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Graft preservation in haploidentical hematopoietic stem cell transplantation with post-transplant cyclophosphamide: single center experience

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Summary

Haploidentical stem cell transplantation (haplo-SCT) is often used as a treatment option in the absence of HLA-matched donor. Cryopreservation of the graft allows pre-preparation of the bone marrow, which has become especially important during the COVID-19 epidemic. As cryopreservation remains to be relatively less studied in the context of haplo-SCT, we conducted a retrospective analysis of its feasibility in our patients. Medical records search identified 113 patients with various oncohematological diseases, who received haplo-SCT with (n=68) or without (n=64) graft cryopreservation between 2015 and 2020. Graft-versus-host disease (GvHD) prevention with post-transplant cyclophosphamide was used in all patients. Both cohorts of patients were comparable in terms of recipient age and gender, disease activity, graft source, and rates of major AB0 incompatibility. Age of donors was significantly higher in cryopreserved graft recipients (45 *vs* 37 years, p=0.017). Rates of acute and chronic GvHD, disease relapse, as well as PFS and OS did not significantly differ between the two studied cohorts. There was also no difference in terms of granulocyte and thrombocyte recovery. Although, in univariate analysis, cryopreservation significantly increased risk of graft rejection (34.3% *vs* 15.4%, p=0.02) and secondary graft failure (19.5% *vs* 4.4%, p=0.02), in multivariate analysis, there was only a trend towards increased risk of secondary graft failure with cryopreservation (p=0.096). As a summary, our data suggest that graft cryopreservation during haplo-SCT with post-transplant cyclophosphamide has no negative impact on key SCT endpoints.

Keywords

Cryopreservation, haploidentical stem cells transplantation, posttransplantation cyclophsphamide.

Introduction

Allogeneic bone marrow transplantation is the only method of therapy, which potentially allows to achieve a cure of the oncohematological disease. However, only 30 percent of people will find a suitable donor within their family. Activation of a donor from the international registry may take a long time and be expensive. In such a situation, the choice of a haploidentical donor is an appropriate option.

Cryopreservation makes it possible to harvest the graft in advance and store it until bone marrow transplantation. In contrast to autologous transplantation, cryopreservation of allograft is performed significantly less frequently. Most often, this procedure is performed, when a long-term transportation of graft is required, there is a risk of preparing an insufficient amount of HSC during one harvesting and for other technical reasons. The outbreak of the COVID-19 epidemic has made significant changes in the work of transplant centers and the frequency of cryopreservation has increased significantly.

The effect of cryopreservation on the results of allogeneic transplantation has been studied in a number of works.

The results of these studies are contradictory and mostly were limited by the data of HLA-matched bone marrow transplantations (BMT) [1-4]. At the same time, the use of cryopreservation in haplo-SCT has practically not been studied.

In this regard, we initiated a study of 113 patients who underwent haplo-SCT at our center from 2015 to 2020.

Materials and methods

Patients and HSCT regimens

The study included data from 113 patients with various oncohematological diseases who underwent allogeneic BMT from a haploidentical donor at the Department of Chemotherapy and Bone Marrow Transplantation No. 2 at the "Almazov National Medical Research Centre". This work was financially supported by the Ministry of Science and Higher Education of the Russian Federation (Agreement No. 075-15-2022-301). Patient characteristics are presented in Table 1. First-line relatives were chosen as donors. Patients were tested for anti-HLA antibodies. In case of detection of donor-specific anti-HLA antibodies, such a donor was excluded.

All patients underwent distinct types of non-myeloablative conditioning regimen, at similar dose intensity. In cases of active disease, cytoreduction with Cytarabine 2000 mg/m^2/d and Fludarabine 30 mg/m^2/d for 5 days was used before non-myeloablative conditioning. All patients underwent the same scheme for the GvHD prophylaxis: Cyclophosphamide 50 mg/m^2 on days 3 and 4, Calcineurin inhibitor (cyclosporine or tacrolimus) from day 5 to 6 months, Mycophenolate mofetil 30 mg/kg from day 5 to day 30 after infusion of hematopoietic stem cells.

