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RESEARCH ARTICLE

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Medium-dose VP-16 Intensified Conditioning Regimen Is Safe in Allogeneic Hematopoietic Stem Cell Transplantation for Acute Lymphoblastic Leukemia

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ABSTRACT

Objective: To explore the effect of medium-dose VP-16 (30mg/kg) intensified TBI/Cy or mBu/Cy conditioning regimens in ALL for allo-HSCT.

Material and Methods: We analyzed the clinical data of 73 ALL patients who received allo-HSCT in Shandong Provincial Hospital during Oct. 2010 to Mar. 2021. The information about primary condition, donor types, OS (overall survival), LFS (leukemia-free survival), GRFS (graft-versus-host disease and/or relapse free survival), RR (relapse rate) and NRM (non-relapse mortality) was collected.

Results: The VP-16 group showed similar 5-year-LFS (59.6% vs. 63.2%, P=0.934), 5-year-OS (65.7% vs. 59.5%, *P*=0.446) and 5-year-GRFS (44.9% vs. 50.2%, *P*=0.925) as the control group. Although the precondition intensity was increased in the VP-16 group, NRM showed a lower trend than that of the control group (0% vs. 13.2%, *P*=0.055).

Conclusion: We concluded that conditioning regimen with medium-dose VP-16 induced similar OS, LFS, GRFS, RR and relatively lower NRM than the control.

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KEYWORDS: Medium-dose VP-16; Conditioning regimen; Allogeneic hematopoietic stem cell transplantation; Acute lymphoblastic leukemia

Introduction

Acute lymphoblastic leukemia (ALL) is a common malignant hematological disease, which originates from hematopoietic stem cells or progenitor cells. As the high recurrence rate and low cure rate of chemotherapy, allogeneic hematopoietic stem cell transplantation (allo-HSCT) is widely applicated and considered to be an important choice for the treatment of ALL [1, 2]. The anti-leukemic effect of allo-HSCT is associated with both the graft versus leukemia (GvL) effect and the direct killing effect of conditioning regimens [3]. GvL effect plays a significant role in allo-HSCT of AML, CML, MDS and so on. But GvL effect is confined in ALL -HSCT, so the conditioning regimen may be of special importance for ALL patients [4].

The busulfan/cyclophosphamide (Bu/Cy) and total body irradiation/cyclophosphamide (TBI/Cy) were the most popular used myeloablative conditioning regimens for ALL-HSCT in China. The estimated 3- years overall survival (OS) were 56.4% and 31.6% for Bu/Cy and TBI/Cy regimen respectively in hematologic malignancy [5]. And no significant differences were observed between the Bu/Cy and TBI/Cy as conditioning regimen for HSCT in hematopoietic reconstitution, disease free survival (DFS), and transplant-related mortality (TRM) [5]. However, recurrence after transplantation is the bottleneck which restrains therapeutic effect and prognosis. Intensified regimens such as Cy/VP/TBI, TBI/TT/Cy, Bu/Cy/MEL, etc., could reduce the probability of recurrence to some extent. At present, they are mainly researched in refractory and/or recurrent patients. Results showed that the 5-year-OS of the standard conditioning and intensified conditioning after HSCT was 23.8% and 64.0%, respectively, and the cumulative recurrence rates were 80.8% and 28.8%, respectively [6]. The results suggested that the intensified conditioning regimen is a favorable factor to improve the survival rate of ALL patients receiving HSCT. Therefore, we have added etoposide (VP-16) to the conditioning regimens of ALL patients who are planning to undergo allo-HSCT to explore better curative effects.

VP-16, a potent inhibitor of DNA topoisomerase, exerts its anti-tumor effect by blocking DNA repair. And it is one of the most effective anticancer drugs for the treatment of malignant tumors, including hematological diseases [7]. VP-16 has been used as an alternative to adding to the conditioning regimen. However, the incidence of non-relapse mortality (NRM) was reported to increase when VP-16 applicated in high dosage (50–60 mg/kg) [8]. It has been reported that ALL patients underwent allo-HSCT preconditioned with TBI/Cy plus medium-dose (30~40 mg/kg) VP-16 had good results, But there is no research on Bu/Cy plus VP-16 yet. In our study, we not only added VP-16 to TBI/Cy but also mostly Bu/Cy to explore the effect of medium-dose (30mg/kg) VP-16 containing regimens for HSCT in ALL [9, 10].

