Post-Transplantation Cyclophosphamide based Graft-Versus-Host-Disease prophylaxis compared to Methotrexate-cyclosporine A in Matched Related Allogeneic Hematopoietic Stem Cell Transplantation

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RESEARCH ARTICLE

Post-transplantation Cyclophosphamide-based Graft-versus-host-disease Prophylaxis Compared to Methotrexate-cyclosporine a in Matched-related Allogeneic Hematopoietic Stem Cell Transplantation

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Abstract

Background and objectives: Post-transplant cyclophosphamide (PTCy) has shown promising results with low rates of severe graft-versus-host-disease (GVHD), either alone or combined with conventional immunosuppression (CIS). However, studies comparing PTCy with CIS as a GVHD prophylaxis are scarce. The study aimed to determine the rates of GVHD and survival outcomes for patients undergoing peripheral blood stem cell transplant (PBSCT) from HLA-matched related donors (MRD) receiving PTCy-based GVHD prophylaxis and compare these outcomes with those of patients receiving methotrexate (MTX) and cyclosporine-A (CsA) as a GVHD prophylaxis.

Patients and methods: Seventy-five patients with advanced hematologic malignancies who underwent MRD allogeneic hematopoietic cell transplantation (allo-HCT) were analyzed prospectively. These patients received PTCy and CSA as a GVHD prophylaxis (therapeutic group) and their outcomes were compared with those of 75 retrospectively collected patients who received methotrexate and CsA as a GVHD prophylaxis (historical group) from the same two transplant centers.

Results: The median recipient age was significantly lower in the MTX/CsA group at 28 years compared to 34 years in the PTCy/CsA group. Peripheral blood was the only graft source used. All patients had a complete MRD, with two patients having a one-antigen mismatched related donor within the PTCy/CsA group. The 1-year cumulative incidence (CI) of chronic GVHD was 13.4% with PTCy/CsA and 38.6% with MTX/CsA (P = .001). Acute GVHD CI across all grades did not differ between the groups, with 10.7% for PTCy/CsA and 14.7% for MTX/CsA (P = .46). At two years, the overall survival (OS) (54.4% vs 67.2%, P = 0.282), disease-free survival (DFS) (54.1% vs 66.1%, P = 0.358), relapse rates (27.4% vs 20.1%, P = 0.245), and non-relapse mortality (NRM) (29.3% vs 25%, P = 0.904) did not differ between PTCy/CsA and MTX/CsA, respectively.

Conclusion: PTCy-based GVHD prophylaxis in MRD transplant is feasible and leads to lower chronic GVHD rates without causing a significantly different risk of relapse or survival than MTX/CsA. More extensive studies are needed to confirm our results.

Keywords: PTCy, GVHD prophylaxis, Chronic GVHD, Matched related donors, Conventional immunosuppression, Methotrexate

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1. Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HCT) is considered as the only curative therapy for many malignant hematological disorders, despite the high rates of non-relapse mortality (NRM), mainly from uncontrollable graft-versus-host disease (GVHD) [1]. Better donor selection, supportive treatment, and GVHD prophylaxis have led to lower rates and severity of acute GVHD; however, chronic GVHD rates have remained almost the same, ranging from 35% to 50% [2]. The standard GVHD prophylaxis in HLA-matched related donor (MRD) comprised the combination of methotrexate (MTX) and calcineurin inhibitors (CNI) with or without mycophenolate mofetil (MMF) since the combination of CsA and MTX in the 1980s. [3,4]. Post-transplant cyclophosphamide (PTCy) was initially used in haploidentical transplants and resulted in low rates of acute grades II-IV, III-IV GVHD, chronic GVHD, and NRM [5]. The use of PTCy as a solo GVHD prophylaxis was assessed in a prospective phase 2 study in which single-agent PTCy was administered on days 3 and 4 to HLA-matched related or unrelated BMT recipient. The incidence of grades II-IV GVHD, grades III-IV GVHD, and chronic GVHD was 43%, 10%, and 10%, respectively [6]. Another study that assessed single-agent PTCy revealed similar rates of grades II-IV GVHD, grades III-IV GVHD, and chronic GVHD, with values of 51%, 15%, and 14%, respectively [7]. The combination of PTCy with immune suppressant was compared to single-agent PTCy in matched sibling and unrelated transplant, and led to a better survival and lower incidence of severe cGVHD with the combination GVHD prophylaxis [8].

