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Features of Immunological Changes in Autologous Hematopoietic Stem Cell Transplantation in Patients with Multiple Myeloma

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ABSTRACT

Intensive treatment of multiple myeloma involves maximum suppression of the tumor clone. The introduction of transplantation techniques into clinical practice has significantly improved the outcomes of multiple myeloma, for which the EBMT research team has developed concepts such as complete and partial remission, progression-free survival and disease-free survival. In this scientific article, we tried to solve the following specific tasks: to study the immunophenotype of plasma cells of the bone marrow of primary patients with multiple myeloma by flow cytometry; to study the immunophenotype of bone marrow plasma cells of healthy donors and compare it with the immunophenotype of primary patients with multiple myeloma; to determine the change in the immunophenotypic characteristics of bone marrow plasma cells in patients with multiple myeloma during treatment: after induction therapy, before and after transplantation of autologous hematopoietic stem cells; to study the qualitative and quantitative composition of plasma cells in the leukoconcentrate collected during the first leukapheresis procedure, and to assess the progression-free survival after transplantation depending on the number of plasma cells transfused.

Keywords: multiple myeloma, plasma cells, bone marrow transplantation.

INTRODUCTION

Modern treatment programs for symptomatic multiple myeloma are based on the principle of early intensification and high-dose consolidation using autologous hematopoietic stem cell transplantation. Autologous transplantation is now considered the "standard" in the treatment of multiple myeloma patients younger than 60-65 years of age.

In the last decade, new drugs with a targeted mechanism of action have been included in the treatment regimens for multiple myeloma. These are a proteasome inhibitor (bortezomib) and immunomodulatory drugs (thalidomide and lenalidomide). The use of new drugs at the stage of induction made it possible to obtain a strict complete response in 25–35% of patients with multiple myeloma. Further high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation in-

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creased the rate of complete immunochemical remissions to 45–50% [1].

Due to the possibility of significant reduction of the tumor mass after autologous transplantation, the sensitivity of standard methods for assessing the effectiveness of multiple myeloma treatment (morphological examination of bone marrow aspirate and immunochemical control of the M-gradient) was insufficient. There was a need for additional use of more sensitive methods for detecting minimal residual disease.

Additional methods of bone marrow examination include immunophenotyping by flow cytometry and molecular biological studies, which are gradually becoming mandatory in many hematological diseases. With the help of these methods, it is possible to obtain more information about the biology of the disease, identify residual tumor cells, assess the effectiveness of treatment [2], as well as to recognise early signs of disease recurrence, thereby predetermining the prognosis of the disease.

The relevance of our study lies in the fact that immunophenotyping of bone marrow plasma cells by flow cytometry is one of the most modern methods for diagnosing hemoblastosis. For example, in monoclonal gammopathy of unknown origin, at the stage of diagnosis using flow cytometry, it became possible to detect clonal plasma cells, which makes it possible to diagnose this nosology in a timely manner [3].

In smouldering myeloma, flow cytometry can detect more than 60% of clonal plasma cells in the bone marrow of patients, which dictates the need for immediate start of specific therapy. In solitary plasmacytoma, based on this method, a new classification was revised and formulated, based on the content of tumor cells in the bone marrow: solitary plasmacytoma without bone marrow involvement and solitary plasmacytoma with minimal bone marrow involvement. In diseases such as amyloidosis and Waldenstrom's macroglobulinemia, flow cytometry, which detects clonal plasma cells in the bone marrow, provides additional information to facilitate a quick and clear diagnosis. Finally, in multiple myeloma, flow cytometry, which is not a standard diagnostic method, is used mainly in difficult diagnostic situations, as well as in the assessment and monitoring of minimal residual disease during treatment and to confirm a strict complete response after therapy [4].

In the examination of a bone marrow sample from a patient with multiple myeloma, the assessment of the simultaneous expression of CD138/CD38 represents the optimal combination of markers for identifying bone marrow plasma cells and distinguishing them from other cell populations and hematopoietic stem cells.