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Patients and methods

Patients

73 ALL patients who received their first allo-HSCT between Oct 2010 to Mar 2021 in the Hematology Department of Shandong Provincial Hospital were enrolled in this retrospective study. At our clinical center, HSCT is recommended for all ALL patients with suitable donors and no contraindications to transplantation, regardless of the level of MRD. Stem cells are derived from peripheral blood or a combination of peripheral blood and bone marrow. Information about the basic characteristics, disease status before transplantation, donor types, conditioning regimens, side effects, complications and survival time were collected and analyzed. The study was approved by the ethics committee of Shandong Provincial Hospital.

Conditioning Regimens

Modified BU/CY (mBu/Cy) was composed of Ara-C (cytarabine) at 2 g/m^2 (2 g/m^2 for one day), Bu at 9.6 mg/kg (3.2mg/kg for 3 days) and Cy (cyclophosphamide) at 3.6 g/m^2 (1.8 g/m^2 for 2 days) [11,12]. Cy/TBI consisted of Cy at 120 mg/kg (60 mg/kg for 2 days) combined with fractionated TBI of 9 Gy (3 Gy×3 fractions). VP-16+Bu/Cy consisted of Bu at 9.6 mg/kg (3.2mg/kg for 3 days), Cy at 120 mg/kg (60 mg/kg for 2 days) and VP-16 at 30mg/kg (15mg/kg for 2 days). VP-16+TBI/Cy was combined Cy/TBI with VP-16 at 30mg/kg (15mg/kg for 2 days) [9]. Prevention of graft-versus-host disease (GVHD) was same for all patients including cyclosporin A (CsA), methotrexate (MTX) and mycophenolate mofetil (MMF), The specific dosage of each drug is as follows (Figure 1): The initial dose of CsA is intravenous infusion of 1.5mg/kg, once every 12 hours, starting from the beginning of the precondition, and changed to oral administration after the disappearance of gastrointestinal symptoms [13]. The amount of CsA decreased gradually at +100d and stopped at 6-9 months after transplantation. Methotrexate was administered by intravenous infusion at 15 mg/m^2 on +1d and 10 mg/m^2 on + 3d+ 6d and + 11d, followed by Calcium Folinate 24 hours after each MTX dose counteracts its toxic response. MMF was administered orally at 1.0 g/d, started at the same time as CsA, halved after implantation, and discontinued 2 to 3 months after transplantation. Anti-thymocyte globulin (AT) (7.5-10mg/kg) was added in haplo- or unrelated-transplantation for GVHD prevention [14]. Cases conditioning with medium-dose VP-16 were defined as the VP-16 group, and the others as the control group.

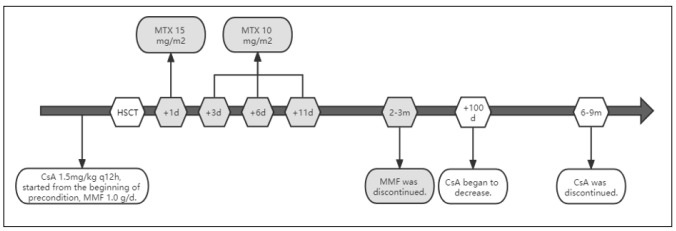

Figure: The application of GVHD-preventive drugs in HSCT

Table: The diagram of the conditioning regimens

Regimens	Drug	Dose(total)	Schedule(day	Donor Type
Modifed BuCy	Ara-C	2–4 g/m^2	−9	MSD-HSCT
	Bu	9.6 mg/kg(iv)	−8 to −6	
	Cy	3.6 g/m^2	−5, −4	
	MeCCNU	250 mg/m^2(po)	− 3	
Cy/TBI	Cy	120 mg/kg	−6, −5	Allo-HSCT
	TBI	9 Gy	−3 to −1	
Modifed BuCy +ATG	Ara-C	4g/m^2	−10, −9	URD,HID-HSCT
	Bu	9.6 mg/kg(iv)	−8 to −6	
	Cy	3.6 g/m^2	−5, −4	
	MeCCNU	250 mg/m^2(po)	− 3	
	ATG	7.5-10 mg	−5 to −2	
VP-16+TBI/Cy	TBI	9 Gy	−8 to −6	Allo-HSCT
	VP-16	30mg/kg	−5, −4	
	Cy	120 mg/kg	−3, −2	
VP-16+Bu/Cy	VP-16	30mg/kg	−8, −7	Allo-HSCT
	Bu	9.6 mg/kg(iv)	−6 to −4	
	Cy	120 mg/kg	−3, −2	