The aims of this study were to evaluate GVHD rates and the survival outcomes of patients with malignant hematological disorders undergoing PBSCT from an MRD using PTCy and cyclosporine-A (CsA) as a GVHD prophylaxis and compare their outcomes to those of a historical group of patients who received MTX and CsA as a GVHD prophylaxis.

2. Patients and methods

2.1. Patients

Between December 2017 and June 2019, 75 patients (therapeutic group) between 18 and 60 years with malignant hematological disorders in CR1 or CR2 undergoing PBSCT from a fully matched related donor (MRD) were prospectively examined. These patients received post-transplantation cyclophosphamide and cyclosporine-A (CsA) as a GVHD prophylaxis. The therapeutic group was compared to a historical group of 75 patients with matched disease characteristics who received cyclosporine-A (CsA) and methotrexate as a GVHD prophylaxis between September 2015 and August 2019. The median CD34 cell dose was almost similar between the two groups. All patients had a fully matched donor, with two patients in the PTCy/CsA group having a single-antigen mismatched related donor. All 150 patients received the transplant at 2 transplant centers. NCI- Cairo University IRB and ethics committee approvals were obtained. Peripheral blood was the only source of stem cells, and myeloablative conditioning (MAC) was administered to both group of patients.

2.2. Treatment protocol

2.2.1. Therapeutic group (PTCy/CsA)

All Patients received the same preparative regimen of intravenous fludarabine 40 mg/m² and oral busulfan 16 mg/kg/total dose on D-5 to D-2. GVHD prophylaxis comprised PTCy 50 mg/kg on days +3 and +4 and cyclosporine-A (CsA) 3 mg/kg/ day, starting on day +5 post-transplant with a trough therapeutic level between 200 and 400 mg/L and tapered from day +90 in the absence of GVHD without the use of G-CSF for support.

2.2.2. Historical group (MTX/CsA)

Three myeloablative preparative regimens were used: busulfan/cyclophosphamide (64%), busulfan/ fludarabine (24%), and TBI/cyclophosphamide (12%). All patients received GVHD prophylaxis with mini-dose MTX (15 mg/m² IV day +1 and 10 mg/m²/ day +3, +6, +11) and CsA starting from day −1, with a trough therapeutic level between 200 and 400 μg/L and tapered from day +90 in the absence of GVHD.

2.3. Definitions of clinical outcomes

Myeloid engraftment was defined as the first of 3 consecutive days when the absolute neutrophil count was ≥5 × 10⁹/L before Day +28. Assessments were not performed for patients who died before Day +28 without engraftment. Platelet engraftment was defined as achieving a platelet count ≥20 × 10⁹/L unsupported by platelet transfusions for seven days. Primary graft failure was defined as the absence of donor-derived myeloid cells at Day +28. Diagnosis of disease recurrence was based on clin-
2.4. End points

The primary endpoint of the current study was the cumulative incidence of cGVHD at 1-year post-transplantation. The secondary endpoints included grade II-IV and III-IV acute GVHD, non-relapse mortality (NRM), relapse rate (RR), neutrophil and platelet engraftment, disease-free survival (DFS), and overall survival (OS). These endpoints were compared between the therapeutic and historical groups.

2.5. Ethics approval and consent to participate

Informed consent was obtained from all patients in accordance with the Declaration of Helsinki, and the protocol was approved by the institutional review board (IRB) and ethics committee.

2.6. Statistical analysis

Data management and statistical analysis were performed using Statistical Package for Social Sciences (SPSS) vs.24.

Numerical data are presented as means and standard deviations or medians and ranges. Categorical data are presented as percentages. Comparisons between the two groups regarding normally distributed numeric variables were performed using the t-test. Non-normally distributed numeric variables were compared using the Mann–Whitney test. For categorical variables, differences were analyzed using the chi-square test and Fisher’s exact test.

The Kaplan and Meier method was used to estimate the OS rates, DFS, NRM, and relapse rate. Comparisons between the different prognostic factors were performed using the Log-rank test. For OS, living patients or patients lost to follow-up were censored on the last known alive date, while DFS patients who neither progressed, relapsed, nor died were censored at the last assessment before loss to follow-up. All p-values are two-sided. P-values <0.05 were considered significant.

