СОПРЯЖЕННОСТЬ МИЕЛОИДНЫХ СУПРЕССОРНЫХ КЛЕТОК С ВОССТАНОВЛЕНИЕМ КРОВЕТВОРЕНИЯ ПОСЛЕ ВЫСОКОДОЗНОЙ ХИМИОТЕРАПИИ ПРИ МНОЖЕСТВЕННОЙ МИЕЛОМЕ

Анмут В.С.[1], Тыринова Т.В.[1, 2], Баторов Е.В.[2], Аристова Т.А.[2], Сизикова С.А.[2], Ушакова Г.Ю.[2], Денисова В.В.[2], Черных Е.Р.[2]

[1] ФГАОУ ВО «Новосибирский национальный исследовательский государственный университет», г. Новосибирск, Россия
[2] ФГБНУ «Научно-исследовательский институт фундаментальной и клинической иммунологии», г. Новосибирск, Россия

Резюме. Супрессорные клетки миелоидного происхождения (МС) играют важную роль в регуляции иммунного ответа при многих патологиях и прежде всего при злокачественных опухолях, однако их роль в приживлении гемопоэтических стволовых клеток и восстановлении кроветворения после высокодозной химиотерапии с аутологичной трансплантацией стволовых клеток остается практически не изученной. Настоящее исследование направлено на изучение зависимости между содержанием субпопуляций МС и показателями крови на этапе восстановления кроветворения после высокодозной химиотерапии с аутологичной трансплантацией гемопоэтических стволовых клеток у пациентов с множественной миеломой (ММ). МС оценивали методом проточной цитометрии в образцах периферической крови на этапе выхода из лейкопении (при количестве лейкоцитов в периферической крови более 1×10^9/л). Количество трансплантируемых $CD34^+CD45^+$ гемопоэтических стволовых клеток составило $4{,}38 \times 10^6$/кг (IQR (3,1-5,6) $\times 10^6$/кг). Длительность выхода из лейкопении варьировала от 8 до 18 дней (Me 12 дней). Содержание МС на этапе выхода из лейкопении не было связано с количеством $CD34^+$ клеток/кг в трансплантате. Относительное содержание моноцитарных МС (М-МС, $CD14^+HLA\text{-}DR^{low/-}$) прямо коррелировало с содержанием моноцитов на этапе выхода из лейкопении ($R = 0{,}417$, $p = 0{,}002$). Для гранулоцитарных МС (Г-МС, $Lin^-HLA\text{-}DR^-CD33^+CD66b^+$) была характерна обратная связь с количеством моноцитов ($R = -0{,}493$, $p = 0{,}0003$), при этом сопряженность с абсолютным содержанием нейтрофилов была слабо выражена ($R = 0{,}273$, $p = 0{,}048$). Содержание лимфоцитов на этапе выхода из лейкопении находилось в обратной связи с Г-МС ($R = -0{,}347$, $p = 0{,}014$) и не коррелировало с М-МС. При анализе длительность лейкопении обратная корреляционная связь с данным показателем была выявлена для процентного и абсолютного содержания М-МС ($R = -0{,}347$, $p = 0{,}018$ и $R = -0{,}469$, $p = 0{,}0008$ соответственно). Множественный регрессионный ана-

Адрес для переписки:

Аристова Татьяна Андреевна
ФГБНУ «Научно-исследовательский институт фундаментальной и клинической иммунологии»
630099, Россия, г. Новосибирск, ул. Ядринцевская, 14.
Тел.: 8 (383) 228-21-01.
E-mail: taris07@mail.ru

Address for correspondence:

Tatyana A. Aristova
Research Institute of Fundamental and Clinical Immunology
14 Yadrintsevskaya St
Novosibirsk
630099 Russian Federation
Phone: +7 (383) 228-21-01.
E-mail: taris07@mail.ru

Образец цитирования:

В.С. Анмут, Т.В. Тыринова, Е.В. Баторов, Т.А. Аристова, С.А. Сизикова, Г.Ю. Ушакова, В.В. Денисова, Е.Р. Черных «Сопряженность миелоидных супрессорных клеток с восстановлением кроветворения после высокодозной химиотерапии при множественной миеломе» // Медицинская иммунология, 2023. Т. 25, № 5. С. 1159-1164. doi: 10.15789/1563-0625-AOM-2700

For citation:

