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Different risk factors of acute and chronic graft-versus-host disease with conventional prophylaxis and posttransplantation cyclophosphamide in matched related and unrelated donor transplantations

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Summary

Novel aspects of allogeneic stem cell transplantation (HSCT) technologies, like use of peripheral blood stem cells (PBSC), or usage of unrelated donors significantly change the risk factors of graft-versus-host disease. Little is known, whether novel prophylaxis regimens also alter the risk factor pattern. In this study we evaluated risk factors of grade II-IV acute GVHD, and moderate or severe (NIH) chronic GVHD in the cohort of 199/344 related/unrelated patients subjected to conventional prophylaxis with calcineurin inhibitor plus methotrexate/mycophenolate mofetil (MMF) ± antithymocyte globuline. Another cohort included 104/365 recipients of related/unrelated grafts with either single-agent posttransplant cyclophosphamide (PTCy), or its combination with tacrolimus and MMF, respectively. We have observed that, for the conventional prophylaxis, the significant factors for acute GVHD were unrelated donor (HR 1.86, 95%CI 1.11-3.19, p=0.0219), salvage disease status at transplant (HR 0.50, 95%CI 0.30-0.79), use of RIC (HR 0.58, 95%CI 0.40-0.85), older age (HR 0.0442, 95%CI 0.96-0.99), higher BMI (HR 0.97, 95%CI 0.97-1.00) and early engraftment (HR 1.55, 95%CI 1.08-2.22). For PTCy prophylaxis, cytomegalovirus serostatus was the only significant factor (HR 0.71, 95%CI 0.54-0.95, p=0.0251). The risk factors of moderate and severe chronic GVHD after conventional prophylaxis were PBSC graft (HR 2.26, 95%CI 1.28-4.11) and previous acute GVHD (HR 3.76, 95%CI 2.32-6.37), while no significant factors were identified for the PTCy prophylaxis. A weak association was found with previous acute GVHD (HR 1.59, 95%CI 0.99-2.54). In conclusion, we have identified the different pattern of GVHD risk factors with conventional prophylaxis and PTCy in related and unrelated donors. Further studies are required to identify the mechanisms behind these observations.

Keywords

Graft-versus-host disease, risk factors, posttransplantation cyclophosphamide.

Introduction

Graft-versus-host disease (GVHD) is one the most life-threatening complications in allogeneic stem cell transplantation (HSCT). With more the 40000 transplants per year, more than 10 thousand patients have this complication [1, 2]. Clinically significant forms of GVHD occur in 20-50% of HSCT recipients, and it is associated with significant mortality and morbidity reaching 30% in severe cases [3, 4]. Only a few large studies have been published with analysis of GVHD risk factors.

Flowers et al. in the cohort of 2941 related and unrelated graft recipients has demonstrated that unrelated donor, HLA mismatch, female donor in male recipient and donor age were the risk factors for both acute and chronic GVHD, while intensity of the conditioning was a predictor of acute GVHD, whereas patient age and peripheral blood stem cell (PBSC) grafting were the predictors of the chronic GVHD. Also GVHD was less frequent in CML than in acute leukemia. The GVHD prophylaxis with antithymocyte immunoglobulin (ATG) did not reach statistical significance [5]. High cellularity of the graft and high prevalence of CD3-positive cells in the graft was another predictor of acute GVHD with conventional prophylaxis, especially in PBSC recipients [6]. In another large study, the use of PBSC compared to bone marrow (BM) was the risk factor for both acute and chronic GVHD [7].

The Center for International Blood and Marrow Transplant Research (CIBMTR) study with data from 226 centers has identified total body irradiation PBSC, ethnicity, poor performance study and positive cytomegalovirus status of donor and recipient as the significant risk factors of acute GVHD [7]. The study also showed that ABO incompatibility was not a significant factor, and the incidence of GVHD in CML is higher probably due to transplantation techniques.

The abovementioned studies were conducted relatively long ago, and were based on population of patients receiving predominantly cyclosporine and methotrexate (MTX) as prophylaxis, and ATG in unrelated donors. However, transplantation technologies have significantly evolved over time. Novel prophylaxis regimens have been introduced, like mTOR inhibitors [8], posttransplant cyclophosphamide (PTCy) [9], TCR alpha/beta cell depletion [10]. No studies have been published on risk factors of GVHD with these novel approaches. In the present study, we searched for risk factors in two large cohorts of patients, one with conventional prophylaxis based on calcineurin inhibitors (CNIs) with MTX/mycophenolate mofetil (MMF) and other, with PTCy prophylaxis. The purpose of this study was to evaluate whether GVHD prophylaxis does change the pattern of risk factors.