Table 1. Characteristics of patients under study

Patients after haplo-SCT	N-113
Age (years)	med. 38 (18-61)
Sex: male/female	47.8%/52.2% (54/59)
Donors	
Age (years)	med. 42 (15-66)
Sex: male/female	48.5%/51.5% (64/68)
Haploidentical SCT	N=132
Cryopreserved graft Fresh graft	51.5% (68) 48.5% (64)
Graft source: Bone marrow Peripheral blood	 10% (11) 90% (121)
CD34+ cells (10^6/kg) TNC (10^8/kg)	4.6 (0.96-12.78) 6.8 (1.5-15.6)
ABO-incompatibility: Matched Major Minor Mixed	 56.1% (74) 25% (33) 13.6% (18) 5.3% (7)

Note: TNC, total nucleated cell count

Cryopreservation technique

Depending on the expected volume of a single cryopreserved dose, the cells were optionally concentrated by centrifugation while maintaining the concentration of nucleated cells less than 400*10^9 *per* liter. The cryoprotectant used was DMSO. The addition of the cryoprotectant was preceded by pre-cooling of the cells to +4°C due to storage in a refrigerator.

Addition of undiluted cryoprotectant to a concentration of 7.5% was carried out on ice. Freezing was performed in a program freezer. Subsequent storage was carried out in nitrogen vapor in the temperature range from -189.3 to -169.7°C.

Endpoints

The primary end points were recovery of hematopoiesis after BMT. Restoration of granulocytopoiesis was taken as the first of three consecutive days with ANC >0.5×10^9/l; recovery of thrombocytopoiesis – the first of seven consecutive days with a platelet level >50×10^9/l, without the need for blood transfusions. Primary graft failure was diagnosed in the absence of increase ANC >0.5×10^9/l within 28 days after BMT, aplasia of hematopoiesis, and the level of donor chimerism in the bone marrow <5%. Transplant rejection was diagnosed when the level of donor chimerism was between 5 and 95% and confirmed remission of the disease in bone marrow examination. Secondary graft failure was defined as reduction of donor chimerism below 5% in bone marrow after primary engraftment.

Secondary endpoints were overall and disease-free survival, assessment of frequency of reactivation of CMV infection, febrile neutropenia, acute and chronic graft GvHD and relapse of disease.

Statistical analysis

The difference between the two groups in assessing categorical factors was carried out using contingency tables with the Fisher`s exact test, quantitative – the Mann-Whitney method. PFS and OS were calculated using Kaplan-Meier analysis. The probability of restoration of granulocytopoiesis and thrombocytopoiesis, development of acute and chronic GvHD, relapse was calculated by the cumulative incidence method. The cumulative frequency of recovery of granulocytopoiesis was assessed on the 30th day after BMT, thrombocytopoiesis on the 100th day after BMT.

Results

Patient characteristics

The study analyzed the results of 132 allogeneic BMT of 113 patients with oncohematological diseases. The main reasons for repeat transplants were graft failure and disease recurrence. The median age of patients was 38 years (18-61). 2 groups were formed, depending on the use of cryopreserved graft (CG) 51.5% (N=68) and fresh graft (FG) 48.5% (N=64). Among the groups, there was no significant difference in age and gender of recipients, disease activity, graft source, and the presence of major AB0 incompatibility. In the cryopreservation group, the age of donors was significantly

higher: 45 (95% CI 37-50) and 37 years (95% CI 29-43) (p=0.017). The level of CD34+ cells and nucleated cells in the graft did not differ in both groups. In most cases peripheral blood was used as graft source – 90%.

Engraftment

The cumulative incidence of recovery of granulocytopoiesis and thrombocytopoiesis did not differ significantly, depending on the use of cryopreservation (Granulocytopoiesis: CG 78.4% (N=57) and FG 86.3% (N=56) (p=0.29); Thrombocytopoiesis: CG 57.8% (N=57) and FG 71.5% (N=56) (p=0.18)). The timing of recovery of granulocytopoiesis and thrombocytopoiesis also did not differ (Granulocytopoiesis: CG 17 days (CI 95% 16-18) and FG 17 days (CI 95% 15-18) (p=0.61); Thrombocytopoiesis: CG 25 days (CI 95% 22-34) and FG 25 days (95% CI 21-32) (p=0.69)). The frequency of primary graft failure did not differ: CG 15.5% and FG 10.5% (p=0.58).

We found, that the use of cryopreservation led to an increase in the incidence of rejection and secondary graft failure. Graft rejection: CG 34.3% (N=15) and FG 15.4% (N=7) (p=0.02); secondary failure: CG 19.5% (N=8) and FG 4.4% (N=2) (p=0.02) (Fig. 1). The median time for the development of graft rejection was 45 days (26-208), secondary graft failure was 85 days (36-134).

