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FROM INBORN ERRORS OF IMMUNITY TO LYMPHOMA – A HEMATOLOGIST'S POINT OF VIEW

OD URODJENIH GREŠAKA IMUNITETA DO LIMFOMA – PERSPEKTIVA HEMATOLOGA

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Summary
After infections, malignancies, lymphomas especially, are the second most frequent cause of death in patients with inborn errors of immunity. Factors predetermining the appearance and aggressiveness of lymphomas include gene defects, defects of immune surveillance and regulation as well as infections with oncogenic viruses. Aggressive non-Hodgkin lymphomas, mostly diffuse large B-cell and Bukit subtypes are predominant in deoxyribonucleic acid repair defects, while Hodgkin lymphoma becomes equally present in patients with defects of immune regulation. Marginal zone and mucosa-associated lymphoid tissue lymphomas, appear to be frequent in defects of antibody production, especially in patients with common variable immune deficiency. The prevalence of Epstein-Barr virus may vary within entities, but there is no entity without at least a few cases of lymphoma and Epstein-Barr virus co-infection. Standard treatment of lymphomas associated with deoxyribonucleic acid repair defects and severe combined deficiencies, is stem cell transplantation. Lymphomas in inborn errors of immunity with a less severe clinical presentation, should be treated with immunochemotherapy and monoclonal antibodies (Brentuximab, Rituximab) wherever feasible. There is no data about the usefulness of checkpoint inhibitors, bi-specific antibodies and T-cells with chimeric antigen receptor. Allogeneic stem cell transplantation represents a major indication for treatment of relapse/refractory lymphomas in any inborn error of immunity. Potential benefit of therapy with Chimeric antigen receptor Natural-killer cells in lymphomas associated with inborn errors of immunity, remains to be seen in future studies.
Key words: Immune System Diseases; Metabolism, Inborn Errors; Lymphoma; Hodgkin Disease; Lymphoma, Non-Hodgkin; Therapeutics

Sažetak
Posle infekcija, maligniteti a naročito limfomi su na drugom mestu kao uzroci smrti pacijenata sa urođenim poremećajima imuniteta. Faktori koji omogućavaju pojavu i agresivnost limfoma su gentski defekti, defekti imunološkog nadzora i regulacije, kao i infekcije onkogenim virusima. Agresivni, ne-Hodgčkinovi limfomi, pretežno difuzni krupnoćelijski B i Burkitov limfom, predominatni su u defektima reparacije dezoksiribonukleinske kiseline, dok je kod bolesnika sa defektom imunske regulacije, učestalost Hodgčkinovog limfoma podjednaka sa prethodnim podtipovima. Marginalno zonalni i limfoidno tkivo povezano sa sluzokožom postaju češći u defektima produkcije antitela, posebno u uobičajenoj varijabilnoj imunodeficijenciji. Prevalencija Epštajn-Barovog virusa varira, ali nema nijednog entiteta u kome bar neki od limfoma nije udružen sa ovom infekcijom. Standardna terapija limfoma udruženih sa defektima reparacije dezoksiribonukleinske kiseline i teškom kombinovanom imunodeficijencijom je transplantacija matične ćelije hematopoeze. Limfome nastale u okviru urođenih grešaka imuniteta sa blažom kliničkom slikom, treba lečiti imunohemoterapijom uz primenu monoklonskih antitela (*Rituksimab, Bretuximab vedotin*) kad god je to moguće. Nema podataka o efikasnosti inhibitora kontrolnih tačaka, bispecifičnih antitela i T-limfocita sa himernim antigenim receptorom kod ovih pacijenata. Alogena transplantacija matičnih ćelija hematopoeze je značajna idnikacija za lečenje relapsirajućih i/ili refraktornih formi limfoma nastalih u bilo kom entitetu sa deficitom imuniteta. Rezultati budućih studija će pokazati potencijalnu korist od terapije ćelijama prirodnim ubicama sa himernim antigenim receptorom.
Ključne reči: bolesti imunog sistema; metaboličke urođene greške; limfom; Hočkinova bolest; non-Hočkinov limfom; terapija

Introduction

There are over 430 acknowledged single gene lesions associated with numerous inborn errors of immunity (IEI), with various clinical presentations, prognosis and complications [1]. Development of malignancy is a common event in many of these entities, with hematological malignancies amounting to 85% of all cancers. Among them, two/thirds are non-Hodgkin lymphomas [2]. Tumorigenesis in IEI is a conse-