Patients and methods

One thousand thirteen adult patients transplanted at the First State I. Pavlov Medical University from 2006 to 2017 were included into the study. All the patients were grafted either from matched related donor (32%) or unrelated donor (68%). In this group, 470 patients received prophylaxis with PTCy, and 543 were subjected to conventional prophylaxis (Table 1). Only patients who successfully engrafted were included in the analysis.

GVHD prophylaxis under conventional regimen included tacrolimus with target concentration of 5 to 15 ng/ml, starting from day-1 until day+120, or cyclosporine A with target concentrations of 150 to 350 ng/ml, starting from day-1 until day+120. The second agent was either MMF 30 mg/kg (day -1 to day+30), or methotrexate 15 mg/m2 (day+1, 10 mg/m^2; day +3, 6). The recipients of unrelated grafts did also receive ATG (ATGAM, Pfizer, Inc.), at 20 mg/kg from day -3 until day -1. In the PTCy group, the prophylaxis consisted of single-agent cyclophosphamide (50 mg/kg) on days +3,+4 for matched related or unrelated bone marrow. In recipients of PBSCs, we used cyclophosphamide (50 mg/kg) on days +3,+4 followed by tacrolimus and MMF (30mg/kg) starting on day +5. In the mismatched grafts, the dose of MMF was increased to 45 mg/kg. Myeloablative conditioning (MAC) in conventional prophylaxis group was performed with oral busulfan (16 mg/kg), and cyclophosphamide (120 mg/kg). In the PTCy group, the majority of patients received MAC containing fludarabine 180 mg/m^2 and busulfan 14 mg/kg. Reduced-intensity conditioning (RIC) was performed with oral busulfan (8 mg/kg) and fludarabine (180 mg/m^2). Minority of patients received conditioning with melphalan (140 mg/m^2) and fludarabine (150 mg/m^2. RIC was performed in patients, who were either older than 40 years, had HSCT-specific co-morbidity index (HCT-CI)≥2, or exhibited, at least, grade 3 hepatotoxicity during the induction therapy. Supportive care did not differ for the two prophylaxis arms.

Statistical analysis

The Consensus Conference criteria were used for acute GVHD grading [11] and National Institutes of Health criteria were used for chronic GVHD grading [12]. Diagnosis of skin GVHD was established either clinically or histologically, the diagnosis of liver GVHD was assessed clinically, whereas gastrointestinal GVHD was specified by pathological examination. Incidence of acute and chronic GVHD was evaluated with cumulative incidence estimates. Time frame for acute GVHD was 125 days, for chronic GVHD, 2 years. Evaluation of risk factors was performed by means of Gray test. Early discontinuation of immunosuppression due to relapse or minimal residual disease was considered a competing risk for aGVHD. Donor lymphocyte infusion was considered a competing risk for cGVHD. Multivariate evaluation and analysis of continuous variables were done using Fine and Grey regression. The variables were selected for the multivariate analysis in case of significance <0.15 obtained in the univariate mode. The cutoff levels for continuous variables were determined in ROC analysis with maximal sum of sensitivity and specificity as a criterion. The analyses were conducted in SAS 9.3 (SAS Institute, Inc.).

Results

The conventional prophylaxis group comprised 199 recipients of matched related grafts and 344 subjects were transplanted from unrelated donors. The PTCy group consisted of 104 matched related transplants, and 27 matched unrelated

Table 1. Patients' characteristics in the study group

Parameter	Percent of patients (total N=1013)
Gender Males Females	 53.35% 46.65%
Age, median years (min-max)	32 (18-70)
Matched related donor (MRD) Unrelated donor (MUD/MMUD)	31.85% 68.15%
HLA mismatched	18.10%
Diagnosis AML ALL CML HL MDS AA NHL MF MPN CLL Other diagnosis	 42.81% 24.75% 10.65% 6.31% 5.82% 3.55% 2.28% 0.69% 1.48% 1.08% 0.40%
Conditioning regimen MAC RIC	 28.71% 71.19%
Salvage recipients	24.48%
Engrafted	91.38%
Calcineurin/mTOR inhibitors No Cyclosporine A Tacrolimus Sirolimus	 15.15% 21.36% 63.49% 1.98%
Second agent in prophylaxis MTX MMF	 32.50% 51.54%
ATG	35.06%
PTCy	46.35%
Mean CD34+ in the graft, *10^6/kg	4.95±2.33

