THE ADDITION OF FLT3 INHIBITOR TO STANDARD INDUCTION CHEMOTHERAPY INCREASES THE RATES OF COMPLETE REMISSIONS IN FLT3-MUTATED ACUTE MYELOID LEUKEMIA

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Introduction: Fms-like tyrosine kinase-3 (FLT3) gene mutations are most frequent molecular abnormalities in acute myeloid leukemia (AML) and internal tandem duplications (ITD) in the juxtamembrane domain occur in ~25% of newly diagnosed cases. The addition of inhibitors of FLT3 to standard induction chemotherapy (IC) is a promising strategy to overcome the historically poor prognosis of FLT3-mutated AML. Here, we evaluate the impact on remission status of the addition of Sorafenib to IC in de novo AML patients, fit for intensive therapy.

Material and methods: This is a retrospective study including 25 previously untreated patients with FLT3-mutated AML. FLT-ITD mutation was detected by fluorescent polymerase chain reaction (PCR) and capillary electrophoresis of PCR products by automatic DNA analyzer at diagnosis and after induction chemotherapy. Patients received frontline Daunorubicin- Cytarabine (DA) "3+7" regimen. Sorafenib was administered at a dose of 400mg daily for 14 days from day +1 on.

Results: The mean age of study population was 60 years (range: 16-74). 14 patients received DA without targeted drug. Only four of them achieved complete remission (CR). Interestingly, all of them had additional nucleophosmin 1 (NPM1) mutation, hence they are stratified into the intermediate risk group. In contrast, among 11 patients receiving Sorafenib, 9 patients achieved CR and all of them were minimal residual disease (MRD) negative at the end of two induction cycles. In addition, 6 of them had FLT3 as sole mutation.

Conclusion: Sorafenib in combination with DA 3+7 is a highly effective treatment regimen, resulting in higher rates of post-induction complete remissions in FLT3+ AML.

THE EFFICACY OF ANTI-THYMOCYTE GLOBULIN AS A METHOD OF IN VIVO T CELL DEPLETION IN CONDITIONING IN PATIENTS WITH ACUTE MYELOID LEUKEMIA UNDERGOING ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION FROM RELATED AND UNRELATED DONORS – SINGLE CENTER ANALYSIS

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Introduction: Acute myeloid leukemia (AML) is a malignant hematological disease characterized by accumulation of malignant hematopoietic immature precursors in the bone marrow. Allogeneic hematopoietic stem cell transplant (HSCT), is the treatment with the biggest curative in these patients. Up to 70% of patients undergoing allogeneic HSCT will suffer graft versus host disease (GvHD) to some extent. One of the options of GvHD prophylaxis is to do in vivo T cell depletion by application of anti-thymocyte globulin (ATG) during conditioning.

Material and methods: In our study we have analyzed 40 patients with AML diagnosed and treated on the Clinic for Hematology in Skopje in the period of 2014 to 2021. ATG was administered on days -3-2-1 before transplant in 19 patients (47%).

Results: We made a comparative analysis of the GvHD rates, infectious complications rates and survival rates. In the ATG group, 15.8% were diagnosed with acute GvHD, and the same percentage accounts for the chronic GvHD. The non ATG group had significantly higher rates of acute GvHD (29%) and chronic GvHD (24%). No inferiority was confirmed regarding fatal infectious rates in the ATG group. The same accounts for the relapse rates (in the non ATG group (19%) compared to the ATG group (16%)).The 3 year OS in patients without ATG was 27.2% compared with 68.2% in patients receiving ATG.

Conclusion:ATG in conditioning for patients with AML undergoing allogeneic HSCT as a method of in vivo T cell depletion is a justified approach contributing to treatment benefits to the patients.

THE IMPACT OF NGS-BASED MINIMAL RESIDUAL DISEASE LEVEL ON CLINICAL OUTCOME IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA

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Introduction: Accurate evaluation of MRD is the most informative tool for treatment decisions in childhood ALL. Using next generation sequencing we studied if extent of MRD, not only its qualitative assessment, would have impact on clinical outcome.

Material and methods: Overall, 50 patients (43 with B-ALL, 7 with T-ALL) were analysed. Patient-specific gene rearrangements in IGH-FR3/TCRG regions were detected at diagnosis and tracked at two timepoints from therapy onset: end of induction (EOI, d33) and before consolidation (d78). DNA was extracted from bone marrow mononuclear cells. The median follow-up was 39 months.

Results: Based on the MRD level, we divided the patients in three groups: MRD<1E-4, 1E-3≥MRD≥1E-4 and MRD>1E-3. Only 40% of the patients showed early MRD clearance at EOI with MRD level <1E-4 or not detectable (ND). This percent nearly doubled before consolidation (78% had ND MRD). Conversely, 60% of the patients had MRD≥1E-4 on d33, whereas 22% remained MRD positive at d78. High MRD level >1E-3 was observed in 34% of the patients (17/50) on d33 and 5 out of 6 relapses occurred in patients from this group. None of the patients with MRD<1E-4 or ND on d33 relapsed. All relapses occurred regardless

of the MRD level on d78: one patient had MRD>1E-3, two patients 1E-3≥MRD≥1E-4 and three had MRD<1E-4 or ND.

Conclusions: High MRD level >1E-3 on d33 is associated with increased relapse risk and should be assigned for treatment intensification. Moreover, for patients with MRD<1E-4 on d33, treatment deintensification should be considered. However, standardisation of this method is needed for routine clinical application.

THE INFLUENCE OF RFC1 A80G GENE POLYMORPHISMS ON METHOTREXATE TOXICITY IN PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA

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Introduction: The reduce folate carrier (RFC1) is the main transporter of methotrexate (MTX) and folate in the cell and his malfunction might be a reason for incidence of toxicities during antifolate therapy. In our study we investigated the clinical relevance of SLC19A1 A80G polymorphism for high dose methotrexate(HD-MTX) related toxicities in children with acute lymphoblastic leukaemia (ALL)

Material and methods: Our study comprised of 65 children with ALL treated with high doses of MTX (5g/m2). Genotyping for RFC1 A80G polymorphisms was performed using the PCR-based RFLPA. Toxic effects were analyzed according to the criteria for toxicity from the protocol ALL BFM 2000 (absence or presence of toxic effects) in correlation with the type of present polymorphism.

Results: In our study patients with AG + GG polymorphisms of RFC1 gene had higher probability for developing anemia as compared with carriers of AA polimorphism [OR (95%CI) 3,400 (0,77 - 14,93), RR (95%CI) 2,125 (0,76 - 5,97) p=0,095], but without statistical significance. Nevertheless, there were not any association between the other types of toxicity and RFC1 A80G polymorphisms

Conclusion: The present study suggests that analyzing RFC1 A80G gene polymorphisms could provide additional information for predicting MTX toxicities. Further multicenter studies with larger data should be performed for future individualization of treatment in childhood ALL.

Key words: RFC1 A80G, polymorphism, methotrexat, toxicities, lymphoblastic leukemia.

MANAGEMENT OF CYTOMEGALOVIRUS REACTIVATION IN ACUTE LEUKEMIA PATIENTS AFTER ALLOGENEIC STEM CELL TRANSPLANTATION – SINGLE CENTER EXPERIENCE

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Introduction: Cytomegalovirus (CMV) reactivation after allogeneic hematopoietic stem cell transplantation (HSCT) still remains one of the major causes of morbidity and mortality in these vulnerable patients. Patients with CMV positive serology are at increased risk for CMV reactivation and early and late nonrelapse mortality.

Materials and methods: We enrolled patients with acute leukemia (AML and ALL) who underwent allogeneic HSCT (related, unrelated or haploidentical) at University Clinic for Hematology – Skopje from 2016 to 2022. CMV reactivation was monitored every two weeks by RQ-PCR in the first 6 months. Preemptive antiviral therapy was administered to all patients with CMV viral load >1000 copies/ml.

