Acute Graft-Versus-Host Disease Prophylaxis With Methotrexate and Cyclosporine After Busulfan and Cyclophosphamide in Patients With Hematologic Malignancies

By Anne von Bueltzingsloewen, Robert Belanger, Claude Perreault, Yvette Bonny, Denis-Claude Roy, Yves Lalonde, Jacques Boileau, Jeannine Kassis, Rene Lavallee, Michel Lacombe, and Martin Gyger

The combination of two powerful immunosuppressive agents, methotrexate (MTX) and cyclosporine (CSP), has resulted in a significant decrease in the morbidity and mortality after allogeneic bone marrow transplantation (BMT). However, the additive toxicities from ablative preparative regimens may lead to suboptimal use of this combined immunoprophylaxis. We evaluated the efficacy and feasibility of administering MTX/CSP with busulfan (4 mg/kg/d for 4 days) and cyclophosphamide (50 mg/kg/d for 4 days) (BuCy4) in 101 consecutive patients with hematologic malignancies categorized into high- and low-risk groups receiving HLA-matched marrow grafts. Postgrafting immunosuppression consisted of MTX short course (15 mg/m² on day 1 and 10 mg/m² on days 3, 6, and 11) and intra-venous CSP (1.5 mg/kg every 12 hours). Eighty-three patients (82.1%) received 100% of MTX calculated dose and 87 (86.1%) achieved a CSP therapeutic level (250 to 600 ng/mL) within a median of 16 days. Seventy-three patients (72.2%) received optimal immunosuppressive therapy comprising a full MTX course and achieving CSP therapeutic concentrations. The Kaplan-Meier estimated incidence of grade II to IV acute graft-versus-host disease (GVHD) was 5.2% for all patients and 5.5% in patients receiving optimal GVHD prophylaxis. Eighty-nine patients (88.2%) survived ≥100 days posttransplant and 43 (48.3%) developed chronic GVHD, the majority of which were de novo (31 of 43). The estimated incidence of relapse was 28.9% for all patients and 14.8% in the low-risk group, with a median follow-up of 24.5 months. High-risk features and the absence of chronic GVHD were significantly associated with relapse (P = .002 and .036, respectively) in multivariate analyses. Projected disease-free survival at 2 years was 52.3% for all patients and 65.2% in low-risk patients. Disease-free survival was significantly improved in optimally treated patients (P = .03) due to a lower incidence of early deaths from acute GVHD and infectious episodes. In conclusion, optimal delivery of MTX/CSP in association with BuCy4 resulted in a near complete abrogation of acute GVHD in HLA-matched transplants and a significantly improved disease-free survival.

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Table 1. Patient Characteristics

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Numbers in parentheses indicate percentages.

According to pretransplant characteristics potentially linked to recurrency of disease post-BMT, High-risk criteria were defined as follows: chronic myelogenous leukemia (CML); acceleration phase, second chronic phase; acute nonlymphocytic leukemia (ANLL); secondary to chemo/radiotherapy, second complete remission (CR2), early relapse; acute lymphoblastic leukemia (ALL); ≥CR2, early relapse. In patients with myelodysplastic syndrome (MDS), those with excess blasts, excess blasts in transformation, and secondary refractory anemia were categorized as high risk. Low-risk criteria were defined as follows: CML in first chronic phase, de novo ANLL in first complete remission (CR1), ALL in CR1, and primary refractory anemia with or without ring sideroblasts. All donor/recipient pairs were HLA genotypically identical, as determined by serological HLA-A, -B, -C, and -Dr typing and results of mixed leukocyte culture.

Preparation for transplant. All patients received a total dose of 16 mg/kg busulfan (administered orally on days -10, -9, -8, and -7) and 900 mg phenytoin 1 day before busulfan initiation, followed by 300 mg daily for 6 days to prevent seizures. Cyclophosphamide (50 mg/kg) was administered intravenously (IV) on days -5, -4, -3, and -2, followed by marrow infusion on day 0. Doses of busulfan were administered according to ideal body weight (or actual weight if less) and those of cyclophosphamide according to actual weight. Patients with ALL received testicular irradiation, 4 Gy/d for 2 consecutive days (days -3 and -2), whereas those with M-4, M-5 ANLL, and ALL received two intrathecal injections of MTX during initiation of systemic therapy (10 mg/m², maximum 15 mg), with leucovorin rescue on days -6 and -2. Those patients were also administered a total of six intrathecal injections of MTX on days 32, 46, 60, 74, 88, and 102 after grafting, as central nervous system prophylaxis. Engraftment was evaluated directly by sex chromosomes and red blood cell antigens. Indirect evidence for engraftment included increasing marrow cellularity and increasing peripheral blood counts.

