Stem Cell Transplantation

Morbidity and non-relapse mortality after allogeneic bone marrow transplantation in adult leukemia patients conditioned with busulfan plus cyclophosphamide: a retrospective comparison of oral versus intravenous busulfan

We retrospectively compared morbidity and non-relapse mortality (NRM) after allogeneic bone marrow transplantation (BMT) in 236 adults with leukemia and myelodysplastic syndrome conditioned with cyclophosphamide plus oral versus intravenous busulfan. Our findings demonstrate that conditioning therapy with intravenous busulfan resulted in lower morbidity and NRM than did oral busulfan.

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Busulfan was administered orally in 181 patients from December 1993 through July 2002 (O-Bu group), and intravenously in 55 patients thereafter (I-Bu group). Patients in the O-Bu group received 1 mg/kg oral busulfan every 6 hours, whereas patients in the I-Bu group received 0.8 mg/kg intravenous busulfan over 2 hours every 6 hours. In all patients, oral or intravenous busulfan was administered for a total of 16 doses from day –7 to day –4, and cyclophosphamide at a dose of 60 mg/kg was given intravenously over 1-2 hours on days –3 and –2. Donor bone marrow was infused on day 0. All patients were prospectively monitored for the occurrence of post-transplant toxicities, including graft-versus-host disease (GVHD), hepatic veno-occlusive disease (VOD), infections, and other transplantation-related toxicities. Toxicities within 100 days after BMT were graded according to NCI Common Terminology Criteria for Adverse Events v3.0, which classifies each toxicity as grades I through to V. Grades III to V toxicities were recorded as severe.

Table 1 shows the pre-transplant characteristics of the patients in the O-Bu and I-Bu groups. Several of these baseline clinico-laboratory factors were not balanced between the two groups at the time of BMT.

Acute GVHD developed in 30.1% of all patients, but there was no significant difference between the O-Bu (29.8%) and I-Bu (30.9%) groups. The incidence of hepatic VOD was significantly higher in the O-Bu group (42.0%) than in the I-Bu group (18.2%) (p=0.001). This significant difference was maintained when only the patients receiving methorexate were analyzed (p=0.003). In addition, 11 patients (6.1%) in the O-Bu group had severe hepatic VOD, compared with none in the I-Bu group. Of toxicities within 100 days after BMT, grade III to V gastrointestinal bleeding (p=0.004), diarrhea (p=0.026), coagulation abnormalities (p=0.007), and metabolic abnormalities (p=0.042) were significantly less frequent in the I-Bu group than in the O-Bu group (Table 2).

With a median follow-up of 1,185 days (range, 48-3,010 days) in the O-Bu group and 290 days (range, 68-484 days) in the I-Bu group among non-relapsed surviving patients, NRM was lower in the I-Bu group (13.8%, 7 non-relapse deaths) than in the O-Bu group (24.4%, 41 non-relapse deaths), this difference being statistically significant (p=0.048; odds ratio, 0.403; 95% confidence interval, 0.164-0.991) after adjustment for unbalanced pre-transplant patient characteristics between the two groups. We also analyzed the effects of post-transplant toxicities on NRM. Of the toxicities that occurred at a significantly higher incidence in the O-Bu group, all except hypomagnesemia were associated with significantly higher NRM.

Table 1. Patients' pre-transplant characteristics.

	O-Bu group (n=181)	*I-Bu group (n=55)*	*p value*
Sex (M/F)	97/84	33/22	0.403
Age, years (≤40 vs. >40)	147/343	35/20	0.007
Diagnosis (AML vs. ALL vs. CML/MPD vs. MDS)	79/36/50/16	20/20/9/6	0.053
Disease status at BMT (low vs. high risk)	129/52	45/10	0.120
ABO incompatibility (no vs. yes)	99/82	27/28	0.466
Sex pair, donor-recipient (female-male vs. other)	44/137	8/47	0.126
Bone marrow donor (sibling vs. unrelated)	138/43	41/14	0.797
Days from diagnosis to BMT (≤140 vs. > 140)	99/82	16/39	0.001
Pre-transplant transfusion, units (≤60 vs. > 60)	95/86	21/34	0.063
History of liver disease prior to BMT (no vs. yes)	159/22	41/14	0.016
AST, IU/L (≤40 vs. > 40)	128/53	36/19	0.458
ALT, IU/L (≤40 vs. > 40)	166/15	41/14	0.001
GVHD prophylaxis (CSA vs CSA/MTX)	29/152	18/37	0.007
Use of antibiotics just before BMT (no vs. yes)	176/5	47/8	0.001
Mononuclear cell dose, $\times 10^8$/kg (≤1.0 vs. > 1.0)	118/61	43/12	0.086
CD34$^+$ cell dose, $\times 10^6$/kg (≤3.0 vs. > 3.0)	74/100	12/43	0.006

AML, acute myelogenous leukemia; ALL, acute lymphoblastic leukemia; CML, chronic myeloid leukemia; MPD, myeloproliferative disorder; MDS, myelodysplastic syndrome; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CSA, cyclosporine; MTX, methotrexate.