Results: 60 patients were included in this study, 33 (55%) of them were man and 27 (45%) were women. The median age of the study cohort was 44 years (15 - 68 years). All patients (100%) were CMV seropositive before transplantation. CMV reactivation was diagnosed in 14 patients (23%) and all of them underwent unrelated or haploidentical HSCT. Valganciclovir was first line therapy. Two patients (14%) were Valganciclovir refractory and Foscarnet therapy was added. One was cured and one died after CMV complications. Totally two patients (14%) died from CMV reactivation and both have GvHD complications.

Conclusion: Despite high CMV seroprevalence in patients, CMV reactivation in North Macedonia posttransplant patients is on the level like Western European countries. Fact that North Macedonia is part of the region with the highest seroprevalence of CMV in the world, close surveillance in the early posttransplant period and CMV prophylaxis in high-risk patients is needed.

HIGH-DOSE CHEMOTHERAPY REGIMENTS IN THERAPY OF NHL DLBCL- SINGLE CENTER EXPERINCE

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Context:Despite advances in the management of aggressive non-Hodgkin's lymphoma, the treatment of relapsed and primary refractory disease continues to be a challenge to the treating hematologist. High-dose chemotherapy (HDT) followed by autologous stem cell transplantation (ASCT) is considered standard in the treatment of patients with relapsed or refractory DLBCL. However, the optimal salvage regimen before ASCT has not yet been established.

Design: This is a retrospective study that analyzed 20 patients with relapsed or refractory DLBCL after anthracycline-based first-line chemotherapy (R-CHOP regiment) who received either R- DexaBEAM (dexamethasone, carmustine, etoposide, cytarabine, and melphalan; n =9) or R-ICE (ifosfamide, carboplatin, and etoposide; n =11) regimen as first salvage chemotherapy. Treatment in a patient, which achieved remission was followed by HDT/ASCT. The patients were diagnosed and treated at the University Clinic of Hematology- Skopje.

Patients and results: The overall response rate (OR) was higher for patients treated with R-ICE (54,5%; 95 % confidence interval -8,03- 20 %) as compared to the R-Dexa BEAM group (44,4 %; 95 % confidence interval -8,8- 16,8 %;)., with higher complete response CR; 36,3 %; vs. 33,3%. Changing regimen due to failure of first salvage therapy was done in 1 patient initially receiving R- ICE, still achieved an OR of 25% with R-Dexa BEAM as second salvage therapy. For all patients proceeding to HDT/ASCT (n=10), a 3-year overall survival was 70 %.

Conclusion: Considering the the small sample size, our data suggest that R-ICE salvage chemotherapy is superior to R-Dexa BEAM for patients with R/R NHL DLBCL for remission induction prior to autologous transplantation.

Key words: DLBCL, High dose chemotherapy, R-ICE, R-Dexa BEAM

MAINTENANCE THERAPY FOR MULTIPLE MYELOMA: HOW LONG TO TREAT?- SINGLE CENTER EXPERIENCE

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Introduction: The outcomes of patients with multiple myeloma (MM) who are eligible for high-dose chemotherapy and autologous stem cell transplant (ASCT) are continuing to improve because of the advancements in pre-ASCT induction regimens with the introduction of the immunomodulatory drugs (IMIDs) and proteasome inhibitors (PIs) and in post-ASCT maintenance strategies with the incorporation of lenalidomide. While maintenance and continuous therapy with lenalidomide is the standard treatment of MM, there is currently no set time period for the optimal duration of maintenance.
Material and methods: From 9.2015 to 9.2022 we retrospectively reviewed 102 patients who underwent ASCT, and 81 (79,4%) of them received maintenance therapy for at least 2 months without progression, without therapy were 21 (20,6%) patients.
We compared the outcomes of patients who received maintenance for 2 years or less (early group) with the patients that received maintenance for 3 or 4 years until relapse.
The number of patients treated with lenalidomide 10mg was 66 (81,5%) patients, with thalidomide 100mg was 12 (14,8%), with lenalidomide 5 mg were 2 (2,5%) and with bortezomib only 1 (1,2%) patient.
Results: Relapse of MM appeared in 17 (16,7%) patients from which 4 of them had no maintenance therapy, 9 were on lenalidomide 10mg and 4 on thalidomide 100mg. Adverse effects of maintenance therapy appeared in 30 (29,4%) patients.
Conclusions: The delayed application of maintenance therapy showed that patients had less relapse of MM. Therefore, it is crucial that minimum therapy should be 24 months with lenalidomide 10mg to improve the outcome.

INGUINAL AND RETROPERITONEAL LYMPHADENOPATHY AS INITIAL PRESENTATION OF ADVANCED PROSTATE CANCER MIMICKING LYMPHOMA

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Introduction: Prostate carcinoma (PCa) is second most common type of cancer in men, with the highest incidence rate in their late 70s. Advanced PCa usually spreads in regional lymph nodes and axial skeleton, followed by the lungs, bladder, liver and adrenal glands. The inguinal lymph nodes are an unusual site of metastases for PCa. We present a case of a patient with PCa with inguinal and retroperitoneal lymphadenopathy as initial presentation
Case presentation: A 63 year old patient presented in the emergency department with diffuse abdominal pain and a lump in the right inguinal region. No urinary tract symptoms were reported.
Contrast-enhanced abdominal computerized tomography revealed retroperitoneal and inguinal lymphadenopathy presence. High index of suspicion for malignant lymphogenous disease was set. Excisional biopsy of the right inguinal nodes was performed. Histopathology showed a metastatic deposit in the lymph nodes originating from the prostate. Offered prostate biopsy was declined by the patient. Initial level of serum Prostatic Specific Antigen (PSA) was >100 ng/ml.
Skeletal scintigraphy with Technetium 99m-methyl diphosphonate was performed, with the finding of multiple focal pathological accumulations of the radiotracer. Hormonal and bisphosphonate therapy was

given by oncologist. Three weeks after treatment initiation, PSA levels decreased to 43ng/ml followed by additional decrease after 2 months (5 ng/ml).
Conclusion: Although inguinal lymph node metastases in prostate cancer are rare initial presentation, certain index of suspicion should be raised. This should lead to timely and proper diagnosis in order to initiate the oncologic treatment with patients with advanced PCa.
Keywords: Inguinal lymphadenopathy, Prostate carcinoma, Metastasis.

MOLECULAR PROFILING OF PATIENTS WITH PHILADELPHIA CHROMOSOME-NEGATIVE MYELOPROLIFERATIVE NEOPLASMS (PH- MPN) FROM RN MACEDONIA

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Introduction: Initial understanding on the pathogenesis of Philadelphia (Ph) chromosome-negative myeloproliferative neoplasms (MPNs) has been achieved with the discovery of mutually exclusive driver somatic mutations in JAK2, CALR and MPL genes leading to constitutive activation of the JAK/STAT signaling pathway. Additional mutations, referred to as non-driver mutations, are assumed to have prognostic implications and are used as clonal markers in triple negative MPN cases.
Materials and methods: To observe the molecular profile of 59 patients with Ph-MPNs, we performed next generation sequencing (NGS) of bone marrow DNA using the Archer Variantplex Myeloid Core panel consisted of 37 MPN-associated genes.
Results: Driver mutations were present in 39/59 (66%) patients, of which 30/39 (77%), 6/39 (15.4%), 3/39 (7.7%) in the JAK2, CALR and MPL gene, respectively. Non-driver mutations were detected in 7/59 (11.9%) triple-negative cases (ASXL1 in 3 and DDX41, CBL, FLT3 and SCF3R in individual patients), while no mutations were detected in the remaining 13/59 (22%) patients. Additional mutations were detected in 9 JAK2V617F positive patients (ASXL1 in 4, DNMT3A and TET2 in 2 each, and RUNX1, TP53 and CBL mutations in one patient each). More than two non-driver mutations were present in only 3 patients associated with poor prognosis.
Conclusion: Our results support previous data on the role of molecular profiling for identifying high-risk MPN patients and for confirming the disease clonality. The fact that 22% of our patients did not show presence of any mutation, raises the possibility that either reactive processes ware in the background of the MPN phenotype or that additional genes should be incorporated in the NGS myeloid panel.