V.S. Anmut, T.V. Tyrinova, E.V. Batorov, T.A. Aristova, S.A. Sizikova, G.Yu. Ushakova, V.V. Denisova, E.R. Chernykh "Association of myeloid-derived suppressor cells with hematopoietic recovery after high-dose chemotherapy in multiple myeloma", Medical Immunology (Russia)/ Meditsinskaya Immunologiya, 2023, Vol. 25, no. 5, pp. 1159-1164. doi: 10.15789/1563-0625-AOM-2700

DOI: 10.15789/1563-0625-AOM-2700

лиз показал зависимость длительности лимфопении от доли циркулирующих М-МС (p = 0,014) и количества трансплантированных CD34+ клеток/кг (p = 0,032). Согласно данным многофакторного дисперсионного анализа значимыми факторами для продолжительности лейкопении являлись количество трансплантированных CD34+ клеток/кг и содержание М-МС. При этом такие клинические параметры как глубина ответа и наличие минимальной остаточной болезни перед проведением высокодозной химиотерапии и трансплантации гемопоэтических стволовых клеток, а также стадия ММ не влияли на длительность восстановления кроветворения. Таким образом, полученные результаты свидетельствуют о сопряженности более высокого содержания М-МС с меньшей длительностью лейкопении после высокодозной химиотерапии с аутологичной трансплантацией стволовых клеток и указывают на позитивную роль М-МС в восстановлении кроветворения в раннем посттрансплантационном периоде у пациентов с ММ.

Ключевые слова: миелоидные супрессорные клетки, множественная миелома, трансплантация, гемопоэтические стволовые клетки, длительность лейкопении, раннее восстановление гемопоэза

ASSOCIATION OF MYELOID-DERIVED SUPPRESSOR CELLS WITH HEMATOPOIETIC RECOVERY AFTER HIGH-DOSE CHEMOTHERAPY IN MULTIPLE MYELOMA

Anmut V.S.[a], Tyrinova T.V.[a, b], Batorov E.V.[b], Aristova T.A.[b], Sizikova S.A.[b], Ushakova G.Yu.[b], Denisova V.V.[b], Chernykh E.R.[b]

[a] *Novosibirsk State University, Novosibirsk, Russian Federation*
[b] *Research Institute of Fundamental and Clinical Immunology, Novosibirsk, Russian Federation*

Abstract. Myeloid-derived suppressor cells (MDSCs) play an important role in the immune response regulation in many pathologies, primarily in malignant tumors, but their role in the hematopoietic stem cell engraftment and the hematopoietic recovery after high-dose chemotherapy and autologous stem cell transplantation remains practically unexplored. This study is aimed at studying the correlation between the number of MDSC subpopulations and blood parameters at the stage of hematopoietic recovery after high-dose chemotherapy and autologous hematopoietic stem cell transplantation in patients with multiple myeloma (MM). Circulating MDSCs were assessed at the stage of leukopenia recovery (absolute leukocyte count in peripheral blood (PB) > 1×10^9/L) by flow cytometry. The number of transplanted $CD34^+CD45^+$ hematopoietic stem cells was 4.38×10^6/kg (IQR $(3.1–5.6) \times 10^6$/kg). The duration of recovery from leukopenia varied from 8 to 18 days (Me 12 days). The number of MDSCs at the engraftment was not associated with the number of $CD34^+$ cells/kg in the graft. The relative number of monocytic MDSCs (M-MDSCs, $CD14^+HLA\text{-}DR^{low/-}$) directly correlated with the number of monocytes at the stage of recovery from leukopenia (R = 0.417, p = 0.002). Granulocytic MDSCs (PMN-MDSCs, $Lin^-HLA\text{-}DR^-CD33^+CD66b^+$) were characterized by an inverse correlation with the number of monocytes (R = -0.493, p = 0.0003) while the association with the absolute number of neutrophils was weak (R = 0.273, p = 0.048). The number of lymphocytes at the stage of recovery from leukopenia had an inverse correlation with PMN-MDSCs (R = -0.347, p = 0.014) and did not correlate with M-MDSCs. When analyzing the duration of leukopenia, an inverse correlation with this indicator was revealed for the percentage and absolute number of M-MDSCs (R = -0.347, p = 0.018 and R = -0.469, p = 0.0008, respectively). Multiple regression analysis showed dependence of the lymphopenia duration on the proportion of circulating M-MDSCs (p = 0.014) and the number of transplanted $CD34^+$ cells/kg (p = 0.032). According to the data of multivariate analysis of variance, the number of transplanted $CD34^+$ cells/kg and the number of M-MDSCs were significant factors for the duration of leukopenia. At the same time, such clinical parameters as the depth of response and minimal residual disease status before high-dose chemotherapy and hematopoietic stem cell transplantation, as well as the MM stage, did not affect the duration of hematopoietic recovery. Thus, the obtained results indicate the association of a higher number of M-MDSCs with a shorter duration of leukopenia after high-dose chemotherapy with autologous stem cell transplantation and indicate a positive role of M-MDSCs in hematopoietic recovery in the early post-transplant period in patients with MM.