AML= acute myeloblastic leukemia; ALL =acute lymphoblastic leukemia; CML= chronic myeloid leukemia; HL= Hodgkin lymphoma; MDS= myelodysplastic syndrome; AA=aplastic anemia; NHL=non-Hodgkin lymphoma MF=myelofibrosis; MPN=myeloproliferative neoplasm; CLL=chronic lymphoid leukemia; MAC=myeloablative regimen; RIC =reduced-intensity conditioning.

HSCTs, with single-agent PTCy prophylaxis. 338 patients received combined prophylaxis with PTCy, tacrolimus and MMF. Among the evaluated patients, 93.4% has engrafted. Among the engrafted patients, 436 received PTCy prophylaxis and 485, conventional GVHD prophylaxis, with a five-year survival of 47%. Incidence of acute GVHD in the whole group was 43.9%. Of them, 18.6% had grade I; 9.8%, grade II; 12.6%, grade III, and 3% had grade IV GVHD. The incidence of chronic GVHD was 31.6%, including 12.6% with mild; 9%, moderate degree, and 10% showed severe GVHD according to NIH criteria. The most common organs involved in chronic GVHD were skin, mucosa, eyes, gastrointestinal tract (GIT) and liver (Fig. 1). Incidence of acute GVHD in the PTCy group was 35%; grade II-IV acute GVHD, 15%; chronic GVHD, 29%. Moderate and severe chronic GVHD was registered in 18% of the cases. Similar incidence rates (resp., 53%, 35%, 35% and 30%) were noted for conventional prophylaxis.

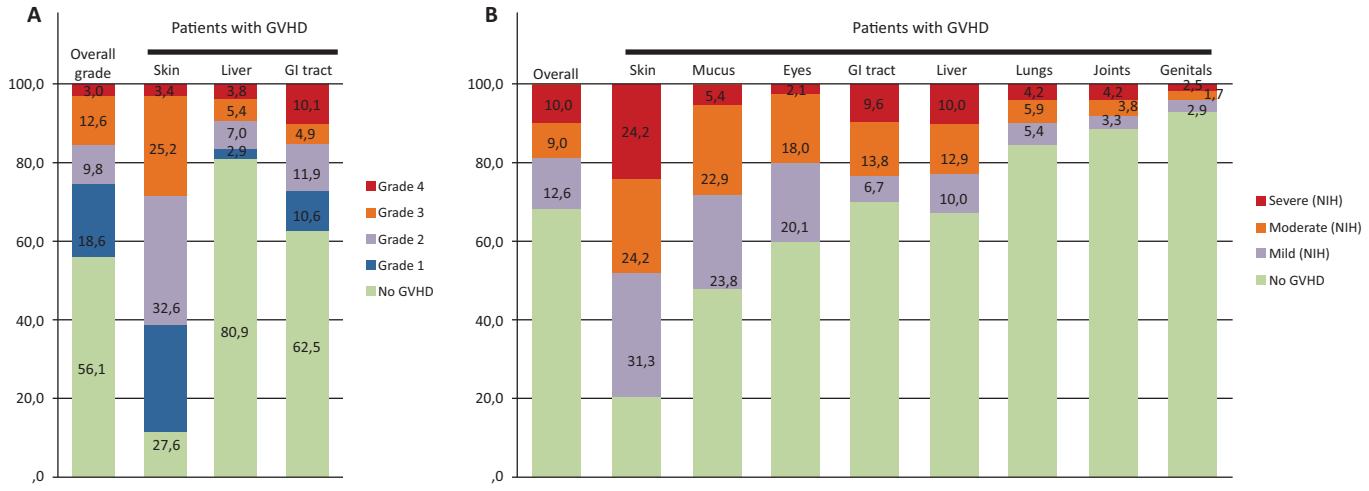

Figure 1. The incidence and severity of acute (A) and chronic GVHD (B). The incidence of organ involvement is calculated only for the patients who developed GVHD

