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# Methotrexate, Cyclosporine, or Both to Prevent Graft-Versus-Host Disease After HLA-Identical Sibling Bone Marrow Transplants for Early Leukemia?

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**Optimal prophylaxis of graft-versus-host disease (GVHD) is controversial. We compared efficacy of three posttransplant immune suppressive regimens in 2,286 recipients of HLA-identical sibling bone marrow transplants for acute lymphoblastic leukemia (ALL) in first remission, acute myelogenous leukemia (AML) in first remission, or chronic myelogenous leukemia (CML) in first chronic phase. Six hundred forty received methotrexate, 977 received cyclosporine, and 669 received combined cyclosporine and methotrexate. In children, the three regimens resulted in similar outcomes. In adults, cyclosporine and methotrexate had comparable risks of acute and chronic GVHD. Compared with methotrexate, cyclosporine was associated with less interstitial pneumonia (relative risk [RR] = 0.6; $P < .001$), less treatment-related mortality (RR = 0.6; $P < .001$), more relapses (RR = 1.6; $P < .05$), and less treatment failure (relapse or death from any cause; RR = 0.7; $P < .001$). Different effects were observed in different leukemias. In ALL, the rate of leukemia relapse was increased with cyclosporine versus methotrexate, with no effect on other outcomes. In AML and CML, interstitial pneumonia, treatment-related mortality, and treatment failures were decreased with cyclosporine, with no increase in relapse. Similar analyses comparing cyclosporine plus methotrexate with cyclosporine alone showed that adults receiving the combination had less acute GVHD (RR = 0.5; $P < .001$), less chronic GVHD (RR = 0.7; $P < .01$), and less interstitial pneumonia (RR = 0.7; $P < .001$). Treatment failure (RR = 0.8; $P < .05$) was marginally reduced. Separate analyses in ALL and AML showed less acute GVHD with combined therapy, but no significant effect on other outcomes. In CML, acute GVHD, interstitial pneumonia, treatment-related mortality, and treatment failure were decreased with combined therapy.**

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GRAFT-VERSUS-HOST disease (GVHD) is an important complication of bone marrow transplants (BMTs) for leukemia. Moderate to severe GVHD occurs in nearly one-half of recipients of HLA-identical sibling transplants, despite posttransplant immune suppressive therapy.[1-3] GVHD, alone or combined with infection or interstitial pneumonia, accounts for a substantial proportion of posttransplant treatment failures.

There is considerable controversy about how best to prevent GVHD. Early studies used methotrexate (MTX).[4] From 1980 to 1985, cyclosporine (CsA) was increasingly used.[5-13] The favorable and unfavorable effects of in vitro depletion of T lymphocytes from the donor BM were reviewed recently by the International Bone Marrow Transplant Registry (IBMTR)[14] and will not be addressed in this report. Currently, the most frequently used GVHD prophylaxis regimen is the combination of CsA and MTX.[15-19]

Seven randomized trials compared MTX and CsA[5-11]; one showed a decreased incidence of acute GVHD with MTX, two a decreased incidence with CsA, whereas four showed no difference. None showed a significant survival advantage for either drug. One study combining data for 274 patients from five of the randomized trials showed no difference in GVHD, relapse, or survival between patients treated with MTX versus CsA.[20]

Some recent studies indicate that combined therapy is more effective in preventing acute GVHD than either drug used alone, although few were randomized.[15-19] One randomized trial reported that patients with acute myelogenous leukemia (AML), but not those with chronic myelogenous leukemia (CML), tended to have more relapses with combined CsA and MTX compared with CsA alone.[19] Another study reported that leukemia patients treated with combined CsA and MTX had increased relapses compared with patients treated with MTX alone.[18] One randomized trial showed a survival benefit for the combination in patients with CML but not AML.[19]

These negative or contradictory results of different randomized and nonrandomized studies are not surprising. Sample sizes often were small. Variables correlated with GVHD, such as age and donor-recipient sex-matching, dif-

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fered in different studies. Also, different methods of GVHD prophylaxis may affect diverse transplant outcomes and may have different effects in various leukemias and remission states.

We used an alternative strategy of analysis using the data base of the IBMTR to study transplant outcomes in 2,286 recipients of HLA-identical sibling transplants for early leukemia receiving MTX (N = 640), CsA (N = 977), or a combination of the two (N = 669). These large numbers allowed us to analyze different leukemias separately and to adjust results for risk factors affecting competing causes of treatment failure.

