Risk-stratified outcomes of nonmyeloablative HLA-haploidentical BMT with high-dose posttransplantation cyclophosphamide


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Key Points

- Nonmyeloablative, related HLA-haploidentical BMT utilizing high-dose posttransplantation cyclophosphamide has a favorable safety profile.
- Risk-stratified relapse and survival outcomes with this approach are comparable to those of HLA-matched BMT.

Introduction

Allogeneic blood or marrow transplantation (BMT) is the only potentially curative treatment of many patients with advanced or poor-risk hematologic malignancies. However, the inability to identify or quickly secure an HLA-matched donor has been a major obstacle. Recent advances in alternative-donor transplantation have expanded allogeneic BMT options to patients who lack HLA-matched donors. Related, partially HLA-mismatched, or haploidentical (haplo) BMT is available to the vast majority of patients and avoids the potential delays associated with matched unrelated donor (MUD) searches. Unfortunately, haplo BMT has historically been associated with excessive graft failure, graft-versus-host disease (GVHD), and nonrelapse mortality (NRM). Methods to reduce GVHD and graft failure have centered on T-cell modulation through ex vivo depletion or increased immunosuppression but are associated with increased risks of infection and relapse. Our group pioneered the use of haplo BMT with high-dose posttransplantation cyclophosphamide (PTCy); when given in a narrow window, PTCy preferentially targets alloreactive proliferating T cells while relatively sparing nonproliferating and regulatory T cells. Our standard related haplo platform has also exclusively used nonmyeloablative (NMA) conditioning because of concerns that myeloablative conditioning might increase the incidence of GVHD. PTCy-based platforms particularly appear to protect against severe (grade III-IV) acute and chronic GVHD, mitigating GVHD and graft failure even after T-cell–replete haplo allografting.

Although numerous groups have now confirmed the acceptable toxicity profile associated with PTCy, haplo BMT remains investigational at many centers. This is because of the historically poor outcomes associated with HLA-mismatched BMT and thus the assumption that HLA matching is critically important. Moreover, concerns have been raised about potentially high relapse rates with PTCy, especially in light of its associated low rates of GVHD. Accordingly, large patient cohorts are still needed to better understand its role, especially with regard to other graft sources. The
heterogeneity of patients included in allogeneic transplant studies makes interpretation of outcomes problematic. Using only diagnosis and pretransplantation remission status, the leading predictors of progression-free survival (PFS) after BMT, the Disease Risk Index (DRI) stratifies allogeneic transplant recipients into low-risk, intermediate-risk, high-risk, and very high-risk disease groups. The DRI has been found to independently risk stratify heterogeneous adult patient cohorts regardless of conditioning intensity and graft source. In 2014, a refined and further validated DRI was published. Reporting outcomes by risk-stratified groups calibrates outcomes to facilitate interpretation of results across studies. However, few recipients of haplo BMT were included in the DRI study cohorts. Furthermore, large outcome studies of haplo BMT based on validated risk-stratification schemes have not yet been described. Here, we report the largest cohort of NMA haplo BMT with PTCy to date and analyze risk-stratified outcomes according to the refined DRI.