MRD MONITORING OF PHILADELPHIA CHROMOSOME-POSITIVE B ALL PATIENTS IN NORTH MACEDONIA - SINGLE CENTRE EXPERIENCE

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Introduction: Ph positive B-ALL is characterized by the presence of BCR-ABL oncoprotein which is crucial in leukemogenesis of this type of ALL. Quantification of BCR-ABL1 transcript levels by real-time quantitative polymerase chain reaction (RQ-PCR) is the gold standard for monitoring therapy response and predict relapse.

Material and methods: In this single-centre retrospective study we will focus on MRD monitoring of adult patients with Ph+ B-ALL using BCR/ ABL1 quantification. We evaluated MRD response based on BCR-ABL1 transcript levels by RQ-PCR in Ph + ALL patients at the University Clinic for Hematology-Skopje between January 2018 and December 2022. First molecular response was evaluated after induction therapy in bone marrow samples and then responses were evaluated at 6, 9 and 12 months after the initiation of treatment.

Results: Eight patients were diagnosed with BCR-ABL positive B-ALL. Five (62.5%) were male and 3 (37.5%) were female. Seven patients were treated by Hyper CVAD regiment + TKI (6 were with Imatinib and 1 of them with Dasatinib). One patient (25 years) was treated by BFM protocol + Imatinib. Two of the patients treated by Hyper CVAD died during induction. At first time point MRD negativity was concluded in 6 patients (75%). Two of them discontinued the treatment and relapsed quickly. Four of the patients completed the treatment and were in complete molecular remission at every follow up and only one continued the treatment with allogenic PBSCT. All four patients in remission continued maintenance therapy including TKI.

Conclusion: MRD measured with BCR/ABL levels after induction/ consolidation and through follow up represents standard tool for monitoring response and predict relapse.

PEGINTERFERON ALFA-2A FOR THE TREATMENT OF PAEDIATRIC ESSENTIAL THROMBOCYTHEMIA - A CASE REPORT

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Introduction;Essential thrombocythemia (ET) is a myeloproliferative disease characterized by high platelet count that cannot be attributed to other causes and megakaryocytic lineage hyperplasia in the bone marrow. Although less common in children, it generally presents with a more benign course compared to adults.

Matherial and methods: This study describes a 17-year-old male with asymptomatic thrombocytosis observed at the age of 9. The patient's platelet count gradually escalated to nearly $3.000x10^9$/L. Past medical history and clinical examination were unremarkable, ruling out secondary thrombocytosis. Genetic analysis failed to identify mutations in JAK2, MPL and CALR genes, nor the BCR-ABL fusion transcript.

A bone marrow trephine biopsy was consistent with ET. Notably, acquired vWD was detected. Treatment with hydroxyurea resulted in only a partial response, prompting the initiation of second-line therapy with subcutaneous PEGinterferon alfa-2A. The patient has been followed on this regimen for an 80-month period

during which the platelet count has remained stable at 400-600x10^9/L. Signs of hemorrhagic or thrombotic complications have not been observed.
This case emphasizes the diagnostic and treatment challenges experienced in paediatric ET. JAK2-V617F, MPL and CALR mutations, commonly associated with myeloproliferative neoplasms in adults, are not clearly correlated with paediatric ET.
Many paediatric patients with clinical and histological features of ET carry a molecular triple wild-type status.
Conclusion: In contrast to well-defined recommendations in adults, there is no standard approach for risk stratification and management in pediatric ET. Long-term follow-up is crucial to optimize therapeutic strategies and gain a comprehensive understanding of paediatric ET.

PROGNOSTIC FACTORS FOR OVERALL SURVIVAL IN PEDIATRIC PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA

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Introduction: Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy. The aim of the study was to analyze the impact of different clinical prognostic factors that might influence the overall survival (OS) of children with ALL.
Material and methods: In this retrospective cohort study were included all newly diagnosed patients with ALL from age 1 to 14 years enrolled in the Department of Hematology and Oncology, University Clinic for Children`s Diseases Skopje between 2010 and 2017. The treatment was based on the intermediate and high risk arm of the ALL IC BFM 2002 protocol. Univariate and multivariate analysis of prognostic factors for OS were performed. OS was estimated by Kaplan-Meier analysis.
Results: Date from 45 (60.8%) males and 29 (39.2%) females were analyzed. In univariate analysis, the older age (≥10 years) ($P < 0.001$), high WBC count at diagnosis (≥50 x 10^9/L) ($P = 0.001$), NCI high risk ($P = 0.003$), prednisone poor response ($P = 0.015$), poor cytomorphological bone marrow response on day 15 during induction ($P = 0.01$) and positive flow cytometry - based minimal residual disease (≥0.01%) at the end of induction ($P = 0.034$) significantly adversely affected OS. Gender, CNS infiltration and immunophenotype had no statistically significant impact on survival. The older age ($P = 0.003$) and high initial WBC count ($P = 0.004$) were significant independent prognostic factors in the multivariate analysis. The patients in the 1-9 age group and those with WBC count at presentation <50 x 10^9/L had superior survival (5-year OS 83.6% ± 5.1% and 88.4% ± 4.5%, respectively).
Conclusion: In this cohort od Macedonian pediatric patients with ALL, an older age and high WBC count at presentation were independent prognostic factors for overall survival.

ROPEGINTERFERON ALPHA 2b IN THE TREATMENT OF YOUNG HIGH RISK PATIENTS WITH Bcr Abl NEGATIVE MYELOPROLIFERATIVE NEOPLASMS SINGLE CENTRE EXPERIENCE

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Introduction: Ropeginterferon alfa-2b is an important therapeutic tool, currently approved only for treatment of patients with Polycythaemia Vera (PV). Nevertheless, many studies are evaluating its efficiency in Essential Thrombocythemia (ET) and Primary Myelofibrosis (PMF) as well. We present our experience with ropeginterferon alfa-2b in 16 young patients with MPNs, diagnosed and treated at the University clinic of hematology in Skopje, North Macedonia.

Material and Methods: The study included 16 patients with BCR-ABL negative MPN. Responses were evaluated by ELN, IWG-MET and EUMNET standardized criteria.

Results: 11pts were female (69%), with average age at diagnosis at 36 years (17-51), 12 had ET, one PV and three patients had hypercellular phase of PMF; JAK2V617F mutation was detected in 62.5%, CALR mutation in 19% and 19% were triple-negative cases. Bone marrow biopsy was performed prior therapy to establish the eventual presence and grade of fibrosis. Splenomegaly was present in four (25%) while three patients underwent splenectomy because of splenic vein thrombosis. In seven pts of which five ET, ropeginterferon alfa-2b was used as first-line treatment. Evaluation of clinicohematologic response was performed every two weeks along with the drug administration. Complete hematological response was observed in 12 patients (75%), with average time to blood count normalization at 8 weeks using average dose of 150mcg (100-250). Side effects were observed in one patient, without needed drug discontinuation.

Conclusion: Ropeginterferon alfa-2b confirmed its effectiveness and supports the necessity to expand its use in the treatment of young high risk patients with ET and PMF.

Keywords: myeloproliferative neoplasm, essential thrombocythemia, polycythaemia vera, ropeginterferon, primary myelofibrosis.

