Clinical features and prognosis of patients with myelodysplastic syndromes who were exposed to atomic bomb radiation in Nagasaki

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M yelodysplastic syndromes comprise a heterogeneous group of clonal hematopoietic stem cell disorders characterized by ineffective hematopoiesis, morphological dysplasia, and leukemic transformation.(1) Most MDS arise primary or de novo without known causative agents, but approximately 15–20% of MDS develop following cytotoxic chemotherapy and/or radiotherapy for a primary malignancy,(2) which are classified as t-MDS or/and t-MDS/t-AML.(3) or, recently, included into therapy-related myeloid neoplasms.(4) It is known that approximately 30% of patients with primary MDS will progress to AML. In order to assess the risk of leukemic transformation and poor survival of primary MDS, several risk-scoring systems have been proposed, such as the IPSS,(5) the IPSS-R,(6) and the WHO Classification-based Prognostic Scoring System.(7)

The pathogenesis of primary MDS remains elusive. A multi-step pathogenesis model has been widely accepted from initial damage to hematopoietic stem cells caused by genotoxic or environmental agents followed by additional genetic or cytogenetic changes. However, the established causative factors for primary MDS also remain elusive. Aging, male sex, and environmental exposure to smoking, benzene, and ionizing radiation have been suggested as risk factors for developing primary MDS in the general population.(8) Of the suggested
risk factors, ionizing radiation is a well-known carcinogen that induces chromosomal and genetic abnormalities. The association between non-therapeutic ionizing radiation and the incidence of primary MDS were reported in a UK case-control study. In the previous study, we found that patients with primary MDS were included who were diagnosed with progressive bone marrow blast counts in bone marrow, cytogenetic examination, the FAB classification, and the 2000 WHO classification. We also accumulated information on outcome data including date of death, date of progression to overt leukemia, and the last recorded follow-up date until March 2014.

After classified into subtypes according to the FAB and WHO classifications, we combined the subtypes into RA, RARS, RAEB/RAEB-t, WHO-RCMD, and WHO-RAEB-1/RAEB-2, because of the small number of cases in this study. Cytogenetic information was obtained as a karyotype report during the routine diagnostic procedure at the respective hospitals, which were described in accordance with the International System for Human Cytogenetic Nomenclature version at the time of diagnosis. Risk category by cytogenetics was then classified into good, intermediate, and poor according to the IPSS, or into very good, good, intermediate, poor, and very poor according to the IPSS-R. Clinical risk was stratified using IPSS (low, INT-1, NT-2, and high). We did not evaluate the IPSS-R prognostic risk categories and the WHO Classification-based Prognostic Scoring System score because data on bone marrow blast percentage and transfusion-dependency were not fully available.

Radiation exposure status. Available data regarding radiation exposure status include sex, age in years at the time of the A-bomb, exposure distance in km from the hypocenter, and death and migration dates. Exposure dose estimate was not available. Age at exposure was treated as a continuous variable, categorized into 5-year groups, or dichotomized (<19 and ≥20 years). Exposure distance in km was categorized into three groups (<1.5, 1.5–2.99, and 3.0–10.0 km). The cut-off values for exposure distance were chosen on the basis of our previous report. Roughly speaking, the cut-off point of exposure distance 1.5 km corresponds to approximate exposure radiation dose of 1 Gy and 3.0 km corresponds to 0.005 Gy, if exposed outside without shielding.

Statistical analysis. Frequencies of categorical variables were compared using the χ²-test or Fisher’s exact test. Continuous variables are presented as the median with ranges and compared with the use of Wilcoxon’s rank-sum test or the Kruskal–Wallis test, or were categorized into several groups as necessary. Cumulative probabilities and the 95% CI of OS and EFS were estimated by the Kaplan–Meier method, and compared between groups using the log-rank test. Overall survival was censored at the time of death or last follow-up. Event-free survival was censored at the time of death, progression to overt leukemia, or last follow-up, whichever occurred first. Effects of factors on OS and EFS were evaluated by using univariate and multivariate Cox regression hazard models. In multivariate analyses, interactions between factors were also tested. Cumulative incidence rate of leukemic transformation was estimated by taking into account the competing risk of non-leukemic death, and compared between groups using Gray’s test. Statistical analyses were carried out using SAS version 9.3 (SAS Institute, Cary, NC, USA), R version 2.12.1 (R Foundation, Vienna, Austria), and EZR version 1.27 (Saitama Medical Center, Jichi Medical University, Saitama, Japan).