## MATERIALS AND METHODS

### *Patients*

Data for 2,286 patients with acute leukemia in first remission or CML in first chronic phase receiving non-T-cell-depleted BMTs between January 1, 1980 and December 31, 1989 from HLA-identical siblings followed by posttransplant immune suppression with MTX and/or CsA were reported to the IBMTR by 158 BMT teams worldwide. Three hundred eighty-four patients were children (<16 years) and 1,902 were adults. Because of different incidence and severity of GVHD in children and adults, the study was designed to analyze these groups separately.

*Children.* The median age of the 384 children was 11 years (range, <1 to 15 years). One hundred twenty-six (33%) were male. Eighty-two (21%) had acute lymphoblastic leukemia (ALL), 231 (60%) had AML, and 71 (18%) had CML. Sixteen (4%) had performance scores less than 90% (50% to 80%). The median interval from diagnosis to transplant was 5 months (range, 1 to 101 months). One hundred eighty-five (48%) transplants were sex-matched; four (1%) were from previously pregnant or transfused females to male recipients. Pretransplant conditioning most often was cyclophosphamide (CY) and total body irradiation (TBI) with or without other drugs (N = 321, 84%). Other regimens included TBI and other drugs (N = 25, 7%), CY and busulfan (N = 33, 9%), and other drug combinations without TBI (N = 5, 1%). The median dose of TBI was 10 Gy (range, 5 to 15.75 Gy) administered in one (N = 125, 33%) or several fractions (N = 221, 58%). Posttransplant immune suppression was with MTX (N = 151, 39%), CsA (N = 144, 38%), or CsA and MTX (N = 89, 23%); 77 (20%) patients also received corticosteroids. The median posttransplant follow-up was 44 months (range, 4 to 119 months).

*Adults.* The median age of the 1,902 adults was 29 years (range, 16 to 62 years). One thousand forty-seven (55%) were male. Three hundred thirty-nine (18%) had ALL, 785 (41%) had AML, and 778 (41%) had CML. One hundred eighty (9%) had performance scores less than 90% (range, 40% to 80%). The median interval from diagnosis to transplant was 7 months (range, 1 to 191 months). One thousand two (53%) transplants were sex-matched; 191 (10%) were from previously pregnant or transfused females to male recipients. The pretransplant conditioning most often was CY and TBI with or without other drugs (N = 1,584, 83%). Other regimens included TBI and other drugs (N = 110, 6%), CY and busulfan (N = 188, 10%), and other drug combinations without TBI (N = 20, 1%). The median dose of TBI was 10 Gy (range, 5 to 15.75 Gy) administered in one (N = 535, 28%) or several fractions (N = 1159, 61%). Posttransplant immune suppression was with MTX (N = 489, 26%), CsA (N = 833, 44%), or CsA and MTX (N = 580, 30%); 475 (25%) patients also received corticosteroids. The median posttransplant follow-up was 39 months (range, 4 to 125 months).

### *Endpoints*

Endpoints analyzed were acute and chronic GVHD, interstitial pneumonia, transplant-related mortality, relapse, treatment failure (relapse or death from any cause), and leukemia-free survival (LFS). Acute GVHD was defined as moderate to severe (grade II to IV) disease using established criteria[3]; patients surviving more than 21 days with evidence of engraftment were considered at risk. Chronic GVHD was determined by clinical criteria in patients surviving more than 90 days with evidence of engraftment.[21] Remission of acute leukemia was defined as absence of detectable leukemia in any site. Relapse and remission of CML were defined by hematologic criteria.[22]

### *Statistical Methods*

To identify differences among the three posttransplant immune suppression groups, patient-, donor-, disease-, and treatment-related variables were compared using $\chi^2$ tests for categorical and Mann-Whitney tests for continuous variables. Variables differing between the groups (age, race, interval from diagnosis to transplant, conditioning regimen [including dose and schedule], cytomegalovirus [CMV] status of donor and recipient, use of CMV-negative blood products, use of prophylactic acyclovir, use of prophylactic Ig, addition of corticosteroids for posttransplant immune suppression, and use of ganciclovir to treat interstitial pneumonia) and other potentially confounding variables (performance score pretransplant, and whether the donor was alloimmunized by prior pregnancy or transfusion) were evaluated to determine their effect on outcomes using Cox proportional hazards regression.[23] A stepwise backward elimination procedure was used. Briefly, all covariates to be considered were entered in an initial regression model that was stratified on disease and year of transplant.[24] Factors not statistically significant ($P > .05$) were removed from the model one at a time with reestimation of all model variables after each step. Variable elimination (or reinsertion) was stopped when all remaining factors were significant at $P < .05$. The reduced model containing significant covariates was used to calculate the relative risks of transplant-related events, relapse, and treatment failure for patients receiving CsA versus those receiving MTX and for patients receiving combined CsA and MTX versus CsA alone. Relative risks were also computed with the addition of acute and chronic GVHD added as time-dependent covariates to determine the effect of GVHD prophylaxis regimens on various outcomes independent of their effect on GVHD.