SEVERE COVID-19 PNEUMONIA IN A CHILD WITH ACUTE LYMPHOBLASTIC LEUKEMIA

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Introduction: Since the beginning of the Covid-19 pandemic, children are more likely than adults to have asymptomatic or mild infection. Children with hematological malignancies could be more susceptible to severe COVID-19 disease due to their immunosuppressive state caused by the malignancy and anticancer treatment.

Case report: A 2-year old girl was diagnosed with standard-risk precursor-B cell acute lymphoblastic leukemia (ETV6-RUNX1 positive) and underwent treatment according to ALL IC BFM 2002 protocol, achieving a complete remission. At the end of the early intensification phase IB the child experienced febrile neutropenia. The workup included a SARS-CoV2 test by real-time reverse transcription polymerase chain

reaction (RT-PCR) in a nasopharyngeal swab sample, which was positive. Blood cell count showed post-chemotherapy aplasia.
The infectious disease was characterized by a severe course complicated with gastrointestinal symptomatology and respiratory failure due to massive bilateral pneumonia requiring supplemental oxygen. Several potential therapies including supportive interventions, intravenous immunoglobulins, oral azithromycin, corticosteroids (dexamethasone), IL-6 inhibitor (tocilizumab) and transfusion of convalescent plasma were applied.
The child responded to this treatment with significant improvement in clinical and pulmonary function, allowing discontinuation of oxygen therapy. The repeated PCR test for COVID was negative for 4 weeks' post-symptom onset. After being cured successfully, she continued intensive chemotherapy according to the protocol followed by prolonged low-intensity maintenance phase and has remained in continuous complete remission.
Conclusion: This case report represents a good example of the severe clinical course of COVID-19 infection in immunosuppressed patient achieving favorable outcome following use of specific therapy.

SEVERE GASTROINTESTINAL PRESENTATION OF HENOCH-SCHÖNLEIN PURPURA WITH DECREASED FACTOR XIII ACTIVITY: A CASE REPORT

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Introduction: Henoch-Schönlein purpura (HSP) is a non-granulomatous, immunoglobulin A-mediated small vessel vasculitis primarily affecting children and young adults. It is characterized by its diverse clinical presentation, often encompassing cutaneous, joint, and renal symptoms. However, a subset of HSP cases exhibits a unique manifestation involving the gastrointestinal system. Here, we report a case of HSP with severe gastrointestinal manifestation.
Case report: A 5-year-old boy, previously healthy, presented two weeks before admission with a purpuric skin rash on his lower limbs. After two weeks, his condition deteriorated, and he was admitted, with new skin changes emerging on his upper limbs, genital and gluteal regions, accompanied by swelling in the joints, genital area, and transient microhematuria. He received oral prednisolone treatment, followed by parenteral prednisolone and a proton pump inhibitor.
On the 7th day, he experienced severe episodes of abdominal pain accompanied by gastrointestinal bleeding (hematochezia) requiring a blood transfusion. Laboratory and imaging data revealed normal findings, except for the low level of factor XIII of 36% (normal range 50-150%). Cryoprecipitate transfusion was given twice, which shortly resulted in a cessation of abdominal pain and gastrointestinal bleeding, but the skin rash still persisted.
Conclusion: The convergence of gastrointestinal symptoms in Henoch-Schönlein purpura, along with cryoprecipitate transfusion for low factor XIII levels, presents a complex treatment scenario. Modifying approaches to match these specific details is essential for achieving improved patient outcomes.
Keywords*:* Henoch-Schönlein purpura; gastrointestinal manifestation; factor XIII; cryoprecipitate

SUCCESSFUL TREATMENT WITH BRENTUXIMAB VEDOTIN AS FIRST-LINE AGENT FOR ADVANCED HODGKIN LYMPHOMA: CASE REPORT

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Introduction: Current guidelines for advanced Hodgkin Lymphoma (HL) recommend adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) or escalated bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) as first-line regimens. ABVD appears to be as effective, with fewer side effects, as escalated BEACOPP. Brentuximab vedotin, a CD30-directed antibody conjugate is approved by the Food and Drug Administration and the European Medicines Agency for the treatment of advanced HL.
Case report: We present you 19-year-old man with a tumor mass on the right side of the neck, with individual lymph nodes (LN) up to 45 mm. Radiological processing verified multiple micronodular changes in the right lung. In the mediastinum in all groups, conglomerates of pathologically enlarged LN, the largest 58mm, in the abdomen up to 37mm. Bone marrow biopsy showed no infiltration by an underlying disease. The patient was found to have clinical stage IVBE Hodgkin's lymphoma, with lung involvement. nodular sclerosis subtype. The value of the International prognostic score was 3. He was treated with the 6 cycles of A-AVD (Brentuximab Vedotin- Adriablastin, Vinblastin, Doxorubicin) protocol with disease remission. Due to the residual positivity of the interim PET CT, the implementation of Involved field radiation therapy is applied. The patient achieved complete remission which was maintained during 8 month follow-up.
Conclusion: A recent advance in the treatment of advanced HL is the shift to molecularly targeted cancer therapy. Brentuximab vedotin specifically targets HL cells. Compared to cytotoxic chemotherapy that is usually used in we conducted brentuximab vedotin with the aim of reducing the toxic effects while maintaining the efficacy, that is achieved.
Key words*:* Hodgkin, lymphoma, brentuximab vedotin, ABVD, efficacy.

SORAFENIB WITH ATRA PLUS CHEMOTHERAPY IN HIGH RISK FLT 3 POSITIVE APL

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Introduction: Acute promyelocytic leukemia (APL) is a unique subtype of acute leukemia characterized by abnormal proliferation of promyelocytes, life-threatening coagulopathy, and the chromosome translocation t(15;17)(q22;q11-12), which results in the PML-RARα fusion protein. This protein destabilizes homeostasis, maturation and hampering the maintenance and differentiation of hematopoietic cells into different lineages, fixing cells in the promyelocyte stage. *FLT3* is a gene that belongs to the class III receptor tyrosine kinase family. Deregulated activation impairs hematopoiesis and will contribute to leukemogenesis. *FLT3* mutations are present in approximately 2% to 38% of APL cases, depending on ITDs or mutations in the tyrosine kinase domain. *FLT3* mutations have been identified as being highly related to hyper leucocytosis.Material and methods: we described two male patients with high-risk APL pml/rar alpha and Flt-3 positive. Patient 1: F.N. 16 years old male presented with hyper leucocytosis WBC:191,Hb 89 Plt:21 and severe hemostasis disorder with hypofibrinogenemia and hemorrhagic syndrome. Patient 2: M.D. 40 year old male, with hyperleukocytosis WBC 53,2 Hb 86 Plt 33. As a high-risk APL we introduce induction therapy with ATRA 45mg/m2 and chemotherapy consisted ARA-C 100mg./m2 (7 days) and antracyclin. From day +1 we add Sorafenib multi-kinase inhibitor in dose 400mg.

during a 14 days.Results: after induction therapy both patient are in complete hematologic and molecular remission. PML-RARA and FLT-3 negative. After consolidation therapy they are still in CR.Conclusion:addition of Sorafenib to standard ATRA plus chemotherapy regimen in high-risk Flt-3 positive APL leads to complete remission and good outcome in this fatal form of acute leukemia.

