Dose-Rate Dependent Differences in Genomic Alterations and Cell Differentiation Stages of Murine Leukemias Induced by Continuous Low-Dose-Rate Gamma-Ray Irradiation

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Abstract

Continuous γ-ray irradiation at low-dose-rate (LDR) of 20 mGy/22h/day for 400 days highly induced leukemias in mice. However, little is known about the mechanism for development of leukemias induced by LDR-irradiation. In this study, relationships between regional chromosomal copy number aberrations and cell differentiation stages were analyzed in leukemias induced by γ-ray irradiation at three different dose rates. C3H/He Nrs mice were irradiated at LDR (total dose of 8 Gy at 20 mGy/22h/day), medium-dose-rate (MDR: total dose of 4 Gy at 400 mGy/22h/day) and high-dose-rate (HDR: total dose of 3 Gy at 1.0 Gy/min). All leukemias were classified into two groups (one with partial hemizygous deletion on chromosome 2 and the other without any deletion) according to array CGH results. The majority of leukemias from non-irradiated mice (non-irradiated leukemias) and LDR radiation-induced leukemias (LDR leukemias) had no deletions around the qE3 region of chromosome 2 and 30% of MDR radiation-induced leukemias (MDR leukemias) and all of HDR radiation-induced leukemias (HDR leukemias) had partial hemizygous deletion on chromosome 2. Differentiation stages of leukemic cells in the bone marrow and spleen cells analyzed by flowcytometry were highly coincident with presence or absence of chromosome 2. Increase of the common lymphoid progenitor-like cell population was frequently found in leukemias without deletion of chromosome 2. In contrast, leukemias with hemizygous deletion of chromosome 2 showed expansion of the common myeloid progenitor-like cell population. Furthermore, transplantation of 100 leukemic cells isolated from each of 7 cell differentiation stages into a syngeneic mouse revealed that leukemic stem cells of leukemias without chromosome 2 deletions were involved in common lymphoid progenitor cells, showing CD45R/B220^{pos} and Gr-1^{pos} phenotypes, while those of leukemias with partial hemizygous deletion on chromosome 2 were involved in hematopoietic stem cells or common myeloid progenitor-like cells. These findings indicate a possibility that γ-ray irradiation at different dose rates might induce leukemic stem cells with different origins and differentiation stages.

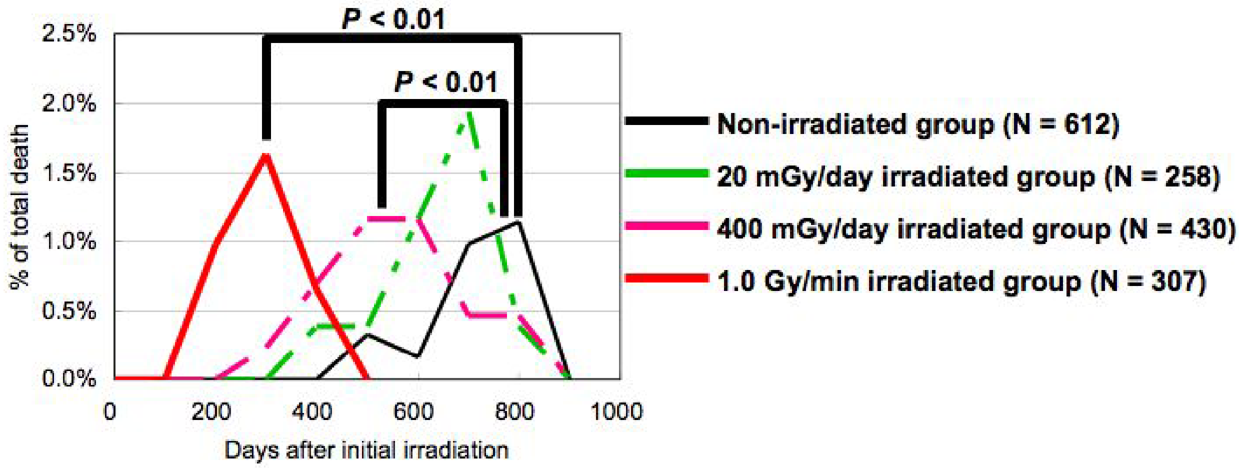

Fig. 1 Comparison of days until onset of leukemias after transplantation of leukemia cells