Actuarial probabilities of acute GVHD, chronic GVHD, interstitial pneumonia, treatment-related mortality, relapse, and LFS were calculated using the life table method.

Results of multivariate analyses were examined for possible influence by differences among centers (1) by entering center size (the average number of allogeneic transplants performed annually) as a covariate; (2) by stratifying on center size; (3) by repeating each analysis after excluding a 5% random sample of teams (this was performed a minimum of three times for each regression equation); and (4) by repeating each analysis after excluding patients from each of the eight largest teams, in turn.

All $P$ values are two-sided and based on multivariate analysis, unless otherwise specified. Because of the large number of comparisons made, we considered only $P$ values <.01 as statistically significant. $P$ values between .01 and .05 are presented to show possible trends, but should be interpreted with caution.

## RESULTS

### *Children*

Patient-, disease-, and transplant-related variables for the three GVHD prophylaxis groups are summarized in Table 1. The probabilities of all outcomes studied were similar, regardless of the regimen used for posttransplant immune suppression. One hundred-day actuarial probabilities of grade II to IV acute GVHD were 34% ± 8% (95% confidence interval) with MTX alone, 37% ± 8% with CsA alone, and 33%

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**Table 1. Patient-, Disease-, Donor-, and Treatment-Related Variables for 384 Children Less Than 16 Years Old Receiving HLA-Identical Sibling BMTs for Early Leukemia**

| Variable | Posttransplant Immune Suppression | | | Univariate P* |
|---|---|---|---|---|
| | MTX | CsA | MTX + CsA | |
| Age (yr), median (range) | 10 (<1-15) | 13 (1-15) | 11 (<1-15) | <.07, NS |
| Race (%) | | | | <.07, <.06 |
| White | 126/151 (83) | 110/144 (76) | 71/89 (80) | |
| Black | 5/151 (3) | 5/144 (3) | 2/89 (2) | |
| Oriental | 11/151 (7) | 8/144 (6) | 11/89 (12) | |
| Other | 9/151 (6) | 21/144 (15) | 5/89 (6) | |
| Disease (%) | | | | |
| ALL | 28/151 (19) | 35/144 (24) | 19/89 (21) | |
| AML | 101/151 (67) | 81/144 (56) | 49/89 (55) | |
| CML | 22/151 (15) | 28/144 (19) | 21/89 (24) | |
| Interval Dx-Tx (mo) | | | | |
| Median (range) | 4 (2-67) | 6 (1-101) | 5 (1-36) | <.0005, <.004 |
| Year of transplant (%) | | | | <.0001, <.0001 |
| 1980-81 | 34/151 (23) | 12/144 (8) | 1/89 (1) | |
| 1982-83 | 62/151 (41) | 39/144 (27) | 2/89 (1) | |
| 1984-85 | 41/151 (27) | 50/144 (35) | 5/89 (3) | |
| 1986-87 | 12/151 (8) | 28/144 (19) | 50/89 (26) | |
| 1988-89 | 2/151 (1) | 15/144 (10) | 31/89 (16) | |
| Conditioning regimen (%) | | | | <.007, <.004 |
| CY + busulfan | 4/151 (3) | 9/144 (6) | 20/89 (22) | |
| CY + TBI | 126/151 (83) | 96/144 (67) | 50/89 (56) | |
| CY + TBI + other drugs | 13/151 (9) | 25/144 (17) | 11/89 (12) | |
| TBI + other drugs | 6/151 (4) | 11/144 (8) | 8/89 (9) | |
| Other | 2/151 (1) | 3/144 (2) | 0/89 (0) | |
| Radiation schedule (%) | | | | <.0001, <.03 |
| Single dose | 76/145 (52) | 39/135 (29) | 10/69 (14) | |
| Fractionated dose | 69/145 (48) | 96/135 (71) | 59/69 (86) | |
| TBI dose (Gy), median (range) | 10 (5-15.75) | 10 (7.7-13.8) | 12 (5-13.4) | <.007, NS |
| Additional post-Tx drugs (%) | | | | <.0009, NS |
| None | 106/151 (70) | 125/144 (87) | 76/89 (85) | |
| Steroids | 44/151 (29) | 19/144 (13) | 13/89 (15) | |
| Other | 1/151 (<1) | — | — | |
| Follow-up (mo), median (range) | 65 (4-119) | 50 (4-105) | 21 (4-109) | <.0003, <.0001 |

Abbreviations: Tx, transplant; Dx, diagnosis; NS, not significant.