SMALL BOWEL PERFORATION IN PATIENT WITH ACUTE MYELOID LEKEMIA-CASE REPORT

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Introduction: Acute leukemia not only affects the hematopoietic system directly but also involves many organs and tissues. The etiology of most leukemic gastrointestinal cornplications is caused by primary invasion by leukernic cells, immunodeficiency with deep neutropenia from the leukemia and antileukemic drugs. Chemotherapy may directly produce necrosis and weakened areas in the bowel wall while destroying the underlying malignant cells. Bacterial, fungal, or viral overgrowth then can invade the bowel and produce ulceration, pseudomembrane formation, or perforation. Gastrointestinal perforation is potentially life-threatening conditions associated with high overall mortality rates of 10% for small bowel obstruction, 20% for large bowel obstruction, 30% for intestinal perforation, and up to 70% for intestinal perforation with diffuse peritonitis. Case report: we present a 48 years old female with AML, treated with DA regimen. After second cycle she present with severe abdominal pain. Abdominal CT scan showed a distended small bowel conglomerate at the level of the ileum with an edematous appearance, and subhepatic and pelvic free fluid in addition to a change from necrotic to ischemic features. The patient was treated in operating theatre, resection of bowel and temporary stoma were performed. She is received 2 cycles Venetoclax Azacytidine and second surgery was obtained.

Conclusion: If abdominal emergency surgery is required due to gastrointestinal perforation in patients with hematological malignancies, temporary or permanent intestinal stoma might be preferred to primary intestinal anastomosis not only to reduce the risk of septic shock due to fecal peritonitis but also to enable treatment of the underlying disease to be continued as quickly as possible.

A CASE REPORT OF ACQUIRED HAEMOPHILIA WITH MASSIVE SKIN AND MUSCLE BLEEDING

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Introduction: Development of autoantibodies directed against plasma coagulation factors may lead to a life-threatening hemorrhage. Generally the autoantibodies are directed against factor VIII. Hence, the condition is called acquired haemophilia A.

Materials and methods: A case of a 66-year-old male presenting with a large hematoma to his left leg and right chest is discussed.

Results: On the day of admission the blood tests revealed hemoglobin level of 76g/L, WBC 12x10(9)/L, and platelet count 693x10(9)/L. Screening hemostasis tests revealed: prothrombin and thrombin time in normal range, but significantly prolonged APTT to 59sec (normal range 26-34). The d-dimers were 3393

microg/L. Factor VIII level was 0.7% and the Bethesda assay confirmed inhibitor titer of 10.2 BU. The bleeding was treated with a by-passing agent rFVIIa. Immunosuppressive treatment was started with Cyclophosphamide 100mg and Prednisone 100mg daily. During the hospital stay the patient deteriorated clinically and developed a hemorrhagic shock. This gradually improved resulting in him being discharged after 25 days of hospital stay.

Conclusions: This case report illustrates a case with acquired hemophilia A with delayed diagnosis and development of a life-threatening condition where the treatment was delayed and the outcome uncertain. Acquired haemophilia should be considered whenever there's a patient with an unexpected massive bleeding, no previous history of a bleeding disorder and prolonged APTT.

A PREDICTIVE INSTRUMENT FOR PROBABILITY OF TREATMENT AT PATIENS WITH ASYMPTOMATIC EARLY-STAGE CHRONIC LYMPHOCYTIC LEUKEMIA-SINGLE CENTER EXPERIENCE

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Introduction: Early-stage patients with chronic lymphocytic leukemia (CLL) are diagnosed without need for treatment, managed with following. The distinct course of the disease is diverse, and planning treatment is barely projected at diagnosis.The aim of the study was first-time evaluation of Iinternational Prognostic Score to predict time to first treatment (TFT) in Macedonian patients with early stage CLL (International Prognostic Score for early-stage CLL IPS-E).

Matheral and methods: Retrospective study of asymptomatic patients with CLL at early stage of disease in a period of time from January 2012 to January 2022. The median follow-up was 60 months (1-120 months). Individual patient data from 120 treatment-naïve CLL patients with Binet A stage were analyzed to composed International Prognostic Score for Early-stage CLL and correlated with time to treatment failure (TTF).We presented IPS-E using three covariates: unmutated immunoglobulin heavy variable gene (IGHV), absolute lymphocyte count higher than 15×10^{9}/L, and presence of palpable lymph nodes. The IPS-E was the sum of the covariates (1 point each), and separated low-risk (score 0), intermediate-risk (score 1), and high-risk (score 2-3) patients showing a distinct TFT.

Results: Using IPS-E patients were distributed in three groups: low risk with 7, 5%, intermediate risk with 44, 1% and high risk patients 48, 3%. Average TFS was 29, 3 months for low-risk group; 28, 6 months for intermediate-risk group and 27; 1 months for high-risk group.

Conclusions: The IPS-E is a simple prognostic model that predicts the probability of treatment necessity in patients with early-stage CLL.

Keywords: chronic lymphocytic leukemia, asymptomatic, early-stage, International Prognostic Score

A RARE CASE OF INFANTILE GENITAL HEMANGIOMA – CASE REPORT

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Introduction: Infantile hemangiomas (IHs) are the most common benign tumors of infancy with a prevalence of 4.5%, less than 1% are in the genital region.
Materials and methods: This is a case of a 5 weeks old infant presenting with an IHs in the genital region.
Results: The physical examination revealed large genital cavernous hemangioma with dimensions 5 cm x 4 cm involving labia majora, labia minora and clitoris, respectively. Also, there were several hemangiomas on the lower abdominal wall. Nonindurated ulcer of size 1 cm x 1 cm with well-defined margins and base covered with granulation tissue was present on the right labia majora. Ultrasonography of the abdomen, brain and heart and ECG were normal. We started therapy with Propranolol 1mg/kg, in inpatient setting, for 24h monitoring of possible side effects. The therapy was well tolerated, without any side effects. After one week we increased the dose of propranolol to 2mg/kg in outpatient setting. Very soon, after two weeks, there was great response to the therapy, the hemangioma started to decrease in the volume and the ulceration was gone. On the age of 16 months we stop the therapy with propranolol when the IHs were almost completely disappeared.
Conclusion: Genital IH are rare but at high risk of ulceration and possible functional impairment. If therapy is indicated, propranolol is effective in the treatment of IH, however, it should be used cautiously, and patients must be closely monitored for adverse effects
Keywords: Infantile hemangioma, Genital hemangioma, Propranolol

ACQUIRED HEMOPHILIA A AND SYSTEMIC CONNECTIVE TISSUE DISEASE: A CASE REPORT

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Introduction: Acquired hemophilia A is a rare, life-threatening condition that manifests itself in spontaneous bleeding, mostly in soft tissues. The diagnosis of this disease should be considered in unexplained bleeding, especially in elderly patients.
Case presentation: An 83-year-old female patient was initially hospitalized at the vascular surgery of the Clinical Center of Montenegro due to deep venous thrombosis (DVT) of the right leg. After being discharged from vascular surgery, she noticed a bruise on the skin of her abdomen, for which she was hospitalized again. Surgical drainage of the hematoma in the anterior abdominal wall and tamponade, then new tamponade and revision were performed. During the second hospitalization, the laboratory findings showed anemia with prolonged aPTT values (Er 2.74, Hg 76, MCV 86, D dimer 3.73, aPTT 113.7, PV normal). A reduced level of factor F VIII (< 0.4 I.U./dl) is found. In a 50:50 mixing study with normal plasma, aPTT and factor VIII did not normalize. The inhibitor level was high (224 BU/mL). The patient was treated with corticosteroids, and intravenous immunoglobulins, and therapeutic plasma exchange with factor VII recombinants was performed. There is a gradual stabilization of the laboratory findings as well as the resolution of the hematoma, there have been no repeated manifestations of cowering. Screening tests were carried out in terms of malignancy and autoimmune diseases. The findings of immunoserology indicated a possible systemic connective tissue disease, which was also confirmed by a rheumatologist. She was treated with pulse doses of corticosteroids. The aPTT values remained stable. Due to previously verified DVT, treatment with rivaroxaban was started. Conclusion. Acquired Hemophilia A can be a reversible coagulopathy. Early diagnosis and early initiation of treatment can lead to the successful resolution of the disease. An adequate approach includes screening for the etiology of acquired hemophilia.
Keywords: acquired hemophilia, inhibitor, etiology, diagnosis, treatment

