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Hematological toxicity of mTOR inhibitors is mild and dose-dependent in patients with tuberous sclerosis and subependymal giant cell astrocytoma

Bartosz Urbański*, Bartłomiej Pawlik, Wojciech Młynarski, Joanna Trelińska

Department of Pediatrics, Oncology and Hematology, Medical University of Lodz, Łódź, Poland

Abstract

Introduction: Everolimus is the primary therapeutic option for patients with tuberous sclerosis complex (TSC) and subependymal giant astrocytoma (SEGA). This study aimed to assess the effect of everolimus, a mammalian-target-of-rapamycin (mTOR) inhibitor, on complete blood count (CBC) parameters in patients with TSC and SEGA.

Material and methods: The study included 18 pediatric patients with TSC-associated SEGA tumors as indications for everolimus treatment. During the standard dose therapy and maintenance phase (<50% of standard dose), CBC results and everolimus whole blood concentrations were collected at five study time points.

Results: Everolimus contributed to decreasing almost all blood cell values. The most severe toxicity occurred six months after therapy commenced. Dose reduction resulted in slightly normalizing parameters, but they did not return to the initial ones in all cases. During the study, only a few instances of cytopenia were reported. The most common abnormality was granulocytopenia, observed in one in three patients. Almost all cytopenias occurred during the standard treatment phase, and none were classified as severe. Hematological toxicity was not the reason for therapy interruption or withdrawal.

Conclusions: A decrease in almost all hematological parameters is widespread during everolimus therapy. Hematological toxicities are rare and mild. The unique abnormality for mTOR inhibitors is microcytosis. Reduction of mTOR inhibitor dose results in a lower frequency of hematological side effects.

Key words: tuberous sclerosis complex, mammalian-target-of-rapamycin inhibitors, subependymal giant cell astrocytoma, hematological toxicity, microcytosis, children

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Introduction

Tuberous sclerosis complex (TSC) is a rare, multisystem disorder caused by mutations in one of the suppressor genes: *TSC1* and *TSC2,* encoding hamartin and tuberin, respectively. These proteins form the protein-complex inhibiting mammalian-target-of-rapamycin (mTOR) pathway, vital in regulating cell proliferation and differentiation. Loss-of-function mutations prevent the synthesis of a correct, functional protein, and lead to hyperactivation of the mTOR pathway [1]. It is estimated that two million people worldwide, both adults and children, suffer from TSC. The clinical characteristics include tumors of the brain, skin, kidneys, lung, and heart that lead to miscellaneous disorders of these organs. Depending on age, the manifestation can vary significantly between individuals and

*Address for correspondence: Bartosz Urbański, Department of Pediatrics, Oncology and Hematology, Medical University of Lodz, Sporna 36/50, 91–738 Łódź, Poland, e-mail: bartosz.urbanski95@gmail.com

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within one individual [2]. About 90% of people with TSC suffer from central nervous system manifestations such as epilepsy, mental retardation, autism spectrum disorder, and/or attention-deficit/hyperactivity disorder [also called TSC-associated neuropsychiatric disorders (TAND)] [3, 4]. In 2021, the International Tuberous Sclerosis Consensus Group updated the TSC diagnostic criteria and surveillance and management recommendations [5].

Many years of research and clinical trials have allowed the introduction of mTOR inhibitors into treating two common presentations of TSC. The EXIST-1 study confirmed the effectiveness and safety of everolimus as a therapeutic option for patients with subependymal giant cell astrocytoma (SEGA) [6]. The EXIST-2 study showed that everolimus is an efficient treatment for renal angiomyolipoma associated with TSC. The most common drug adverse events during the EXIST-2 study were stomatitis, nasopharyngitis, and acne-like skin lesions. Hematological complications were reported in a small percentage of patients. The most common were anemia (n = 10, 13%) and leukopenia (n = = 8, 10%). However, none of the cases was classified as 3+ as defined by the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0 (CTCAE v3.0) [7, 8]. The results of our EMINENTS study show that it is possible to minimize adverse effects of everolimus therapy while maintaining adequate control of SEGA using a maintenance dose of the mTOR inhibitor [9].

The aim of this study was to assess the effect of everolimus on hematological parameters in patients with TSC treated due to a SEGA tumor during the standard dose treatment, and after the dose reduction.