* Based on $\chi^2$ for categorical and Mann-Whitney for continuous variables; first *P* value refers to comparison of MTX with CsA, the second to comparison of CsA with MTX + CsA.

± 10% with CsA and MTX (*P* = NS). Two-year probabilities of chronic GVHD were 31% ± 9% with MTX alone, 31% ± 9% with CsA alone, and 36% ± 12% with CsA and MTX (*P* = NS). Two-year probabilities of interstitial pneumonia were 20% ± 7% with MTX alone, 9% ± 5% with CsA alone, and 14% ± 9% with CsA and MTX (*P* = NS). Two-year probabilities of treatment-related mortality were 25% ± 7% with MTX alone, 19% ± 7% with CsA alone, and 17% ± 9% with CsA and MTX (*P* = NS). Two-year probabilities of relapse were 18% ± 7% with MTX alone, 16% ± 7% with CsA alone, and 23% ± 2% with CsA and MTX (*P* = NS). Two-year probabilities of LFS were 62% ± 8% with MTX alone, 68% ± 8% with CsA alone, and 63% ± 12% with CsA and MTX (*P* = NS). Risks of acute and chronic GVHD, interstitial pneumonia, treatment-related mortality, relapse, and treatment failure were not significantly different for the three methods of GVHD prophylaxis in multivariate analyses adjusting for patient-, disease-, and transplant-related variables. This was true whether different leukemias were analyzed together or separately.

*Adults*

Patient-, disease-, and transplant-related variables for the three GVHD prophylaxis groups are summarized in Table 2.

*CsA versus MTX.* Actuarial probabilities and relative risks of transplant outcomes including acute and chronic GVHD, interstitial pneumonia, treatment-related mortality, relapse, and LFS (or treatment failure) are indicated in Table 3 and Fig 1.

Overall, CsA and MTX (reference group) had comparable risks of acute and chronic GVHD (Fig 1A and B). CsA was associated with less interstitial pneumonia (Fig 1C). This association persisted after adjusting for acute GVHD. Treatment-related mortality (Fig 1D) was also less with CsA, even after adjusting for acute GVHD. Relapse risk (Fig 1E) was marginally higher with CsA, with and without adjustment for GVHD. Treatment failure was less and LFS (Fig 1F) was higher with CsA, even after adjusting for GVHD.

Separate analyses were also performed for each leukemia. In ALL, there was no significant effect on any outcome except

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**Table 2. Patient-, Disease-, Donor-, and Treatment-Related Variables for 1,902 Adults (≥16 years) Receiving HLA-Identical Sibling BMTs for Early Leukemia**