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Abbreviations

ADA	– Adenosine deaminase
AIDS	– Acquired Immune deficiency syndrome
ALPS	– Autoimmune lymphoproliferative syndrome
APDS	– Activated PI3 kinase-δ syndrome
APO1	– Apoptosis antigen 1
ATM	– Ataxia Telangiectasia Molecule
CAR-NK cells	– Chimeric Antigen Receptor Natural Killer Cells
CAR-T cells	– Chimeric Antigen Receptor T cells
CMV	– Cytomegalovirus
CTLA4	– Cytotoxic T-lymphocyte associated protein 4
CVID	– Common Variable Immunodeficiency
DLBCL	– Diffuse large B-cell lymphoma
DNA	– Deoxyribonucleic acid
DOCK8	– Dedicator of Cytokinesis 8
EBV	– Epstein Barr Virus
FAS	– apoptosis stimulating fragment
FL	– Follicular lymphoma
G-CSF	– Granulocyte Colony Stimulating Factor
GVHD	– Graft Versus Host Disease
HHV	– Human herpes virus
HLA	– Human Leukocyte Antigen
HSCT	– hematopoietic stem cell transplantation
ICOS	– Inducible T-cell Costimulator
IEI	– inborn errors of Immunity
ITK -IL-2	– Inducible T-cell kinase
IUIS	– International Union of Immunological Societies
NCCN	– National Comprehensive Cancer Network
NFκB1	– Nuclear Factor Kappa Light-chain Enhancer of Activated B cells
PD-1	– Programed cell Death protein 1
PET	– Positron Emission Tomography
PIK3CD	– Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta
PIK3R1	– Phosphoinositide-3-kinase regulatory subunit 1
TNFRSF6	– Tumor necrosis factor receptor superfamily member 6 (Known as FasR)

quence of the complex interplay of many factors. The type of gene defect, combined with defects of immune surveillance and regulation, may predetermine the aggressiveness of lymphoid malignancy. Infection with oncogenic viruses such as, Epstein Barr Virus (EBV), Human herpes virus (HHV) or Cytomegalovirus (CMV), additionally contribute to biology and clinical behavior of lymphomas in IEI setting.

In spite of considerable breakthroughs in understanding and diagnostics of IEI, there are still unsolved issues about management of lymphomas in this susceptible population. The aim of this review is to give a critical view on the characteristics of lymphomas according to type of defects in IEI, and to give an update on current and emerging treatment options.

Characteristics of lymphomas according to IEI entity

The systematic review of Riaz and colleagues has elegantly shown a strong association between IEI entities and subtypes of lymphomas. In deoxyribonucleic acid (DNA) repair defects, the majority of lymphomas were aggressive and originated from

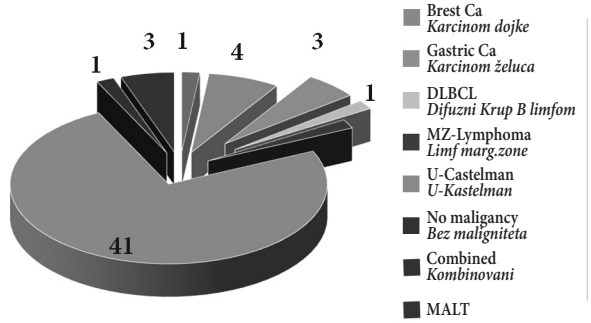

Figure 1. Number malignancies in adult CVID patients from joined cohort from University Clinic Centre Serbia-Belgrade and University Clinical Centre Nis (January 1st 2011 - August 15th 2021)

Slika 1. *Broj odraslih pacijenata sa malignitetom i CVID u objedinjenoj kohorti bolesnika Univerzitetskog kliničkog centra Srbije-Beograd i Univerzitetskog kliničkog centra u Nišu (od 1. januara 2011 do 15. avgusta 2021. godine)*

germinative center B-cells. The highest number of reported cases were patients with Ataxia Telangiectasia and Nijmegen Breakage Syndrome, which had mainly developed Diffuse large B-cell lymphoma (DLBLC) and less frequently Burkitt lymphoma [3]. Both lymphoma types originate from B-cells undergoing affinity maturation in the germinative centers of the lymph nodes. High incidence of DLBCL is therefore highly expected in defective DNA repair setting, since DNA breakage and repair are common events during isotype switching and affinity maturation. It is noteworthy that chronic antigenic stimulation and infection with EBV, contribute to dysregulated B and T-cell proliferation in this patient subgroup.

