Prikaz slučaja / Case report

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Akutna limfoblastna leukemija

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Sažetak

Uvod. Akutna limfoblastna leukemija (ALL) je heterogena bolest koju karakteriše klonalno bujanje i nagomilavanje nezrelih limfoidnih ćelija u koštanoj srži i limfoidnim organima. Etiologija nastanka nije poznata, ali se u vezu dovode izloženost radijaciji, određenim hemikalijama i genetika. Bolest karakteriše nagli početak. U kliničkoj slici prevladava prisustvo opštih simptoma: umor, malaksalost, noćno znojenje, gubitak telesne mase, febrilnost. Dijagnoza se postavlja na osnovu anamneze, fizikalnog nalaza, analize krvi, biopsije koštane srži, citogenetskih i imunohistohemijskih testiranja. Osnovu lečenja čini polihemioterapija, radioterapija, transplantacija matičnih ćelija hematopoeze.

Prikaz bolesnika. U radu je prikazan pacijent starosti 20 godina. Prvi put se javio lekaru zbog bola u vratu. Lečen je od strane fizijatra. Nakon završene fizikalne terapije, u krvnoj slici je viđena pancitopenija. Izabrani lekar ga upućuje hematologu gde bivaju nastavljena ispitivanja i postavljena dijagnoza ALL. Lečenje je započeto hemioterapijom po predviđenom protokolu. Potom je urađena srodna alogena transplantacija matičnih ćelija hematopoeze. U daljem kliničkom toku rađene su redovne hematološke procene i procena MRD nalaza. Sve vreme se održavala morfološka kompletna remisija, ali uz pozitivan MRD nalaz. Primenjena je terapija monoklonskim antiCD22 antitelom na koju je dobro odgovorio. Osam meseci kasnije se utvrđuje relaps B-ALL. Dolazi do pogoršanja opšteg stanja bolesnika i uprkos primenjenoj intenzivnoj terapiji dolazi do nastupanja letalnog ishoda.

Zaključak. Akutna limfoblastna leukemija je bolest čiji ishod zavisi od mnogobrojnih faktora. Zbog atipične simptomatologije treba razmišljati o ovoj bolesti kako bi se skratilo vreme do postavljanja dijagnoze, omogućilo pravovremeno lečenje, a samim tim uticalo i na ishod bolesti.

Ključne reči: leukemija, mlada osoba, rana dijagnostika

Acute lymphoblastic leukemia

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Abstract

Introduction. Acute lymphoblastic leukemia (ALL) is a heterogeneous disease distinguished by clonal replication and piling of immature lymphoid cells in the bone marrow and lymph organs. The etiology is unknown but radiation and some chemical exposure, as well as genetics, might play a role. The disease onset is abrupt. Clinical presentation is characterized by a variety of general symptoms: fatigue, malaise, night sweats, weight loss, fever. The diagnosis is based on a patient`s history, physical examination, blood tests, bone marrow biopsy, cytogenetic, and immunohistochemical tests. Core treatments are poly-chemotherapy, radiation therapy, hematopoietic stem cell transplantation.

Case report. We presented a 20-year-old patient. On his first visit, he complained of neck pain. He was treated by a physiotherapist. After he finished with physical therapy we noticed pancytopenia in his lab work. His general practitioner (GP) referred him to a hematologist where further medical examinations were performed and ALL diagnosis was made. The treatment started with a chemotherapy regimen. An allogeneic hematopoietic stem cell transplantation was performed afterward. In the follow-up, regular haematologic assessments were done, as well as, the assessment of MRD (Minimal Residual Disease). Complete morphologic remission was maintained the whole time but with positive MRD findings. He received an antiCD22 monoclonal antibody therapy and the therapeutic response was good. Eight months later B-ALL relapse was confirmed. The patient`s general condition got worse and in spite of an intensive therapy the patient died.

Conclusion. Acute lymphoblastic leukemia is a disease whose outcome depends on many a factor. Due to atypical symptoms, it should be taken into consideration to shorten the time to diagnosis, provide timely treatment and thus influence the disease outcome.

