5, carboplatin 400 mg/m^2 №1. Partial response was achieved according to PET-CT data (20.01.2020) (Fig. 3).

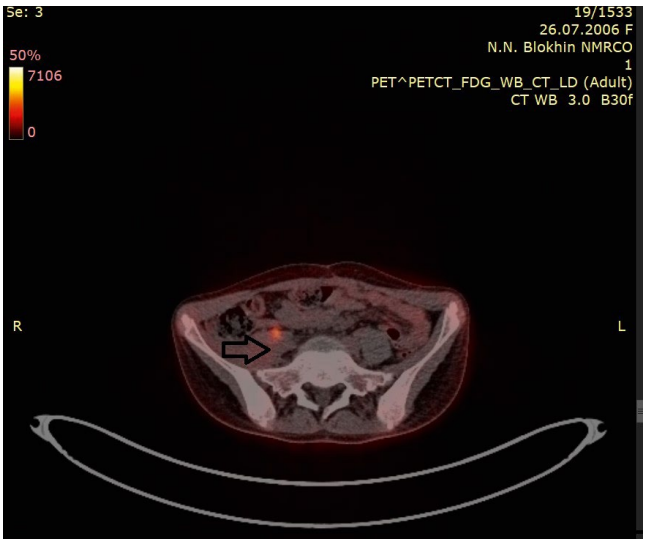


Figure 3. PET-CT scan after 3rd-line therapy in ALCL patient. Black arrow demonstrates diffuse thickening of right iliac muscle with local metabolic activity

On 26.03.2020, the patient underwent auto-HSCT in RM Gorbacheva Research Institute (St. Petersburg) with BeEAM conditioning regimen (bendamustine 160 mg/m^2 №2, cytarabine 400 mg/m^2 №4, etoposide 200 mg/m^2 №4, melphalan 140 mg/m^2 №1). A total of 3.2×10^6 CD34+ cells were reinfused. Prior to beginning the conditioning regimen, the patient progressed with right forearm involvement, confirmed by ALCL-positive cytology. Due to limited options for the remission reinduction and their presumably low efficiency, it was decided to proceed with auto-HSCT in the progression state. Posttransplant period was, generally, well tolerated, with febrile neutropenia and mucositis. Crizotinib 250 mg was initiated post-HSCT twice daily, in order to prevent progression. Three months after transplantation, the malignancy progression was registered with involvement of iliac muscle and right forearm. Glucocorticoid therapy was started to control the disease.

The 4th-line therapy at the N. N. Blokhin Research Center of Oncology consisted of VIGEPD №2 (gemcitabine 1000 mg/m^2 №3, vinorelbine 30 mg/m^2 №2, dacarbazine 375 mg/m^2, prednisolone 20 mg/m^2)+ brentuximab vedotin №2 and crizotinib (08.2020-09.2020). Infection complications and cytopenia were registered after the therapy. Partial remission was achieved, and patient was readmitted to RM Gorbacheva Research Institute for haploidentical HSCT (haplo-HSCT). On the 1st day of conditioning regimen, the patient experienced puffiness of the right forearm in the area of previous tumor location, and the disease progression could not be ruled out. Haplo-HSCT (26.10.2020) was performed from father, with conditioning by fludarabine (90 mg/m^2) and bendamustine (390 mg/m^2). Graft-versus-host disease (GVHD) prophylaxis consisted of posttransplant cyclophosphamide (100 mg/m^2), tacrolimus and sirolimus. Posttransplant period was complicated by steroid-refractory acute skin GVHD Stage 2 (Day+42) that responded to ruxolitinib (10 mg/day). Bacterial pneumonia was diagnosed on Day +73 followed by complete recovery after combined antibacterial therapy (meropenem+vancomycin). As seen from Fig. 4, no lymphoma signs are observed by PET-CT from February 2022. At the present moment (1.5 years after haplo-HSCT), the patient is clinically disease-free, without symptoms of GVHD and with excellent transplant function, due to full donor chimerism.

