Acute Graft Versus Host Disease in Hematopoietic Stem Cell Allotransplant Recipients

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Introduction: The transplantation of hematopoietic stem cells (HSCT) is a therapeutic intervention where the hematopoietic stem cells and the cells originating from them are being removed and replaced by the normal stem cells of donor or the patient him/her-self. HSCT today represent standardized biological manipulation for treating malignant, genetic and autoimmune diseases. The application of allogeneic hematopoietic stem cell transplantation (HSCT) is limited by life-threatening complications such as severe or acute graft-versus-host disease (GVHD). Despite intensive prophylaxis with immunosuppressive agents, the incidence of GVHD occurs in 9-50% of patients undergoing transplant with an identical HLA sibling matched donor and 75% of patients undergoing unrelated HLA donors.

Aim of study: To evaluate our experiences in GVHD prophylaxis and treatment after alloHSCT, GVHD incidence and prognostic factors and administration of new immunosuppressive regiments. Can we recognize clinical parameters which are associated with occurrence and severity of graft-versus-host disease? Patients and methods: Starting from September 2000 till September 2010, 63 patients (36 males and 27 females) at the age of 16-56 (median range 33 years) with hematological malignancies were treated with alloHSCT on Department of Hematology, Clinical Centre, Skopje. In 10 patients bone marrow was used as source of stem cells and in 53 patients stem cells were obtained from peripheral blood. From the group of 63 patients, 26 patients had active disease at the time of transplantation. GVHD prophylaxis was accomplished with combination of cyclosporine and methotrexate (Seattle regimen) or more intensive immunosuppression regiments.

Results: GVHD was noticed in 30 patients (47,6%) and in 33 patients (52,4%) a manifestation of GVHD was noticed. Acute GVHD was noticed in 24 patients (38%) and chronic GVHD in 20 patients (31,7%) The remaining 32 patients (45%) achieved complete clinical and hematological remission. Lethal outcome was confirmed in 31(49%) patients (9 from chrGVHD, 6 from acute GVHD, 16 from disease relapse). Conclusion: The incidence of acute GVHD in our study was 38% and 31% for chronic GVHD. The most common GVHD reaction was registered in female donors and male recipients, with higher GVHD incidence in elderly patients. In all patients stem cells were obtained from peripheral blood. Active disease, sex, source of hematopoietic cells, age and conditional regiments are the most significant predictive factors with the high incidence of GVHD. Key words: acute graft versus host disease in hematopoietic stem cell allotransplant recipients.
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2. MATERIAL AND METHODS

Starting from September 2000 till September 2010, 63 patients (36 males and 27 females) at the age of 16-56 (median range 33 years) with hematological malignancies were treated with al-loHSCT on Clinic of Haematology. In 10 patients bone marrow was used as source of stem cells and in 53 patients stem cells were obtained from peripheral blood. From the group of 63 patients, 26 patients have active disease at the time of transplantation.

The first 3 weeks after the allogeneic HSCT CsA shall be applied in doses of 3 mg/kg IV.+ MTX and then orally depending on the cyclosporinemia in two day doses. The other preventive protocols for aGVHD shall be performed with application of mycophenolate mophetil 1,5-3 gr/kg per day +30 in combination with CsA in the standard doses and/or in combination of CsA with corticosteroids (methylprednisolone) 1mg/kg/day. The individualization in maintaining the cyclosporinemia in the ref-

perfect HLA ma GVHD match of a related donor, the chances of incompatibility of unknown sites are in the framework of 40-50%. (21, 22, 23, 24). NK cells have the ability to cause GVHD reaction without the mediation of T-cells, chemokinesis of mononuclear phagocytes and damage of target organs, through recipient’s target cell apoptosis. MNC or non-MNC minor Ag can be found in all cells and tissues and in the process of transplantation they are transferred between the donor and the recipient. In normal circumstances these antigens shall be recognized by the recipient’s immune system and any alien tissue and cells shall be rejected. But if the recipient is has a defined immune system then the immune competent cells contained in the graft shall recognize the recipient’s antigens as alien and shall indicate GVHD.(3, 8). The proactive allo-reactivity occurring in HLA mismatch transplantation results in decreasing the patients’ GVHD and increasing the GVL effect. This paradoxical effect “perfect mismatch” is observed by NK inhibitory receptors of donor’s cells and KIR ligands (polymorphic cell surface molecules presented in “natural killer” cells with antigen marks CD56, CD16, CD3) of recipient’s hematopoietic cells. In future the genotype of the patients and the panel of cytokines, chemokines and pharmacogens shall be sufficient without any classification of histological compatibility and may be predicted the risk of transplantation and the toxicity associated with it. (12) The main question of the future is if the GV effect can be separated from the GVH manipulating the transplanted immune system. The potential target of GV effect is the normal recipient allogens or recognizing the tumor associated antigens (13).