3. Results

3.1. Patients and donor characteristics

Seventy-five prospectively studied patients who received PTCy/CsA as a GVHD prophylaxis (therapeutic group) were compared to 75 retrospectively collected patients who received MTX/CsA for GVHD prophylaxis (historical group) from the same transplant centers. Two patients in the therapeutic group had a one-antigen mismatched related donor, while the remaining patients had a fully matched related donor. There were no significant differences between the characteristics of both groups, except patient age. The patient and donor characteristics are summarized in Table 1.

3.2. OS and DFS

No significant difference was found in the 2-year OS, 54.4% vs. 67.2% (P = .282; Fig. 1), or 2-year DFS rates, 54.4% vs. 66.1% (P = .358; Fig. 2), between the PTCy/CsA and MTX/CsA groups, respectively.

Univariate analysis of multiple factors (diagnosis, BMI, creatinine clearance, donor’s age, recipient’s age, and sex disparity) revealed that the factors had no significant impact on the OS or DFS in both groups, except for creatinine clearance levels. Patients in the PTCy/CsA group with creatinine clearance ≥90 ml/minute had a superior one-year OS (72.1% vs. 35.7%) (P = .003; Fig. 3) and DFS (73.7% vs. 41.7%) (P = .011; Fig. 4) compared to those with lower values.
3.4. GVHD

The cumulative incidence of acute GVHD across all grades was 10.7% (CI 5.2%–19.1%) and 14.7% (CI 8.1%–23.9%) in patients receiving PTCy/CsA and MTX/CsA, respectively (P = .46).

In the PTCy group, grade II acute GVHD occurred in 5 patients, while grade III aGVHD was observed in three patients, with the skin being the most affected site (75%). Further, 87.5% of patients responded to steroids while 12.5% required second-line treatment; none of the patients died from aGVHD.

Grade II aGVHD occurred in 6 patients and grade III aGVHD occurred in 5 patients in the MTX/CsA group, with the gastro-intestinal tract (GIT) being the most affected organ. Of the patients, 63.5% were steroid sensitive and the remaining 36.5% required second-line treatment; none of the patients died from aGVHD.

Univariate analysis of multiple risk factors to derive their impact on the rates of aGVHD revealed higher rates in patients with seropositive hepatitis C virus (HCV) in the MTX/CsA group (P = .04). Of note, none of the other factors (diagnosis, BMI, donor’s/recipient’s age and sex disparity) had any impact on the rates of aGVHD in both groups.

For patients surviving more than 100 days post-transplant, the cumulative incidence of chronic GVHD was 13.4% (CI 6.9%–23.1%), with occurrence in 9 of the 67 patients receiving PTCy/CsA prophylaxis. On the other hand, a higher cumulative incidence of 38.6% (CI 26.8%–51.5%) (P = .001) was observed with MTX/CsA as chronic GVHD occurred in 22 of the 57 patients. Within the PTCy/CsA group, moderate cGVHD was observed in