| Variable | Posttransplant Immune Suppression | | | Univariate P* |
|---|---|---|---|---|
| | MTX | CsA | MTX + CsA | |
| Age (yr), median (range) | 27 (16-48) | 30 (16-54) | 31 (16-62) | <.0002, <.004 |
| Race (%) | | | | <.0001, <.0004 |
| White | 443/487 (91) | 700/823 (85) | 523/573 (91) | |
| Black | 15/487 (3) | 13/823 (2) | 9/573 (2) | |
| Oriental | 19/487 (4) | 42/823 (5) | 18/573 (3) | |
| Other | 10/487 (2) | 68/823 (8) | 23/573 (4) | |
| Disease (%) | | | | <.0001, <.004 |
| ALL | 106/489 (22) | 149/833 (18) | 84/580 (14) | |
| AML | 254/489 (52) | 332/833 (40) | 199/580 (34) | |
| CML | 129/489 (26) | 352/833 (42) | 297/580 (51) | |
| Interval Dx-Tx (mo) | | | | |
| Median (range) | 6 (1-191) | 7 (1-144) | 8 (1-116) | <.0002, NS |
| Year of transplant (%) | | | | <.0001, <.0001 |
| 1980-81 | 88/489 (18) | 47/833 (6) | 3/580 (1) | |
| 1982-83 | 178/489 (36) | 150/833 (18) | 4/580 (1) | |
| 1984-85 | 155/489 (32) | 292/833 (35) | 46/580 (8) | |
| 1986-87 | 60/489 (12) | 242/833 (29) | 305/580 (53) | |
| 1988-89 | 8/489 (2) | 102/833 (12) | 222/580 (38) | |
| Conditioning regimen (%) | | | | <.0001, <.002 |
| CY + busulfan | 12/489 (2) | 88/833 (11) | 88/580 (15) | |
| CY + TBI | 378/489 (77) | 513/833 (62) | 354/580 (61) | |
| CY + TBI + other drugs | 73/489 (15) | 162/833 (19) | 104/580 (18) | |
| TBI + other drugs | 19/489 (4) | 66/833 (8) | 25/580 (4) | |
| Other | 7/489 (1) | 4/833 (<1) | 9/580 (2) | |
| Radiation schedule (%) | | | | <.0001, NS |
| Single dose | 197/474 (42) | 217/744 (29) | 121/484 (25) | |
| Fractionated dose | 277/474 (58) | 527/744 (71) | 363/484 (75) | |
| TBI dose (Gy), median (range) | 10.2 (5-15.75) | 10.2 (5-15.75) | 12 (5-14.4) | <.0003, <.09 |
| Additional post-Tx drugs (%) | | | | <.004, <.0001 |
| None | 316/489 (65) | 603/833 (72) | 504/580 (87) | |
| Steroids | 171/489 (35) | 228/833 (27) | 76/580 (13) | |
| Other | 2/489 (<1) | 2/833 (<1) | — | |
| Follow-up (mo), median (range) | 63 (4-125) | 48 (4-123) | 24 (3-109) | <.0001, <.0001 |

Abbreviations: Tx, transplant; Dx, diagnosis; NS, not significant.

* Based on $\chi^2$ for categorical and Mann-Whitney for continuous variables; first $P$ value refers to comparison of MTX with CsA, the second to comparison of CsA with MTX + CsA.

leukemia relapse, which was marginally increased with CsA. This persisted after adjusting for GVHD. In AML, interstitial pneumonia, treatment-related mortality, and treatment-failure were decreased with CsA. The latter association persisted, albeit less significantly, after adjusting for GVHD. In CML, there was also less interstitial pneumonia, treatment-related mortality, and treatment failure with CsA. These decreases persisted, with lower statistical significance, after adjusting for GVHD.

*CsA and MTX versus CY.* Actuarial probabilities and relative risks of transplant outcomes for patients receiving CsA and MTX compared with those receiving CY alone (reference group) are indicated in Table 4 and Fig 1. Overall, the combination was associated with less acute GVHD (Fig 1A), less chronic GVHD (Fig 1B), and less interstitial pneumonia (Fig 1C), but not with significantly less treatment-related mortality (Fig 1D). This was due to increased deaths from infection in the absence of GVHD in the group receiving combined therapy. Deaths from infection accounted for 11% of nonrelapse deaths with CsA alone, compared with 24% with CsA plus MTX ($P < .01$). Treatment failure was marginally decreased and LFS was marginally increased with combined therapy (Fig 1F). These associations were not significant after adjusting for GVHD.

In ALL and AML, CsA plus MTX significantly decreased acute GVHD with no effects on other transplant outcomes. In CML, acute GVHD was also decreased, as were interstitial pneumonia, treatment-related mortality, and treatment failure. These decreases were no longer significant after adjusting for GVHD, except for a marginal decrease in interstitial pneumonia.

## DISCUSSION

This study examined the effects of the three most commonly used immune suppressive treatments to prevent GVHD in recipients of HLA-identical sibling transplants with leukemia. These data show that results vary depending on age, leukemia type, and endpoints analyzed.

In children, there was no advantage to any specific GVHD prophylaxis regimen studied for any endpoint considered.

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**Table 3. Comparison of CsA Versus MTX (reference group, relative risk = 1.0). Two-Year Probability (±95% confidence intervals) and Relative Risk of Transplant Outcome in Adults After HLA-Identical Sibling BMTs for Early Leukemia**

