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# Prospective multicenter phase II study of myeloablative conditioning consisted of intravenous busulfan and fludarabine +/- total body irradiation for older patients (55 years and older): Results of the JSCT FB09 study.

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Introduction: Allogeneic hematopoietic stem cell transplantation (allo-SCT) using reduced-intensity conditioning has been widely applied to those who are not eligible for conventional conditioning, such as elderly patients. However, benefit provided by reduced toxicity has been offset by increased incidence of relapse. So far, the optimal conditioning for elderly patients has not been established. To investigate whether myeloablative dose of intravenous busulfan (ivBu) can be used for elderly recipients, multicenter phase II study has been conducted. Design and Methods: This study started in September 2009, and 32 centers have participated. The protocol was approved by each institutional review board (Trial identifier: UMIN000002426). Patients aged from 55 to 70 with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) who

were in 0-2 ECOG PS and were planned for allo-SCT (bone marrow (BM), peripheral blood (PB), and cord blood (CB)) without end organ damage were enrolled after obtaining written informed consent. Pretransplant conditioining consisted of 30 mg/m$^2$ of fludarabine (Flu) for 6 days (total 180 mg/m$^2$) and 3.2 mg/kg of ivBu for 4 days (divided by 4 daily, total 12.8 mg/kg). Four gray of total body irradiation (TBI) was used for all cord blood transplant recipients, whereas 2 gray of TBI was used in other stem cell sources except a matched related donor according to each institutional policy. Calcineurine inhibitors (cyclosporine or tacrolimus) + short term methotrexate were used as GVHD prophylaxis for BM or PB recipients, while tacrolimus + mycophenolate mofetil were used for CB recipients. Donor cell engraftment and 60 day-survival were assessed as a primary end point to evaluate feasibility of this protocol for elderly patients. Pharmacokinetic analysis of ivBu measured by HPLC was also performed at institutes in which a separate protocol on PK study was approved. Results: Thirty-eight patients were enrolled. Median age was 60 (55-68), 22 were male, and 16 were female. Thirty-one were AML and 7 were MDS. Donors were 8 matched related BM/PB, 2 1-Ag/allele-mismatched related BM/PB, 8 matched unrelated BM, 4 1-Ag/allele-mismatched unrelated BM, and 16 ≤2-Ag-mismatched CB. So far, 31 patients have passed 60-day-point post-transplant, and 26 CRFs have been obtained. All the reported recipients have engrafted (25/25) with complete donor-type chimerism, except one who died before engraftment due to cerebral hemorrhage (male CB recipient, 62y). There were 2 cases of grade IV toxicity observed (1 SOS and 1 hyperbilirubinemia likely to be caused by GVHD) within 60 days post-transplant. There were 3 deaths post-engraftment due to DAH (1 male CB recipient, 62y, day 63), SOS (1 male CB recipient, 55y, day 69), and GVHD (1 male UBM recipient, 61y, day 81). No relapse was observed up to day 60. Overall survival and event-free survival were estimated to be 84 % and 77 % at 100 days post-transplant. PK study obtained from 10 patients showed comparable AUC level (1043 (820-1233) μmol·min/L) as that from younger patients, and there were no clinically significant increase of serum concentration observed. Conclusions: Myeloablative conditioning using Flu/ivBu12.8 mg/kg +/- TBI was well tolerated with acceptable low toxicities and was sufficient to allow donor cell-engraftment post allo-SCT for elderly patients with AML or MDS. Longer follow up and another prospective multicenter study enrolling more patients are required to evaluate the eventual survival benefit by reducing

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