The incidence and biology of lymphoma subtypes differ in patients with immune regulation defects such as autoimmune lymphoproliferative syndrome (ALPS) and activated PI3 kinase-δ syndrome (APDS). Defects in FAS mediated (TNFRSF6, CD95, and APO1) and other apoptotic pathways in ALPS, lead to lymphoproliferation with a 14-fold risk for non-Hodgkin lymphoma and a 53-fold risk of Hodgkin lymphoma development [4]. This comes as no surprise, since Hodgkin Reed-Sternberg cells have features of activated B-cells, engaged in complex interaction with surrounding reactive tumor microenvironment.

In APDS, gain or loss of function of subunits with regulatory role within PI3 kinase δ pathway, have deleterious effects on T- and B-cell functions. T-cells in APDS are susceptible to apoptosis and cellular senescence, while B-cells could not undergo isotype switching and poorly respond to follicular T-helper cells stimuli [5]. Further lymphoproliferation is driven by EBV infection, whose presence is detected in 30% of APDS patients, of whom 20% develop B-cell lymphoma [6]. For that reason, apart from highly prevalent Hodgkin lymphoma and DLBCL, landscape of lymphoma entities is enriched with MALT and marginal zone B-cell lymphomas.

[7]. The later subtypes develop from primed B-cells residing outside the lymph nodes.

Another disease classified as an immune regulation defect, is X-linked lymphoproliferative disease type XLP1. The lymphoma most commonly diagnosed in this entity is DLBCL, with EBV present in 50% of cases. Straightforward association of EBV with hemophagocytic lymphohistiocytosis and lymphomas has placed this disease among defects with high susceptibility to EBV in latest IUIS 2019 classification [1].

Finally, a group of diseases known as Tregopathies, due to defects of CTLA-4 check point molecule or its accompanying molecules, evolve into lymphomas with frequent EBV positivity [8].

Within the defects of antibody production, Common variable immunodeficiency (CVID) is the most common symptomatic IEI in adults. Adult patients with CVID have 30-fold higher tendency to develop lymphomas, and usually appear in CVID lasting more than 14 years, with average diagnosis in 4^{th} -6^{th} decade [9]. In lymphomas diagnosed in CVID, EBV infection was associated in 31% of cases [2, 9].

When looking at lymphoma entities found in CVID, there is a shift towards Marginal zone and MALT lymphomas, making these subtypes equally or even more frequent than DLBCL and Hodgkin lymphoma. Apart from reports from western national registries, this tendency has been observed in some parts of the Balkans, in Northern Macedonia (unpublished data). Likewise, similar distribution of lymphoma subtypes was found in our joint cohort with 55 patients from two University Clinical Centers Serbia (Belgrade) and Nis, during a 10-year follow up. Of them, 3 patients (5.45%) had DLBCL, another 3 (5.45%) had MALT lymphoma and 1 (1.81%) had Marginal zone B-cell lymphoma **(Figure 1)**. In accordance to data from other studies, our cohort showed a striking absence of follicular lymphomas (FL) in CVID patients [9]. Its noteworthy mentioning that FL holds the second place in overall lymphoma incidence in human population in the western hemisphere, right behind DLBCL. This discrepancy of FL incidence in CVID versus normal population, is probably due to defective signaling (ICOS, PIK3CD, NFKB-1 or PIK3R1 mutations) within germinative centers in CVID patients. The lack of sufficient signals abort the formation of germinative center reaction, which is a prerequisite for the development of FL. It has been hypothesized that malignant B-cells need several reentries into the follicular center, in order to "highjack it" and establish a malignant lymphoma [10, 11].

Therapy of lymphomas in IEI patients

General rules

A literature search for treatment of lymphomas associated with IEI, gave limited data containing mostly case reports and case series. Therefore, the decision on treatment is based on individual judgment and experience of the hematologist or pediatrician.

In general, treatment options do not differ significantly from therapy of immunocompetent patients.