Results

Patient characteristics. Among 226 patients, 86 were not evaluable for IPSS or IPSS-R due to the lack of information.
Therefore, a total of 140 patients who were evaluable for IPSS was included in this analysis. Of those, 31 (22.1%) were exposed at a distance within 1.5 km, 35 (25.0%) at 1.5–2.99 km, and 74 (52.9%) at over 3.0 km.

Demographic characteristics of the 140 patients are given in the left column of Table 1. Of the 140 patients, 73 (52%) were male, and 106 (75.7%) were exposed at an age younger than 20 years, with median exposure age of 15.5 years (range, 0.3–40.6 years), and 78 (56%) were diagnosed in the period 1995–2004. Median age at diagnosis was 72.0 years (range, 42.0–94.6 years). The median latency from the time of A-bombing to the date of MDS diagnosis was 55.6 years (range, 39.7–67.8 years).

Clinical characteristics of the 140 patients are given in the left column of Table 2. According to the FAB classification, 95 (68%) were classified into RAEB/RAEB-t. According to the WHO classification, 94 (66%) were classified into RAEB/RAEB-t. According to the IPSS-R cytogenetics, 51 (44%) were classified into the INT/poor/very poor group.

R cytogenetics, 51 (44%) were classified into the INT/poor/very poor group.

There were no statistically significant differences among exposure distance groups in the OS (Fig. 1a) and EFS (Fig. 1b), although patients exposed at <1.5 km tended toward worse OS and EFS than those exposed at 3.0–10.0 km, in particular at the time of the 10-year follow-up.

There was also no statistically significant difference among exposure distance groups in the CIR of progression to overt leukemia (Fig. 2a), although patients exposed at <1.5 km and 1.5–2.99 km tended to have a higher progression to overt leukemia. When we analyzed CIRs of progression to overt leukemia and deaths without leukemic transformation as a competing event by exposure distance, patients who were exposed at <1.5 km and 1.5–2.99 km tended to progress to overt leukemia.

### Table 1. Demographic characteristics of patients with myelodysplastic syndromes who were exposed to atomic bomb radiation in Nagasaki, grouped by radiation exposure status

| Characteristics | n (%) or median (range) | Exposure distance† | P for difference among three groups | P for difference between <1.5 km vs ≥3.0 km |
|-----------------|------------------------|-------------------|-----------------------------------|------------------------------------------|
| No. of patients | 140                    | 31 35 74          |                                   |                                          |
| Sex             |                        |                   |                                   |                                          |
| Male            | 73 (52)                | 16 (52) 21 (60)   | 36 (49)                           | 0.54 0.78                                |
| Female          | 67 (48)                | 15 (48) 14 (40)   | 38 (51)                           |                                          |
| Age at exposure‡ |                       |                   |                                   |                                          |
| <20             | 106 (76)               | 25 (81) 28 (80)   | 53 (72)                           | 0.48 0.34                                |
| ≥20             | 34 (24)                | 6 (19) 7 (20)     | 21 (28)                           |                                          |
| Age at diagnosis§ |                      |                   |                                   |                                          |
| <2             | 70 (50)                | 14 (45) 17 (49)   | 39 (53)                           | 0.77 0.78                                |
| ≥2             | 70 (50)                | 17 (55) 18 (51)   | 35 (47)                           |                                          |
| Year of diagnosis |                     |                   |                                   |                                          |
| 1985–1994       | 24 (17)                | 5 (16) 6 (17)     | 13 (18)                           | 0.94 0.70                                |
| 1995–2004       | 78 (56)                | 19 (61) 20 (54)   | 39 (53)                           |                                          |
| 2005–2013       | 38 (27)                | 7 (23) 9 (25)     | 22 (30)                           |                                          |
| Time from exposure, years | 55.6 (39.7–67.8) | 55.6 (39.7–67.5) | 55.4 (40.2–89.9) | 0.88 0.62                                |