**Patients and methods**

**Eligibility and treatment**

This institutional review board–approved study retrospectively evaluated 372 consecutive hematologic malignancies patients aged ≥18 years who received NMA haplo BMT with high-dose PTCy at Johns Hopkins between 2002 and 2012. Patients were treated in institutional review board–approved prospective clinical trials of this transplantation platform (86%), in most cases phase 2 trials, or similarly off study. Reasons for off-study treatment included insurance restrictions, completed protocol accrual, and rarely protocol ineligibility. Two-hundred fifteen patients (58%) were included in previous manuscripts. Eligibility for NMA BMT included, per institutional guidelines, age ≤75 years, Eastern Cooperative Oncology Group performance status ≤2, left ventricular ejection fraction ≥35%, forced expiratory volume in the first second and functional vital capacity ≥40% of predicted (≥60% of predicted after thoracic or mantle radiation), not on dialysis, and absence of uncontrolled infection. Complete remission (CR) was standardly required for acute leukemias and partial remission (PR) or better for aggressive lymphomas. Donors were first-degree relatives or half siblings who were HLA-haploidentical based on molecular typing at HLA-A, -B, -Cw, -DRB1, and -DQB1. The study excluded recipients of phenotypically HLA-matched transplants, second allogeneic transplants, or regimens other than the following. All patients received fludarabine (30 mg/m² IV, days −6 to −2, renally adjusted), Cy (14.5 mg/kg IV, days −6 and −5), total body irradiation (200 cGy, day −1), and T-cell–replete bone marrow grafting (day 0) as previously described. GVHD prophylaxis consisted of high-dose PTCy (50 mg/kg IV, days +3 and +4) with mesna, mycophenolate mofetil (days +5-35), and tacrolimus (initiated day 5). In the absence of GVHD or graft failure, tacrolimus was stopped without taper at day 90 (n = 45) or day 180 (n = 327). Filgrastim was administered from day 5 until neutrophil recovery to ≥1000/µL. Recipients of posttransplantation consolidation or maintenance therapy (eg, imatinib or rituximab) were included in this study. Supportive care was delivered according to good medical practice.

**DRI scoring**

The DRI risk group is a composite of disease risk (diagnosis) and stage risk (pretransplantation disease status). The refined DRI was scored as published and analyzed by collapsing the initial 4-group index into a 3-group index (low-, intermediate-, and high/very high-risk disease) as validated. For example, Hodgkin lymphoma in PR was classified as intermediate risk and aggressive non-Hodgkin lymphoma (NHL) in refractory relapse as very high risk (supplemental Table 1, available on the Blood Web site). Pretransplantation remission status was based on standard response criteria, for acute leukemia, CR was defined as morphologic CR (<5% blasts in the marrow by CD34+ immunohistochemistry and flow cytometry). Disease risk in acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS) incorporated the cytogenetic risk criteria used in the refined DRI paper. For cytogenetic risk in de novo AML, t(8;21), inv(16), or t(15;17) was considered favorable in the absence of a complex karyotype (≥4 abnormalities), complex karyotype was adverse, and all other cytogenetics were intermediate. In MDS, the refined DRI group was based on blast percentage at diagnosis, pretransplantation remission status, and cytogenetic risk, wherein abnormal chromosome 7 or ≥4 abnormalities were considered adverse and normal cytogenetics or any other abnormalities were considered intermediate. For AML arising from MDS, this study used MDS cytogenetic risk criteria.

**Statistical methods**

The primary end point was to evaluate risk-stratified disease and survival outcomes based on the refined DRI. Differences in group characteristics were compared with Fisher exact or Kruskal-Wallis tests. Time-to-event end points were measured from the date of transplantation. PFS was defined as time to progression/relapse, unplanned treatment of disease persistence, or death from any cause. Disease-free survival was defined as time to disease persistence, relapse, or death. Failure-free patients were censored at the time of last evaluation. PFS, disease-free survival, and overall survival (OS) were estimated using the Kaplan-Meier method and compared with stratified log-rank tests or Cox proportional hazards models, with P values stratified by BMT year (2002-2008 vs later). Cumulative incidences (CIs) of relapse, NRM, count recovery, and GVHD were estimated and compared using competing-risk methods. All regression models of time-to-event end points were also stratified by BMT year. Multivariable models retained patient age regardless of P value and otherwise used backward stepwise selection with a retention P ≤ .15. All P values are 2 sided and unadjusted for multiple comparisons, with significance based on P ≤ .05. Statistical analysis was performed with R, version 3.0.2.

Relapse, progression, and unplanned treatment of disease persistence were considered competing risks for NRM and vice versa. Graft failure was defined as ≤5% donor chimerism in peripheral blood and/or bone marrow by day 60 without detected bone marrow disease. Acute GVHD was scored using the modified Keystone Criteria, and chronic GVHD was evaluated by National Institutes of Health Consensus Criteria.