The most important markers by which tumor myeloma cells can be distinguished from normal bone marrow plasma cells are CD45, CD19, CD117, and CD56 in the CD138+/CD38+ plasma cell population.

A study of the residual tumor population of bone marrow plasma cells after completion of a high-dose multiple myeloma treatment program will contribute to the evaluation of the effectiveness of therapy.

In our study, the immunophenotype of bone marrow plasma cells in patients with multiple myeloma was studied in detail, both at the time of diagnosis of the disease and during treatment, which included high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation. When studying the publications of domestic and foreign authors, we did not find any reports indicating the possibility of changing the immunophenotype of myeloma cells or a combination of aberrant markers in the process of transplant treatment, which gives reason to consider this problem urgent.

The study aimed to study the immunophenotypic characteristics of bone marrow plasma cells in patients with multiple myeloma before and after transplantation of autologous hematopoietic blood stem cells.

MATERIAL AND METHODS

The study included 54 patients with multiple myeloma (25 men and 29 women). The study was prospective. The age of the patients ranged from 26 years to 74 years (median 54 years).

During the diagnosis (before the start of specific therapy), all patients underwent morphological examination of bone marrow aspirate, clinical and biochemical blood tests, immunochemical examination of blood serum and daily urine, and X-ray examination of skeletal bones.

The diagnosis of multiple myeloma was made according to the criteria developed by the International Working Group on Multiple Myeloma (IMWG, 2014):

• Bone marrow punctate examination revealed between 1.6% and 60.5% of plasma cells.

• Hemoglobin (Hb) levels ranged from 76 to 156 g/L, with 22 (41%) patients showing anemia (Hb < 100 g/L).

• In the biochemical blood test, the creatinine level ranged from 75 to 451 μmol/L, while in 21 patients (39%) it exceeded 177 μmol/L. The calcium level was from 2.09 to 2.81 mmol/L, while in 20 (37%) patients it exceeded the normal value.

• The level of β2-microglobulin ranged from 1.9 mg/L to >12 mg/L, with 30 (55.5%) patients exceeding normal values (>3.5 mg/L).

• X-ray and computed tomography of the osteoarticular system: 18 (33.3%) patients had osteodestruction of various localization; 17 (31.4%) patients had soft tissue components in the femur, spine, ilium, clavicle, sternum, and 10 (18.5%) patients had compression fractures of the lumbar and thoracic vertebrae, and clavicle.

Most often, patients in our study were diagnosed with stage II and III multiple myeloma. In 21 patients (39%), myeloma nephropathy (B-substage) was detected. Immunochemical examination of blood serum and daily urine by electrophoresis and immunofixation revealed paraproteinemia G (κ/λ) most often in 28 (51.8%) of 54 patients; paraprotein A (κ/λ) – in 14 (26%) out of 54; paraprotein Dκ – in 1 (1.8%) out of 54; isolated proteinemia and proteinuria BJ in 11 (20.4%).

Induction therapy was performed according to the VD, VCD, and PAD schemes. In case of insufficient antitumor response, lenalidomide (Rd) was included in the induction regimens.

Upon completion of the induction stage, patients candidates for autologous hematopoietic stem cell transplantation underwent mobilization according to a single protocol (CF 4 g/m2 + G-colon-stimulating factor 5 μg/kg/day) and collection of hematopoietic stem cells. 3-to 6 months after mobilization, the patients underwent high-dose chemotherapy using melphalan at a dose of 200 mg/m2, followed by single or double transplantation of autologous hematopoietic stem cells.

The antitumor response was assessed according to criteria developed by the International Myeloma Working Group (IMWG, 2011):

– Immunophenotyping of bone marrow plasma cells was performed in 24 patients with multiple myeloma at the time of diagnosis. In 30 patients, the plasma cell immunophenotype was determined during treatment: after completion of the induction stage of treatment (before the mobilization of hematopoietic stem cells), before the 1st autologous hematopoietic stem cell transplantation, then 2-8 months after the 1st autologous hematopoietic stem cell transplantation, and 12-18 months after the 2nd autologous hematopoietic stem cell transplantation.