AUTOIMMUNE CYTOPENIAS IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA: SINGLE CENTER EXPERIENCE

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Objective: Autoimmune cytopenias, particularly autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP), complicate up to 25% of chronic lymphocytic leukemia (CLL) patients. Their occurrence correlates with a more aggressive disease. AIHA and ITP are more frequently found in patients with unfavorable biological risk factors for CLL. The aim of this study was evaluation of autoimmune cytopenias in chronic lymphocytic leukemia patients from Republic of North Macedonia in correlation with genetic structure of pathologic B lymphocyte.
Methodology: This is a retrospective study of patients with CLL, diagnosed and followed in the period between January 2012 and January 2022. Individual data from 100 treatment naïve CLL patients were analyzed, and mutational status and configuration of IGHV-IGHD-IGHJ rearrangements and genetics were analyzed using reverse transcriptase– polymerase chain reaction (RT-PCR) and sequencing methodology at the center for bimolecular pharmaceutical analyses, faculty of pharmacy, Skopje, Republic of North Macedonia.
Results: Our evaluation have shown that 10% of CLL patients had AIHA and 4% had ITP. Most of the patients were male (90%) with Binet B stage (60%) and unmuteted IGHV genes (70%). The most frequently expressed IGHV subgroup was IGHV1-69 (71%), followed by IGHV3-13 and IGHV4-4 (14%). The genetic results presented unfavorable cytogenetics with 11q deletions and NOTHCH mutation.
Conclusion: The results of our study are consistent with published studies with pecific molecular signature.

CLINICAL FEATURES AND OUTCOMES IN NEWLY DIAGNOSED PAEDIATRIC IMMUNE THROMBOCYTOPENIA

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Introduction: Immune thrombocytopenia (ITP) is a disease associated with autoimmune destruction of platelets. In 50-65% of cases, infection is the triggering factor.
Aim:The aim of this study was evaluation of clinical features and outcomes in newly diagnosed ITP patients in the last five years in our clinic.
Methods:We analysed the data of 184 patients aged between 1-14 years, regarding their gender, clinical presentations, history of infections, treatment response ant outcome.
Results:Out of 184 cases, 93 were male (50.5%) and 91 were female (49.5%). One hundred thirty (70.6%) had hemorrhagic syndrome (bruises, petechiae, epistaxis or gingival bleeding) and 121 (54.8%) had a previous infection. A hundred and eight (108) (58.7%) had severe, 46 (25%) had moderate, and 30 (16.3%) a mild form of ITP. Spontaneous remission was observed in 48 patients. We treated 24 (18%) patients with IVIG. Fourteen patients improved their platelet counts within 3-5 days, and the rest 10 within 10 days. One hundred thirty-six (85%) patients were treated with corticosteroids, and in 92 patients the platelet count improved within 3-5 days and in 44 (32.2%) within the 10th day of treatment.

Conclusion:The most common age at diagnosis was 4 years, with no difference between genders. A faster therapeutic effect (in the first five days) was observed in patients treated with IVIG than in patients treated with corticosteroids. The majority of patients (147-79.8%) had acute ITP and 37 patients (20.2%) developed chronic disease.

Keywords:Paediatric ITP, IVIG, corticosteroids in thrombocytopenia

CLINICAL PRESENTATION AND OUTCOMES OF PAEDIATRIC AUTOIMMUNE HEMOLYTIC ANEMIA – A RETROSPECTIVE ANALYSIS

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Autoimmune hemolytic anemia (AIHA) is a rare disease in childhood characterized by autoantibodies against erythrocyte membrane, causing excessive or uncompensated hemolysis and a clinical range from mild to severe life-threatening anemia.

We conducted a retrospective study of 18 AIHA patients treated at the University Children's Hospital Skopje between 2018 and 2022.

The mean age at diagnosis was 4.92 years, with 61% males and 39% females. Common manifestations included fever, jaundice, hepatomegaly or splenomegaly, with 61% exhibiting two or more features. The mean hemoglobin level at presentation was 63 g/L, necessitating red blood cell transfusion in all cases. Direct antiglobulin test (DAT) was negative in only one patient. Indirect antiglobulin test (IAT) was positive in 50%. Acute transient AIHA was observed in 16 patients, while 2 patients had chronic AIHA. Notably, both chronic patients were also diagnosed with Gilbert's syndrome. Primary AIHA was diagnosed in 44% of the cohort and all of them achieved remission after an average 4-week corticosteroid treatment. Secondary AIHA was identified in 56%, predominantly associated with infections, while one patient had Evans syndrome and one had autoimmune pancreatitis. Patients with chronic secondary AIHA received a combination of corticosteroids, immunoglobulins, rituximab and immunosuppressants. All other secondary AIHA patients responded well to corticosteroid monotherapy or a short course of immunoglobulins.

Secondary AIHA patients experienced a prolonged recovery compared to those with primary AIHA, who achieved complete remission. These findings highlight the importance of appropriate investigation and treatment strategies for AIHA.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS OF ELTROMBOPAG: A RETROSPECTIVE STUDY FROM THE CLINICAL PHARMACIST PERSPECTIVE

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Introduction: Thrombopoietin is the main cytokine regulating megakaryopoiesis and platelet production. Eltrombopag interacts with the transmembrane domain of thrombopoietin receptors and initiates signaling cascades inducing proliferation and differentiation from bone marrow progenitor cells. The aim of the study was to determine drug interaction at patients that are receiving Eltrombopag along with other medications.
Materials and methods: A retrospective, longitudinal study was conducted at the Hematology Clinic in Skopje, N. Macedonia. A clinical pharmacist, focusing on Eltrombopag and concomitant medications interactions, reviewed a total number of 16 patient's histories for the period of 6 months (January-June 2023). Anamnestic data on additional drugs, herbal supplements, vitamins, minerals were also taken. Potential drug interactions were identified using Stockley's interactions checker, categorized by severity and subclassified into co-administered drugs altering pharmacokinetics.
Results: A total number of 73 interactions were identified, of which 23 (31.51%) were with moderate clinical relevance, 14 (19.18%) were with no clinical importance and required counseling about possible adverse effects and additional monitoring. The rest of 36 (49,32%) interactions were without clinical significance. Additionally, we determine that 7 (9.59%) of total interactions directly related to patients receiving Eltrombopag (ciclosporin, atorvastatin, rosuvastatin, dexamethasone, prednisolone, valsartan, and magnesium) and categorized as moderate and needs close monitoring.
Conclusion: This study demonstrates toxicity potential of Eltrombopag at patients associated with concomitant medicines. Close collaboration of physicians and clinical pharmacists is necessary in all cases where patients are receiving Eltrombopag along with other medications in order all significant interactions to be identified, prevented and managed.

DISCONTINUATION OF IMATINIB TREATMENT IN PATIENTS WITH CML IN PATIENT WITH DEEP MOLECULAR RESPONSE–SINGLE CENTRE EXPERIENCE.

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Introduction: Tyrosine kinase inhibitors (TKIs) represent a major breakthrough in the treatment of patients with chronic myeloid leukemia (CML). These agents have transformed CML from a disease with a dismal prognosis into a more indolent disease with survival comparable to that of the general population. Studies in CML patients with a sustained deep molecular response have demonstrated that stopping TKI therapy is feasible and safe. Current available data show that 40% to 60% of patients who stop therapy relapse and molecular relapses typically occur within first 6 months after treatment discontinuation, but nearly all relapsing patients regain molecular response upon reinitiating of the TKI.