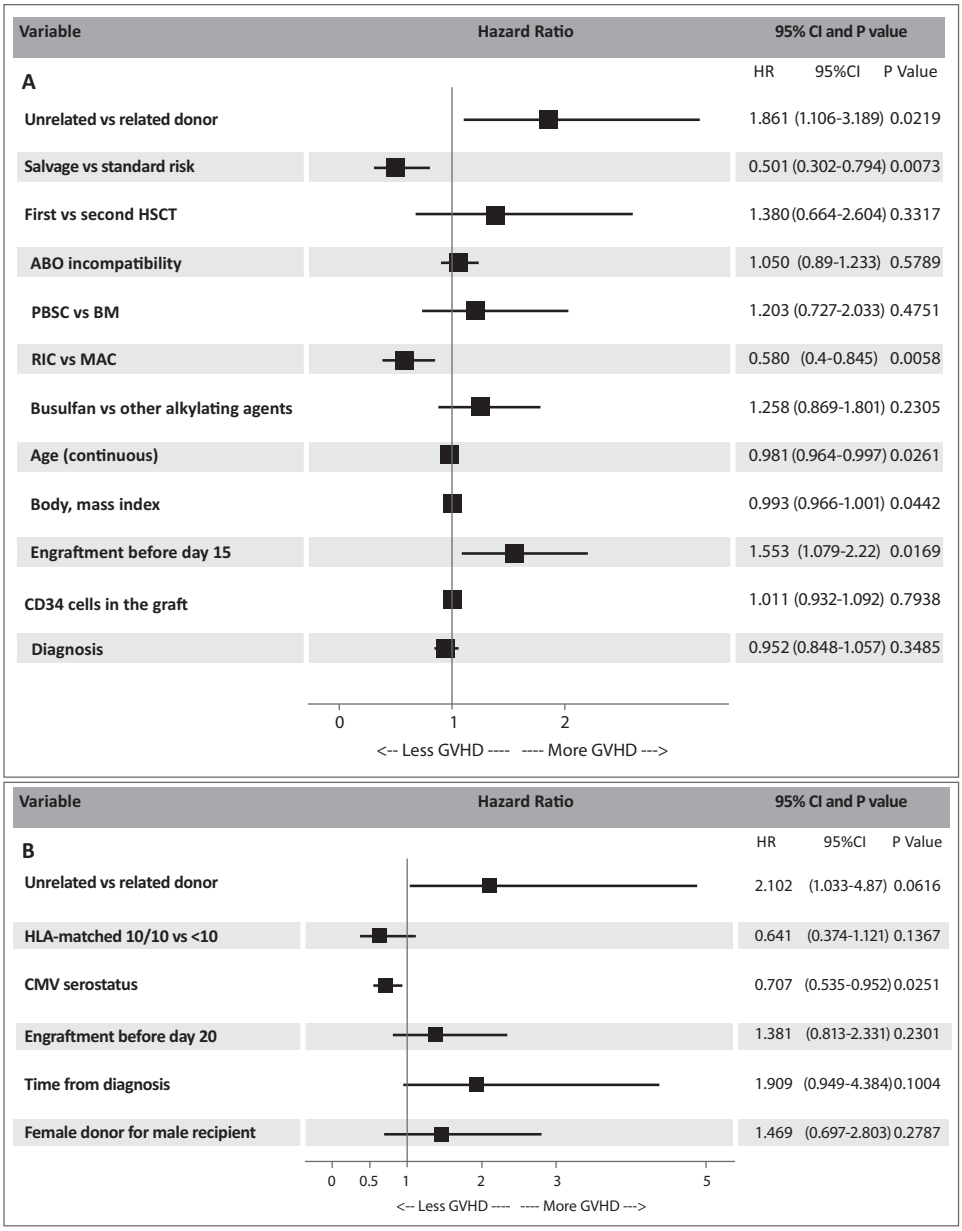

Figure 2. Risk factors of acute GVHD grade II-IV after conventional prophylaxis (A) and posttransplant cyclophosphamide (B). Number of CD34+ cells in the graft, age and BMI are continuous variables, all the others are logistic