†The cut-off values of 1.5 and 3.0 km were chosen according to previous studies.‡ The cut-off point of exposure distance 1.5 km corresponds to an approximate exposure radiation dose of 1 Gy, and 3.0 km corresponds to 0.005 Gy, if exposed outside. §Cut-off value of 20 years was chosen according to previous studies. ‖Cut-off value of 72 years was chosen according to median.
leukemia earlier, within 10 years after the diagnosis of MDS (Fig. 2b, c), although there was no statistical significance. In fact, patients exposed at <1.5 km tended toward a shorter interval from MDS diagnosis to overt leukemia (median, 0.9 years) (Table 3). In contrast, in patients who were exposed at 3.0–10.0 km, the CIR of non-leukemia death was greater among three groups (Table 3). In particular, abnormal karyotype was observed in 77% of patients exposed at <1.5 km; the rate of which is similar to those of t-MDS exposed to cytotoxic agents. It is well known that the cytogenetic risk categories of currently available prognostic scoring systems for de novo MDS (IPSS and IPSS-R) are highly significant factors for the prognosis of MDS. However, exposure distance was not a statistically significant independent risk factor for the progression of overt leukemia, nor OS, although patients exposed at the more proximal distance tended toward a shorter interval from MDS diagnosis to overt leukemia. It is possible that the number of cases in this study was not large enough to properly reflect the prognostic power of “the distance from the hypocenter”, or the prognostic impact of karyotype might be different between MDS related to A-bomb radiation and general MDS such as de novo and therapy-related.

### Discussion

This is the first study evaluating the impact of A-bomb exposure status in terms of clinical characteristics, progression to overt leukemia, and survival of primary MDS that occurred in Nagasaki A-bomb survivors. The major findings in the present study were that “the more proximally exposed to A-bomb (probably exposed to the higher radiation dose)” was associated with developing MDS having a higher risk of cytogenetic abnormalities such as IPSS INT/poor cytogenetic and IPSS-R INT/poor/very poor cytogenetic categories. In particular, abnormal karyotype was observed in 77% of patients exposed at <1.5 km, the rate of which is similar to those of t-MDS exposed to cytotoxic agents. It is well known that the cytogenetic risk categories of currently available prognostic scoring systems for de novo MDS (IPSS and IPSS-R) are highly significant factors for the prognosis of MDS. However, exposure distance was not a statistically significant independent risk factor for the progression of overt leukemia, nor OS, although patients exposed at the more proximal distance tended toward a shorter interval from MDS diagnosis to overt leukemia. It is possible that the number of cases in this study was not large enough to properly reflect the prognostic power of “the distance from the hypocenter”, or the prognostic impact of karyotype might be different between MDS related to A-bomb radiation and general MDS such as de novo and therapy-related.

Although there was no statistically significant difference among exposure distance groups, the present study revealed that OS (Fig. 1a) and EFS (Fig. 1b) were lower in patients exposed at >2.5 km from the hypocenter compared to those exposed at <1.5 km (P = 0.001 vs >2.5 km, 0.001 vs >2.5 km). This suggests that exposure distance is an important factor in the prognosis of MDS.

### Table 2. Clinical characteristics of patients with myelodysplastic syndromes who were exposed to atomic bomb radiation in Nagasaki, grouped by radiation exposure status

