CONCISE REPORT

Hyperacute Graft-v-Host Disease in Patients Not Given Immunosuppression After Allogeneic Marrow Transplantation

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Sixteen patients with leukemia in relapse or second to third remission, 5 to 27 years old (median, 17), were given cyclophosphamide (60 mg/kg × 2) and total body irradiation (2.25 Gy for each of seven days) followed by unmodified marrow grafts from HLA-identical siblings. Patients did not receive posttransplant immunosuppression and were followed a median of nine months (range, 5–17). Prompt engraftment was sustained in 12 patients with a median time of 16 days (range, 10 to 63) to achieve 500 neutrophils/mm^3. One patient failed to engraft, one had delayed engraftment, and two had late poor graft function. All 15 with engraftment developed moderate to life-threatening graft-v-host disease (GVHD, eight grade II and seven grade III-IV). This syndrome was hyperacute (median onset eight days [range, 7 to 29] posttransplant) and manifest by severe skin disease (14 patients at stage 3 and one at stage 4), fever (ten patients), and liver (four patients, stage 3-4) or gut (four patients, stage 3-4) involvement. Serial tissue biopsies confirmed acute GVHD in 13 of 15 patients. Ten were treated with antithymocyte globulin and cyclosporine (four survive), and four with corticosteroids (two survive). Actuarial survival to 17 months was 37%. Causes of death included interstitial pneumonia (four), infection (three), graft failure (one), venocclusive disease (one), and relapse of leukemia (one). Age-matched controls receiving standard methotrexate after transplant had comparable relapse-free survival but only a 25% incidence of grade II-IV acute GVHD ($P < .0001$). We conclude that deleting posttransplant immunosuppression is associated with frequent and severe hyperacute GVHD, infectious complications, and occasional poor graft function.

ACUTE graft-v-host disease (GVHD) and associated infection and interstitial pneumonia (IP) remain major determinants of morbidity and mortality following HLA-identical marrow transplantation. Demonstration that GVHD could be averted or modified in animals if immunosuppressive agents such as methotrexate (MTX), cyclophosphamide (CY), or cyclosporine (CsA) were given after transplant led to direct clinical application.[1–4] However, immunosuppressive agents may contribute to delayed engraftment, IP, or infection and might not always be needed in humans. Moreover, previous clinical trials comparing different prophylaxis regimens could be invalidated if compared agents were equally ineffective in preventing GVHD.

The first study deleting immunosuppression after allogeneic transplant reported no difference in incidence or severity of acute GVHD in patients who did or did not receive MTX.[5] However, MTX recipients appeared to have more GVHD than expected for their age. Based upon these findings, it seemed justified to study young patients not given immunosuppression after marrow grafting. We report the incidence and severity of GVHD, IP, and infection in this trial and compare results with age-matched historic controls who differed only by receiving standard MTX.

MATERIALS AND METHODS

From March 1984 to March 1985, 16 study patients <30 years of age did not receive posttransplant immunosuppression. Protocols and consent forms were approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center. Attending physicians fully outlined the advantages and disadvantages of the procedure. Controls were derived from a randomized trial of patients less than age 30 conducted from Dec 1980 to July 1984 comparing standard MTX to other MTX-based regimens.[6] A total of 44 patients in that trial received standard intravenous (IV) MTX, 15 mg/m^2 day 1 and 10 mg/m^2 days 3, 6, and 11, then weekly to day 102.[2]

Patient characteristics are shown in Table 1. Patients in both groups received CY (60 mg/kg × 2), followed by 15.75 Gy total body irradiation (TBI, 2.25 Gy daily × 7). Both groups were comparable for factors influencing GVHD[7] and received unmodified marrow from HLA-identical siblings.[2] Engraftment was confirmed by peripheral counts, marrow aspirates, and cytogenetic markers. The assessment, grading, and treatment of acute and chronic GVHD have been described.[2,8] Grade II-IV acute GVHD was treated with prednisolone (2 mg/kg/d) or antithymocyte globulin (ATG, 15 mg/kg × 3) and CsA (3 mg/kg/d IV or 12.5 mg/kg/d orally).[9]