Keywords: leukemia, young person, early diagnosis

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Uvod

Akutna limfoblastna leukemija (ALL) je heterogena bolest koju karakteriše klonalno bujanje i nagomilavanje nezrelih limfoidnih ćelija (limfoblasta) u koštanoj srži i limfoidnim organima. Učestalost ALL u Evropi je 1,28/100.000 sa značajnim varijacijama u odnosu na starosnu dob[1]. Najveći procenat obolelih, oko 80%, registruje se u dečijoj populaciji sa stopom preživljavanja od 90%, dok odrasli imaju lošiju prognozu[2]. Za većinu slučajeva bolesti ne postoji jasan uzrok nastanka, a smatra se da su faktori rizika izloženost radijaciji, određenim hemikalijama i genetika[3]. Manje od 3% slučajeva može biti udruženo sa Daunovim i Klinefelterovim sindromom, Fankonijevom anemijom, ataksijom-telangiektazijom[4,5,6].

Klasifikacija ALL je važna kako bi se definisao terapijski pristup i predvidela prognoza. Prema citomorfološkoj Francusko-Američko-Britanskoj (FAB) klasifikaciji postoje 3 podtipa: L1, L2, L3[7] (Tabela 1). Prema imunološkoj klasifikaciji ALL se deli na B i T ALL sa karakterističnim fenotipskim podtipovima. B ALL obuhvata podtipove: pre-pre B ALL, common B-ALL, pre-B ALL i B-cell ALL, dok većina T ALL ima tipični fenotip[8].

Introduction

Acute lymphoblastic leukemia (ALL) is a heterogeneous disease distinguished by clonal replication and piling of immature lymphoid cells (lymphoblasts) in the bone marrow and lymph organs. The prevalence of ALL in Europe is 1,28/100.000 with significant variations concerning age[1]. The largest percentage of the diseased, around 80%, is registered in children with a survival rate of over 90% while adults have a worse prognosis[2]. For the majority of the disease cases, there is no clear cause but radiation, exposure to some chemicals, and genetics are considered risk factors[3]. Less than 3% of cases may be associated with Down and Klinefelter syndrome, Fanconi anemia, ataxia-telangiectasia.[4,5,6].

An ALL classification is important so we could define a therapeutic protocol and foresee the prognosis. According to French-American-British (FAB) cytomorphologic classificastion there are 3 subtypes: L1, L2, L3[7] (Table 1). According to immunological classification, ALL is divided into B and T ALL with characteristical phenotype subtypes. B ALL encompasses subtypes: pre-pre B ALL, common B-ALL, pre-B ALL, and B-cell ALL, while the majority of T ALLs have got typical phenotype[8].

Tabela 1. FAB klasifikacija akutne limfoblastne leukemije/
Table 1. FAB classification of acute lymphoblastic leukemia

	L1	L2	L3
Ćelijska populacija/ Cell population	Homogena/ Homogenous	Heterogena u veličini i obliku/ Heterogenous in size and shape	Homogena/ Homogenous
Veličina ćelije/ Cell size	Male ćelije/ Small cells	Velike i male ćelije/ Large and small cells	Velike ćelije/ Large cells
Odnos jedra/citoplazme/ Nucleus/cytoplasmic ratio	↑	↓	↓
Nukleolus/ Nucleolus	Neupadljiv/ Sparse	Prominentan (1–2)/ Prominent (1–2)	Prominentan/ Prominent
Citoplazma/ Cytoplasm	Oskudna/ Sparse	Obilna/ Abundant	Bazofilna sa vakuolizacijom/ Basofils with vacuolization
Uzrast/ Age: **Deca/ Children**	85%	14%	1%
Odrasli/ Adults	31%	60%	9%

Bolest karakteriše nagli početak. U kliničkoj slici dominira prisustvo opštih, tzv. B simptoma: umor, malaksalost, noćno znojenje, gubitak telesne mase, febrilnost[9]. Simptomi su posledica "zamene" normalnih ćelija krvi malignim ćelijama. Usled smanjenja crvenih krvnih zrnaca javljaju se znaci i simptomi anemije, češće infekcije zbog smanjenog broja funkcionalnih belih krvnih zrnaca, a spontana krvarenja usled

The disease onset is abrupt. Clinical presentation is dominated by general, so called, B symptoms: fatigue, malaise, night sweats, weight loss, fever[9]. Symptoms are the consequence of normal cells being "switched" with malignant cells. Due to the reduction of red blood cells the signs and symptoms of anemia appear, frequent infections are present because of the lack of functional white blood cells, and

smanjenja broja krvnih pločica. U objektivnom nalazu konstatuju se uvećane limfne žlezde, uvećana jetra i slezina.