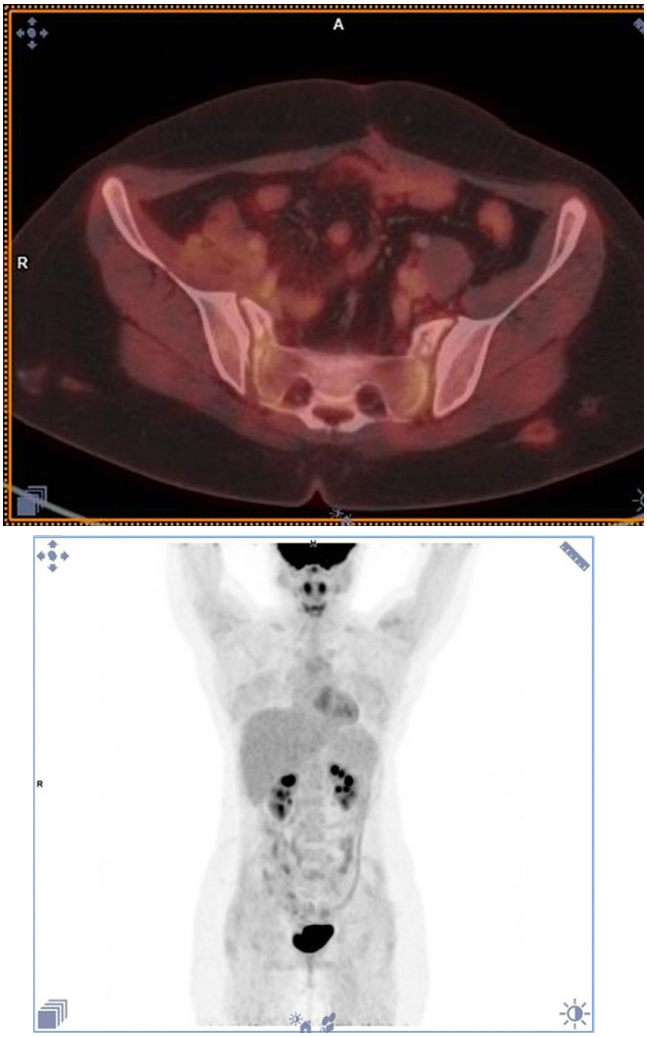


Figure 4. PET-CT scan after haplo-HSCT in ALCL patient

Discussion

The present case report demonstrates wide therapeutic options for the treatment of R-R ALCL, ALK+. Taken together, they result in high chance of curation, even in refractory patients following several relapses. The treatment resistance may be registered to any known therapeutic modes (chemotherapy, targeted therapy, immunotherapy, HSCT). The mechanisms of resistance are diverse, including tumor clonal evolution, presence of residual tumor stem cells, various intercellular and intracellular mechanisms (for example, PDL-1 expression levels, etc.) [12]. Nowadays, the majority of patients with ALK+ ALCL enter continuous remission after first-line therapy. There is higher incidence of relapsed

or refractory course of disease in cases of primary misdiagnosis and inadequate first-line therapy. Our patient received initial therapy according to the leiomyosarcoma protocol, thus being a probable factor of refractory course. After assessing correct diagnosis, the patient received therapy according to NHL-BFM-like protocol with complete response achieved. However, a relapse developed several months after finishing the protocol. Hence, the case could be regarded as early relapse or primary refractory state. Second-line therapy was based on high-dose methotrexate and vinblastine, the two highly effective drugs in this clinical setting. After initial response, the disease progressed and third-line therapy was started which consisted of ICE combined with brentuximab vedotin (BV). ICE is a classical regimen for R-R NHL, whereas BV is an established targeted drug for CD 30+ lymphomas [13]. In our case, this drug combination resulted in partial remission. Unfortunately, auto-HSCT was performed in progression, since the tumor appeared on right forearm several days prior to conditioning. Therefore, starting auto-HSCT in progression was a controversial decision. In general, the results of auto-HSCT in progression of ALCL are disappointing, and the transplant is not recommended in such cases [14]. We performed transplantation due to limited options for remission induction in heavily pretreated patient, relatively good somatic status and the intention-to-treat strategy. We used BeEAM, a conditioning regimen standard for lymphomas [15]. Toxicity of auto-HSCT is similar to high-dose chemotherapy, and usually manifests as mucositis, cytopenia and febrile neutropenia [16].