### Table 1. Patient and donor characteristics.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group A (PTCy/CsA)</th>
<th>Group B (MTX/CsA)</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Donor age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>34 years (12–58)</td>
<td>27 years (12–60)</td>
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<tr>
<td>&lt;29</td>
<td>31 (41.3)</td>
<td>43 (57.3)</td>
<td>.060</td>
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<tr>
<td>30–49</td>
<td>33 (44.0)</td>
<td>28 (37.3)</td>
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</tr>
<tr>
<td>≥50</td>
<td>11 (14.7)</td>
<td>4 (5.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Recipient age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>34 years (19–60)</td>
<td>28 years (16–58)</td>
<td></td>
</tr>
<tr>
<td>&lt;29</td>
<td>23 (30.7)</td>
<td>40 (53.3)</td>
<td>.017</td>
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<tr>
<td>30–49</td>
<td>46 (61.3)</td>
<td>32 (42.7)</td>
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</tr>
<tr>
<td>≥50</td>
<td>6 (8.0)</td>
<td>3 (4.0)</td>
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<tr>
<td><strong>Recipient sex</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>26 (34.7)</td>
<td>34 (45.3)</td>
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<tr>
<td>Male</td>
<td>49 (65.3)</td>
<td>41 (54.7)</td>
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</tr>
<tr>
<td><strong>Donor sex</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Female</td>
<td>32 (42.7)</td>
<td>29 (38.7)</td>
<td>.618</td>
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<tr>
<td>Male</td>
<td>43 (57.3)</td>
<td>46 (61.3)</td>
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<tr>
<td><strong>Diagnosis</strong></td>
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<td>AML</td>
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<td>43 (57.3)</td>
<td>.061</td>
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<tr>
<td>CML</td>
<td>7 (9.3)</td>
<td>12 (16.0)</td>
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<tr>
<td>MDS</td>
<td>12 (16.0)</td>
<td>9 (12.0)</td>
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<tr>
<td>ALL</td>
<td>1 (1.3)</td>
<td>10 (13.4)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>2 (2.7)</td>
<td>1 (1.3)</td>
<td></td>
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<tr>
<td><strong>Creatinine clearance</strong></td>
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<tr>
<td>60–89 ml/minute</td>
<td>14 (18.7)</td>
<td>6 (14.3)</td>
<td>.546</td>
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<tr>
<td>&gt;90 ml/minute</td>
<td>61 (81.3)</td>
<td>36 (85.7)</td>
<td></td>
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<tr>
<td><strong>Recipient/HCV Antibody</strong></td>
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<tr>
<td>Negative</td>
<td>67 (89.3)</td>
<td>71 (94.7)</td>
<td>.229</td>
</tr>
<tr>
<td>Positive</td>
<td>8 (10.7)</td>
<td>4 (5.3)</td>
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</tr>
<tr>
<td><strong>CMV</strong></td>
<td></td>
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<tr>
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<td>57 (76)</td>
<td>65 (86.7)</td>
<td>.533</td>
</tr>
<tr>
<td>CMV viremia</td>
<td>15 (20)</td>
<td>10 (13.3)</td>
<td></td>
</tr>
<tr>
<td>CMV disease</td>
<td>3 (4)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td><strong>Recipient/HBs antibody</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>65 (86.7)</td>
<td>57 (76.0)</td>
<td>.094</td>
</tr>
<tr>
<td>Positive</td>
<td>10 (13.3)</td>
<td>18 (24.0)</td>
<td></td>
</tr>
</tbody>
</table>

Note: AML, Acute Myeloid Leukemia; CML, Chronic Myeloid Leukemia; MDS, Myelodysplastic Syndrome; ALL, Acute Lymphoblastic Lymphoma; HCV, Hepatitis C virus; CMV, Cytomegalovirus; HBs, Hepatitis B surface.

* Data were only collected for 42 patients.
88.8% of patients, while severe cGVHD was observed in the remaining patients. The liver was the most involved organ in the occurrence of GVHD, and no patient died owing to GVHD. In the MTX/CsA group, 59% of patients had mild cGVHD, while approximately 32% and 9% had moderate and severe cGVHD, respectively. The skin and mucus membranes were the most affected sites, and three patients died due to cGVHD.

Univariate analysis of multiple risk factors revealed higher rates of cGVHD in patients with female donors to male recipients (F-M) in the MTX/CsA group (P = 0.05) and patients with seropositive HCV in the PTCy/CsA group (P = 0.01). None of the remaining factors (initial diagnosis/BMI/donor’s or recipient’s age) impacted the rates of cGVHD.

3.5. Toxicity and NRM

The 2-year non-relapse mortality (NRM) was similar (29.3% vs. 25%, P = .904; Fig. 5), and infection-related
mortality was the leading cause of NRM in both groups. In the PTCy/CsA group, sinusoidal occlusive syndrome (SOS) and fulminant hepatitis were each responsible for approximately 11.8% of NRM, while infection served as the cause for the remaining NRM. In the MTX/CsA group, infection-related mortality occurred in approximately 67% of patients, while each GVHD-related mortality and SOS accounted for approximately 16.5% of the NRM. After allo-HCT, 45% of the NRM occurred during the first 100 days post-transplant in the PTCy-based GVHD prophylaxis group and 83.3% in the conventional group.

A significantly higher number of hemorrhagic cystitis was observed in the PTCy/CsA group (approximately 23%) relative to the MTX/CsA group (approximately 7%) (P = .006). On the other hand, more occurrences of higher grades of oral mucositis G III-IV were observed in patients receiving methotrexate (42.7%) than patients receiving PTCy (25.3%).