Dijagnoza se postavlja na osnovu anamneze, fizikalnog nalaza, analize krvi, biopsije koštane srži, citogenetskih i imunohistohemijskih testiranja. U krvnoj slici je snižen broj eritrocita, trombocita, dok je broj leukocita kod odraslih najčešće visok. Mogu biti povišene vrednosti laktat dehidrogenaze i mokraćne kiseline. Konačna dijagnoza postavlja se biopsijom koštane srži.

Lečenje se započinje odmah po postavljanju dijagnoze i prolazi kroz 3 stadijuma: fazu indukcije, fazu konsolidacije i fazu održavanja. Osnovu lečenja čini polihemioterapija, dok je transplantacija matičnih ćelija hematopoeze i dalje zlatni standard. Cilj lečenja je da se postigne kompletna remisija, odnosno da se unište sve maligne ćelije kako bi u koštanoj srži ponovo mogle da rastu normalne ćelije krvi.

Kontrola bolesti vrši se procenom minimalne rezidualne bolesti (MRD nalaza) metodom protočne citometrije i nalazom mijelograma. Minimalna rezidualna bolest predstavlja broj leukemijskih ćelija koje ostaju u krvi posle lečenja, a nalaz se definiše kao pozitivan ili negativan, shodno tome da li su leukemijske ćelije otkrivene ili ne.

Petogodišnje preživljavanje kod pacijenata kod kojih se ne registruje minimalna rezidualna bolest nakon transplantacije je 75%, dok je kod pacijenata sa pozitivnim MRD nalazom procenat preživljavanja 33%[10,11,12].

spontaneous bleeding is frequent due to the reduced number of platelets. Physical examination may show enlarged lymph nodes, liver, and spleen.

The disease is diagnosed based on the patient`s history, physical examination, blood tests, bone marrow biopsy, cytogenetic, and immunohistochemical tests. Blood count shows a reduced number of erythrocytes, and platelets, while the number of leucocytes is mostly high in adults. The levels of LDH (lactate dehydrogenase) and uric acid may be high, as well. The final diagnosis is made after a bone marrow biopsy.

The treatment is started right after the diagnosis and has three phases: induction phase, consolidation phase, and maintenance phase. The treatment core is polychemotherapy, while hematopoietic stem cell transplantation is still the golden standard. The treatment goal is to achieve complete remission and destroy all malignant cells so bone marrow can produce normal blood cells again.

Controls are performed by assessing MRD (Minimal Residual Disease), by using flow cytometry and myelogram findings. Minimal Residual Disease is the number of leukemic cells remaining in the blood after the treatment and the result is defined as positive or negative based on whether the leukemic cells are found or not.

The five-year survival rate in patients without Minimal Residual Disease after transplantation is 75%, while in patients with positive MRD findings, it`s 33%[10,11,12].

Prikaz bolesnika

U radu je prikazan pacijent starosti 20 godina kome je dijagnoza pre-B akutne limfoblastne leukemije, normalnog kariotipa, bez neuroleukemije postavljena decembra 2018. godine. Prvi put se javio lekaru zbog bola u vratu. Pregledan je od strane fizijatra koji je propisao seriju fizikalne terapije. Tegobe su se održavale i po završetku fizikalne terapije. Prisutni su bili i malaksalost, umor, bolovi u kostima i mišićima, pojava modrica po koži. Daljim ispitivanjima u krvnoj slici je viđena pancitopenija (Le 2,9x10^9/l, le formula: Ly 15%, Gr 9%, blasti 76%, Er 4x10^{12}/l, Hb 95 g/L, Hct 0,30 l/l, Tr 68x10^9/l). Na objektivnom pregledu utvrđena je cervikalna limfadenopatija (koja je i bila uzrok pojave bola), uvećana jetra i slezina, što je potvrđeno i ultrazvučnim pregledom. Izabrani lekar ga upućuje hematologu u UKCS gde bivaju nastavljena ispitivanja. Dijagnoza je postavljena analizom periferne krvi, razmaza koštane srži, imunofenotipizacijom i protočnom citometrijom, analizom kariotipa i molekularno-genetskim ispitivanjima.