Keywords: myeloid-derived suppressor cells, multiple myeloma, transplantation, hematopoietic stem cells, duration of leukopenia, early hematopoietic recovery

The study was funded by budget of Research Institute of Fundamental and Clinical Immunology (theme No. 122011800108-0).

Introduction

Myeloid-derived suppressor cells (MDSCs) play an important role in the immune response regulation in many pathologies, primarily in tumors [6]. MDSCs release a suppressor activity towards innate and adaptive immune cells *in vitro* and *in vivo* with the most pronounced suppressor activity against T cells [5]. In humans, monocytic MDSCs (M-MDSCs, $CD14^+HLA\text{-}DR^{low/-}$), granulocytic, or polymorphonuclear, MDSCs with a phenotype similar to neutrophils (PMN-MDSCs, $CD11b^+CD33^+CD14^-CD15^+$ ($CD66b^+$) $HLA^-DR^{low/-}$) and immature MDSCs (E-MDSCs) with the Lin^- (CD3, CD14, CD15, CD19, CD56) HLA-DR$CD33^+$) phenotype have been described [1, 2].

In solid tumors, the number of MDSCs increases and correlates with tumor size, stage and poor prognosis [5]. In hemoblastosis, especially in patients with hematopoietic stem cell transplantation (HSCT) the MDSC population is less studied and the role of MDSCs is not clear [11]. MDSCs of donor origin presented in the allograft can suppress the graft-versus-host reaction [4], playing a positive role. There is much less clarity regarding the role of MDSCs in autologous HSCT (auto-HSCT). Since early reconstitution of lymphocytes is provided by homeostatic proliferation of T cells transplanted as a part of the graft, MDSC suppressive activity against T cells can reduce the effectiveness of immune reconstitution after auto-HSCT.

Multiple myeloma (MM) is a malignant lymphoproliferative disease characterized by infiltration of the bone marrow by tumor plasma cells secreting monoclonal immunoglobulin and/or free light chains. Despite advances in therapy, MM still remains an incurable disease with a 5-year survival rate of just over 50% [12]. At the same time, high-dose chemotherapy (HDCT) with auto-HSCT is an important and effective standard of treatment for MM. One of the prognostically favorable factors associated with successful HSCT and greater overall survival after HDCT and auto-HSCT is a faster and more stable hematopoietic recovery [8, 10]. The study of the immune reconstitution mechanisms and the search for prognostic factors affecting the hematopoietic recovery after HSCT attracts special attention in terms of optimizing therapy and predicting the development of infectious complications and MM relapse. However, there is no information about the possible role of MDSCs in the regulation of autologous hematopoietic stem cell (HSC) engrafting after HDCT and the hematopoietic recovery.

The aim of this study was to find the relationship between the number of MDSC subpopulations and the hematopoietic recovery after HPCT and auto-HSCT in patients with MM.

Materials and methods

The study included 55 patients (30 women and 25 men) with MM aged 38 to 72 years (Me 54 years), who underwent HDCT with auto-HSCT. A complete or very good partial response (CR/VGPR) was achieved in 37 patients; a partial response (PR) was achieved in 18 patients at the time of HSC transplantation. Auto-HSCT was performed with a conditioning regimen of melphalan 200 mg/m^2, or 140 mg/m^2 in patients with impaired renal function. The median number of $CD34^+CD45^+$ hematopoietic stem cells was 4.38×10^6/kg (IQR (3.1-5.6) $\times 10^6$/kg).