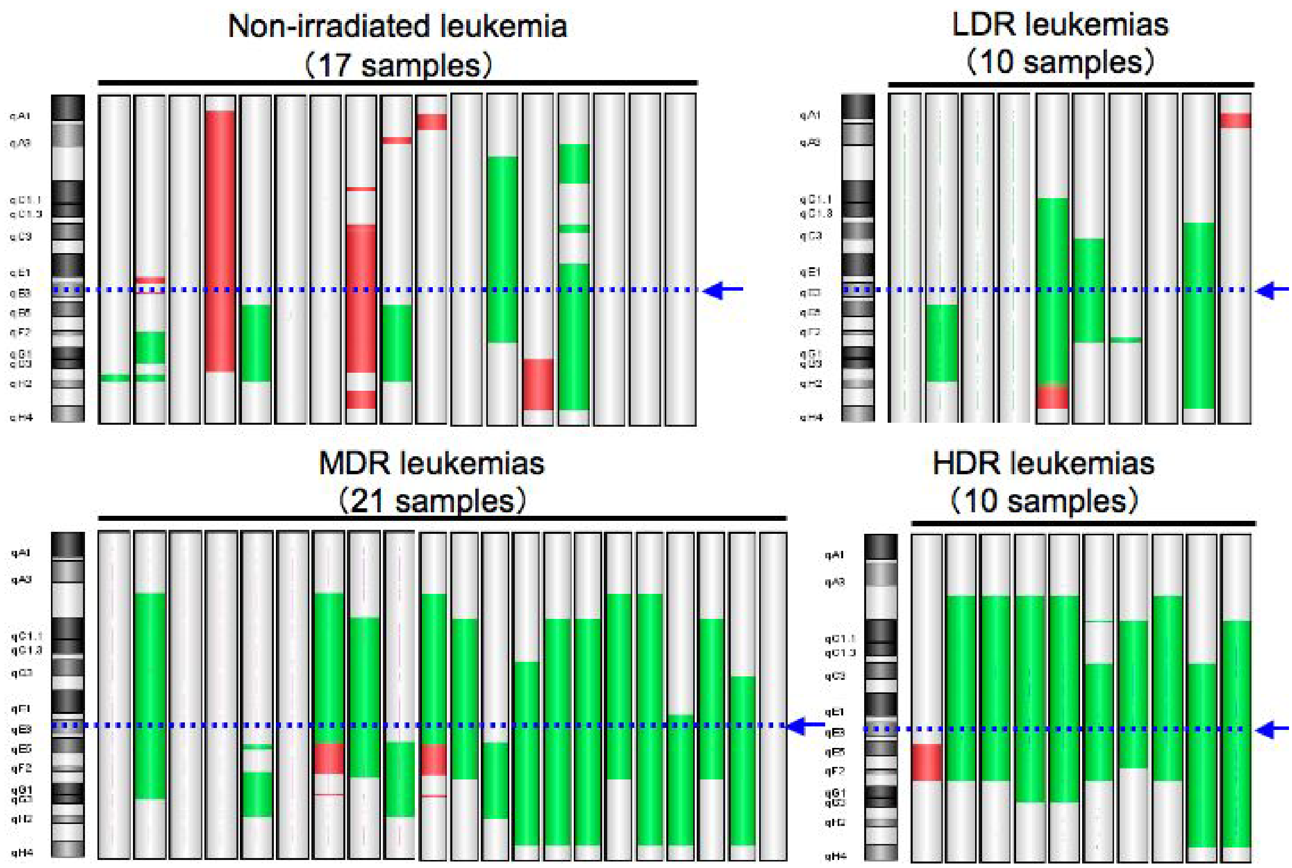

Fig. 2 Chromosomal aberrations among four leukemia groups (Non-irradiated, LDR, MDR and HDR leukemias). Red and green regions on each chromosome showed regions with gain and loss, respectively. Blue dotted lines indicate the region of mapping of the *PU.1* locus.