Selection of treatment depends on lymphoma subtype, stage of the disease, patient's age, and comorbidity status. Staging procedure is therefore critical and should be identical to management of non-IEI lymphoma cases, except for patients with DNA repair defects. It is generally acknowledged that diagnostics using X-rays or PET scan as well as radiotherapy, should be strictly avoided in this radio-sensitive subgroup.

Response and overall survival to standard chemotherapy, was inferior in IEI patients as compared to patients without immunodeficiency. Dismal outcomes were due to poorer tolerability of chemotherapy and susceptibility to infectious agents [12]. Besides the need for vigorous treatment of infections, one may advocate the use of antimicrobial prophylaxis. In the absence of clear data, some preventive strategies could be taken from NCCN clinical practice guidelines for AIDS related lymphomas. According to recommendations, granulocyte colony-stimulating factors (G-CSF) and quinolones should be used until resolution of neutropenia, and trimethoprim sulfamethoxazole should be given for pneumocystis jirovecci prophylaxis.

High toxicity rate of epipodophyllotoxins (Etoposide) and alkylating agents (Cyclophosphamide) in patients with DNA repair defects requires its avoidance or dose modifications [13].

Monoclonal antibodies in treatment of lymphomas associated in IEI

Various combinations of chemotherapy with anti-CD20 monoclonal antibody have been gradually introduced, both for pediatric and adult IEI patients with DLBCL [3, 14]. In non IEI patients with DLBCL, FL or chronic lymphocytic leukemia, a type II glycoengineered anti-CD20 monoclonal antibody obinutuzumab has been adapted for standard treatment. Currently there is no data about the use of obinutuzumab in lymphomas associated with IEI. Preclinical studies showed that its effectiveness relies on antibody dependent cell cytotoxicity mediated by pool of NK lymphocytes. This may raise a concern about efficacy of obinutuzumab in IEI with depleted or deficient NK cell function.

Recent study of Pincez and coworkers has brought into focus the beneficial effects of immunoconjugates for selected lymphoma subtypes derived in IEI. Authors have used Brentuximab vedotin, an anti-CD30 monoclonal antibody coupled with microtubule disrupter -monomethyl auristatin E, in 7 IEI patients, of which 6 were carrying DOCK8, ATM, ITK, CD27, ADA, SH2D1A genetic lesions. The drug was given as first line in two anaplastic large cell lymphomas, one DLBCL, one prolymphocytic leukemia case and in one case with mucocutaneous ulcer. Brentuximab was given as second line treatment in 2 patients with relapse/refractory Hodgkin lymphoma. Malignant cells in all cases expressed CD30 molecule, but it varied from 30-100%. This approach induced response

and/or remission in 5 patients, bridging towards hematopoietic stem cell transplantation (HSCT) [15]. This was not the only proof of brentuximab efficacy, since two cases of successful treatment of Hodgkin lymphoma, in patients with CVID and Ataxia telangiectasia, were reported earlier [16, 17].

A recent breakthrough in treatment of lymphomas has been achieved with the introduction of bispecific antibodies. Bispecific antibodies engage domains on the surface of tumor cells with domains of unspecific T-cells, putting them into close proximity. Net result is an activation of T-cells and stimulation of tumor destruction. Unfortunately, certain IEI entities frequently lack functional T-cells, making this approach of limited use in these subtypes. Until now, there is no data about their efficacy in IEI patients with lymphomas.

Another established group of monoclonal antibodies known as "check point inhibitors", act through blocking the inhibitory signals mediated through PD-1 or CTLA-4 receptors. The physiological role of PD-1 and CTLA-4 molecules is to control potential auto-reactive clones and block autoimmune reactions. Abuse by overexpression of PD-1, on the surface of malignant lymphoma cells, particularly on Reed-Sternberg cells, results in resistance to anti-tumor cellular response and tumor progression. Introduction of checkpoint inhibitors in treatment led to satisfactory response rates even in cases with defective T-cell response, seen both in AIDS related Hodgkin and non-Hodgkin lymphomas [18–20]. Important adverse reaction seen throughout the treatment with checkpoint inhibitors, is the appearance of autoimmune diseases or its exacerbation. So far, there is no data about the use of these drugs in patients with IEI related lymphomas. Nevertheless, numerous IEI entities including immune regulation defects, tregopathies, CVID and even some syndromic IEI, may present with autoimmune phenomena and autoimmune diseases. Application of check-point inhibitors, therefore poses a serious threat of life-threatening exacerbation of autoimmune reactions. This was reported in 5 patients with various IEI including DOCK8, CD40 deficit and CVID whose clinical state worsened after minimal dose of pembrolizumab, received to treat progressive multifocal leukoencephalopathy [21].