To assess the number of MDSCs, mononuclear cells (MNCs) at the stage of recovery from leukopenia (number of leukocytes in peripheral blood (PB) $> 1 \times 10^9$/L) were isolated from PB by standard centrifugation of whole heparinized venous blood in a ficoll-verografin density gradient (p = 1.077). Flow cytometry (BD FACSCanto II, USA) was used to study the relative number of PMN-MDSCs ($Lin^-HLA\text{-}DR^-CD33^+CD66b^+$), M-MDSCs ($CD14^+HLA\text{-}DR^{low/-}$), and P-MDSCs ($Lin^-HLA\text{-}DR^-CD33^+CD66b^-$) among MNCs using anti-Lineage Cocktail 1 (CD3, CD14, CD16, CD19, CD20, CD56; FITC, BD Biosciences, USA), anti-CD14 (FITC, BD Biosciences), anti-CD33 (PerCP-Cy5.5, BD Biosciences), anti-CD66b (APC, BioLegend, USA), anti-HLA-DR (APC-Cy7, PerCP, BD Biosciences). Isotype antibodies conjugated with similar fluorochromes were used as a negative control.

Statistical data processing was performed using the Statistica 6.0 (StatSoft) and GraphPad Prism 8 software packages. Correlation analysis was performed using the Spearman rank correlation test. Additionally, linear regression analysis and multivariate analysis of variance were performed. Differences were considered statistically significant at $p < 0.05$.

Results and discussion

The duration of recovery from leukopenia (leukocytes in the PB $> 1 \times 10^9$/L, platelets $> 50 \times 10^9$/L) in patients with MM after HDCT and auto-HSCT varied from 8 to 18 days (Me 12 days, IQR 11-14 days). The number of leukocytes and platelets counted at this stage is shown in Table 1.

Since the number of transplanted $CD34^+$ HSCs is one of the important factors of immune reconstitution, we conducted a correlation analysis of the transplanted $CD34^+$ cells/kg with hematopoietic recovery indicators. The duration of leukopenia was in a reverse association with transplanted $CD34^+$ cells/kg (R = -0.305, p = 0.008). A significant de-

TABLE 1. PARAMETERS OF HEMATOPOIETIC RECOVERY AFTER AUTO-HSCT IN MULTIPLE MYELOMA

Parameter	Me ($Q_{0.25}$-$Q_{0.75}$)	Min-max
Neutrophils (× 10^9/L)	1.26 (0.78-2.44)	0.22-7.95
Thrombocytes (× 10^9/L)	65 (47-90)	7-243
Monocytes (× 10^9/L)	0.12 (0.05-0.25)	0.005-1.560
Lymphocytes (× 10^9/L)	0.48 (0.33-0.79)	0.02-2.68
M-MDSCs (%)	3.4 (2.0-6.9)	0.3-19.1
M-MDSCs (× 10^6/mL)	26.8 (14.1-68.8)	4.4-350.0
PMN-MDSCs (%)	0.32 (0.03-0.90)	0.001-15.540
PMN-MDSCs (× 10^6/mL)	2.90 (0.43-7.47)	0.02-148.40
E-MDSCs (%)	0.63 (0.39-1.19)	0.09-2.55
E-MDSCs (× 10^6/mL)	5.5 (3.7-10.5)	0.6-34.3