The acute GVHD is defined as a syndrome that appears in the first 100 days after the HSCT in related and unrelated transplantations. The transplantation practice shows that the acute GVHD may occur 100 days after HSCT, too. The time of acute GVHD occurrence may help us predict the disease outcome, that is the liver acute GVHD has bad prediction and high percentage of unrelapsed mortality (11, 20, 22). The acute GVHD directly depends on the histological barrier, number of T lymphocytes, donor’s and recipient’s characteristics, prophylactic protocols, conditioning protocols (chemo/radiotherapy), patient’s age, AB0 incompatibility, donorrecipient’s sex mismatch, donor’s/recipient’s active state, etc. (19). The acute of form of GVHD clinic manifestations are presented by changes in skin, GIT and liver. The genetic predisposition and the other HLA antigen differences (genetic polymorphism of cytokines, pharmacogens polymorphism that infiltrates the metabolism of drugs used in conditioning protocols) can be associated with the GVHD occurrence. Clinic manifestations and grades of AGVHD standardized by Glucksberg in 1974 and by the IBMTR Consensus Conference. The acute GVHD is manifested clinically by maculopapular rash which is not specific and looks like a drug allergic dermatitis. It appears on the soles, palms and after that on the skin of the face and/or generalized dermatitis. The dominant symptom of AGVHD in getting GIT is nausea and watery green diarrhoea. The liver taken from an acute form of GVHD is manifested like cholestatic hepatoapathy. GVHD also involves the immune system delaying the immunologic recovery, which results in prolonged immunodeficiency. This is manifested by infections and the risk of further deterioration of immunosuppressive GVHD therapy. The capacity of the epithelial tissue to become a GVHD target organ depends on the degree of differentiation. This is the reason why the acute GVHD gets primarily the epithelial cells with low differentiation. Histological biopsy staging is not used for grading the acute GVHD. Today the grading score system including clinic skin manifestations, GIT, liver and performance status, has been accepted. (2) The surface molecules as (CD4 and CD8) of T-lymphocytes are very important for the reaction of transplant against recipient. The corticosteroids have a proven ability to lysis the lymphocytes and their proven anti-inflammatory effect. When treating AGVHD methylprednisolonom is applied in doses of 10mg/kg per day, five days, then ten days in doses of 2 mg/kg per day and after that then check the condition of the patient. It no improvement is made the therapy shall continue applying higher doses of corticosteroids (methylprednisolonom 20 mg/kg per day) or different salvage protocols are used such as: ATG, different monoclonal antibodies (OKT3, anti IL-2, CD25, anti TNF-α). (9, 10). The response of AGVHD treatment depends of many factors, such as degree of AGVHD, beginning time and response to the initial treatment.