We conducted an additional analysis to clarify other factors that influenced the functionality of the graft in the long term. It was found, that the age of donors in the groups of patients with rejection and secondary graft failure was significantly older: graft rejection 52.5 (95% CI 43-54) and 36.5 (95% CI 29-43) years (p=0, 0003); secondary graft failure 51.5 (95% CI 26-58) and 37 (95% CI 32-43) years (p=0.026). In multivariate analysis, the advanced age of the donor led to a significant increase in the incidence of graft rejection (HR 1.077, 95% CI 1.023-1.134, p=0.005). At the same time, in a multivariate analysis of secondary graft failure, the age of the donor had no effect, but there was a statistical trend towards worsening results with cryopreservation (HR 4.204, 95% CI 0.776-22.773, p=0.096).

GvHD and infectious complications

The use of cryopreservation did not have a significant effect on the incidence of acute and chronic GvHD after haplodentical BMT. Cumulative frequency of acute GvHD grades 1-4: CG 58.3% (N=27) and FG 68.5% (N=35) (p=0.33); acute GvHD grades 3-4: CG 8.2% (N=4) and NT 21.7% (N=10) (p=0.17); chronic GvHD: CG 27.8% (N=7) and FG 14.5% (N=5) (p=0.23). Cryopreservation also did not lead to an increase in the incidence of infectious complications. The development of CMV infection during the first 6 months and febrile neutropenia within 30 days after BMT did not differ significantly in both groups. CMV: CG 83.6% (N=45) and FG 84.4% (N=45) (p=0.62); febrile neutropenia: CG 86.4% (N=51) and FG 89.8% (N=59) (p=0.19) (Fig. 2).

Relapse and survival

The use of cryopreservation did not lead to an increase in 30-day mortality: CG 19.4% and FG 12.5% (p=0.34). At the same time, there was a trend towards an increase in 100-day

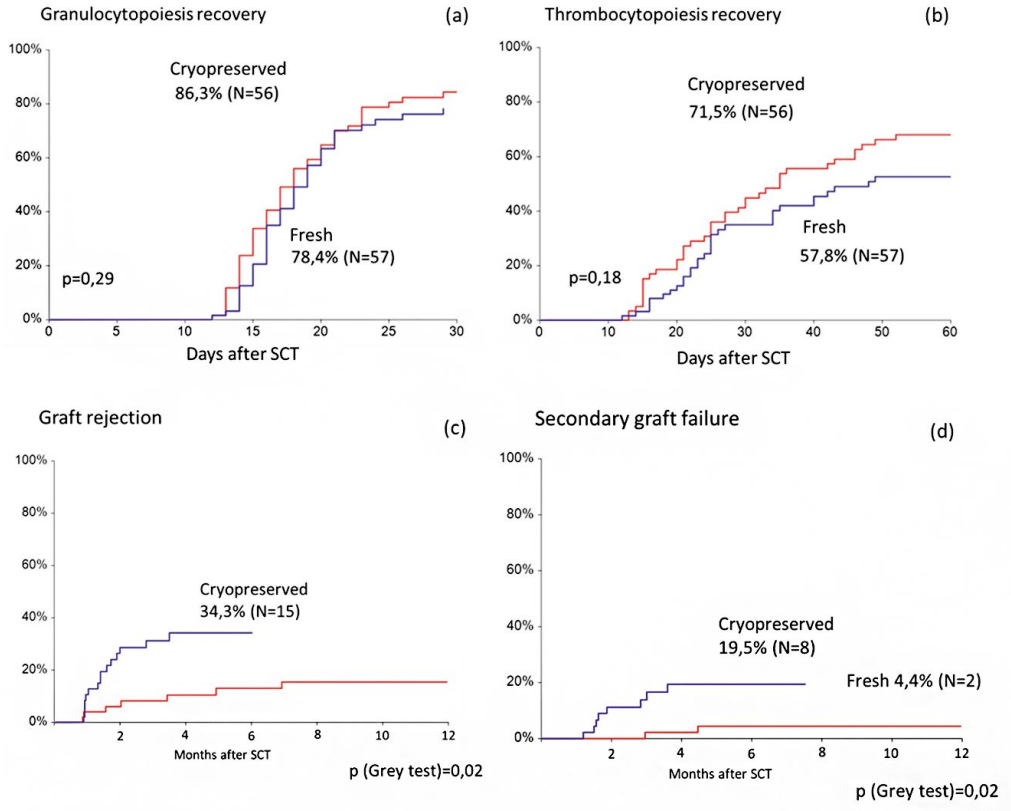

Figure 1. Cumulative incidence of granulocytopoiesis (a) and thrombocypoiesis recovery (b), graft rejection (c) and secondary graft failure after haplo-SCT