Cells with chimeric-antigen receptor in treatment of lymphomas associated in IEI

In 2017 and 2018 FDA approved the use of T-cells with chimeric-antigen-receptor (CAR-T cells) for relapsed/refractory B-cell acute leukemia and lymphomas. These autologous cells with "ex vivo" modified T-cell receptor, were able to induce very high responses in patients resistant/refractory B-cell malignancies [22]. Furthermore, applicability and effectiveness of CAR-T cells, was shown even in case reports with AIDS related relapse/refractory lymphomas [23, 24]. In spite of encouraging results, production of autologous CAR-T cells and their efficacy could be hampered by low number of mobilized T-cells, T-cell exhaustion, immune or age-related T-cell senescence, prior therapies, unrecognized underlying genetic defects and many other patient or procedure related factors [25, 26]. Obviously, the concerns mentioned above invariably apply for the majority of IEI patients. Currently, there is no data concerning the use of CAR-T cells or treatment of lymphomas associated with IEI.

A promising approach that might overcome this problem both in IEI and non-IEI patients with lymphomas is development off-the-shelf, ready to use CAR-NK cells.

CAR–NK cell receptor construct is same as in CAR-T cells. The advantages over CAR-T cells is in the absence of alloreactivity, ability to overcome immune evasion by tumor, as well as the absence of cytokine release syndrome and neurotoxicity caused by cell activity [27]. The proof of effectiveness of this concept is the overall response rate in 8/11 patients (73%) with 7 complete responses in a recent pilot study. Of patients with complete remission, 3 had relapse/refractory chronic lymphocytic leukemia and 4 had relapse/refractory non-Hodgkin lymphomas [28]. Meanwhile, the number of phase I and II clinical trials with patients with hematological malignancies is rapidly growing [27]. Having in mind the rationale behind the use of CAR-NK cells, we might expect that this strategy may be feasible in treatment of hematological malignancies associated with IEI. The following years will provide the clue for this assumption.

Hematopoietic stem cell transplant in treatment of lymphomas associated with IEI

Hematopoietic stem cell transplantation (HSCT) is considered the "standard of care" and major therapeutic option particularly in children with severe combined IEI [29]. The decision to undergo HSCT in adolescents, young adults with milder forms of IEI, has become challenging, due to high transplant related morbidity and mortality on one side, and improved conventional management and extended overall survival. In spite of these changes, the development of malignancy associated with IEI still remains one of the major indications for HSCT [29]. Optimal timing for Hematopoietic stem cell transplantation (HSCT) in IEI associated lymphoid malignancies should be in remission of very good partial response. Decisions about stem cell source, conditioning regimes need to take in consideration age, autoimmune manifestations, organ function damage, past and present infections and many other issues [30]. In general, improvement in HLA typing, adoption of reduced intensity regimens, increased availability of alternative stem cell sources and improved methods of GVHD prophylaxis improved outcomes in HSCT in all IEI patents, especially in adolescents and young adults [30–32].

Conclusion

Improvements in understanding, diagnostic and management of patients with inborn errors of immunity extended overall survival and life expectancy, making the appearance of lymphomas no longer limited to childhood. The burden of such patients is there-

fore growing, creating therapeutic challenges both to pediatricians and hematologists. The spectrum of lymphoma subtypes associated with inborn errors of immunity is wide, frequently depending on the type of underlying inborn error defect. Diagnostics and treatment strategies should acknowledge risks and limitations in sensitive patients with deoxyribonucleic acid repair defects. Hematopoietic stem cell transplantation is the standard of care for patients with severe immune defects and short life expectancy even without malignancy. In those with a milder clinical picture and better survival, transplantation should be the treatment of choice for relapsed/refractory lymphomas. Treatment should rely on chemotherapy with the addition of appropriate monoclonal antibodies (rituximab, brentuximab vedotin) wherever feasible. The applicability and effectiveness of new "ready to use, off the shelf" approaches with Chimeric Antigen Receptor Natural Killer cells remains to be elucidated in near future.

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