– Bone marrow immunophenotyping of healthy donors was performed as a control. The age of the donors ranged from 24 to 50 years (median age 34 years), of which 4 were men and 3 were women. Samples were taken during the exfusion of bone marrow suspension for subsequent transplantation to siblings.

The material for the study was bone marrow aspirate before and during specific therapy, as well as leukoconcentrate collected as a result of hematopoietic stem cell mobilization.

Immunophenotyping was performed using the method of 4-color flow cytometry on Cytomics FC500 (Beckman Coulter (BC), USA). CXP Cytometer software was used for data collection, and CXP Analysis was used for data analysis.

A total of 134 studies of the immunophenotype of bone marrow plasma cells were performed. Of these, 107 bone marrow samples, 20 leukoconcentrates were collected during the first leukapheresis procedure, and 7 bone marrow studies from healthy donors.

In the study, 6 monoclonal antibodies to antigens were used: CD138, CD38, CD45, CD19, CD117, and CD56.

To isolate the plasma cell population and study minimal residual disease, the A. Rawstron protocol was taken as a basis [5]. The required number of events in the CD138/CD38 gate was at least 50. In the case of minimal residual disease assessment, up to 500,000 events were collected. For diagnostic purposes, 50,000 events were sufficient at the time of diagnosis.

In the first gate, all nucleated bone marrow cells were isolated according to the characteristics of lateral light scattering (SSC) and CD45 expression, then the plasma cell gate was established according to the co-expression of CD138+/CD38+, the final gate of plasma cells was determined by direct light scattering (FSC) and side light scattering (SSC), in which the population was once again cleared of debris.

By analyzing the cells of the sample representing such a negative control, the threshold levels of fluorescence (the boundaries between the so-called "antigen-positive" and "antigen-negative" objects) were marked on the logarithmic scale of fluorescence intensity.

To analyze the collected information, classical methods of descriptive statistics, frequency, variance, regression analysis and survival analysis were used. The T-test was used for the linked samples, and the Wilcoxon test was used to calculate the median. When calculating the value of P (< 0.05), a test was used according to the McNemar method, and the Bonferroni correction was also used. Data conversion and analysis were carried out using the SAS 9.4 analytical package and Dell Statistica 13.1.

RESULTS AND DISCUSSION

Immunophenotypic characteristics of bone marrow plasma cells in primary patients with multiple myeloma Bone marrow cell immunophenotyping using 4-color flow cytometry was performed in 24 patients at the time of diagnosis of multiple myeloma. The study included the detection of CD19/CD117/CD56

markers in the CD138+/CD38+/CD45dim/plasma cell population.

The guidelines "Study of minimal residual disease by multiparametric flow cytometry" [6] indicate that the most common immunophenotype of normal plasma cells is represented by the following markers: CD38+/bright, CD138+/bright, CD19+, CD45+/-, CD20-, CD27+, CD28-, CD56-, CD81+, CD117-, CD200-/+, and the immunophenotype of myeloma cells is characterized by the following markers: CD38+/low, CD19-, CD45dim/-, CD20+, CD27-/low, CD28+, CD56+/bright, CD8-/ low, CD117+, CD200bright.

At the same time, the authors noted that a small population of normal plasma cells (< 30%) may have expression of a marker characteristic of tumor cells (CD56+) and no expression of CD19 and CD45.

Various variants of plasma cell immunophenotype were identified by us in patients with multiple myeloma at the time of diagnosis of the disease. Due to the uniformity of expression of CD138+/CD38+/CD45dim/, these markers were not included in this list. For example, CD19-/CD117+/CD56+, an aberrant immunophenotype that fully corresponds to the classic immunophenotype of myeloma cells, was found in only 4 (16.7%) patients. The CD19+/CD117+/CD56+ immunophenotype, characterized by the expression of aberrant markers CD117 and CD56, as well as the presence of expression of the CD19 marker, was observed in 6 (25%) patients.