| | | ALL + AML + CML (N = 1,322) | | | ALL (N = 255) | | | AML (N = 586) | | | CML (N = 481) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Outcome | Drug | Prob (%) | RR* | RR† | Prob (%) | RR* | RR† | Prob (%) | RR* | RR† | Prob (%) | RR* | RR† |
| AGVHD | MTX | 50 ± 5 | | | 50 ± 10 | | | 45 ± 7 | | | 59 ± 9 | | |
| | CsA | 43 ± 3 | 0.9 | — | 39 ± 8 | 0.9 | — | 40 ± 5 | 1.0 | — | 47 ± 5 | 0.9 | — |
| CGVHD | MTX | 50 ± 6 | | | 46 ± 13 | | | 50 ± 8 | | | 55 ± 12 | | |
| | CsA | 53 ± 4 | 0.9 | 0.9 | 53 ± 10 | 1.3 | 1.4 | 47 ± 7 | 0.7 | 0.8 | 61 ± 6 | 1.0 | 1.0 |
| IPn | MTX | 35 ± 5 | | | 25 ± 9 | | | 32 ± 6 | | | 48 ± 10 | | |
| | CsA | 26 ± 3 | 0.6‡ | 0.7§ | 21 ± 7 | 0.9 | 1.0 | 23 ± 5 | 0.7‖ | 0.7 | 32 ± 5 | 0.5‡ | 0.6§ |
| TRM | MTX | 47 ± 5 | | | 42 ± 10 | | | 45 ± 6 | | | 57 ± 9 | | |
| | CsA | 35 ± 3 | 0.6‡ | 0.7§ | 34 ± 8 | 0.9 | 1.0 | 29 ± 5 | 0.5‡ | 0.6‡ | 42 ± 5 | 0.6‡ | 0.8 |
| Relapse | MTX | 11 ± 4 | | | 12 ± 8 | | | 11 ± 5 | | | 11 ± 8 | | |
| | CsA | 14 ± 3 | 1.6‖ | 1.5‖ | 22 ± 8 | 2.2‖ | 2.2‖ | 19 ± 5 | 1.6 | 1.6 | 6 ± 3 | 0.9 | 0.8 |
| LFS¶ | MTX | 47 ± 5 | | | 51 ± 10 | | | 49 ± 6 | | | 39 ± 9 | | |
| | CsA | 56 ± 3 | 0.7‡ | 0.8‖ | 52 ± 9 | 1.1 | 1.2 | 58 ± 6 | 0.7§ | 0.7‖ | 54 ± 5 | 0.6§ | 0.8 |

Abbreviations: RR, relative risk; AGVHD, acute GVHD; CGVHD, chronic GVHD; IPn, interstitial pneumonia; TRM, transplant-related mortality.

* RR adjusted for age, race, interval from diagnosis to transplant, alloimmune female donor for male recipient, donor/recipient CMV status, CMV-negative blood products, prophylactic acyclovir, use of prophylactic immune globulin, conditioning regimen, addition of corticosteroids for GVHD prophylaxis, and use of ganciclovir.

† RR also adjusted for GVHD.

‡ $P < .001$.

§ $P < .01$.

‖ $P < .05$.

¶ RR here refers to risk of treatment failure (relapse or death).

This is perhaps not surprising because GVHD is considered less of a problem in children than adults.

In adults, CsA resulted in less treatment-related mortality and higher LFS rates than MTX. These benefits were detected in AML and CML but not in ALL. Interestingly, higher LFS rates resulted from less interstitial pneumonia and lower treatment-related mortality rather than decreased acute or chronic GVHD. Leukemia relapse was marginally higher with CsA in ALL but not in AML or CML. This increase in ALL persisted even after adjusting for GVHD and is consistent with a prior IBMTR study.[25] Long-term results of two randomized trials comparing MTX with CsA after transplants for leukemia also show a decreased incidence of relapse with MTX.[9,12]

Combined CsA and MTX resulted in less acute GVHD than CsA alone. Reductions in chronic GVHD and interstitial pneumonia were also detected in some instances, but were not significant after adjusting for acute GVHD. The major impact of combined therapy was in CML, in which treatment-related mortality and treatment failure were significantly decreased. These effects are probably the result of less GVHD, because they were no longer significant after this adjustment. There is no evidence that combined therapy increased relapse.

Our results agree with some but disagree with other reports of randomized trials comparing CsA, MTX, and the combination. This is not surprising in view of the complexity of issues addressed and the small numbers of patients studied in most trials. Most studies combined results in children and adults as well as leukemias and remission states. In none was it possible to stratify or adjust for important variables influencing transplant outcome. The impact of these limitations is illustrated by the observation that patients receiving MTX alone in these trials had grade II to IV acute GVHD incidences ranging from 21% to 71%.[5-11] This difference is much greater than differences observed between the treatment arms in any of these reports.

Two additional aspects of our study warrant further discussion: the impact of MTX on interstitial pneumonia and the impact of GVHD prophylaxis on leukemia relapse.