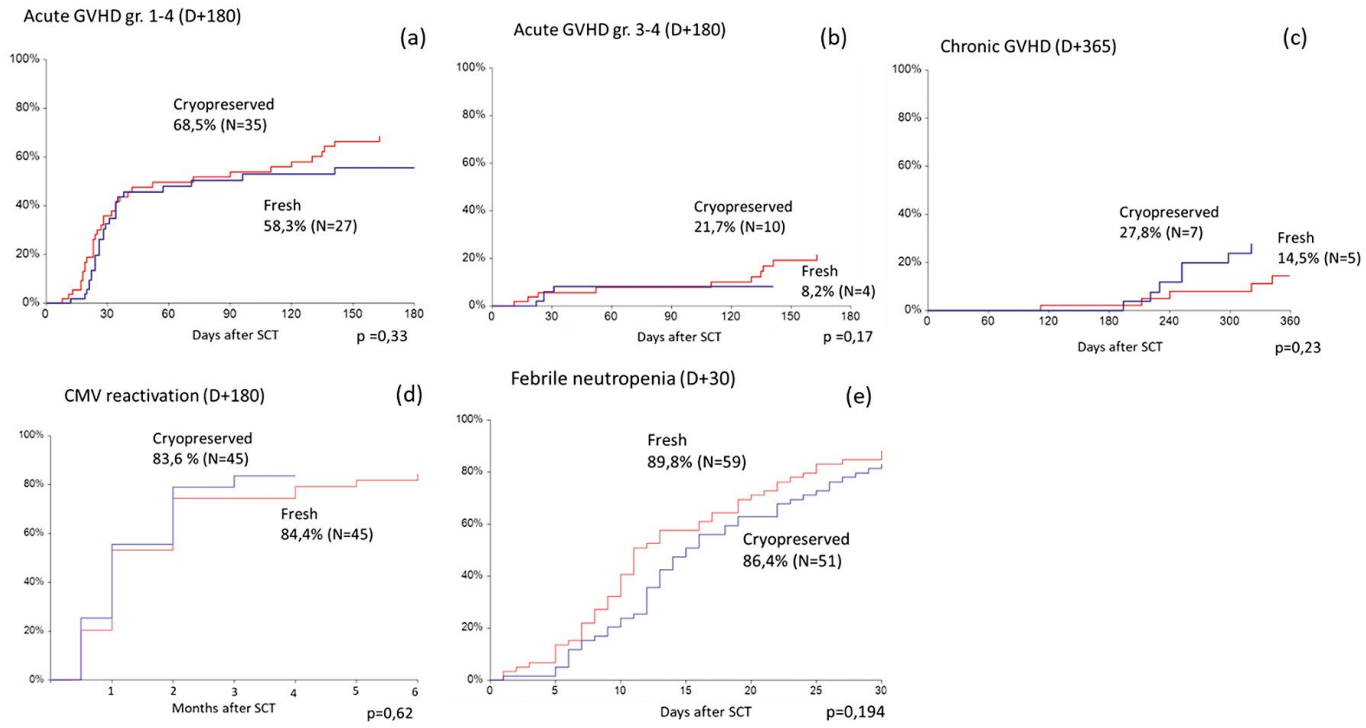

Figure 2. Cumulative incidence of acute GvHD gr. 1-4 (a), acute GvHD gr. 3-4 (b), chronic GvHD (c), CMV reactivation (d) and febrile neutropenia (e) after haplo-SCT