The CD19-/CD117-/CD56- immunophenotype, characterized not only by the absence of expression of CD117 and CD56 markers but also by the absence of CD19 expression, which would be more consistent with normal plasma cells, was detected in 4 (16.7%) patients.

The CD19+/CD117-/CD56+ immunophenotype, represented by expression of the CD19 marker, expression of the aberrant marker CD56, and absence of CD117 expression, was noted in only 1 (4.1%) patient. The CD19-/CD117-/CD56+ immunophenotype, characterized by expression of the aberrant marker CD56 and the absence of CD117 and CD19 markers of plasma cells, was found in 9 (37.5%) patients. It was this combination of the studied markers in patients with multiple myeloma that was most common in our study.

As noted above, the immunophenotype of tumor plasma cells is represented by the following characteristics of the CD138+/CD38+/CD45-/dim/CD19/CD117+/CD56+ markers. When each of the aberrant markers was examined separately, CD56 expression was most often detected in 20 (83.3%) of 24 patients. Lack of expression of the CD19 marker was observed in 17 (70.83%) of 24 patients. CD117 expression was detected in 10 (41.66%) of 24 patients.

In the study of the immunophenotype of bone marrow plasma cells, 7 healthy bone marrow donors were considered as a control group. The CD138+/CD38+ PC content in the bone marrow of healthy donors ranged from 0.07% to 0.72% (median 0.39%).

All donors had strong expression of CD138+/CD38+ and no expression of the CD117 marker. As for the CD45 marker, 4 donors had expression of this marker, and the remaining 3 did not.

In donors, we found 4 types of bone marrow plasma cell immunophenotype in terms of the expression or absence of CD45, CD19, and CD56 markers. Immunophenotype CD138+/CD38+/CD45+/CD19-/CD117-/CD56+ was detected slightly more often in 3 cases. Immunophenotype CD138+/CD38+/CD45-/CD19-/CD117-/CD56+ was determined in 2 cases.

The diversity of the phenotype of plasma cells of donors is evidenced by some foreign publications. For example, in a study [7], bone marrow immunophenotyping was performed in 11 healthy donors using flow cytometry. In his study, the author also identified 4 types of plasma cells characterized by the presence or absence of expression of CD19, CD56 markers: CD19+/CD56-; CD19-/CD56+; CD19-/CD56-; CD19+/CD56+.

Thus, the results of our study by flow cytometry confirmed the pronounced heterogeneity of the plasma cell phenotype in both patients with multiple myeloma and healthy donors.

Immunophenotyping of bone marrow cells was performed in 36 patients with multiple myeloma during treatment: after completion of induction therapy (or before mobilization of hematopoietic stem cells), before and after transplantation of autologous hematopoietic stem cells.

As the plasma cells of the bone marrow of all 36 patients were characterized by CD138/CD38 expression and weak/negative CD45dim/- expression during treatment, these results were not included in the analysis.

The expression rate of CD19+/- and CD56+/- markers in the stages before hematopoietic stem cell mobilization, before and after autologous hematopoietic stem cell transplantation remained practically unchanged. As for the expression of CD117, the frequency of the presence/absence of this marker still changed slightly at the stage before the 1st autologous hematopoietic stem cell transplantation and returned to the initial level after the completion of transplant treatment.

Examination of the bone marrow of patients with multiple myeloma (n = 30) revealed 7 varieties of combinations of aberrant markers of plasma cells before the mobilization of hematopoietic stem cells: CD19-/CD117-/CD56+, CD19+/CD117-/CD56+, CD19-/CD117-/CD56-, CD19-/CD117+/CD56+, CD19-/CD117+/CD56-, CD19+/CD117+/CD56-, CD19+/CD117+/CD56+. At the same time, the most common immunophenotype of plasma cells at this stage of treatment was CD19+/CD117+/CD56+ in 14 patients and CD19-/CD117-/CD56- in 7 patients. It was this combination of markers that remained the most common at all stages of treatment.