Material and methods

Study design

The study included patients meeting the following criteria: age under 18 years, a definite diagnosis of TSC, and everolimus treatment due to a SEGA tumor. The initial study group consisted of 28 patients recruited at the Department of Pediatrics, Oncology and Hematology in Lodz, Poland between 14 December, 2011 and 16 March, 2018. The study was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by the Bioethics Committee of the Medical University of Lodz (# RNN/306/13/KE). All individuals, or their legal representatives, gave their written informed consent to participate.

Therapy protocol

The standard treatment regimen consisted of everolimus administration *per os* once daily at the same time every day, consistently either with or without food. The starting dose of everolimus for children was calculated according to the body surface area (BSA): 2.5 mg for patients with a BSA ≤1.2 m^2, 5 mg for patients with a BSA between 1.3 and 2.1 m^2, and 7.5 mg for patients with a BSA ≥2.2 m^2. Dosing was titrated to achieve therapeutic blood concentrations (5 to 15 ng/mL) [10].

After at least one year of full-dose therapy in the group of patients with reduction or stabilization of SEGA volume, the dose of everolimus was reduced to three times a week (Monday, Wednesday, and Friday) with the same daily dose (maintenance phase).

Laboratory parameters measurements

At five study time points (0 — before the introduction of treatment, 3 — after three months, 6 — after six months, 12 — after 12 months of full-dose treatment, and MT — after at least 12 months of maintenance therapy), the whole blood concentration of everolimus and the following parameters of complete blood count (CBC) were collected: red blood cell (RBC) count, hemoglobin (Hb) concentration, hematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), white blood cell (WBC) count, granulocyte (GRA) count, lymphocyte (LYMPH) count, and platelets (PLT) count. Hematological values at study time points were additionally assessed using the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) [11]. The everolimus whole blood concentration was measured using ultra-performance liquid chromatography/tandem mass spectrometry (UPLC/MS/MS) [12]. To unify measurements and increase the reliability of the study, complete blood counts from maintenance therapy were collected on the same day of the week for the whole study group.

Statistical analysis

Statistical analysis was performed using GraphPad Prism 9.2. The conformity of the data distribution to the requirements of the Gaussian distribution was checked by the Shapiro–Wilk test. Continuous variables are presented as medians with interquartile ranges (IQRs) or mean with SD and were compared using the Friedman with a post hoc Dunn's multiple comparisons test to analyze differences between more than two groups or a Wilcoxon matched-pairs signed rank test (for nonparametric variables) or a paired *t*-test (from parametric variables) to examine differences between two groups. Correlations were made using the Spearman or Pearson correlation tests respectively. A *p*-value of ≤0.05 was considered significant.

Results

Initially, 28 patients who met the inclusion criteria were enrolled on the study. In seven cases, the follow-up time was too short to collect five study time points for inclusion in the study. In three patients, the reduction attempt was unsuccessful. Finally, 18 patients were eligible for the study and were included in the data analysis (Figure 1).

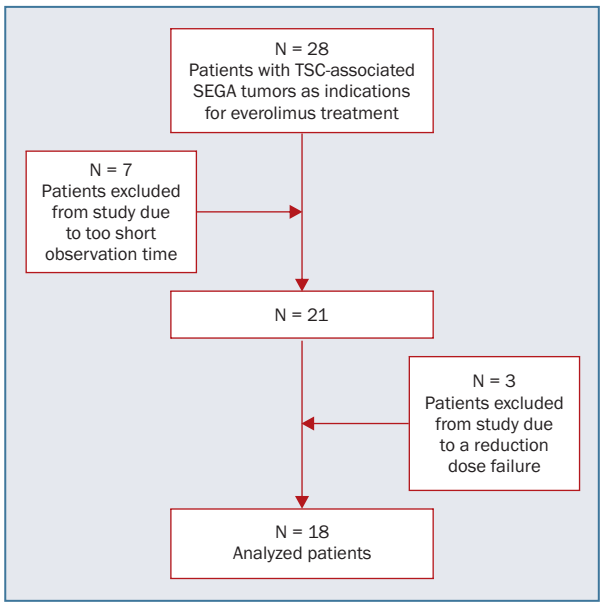

Figure 1. Flow chart of patient recruitment; TSC — tuberous sclerosis complex; SEGA — subependymal giant astrocytoma