1. Using bone marrow from an allo-sensitive female donor in male recipient shall increase twice or trice the risk of acute GVHD occurrence (1). Using donor’s viable lymphocytes for re-induction of remission in patients who had relapse of leukemia after hematopoietic stem cell transplantation is controversial because DLI leads to a higher risk of acute GVHD (12, 15, 26). Treating the reaction of transplant against recipient. The corticosteroids have a proven role in the treatment of AGVHD with their ability to lysis the lymphocytes and their proven anti-inflammatory effect. When treating AGVHD methylprednisolonom is applied in doses of 10mg/kg per day, five days, then ten days in doses of 2 mg/kg per day and after that then check the condition of the patient. It no improvement is made the therapy shall continue applying higher doses of corticosteroids (methylprednisolonom 20 mg/kg per day) or different salvage protocols are used such as: ATG, different monoclonal antibodies (OKT3, anti IL-2, CD25, anti TNF-α). (9, 10). The response of AGVHD treatment depends of many factors, such as degree of AGVHD, beginning time and response to the initial treatment.
order to be cured, and to see if we can make a systematization of the these risk factors individually for each patient. This shall be a foundation for optimization of the therapeutic approach on one hand and on the other to show if all these risk factors shall confirm their specificity and sensitivity using comparison of more standard prognostic risk factors. The optimization of the therapeutic approach is of great significance for the patients with multiple positive risk factors, who need more aggressive GVHD prophylactics. The first risk factor of our group that correlates with the world risk factors result in developing GVHD is the age of a patient over 40. According to the crossed relation it is a statistically significant risk that increases the chance of GVHD registration almost twice. Also the age of the donor over 40 according to the crossed relation is a statistically significant risk that increases the chance of GVHD registration in the recipients for one and half times. The positive allo-immunization status of the donor develop GVHD) and confirms the statistic significance of the world experience. Knowing the mechanism of the reaction, the benefit of the GVL effect is desirable as a reaction and its occurrence is associated with lower incidence of relapse in the hematological diseases (7, 13). In the group we have researched, of all 63 patients 16 patients (or 25.3%) have developed relapse without GVHD occurrence. But still the mortality is 23.8% or 31 patients of the total number. 75% of the patients survive for 500 days - those who were only on corticosteroids, and 25% of the patients survive for the same period even not responding to the straight-line therapies and other immunosuppressants. These risk factors are considered to be important because the patients who have increased risk of developing GVHD, should have been treated with a more aggressive prophylactic therapy (4, 16). All achieved parameters have been included into the multi-variant analysis the in order to define or stratify with what size of risk the patient shall be treated in
showed that GVHD has been registered in 72.2% of the patients and negative allo-immunization status of the donor has been registered in 37.8%. The chance of GVHD occurrence in patients who received allograft of donors with positive allo-immunization status is increased twice. Our experience according to the source of stem cells and GVHD occurrence is statistically insignificant because the group of patients who have received fresh bone marrow, is very small. According to the conditioning protocols depending on the application of myeloablative or non-myeloablative protocols our experience is also insignificant because this group is also very small to indicate statistical significance in GVHD occurrence. According to the GVHD type of prophylactics, the group of patients who have received preventive therapy by Seattle and other immunosuppressants, is too small, and for this reason there is only insignificant statistic dependence. The incidence of acute GVHD in the big random studies in the world indicates to the fact that the acute GVHD occurs in 20-80%. The data presented in our study indicate that the acute GVHD occurs in 38.1% of the total group of patients treated with allogeneic transplantation. Our researched group the acute GVHD in grade I and II stage occurred in 11 patients or 45.8% and grade III and IV stage occurred in 13 patients or 54.2%. All our patients with grade III and IV had extensive form of the disease in all three target organs and ended lethal. Our group of patients who had developed grade I and II are young under 40 with one or two positive risk factors, they are alive and do not relapsed the basic disease. 60% of the group of our patients who had developed III and IV grade developed chronic form of GVHD and existed of the same reason.

4. CONCLUSION

The incidence of acute GVHD in our study was 38% and 31% of chronic GVHD. The cumulative survival of the patients with a GVHD: the difference in the survival compared to the presence or the absence of GVHD is being registered during a period between 900 to 1800 days (49% of the patients don’t have a GVHD, 45% have a GVHD) in the period which follows the survival gets equal, whereas 25% of the examined survive for 115 days, 50% survive for 706 days, and 49% survive for more than 1000 days. The univariate analysis has shown that the statistical significance as a prognosis markers for GVHD are: the stadium of disease, the days of the occurrence of aGVHD and hGVHD since the days of the transplantation, the form of manifestation with GVHD (gradus I, II, vs. transplantation, the form of the manifestation of aGVHD, as well as the respondents who responded to the first line therapy of GVHD, as well as those patients who developed hGVHD “denovo” type, and whether they’ve responded to the first line therapy of hGVHD. Those are important for identification of the patients, through which a basis for an individual assessment of each patient would be made during the each therapy approach. The curve of survival has shown that those patients which showed relapse of the basic disease and who are primarily resistant to the first line immunosup-

**Figure 4.** Survival curve of patients according to the occurrence of acute GVHD/days

**Figure 5.** Cumulative survival of patients according to the manifestation of acute GVHD

**Figure 6.** Cumulative survival of patients according to the occurrence of relapse

**Figure 7.** Cutaneous findings in the patients with GVHD and with active disease before HSCT
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pressive therapy and to the acute form of GVHD are candidates for a more aggressive immunomodulation and a usage of new types of cell and molecular therapy. However most of patients with GVHD who have active disease at the time of transplantation, and the question arises whether these patients can recognize and immunosuppressive and immunomodulation before and to develop clinical GVHD with uncontrollable fatal end. From our study this is a clinical benefit.

REFERENCES