3.6. Relapse

The 2-year relapse rates were comparable between both groups (27.4% vs. 20.1%, P = .175; Fig. 6). Fourteen patients relapsed in the PTCy/CsA group, 78.5% of which relapsed early during the first 12 months post HCT; none of these patients received donor-lymphocyte infusion. Among the 11 patients who experienced a relapse in the MTX/CsA group, approximately 64% relapsed within the first 12 months post HCT, and one patient received donor-lymphocyte infusion.
4. Discussion

GVHD remains as the leading cause of morbidity and transplant-related mortality. HLA-identical sibling donor is still considered the preferred source for allo-HCT to decrease the risk of GVHD; however, the second major modifiable risk factor is the use of GVHD prophylaxis. Unfortunately, the standard GVHD prophylaxis (methotrexate and CNI) has not changed in more than 30 years [3], despite the significant rate of occurrence of GVHD.

Post-transplantation cyclophosphamide was initially used in haploidentical HCT, leading to comparable outcomes with MRD and MUD [11]. Promising results were also obtained using PTCy either as a single agent for GVHD prophylaxis [6] or combined with another immunosuppressant in HLA-matched donors [7,12]. However, only few studies compared conventional GVHD prophylaxis with PTCy/CSA in matched-related transplants. Despite the risk of increased cGVHD, PBSCs are now a common stem cell source due to convenience, better disease control, and earlier engraftment [15,16]. The increased risk of cGVHD may be abolished using cyclophosphamide-based prophylaxis according to the lower observed rates.

In this study, we compared the efficacy of PTCy GVHD prophylaxis in combination with CSA only to a retrospectively collected group of patients who received conventional immunosuppression using
CsA and methotrexate in adult patients undergoing HCT from MRD using mobilized PBSCs. A significant reduction in the one-year cumulative incidence of chronic GVHD was observed with the PTCy-based GVHD prophylaxis. On the other hand, no significant impact on the rates of acute GVHD, NRM, relapse rates, OS, and DFS was observed between the two groups.

A recent prospective trial compared PTCy-based GVHD prophylaxis and CsA to CsA and mycophenolic acid in matched related and unrelated peripheral blood allo-HCT after non-myeloablative conditioning. The Hovon-96 trial revealed a lower two-year cumulative incidence of chronic extensive GVHD of 16% versus 48% (HR: 0.36, 95%CI: 0.21–0.64, p < 0.001); however, there was no difference in the rates of relapse incidence (32% and 26%), progression-free (60% and 58%), and OS (69% and 63%) between the two treatment arms [13]. In another retrospective study by Kwon and colleagues, conventional GVHD prophylaxis with methotrexate/cyclosporin A was compared to PTCy-based regimen with additional immunosuppression. These researchers found similar 2-year OS rates (78% vs 56%), EFS (62.5% vs 48%), relapse (28% vs 27%), and NRM (8.8% vs 24%). In addition, lower rates of chronic GVHD were observed that were non-significant, which may be attributed to the small sample size [14].

In the present study, the low chronic GVHD cumulative incidence with PTCy (13.4% vs 38.6%; P = .01) and the similar 2-year OS (54.4% vs. 67.2%; P = .282), DFS (54.4% vs. 66.1%; P = .358), NRM (29.3% vs. 25%; P = .904), and relapse rates (27.4% vs. 20.1%; P = .175) align with those of prior studies [13,14]. No difference in the incidence of acute GVHD was found between the two studied groups, aligning with the results obtained by Mehta and colleagues who found similar grade II–IV (37% vs. 36%, P = 0.8) and grade III–IV (17% vs. 12%, P = 0.5) acute GVHD in patients with one-antigen MMUD receiving PTCy, tacrolimus, and mycophenolate mofetil (MMF) compared to anti-thymocyte globulin, tacrolimus, and methotrexate compared to the group receiving PTCy, tacrolimus, and mycophenolate mofetil (MMF) [16].

More occurrences of higher grades of oral mucositis G III-IV were observed in patients receiving methotrexate (42.7%) than patients receiving PTCy (25.3%). This result was consistent with that of Ying and coworkers who found significantly lower rates and severity of oral mucositis with PTCy than with MTX [19].

5. Conclusion
In conclusion, within the limitations of the study design, short follow-up period, and the small sample size, our findings revealed that the addition of post-transplantation cyclophosphamide as a GVHD prophylaxis in HLA-matched related donors PBSCT can lower the rates of chronic GVHD without significantly impacting survival compared to conventional GVHD prophylaxis. More patients and prospective trials are needed to confirm those results.

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Conflict of interest
The authors declare no conflict of interests or financial disclosures.

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