

The role and significance of MDSC-like myeloid blasts in immune-tolerance of AML

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Myeloid-derived suppressor cells (MDSCs) is a heterogenous cell population, consisting of myeloid progenitor cells and immature myeloid cells and having an ability to suppress T-cell function. Due to their suppressive effects on immunity, MDSCs can lead to facilitate tumor development and growth, and has been known to be associated with poor prognosis in various solid cancers. However, the role of MDSC in myeloid neoplasm are unclear. So, we elucidated the role of leukemic subpopulation showing CD11b + CD33 + HLA-DR- immunophenotype, which resembles MDSCs. CD11b + CD33 + HLA-DR- blast were isolated using flow-cytometry from bone marrow mononuclear cell sample, which were collected at the time of diagnosis by Acute Leukemia Cohort Study in Severance. The clinical impact of MDSC-like blasts was retrospectively reviewed in 63 patients. CD33 + HLA-DR- leukemic cells from each patients showed various range of expression for CD11b (Mean±SD, 21.02±22.19%). MDSCs can be divided into two subtypes, monocytic MDSC expressing CD14 and granulocytic MDSC expressing CD15, and CD14 expression on MDSC-like blast expression was more frequent than CD15 expression (67.5% vs. 39.3%). To figure out the immunosuppressive activity in MDSC-like blasts, Arg1 and iNOS expression were checked, and MDSC-like blasts showed significantly higher expression of Arg1 (77.1% vs. 38.5%, $p < 0.001$) and iNOS (33.0% vs. 1.1%, $p < 0.0001$) compared to non-MDSC-like blasts. Compared to 'Lower MDSC group', WBC count, serum LDH, fraction of blasts in bone marrow, and frequency of adverse cytogenetics were significantly higher in 'Higher MDSC group'. Patients in 'High MDSC group' had significantly shorter overall survival (331±42 vs. 758±114 days, $p = 0.027$). On multivariate analysis, higher fraction of CD11b + CD33 + HLA-DR- leukemic cells (HR 2.966, 95%CI 1.086-8.095, $p = 0.034$), old age ($p = 0.001$), adverse cytogenetics ($p = 0.013$), and FAB classification ($p = 0.035$) were poor prognosis factors. CD33 + HLA-DR- MDSC-like blasts subgroup is existed in myeloid leukemic blasts with various range. Because they suppressed T cell immunity, also showed adverse prognostic effect on survival, MDSC-like blasts might play a certain role in immune-tolerance in leukemia.

The sequence of TBI and cyclophosphamide in acute leukemia with alloHCT as a risk factor for BOS

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Introduction: Total body irradiation (TBI) plus cyclophosphamide (CY) has been used as a transplantation conditioning regimen for more than 30 years. TBI based regimens have been known to be associated with higher incidence of acute GVHD, long-term pulmonary and ocular complications caused by cytokine effects and endothelial damage. Several previous data discussed about the sequence of CY and other toxic regimens in association with several complications. In this study, we tried to compare the clinical outcomes between TBI plus CY vs. CY plus TBI. **Methods:** We conducted a retrospective analysis of 213 acute leukemia patients (AML (n = 146) and ALL (n = 67)) who underwent allogeneic hematopoietic cell transplantation (allo-HCT) between January 2006 and December 2013. All patients received conditioning regimen consisted of TBI followed by CY (TBI-CY, n = 114) or CY followed by TBI (CY-TBI, n = 99). All 213 patients were transplanted from HLA-matched sibling donors and achieve complete remission on first induction chemotherapy. We analyzed the incidence of acute and chronic GVHD, and bronchiolitis-obliterans syndrome (BOS) according to the sequence of the regimen. **Results:** Between the 2 groups (TBI-CY vs. CY-TBI), 5-year OS (68.4% vs. 69.4%, $p = 0.998$), DFS (65.4% vs. 67.2%, $p = 0.633$), CIR (20.9% vs. 16.2%, $p = 0.40$), and NRM (13.8% vs. 14.4%, $p = 0.87$) was not significantly different, Acute GVHD was not significantly different between the 2 groups (61.0% vs. 54.5%, $p = 0.469$), chronic GVHD also shown no statically significant between the 2 groups (55.1 vs 49.5 $p = 0.684$) BOS was more common in TBI-CY group (16.3% vs. 6.1%, $p = 0.017$). For BOS, our data showed lower pre-transplantation pulmonary function test (FEV1/FVC < 70) and PB as a stem cell source was associated with higher incidence of BOS. Final multivariate analysis also revealed that TBI-CY (HR = 2.40, 95%CI 1.0-5.7, $p = 0.048$), PB stem cell source (HR = 3.10, 95%CI 1.4-6.6, $p = 0.034$) FEV1/FVC < 70 (HR 3.070, 95%CI 1.6-5.8 $p = 0.006$) was significantly associated with BOS. **Conclusions:** Sequence of TBI-CY was significantly associated with development of BOS compared to CY-TBI, although OS, CIR rate and incidence of acute/chronic GVHD were not significantly different.