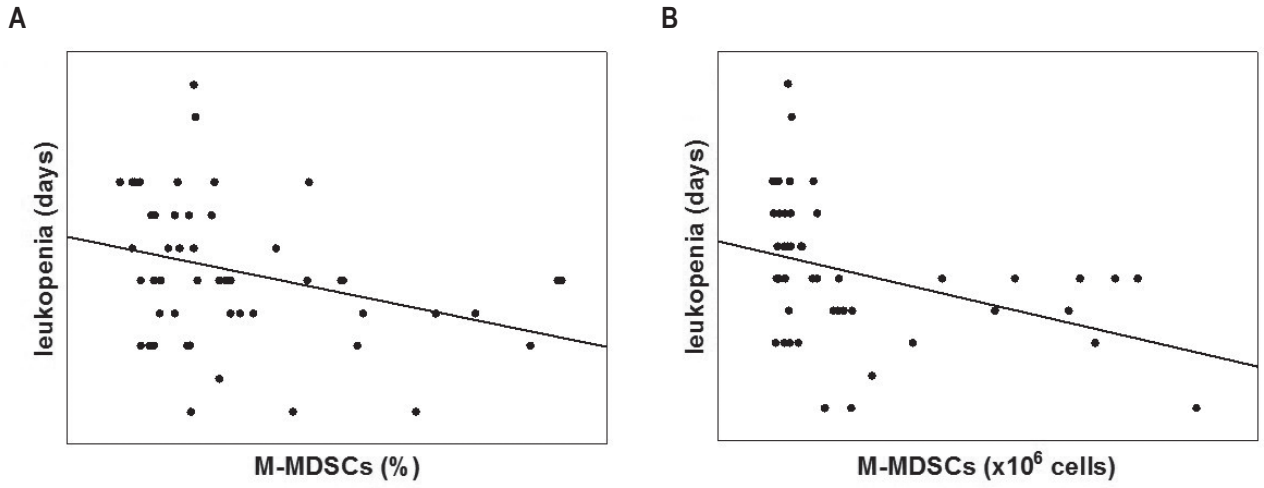

Figure 1. Association of leukopenia duration and numbers of M-MDSCs at the stage of recovery from leukopenia after high-dose chemotherapy

TABLE 2. MULTIVARIATE ANALYSIS OF THE CLINICAL PARAMETERS' INFLUENCE ON THE DURATION OF LEUKOPENIA AFTER AUTO-HSCT IN PATIENTS WITH MULTIPLE MYELOMA

Factorial ANOVA	F-value	p-value
$CD34^+$ cells/kg (> Me *vs* < Me)	6.95	0.01
M-MDSCs, % (> Me *vs* < Me)	7.66	0.008
Response (CR *vs* PR)	0.33	0.57
MRD (positive *vs* negative status)	0.15	0.70
Stage at diagnosis (II *vs* III Durie–Salmon stage)	0.003	0.96

Note. Response, the depth of the response before the HDCT; CR, complete response; PR, partial response; MRD, minimal residual disease before HDCT

pendence on the transplanted CD34+ cells/kg was found only for the absolute number of platelets (R = 0.378, p = 0.0007) among all the analyzed parameters. A similar relationship with the number of monocytes was weak (R = 0.250, p = 0.03). The number of MDSC subpopulations at the stage of recovery from leukopenia was not associated with the CD34+ cells/kg in the graft.

In order to assess the importance of MDSCs in terms of hematopoietic recovery after HPCT and auto-HSCT, we compared the number of MDSCs with the number of other blood cells populations. The relative number of M-MDSCs directly correlated with the number of monocytes (R = 0.417, p = 0.002). PMN-MDSCs was characterized by an inverse relationship with the number of monocytes (R = -0.493, p = 0.0003). At the same time, PMN-MDSCs and the absolute number of neutrophils were revealed to have weak positive correlation (R = 0.273, p = 0.048). In addition, an inverse significant correlation was found between the proportion of PMN-MDSCs and the number of lymphocytes (R = -0.347, p = 0.014). When analyzing the duration of leukopenia, it turned out that this indicator was associated only with the number of M-MDSCs. The duration of leukopenia had an inverse correlation with the percentage and absolute number of M-MDSCs (R = -0.347, p = 0.018 and R = -0.469, p = 0.0008, respectively; Figure 1), which indicates the association of a higher number of M-MDSCs with earlier recovery of hematopoiesis after HDCT and infusion of autologous HSCs.

Multiple regression analysis confirmed the dependence (determination coefficient R^2 0.241, F-test 3.45, p = 0.015) of the duration of leukopenia on the proportion of circulating M-MDSCs (p = 0.014) and the number of transplanted CD34+ cells/kg (p = 0.032). According to regression analysis, the proportion of circulating PMN-MDSCs and E-MDSCs did not affect the duration of leukopenia (p = 0.14 and p = 0.66, respectively) at the same time. A similar pattern was found for the absolute number of M-MDSCs (p = 0.048).

At the final stage we tried to find the most significant factors associated with a shorter duration of leukopenia using multivariate analysis of variance (Table 2). The number of transplanted CD34+ cells/kg and the number of M-MDSCs were significant factors for the duration of leukopenia. At the same time, such clinical parameters as the depth of response and the presence or absence of minimal residual disease before HDCT, as well as the MM stage, did not affect the duration of hematopoiesis recovery.