Posttransplant period in our patient proceeded typically, without unusual complications. In general, total body irradiation (TBI) is not indicated for lymphoma patients, due to its efficiency similar to the cytostatic drug-based conditioning regimens, and higher incidence of late side effects [17, 18]. According to CIBMTR data BEAM, TBI and BuCy (busulfan+cyclophosphamide) are equally effective in auto-HSCT as conditioning regimens for NHL therapy [19]. BEAM is a non-myeloablative conditioning as most patients recover hematopoiesis even without reinfusion of hematopoietic stem cells. Auto-HSCT shortens cytopenia and reduces complications [20].

Our patient progressed 3 months after auto-HSCT. Relapses and progression after auto-HSCT are common in the patients with R-R NHL, despite modern treatment options and are still a challenge in all but ALK+ ALCL [10,11,21]. Hopefully, one more remission could be achieved after ViGePD scheme combined with targeted therapy (BV+crizotinib). This protocol earlier demonstrated efficiency in pretreated R-R NHL [22]. The idea was to add gemcitabine which was not previously used in the therapy. The remission state was considered till the first day of conditioning for allo-HSCT, when clinical progression with the involvement of right forearm was suspected. Allogeneic HSCT was not cancelled. There are data supporting its effectiveness despite absence of remission in ALK+ ALCL. The patients who receive allo-HSCT after relapse post auto-HSCT, or in ALCL progression, may be cured. Thus, the progression state is not desirable but it is not a contraindication for HSCT [11, 23].

Non-myeloablative conditioning (fludarabine and bendamustine) was used prior to haplo-HSCT. This conditioning regimen demonstrated effectiveness, and low level of toxicity in lymphoma patients [24]. It is also the proven fact that GVT effect plays major role in this clinical setting [25]. We did not apply intensive regimen, due to chemoresistance and four chemotherapy lines in previous history of this patient. This strategy appeared effective and safe, despite evidence of clinical progression and heavy pretreatment. Moderate complications of early posttransplant period (acute GVHD and pneumonia) were manageable and time-limited. The patient still maintains the remission state being also free of significant GVHD for 1.5 years.

In conclusion, a wide range of therapeutic options could be offered to the patients with ALK+ ALCL, e.g., chemotherapy, targeted therapy, HSCT that make this clinical subgroup unique among other R-R NHLs, due to favorable prognosis even in case of failure at the first line of therapy.

Conflict of interests

No conflicts of interest reported.

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Клинический случай успешной терапии рецидивирующей/рефрактерной анапластической крупноклеточной лимфомы у подростка

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Резюме

Представленный клинический случай отражает современные возможности лечения ALK-позитивной рецидивирующей/рефрактерной (Р-Р) анапластической крупноклеточной лимфомы у детей и подростков. Для этого варианта лимфомы даже в случае Р-Р течения шанс на излечение остается относительно неплохим благодаря наличию эффективной таргетной терапии и высокой эффективности аллогенной трансплантации гемопоэтических стволовых клеток, которая может успешно применяться при данной патологии в том числе у пациентов вне ремиссии.

Ключевые слова

Анапластическая крупноклеточная лимфома, ALK+, рецидивирующее/рефрактерное течение, таргетная терапия, трансплантация гемопоэтических стволовых клеток.