Materials and methods: In our Clinic we have attempted to stop Imatinib treatment in 18 patients in the last 6 years. Median age of this group of patients was 48.4 years (range 21-74 years), and 77% were female (14 females, 4 male). Median duration of CML before stopping Imatinib treatment was 8.6 years (range 2-19 years), while median duration of TKI treatment before stopping Imatinib was 6.5 years (range 1-13 years).

Results: Successful stop of Imatinib treatment was registered in 11(61%) of patients. Median duration of the period without treatment in our group of patients is 23.3 months (range 3-76 months). All patients who restarted therapy with Imatinib after unsuccessful stop, achieved deep molecular remission 6 months after reintroducing Imatinib treatment.

Conclusion: Our results are similar to already reported data in other studies and confirmed that stopping of Imatinib treatment is safe and possible in selected number of cases of CML patients in sustained deep molecular response.

EVALUATION OF IMMUNOLOGICAL CHANGES IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA DURING CHEMOTHERAPY

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Introduction: Acute lymphoblastic leukemia (ALL) is the most common malignant disease in childhood. Chemotherapy and the malignant disease itself cause suppression of the immune system and the development of secondary immune deficiency.

Materials and methods: This study includes 17 children aged 2 to 12 years, with newly diagnosed ALL, treated at the Oncology Department at the University Clinic for Children's Diseases - Skopje over a period of 1 year. All children were treated according to the BFM-ALL-IC 2002 protocol. The total number of Leukocytes (neutrophils, lymphocytes), the level of immunoglobulins (Ig) in serum (IgA, IgG, IgM), IgG subclasses, and lymphocyte subpopulations (CD3, CD4, CD19, CD45) were analyzed at 3-time points: before the start of chemotherapy, after completion of the induction phase of therapy and after completion of the reinduction phase.

Results: IgM in serum has the lowest values after completion of the induction phase, t (0.33 vs 0.76, p=0.002). An overall statistically significant difference was found for p=0.02 for subclass IgG1, p=0.015 for subclass IgG2, p=0.014 for subclass IgG3, and p=0.027 for subclass IgG4. For p=0.017, an overall statistically significant difference in the values of CD19 cells between the three-time points was confirmed. CD19 cells were with significantly lower values after the induction phase compared to the initial ones (1.22 vs 15.3, p=0.008) and significantly lower values at the end of therapy compared to the values before therapy (2.5 vs 15.3, p=0.021)

Conclusion: Modern multiagent chemotherapy in the immune system of children with ALL leads to secondary immunodeficiency. Detection of secondary immune deficiency is important for successful and much more easy treatment.

EXPERIENCE OF THE DIAGNOSIS AND TREATMENT OF VISCERAL LEISCHMANIASIS IN PEDIATRIC POPULATION AT UNIVERSITY CLINIC FOR CHILDREN'S DISEASES IN THE PERIOD 1990-2023

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Visceral leishmaniasis (Kala – Azar), is a vector borne disease caused by a protozoan of the Leishmania genus complex. A phlebotomus/ sand fly transmits the parasite from person to person or via animal reservoir. The infected person may express mild to severe clinical manifestation but there are five obligatory characteristics: organomegaly (massive splenomegaly and moderate hepatomegaly), prolonged fever, anemia, trombocytopenia, dysproteinemia/ hypergammaglobulinemia. The diagnostic methods were: demonstration of amastigotes in bone marrow aspirate (BMA), IFAT or Real time PCR. The treatment untill April 2019 was with Glucantime-D,after that with liposomal Amphotericin B.

In the period of 1990 to 2023 on the UC for Children's diseases, were diagnosed and treated 101 children with VL. The analysed data is regarding age, sex, clinical presentation and treatment. 80% are under age of 5, equal gender presentation, mainly from Skopje, Strumica, Prilep, Debar and Kumanovo.The dominant symptom was prolonged high fever -83 %, anemia- 92%, thrombocytopenia or pancytopenia -85%, hipergammaglobulinemia- 80 %, hepatosplenomegaly -60% Diagnosis was confirmed by BMA in 90% , IFAT in 10%, hepatic or lymph node biopsy -4% ,PCR – 2 %. Glucantime was applied in 74 patients, Amphotericin B – 13 pct.

Macedonia is an endemic area for VL. It always should be taken in consideration when having a child with prolong fever and organomegaly followed by hematological cytopenias. The diagnostic method is simple and the treatment is highly effective.

EXTRACORPOREAL PHOTOPHERESIS FOR CHRONIC GvHD TREATMENT IN PATIENTS UNDERGOING ALLOGENEIC STEM CELL TRANSPLANTATION – CASE REPORT

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Introduction: Up to 70% of patients undergoing allogeneic HSCT will suffer graft versus host disease (GvHD) to some extent. According to data of prospective studies ECP is able to provide overall response rates in cGvHD in 71% of patients with cutaneous manifestations, in 62% of patients with cGvHD of the gut, 58% of patients with hepatic manifestation, 63% of patient with cGvHD of the mouth.
Material and methods: We have performed ECP in 7 patients treated with allogeneic HSCT. Using the standard 1500ml of processed blood. As anticoagulation method we used unfractionated heparin. Peripheral venous access was used in 71% od the patients. The protocol included 2 procedures in 2 consecutive days as 1 cycle. We have started with 1 cycle every 2 weeks for the first 3 months, then 1 monthly until 1 year.
Results: The overall response rate in our patients with cutaneous cGvHD was 73%, and with hepatic cGvHD around 60%. In a patient with SAA treated with MUD allogeneic HSCT, who suffered from cutaneous and hepatic cGvHD refractory to 3 lines of immunosuppression therapy, we started ECP with the standard protocol for 1 year. We achieved a complete response measured by normalization of the liver enzymes, bilirubin levels and alkaline phosphatase. The skin lesions were in almost full regression, and there was no need of additional immunosuppressive therapy.
Conclusion:ECP is a safe and effective immunomodulatory therapeutic approach in patients treated with allogeneic HSCT suffering from chronic GvHD

GLANZMANN THROMBASTHENIA - A CASE REPORT OF RARE BLEEDING DISORDER

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Introduction: Glanzmann thrombasthenia (GT) is a rare autosomal recessive bleeding disorder associated with severe platelet dysfunction. GT is due to quantitative or qualitative defects of the platelet membrane integrins αIIb and β3, resulting from mutations in ITGA2B and/or ITGB3 genes. These integrins form platelet glycoprotein GP IIb/IIIa, which acts as the platelet fibrinogen receptor, and is thus essential molecule to platelet aggregation and hemostasis. Patients tend to present in early childhood with easy bruising and severe mucocutaneous bleeding.
Case report: A 2-year-old girl presented with recurrent massive epistaxis from infancy often associated with consecutive severe anemia. Additionally, she had a history of easy and spontaneous bruising in her extremities and prolonged bleeding following immunization. Family history was unremarkable and there were no known bleeding disorders in the family. Investigations revealed normal platelet count and normal morphology on peripheral blood smear. Screening test of the hemostatic system (PT, APTT and TT) was normal. Von Willebrand disease was ruled out as well. Platelet aggregation studies showed normal platelet aggregation with ristocetin and very reduced platelet aggregation with ADP and collagen. The GPIIb-IIIa expression rate`s by flow cytometry were markedly decreased confirming the diagnosis of GT. Epistaxis were successfully managed with supportive care including a nasal pack insertion and antifibrinolytic therapy. Platelet transfusion was given only in one excessive episode.

Conclusion: GT is a rare inherited bleeding disorder but should always be considered as differential diagnosis while evaluating any case of bleeding disorder. With careful early diagnosis and proper supportive care, GT has a very good prognosis.

HOW TO TREAT HISTIOCYTIC SARCOMA, A RARE MALIGNANT TUMOUR?