**Results**

**Overall outcomes**

Baseline patient and transplant characteristics overall and by refined DRI group are shown in Table 1. The disease types and stages in each DRI group are shown in supplemental Table 1. The median age at BMT was 55 (range 18-75) years, and 131 patients (35%) were aged ≥60 years. Seventy-one patients (19%) had prior autologous BMT. The most common diagnoses were aggressive NHL and AML, followed by indolent B-cell neoplasms. By refined DRI grouping, 71 patients (19%) were categorized as low risk, 241 (65%) as intermediate risk, and 60 patients (16%) as either high risk (13%) or very high risk (3%). In the majority of patients (81%), the risk groups were concordant between the original and refined DRIs.

The median follow-up was 4.1 years overall by the reverse Kaplan-Meier method and 3.7 (range 0.5-11.4) years in surviving patients. On competing-risk analysis, the estimated CIs of neutrophil recovery was 90% (95% confidence interval [CI], 86%-93%) by day 30 (median 17 days). The probability of platelet recovery to 20 000/µL was 88% (95% CI, 84%-91%) by day 60 (median 25 days). Primary or secondary graft failure occurred in 8.2% (95% CI, 5.6%-11.5%) of evaluable patients and was in most cases accompanied by autologous hematopoietic recovery.

Table 2 summarizes risk-stratified survival, relapse, and NRM estimates with 95% CIs. For the entire cohort, the 3-year probabilities
of PFS, OS, and relapse were 40%, 50%, and 46%, respectively (Figure 1A-B). The estimated CUL of NRM was 8% at day 180 (Figure 1B). The estimated 180-day CULs of grade II-IV and grade III-IV acute GVHD were 32% (95% CI, 27%-36%) and 4% (95% CI, 2%-6%), respectively (Figure 1C). Grade II-IV acute GVHD was first diagnosed at a median of 42 (range 14-236) days posttransplantation, with 3 of the 121 cases occurring after day 180. The estimated 2-year CUL of chronic GVHD was 13% (95% CI, 10%-17%; Figure 1D).

Results by refined DRI

The refined DRI groups were well balanced for most patient and transplant characteristics (Table 1). There were no statistically significant differences in histology (lymphoid vs myeloid), hematopoietic cell transplantation–specific comorbidity index (HCT-CI) risk category, median graft doses, or patient cytomegalovirus serostatus. However, patient age was statistically significantly higher in poorer-risk DRI groups (Table 1).

Disease and survival outcomes with 95% CI, grouped by the refined DRI, are shown in Table 2. In low-, intermediate-, and high/very high-risk groups, the 3-year PFS estimates were 65%, 37%, and 22%, and 3-year OS estimates were 71%, 48%, and 35%, respectively (all \( P \) values \( \leq .0001 \); Figure 2A-B). The probability of relapse differed significantly between the DRI groups (\( P < .0001 \); Figure 2C), being greater in both the intermediate- and high/very high-risk groups compared with the low-risk group. There was no statistically significant association between DRI risk group and NRM.
suggesting that the PFS and OS differences were attributable primarily to differences in relapse risk. Within a DRI stratum, relapse rates were similar in the 2 groups that are large enough for such a comparison: intermediate-risk aggressive NHL ($n = 84$) and intermediate-risk AML ($n = 64$) (Figure 3). In these subsets of NHL and AML, the 3-year probabilities of relapse were 39% (95% CI, 28%-50%) and 45% (95% CI, 32%-57%), respectively, with corresponding 3-year PFS probabilities of 45% (95% CI, 35%-57%) and 41% (95% CI, 31%-56%).