For the conventional prophylaxis group, the following factors were revealed in the univariate analysis with significance >0.15 for acute GVHD grade II-IV development: unrelated donor (p<0.0001), salvage group (p=0.0014), number of HSCT (p=0.1064), ABO incompatibility (p=0.0709), cytomegalovirus (CMV) serostatus (p=0.1487), graft source (p=0.0004 conditioning intensity (p=0.0003), alkylating agents in the conditioning (0.1377), age of the recipient (0.0002), CD34 cell number in the graft (p<0.0001), engraftment time (p<0.0001), diagnosis (p=0.0379), body mass index (BMI) (p=0.0220). These parameters were included into the multivariate model where only unrelated donor (HR 1.86, 95%CI 1.11-3.19, p=0.0219), salvage disease status at transplant (HR 0.50, 95%CI 0.30-0.79), use of RIC (HR 0.58, 95%CI 0.40-0.85), older age (HR 0.0442, 95%CI 0.96-0.99), higher BMI (HR 0.97, 95%CI 0.97-1.00) and engraftment before day +15 (HR 1.55, 95%CI 1.08-2.22) significantly affected the incidence of acute GVHD grade II-IV (Figure 2A). The BMI cut-off value was 28 kg/m^2 indicating that obese patients had less acute GVHD. Despite common risk factor of graft source, the fast engraftment was more significant than the graft source factor (p=0.48), despite the fact that fast engraftment occurred more often in the PBSC recipients (32% *vs* 17%, p<0.0001).

In the univariate analysis of PTCy group, only unrelated donor (p=0.0170), HLA matching (p=0.0347), number of HSCT (p=0.0592), recipient gender (p=0.0592), CMV serostatus (p=0.0592), female donor for male recipient (p=0.0706), time of engraftment (p=0.0037), and time from diagnosis to transplant were shown to be significant factors (p<0.0001). Since the recipient gender was significant because of female-male combination, only that factor was included in the multivariate analysis. Also in ROC analysis, the cut-off for engraftment time was different: 20 days instead of 15. These parameters were added to the multivariate model where CMV serostatus was the only significant factor (HR 0.71, 95%CI 0.54-0.95, p=0.0251). The highest incidence was in the -/- pair of donor / recipient (32%), lower in the +/- pair (20%) and the lowest in the CMV-positive recipients (13% with +/+ pair *vs* 15% with -/+ pair).

The univariate analysis in conventional prophylaxis group revealed unrelated donor (p=0.0002), salvage group (p=0.0635), cytomegalovirus serostatus (p=0.0248), graft source (p<0.0001), age (p=0.1360), number of CD34 cells in the graft (p=0.0047), engraftment at <15 days (p=0.0013), time from diagnosis to transplantation (p=0.1151), diagnosis (p=0.0205) and previous acute GVHD (p<.0001) as significant factors for moderate and severe chronic GVHD. In the PTCy group, the univariate analysis revealed unrelated donor (p=0.0980), donor gender (p=0.0138), graft source (p=0.0805), male recipient with female donor (p=0.1082), number of CD34+ cells in the graft (p=0.0272), time to engraftment (p=0.0302) and previous acute GVHD (p=0.0929), as predisposing factors for chronic GVHD. In the multivariate model with conventional GVHD prophylaxis, only PBSC graft (HR 2.26, 95%CI 1.28-4.11) and previous acute GVHD (HR 3.76, 95%CI 2.32-6.37) were significant risk factors for moderate and severe chronic GVHD (Figure 3A).