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Introduction: Histiocytic sarcoma (HS) is an extremely rare malignant neoplasm, accounting for less than 1% of all hemato-lymphoid neoplasms. The tumour cells are derived from monocyte/macrophage lineage and express histiocytic markers, including CD68, CD163, and Lysozyme.
Case report: A 60-year-old man presented with a right-sided neck tumour mass measuring 49mm×39mmx39mm. Microscopy of the lesion revealed a markedly pleomorphic tumour, composed of large cells with vesicular nuclei. Immunohistochemical staining of the tumour cells revealed that LCA S100, CD33, CD68, CD163, CD31, CD4, CD10 and Vimentin were positive.
Radiology evaluation pointed to enlarged nodes at axillae and inguinal regions. Bone marrow biopsy confirmed bone involvement. The patient received systemic chemotherapy (cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone [CHOEP] regimen). After three cycles of chemotherapy, PET CT imaging revealed a hypermetabolic cervical lymph node (21× 24mm), SUV max 21.74. The chemotherapy regimen was changed to ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin). Three cycles of therapy were applied and then an autologous stem cell transplant was performed. Control PET CT revealed hypermetabolic cervical lymph node (10x6x7 mm), SUV max 4,09. Radiotherapy had been applied on the right side of the neck, including radiation at the base of the tumour Control PET CT confirmed remission which persist for tree years of follow-up.
Conclusion: HS is an extremely rare malignant neoplasm of the monocytic/macrophage lineage, with no standardized chemotherapy regimen for the multisystemic disease. Metastatic patients have a more aggressive clinical course. High-dose chemotherapy including autologous stem cell transplantation may be an adequate therapy approach.
Key words: Histiocytic sarcoma, markers, CHOEP, ESHAP, stem cell transplantation

QUALITY OF LIFE IN PATIENTS TREATED WITH HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Introduction: Analyzing quality of life undoubtedly incorporates physical, psychological, emotional, and social components as an integral part of the clinical assessment.
Material and methods: Our study included 80 patients treated with autologous and allogeneic HPSCT at University Clinic for Hematology -Skopje. A questionnaire created by the FACIT organization was used, filled in through a standardized interview. All patients were analyzed after the HPSCT and at 6 months and 12 months for patients with autologous and allogeneic HPSCT respectively. Physical, social/family, emotional and functional well-being sections were of greatest interest in our analysis. A separate specialized scale for additional concerns was added.
Results: 85% of patients were treated with autologous HPSCT and 15% with allogeneic HPSCT. The quality of life after performing HPSCT in all patients had a score range of 82.5 and improved by 30%, reaching 107.1 at next assessment. In patients treated with autologous HPSCT the functional scale was 11.9

and improved by 70%. The quality of life after performing HPSCT at these patients had a value of 74.3, with a significant improvement of 49% to the value of 110.9. In patients treated with allogeneic HPSCT, the lowest value of 10.1 was observed at the additional concerning scale, double improved by 1 year. The quality of life after performing HPSCT in these patients had a value of 68.2, with a significant improvement of 36% to 92.7. An unfavorable factor affecting the quality of life is the occurrence of GVHD complication, observed in 3%.

Conclusion: HPSCT in the treatment of hematological diseases is a complex intervention that affects the quality of life of patients.

INFLUENCE OF SINGLE NUCLEOTIDE POLYMORPHISMS IN MTHFR GENES ON OCCURRENCE OF HAEMATOLOGICAL SIDE EFFECTS CAUSED BYMTX IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Introduction: Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease that leads to progressive disability, systemic complications, early death. Methotrexate (MTX) is the disease-modifying anti-rheumatic drug of first choice in RA. Treatment discontinuation due to toxicity is present in approximately 30% of patients, with the most common gastrointestinal, haematological and elevated transaminase as adverse events (AEs). Polymorphisms of MTHFR that cause mild deficiencies in enzyme activity have been identified and it has been suggested that a reduced enzyme activity could lead to an increased risk for MTX-related toxicity.

Aim of the study: to investigate influence of Single Nucleotide Polymorphisms(SNP's) in MTHFR gene on the occurrence of the haematological AE's due to MTX in patients with RA.

Material and methods: 78 patients with active RA (ACR 1997) were included in the study to receive oral MTX in dose of 15mg. weakly in the period of 180 days. Median age:56 years Female: 59 Male:19. All patients were monitored in haematological AE's. SNP's polymorphism in MTHFR were performed using PCR method: 677C>T (rs1801133) and 1298A>C (rs1801131).

Results: AE's were present in 20 patients 20/78(25.6%). Haematological AE's: 6/78pts (7,7%) (anaemia 2, neutropenia 2, pancytopenia 2). Discontinuation of therapy due to AE was conducted in 13 patients (16.7%). Hematologic AEs were recorded in 2 pts with the CC genotype for MTHFR C677T, 2 pts with the CT genotype for MTHFR C677T, and in 2 pts with the AC genotype for the MTHFR A1298C polymorphism.

Conclusion: Genetic predictors are an excellent tool for the selection of therapy in patients with RA.

PREGNANCY RELATED ACQUIRED HAEMOPHILIA A- CASE REPORT

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Introduction: Acquired hemophilia A (AHA) is a rare bleeding disorder caused by neutralizing autoantibodies called inhibitors, against coagulation factor VIII (FVIII) and it's occurs without a previous history of bleeding. Approximately 50% of this disease derives from basic conditions, such as autoimmune diseases, cancer, and pregnancy.
Material and methods: We report a 24-year-old postpartum female with acquired hemophilia A who initially presented with hematoma and pain on the right leg and left forearm and when first line therapy doesn't work, presented with new hematomas in the gluteal region and in the left hand. Laboratory analyzes in this patient showed: activated prothrombin time was (PT) 13″ (13″) and activated partial thromboplastin time (aPTT) was 110″ (22″). The factor VIII activity was 0.19%. Furthermore, Bethesda assay showed a FVIII antibody titer of 66 Bethesda units (BUs).
Results: The treatment requires a 2-pronged approach: treatment of the bleeding and elimination of the inhibitor. After hemostatic agents and immunosuppressive were used and inhibitors were eradicated, the patient achieved complete remission.
Conclusion: It is essential to recognize the development of disease earlier in pregnant woman.

SYNTHETIC DATA IN EVIDENCING HYPOTHESIS FOR GRANT APPLICATION TO COLLECT LARGE DATASET OF ROUTINE HEMATOLOGY TESTING: A CALL FOR NEW NARRATIVE?

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Introduction: Artificially generated or Synthetic data (SD) is helping the researchers in making data more accessible for their research and development, even carrying major limitations like 'questionable replication of the content and properties of original dataset' and others.
Material and Methodology: For present study, we used synthetic data approach for hypothesis testing in routine hematology laboratory to strengthen our proposal of collecting large dataset. After, the introduction of extended analytical channels in advance CBC analyzers potential morphological parameters (cell population data) are routinely generated. Focusing more than a hundred parameters against every analysis to read any specific deviational trend (fingerprint) is a real challenge that becomes opportunity for machine learning (ML). Data were extracted, labeled, and pre processed for application of ML models through computer command language (Python).
Results: A total of 5860 cases belong 65 study groups was an original dataset. At this point, the highest accuracy for our ML model was remained as higher as just of 45%. Next, data synthesis step was performed for getting double number (11720) of total cases, and similarly ML models were called. In results, worth discussing points including a noticeable accuracy of 85.61% with 91.92% precision for random forest classifier followed by decision tree, support vector machine, logistic regression, Knearest neighbor, stochastic decent, and Gaussian naïve bayers were noted.
Conclusion: Although for present study synthetic data bridge data access gap to evidence our hypothesis at grant application stage while the original real data remains the preferred choice as we requested in our proposal to funding agency. It is a call for new narrative to examine synthetic data's validity and its utility in research through future discussions and studies for awareness among our hematology community.