Lečenje je započeto hemioterapijom po protokolu *Hyper CVAD*, ukupno V ciklusa, nakon čega je pacijent postigao kompletnu remisiju. Sprovedeno je i profilaktičko zračenje CNS. Potom je urađena srodna alogena transplantacija matičnih ćelija hematopoeze, imajući u vidu da se radilo o bolesti visokog rizika (imunološki podtip pre-B ALL). Do-

Case report

We presented a 20-year-old patient diagnosed with pre-B acute lymphoblastic leukemia in 2018, with normal karyotype, without neuro-leukemia. He first paid a visit to his doctor due to the neck pain. He was examined by a physiotherapist who recommended a series of physical therapies. His health problems didn`t improve after physical therapy. He felt weak, fatigued, had bone and muscle pain, and bruises appeared on his skin. Further examination revealed pancytopenia in his CBC (WBC 2,9x10^9/l, le formula: Ly 15%, Gr 9%, blasts 76%, RBC 4x10^{12}/l, Hb 95 g/L, Hct 0,30 l/l, Plt 68x10^9/l). Physical examination revealed cervical lymphadenopathy (which initially caused neck pain), and enlarged liver and spleen, which was sonographically confirmed. His GP referred him to a hematologist at the University Clinical Center of Serbia where further examinations were performed. The diagnosis was made based on the analysis of the peripheral blood, and bone marrow smear, by using immunophenotyping, flow cytometry, karyotype analysis, and molecular-genetic research.

Treatment started with chemotherapy, *Hyper CVAD* protocol, 5 cycles in total, after which the patient achieved total remission. Prophylactic radiation of CNS was performed. Afterward, an allogeneic hematopoietic stem cell transplantation was performed, considering it was a high-risk

nor je bio rođeni brat sa minor krvno-grupnom neusklađenosti (bolesnik krvna grupa AB Rh+, donor krvna grupa B Rh+). Procedura je protekla bez komplikacija. Primenjena je profilaksa antibioticima, antiviroticima, antimikoticima, kao i predviđenim dozama imunoglobulina. Posttransplantacioni tok je komplikovan reaktivacijom BK virusa (familija Polyomaviridae, rod Polyoma virusa), mukozitisom i furunkulitisom kože. Hematološkom procenom bolesti tri meseca po transplantaciji, MRD nalaz bio je pozitivan, kao i nalaz mijelograma zbog čega je pacijent morao primiti donorske limfocite (donor rođeni brat). Kod pacijenta je došlo do zamene krvne grupe, koji sada ima donorsku krvnu grupu. U daljem kliničkom toku rađene su redovne hematološke procene, sve vreme se održavala morfološka kompletna remisija uz pozitivan MRD, ali uz značajno smanjenje leukemijskih ćelija u koštanoj srži, dok je nalaz u perifernoj krvi bio negativan. Lečenje je nastavljeno primenom monoklonskog antiCD22 antitela, inotuzumab ozogamicin. Nakon primene leka urađena je hematološka procena: mijelogram je pokazao morfološku kompletnu remisiju, a MRD je takođe bio negativan. Nastavljeno je dalje praćenje bolesnika. Osam meseci od primene monoklonskog antitela, kod pacijenta dolazi do pojave febrilnosti, malaksalosti, pojave spontanih modrica po koži, krvarenja od strane unutrašnjih hemoroida. Konstatuje se relaps B-ALL. U nalazima krvne slike: Le 167,1x10^9/l, le formula: Gr 1%, Ly 8%, blasti 91%, Er 3,5x10^{12}/l, Hb 130 g/L, Hct 0,29 l/l, Tr 59x10^9/l. Neposredno po prijemu bolesnika započeta je citoreduktivna terapija primenom 6-merkaptopurina i deksametazona. Drugog dana hospitalizacije dolazi do pogoršanja opšteg stanja bolesnika, razvoja ARDS, diseminovane intravaskularne koagulacije, laboratorijskih i kliničkih znakova sepse (izolovana E. coli). Dolazi do pojave crnih prolivastih stolica. Zbog navedenog, primenjena je intenzivna antibiotska terapija (meropenem, vankomicin, levofloksacin), simptomatska (hepatoprotektivi, kardiotonici, diuretici) i suportivna terapija (supstitucija derivatima krvi, elektroliti i albumini), nakon čega dolazi do poboljšanja stanja. Konzilijarnom odlukom sprovedena je hemioterapija primenom "salvage" protokola *Flag-5*. Navedena terapija bila je praćena aplazijom koštane srži, koja se komplikovala pojavom febrilne neutropenije i epistakse. Učinjen je i RTG pluća na kome je u desnom srednjem plućnom polju viđena homogena senka pneumonične plućne konsolidacije. Dalje dolazi do pojave dezorijentisanosti, biva konsultovan neurolog koji traži CT endokranijuma na kome bivaju uočeni hemoragični fokusi okcipitalno parasagitalno. Primenjena je antiedematozna terapija uz intenzivne simptomatske i suportivne mere. Međutim, i pored primenjene terapije dolazi do pogoršanja opšteg stanja i nastupanja letalnog ishoda.