Table I. Study group characteristics

Characteristic	Median (interquartile range) or number [%]
Sex (n) [%]: • male • female	 12 (67%) 6 (33%)
Age at start of study [years]	12.5 (8.5–14.8)
Full-dose treatment duration [months]	12.5 (12.0–17.8)
Maintenance phase duration [months]	85.0 (65.3–102.8)
Everolimus concentration during full-dose treatment [ng/mL]	5.85 (4.40–8.38)
Everolimus concentration during maintenance phase [ng/mL]	1.85 (1.50–2.78)
Everolimus dose at study entrance [mg/m^2/week]	23.2 (18.9–26.0)
Everolimus full dose during intensive treatment [mg/m^2/week]	39.4 (30.9–49.5)
Everolimus dose at start of maintenance phase [mg/m^2/week]	15.8 (13.0–20.6)

The median of the initial everolimus dose was 23.2 mg/m^2/week (IQR: 18.9–26.0) and increased during the standard therapy phase to a total dose of 39.4 mg/m^2/week (IQR: 30.9–49.5). This phase lasted for 12.5 months (IQR: 12.0–17.8). The median of the everolimus dose at the start of the maintenance phase was 15.8 mg/m^2/week (IQR: 13.0–20.6). The observation time after dose reduction lasted 85 months (IQR: 65.3–102.8). The study group characteristics are set out in Table I.

Everolimus concentration

The everolimus blood concentration gradually increased during the intensive treatment phase (5.04 ng/mL at time point 3; 5.36 ng/mL at time point 6) and reached a peak after 12 months of treatment (8.14 ng/mL, $p = 0.0046$) (Figure 2A). During the maintenance phase, the concentration significantly decreased under 5 ng/mL (1.85 ng/mL at time point MT, $p < 0.0001$) (Figure 2B). On this basis, we attempted to observe changes in CBC under the influence of mTOR inhibitor therapy.

Red blood cells parameters

Hemoglobin concentration (Hb) decreased significantly after three months of everolimus treatment (12.5 g/dL vs. 13.3 g/dL, $p = 0.01$) and remained at a similar level throughout the standard therapy regimen (six and 12 months) and after at least 12 months of the maintenance phase (Figure 3).

We observed a decrease in mean corpuscular volume (MCV) after three months (86.0 fL vs. 77.5 fL, $p = 0.02$) with the peak of microcytosis after six months (77.5 fL vs. 75.0 fL, $p = 0.03$) of the standard dose of everolimus. During the maintenance phase, MCV values were increasing (76.5 fL vs. 80.0 fL, $p = 0.02$), but they did not come back to the initial ones (80.0 fL vs. 86.0 fL, $p < 0.00001$) (Figure 4).

Similar observations were obtained for MCH. MCHC remained stable during the whole study. An increase in RBC count after six months (4.78×10^6/μL vs. 4.52×10^6/μL, $p = 0.0047$) and after 12 months (4.95×10^6/μL vs. 4.52×10^6/μL, $p = 0.0005$) compared to the initial ones was revealed. Subsequently, the erythrocyte values stayed stable during the maintenance phase.

Hematocrit (Hct) at all the study time points during intensive therapy (after three, six, and 12 months) was lower than at baseline. After the dose reduction, Hct returned to the value before the treatment commenced.

White blood cell count

Parameters of white blood cell (WBC) lineage were significantly lower after six and 12 months of standard-dose treatment compared to the initial ones (WBC 5.95×10^3/μL and 6.00×10^3/μL, respectively vs. 6.35×10^3/μL) (Figure 5A). After everolimus dose reduction at time point MT, WBC increased compared to time point 12 (6.95×10^3/μL vs. 6.00×10^3/μL, $p = 0.0001$), and measurements came back to the initial values (Figure 5B). Granulocytes count decrease was significant after 12 months of the standard everolimus dose compared to the baseline values (2.50×10^3/μL vs. 3.16×10^3/μL, $p = 0.0347$) (Figure 5C). After the everolimus dose reduction, an indicative increase in granulocyte count was observed, similar to values at the beginning (Figure 5D).