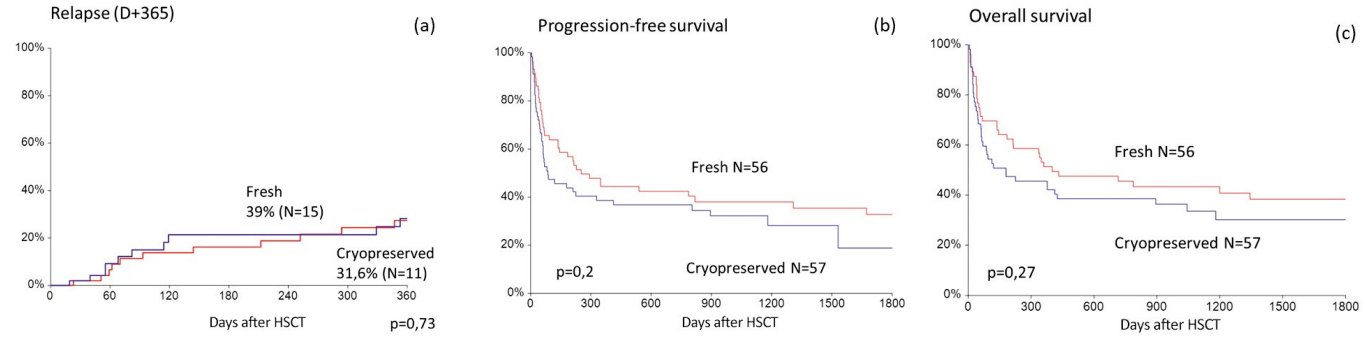

Figure 3. Cumulative incidence of relapse (a), progression-free (b) and overall survival (c) after haplo-SCT

mortality with the use of cryopreservation: CG 43.3% and FG 27% (p=0.062). 1 year OS and DFS did not differ significantly in both groups. OS: CG 45.6% and FG 51.8% (p=0.382). PFS: CG 38.6% and FG 45.8% (p=0.303) (Fig. 3).

Discussion

Thanks to graft cryopreservation, hematopoietic stem cells are stored regardless of the timing of the bone marrow transplantation procedure. The main reasons why cryopreservation is carried out include: the impossibility of immediate infusion of HSC, which is most important in autologous BMT; risk of insufficient HSC level during graft cryopreservation; donor unavailability during BMT; long-term graft transport. The main risks of this procedure are associated with the negative impact of cryopreservation on the graft, as well as the toxic effect of cryopreservative agents on the recipient's body. In most cases, cryopreservation begins after it is known for certain that the graft has been received at the transplant center and a satisfactory amount of HSC has been prepared.

The impact of the cryopreservation process on the graft has been studied in a number of works. In the process of cryopreservation, a negative effect on the hematopoietic stem cells themselves can occur, which is manifested in a decrease in the level of colony-forming units from thawed transplant samples [5, 6]. A deterioration in immune recovery after BMT has also been shown, which may be associated with the effect of cryopreservation on immune cells in the graft [7-9]. Cryoprotectant are used to preserve their viability. The most commonly used are dimethyl sulfoxide (DMSO) and hydroxyethyl starch [10]. DMSO is used at concentrations from 5% to 10%, and according to a number of studies,

a change in concentration does not affect graft engraftment. At the same time, most of the studies were carried out when performing autologous BMT [11, 12]. In our study, DMSO was used at a concentration of 7.5%.

Due to the COVID-19 epidemic, the relevance of the use of cryopreservation increased in past few years. All this has led to appearance of new research on the subject. The results of studies vary. In most cases studies are limited to groups of patients after HLA-matched BMT. Kanda Y. and colleagues evaluated the impact of cryopreservation on 112 patients in Japan after an HLA-matched unrelated BMT. The results of BMT did not differ depending on the use of cryopreservation and the source of HSC [13]. In another large multicenter study, Hsu JW. and colleagues analyzed 7397 patients after HLA-matched SCT. The patients were divided into groups according to the source of the graft: bone marrow, peripheral blood from related donor and peripheral blood from unrelated donor. Cryopreservation didn`t altered the results, if bone marrow has been used. In contrast, cryopreservation of related donor with peripheral blood stem cells was associated with decreased platelet recovery and an increased risk of acute GvHD. Cryopreservation of unrelated peripheral blood stem cells was associated with delayed engraftment of neutrophils and platelets as well as an increased risk of NRM and decreased PFS and OS [14].