disease (immunologic subtype pre-B ALL). The donor was his brother with minor blood type inconsistency (the patient had AB Rh+ blood type and the donor B Rh+). The procedure went without any complications. Antibiotic, antiviral, and antimycotic prophylaxis was applied, as well as, adequate doses of immunoglobulins. The posttransplantation course was complicated by reactivation of the BK virus (Polyomaviridae family, Polyomavirus strain), mucositis, and cutaneous furuncle. Hematologic assessment three months after transplantation showed positive MRD, as well as a myelogram, and therefore the patient received donor lymphocytes (the donor was his brother). The patient`s blood type was replaced then by the donor`s. The further clinical course included regular hematological assessment. Complete morphologic remission was maintained with positive MRD but a significant decrease of leukemic cells in the bone marrow, while the findings in the peripherial blood were negative. The treatment was continued with an antiCD22 monoclonal antibody therapy, inotuzumab ozogamicin. After the medication application, a hematologic assessment was made – the myelogram showed complete morphologic remission, and MRD was also negative. Further follow-up was continued. Eight months after the application of monoclonal antibody fever appeared, as well as malaise, spontaneous bruises, and bleeding of internal hemorrhoides. The B-ALL relapse was noted. The CBC findings: WBC 167,1x10^9/l, le formula: Gr 1%, Ly 8%, blasts 91%, RBC 3,5x10^{12}/l, Hb 130 g/L, Hct 0,29 l/l, Plt 59x10^9/l. Right after the patient`s admission, cytoreductive therapy was started with 6-mercaptopurine and dexamethason. On the second day of hospitalization the patient`s general state got worse, ARDS developed, disseminated intravascular coagulation, and lab and clinical signs of sepsis (E. Coli was isolated). Tarry, diarrhoeic stools appeared. Due to all this, intensive antibiotic therapy was applied (meropenem, vancomycin, levofloxacin), symptomatic therapy (hepatoprotectives, cardiotonics, diuretics), and supportive therapy (blood derivates substitution, electrolytes, and albumins), after which his condition went for the worse. The consular decision was to apply "salvage" chemotherapy, *Flag-5* protocol. This therapy led to bone marrow aplasia which was complicated by the appearance of febrile neutropenia and epistaxis. A chest X-ray was performed and it showed homogenous pneumonic lung consolidation in the right middle field. Further on, disorientation appeared, and therefore a neurologist was consulted. He ordered a head CT scan which showed hemorrhagic focuses in the occipital parasagittal region. The patient received antiedematous therapy with intensive symptomatic and supportive measures. However, even with all applied therapy the patient`s general condition got worse and led to a lethal outcome.

Diskusija

Akutna limfoblastna leukemija je malignitet krvi kod koga je važno što pre započeti sa lečenjem. Prisutni znaci i simptomi ALL su prilično nespecifični, pa su poremećeni parametri u krvnoj slici alarm za upućivanje pacijenta hematologu. Određivanje stadijuma bolesti i profila rizika pacijenta se sprovode kako bi se definisali podtipovi ALL i tako napravio plan i protokol lečenja. Lečenje se sastoji iz dve faze, faza indukcije remisije i faza održavanja remisije. Faza indukcije remisije je prva faza i ima za cilj da "ubije" leukemijski aktivne ćelije i dovede bolest u remisiju. Faza održavanja je druga faza i u njoj treba da se unište preostale leukemijske ćelije koje nisu aktivne, a koje bi mogle postati[13]. Takođe, često se vrši i profilaktičko zračenje CNS, što je bio slučaj i kod našeg pacijenta.

Standardno lečenje ALL obuhvata hemioterapiju, radioterapiju, transplantaciju matičnih ćelija hematopoeze, palijativnu terapiju. Novi koraci u lečenju podrazumevaju primenu imunoterapije (oblik biološke terapije). Sa razvojem medicine neprekidno se vrše klinička ispitivanja novih lekova kod ALL u koje mogu biti uključeni oboleli od ALL uz njihovu saglasnost[13].

Prognoza bolesti zavisi od više faktora: starosti pacijenta, pola, tumorske mase, broja leukocita, broja trombocita, vrednosti hemoglobina, vremena potrebnog da se postigne kompletna remisija, leukemije CNS. Sa povećanjem starosti smanjuje se broj postignutih remisija. Loš prognostički znak predstavlja ekstremno uvećanje limfnih žlezda, slezine, jetre, kao i prisutnost tumora medijastinuma[14].