Table 3 presents univariable analyses of selected validated prognostic indices for allogeneic BMT outcomes, namely the refined DRI, HCT-CI, and comorbidity-age index. In univariable analyses, the refined DRI group was statistically associated with relapse risk, PFS, and OS. In contrast, in this study, neither the HCT-CI risk category nor the comorbidity-age index ($<3$ vs $\geq3$) was statistically significantly associated with OS. Multivariable analyses adjusted for patient age and other baseline characteristics are shown in Table 3. The refined DRI group was found

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<table>
<thead>
<tr>
<th>Variable: refined DRI group</th>
<th>Probability (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRM (CuI)</td>
<td></td>
</tr>
<tr>
<td>Day 180</td>
<td>0.08 (0.05-0.11)</td>
</tr>
<tr>
<td>1 y</td>
<td>0.11 (0.08-0.14)</td>
</tr>
<tr>
<td>Relapse (CuI)</td>
<td></td>
</tr>
<tr>
<td>1 y</td>
<td>0.37 (0.32-0.42)</td>
</tr>
<tr>
<td>3 y</td>
<td>0.46 (0.41-0.51)</td>
</tr>
<tr>
<td>PFS</td>
<td></td>
</tr>
<tr>
<td>1 y</td>
<td>0.52 (0.47-0.57)</td>
</tr>
<tr>
<td>3 y</td>
<td>0.40 (0.35-0.45)</td>
</tr>
<tr>
<td>DFS</td>
<td></td>
</tr>
<tr>
<td>1 y</td>
<td>0.51 (0.46-0.57)</td>
</tr>
<tr>
<td>3 y</td>
<td>0.61 (0.57-0.66)</td>
</tr>
<tr>
<td>OS</td>
<td></td>
</tr>
<tr>
<td>1 y</td>
<td>0.68 (0.63-0.73)</td>
</tr>
<tr>
<td>3 y</td>
<td>0.50 (0.45-0.56)</td>
</tr>
</tbody>
</table>

DFS, disease-free survival.

*P for differences between refined DRI risk groups, with stratification by BMT year.

Figure 1. Overall outcomes of NMA haplo BMT with high-dose posttransplantation cyclophosphamide. (A) Progression-free and overall survival. (B-D) Cumulative incidences by competing-risk analysis of relapse and nonrelapse mortality (B), acute graft-versus-host disease (C), and any chronic graft-versus-host disease (D). Point estimates are provided in Table 2.
to be independently associated with relapse risk, PFS, and OS (each \( P < .001 \)). In multivariable models of relapse, as compared with the low-risk DRI group, the intermediate-risk group had a >3-fold increased relapse risk (hazard ratio [HR], 3.30; \( P < .0001 \)) and the high/very high-risk group had a >5-fold increased risk (HR, 5.27; \( P < .0001 \)). The refined DRI group was not statistically significantly associated with NRM on multivariable analysis. The differential relapse risk in DRI groups appeared to translate into marked differences in PFS and OS probabilities. In multivariable models of PFS, as compared with the low-risk DRI group, the HR was >2-fold greater in both the intermediate-risk group (HR, 2.34; \( P = .0001 \)) and high/very high-risk groups (HR, 3.06; \( P < .0001 \)). Similarly, in multivariable models of OS, HRs in both the intermediate-risk and high/very high-risk groups were >2-fold greater (HR, 2.11; \( P = .0009 \) for intermediate-risk DRI; HR, 2.79; \( P = .0001 \) for high/very high-risk DRI).

**Discussion**

Approximately 70% of patients in need of allogeneic BMT lack an HLA-matched related donor, and the unrelated donor registry match rates can be as low as 16% for certain ethnicities, such as African Americans and Hispanics.\(^2\) Furthermore, patients may relapse while awaiting the identification of a MUD. In contrast, haplo donors can be identified for the vast majority of patients, without the at times prohibitive waits associated with unrelated-donor transplants. However, historically haplo BMT has been associated with prohibitive toxicities.\(^2,5\) The development of high-dose PTCy has significantly reduced the rates of GVHD, graft failure, and NRM associated with haplo BMT. Nevertheless, haplo BMT remains investigational at many centers. In the largest cohort of NMA haplo BMT with PTCy to date,
we demonstrate the favorable safety profile of this transplantation platform. The incidences of severe acute and any chronic GVHD were very low, supporting the role of PTCy in GVHD prevention. Graft failure rates were acceptable and usually accompanied by autologous hematopoietic recovery. The 6-month probability of NRM was 8%, indicating the need for further refinement of prognostic tools. Similarly, in the refined DRI validation study, the majority (63%) of patients were categorized as intermediate risk, with 14% of patients being low risk, 20% high risk, and 4% very high risk.16 For disease-specific studies, more detailed risk-stratification tools are needed.