In general, the present study showed for the first time that the number of MDSC subpopulations at the stage of recovery from leukopenia after HDCT and auto-HSCT is not linearly related to the number of transplanted CD34+ cells/kg but correlates with the number of other types of leukocytes and platelets during the hematopoietic recovery. In addition, M-MDSCs along with the number of transplanted CD34+ cells/kg are significant factors for an earlier recovery from leukopenia after HSC transplantation. Indeed, the factors affecting the efficiency and duration of hematopoietic recovery in auto-HSCT in patients with MM are the number of CD34+ cells in auto-graft, an early stage of the disease, conditioning regimen, age [7, 8, 9]. Our findings about association between faster recovery from leukopenia and higher number of circulating M-MDSCs may indicate that MDSCs not only have the ability to maintain the stem properties of tumor cells [3], but may also be involved in the microenvironment recovery needed for effective HSC functioning in the bone marrow of patients after HDCT. However, further studies are required to confirm this assumption.

The positive correlation found between M-MDSCs and monocytes, as well as between PMN-MDSCs and neutrophils, indicates the common origin of these cell populations while the inverse correlation between PMN-MDSCs and monocytes indicates competitive lines of cell differentiation from common myeloid progenitors.

Conclusion

Thus, the revealed relationship between MDSCs and the efficiency of leukocyte recovery in patients with MM after HDCT and auto-HSCT demonstrates a new role for MDSCs. Since the rapid hematopoietic recovery is an important factor in terms of possible complications and transplantation outcomes, it can be assumed that M-MDSCs can play a positive role at the stage of recovery from leukopenia contributing to the rapid engraftment of HSCs and the beginning of hematopoiesis.

References

1. Bronte V., Brandau S., Chen S.H., Colombo M.P., Frey A.B., Greten T.F., Mandruzzato S., Murray P.J., Ochoa A., Ostrand-Rosenberg S., Rodriguez P.C., Sica A., Umansky V., Vonderheide R.H., Gabrilovich D.I. Recommendations for myeloid-derived suppressor cell nomenclature and characterization standards. *Nat. Commun., 2016, Vol. 7, 12150.* doi: 10.1038/ncomms12150.

2. Condamine T., Gabrilovich D.I. Molecular mechanisms regulating myeloid-derived suppressor cell differentiation and function. *Trends Immunol., 2011, Vol. 32, no. 1, pp. 19-25.*

3. de Veirman K., Menu E., Maes K., de Beule N., de Smedt E., Maes A., Vlummens P., Fostier K., Kassambara A., Moreaux J., van Ginderachter J.A., de Bruyne E., Vanderkerken K., van Valckenborgh E. Myeloid-

derived suppressor cells induce multiple myeloma cell survival by activating the AMPK pathway. *Cancer Lett., 2019, Vol. 442, pp. 233-241.*

4. Demosthenous C., Sakellari I., Douka V., Papayanni P.G., Anagnostopoulos A., Gavriilaki E. The role of myeloid-derived suppressor cells (MDSCs) in graft-versus-host disease (GVHD). *J. Clin. Med., 2021, Vol. 10, no. 10, 2050.* doi: 10.3390/jcm10102050.

5. Gabrilovich D.I. Myeloid-derived suppressor cells. *Cancer Immunol. Res., 2017, Vol. 5, no. 1, p. 3-8.*

6. Ge Y., Cheng D., Jia Q., Xiong H., Zhang J. Mechanisms underlying the role of myeloid-derived suppressor cells in clinical diseases: good or bad. *Immune Netw., 2021, Vol. 21, no. 3, e21.* doi:10.4110/in.2021.21.e21.

7. Gonçalves T.L., Benvegnù D.M., Bonfanti G. Specific factors influence the success of autologous and allogeneic hematopoietic stem cell transplantation. *Oxid. Med. Cell. Longev., 2009, Vol. 2, no. 2, pp. 82-87.*

8. Grubovic R.M., Georgievski B., Cevreska L., Genadieva-Stavric S., Grubovic M.R. Analysis of factors that influence hematopoietic recovery in autologous transplanted patients with hematopoietic stem cells from peripheral blood. *Open Access Maced. J. Med. Sci., 2018, Vol. 5, no. 3, pp. 324-321.*