Glavni razlog mortaliteta ovih pacijenata su teške infekcije, kako bakterijske, tako i gljivične, sepsa.

Stope potpune remisije su visoke, posebno među decom (čak 100%). Međutim, dugotrajno preživljavanje nakon 10 godina je u rasponu od 63% za decu i 25–35% za odrasle[15]. Ovi podaci nagoveštavaju da i dalje postoji potreba za novim terapijama i terapijskim protokolima za održavanje remisije i produženje preživljavanja.

Zaključak

Akutna limfoblastna leukemija je bolest čiji ishod zavisi od brojnih faktora, prvenstveno starosti pacijenta, ali i citogenetsko molekularnih promena i koja se može veoma dobro kontrolisati ako se pravovremeno otkrije i ako se lečenje započne na vreme. Zbog atipične simptomatologije treba razmišljati o ovoj bolesti kako bi se skratilo vreme do postavljanja dijagnoze, omogućilo pravovremeno lečenje, a samim tim uticalo i na ishod bolesti. Treba naglasiti značaj dobro uzete anamneze i adekvatnog pregleda lekara opšte medicine pri svakom kontaktu sa pacijentom, bez obzira na vremensko ograničenje pregleda i opterećenost lekara primarne zdrav-

Discussion

Acute lymphoblastic leukemia is a malignant blood disease and it is of utmost importance to start the treatment as early as possible. The existing signs and symptoms of ALL are very unspecific, so CBC parameters` disorder should be an alarm to forward the patient to a hematologist. The disease staging and determination of the patient`s risk profile are performed to define ALL subtypes and thus make the treatment plan and protocol. The treatment consists of two phases – phase of remission induction, and phase of remission mainteinance. The remission induction phase is the first phase and it aims to "kill" active leukemic cells and lead the disease to remission. The mainteinance phase is the second phase and it implies the destruction of the leftover leukemic cells, which are not active but could become active.[13] Also, prophylactic radiation of the CNS is often performed, which was the case in our patient, as well.

Standardno treatment of ALL includes chemotherapy, radiation therapy, hematopoietic stem cell transplantation, and palliative therapy. New steps in the treatment imply the application of immunotherapy (a form of biologics). As a part of medical progress, there is continuous research with new medications for ALL, and ALL patients may enter them if they give their consent.[13]

The disease prognosis depends on many a factor: patient`s age, gender, tumor mass, number of leucocytes, number of platelets, hemoglobin values, the time necessary to achieve complete remission, and CNS leukemia. With older age, the number of achieved remissions decreases. A bad prognostic sign is an extreme enlargement of lymph nodes, spleen, liver, and tumor presence in the mediastinum.[14]

The main mortality reasons for these patients are severe infections, bacterial but mycotic, as well, and sepsis.

The full remission rates are high, especially among children (even 100%). However, long-term survival after 10 years varies from 63% for children to 25–35% for adults[15]. These data imply there is still the need for new therapies and therapeutic protocols to maintain remission and prolong survival.

Conclusion

Acute lymphoblastic leukemia is a disease whose outcome depends on numerous factors, first of all, the patient`s age but also cytogenetic molecular changes. It may be well controlled if it`s discovered on time and the treatment is initiated right away. Due to the atypical symptoms, we should bear it in mind to shorten the time to diagnosis, enable timely treatment, and therefore influence the disease outcome. The patient`s history is very important, as well as, the physical examination performed by the GP at every patient`s visit despite

stvene zaštite. Značajnu ulogu imaju preventivni pregledi, kao i redovne provere analiza krvi, a na osnovu kojih se u ordinaciji lekara opšte medicine najčešće i javlja sumnja na ovu bolest. Lečenje se sprovodi na sekundarnom ili tercijarnom nivou, a izabrani lekar je taj koji prati efekte terapije u ambulantnim uslovima i komplikacije od istih. Treba naglasiti da je u lečenju ovakvih pacijenata neophodan multidisciplinarni pristup kako bi se postigao željeni cilj.

time limitations and GP`s work overload. Preventive check-ups are of great importance, but also regular CBC checks at GP`s, which can lead us to suspect the occurancce of the disease. The treatment is carried out on the secondary and tertiary level and the GPs are the ones to follow the therapy effects and complications in their offices. It should be stressed, the multidisciplinary approch in the treatment of these patients is necessary to achieve the desired goal.

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