Ara-C, cytarabine; allo-HSCT, allogeneic stem cell transplantation; ATG, antithymocyte globulin; Bu, busulfan; Cy, cyclophosphamide; IV, intravenous; HID, Haploidentical donor; MSD, matched sibling donor; MeCCNU, Semustine; PO, Oral; TBI, Total body irradiation; URD, unrelated donor

Definitions

Neutrophil engraftment time is defined as the first day of absolute neutrophil count > 0.5×10^9/L for at least 3 days, and platelet engraftment time is defined as the first day of an untransfused platelet count >20×10^9/L for more than 7 days [15]. Acute GVHD (aGVHD) is graded according to Thomas [16] and Glucksberg criteria, and chronic GVHD (cGVHD) is defined as limited or extensive according to the criteria of National Institutes of Health (NIH) [15,16]. Regimen-related toxicity (RRT) is assessed according to Bearman's criteria [17]. LFS refers to the period from transplantation to relapse or death from any cause. OS is measured from the time of transplantation until death [15]. GRFS is defined as time from transplantation to events including grade III~IV aGVHD, systemic therapy-requiring cGVHD, relapse or death [18]. NRM is defined as death during a sustained remission.

Statistical Analysis

Mann-Whitney U test is used for numerical variables, and Chi2 or Fisher's test is used for categorical variables. Kaplan-Meier survival analysis and log-rank test were used to compare the time-dependent rates. Multivariate analyzes was analyzed by the Cox proportional hazard model (when the P value in the univariate analysis was less than 0.2, it entered to multivariate analyze). Using SPSS 25.0 for statistical analysis, P<0.05 is considered to have statistical differences.

Results

Basic Characters of Patients

The basic characters of patients were summarized in Table 1. There were 35 cases in the VP-16 group and 38 cases in control group. There are not significant different between the two groups among the factors as gender, age, immunotype of the disease and Ph chromosome status. Majority of patients (68/73, 94.5%) underwent allo-HSCT at CR status. The proportion of recurrent/refractory (R/R) patients did not differ significantly between the two groups (18.4% vs. 20%, P=0.864). 9 patients (25.7%) in the VP-16 group and 11 patients (28.9%) in control group underwent HSCT from the human leukocyte antigen (HLA)-allele matched related donors, 2 patients (all in the VP-16 group) received transplantation from matched unrelated donor, others received related haploidentical transplantation (HID).The donor types, median mononuclear cell (MNC) and CD34+ cell numbers were all without significant difference between the two groups.

Engraftment, GVHD and RRT

All patients achieved neutrophil engraftment and the median engraftment time was both 12 days in the two groups. 32 patients (91.4%) achieved platelet engraftment in the VP-16 group, while 36 cases (94.7%) achieved engraftment in control group. The median platelet engraftment time was also the same in both groups, at 13 days. (Table 2)

The median onset time of aGVHD in the VP-16 group was earlier than that in the control group (15d vs 30d, P=0.013), but there was no significant difference in the incidence of all grades of aGVHD (57.1% vs 44.7%, P=0. 352) and severe (grade III~IV) aGVHD (11.4% vs 13.2%, P=0.703) between the two groups. 6 patients in both groups developed cGVHD, and the median time of onset in the VP-16 group was significantly longer than the control group (180d vs 359d, P=0.028) (Table 3).

The most common RRT of these patients is hemorrhagic cystitis (35/73, 47.95%), which has a lower incidence in the VP-16 group (37.2% vs. 57.9%, P=0.076). The second is mucosal toxicity (32/73, 43.84%), especially oral mucosal toxicity, which was more common in the VP-16 group but without significant difference (51.4% vs. 36.8%, P=0.210). Occurrence of Gastrointestinal toxicity was 28.6% and 39.5% in the two group (P=0.529). Other organ toxicities like arrhythmia, hepatic function lesion and so on were rarely happened and both occurred without significant differences between the two groups (Table 4).

Survival, RR and NRM

Up to the last follow-up in Mar. 2021, 22 cases died (17 due to relapse and 5 due to NRM) and 51 cases are still alive. The estimated-5 years OS in the VP-16 group were slightly higher than the control group but without significant difference, and there was no significant difference in 5-year LFS and GRFS between the two groups. (65.7% vs. 59.5%, *P*=0.446; 59.6% vs. 63.2%, *P*=0. 934; 44.9% vs. 50.2%, *P*=0. 925). (Figure 1). 10 patients (28.6%) relapsed after transplantation in the VP-16 group, the median relapse time was 17 months, while 12 (31.6%) patients relapsed with median time of 20 months in the control group (P=0.780). There were no NRM cases in the VP-16 group and 5 patients died of NRM in the control group with a median time of 5 months (range: 3~19months) (*P*=0.055) (Table 5).