GVHD prophylaxis. MTX was administered at a dose of 15 mg/m² of body surface area IV on day 1 and 10 mg/m² on days 3, 6, and 11 after grafting. There was no dose reduction schedule for MTX; however, the drug was withheld in patients with aspartate aminotransferase (AST) ≥500 U/L and/or a creatinine level ≥177 μmol/L. CSP was begun on the day before transplantation and was infused IV over 2 hours at a dose of 1.5 mg/kg (ideal weight or actual weight if less) every 12 hours until the patient recovered from conditioning regimen-induced gastrointestinal toxicity. Thereafter, the patient orally received 5 mg/kg CSP every 12 hours. The full dose of CSP was administered until day 50, after which it was decreased by 10% every 2 weeks. If the serum creatinine level increased 50% above the day 0 baseline value, the dose was reduced by 50%. The dose was further reduced by 50% if the serum creatinine level doubled above the day 0 baseline value. The drug was withheld if the creatinine level exceeded 177 μmol/L. Patients requiring ≥50% dose reduction received IV methylprednisolone or oral prednisone 0.5 mg/kg every 12 hours until resumption of full dose of CSP. If steroids were continued for more than 14 days, the drug was slowly tapered at a rate of 10 mg per week. CSP trough levels, as measured by radioimmunoassay using a specific monoclonal antibody without any significant cross-reactivity with CSP metabolites (cyclo-trac, sp-whole blood; Incstar Corporation, Stillwater, MN) were monitored three times weekly. Levels of 250 to 600 ng/mL were considered therapeutic. CSP after day 5 was steadily increased by 25% of initial dose until therapeutic levels were reached, and reduced by 25% in patients with toxic serum trough levels. Acute and chronic GVHD were graded according to criteria proposed by the Seattle team.25-28 Primary therapy of established grade II to IV acute GVHD consisted initially of methylprednisolone. 2.5 mg IV every 12 hours for 4 consecutive days, after which the patient’s status was reevaluated. Progressive chronic GVHD was treated with alternate day CSP/prednisone, whereas patients with quiescent and de novo GVHD received prednisone 1 mg/kg/day for 1 month.

Bone marrow donors. All donations were performed under general anesthesia and patients were discharged between 1 and 2 days after marrow harvest. No complication of the marrow harvest procedure occurred.

Supportive care. All patients were treated in single patient’s room equipped with high-efficiency particulate air filtration (HEPA-filtered). To reduce CSP nephrotoxicity, patients received daily glucocorticoid magnesium supplements. Also, a non-nephrotoxic broad spectrum antibiotic (cefazidime) was initiated if fever developed during aplasia. Amphotericin B (0.6 mg/kg) was administered if fever persisted for 5 consecutive days despite the initiation of cefazidime. Seropositive patients for herpes simplex virus (HSV) received acyclovir 250 mg/m² every 12 hours IV from day 0 until day 21 posttransplantation. Patients with cytomegalovirus (CMV) seropositivity or with a CMV-seropositive donor received IV acyclovir, 500 mg/m² every 8 hours, from day -5 to day +30. CMV-seronegative blood products were used in all seronegative recipients. All blood products were irradiated (25 Gy). Patients with clinical and enzymatic suspicion of veno-occlusive disease (VOD)25 were treated with IV methylprednisolone, 0.5 mg/kg every 12 hours, strict fluid restriction and a combination of furosamide and spironolactone. Trimethoprim-sulfamethoxazole was administered after 6 months without transplant for Pneumocystis carinii prophylaxis.