We previously reported that prophylaxis of GVHD using MTX is associated with more interstitial pneumonia than CsA alone.[26,27] This was confirmed in this study, predominantly in persons with CML and to a lesser extent in AML; there was no increase in ALL. The effect persisted even after adjusting for GVHD and is consistent with a direct toxic effect of MTX. In contrast, there was no evidence that adding a brief course of MTX to CsA increased interstitial pneumonia over that observed with CsA alone.

This study is also consistent with our prior finding that use of MTX is associated with fewer relapses in ALL than use of CsA. However, there is no evidence that different GVHD prophylaxis affects the risk of leukemia relapse in AML or CML. Although one study reported more relapses with CsA and MTX than with either drug alone,[18] we found no evidence that combined therapy has more relapses than CsA alone. Reasons for this disparity are unclear. The present study involved considerably more patients and was adjusted for GVHD and for other variables influencing relapse.

Different strategies to prevent GVHD may affect diverse endpoints, such as interstitial pneumonia and relapse, differently. Consequently, the most important endpoint to evaluate is treatment failure. The data we present suggest that in children no specific GVHD prophylaxis is superior. In adults, CsA, when compared with MTX, is associated with fewer treatment failures in AML and CML but not in ALL.

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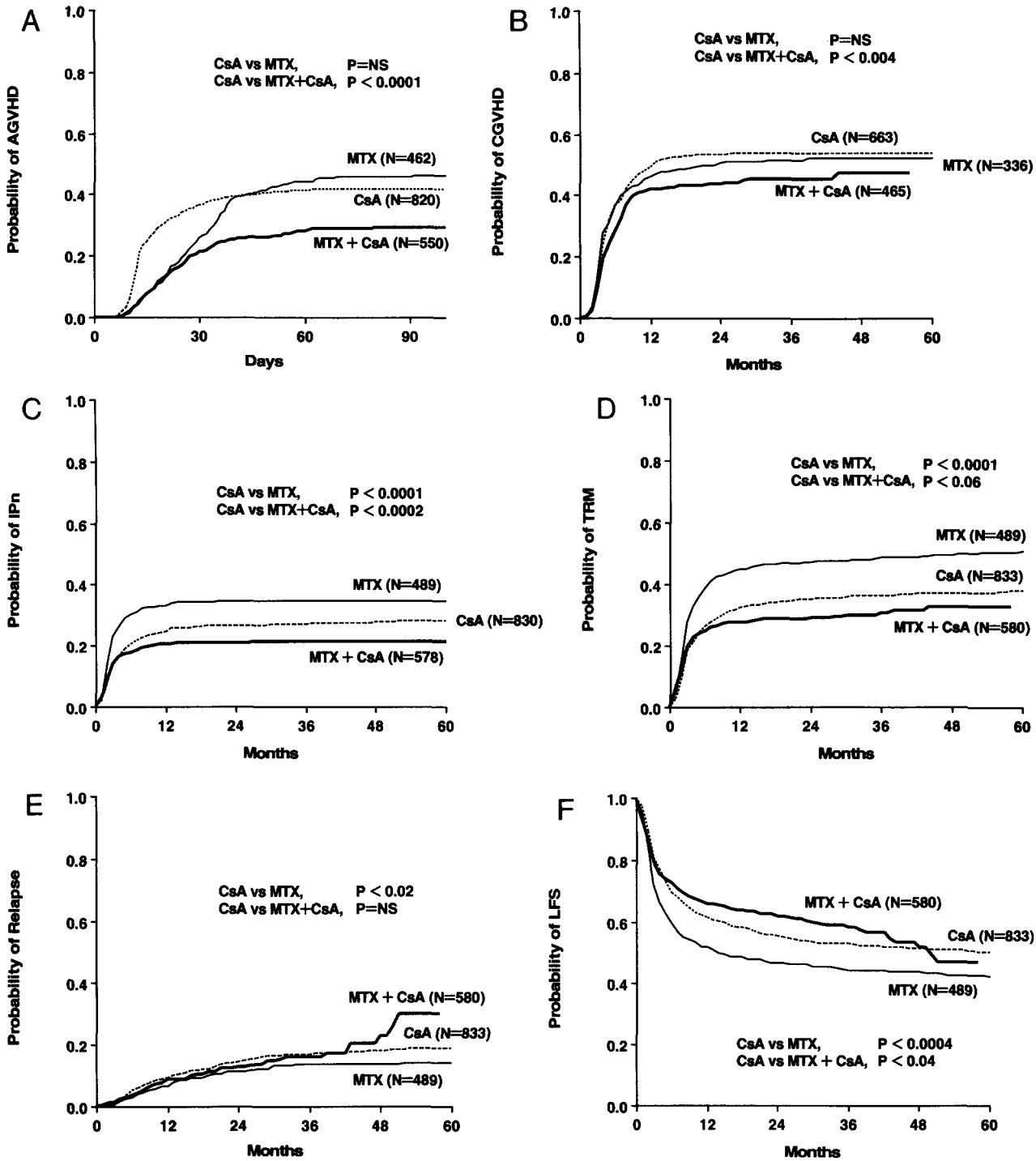