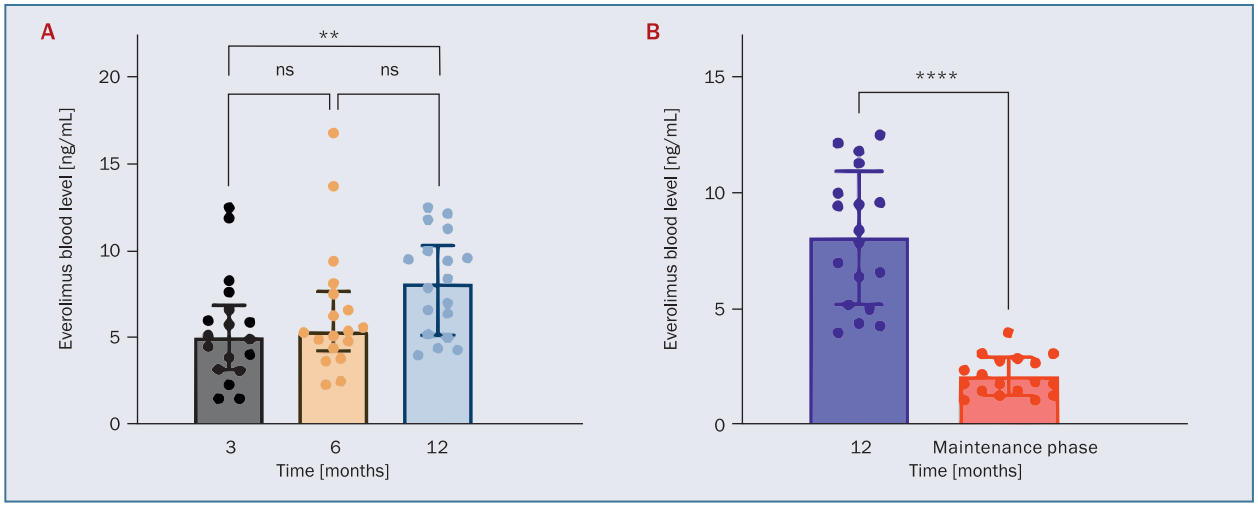

Figure 2. Everolimus blood concentration at study time points. Data from 18 patients is presented as (**A**) median with interquartile range or (**B**) mean with standard deviation. Statistically significant differences in everolimus blood level between months of follow-up: ***p* <0.01, *****p* <0.0001, ns — no significance (Friedman test with Dunn's multiple comparisons or Paired *t*-test)

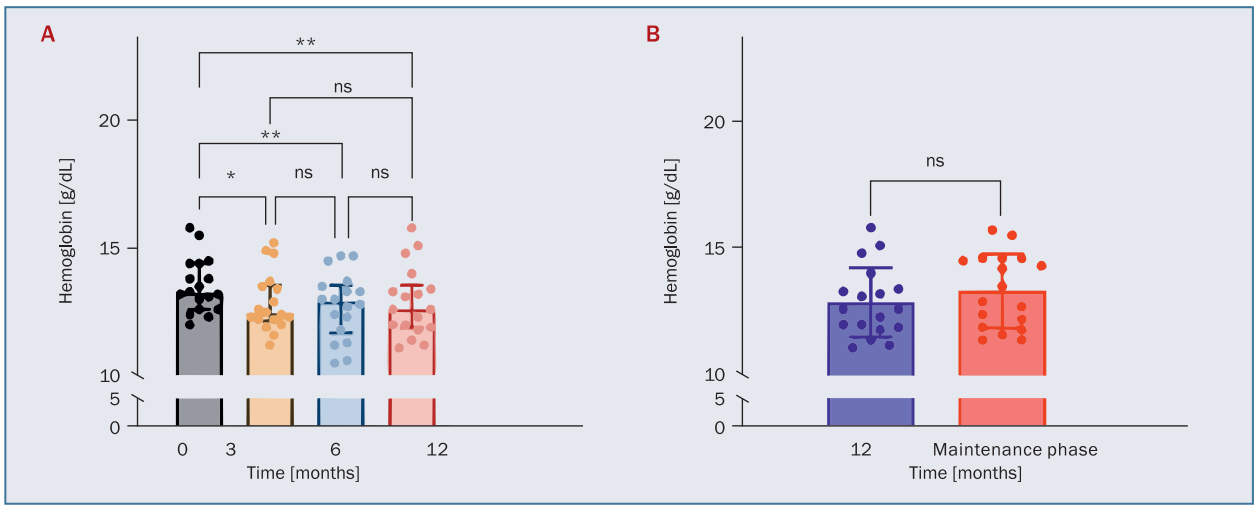

Figure 3. Hemoglobin level at study time points. Data from 18 patients is presented as (**A**) median with interquartile range or (**B**) mean with standard deviation. Statistically significant differences in hemoglobin concentration between months of follow-up: **p* <0.05, ***p* <0.01, *****p* <0.0001; ns — no significance (Friedman test with Dunn's multiple comparisons or Paired *t*-test)