In the study of bone marrow patients with multiple myeloma (n = 31) before the 1st transplantation of autologous hematopoietic stem cells, we noted 4 types of immunophenotype of bone marrow plasma cells: CD19-/CD117-/CD56+, CD19+/CD117-/CD56+, CD19-/CD117-/CD56-, CD19+/CD117+/CD56+. The CD19-/CD117-/CD56+ immunophenotype was detected in 6 patients, CD19+/CD117-/CD56+ in 3 patients, CD19+/CD117+/CD56+ in 12 patients, and CD19-/CD117-/CD56- in 10 patients.

Thus, it is important to note that CD19-/CD117+/CD56+, CD19-/CD117+/CD56- and CD19+/CD117+/CD56- combinations of aberrant markers on plasma cells disappeared after cyclophosphamide administration.

Bone marrow immunophenotyping was performed in 17 patients with multiple myeloma after the 1st autologous hematopoietic stem cell transplantation. 5 types of immunophenotype were identified at the previous stages of treatment (before the mobilization of hematopoietic stem cells): CD19-/CD117-/CD56+, CD19-/CD117+/CD56+, CD19-/CD117+/CD56-, CD19-/CD117-/CD56-, CD19+/CD117+/CD56+. The most common among them were still CD19-/CD117-/CD56- (n = 5), CD19+/CD117+/CD56+ (n = 8). However, the CD19+/CD117-/CD56+ immunophenotype, which occurred at the previous stage of treatment (before the 1st autologous hematopoietic stem cell transplantation), disappeared.

Thus, during the immunophenotyping of the bone marrow of patients with multiple myeloma in the course of treatment, a change in the immunophenotype of plasma cells against the background of the therapy was revealed. The most commonly detected bone marrow plasma immunophenotype at all stages of treatment was CD138+/CD38+/CD45dim/-/CD19+/CD117+/CD56+ and CD138+/CD38+/CD45dim/-/CD19-/CD117-/CD56-.

Next, we calculated the total number of plasma cells CD138+/CD38+ and plasma cells with aberrant expression in the bone marrow before and after the 1st transplantation of autologous hematopoietic stem cells.

The total number of CD138+/CD38+ plasma cells in the bone marrow before autologous hematopoietic stem cell transplantation was 0.827±0.148%, and after autologous hematopoietic stem cell transplantation decreased to 0.559±0.116%. The content of plasma cells with aberrant expression of the studied plasma cell markers also decreased after autologous hematopoietic stem cell transplantation compared to pre-transplant rates: 0.339±0.134% versus 0.559±0.116%.

Significant differences in the comparison confirm the pronounced myelosuppressive and antitumor effect of high-dose melphalan used as pre-transplant conditioning in patients with multiple myeloma.

Immunophenotyping of plasma cells in leukoconcentrate collected as a result of hematopoietic stem cell mobilization Immunophenotyping of plasma cells in leukoconcentrate collected during the first leukapheresis procedure was performed in 20 patients with multiple myeloma. The total number of CD138+/CD38+ plasma cells in the leukoconcentrate was assessed by flow cytometry, among which the presence or absence of expression of each of the aberrant markers of plasma cells was revealed: CD19, CD117, CD56. The CD34+ cell count in the leukoconcentrate collected during the first leukapheresis procedure ranged from 2.33 to 48.6 x 106 cells/kg (median = 10.8).

Based on the results obtained, the dependence of the content of plasma cells with aberrant expression of markers in the leukoconcentrate on the total number of plasma cells collected during the first leukapheresis procedure was analyzed.

We assessed overall and progression-free survival in 20 patients. In 7 patients, no relapse/progression of the disease was detected within 20–60 months (median 48 months) after autologous hematopoietic stem cell transplantation. In the other 13 patients, recurrence/progression of multiple myeloma was observed 7–58 months (median 23 months) after autologous hematopoietic stem cell transplantation.

At the time of analysis of the results, 17 patients were alive (median duration of follow-up was 47 months), of which 3 patients died 8, 35 and 47 months after autologous hematopoietic stem cell transplantation from disease progression.