Univariate and Multivariate Analysis

In the univariate and multivariate analysis, we analyzed the effect of VP-16 on the prognosis of ALL. Besides conditioning regimens (Bu/Cy or TBI/Cy), other characters as age (≤ 35 or>35), gender, immune subtype (T-ALL or B-ALL), Ph chromosome, disease risk stratification (high risk or standard risk), disease status at HSCT (CR1, CR2 or NR), minimum residual disease (MRD), the compatibility of HLA and blood type of donor and recipient (matched or mismatched) were also listed as variables in the univariate and multivariate analysis [19]. The results indicated that whether conditioning regimen contained VP-16 have no significant impact on the survival, RR and NRM (OS: *P*=0.446, LFS: *P*=0.934, GRFS: *P*=0.925, RR: P=0.783, NRM: *P*=0.200). Among other risk factors, MRD was an independent risk factor for OS, LFS, GRFS and RR (*P*=0.006, OR: 0.297; *P*=0.004, OR: 0.280; *P*=0.001, OR: 0.275; *P*=0.007, OR: 5.192). Female donors are associated with a higher incidence of cGVHD (*P*=0.033,

OR=4.182), and the presence of MRD is an independent risk factor for severe aGVHD (P=0.016, OR=10.608) (Table 6).

Discussion

ALL is one of the most common leukemia both in adults and pediatric. Despite a high rate of response to combination chemotherapy, many patients experienced recurrence and the 5-year OS of adult patients are only 30~40% [20, 21]. Moreover, R/R patients usually have a poor prognosis. Thus allo-HSCT, which could decrease recurrence rate and increase survival duration, has become an effective therapeutic option for ALL patients. The reported 3- to 5-year OS is between 40% to 60% for HSCT in ALL. The study published by Center for International Blood and Marrow Transplant Research (CIBMTR) reported PFS and OS of 41% and 53% respectively [22]. But relapse is still the leading cause of death [23]. Researches have shown that among the deaths beyond 100d after unrelated and identical sibling transplantation, recurrence accounted for 46% and 57%, respectively [24]. In China, the cumulative incidence (CI) of 10-year RRT in patients has undergone haploidentical and HLA-identical sibling transplantation was 15.6% and 16.7%, respectively [24]. This highlights the need to reduce relapse in patients undergoing HSCT. The rapid development of HID HSCT has made it possible for almost every patient to have a donor, especially in China, where there is a shortage of MSD due to the family planning policy. Nine years ago, the number of HID HSCT in China exceeded that of MSD HSCT. By 2019, HID HSCT had accounted for more than 60% of allo-HSCT. And in hematological malignancies, the haploid "Beijing protocol" could provide similar outcomes to MSD HSCT [25-27].

Conditioning regimen is the initial and important part of allo-HSCT in ALL. It is closely related to the RR and transplantation complication [29]. HSCT precondition can be divided into three groups as myeloablative conditioning (MAC), reduced-intensity conditioning (RIC) and intensified conditioning (IC) according to intensity of the regimens. MAC as TBI/Cy and Bu/Cy are suit for most of the patients and are popularly applied in the world. The modified BU/CY regimen was shown to have a lower recurrence rate and a lower incidence and severity of GVHD [28]. Compared with MAC, RIC are often used in old patients or patients with organ dysfunctions to reduce side effects and treatment related mortality. IC is generally based on MAC, and drugs such as Ara-C, VP-16, Melphalan, Fludarabine, or Tespamin are added to kill as many leukemia cells as possible. IC is often used in R/R diseases to reduce relapses and improve outcomes [14]. The CI of recurrence in the IC group was significantly lower than that in the standard conditioning group (P = 0.0013) [30]. But IC is often associated with significant organotoxicity and increased treatment-related mortality, which limits its wide application. So, which disease, which patients and under what conditions are suitable for IC is still under study.

VP-16 is a highly effective drug in the treatment of hematological tumors [5]. It can not only directly kill leukemia cells but also exert synergistic cytocidal effects with Cy [31]. Moreover, VP-16 could act on generation cycle and up-regulate cytokines such as interleukin-8, which may play an essential role during engraftment after HSCT [32]. These pharmacokinetic features of VP-16 provide therapeutic advantages to reduce relapse and improve prognosis. Thus VP-16 has been used in conditioning regimens for hematological malignancies [6].