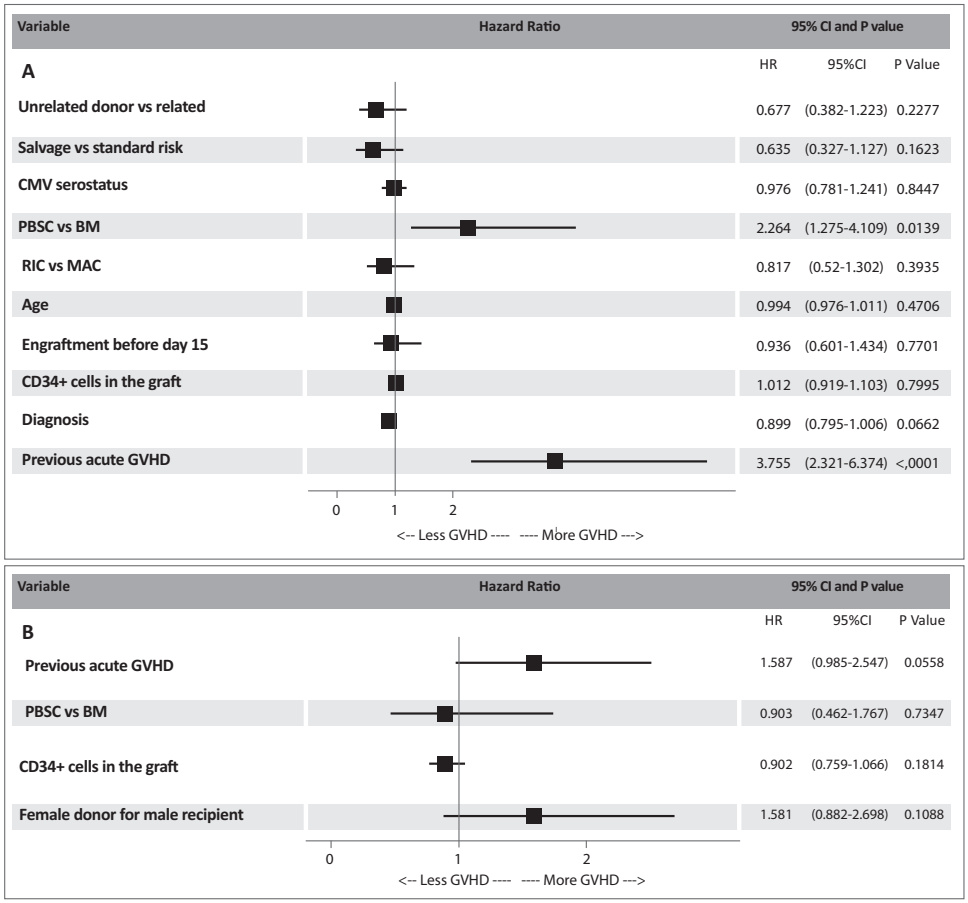

Figure 3. Risk factors for moderate and severe chronic GVHD with conventional prophylaxis (A) and posttransplantation cyclophosphamide (B)

Modeling in the PTCy group demonstrated only a weak statistical significance for previous acute GVHD (HR 1.59, 95%CI 0.99-2.54), while all the other factors were non-significant (Figure 3B).

Regarding mild acute GVHD (grade I-II) which is usually favorable for prognosis in the conventional prophylaxis group, only the CD34 cell dose increased the probability of this condition (HR 1.08, 95%CI 1.01-1.150, p=0.0133). The other variables were not significantly different. With PTCy prophylaxis, the unrelated donorship was associated with increased probability of grade I-II acute GVHD (HR 3.26, 95%CI 1.26-8.39, p=0.0145). Also a combination of a female donor/ male recipient had week statistical significance (HR 1.87, 0.94-3.72, p=0.0761). No predictors were determined for mild chronic GVHD in conventional prophylaxis patients, whereas, with PTCy, the CMV-positive recipient serostatus was protective against this condition (HR 0.675, 0.496-0.918, p=0.0123). Mild chronic GVHD was lowest in +/+ CMV positive donor/ recipient (6%), being highest in -/+ (15%) and +/- (19%) combinations. In the both CMV-negative pairs, mild chronic GVHD rate was also substantial (14%).

Discussion

In this relatively large study, we have confirmed that the novel prophylaxis regimens may dramatically change the landscape of risk factors which was not demonstrated before. Previous registry studies mostly documented only evolutional changes in the risk factors due to other aspects of HSCT. In the era of only BM transplantation from matched siblings with cyclosporine and methotrexate as prophylaxis, the predominant risk factors were female donor for male recipient, pregnancy history and older recipient age [13]. The subsequent CIBMTR study identified the risk factors of PBSC use, ethnicity, TBI *versus* busulfan-based conditioning, and positive CMV serostatus [7]. After broad introduction of unrelated transplants, it became obvious that GVHD incidence is higher than after sibling transplants [14]. Additional risks of GVHD are associated with partial HLA mismatches [15] and non-HLA allele mismatches [16]. Furthermore, the donor age was also identified as risk factor in unrelated HSCT [17]. Nonetheless the recent mathematical analysis indicates that the predictive potential of clinical parameters is relatively low [18]. Thus, the risk factors of GVHD were slowly evolving, due to implementation of novel cell sources and donor types. We, however, confirm that the use of PTCy completely abolished the previously significant risk factors.