RESULTS

Engraftment. Engraftment was more rapid in those not receiving MTX (Table 2). Only one patient failed to engraft: due to electrocardiographic abnormalities, she received only 60 mg/kg CY followed by 15.75 Gy TBI. Three others not receiving immunosuppression had graft problems: one had delayed myeloid and platelet recovery despite early GVHD

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Table 1. Patient Characteristics

Factor	Posttransplant Regimen: No Immunosuppression	Posttransplant Regimen: Standard MTX
No. of patients	16	44
Patient age		
Median (range) in years	17 (5–27)	19 (1–29)
No. <10 yr old	4 (25%)	10 (22%)
Patient sex (M/F)	9/7	27/17
Patient–donor sex mismatch	9 (56%)	24 (55%)
Diagnosis		
Refractory ANL/ALL	1/0	1/0
Relapse ANL/ALL	3/1	11/12
2nd-3rd remission ANL/ALL	2/7	0/6
CML acceleration/blast crisis	1/1	3/9
Lymphoma	0	2
Median (range) no. of marrow cells infused ($\times 10^{-8}$/kg)	2.6 (1.2–5.1)	2.2 (0.9–11.5)
Median (range) follow-up in months	9 (5–17)	32 (14–56)

MTX, methotrexate; ANL, acute nonlymphoblastic leukemia; ALL, acute lymphoblastic leukemia; and CML, chronic myelogenous leukemia.

(63 days to 500 neutrophils/mm^3) and two had late graft failure after acute GVHD development.

Hyperacute GVHD. All 15 study patients who engrafted developed grade II-IV acute GVHD (Table 2). The onset was hyperacute (median, day 8) and associated with stage 3-4 skin disease (generalized erythroderma or desquamation) in all 15 patients. Fever ≥40 °C accompanied the onset in ten patients. Hepatic and enteric GVHD developed in most patients but was less severe than the dermal component: four had stage 3-4 liver disease (bilirubin ≥6 mg/dL) and four had stage 3-4 gut disease (diarrhea ≥1,500 mL/d, severe pain or ileus). Although difficult to distinguish between early GVHD and the histologic effects of chemoradiotherapy,[10] serial skin, liver, or gut biopsies confirmed GVHD in 13 patients. Treatment of hyperacute GVHD was started eight to 22 days (median, day 10) after transplant; ten patients received ATG and CsA (four survive) and four received corticosteroids (two survive). Six had sustained response, four had no benefit, and four had response followed by GVHD flare on tapering therapy.

Table 2. Posttransplant Regimen and Course

Factor	Posttransplant Regimen: No Immunosuppression	Posttransplant Regimen: Standard MTX
No. of engrafted patients	15	44
Median (range) day to 500 neutrophils/mm^3	16 (10–63)	24 (17–35)
Median (range) day to last platelet transfusion*	45 (12–131)	32 (16–92)
Overall grade acute GVHD		
0 (None)	0	22
I (Mild)	0	12
II (Moderate)	8	1
III-IV (Severe, life-threatening)	7	9
Onset grade I-IV acute GVHD		
Median (range) day of onset	8 (7–29)	25 (11–65)
No. with onset ≤ day 14	11 (73%)	4 (18%)
No. with stage 3–4 GVHD/total with stage 1–4 GVHD of:		
Skin	15/15	6/22
Liver	4/7	6/8
Gut	4/10	3/6
No. with interstitial pneumonia	4 (27%)	9 (20%)
No. with relapse of leukemia	1 (7%)	13 (30%)
No. with chronic GVHD/total no. surviving ≥180 days	2/6 (33%)	9/27 (33%)

MTX, methotrexate.
*Among patients surviving ≥85 days. Day 0 is the day of transplant.

Fig 1 depicts the incidence and time to onset of GVHD. Patients receiving MTX had a 25% incidence of grade II-IV acute GVHD compared with 100% incidence in those not given immunosuppression ($P < .0001$).

Infection and survival. Six of 16 study patients developed bacteremia, two cytomegalovirus (CMV) viremia, one aspergillus pneumonia, one toxoplasmosis, and one fulminant hepatic varicella. Four had IP (two pneumocystitis, one CMV, and one idiopathic) and three had hepatic venocclusive disease (VOD). Chronic GVHD developed in two of six surviving ≥180 days. Four study patients died of IP, three of infection, and one each of graft failure, VOD, and relapse. Fig 2 presents actuarial survival. Although relapse-free survival was comparable in study patients and controls, death from nonrelapse causes was increased in the no immunosuppression group ($P = .067$).