The lymphocyte count remained stable throughout the study.

Platelet count

The platelet count (PLT) did not differ significantly between study time points 0, 3, and 6 months of standard-dose treatment. A decrease of PLT was observed at time point 12 compared to time point 0 (232.5 × 10^3/μL vs. 262.0 × 10^3/μL, p = 0.012). After the dose reduction, PLT increased to its initial value.

The changes in CBC throughout the study are set out in Table II.

Most of the presented values were within the normal ranges. Only 1/18 (5.56%) cases of anemia, 2/18 (11.1%) cases of leukopenia, 6/18 (33.3%) cases of granulocytopenia, and 2/18 (11.1%) cases of thrombocytopenia were revealed. Almost all cytopenias occurred during the intensive treatment phase. Moreover, none of the abnormalities was classified as 3+ as defined by the CTCAE v4.0 (Table III). Hematological toxicity did not lead to dose interruption or the cessation of treatment in any patient.

Discussion

Due to the critical role of the mTOR pathway in the cell cycle, mTOR inhibitors have found applications in many fields of modern medicine, mainly in transplantology and oncology [13]. Hematological adverse effects have been

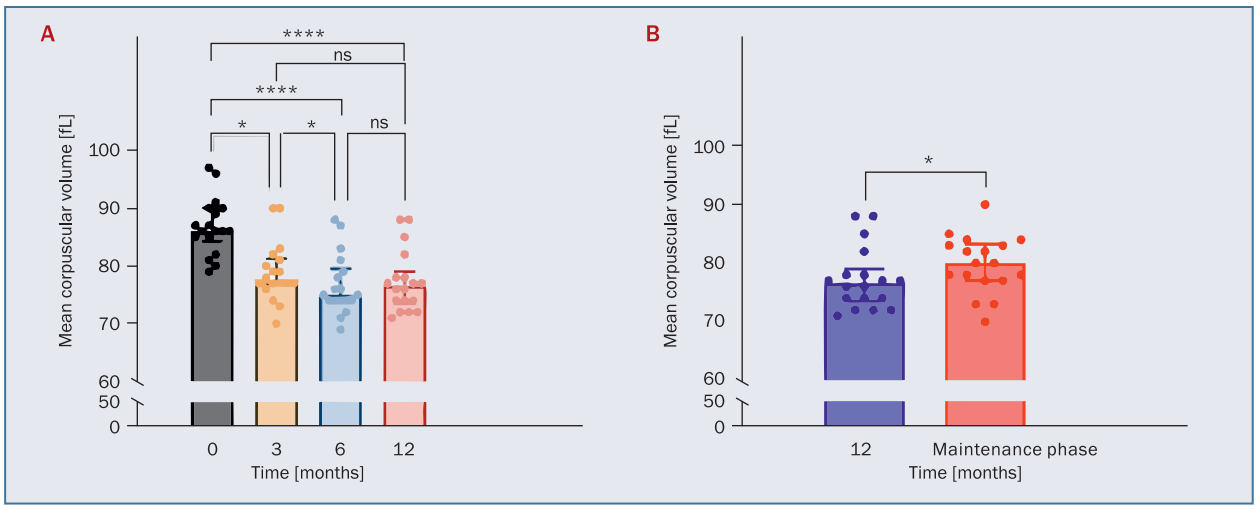

Figure 4A, B. Mean corpuscular volume at study time points. Data from 18 patients is presented as median with interquartile range. Statistically significant differences in mean corpuscular volume level between months of follow-up: *p <0.05, ****p <0.0001, ns — no significance (Friedman test with Dunn's multiple comparisons or Wilcoxon matched-pairs signed rank test)