9. Hassan M.N., Fauzi H.M., Husin A., Mustaffa R., Hassan R., Ibrahim M.I., Noor N.H.M. Autologous peripheral blood stem cell transplantation among lymphoproliferative disease patients: factors influencing engraftment. *Oman Med. J., 2019, Vol. 34, no. 1, pp. 34-43.*

10. Hegerova L., Gertz M., Lacy M., Dispenzieri A., Buadi F., Hayman S.R., Dingli D., Porrata L.F., Kumar S. Measures of immune recovery following autologous stem cell transplantation for multiple myeloma and outcome. *J. Clin. Oncol., 2013, Vol. 31, Iss. 15 Suppl., pp. 8581-8581.*

11. Lv M., Wang K., Huang X.J. Myeloid-derived suppressor cells in hematological malignancies: friends or foes. *J. Hematol. Oncol., 2019, Vol. 12, no. 1, 105.* doi: 10.1186/s13045-019-0797-3.

12. Stalker M.E., Mark T.M. Clinical management of triple-class refractory multiple myeloma: a review of current strategies and emerging therapies. *Curr. Oncol., 2022, Vol. 29, no. 7, pp. 4464-4477.*

Авторы:

Анмут В.С. *— студент, Институт медицины и психологии В. Зельмана ФГАОУ ВО «Новосибирский национальный исследовательский государственный университет», г. Новосибирск, Россия*

Тыринова Т.В. *— д.б.н., ведущий научный сотрудник ФГБНУ «Научно-исследовательский институт фундаментальной и клинической иммунологии»; старший преподаватель кафедры иммунологии, Институт медицины и психологии В. Зельмана ФГАОУ ВО «Новосибирский национальный исследовательский государственный университет», г. Новосибирск, Россия*

Баторов Е.В. *— к.м.н., старший научный сотрудник ФГБНУ «Научно-исследовательский институт фундаментальной и клинической иммунологии», г. Новосибирск, Россия*

Аристова Т.А. *— врач-гематолог ФГБНУ «Научно-исследовательский институт фундаментальной и клинической иммунологии», г. Новосибирск, Россия*

Сизикова С.А. *— к.м.н., врач-гематолог ФГБНУ «Научно-исследовательский институт фундаментальной и клинической иммунологии», г. Новосибирск, Россия*

Ушакова Г.Ю. *— к.м.н., врач-гематолог ФГБНУ «Научно-исследовательский институт фундаментальной и клинической иммунологии», г. Новосибирск, Россия*

Денисова В.В. *— к.м.н., заведующая отделением ФГБНУ «Научно-исследовательский институт фундаментальной и клинической иммунологии», г. Новосибирск, Россия*

Черных Е.Р. *— д.м.н., профессор, член-корреспондент РАН, заведующая лабораторией ФГБНУ «Научно-исследовательский институт фундаментальной и клинической иммунологии», г. Новосибирск, Россия*

Authors:

Anmut V.S., *Student, V. Zelman Institute of Medicine and Psychology, Novosibirsk State University, Novosibirsk, Russian Federation*

Tyrinova T.V., *PhD, MD (Biology), Leading Research Associate, Research Institute of Fundamental and Clinical Immunology, Novosibirsk, Russian Federation; Senior Lecturer, Department of Immunology, V. Zelman Institute of Medicine and Psychology, Novosibirsk State University, Novosibirsk, Russian Federation*

Batorov E.V., *PhD (Medicine), Senior Research Associate, Research Institute of Fundamental and Clinical Immunology, Novosibirsk, Russian Federation*

Aristova T.A., *Hematologist, Research Institute of Fundamental and Clinical Immunology, Novosibirsk, Russian Federation*

Sizikova S.A., *PhD (Medicine), Hematologist, Research Institute of Fundamental and Clinical Immunology, Novosibirsk, Russian Federation*

Ushakova G.Yu., *PhD (Medicine), Hematologist, Research Institute of Fundamental and Clinical Immunology, Novosibirsk, Russian Federation*

Denisova V.V., *PhD (Medicine), Head of Department, Research Institute of Fundamental and Clinical Immunology, Novosibirsk, Russian Federation*

Chernykh E.R., *PhD, MD (Medicine), Professor, Corresponding Member, Russian Academy of Sciences, Head of Laboratory, Research Institute of Fundamental and Clinical Immunology, Novosibirsk, Russian Federation*

Поступила 11.04.2023
Принята к печати 13.04.2023

Received 11.04.2023
Accepted 13.04.2023