DISCUSSION

Based upon controlled studies in experimental animals, patients have routinely received posttransplant immunosuppression to prevent or ameliorate GVHD. The efficacy and toxicity of prophylaxis are incompletely understood since few patients have not received immunosuppression after transplant. We selected young patients with advanced leukemia for this pilot study since there might be either no increase in GVHD if prophylaxis were deleted,[5] or a possible antileukemic benefit if GVHD were augmented.[11] If these pilot data suggested no additional hazard, we proposed a subsequent randomized trial comparing MTX and placebo.

We found, however, that deleting posttransplant immunosuppression was associated with development of grade II-IV

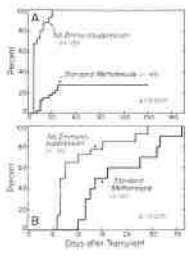

Fig 1. Kaplan-Meier estimates (generalized Wilcoxon test statistic). (A) Probability of developing grade II-IV acute GVHD. (B) Time to onset of grade II-IV acute GVHD. One patient in the no immunosuppression group failed to engraft and is excluded from analysis.

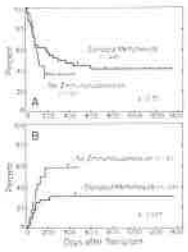

Fig 2. Kaplan-Meier estimates (generalized Savage test statistic). (A) Probability of relapse-free survival. Vertical marks represent patients surviving in remission as of Aug 1, 1985. The actuarial estimate of relapse of leukemia was 11% in the no immunosuppression group and 40% in the standard methotrexate group (P = .27). (B) Probability of death from nonrelapse (ie, transplant-related) causes. Patients are censored from analysis at the time of relapse.

GVHD in all 15 patients who achieved engraftment. This hyperacute syndrome included severe skin disease and fever beginning seven to 14 days after transplant. Features were sufficiently severe to require prompt treatment. Although response was often dramatic and perhaps blunted development of severe liver and gut involvement, GVHD flare was observed when therapy was tapered in four of ten who initially responded. Survival was poor with most deaths resulting from IP or infection. In contrast to others,[5,12] we noted an equal incidence of IP in those who did and did not receive MTX. Any lessening of pulmonary toxicity in patients not given MTX may be offset by increased GVHD and associated immunodeficiency.[13]

Age-matched controls given the same CY and TBI preparation and standard MTX after transplant had a 25% incidence of grade II-IV acute GVHD.[6] This agrees with other reports of infrequent GVHD in young patients receiving MTX[14,15] but differs from the study by Lazarus et al where 24 of 34 patients (71%) (median age, 12 years) given standard MTX developed grade II-IV acute GVHD.[5] The high incidence in the MTX controls may explain why that study found no increase in GVHD in 21 patients not given MTX.

The development of graft problems in four of our 16 study patients was not expected. One patient given a reduced dose of CY failed to engraft despite 15.75 Gy TBI. Three developed severe early GVHD with either delayed myeloid recovery or poor late graft function. We have observed such "lymphoid" grafts in GVHD patients who required marrow reinfusion to correct poor myeloid and platelet recovery.[16] Alternatively, deleting posttransplant immunosuppression could encumber engraftment. Studies in dogs suggested that MTX facilitated engraftment but the mechanism of the effect was never clear.[17]

The present data would refute the theory that previous trials of single agent prophylaxis were ineffective in preventing GVHD. Moreover, both animal[18] and clinical studies[14] have reported a reduction in the incidence of GVHD when multiagent immunosuppression was given after transplant. A recent trial comparing CsA to a combination of CsA and MTX showed both a reduction in GVHD and an increase in survival in patients receiving combination prophylaxis.[19] Such studies illustrate the interrelationship of graft function, GVHD, immunosuppression, IP, infection, and survival following allogeneic transplant. We conclude from the present study that deleting posttransplant immunosuppression is associated with frequent and severe hyperacute GVHD. Elimination of MTX does not appear to prevent IP or infectious complications. Occasional poor graft function may result from deletion of posttransplant immunosuppression, development of GVHD, or other factors.

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