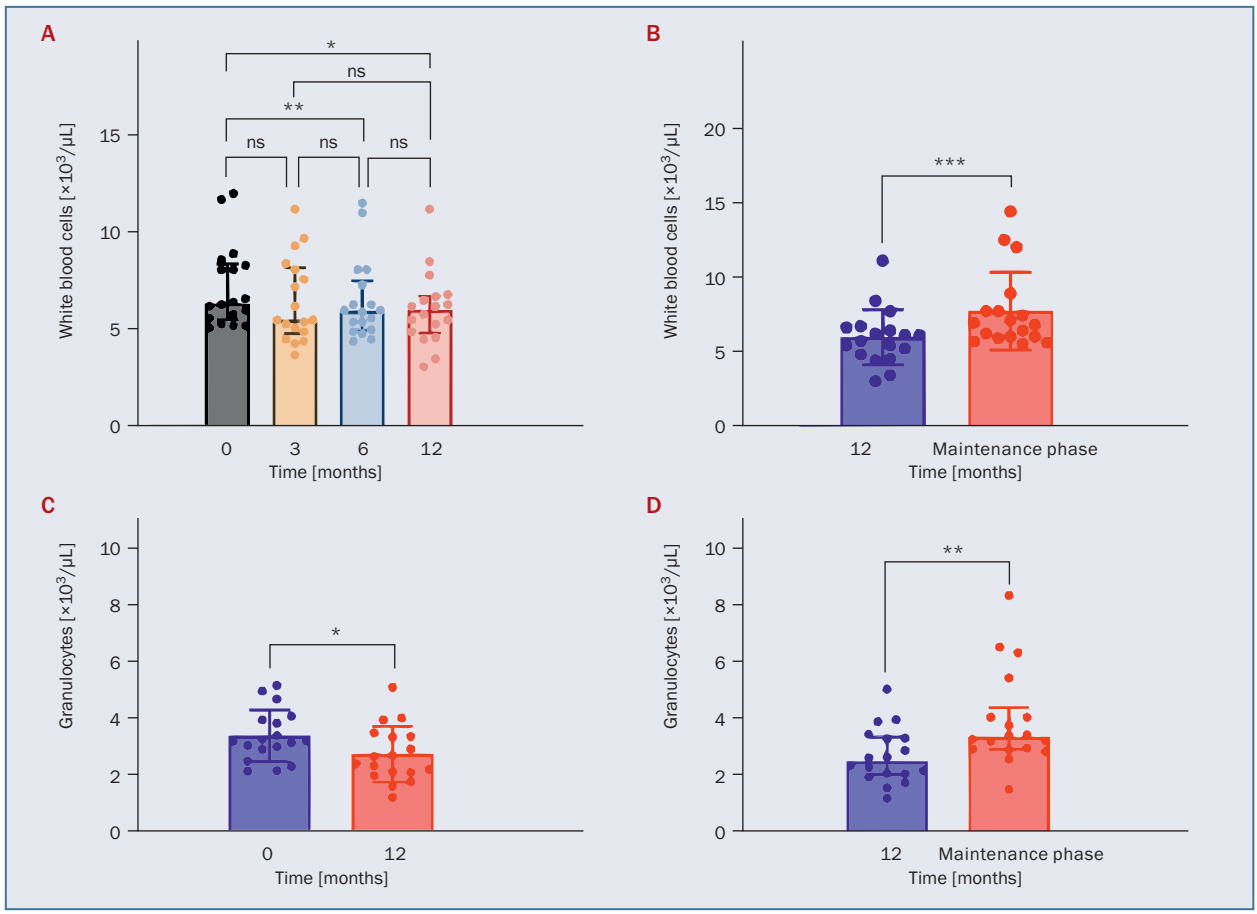

Figure 5. White blood cell count and granulocyte count at study time points. Data from 18 patients is presented as (**A, D**) median with interquartile range or (**B, C**) mean with standard deviation (SD). Statistically significant differences in white blood cell count (**A, B**) and granulocyte count (**C, D**) between months of follow-up: *p <0.05, **p <0.01, ***p <0.001, ns — no significance (Friedman test with Dunn's multiple comparisons, Paired t-test or Wilcoxon matched-pairs signed rank test)