Statistical methods. Event times were measured from date of transplantation to date of relapse, death, or last follow-up examination. DFS was defined as time until relapse or death, whichever occurred first. The Fisher’s exact probability test or likelihood ratio test were used to test independent pretransplant risk factors for significant association with acute/chronic GVHD and relapse. These risk factors were type of hematologic malignancy, categorization into
high- or low-risk group, donor/recipient age, ABO compatibility, donor/recipient sex combinations, donor parity, CMV status, percent of calculated MTX dose administered, achievement of a CSP therapeutic serum trough level, steroid administration, acute GVHD (for chronic GVHD and relapse), and chronic GVHD (for relapse). A logistic regression model was performed to determine possible multivariate relation between risk factors and events such as relapse and acute and chronic GVHD. The same tests were used to evaluate whether variables such as hematologic malignancy, categorization into high- and low-risk groups, and recipient age could have influenced compliance to MTX and CSP. All tests were performed at the nominal 5% level of significance and were two-sided. Cumulative incidence curves for grade II to IV acute GVHD, chronic GVHD, and relapse were generated with Kaplan-Meier estimates taking into account time of death and time to follow-up (treated as censored values). Only patients who survived ≥100 days posttransplant were included in the analyses of chronic GVHD. The probability of DFS was estimated by the method of Kaplan-Meier. Comparisons of acute GVHD and relapse cumulative incidence and DFS curves between different groups of patients were performed through the Wilcoxon test.

RESULTS

Engraftment and early toxicity. Ninety-seven patients showed evidence of engraftment. Of the remaining four patients, three died too early to evaluate the fate of the graft and one died in BM failure with an absolute neutrophil count (ANC) <0.1 × 10^9/L on day 29 in a severe septicemic status. Two patients died before achieving a platelet count ≥20 × 10^9/L. The median time to reach an ANC ≥0.5 × 10^9/L for 3 consecutive days was 21 days (range, 11 to 37 days) and 24 days for a platelet count ≥20 × 10^9/L (range, 12 to 82 days). Mucosal, hepatic, and renal toxicities were most frequently observed. All but three patients had mild to severe oral mucositis. Hepatic dysfunction with elevated bilirubin levels and/or increased AST occurred in 86 patients. Eighteen patients presented with clinical symptoms of VOD, which is often observed. All but three patients had mild to severe hepatic toxicity. Renal toxicity in 12, three, and two patients, respectively. One patient died at day +8 posttransplant before receiving the last MTX dose. Increased creatinine levels led to CSP reduction in 35 patients or discontinuation in 34 at a median of 21 days posttransplant (range, 3 to 47 days). Initial diagnosis, risk factors for relapse, and recipient age did not affect either compliance to MTX or achievement of CSP therapeutic concentrations. The Kaplan-Meier estimated incidence of acute grade II to IV GVHD was 9.2% for all patients (Fig 1). Initial diagnosis, risk of relapse, donor/recipient age, donor/recipient sex combination, donor parity, CMV status, ABO compatibility, steroid intake, compliance to MTX, and CSP subtherapeutic serum trough levels were not significantly associated with the onset of acute GVHD in univariate and multivariate analyses. However, the cumulative incidence of acute GVHD was significantly lower in patients with optimal immunosuppressive compliance when compared with the suboptimal group (P = .02). We attempted to determine whether time to achieve a therapeutic CSP level had an influence on the occurrence of acute GVHD. We observed that achieving a therapeutic CSP level by day 16 had no influence on the incidence of acute GVHD (P = .57); in contrast, the occurrence of acute GVHD was significantly more frequent in patients with subtherapeutic CSP levels by day 20 (P = .02).

Chronic GVHD. Eighty-eight patients (87.1%) survived 100 days posttransplant and, hence, were at risk for chronic GVHD. Forty-three patients (48.3%) developed chronic GVHD (31 de novo, 10 quiescent, and 2 progressive). The Kaplan-Meier estimated incidence of chronic GVHD was 50.6% for all patients (Fig 2). Univariate analysis of risk factors known to be associated with chronic GVHD showed CML diagnosis (P = .005) and donor/recipient age (P = .006/P = .002) to be significantly associated with chronic GVHD. Multivariate logistic regression analysis showed only CML diagnosis (P = .001) to be significantly associated with chronic GVHD. Steroid intake, compliance to MTX, and achieve-

Fig 1. Kaplan-Meier estimated incidence of acute grade II to IV GVHD in 101 patients administered HLA-matched marrow grafts receiving MTX/CSP immunoprophylaxis in combination with BuCy4.
ment of CSP subtherapeutic levels did not significantly alter the onset of chronic GVHD. All living patients with chronic GVHD have Karnofsky scores ≥90 except for three with scores ≥70.