**Fig 1. Actuarial probability of (A) acute GVHD, (B) chronic GVHD, (C) interstitial pneumonia, (D) treatment-related mortality, (E) relapse, and (F) LFS after HLA-identical sibling transplants for early leukemia in adults according to method of GVHD prophylaxis. *P* values are from multivariate analyses (Tables 3 and 4).**

Combined CsA and MTX is superior to CsA in CML but not in ALL or AML.

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**Table 4. Comparison of Combined MTX and CsA Versus CsA (reference group, relative risk = 1.0). Two-Year Probabilities (±95% confidence intervals) and Relative Risks of Transplant Outcome in Adults After HLA-Identical Sibling BMTs for Early Leukemia**

| | | ALL + AML + CML (N = 1,413) | | | ALL (N = 233) | | | AML (N = 531) | | | CML (N = 649) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Outcome | Drug | Prob (%) | RR* | RR† | Prob (%) | RR* | RR† | Prob (%) | RR* | RR† | Prob (%) | RR* | RR† |
| AGVHD | CsA | 43 ± 3 | | | 39 ± 8 | | | 40 ± 5 | | | 47 ± 5 | | |
| | MTX + CsA | 29 ± 4 | 0.5‡ | — | 19 ± 9 | 0.4§ | — | 27 ± 7 | 0.6§ | — | 32 ± 6 | 0.6‡ | — |
| CGVHD | CsA | 53 ± 4 | | | 53 ± 10 | | | 47 ± 7 | | | 61 ± 6 | | |
| | MTX + CsA | 44 ± 5 | 0.7§ | 0.8‖ | 29 ± 12 | 0.6 | 0.7 | 40 ± 9 | 0.8 | 0.9 | 50 ± 7 | 0.8 | 0.8 |
| IPn | CsA | 26 ± 3 | | | 21 ± 7 | | | 23 ± 5 | | | 32 ± 5 | | |
| | MTX + CsA | 21 ± 4 | 0.7‡ | 0.9 | 17 ± 9 | 0.9 | 1.0 | 21 ± 6 | 1.0 | 1.2 | 22 ± 5 | 0.6§ | 0.7‖ |
| TRM | CsA | 35 ± 3 | | | 34 ± 8 | | | 29 ± 5 | | | 42 ± 5 | | |
| | MTX + CsA | 29 ± 4 | 0.8 | 1.1 | 28 ± 10 | 0.9 | 1.1 | 30 ± 5 | 1.3 | 1.6‖ | 28 ± 5 | 0.6§ | 0.8 |
| Relapse | CsA | 14 ± 3 | | | 22 ± 8 | | | 19 ± 5 | | | 6 ± 3 | | |
| | MTX + CsA | 13 ± 4 | 1.0 | 1.4 | 23 ± 11 | 1.0 | 0.9 | 16 ± 7 | 0.8 | 0.7 | 7 ± 4 | 1.4 | 1.3 |
| LFS¶ | CsA | 56 ± 3 | | | 52 ± 9 | | | 58 ± 6 | | | 54 ± 5 | | |
| | MTX + CsA | 62 ± 4 | 0.8‖ | 1.0 | 55 ± 11 | 0.9 | 1.1 | 59 ± 7 | 1.1 | 1.2 | 66 ± 6 | 0.7§ | 0.9 |

Abbreviations: RR, relative risk; AGVHD, acute GVHD; CGVHD, chronic GVHD; IPn, interstitial pneumonia; TRM, transplant-related mortality.

* RR adjusted for age, race, interval from diagnosis to transplant, alloimmune female donor for male recipient, donor/recipient CMV status, CMV-negative blood products, prophylactic acyclovir, use of prophylactic immune globulin, conditioning regimen, addition of corticosteroids for GVHD prophylaxis, and use of ganciclovir.

† RR also adjusted for GVHD.

‡ $P < .001$.

§ $P < .01$.

‖ $P < .05$.

¶ RR here refers to risk of treatment failure (relapse or death).

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