Until recently, busulfan has been available only as an oral formulation. Oral busulfan does, however, show wide variability in bioavailability,[1] thus hampering the effectiveness of conditioning regimens. Hepatic VOD is one of the major toxicities of oral busulfan plus cyclophosphamide.[2-4] We found that the incidence of hepatic VOD was significantly lower in the I-Bu group than in the O-Bu group, in agreement with previous studies reporting a low incidence of hepatic VOD in patients treated with intravenous busulfan.[5] This may be because erratic absorption and a hepatic first pass effect of oral busulfan are avoided.[6,7] We also found that the incidences of severe gastrointestinal bleeding and diarrhea were significantly higher in the O-Bu group than in the I-Bu group, suggesting that patients receiving high dose oral busulfan may be more susceptible to gastrointestinal mucosal injury. This finding may be related to the erratic absorption of the drug in that gastrointestinal epithelium is the tissue that absorbs oral busulfan and localized exposure to high busulfan concentrations may increase cell death.[8] The lower incidence of post-transplant toxicities in the I-Bu group translated into decreased NRM.

Our results have some limitations, mostly due to the fact that the study was retrospective. Although we tried to adjust for several unbalanced factors between two groups through multivariate analysis, the different time periods in which the patients in the two groups were treated might also have influenced the results. Pharmacokinetic monitoring of oral busulfan has been reported to reduce NRM.[9,10]

Table 2. Incidence of severe toxicities within 100 days after allogeneic BMT.*

	O-Bu group/I-Bu group (%)	p value
Pulmonary toxicities	7.7/5.5	0.567
Pleural effusion	2.2/1.8	0.860
Pulmonary infiltrates	7.2/5.5	0.655
Pneumothorax	0.6/0.0	0.581
Cardiac toxicities	1.1/0.0	0.434
Hypertension	0.6/0.0	0.581
Pericardial effusion	0.6/0.0	0.581
Bleeding complications	26.0/16.4	0.143
CNS bleeding	3.9/0.0	0.139
GI bleeding	19.3/5.5	0.014
Hematuria	6.6/10.9	0.295
Other bleeding	2.8/1.8	0.697
GI toxicities	76.1/69.1	0.296
Stomatitis	60.8/49.1	0.124
Nausea/vomiting	27.1/30.9	0.579
Diarrhea	14.9/3.9	0.026
Pancreatitis	1.1/0.0	0.434
Ascites	4.4/0.0	0.113
Hepatic toxicities	57.5/49.1	0.274
AST, increase	29.8/25.5	0.530
ALT, increase	48.1/45.5	0.734
ALP, increase	1.7/0.0	0.335
Bilirubin, increase	22.1/10.9	0.067
Albumin, decrease	12.2/5.5	0.157
Renal toxicities		
Serum Cr, increase	2.2/0.0	0.266
Infectious complications		
Febrile neutropenia	89.0/90.9	0.679
Coagulation abnormalities	28.7/10.9	0.007
PT prolongation	7.8/0.0	0.033
aPTT prolongation	24.9/10.9	0.028
Thrombotic microangiopathy	2.2/0.0	0.266
Metabolic abnormalities	86.7/74.5	0.031
Hyper- or hypo-calcemia	0.6/0.0	0.579
Hyperphosphatemia	28.5/27.3	0.861
Hypercholesterolemia	1.1/0.0	0.434
Hyperuricemia	5.6/5.5	0.977
Hyperglycemia	42.5/34.5	0.290
Hypoglycemia	4.4/3.6	0.801
Hypernatremia	3.9/3.6	0.938
Hyponatremia	64.1/38.2	0.001
Hyperkalemia	7.7/7.3	0.910
Hypokalemia	49.2/40.0	0.233
Hypermagnesemia	3.9/0.0	0.139
Hypomagnesemia	20.4/7.3	0.024
Neurologic toxicities	2.8/0.0	0.213
Seizure	0.6/0.0	0.337
Decrease of consciousness	1.7/0.0	0.581
Other	0.6/0.0	0.581

** Toxicities were graded by CTCAE v3.0 and grades III to V toxicities were recorded as severe. GI, gastrointestinal; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; Cr, creatinine; PT, prothrombine time; aPTT, activated partial thromboplastin time*

Because we did not perform pharmacokinetic studies of oral busulfan, we could not compare the cost-benefit issue of intravenous busulfan and targeted oral busulfan. The only way to truly compare the 2 formulations would be to conduct a prospective, randomized comparison.

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