A retrospective study by the Acute Leukemia Working Party indicated that high dose VP-16 (60 mg/kg) /TBI appeared to be more effective than Cy/TBI for relapse adult ALL (RR: 17% vs. 30%; LFS: 60% vs. 50%) [3]. Nevertheless, it also has a higher risk of NRM (24~47%), especially in older patients [33, 34]. Compared with the significant toxicity of high dose VP-16, the safety and efficacies of medium-dose (30 mg/ kg) VP-16 plus TBI/Cy conditioning regimens, were validated for adult ALL patients [9, 35, 36].

It has been proved that medium-dose VP-16/TBI/Cy significantly reduced relapse rate compared with TBI/Cy with a corresponding improvement in LFS (RR, 0.75; 95%CI, 0.56-1.00; P = 0.05) [36]. Meanwhile, the addition of medium-dose VP-16 did not increase the incidence of post-transplant complications or NRM [36]. The Bu/Cy regimen was also widely used and achieved remarkable results both in HLA-matched sibling donor (MSD)-HSCT and HID-HSCT [14]. Studies showed that Bu/Cy regimen played a reliable role in ALL-HSCT [37]. When added with VP-16 (60mg/kg), the Bu/Cy regimen could achieve long-term survival in patients with high-risk or advanced myeloid malignancies [38]. But the effect of Bu/Cy combined with medium-dose VP-16 as precondition in ALL was still uncertain. In our study, we not only added VP-16 to Cy/TBI (n=5) but also mostly Bu/Cy (n=30) to research the effect of medium-dose VP-16-containing regimens for ALL HSCT.

Recurrence is the main cause of treatment failure after allo-HSCT, especially for NR patients. Relapse rates have been demonstrated ranging from 28–69% after HSCT depending on the different precondition regimens and patients' baseline conditions [4]. And relapse was significantly associated with poor prognosis. The intensity of precondition is acritical factor for stable remission in recurrent patients undergoing allo-HSCT. In our cohort, most (14/21) of relapse happened within the first year after transplantation, and then entered a stable plateau without recurrence. Incidence of relapse within the first year after allo-HSCT was the critical factor to influence the long-term survival. Thus, strict and active follow-up and reexamination in the first year after HSCT were needed.

RRT is another issue to be considered. VP-16 is mainly metabolized by kidney and excreted by urine. Its adverse reactions include bone marrow suppression, digestive tract reactions (anorexia, nausea and vomiting, stomatitis, abdominalgia and diarrhea), skin toxicity and neurotoxicity. It has been showed that high-dose VP-16-containing regimens resulted in high incidence of RRT (especially mucosal and gastrointestinal toxicity) and NRM [33]. Hence, medium dose VP-16 was used for treatment with the attempt to minimize the side effects while obtain the antileukemia effect. In our study, there was no NRM in VP-16 group while incidence of NRM was higher in the control group (0% vs 13.5%, P=0.055). The superior incidence of NRM might rely to the limited number of our cohort. But in another large number study, NRM in

the VP-16/TBI/CY group is also significantly lower than TBI/CY group [34]. All these data illustrated medium-dose-VP-16 did not increase NRM although with higher RRT. Our data also indicated that complications in the VP-16-containing regimens could be well tolerated. Medium-dose VP-16 did not induce fatal complications and could be safely applied in conditioning regimens.

In terms of GVHD, our results showed that incidence of aGVHD in VP-16 group had no significant statistical difference with the control group. This indicated that medium-dose VP-16 did not increase the mortality caused by GVHD and was safe enough for application. MRD was significantly related with OS, LFS, GRFS and RR in ALL transplantation [39]. MRD status at HSCT was identified as a critical prognostic factor for survival. Lower pretransplant-MRD was related to good prognosis with higher OS, LFS and lower RR [40]. This suggests that negative pretransplant-MRD is of vital importance in ALL. On account of limit of cases and biases of retrospective research, Medium-dose VP-16 intensified conditioning had no significant effect on any of the end-points in this study. But even VP-16 group contained more positive-MRD and R/R patients; they achieved similar RR and OS as the control group. The results might suggest that medium-dose VP-16-intensified regimens are especially effective for positive-MRD and R/R patients.

Conclusion

In conclusion, we studied the effects of medium-dose VP-16 combined with BU/Cy and TBI/Cy as conditioning regimens for allo-HSCT in ALL patients. We found that the intensified conditioning regimens with medium-dose (30mg/kg) VP-16 did not increase NRM, GVHD, and other adverse effects. However, the conditioning regimen containing VP-16 did not improve the OS, LFS or GRFS of patients, which may be due to the characteristics of retrospective studies and the limited cases number of our study. Large-scale retrospective or prospective studies of this regimen are needed to verify its effectiveness.

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