Risk-stratified disease and survival outcomes after NMA haplo BMT with PTCy also appear comparable to those of reduced-intensity conditioned, HLA-matched BMT.29-32 For example, emerging data suggest that tyrosine kinase inhibitors incorporated novel posttransplantation strategies to reduce relapse. The present data suggest that the index is helpful regardless of HLA-mismatching and the type of postgrafting immunosuppression. However, the refined DRI categorized 65% of patients in the present study as intermediate risk, indicating the need for further refinement of prognostic tools. Similarly, in the refined DRI validation study, the majority (63%) of patients were categorized as intermediate risk, with 14% of patients being low risk, 20% high risk, and 4% very high risk.16 For disease-specific studies, more detailed risk-stratification tools are needed.

With the greatly expanded ability to safely find donors, disease relapse becomes the major area for improvement, especially in high-risk and very high-risk patients. Evaluation of more intensive conditioning regimens is warranted, and the favorable toxicity profile associated with the PTCy platform also provides an ideal setting to incorporate novel posttransplantation strategies to reduce relapse. For example, emerging data suggest that tyrosine kinase inhibitors can reduce relapse after BMT for both fms-like tyrosine kinase 3 internal tandem duplication AML33 and Philadelphia-chromosome-positive leukemia. Integrating novel immunologic agents with allogeneic BMT also holds promise for relapse reduction and improved survival in patients with poor-risk or advanced hematologic malignancies. However, approaches for reducing relapse, such as more intensive conditioning regimens, could also increase toxicities without improving overall outcomes. Thus, approaches for relapse reduction need to be carefully studied in prospective clinical trials. We initially developed our haplo BMT platform exclusively using NMA conditioning, and it remains our standard for haplo BMT because of toxicity concerns with myeloablative conditioning. More recently, we are testing haplo BMT with more intensive conditioning, but early results suggest that a small improvement in disease control is potentially offset by increased NRM, leading to PFS and OS outcomes similar to those seen with NMA conditioning.34