Clinical data on the safety of cryopreservation after haploidentical BMT are rare. Hamandi M. and colleagues studied the results of 274 patients with various oncohematological diseases after allogeneic BMT. Most of the patients were transplanted from a haploidentical donor and peripheral blood was used as a source of HSC. Schemes with the inclusion of post-transplant cyclophosphamide were used for GvHD prophylaxis. The results of hematopoiesis recovery and survival after BMT did not differ depending on the use of cryopreservation [15].

A feature of our study was that all patients underwent haploidentical BMT with the same scheme GvHD prophylaxis, using post-transplant cyclophosphamide. A total of 132 transplant cases performed at our center were included in our study. All patients underwent a non-myelooblative conditioning regimen. Graft cryopreservation was performed in half of the patients.

Our results correspond with data of most studies. Using of transplant cryopreservation didn`t influenced recovery of hemopoiesis or risk of primary graft failure. The incidence of acute and chronic GvHD, relapse, and survival after allogeneic BMT also did not differ significantly in both groups.

At the same time, according to the results of our study, it was found that the use of cryopreservation of the graft led to a significant deterioration in the long-term results of the graft functionality. In univariate analysis, there was an increase in the incidence of graft rejection and secondary graft failure: 34.3% and 15.4% (p=0.02); 19.5% and 4.4% (N=2) (p=0.02), respectively. However, this effect was not observed in multivariate analysis, although there was a trend towards an increase in the frequency of secondary graft failure (p=0.096). Among the factors, included in the multivariate analysis, only donor age resulted in a significant increase in the incidence of graft rejection (p=0.005). In our study, the age of donors whose transplant was cryopreserved, was significantly higher: 45 and 37 years (p=0.017). This is due to the fact that when choosing elderly donors, the risk of preparing an insufficient amount of HSC increases, and there may be other reasons that will become a contraindication for donation.

The advanced age of the donor is a known factor leading to poor results of BMT, and in some studies had a negative impact on graft engraftment, but the reason for this is not fully understood [16-18].

Conclusion

Cryopreservation of graft is a safe technique for performing haploidentical BMT from a related donor with post-transplant cyclophosphamide as GvHD prophylaxis and does not lead to worsening of OS and PFS. Although, there may be a tendency to increase risk of secondary graft failure. To further study the effect of cryopreservation on the results of BMT, multicenter randomized trials are needed.

Conflict of interest

None declared.

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Применение криоконсервации при трансплантации аллогенных гемопоэтических стволовых клеток от гаплоидентичного донора с использованием посттрансплантационного циклофосфамида – опыт одного центра

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Резюме

Проведение гаплоидентичной трансплантации костного мозга (гапло-ТКМ) является подходящей альтернативой в случае отсутствия HLA-совместимого донора. Криоконсервация позволяет провести заготовку донорских гемопоэтических стволовых клеток заранее, что стало особо актуальным в период эпидемии COVID-19. Применение криоконсервации остается относительно малоизученным при проведении гапло-ТКМ, в связи с этим нами было проведено ретроспективное исследование применения криоконсервации у наших пациентов. При анализе медицинской документации были выбраны 113 пациентов с различными онкогематологическими заболеваниями, которым была проведена гапло-ТКМ с (n=68) или без (n=64) применения криоконсервации с 2015 по 2020 гг. У всех пациентов проводилась профилактика реакции «трансплантат против хозяина» (РТПХ) с использованием посттрансплантационного циклофосфамида. Обе группы пациентов были сопоставимы по полу и возрасту реципиентов, активности заболевания, источнику трансплантата и большой АВ0-несовместимости. В группе пациентов с криоконсервацией возраст доноров был значимо старше (45 против 37 лет, p=0,017). Частота острой и хронической РТПХ, рецидив заболевания, безпрогрессивная и общая выживаемость не отличались между двумя группами. Также не было разницы в сроках восстановления гранулоцитопоэза и тромбоцитопоэза. При однофакторном анализе применение криоконсервации приводило к значимому увеличению частоты развития отторжения (34,3% против 15,4%, p=0,02) и вторичного неприживления трансплантата (19,5% против 4,4%, p=0,02). При многофакторном анализе наблюдался лишь тренд к увеличению вторичного неприживления трансплантата при применении криоконсервации (p=0,096). Наши данные позволяют сделать вывод, что криоконсервация трансплантата не приводит к ухудшению результатов основных параметров гапло-ТКМ.

Ключевые слова

Криоконсервация, гаплоидентичная трансплантация гемопоэтических стволовых клеток, посттрансплантационный циклофосфамид.