In analyzing the timing of relapse/progression of multiple myeloma, we noted that in 8 cases relapse/progression was observed within the first 24 months, in 4 patients there was no relapse/progression within the first 24

months, and in 8 patients there was no relapse/progression within > 40 months after autologous hematopoietic stem cell transplantation.

The mean number of transfused plasma cells with aberrant expression turned out to be almost the same both in patients with early relapse/progression (within the first 24 months) and in patients whose relapse-free survival exceeded 40 months.

Thus, in our study, there was no significant dependence of the relapse/progression time after autologous hematopoietic stem cell transplantation on the number of transfused plasma cells with aberrant expression.

CONCLUSION

The study of the immunophenotype of plasma cells in primary multiple myeloma revealed a pronounced heterogeneity of tumor cells. Thus, the immunophenotype characterized by the markers CD138+/CD38+/CD45-/CD19-/CD117-/CD56+ was detected in 37.5% of patients, and the markers CD138+/CD38+/CD45-/CD19+/CD117+/CD56+ were detected in 25% of patients. At the same time, aberrants for CD19- were observed in 70.8% of cases, for CD117+ in 41.7% and for CD56+ in 83.3% of cases.

In the course of treatment of multiple myeloma, the frequency of expression of CD19, CD117, and CD56 markers did not change, while the combinations of these aberrant markers on plasma cells differed after the use of high doses of cyclophosphamide and melphalan. There was a significant (p=0.03) decrease in the total number of plasma cells in the bone marrow (from 0.827±0.148 to 0.559±0.116) and plasma cells with an aberrant immunophenotype (from 0.588±0.12 to 0.339±0.134) after transplantation of autologous hematopoietic stem cells. In 6 (35%) patients with multiple myeloma after the 1st transplantation, minimal residual disease was achieved - negativity.

A significant (p=0.0004) direct relationship between the number of plasma cells with aberrant expression and the total number of plasma cells collected in the leucoconcentrate as a result of hematopoietic stem cell mobilization was revealed. It has been shown that the timing of recurrence/progression of multiple myeloma after autologous transplantation does not depend on the number of transfused plasma cells with aberrant expression of markers.

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MIYELOM KASALLIGI BILAN HASTALANGAN BEMORLARDA AUTOLOGIK GEMAPOETIK O'ZAK HUJAYRALARINI TRANSPLANTATSIYA QILISHDA IMMUNOLOGIK O'ZGARISHLARNING XUSUSIYATLARI

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ABSTRAKT

Ko'p miyelomani intensiv davolash o'simta kloni maksimal darajada bostirishni o'z ichiga oladi. Klinik amaliyotga transplantatsiya usullarini joriy etish ko'p miyeloma natijalarini sezilarli darajada yaxshiladi. Buning uchun EBMT tadqiqot guruhi to'liq va qisman remissiya, prognozsiz tiriklik va kasalliksiz tiriklik kabi tushunchalarni ishlab chiqdi. Ushbu ilmiy maqolada quyidagi muayyan vazifalarni yechishga harakat qildik: oqim sitometriyasi bo'yicha ko'p miyelomali birlamchi bemorlarning suyak iligi plazma hujayralari immunopenotipini o'rganish; sog'lom donorlarning suyak iligi plazma hujayralarining immunopenotipini o'rganish va uni ko'p miyelomali birlamchi bemorlarning immunopenotiplari bilan taqqoslash; davolash paytida ko'p miyeloma bilan og'rilgan bemorlarda suyak iligi plazma hujayralarining immunofenotipik xususiyatlarining o'zgarishini aniqlash uchun: induksion terapiyadan so'ng, autolog gematopoietik bo'g'im hujayralarini transplantatsiya qilishdan oldin va keyin; birinchi leykopherez jarayonida to'plangan leykokonsentratdagi plazma hujayralarining sifat va miqdoriy tarkibini o'rganish, transfüze qilingan plazma hujayralari soniga qarab transplantatsiyadan so'ng progressiyasiz yashashni baholash.

Tayanch so'zlar: ko'p miyeloma, plazma hujayralari, suyak iligi transplantatsiyasi.