Table 3. Univariable and multivariable analyses of NMA-haplo BMT

<table>
<thead>
<tr>
<th>Variables</th>
<th>PFS (HR 95% CI)</th>
<th>OS (HR 95% CI)</th>
<th>Relapse (SDHR 95% CI)</th>
<th>NRM (HR 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refined DRI group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>2.55 (1.67-3.87)</td>
<td>&lt;.0001</td>
<td>2.23 (1.44-3.45)</td>
<td>3.32 (1.90-5.78)</td>
</tr>
<tr>
<td>High/very high risk</td>
<td>3.37 (2.10-5.41)</td>
<td>&lt;.0001</td>
<td>2.86 (1.74-4.72)</td>
<td>5.29 (2.89-9.66)</td>
</tr>
<tr>
<td>HCT-CI score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 (low risk)</td>
<td>NT‡</td>
<td>Ref</td>
<td>NT</td>
<td>Ref</td>
</tr>
<tr>
<td>1-2 (intermediate risk)</td>
<td>1.11 (0.77-1.56)</td>
<td>.59</td>
<td>1.14 (0.55-2.34)</td>
<td>.73</td>
</tr>
<tr>
<td>≥3 (high risk)</td>
<td>1.27 (0.88-1.81)</td>
<td>.20</td>
<td>1.60 (0.78-3.25)</td>
<td>.20</td>
</tr>
<tr>
<td>Comorbidity-age index</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-2 (low risk)</td>
<td>NT‡</td>
<td>Ref</td>
<td>NT</td>
<td>Ref</td>
</tr>
<tr>
<td>≥3 (high risk)</td>
<td>1.17 (0.89-1.55)</td>
<td>.26</td>
<td>1.37 (0.81-2.34)</td>
<td>.24</td>
</tr>
<tr>
<td>Multivariable†‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient age by decade§</td>
<td>1.07 (0.96-1.18)</td>
<td>.24</td>
<td>1.10 (0.98-1.23)</td>
<td>.10</td>
</tr>
<tr>
<td>Female donor for male patient (vs other)</td>
<td>1.26 (0.95-1.68)</td>
<td>.11</td>
<td>1.34 (0.99-1.81)</td>
<td>.06</td>
</tr>
<tr>
<td>Female donor for female patient (vs male)</td>
<td>1.27 (0.88-1.81)</td>
<td>.20</td>
<td>1.60 (0.78-3.25)</td>
<td>.20</td>
</tr>
<tr>
<td>Female donor for male patient (vs other)</td>
<td>1.26 (0.95-1.68)</td>
<td>.11</td>
<td>1.34 (0.99-1.81)</td>
<td>.06</td>
</tr>
<tr>
<td>Patient CMV positive (vs negative)</td>
<td>1.34 (1.03-1.74)</td>
<td>.03</td>
<td>1.31 (1.00-1.76)</td>
<td>.05</td>
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<tr>
<td>Patient CMV positive (vs negative)</td>
<td>1.34 (1.03-1.74)</td>
<td>.03</td>
<td>1.31 (1.00-1.76)</td>
<td>.05</td>
</tr>
<tr>
<td>CD3 dose ≥ 3.84 x 10^6 /kg (vs less)</td>
<td>0.77 (0.59-1.01)</td>
<td>.66</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>CD3 dose ≥ 3.84 x 10^6 /kg (vs less)</td>
<td>0.77 (0.59-1.01)</td>
<td>.66</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>
| CMV, cytomegalovirus; NR, not retained in final model; NT, not tested; ref, reference category.
| *All models were stratified by BMT year (2002-2008 vs later).
| †Index is validated for NRM and OS only.
| ‡All models also considered donor age (continuous), CMV matching, and for NRM and OS, the HCT-CI score.
| §Increasing age by decade as a continuous variable.

**Refined DRI study cohort.**15 The survival differences among risk groups appeared to be driven by differences in relapse risk. The present data suggest that the index is helpful regardless of HLA-mismatching and the type of postgrafting immunosuppression. However, the refined DRI categorized 65% of patients in the present study as intermediate risk, indicating the need for further refinement of prognostic tools. Similarly, in the refined DRI validation study, the majority (63%) of patients were categorized as intermediate risk, with 14% of patients being low risk, 20% high risk, and 4% very high risk. For disease-specific studies, more detailed risk-stratification tools are needed.

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To the best of our knowledge, this is the largest published study to date of HLA-haplo BMT after NMA or reduced-intensity conditioning. The encouraging results in this series of NMA haplo BMT with PTCy support its role as a viable alternative-donor transplantation platform. The results furthermore suggest that virtually no patient should any longer be denied allogeneic BMT because of lack of an HLA-matched donor. Prospective randomized trials, such as the ongoing BMT Clinical Trials Network comparison of NMA double umbilical cord blood transplantation and haplo BMT, are necessary to help prioritize alternative-donor transplantation approaches.

Acknowledgments

The authors thank the Cell Therapy Laboratory at Johns Hopkins for manuscript. Conflict-of-interest disclosure: The authors declare no competing financial interests.

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References


Authorship

Contribution: S.R.M. and Y.L.K. were involved in the study’s conception and design, data collection, analysis, and interpretation, primary writing of the manuscript, and manuscript revisions; R.J.J. and E.J.F. were also involved in conception and design, data collection, data analysis and interpretation, and manuscript revisions; H.-L.T. and G.L.R. statistically analyzed and interpreted the data and revised the manuscript; J.A.K., M.M.S., J.B.-M., C.G.K., K.P., H.J.S., R.A.B., D.E.G., C.A.H., K.W.P., G.T.P., A.E.D., I.G., W.H.M., I.B., M.A.M., L.J.S., B.D.S., M.J.L., R.F.A., and L.L. were involved in data collection; J.A.K., C.G.K., and R.A.B. also revised the manuscript; and all authors approved the manuscript.

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