It has been previously published that HLA matching is not a significant factor with PTCy prophylaxis [19], and this was confirmed in the current study. Nonetheless, the difference between matched sibling and unrelated donor had a tendency to significance, which was also confirmed in our group of patients. What was not established earlier is the preventive role of CMV-positive serology in recipient, despite a weak statistical trend in the EBMT study [20]. The probable reason for that is different prevalence of CMV seropositivity in Russia, Europe and the USA. In Russia, the CMV seroprevalence is above 85% [21, 22, 23]. The CMV seropositivity is unlikely to represent the reason for differences, but, rather, it may be a consequence of changes in immune system that, probably, led to decreased GVHD incidence. It was demonstrated that CMV causes expansion of T-regulatory cells [24] and upregulation of IL-33 pathway, which protects against lethal GVHD in animal models [25, 26]. The significance of this factor with no such evidence for conventional prophylaxis [7] indicates the presence of different immunological mechanisms behind PTCy prophylaxis that still should be elucidated.

The risk factors identified for moderate and severe chronic GVHD with conventional prophylaxis were similar to the ones previously reported [27, 28]. The history of severe acute GVHD was the most predominant risk factor. However, no risk factors were identified for PTCy, probably due to low incidence of this complication and low incidence of preceding acute GVHD in the study cohort. Contrary to this data, the European Registry Study defined recipient age, use of PBSC and combination prophylaxis as the risk factors [20]. The differences might be due to different PTCy schedule (day +3, +5), use of cyclosporine instead of tacrolimus, duration of immunosuppression [29]. The absence of differences between PBSC and BM is explained by single-agent PTCy prophylaxis in the matched bone marrow group and combination with tacrolimus and MMF in the PBSC group, which alleviated the differences.

In conclusion, this study identified the changing pattern of GVHD risk factors with introduction of novel prophylaxis regimens in related and unrelated HSCT grafts. Further studies are required to elucidate the biological mechanisms behind these changes.

Conflicts of interest

No conflicts of interest are reported by the authors.

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Различия факторов риска острой и хронической реакции «трансплантат против хозяина» при классической профилактике и использовании посттрансплантационного циклофосфана при родственных и неродственных трансплантациях

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Резюме

Изменения технологии аллогенной трансплантации гемопоэтических стволовых клеток (алло-ТГСК), например, внедрение заготовки периферических стволовых клеток крови (СКПК) и трансплантация от неродственного донора привели к значимым изменениям факторов риска реакции «трансплантат против хозяина» (РТПХ). В настоящий момент ограничено число публикаций, оценивавших влияние новых режимов профилактики РТПХ на факторы риска этого осложнения. Было проведено исследование на двух когортах пациентов. В первую, с классической профилактикой РТПХ вошло 199/344 родственных и неродственных трансплантаций, соответственно, с профилактикой циклоспорином А (ЦСА) и ММФ±атитимоцитарный глобулин. Во вторую когорту пациентов вошли 104/365 родственных и неродственных трансплантаций, соответственно, с профилактикой посттрансплантационным циклофосфаном (ПТЦф) в качестве монотерапии или в комбинации с такролимусом и ММФ. При классической профилактике значимыми оказались трансплантация от неродственного донора (HR 1.86, 95%CI 1.11-3.19, p=0.0219), принадлежность к группе спасения (HR 0.50, 95%CI 0.30-0.79), использование режимов кондиционирования со сниженной токсичностью (HR 0.58, 95%CI 0.40-0.85), пожилой возраст (HR 0.0442, 95%CI 0.96-0.99), высокий ИМТ (HR 0.97, 95%CI 0.97-1.00) и раннее приживление (HR 1.55, 95%CI 1.08-2.22). Для ПТЦф единственным значимым фактором оказался цитомегаловирусный серостатус донора и реципиента (HR 0.71, 95%CI 0.54-0.95, p=0.0251). Для хронической РТПХ средней и тяжелой степени при классической профилактике выявлены следующие факторы риска: использование СКПК (HR 2.26, 95%CI 1.28-4.11) и наличие предшествовавшей острой РТПХ (HR 3.76, 95%CI 2.32-6.37). Для профилактики с ПТЦф ни одного значимого

фактора риска не выявлено. Слабую статистическую взаимосвязь демонстрировал анамнез острой РТПХ (HR 1.59, 95%CI 0.99-2.54). В заключении, исследование продемонстрировало значимые различия в факторах риска РТПХ между классической профилактикой и профилактикой на основе ПТЦф. Требуются дальнейшие исследования для изучения биологических основ этих различий.

Ключевые слова

Реакция «трансплантат против хозяина», факторы риска, посттрансплантационный циклофосфан.