Table II. Complete blood count during study

CBC parameter [unit]	0-month median [IQR]	Three months median [IQR]	Six months median [IQR]	12 months median [IQR]	MT median [IQR]	*p* (12 months vs. MT)
RBC [× 10^6/μL]	4.52 [4.34–4.87]	4.84 [4.58–5.02]	4.78 [4.51–5.27]	4.95 [4.61–5.33]	5.03 [4.28–5.51]	0.9747
Hct [%]	39.7 [37.4–41.3]	37.2 [35.9–39.6]	38.9 [34.1–40.2]	37.7 [34.9–40.0]	39.3 [35.8–43.0]	0.0108
Hb [g/dL]	13.3 [12.6–14.4]	12.5 [12.2–13.6]	12.9 [11.7–13.6]	12.6 [11.9–13.6]	13.2 [11.9–14.6]	0.0540
MCV [fL]	86.0 [84.3–90.0]	77.5 [76.8–81.3]	75.0 [74.0–79.5]	76.5 [73.5–79.0]	80.0 [77.0–83.3]	0.0229
MCH [pg]	29.1 [28.1–30.5]	26.2 [25.5–27.2]	25.2 [24.6–27.9]	26.0 [24.4–27.5]	27.2 [25.7–28.3]	0.1038
MCHC [g/dL]	34.0 [33.7–34.2]	33.9 [33.3–34.1]	33.4 [33.0–34.0]	34.1 [33.3–34.3]	33.9 [33.1–34.3]	0.6974
WBC [× 10^3/μL]	6.35 [5.53–8.38]	5.50 [4.80–8.18]	5.95 [4.98–7.50]	6.00 [4.83–6.73]	6.95 [6.08–8.10]	0.0001
GRA [× 10^3/μL]	3.16 [2.78–3.94]	2.47 [2.03–3.48]	2.74 [2.46–3.43]	2.50 [2.04–3.35]	3.36 [2.93–4.40]	0.0015
LYMPH [× 10^3/μL]	3.09 [1.88–3.94]	2.88 [2.31–3.97]	2.96 [1.92–3.70]	2.76 [2.00–3.28]	2.91 [2.32–4.07]	0.0898
PLT [× 10^3/μL]	262.0 [226.8–321.8]	282.0 [224.8–318.3]	238.5 [199.0–311.3]	232.5 [192.0–288.5]	297.5 [227.3–333.5]	<0.0001

CBC — complete blood count; IQR — interquartile range; MT — maintenance therapy; RBC — red blood cells; Hct — hematocrit; Hb — hemoglobin; MCV — mean corpuscular volume; MCH — mean corpuscular hemoglobin; MCHC — mean corpuscular hemoglobin concentration; WBC — white blood cells; GRA — granulocytes; LYMPH — lymphocytes; PLT — platelets

Table III. Hematological adverse events according to Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0)

Adverse event	Full-dose therapy		Maintenance therapy	
	In total [%]	Grade ≥3	In total [%]	Grade ≥3
Anemia	1/18 (5.56%)	0	0	0
Leukopenia	2/18 (11.1%)	0	0	0
Granulocytopenia	6/18 (33.3%)	0	1/18 (5.56%)	0
Thrombocytopenia	2/18 (11.1%)	0	1/18 (5.56%)	0

shown to be the most common in patients treated with mTOR inhibitors, mainly sirolimus, after renal and heart transplantation [14, 15]. Hematological complications in patients with TSC have been poorly explored. This may be caused by the limited cohort size of previous studies and benign abnormalities [16, 17]. The results of our study are consistent with the data published so far.

The basis of our study was that after introducing the intensive treatment phase, everolimus blood concentration gradually increased and peaked after 12 months of therapy. During the maintenance phase, the concentration significantly decreased. Our study confirmed that mTOR inhibitor causes a decrease in the value of almost all blood cells. In most parameters, the peak of toxicity occurred six months after commencing therapy, and then parameters reached a plateau and did not exacerbate.