Leukemic recurrence. The estimated relapse rate at 2 years was 28.9% for all patients and 14.8% in those with low-risk features. The median follow-up was 24.5 months (range, 6 to 58 months). Leukemic recurrence was seen in 18 patients (ANLL, 5 of 26; ALL, 5 of 22; CML, 4 of 38; MDS, 4 of 15) at a median of 12 months (range, 3 to 28 months). Thirteen of 18 (72.2%) relapses occurred in high-risk patients. Univariate analyses showed relapse to be significantly associated with high-risk categorization (P = .003). In multivariate logistic regression analyses, high-risk features and absence of chronic GVHD were found to be significantly associated with relapse (P = .002 and P = .036, respectively). Three patients are alive in second complete remission, one after a second BMT and two after standard rescue chemotherapy. One CML patient in hematologic relapse remains Philadelphia chromosome-positive after interferon α2b.

Survival and cause of death. Projected DFS at 2 years was 52.3% for all patients and 65.2% in those with low-risk features. DFS was significantly improved in low-risk patients (P = .007) (Fig 3) and in those receiving optimal GVHD prophylaxis (P = .03). Early posttransplant survival at 3 months in patients with optimal/suboptimal GVHD prophylaxis was 94.6% and 69.1%, respectively. This was attributable to a lower incidence of early deaths from acute GVHD and infectious episodes. Thirty-five patients died posttransplant. Complications related to acute and chronic GVHD were responsible for death in five and four patients, respectively; the death rate from these complications in patients given optimal GVHD prophylaxis was 2% in both. Fourteen patients died of relapse. Six patients experienced fatal infection (1 septicemia, 1 hepatic and cerebral mycosis, 2 severe colitis, 2 viral encephalitis). Idiopathic interstitial pneumonitis was responsible for death in one patient. Finally, five patients presented miscellaneous lethal complications (1 hemorrhage, 1 toxic encephalopathy, 1 CNS lymphoma, 1 accident, 1 suicide).

DISCUSSION

The success of allogeneic BMT in hematologic malignancies is intimately related to the conditioning regimen’s tumoricidal potential and to the prevention of morbid and often lethal complications associated with the occurrence of acute GVHD. When tested in a prospective trial in patients with ANLL and CML, MTX/CSP combination, in association with the CY-TBI preparative regimen, reduced the overall incidence of acute GVHD to 33%, compared with 54% for those receiving CSP alone. Similar findings were reported by others after CY-TBI. However, these encouraging results were offset by an increased incidence of leukemic recurrences, mostly in patients with ANLL.

MTX/CSP has been administered in 35 patients in association with a shortened BuCy regimen (cyclophosphamide 60 mg/kg/d for 2 days) with significant hepatic toxicity. This is the first study using the combined immunoprophylaxis MTX/CSP with the highly tumoricidal BuCy4 preparative regimen, as originally reported by Santos et al. Of major concern was the possibility that regimen-related toxicity could lead to unacceptable MTX/CSP dose reductions, thereby impairing the efficacy of this drug combination in preventing acute GVHD. Indeed, in an initial study with CY-TBI, only 58% of the patients received 100% of MTX calculated dose. In our study, 82.1% of the patients received 100% of the MTX calculated dose and 86.1% achieved a therapeutic CSP serum trough level, with a mean of 143% of projected dose. Seventy-three patients had an optimal immunosuppressive prophylaxis receiving full MTX course and achieving a therapeutic CSP level. This combined immunoprophylaxis resulted in a Kaplan-Meier estimated incidence of grade II to IV acute GVHD of only 9.2% for all patients, with an overall mortality related to acute GVHD of 5%. The 5.5% Kaplan-Meier estimated probability of acute GVHD in patients with optimal prophylaxis was comparable or lower to the results obtained after T-cell depletion. It is noteworthy that neither full MTX course nor achievement of a CSP therapeutic
level, when analyzed independently, were significantly associated with a decreased incidence of acute GVHD. Thus, in this study, full MTX delivery with achievement of a CSP therapeutic trough level proved to be essential in preventing acute GVHD. During the early posttransplant period, MTX probably plays a major role in inducing tolerance against donor lymphocyte proliferating in response to alloantigens. The marginal contribution of CSP in preventing acute GVHD within that specific period has been emphasized in a recent study from Seattle using MTX/CSP in which CSP was reduced by 50% during the first 15 days of transplantation without any adverse effects in the incidence, time of onset, and severity of acute GVHD. This is in accordance with our study in which occurrence of acute GVHD was not influenced by achieving a therapeutic CSP trough level by day 16. Yee et al. who studied the relation between CSP concentrations and acute GVHD, did not find any correlation during the first week posttransplant. However they observed that after the first week low CSP trough levels for a given week were significantly associated with the risk of developing acute GVHD during the following week. The significantly reduced incidence of acute GVHD observed in our patients achieving CSP therapeutic concentration by day 20 corroborates these findings. These observations suggest that CSP may have a marginal impact on GVHD prevention during the early posttransplant period, contrasting with its important role once MTX is ceased. Results from studies using short-course MTX alone to prevent acute GVHD confirmed the role played by CSP.

The compliance to MTX/CSP observed in this study is superior to the one reported by the Seattle group, mostly with regards to percent of MTX calculated dose administration. Several factors are likely to explain this discrepancy. First, the Seattle team's guidelines for altering the projected MTX dose may be more rigid. In our study, MTX was omitted only in patients with AST ≥500 U/L and/or in patients with a creatinine value of 177 μmol/l. All other patients were supposed to receive 100% of the calculated MTX projected dose, although three patients had one dose omitted for mucosal toxicity. Also, to limit renal toxicity, CSP was monitored on a regular basis, three times weekly, with a 50% dose reduction when creatinine levels were increased 50% above the baseline value (compared with a creatinine level doubling in the Seattle group). This precocious lowering of CSP may have helped in sparing renal function. Furthermore, all nephrotoxic antibiotics were avoided if possible. None of the patients received aminoglycosides as first line broad spectrum antibiotics. Amphoterin B was administered to only 34.6% of our patients for a median of 9 days (range, 2 to 42 days). Finally, 63 patients received oral or intravenous steroids for various reasons (CSP dose reductions, VOD, pulmonary toxicity). In contrast to the Seattle data, the addition of steroids had no significant adverse effect on the cumulative incidence of acute or chronic GVHD. However, steroids may have contributed to the high compliance to MTX/CSP administration through inhibition of inflammatory acute phase reactants such as tumor necrosis factor α (TNFα), interleukin-1 (IL-1), IL-6, and IL-8. This is in agreement with results from a recent Seattle study in which the percentage of MTX calculated dose administered was significantly higher in patients receiving steroids. Steroid inhibition of early inflammatory cytokines may have also contributed to the low grade of regimen-related hepatic toxicity.

The overall estimated relapse rate at 2 years posttransplant was 28.9%; however, despite a low acute GVHD incidence, the projected relapse rate in low-risk patients was only 14.8%. Two factors are likely to explain this phenomenon. Since its original description, BuCy has been widely recognized as a highly effective tumoricidal regimen. Moreover, the high incidence of chronic GVHD may have precluded disease recurrence through the hitherto recognized GVHD linked antileukemic effect. Indeed, 48.3% of our patients developed chronic GVHD. Fortunately, 72.1% of these were de novo chronic GVHD occurring at the very end of CSP tapering and responding well to steroid therapy. We have no obvious explanation for this high incidence of de novo chronic GVHD and, in contrast to the Seattle study, steroids delivery was not significantly associated with chronic GVHD. Unexpectedly, CML was found to be significantly related to the incidence of chronic GVHD. It is unclear whether this finding can be explained by the disease itself or by the age of the patients with CML. Indeed, 50% of the patients over 40 years of age were in the CML group. Disease recurrence was the major cause of treatment failure in this study. The most statistically significant factor associated with relapse was high-risk pretransplant characteristics, emphasizing the need for improved tumoricidal preparative regimens or innovative posttransplant therapeutic strategies.

The combination of MTX/CSP proved highly effective in preventing acute GVHD in this study. Achievement of optimal GVHD prophylaxis, both in the early posttransplant period through a full course of MTX administration and in the late posttransplant period with therapeutic CSP levels, resulted in a low incidence of acute GVHD, minimal treatment-related mortality, and significantly improved DFS.

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REFERENCES


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