Significantly, the observed changes were usually within the laboratory reference range. We reported only a few cases of anemia, leukopenia, granulocytopenia, and thrombocytopenia, which were compatible with observations from the EXIST-2 study [7]. Interestingly, we observed granulocyte deficiency in one-third of patients, which might increase the risk of infection and, consequently, therapy cessation. Nevertheless, all hematological adverse events were classified as mild according to CTCAE v4.0. We did not reveal any case of withdrawal from the therapy due to hematological toxicity. Interestingly, in our study, values of lymphocytes remained relatively constant. Based on a wide range of literature, mTOR inhibitors impair hematopoiesis by inhibiting cytokine-driven proliferation. Everolimus restrains transduction of glycoprotein 130β chain signal, which is also present in many cytokine receptors,

including interleukin-3, interleukin-11, erythropoietin and granulocyte colony-stimulating factor, and thus leads to bone marrow suppression [18, 19].

Another important observation from our study is the resolution of almost all hematological abnormalities after the reduction of the everolimus dose. Mild granulocytopenia, as well as thrombocytopenia, were noticed in one case. This proves that maintenance treatment with everolimus is a sufficient therapeutic option after effective standard-dose therapy [9]. The dose reduction resulted in a parameters increase, but only hematocrit, leukocytes and thrombocytes returned to the values before the treatment commenced.

Particular attention should be paid to red blood cell lineage changes. The most relevant and characteristic hematological complication was the microcytosis persisting despite the everolimus dose reduction. Interestingly, simultaneous with the MCV decrease, a gradual increase in erythrocyte count was noticed. Eventually, this did not contribute to the full compensation for microcytosis, as hemoglobin concentration progressively declined during the standard-dose therapy. Nevertheless, only one case of mild anemia was found throughout our study. Sirolimus and everolimus have been widely described as post-transplantation anemia (PTA)-associated immunosuppressive medications [20, 21]. Friend et al. [22] observed that hemoglobin levels in their study group normalized over the observation time, while microcytosis was persistent and progressive. In our research, we noticed a similar observation, but the increase in hemoglobin concentration during the maintenance phase was statistically insignificant. Similarly, leukocytes and thrombocytes returned to the initial values after dose reduction. This is strong evidence for the involvement of many mechanisms in mTOR-induced cytopenias. While bone marrow suppression is a convincing explanation for thrombocytopenia and leukopenia, the etiology of disorders in red blood cells is still elusive. Sofroniadou et al. [23] brought together the potential mechanisms of this unique phenomenon. Different but not mutually exclusive hypotheses included globin production defects, erythropoietin resistance, chronic inflammatory state, and iron homeostasis disorders [23]. Indeed, the mTOR pathway plays a significant role in erythropoiesis's early stages as a promoter of erythroblast proliferation. However, as the process progresses, mTOR activity weakens. The sensitivity of precursor cells to the everolimus varies depending on the maturation stage [24]. Regardless of iron availability, mTOR inhibitors cause a decline in MCV, which excludes pure iron deficiency as the explanation for the microcytosis [25, 26].

Notably, the relatively least affected blood cell population was platelets. Only after 12 months, under the influence of a high everolimus concentration, was the megakaryocytic lineage suppressed significantly. However, platelets returned to the initial values during the maintenance therapy. As observed in another study, thrombocyte count demonstrates the clearest dose-dependent toxicity during mTOR inhibitor treatment only in medium and high-dose groups [18].

The incidence of TSC is estimated at one case per 6,000–10,000 live births. SEGAs are diagnosed in 10–15% of patients with TSC and are often the cause of death [2]. Consequently, our study analyzed hematological complications of a specific group of drugs in pediatric patients with one clinical presentation of a rare disease. All these features prove the uniqueness and valence of this observation, despite the relatively small study group. Further studies on drug mechanisms and toxicity in TSC patients are necessary.

Conclusions

A decrease in almost all hematological parameters is widespread during everolimus therapy; however, hematological toxicities defined by the CTCAE are rare and not severe. The most relevant and unique abnormality for mTOR inhibitors is microcytosis. Along with reducing the dose, the CBC parameter normalizes and becomes close to the initial values. Hematological adverse effects are rarely a reason for withdrawal from the therapy due to their benign character.

Authors' contributions

BU — conceptualization, formal research, interpretation of data, writing — original draft. BP — visualization, statistical analysis. WM — conceptualization, writing — review and editing. JT — conceptualization, writing — review and editing, supervision. All authors have read and agreed to the published version of manuscript.

Conflict of interest

The authors declare no conflict of interest.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments and uniform requirements for manuscripts submitted to biomedical journals.

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