| Characteristics | n (%) or median (range) | Exposure distance | P for difference among three groups | P for difference between <1.5 km vs ≥3.0 km |
|-----------------|-------------------------|------------------|-----------------------------------|-------------------------------------|
| No. of patients | 140                     | 31               | 35                                | 74                                  |
| FAB classification |                        |                  |                                   |                                     |
| RA/RARS         | 95 (68)                 | 20 (65)          | 24 (68)                           | 51 (69)                             | 0.950 0.720 |
| RAEB/RAEB-t     | 38 (27)                 | 10 (32)          | 9 (26)                            | 19 (26)                             | 0.530 0.830 |
| CMML            | 7 (5)                   | 1 (3)            | 2 (6)                             | 4 (5)                               |                                     |
| WHO 2000 classification, n (%) |        |                  |                                   |                                     |
| RA/RARS         | 68 (49)                 | 13 (42)          | 20 (57)                           | 35 (47)                             | 0.530 0.830 |
| RAEB/RAEB-t     | 33 (23)                 | 9 (29)           | 6 (17)                            | 18 (24)                             |                                     |
| RAEB/RAEB-t/RCMD | 36 (26)                 | 8 (29)           | 10 (33)                           | 18 (25)                             |                                     |
| Raeb/RAEB-t     | 33 (23)                 | 9 (29)           | 6 (17)                            | 18 (24)                             |                                     |
| RAEB/RAEB-t/RCMD | 36 (26)                 | 8 (29)           | 10 (33)                           | 18 (25)                             |                                     |
| Others          | 13 (9)                  | 2 (6)            | 5 (14)                            | 6 (8)                               |                                     |
| Blood counts, median (range)† | |                  |                                   |                                     |
| Hemoglobin, g/dL | 8.6 (3.2–14.6)         | 7.6 (5.5–12.4)   | 9.1 (5.6–14.6)                    | 8.9 (3.2–13.5)                      | 0.340 0.760 |
| ANC, ×10^9/L     | 1.5 (0.1–31.7)          | 1.5 (0.1–31.7)   | 2.0 (0.2–7.5)                     | 1.3 (0.1–10.5)                      | 0.270 0.640 |
| Platelets, ×10^9/L | 83.0 (0.2–858)         | 119 (29–434)     | 76.5 (26–858)                     | 77.0 (0.2–440)                      | 0.060 0.020 |
| Karyotype abnormality |                        |                  |                                   |                                     |
| Normal          | 63 (45)                 | 7 (23)           | 15 (43)                           | 41 (55)                             | 0.008 0.020 |
| Abnormal        | 77 (55)                 | 24 (77)          | 20 (57)                           | 33 (45)                             | 0.240 0.560 |
| IPSS cytogenia  | 0/1                     | 47 (34)          | 11 (36)                           | 14 (40)                             | 0.007 0.001 |
| 2/3             | 93 (66)                 | 20 (64)          | 21 (60)                           | 52 (70)                             |                                     |
| IPSS cytogenetics |                        |                  |                                   |                                     |
| Good            | 78 (56)                 | 9 (29)           | 19 (54)                           | 50 (68)                             | 0.007 0.001 |
| Intermediate    | 35 (25)                 | 11 (35)          | 10 (29)                           | 14 (19)                             |                                     |
| Poor            | 27 (19)                 | 11 (35)          | 6 (17)                            | 10 (13)                             |                                     |
| IPSS score      | 0.060 0.020             |                  |                                   |                                     |
| Low (0)/INT-1 (0.5–1) | 102 (73)            | 20 (65)          | 26 (74)                           | 56 (76)                             | 0.490 0.240 |
| Low (1.5–2.5)/high (≥2.5) | 38 (27)               | 11 (35)          | 9 (26)                            | 18 (24)                             |                                     |
| IPSS-R cytogenetics |                        |                  |                                   |                                     |
| Very good/good  | 66 (56)                 | 7 (24)           | 12 (50)                           | 47 (73)                             | <0.001 <0.001 |
| INT/ poor/ very poor | 51 (44)             | 22 (76)          | 12 (50)                           | 17 (27)                             |                                     |
| N.A.            | 23                      | 2                | 11                                | 10                                  |                                     |

†Full data of blood counts data available from only 97 patients. ANC, absolute neutrophil count; CMML, chronic myelomonocytic leukemia; FAB, French-American-British; INT, intermediate; IPSS, International Prognostic Scoring System; IPSS-R, revised IPSS; N.A., not available; RA, refractory anemia; RAEB, RA with excess of blasts; RAEB-t, RAEB in transformation; RARS, RA with ringed sideroblasts; RCMD, RA with multilineage dysplasia.
exposed at <1.5 km than those exposed >1.5 km, in particular at the time of approximately 10 years follow-up. This may reflect in part the difference in the interval from MDS diagnosis to overt leukemia among exposure distance groups (Table 2, Fig. 2), which may be due to the higher frequency of abnormal karyotype and the poorer cytogenetic abnormalities in those exposed at <1.5 km than those in other categories (Table 2).

Few studies have investigated the clinical characteristics of primary MDS after accidental radiation exposure. Recently, Gluzman et al.\(^1\) reported data on MDS among clean-up workers who were exposed to radiation at the Chernobyl nuclear power plant accident during 1986–1987 (exposure dose range, 0.075–0.25 Gy). They diagnosed 23 MDS and five CMML cases based on the WHO classification during 1996–2012, but did not assess the effect of exposure dose on the clinical course. Instead, they reported that 15.2% of AML cases were accompanied with myelodysplasia, contrary to 1.5% in those among the non-exposed population, suggesting that overt AML developed more frequently following preceding MDS among the Chernobyl clean-up workers. This is an important point of view because researchers of the University of Chicago (Chicago, IL, USA) reported approximately 70% patients with t-AML had characteristics of myelodysplasia, regardless of the treatment content.\(^1\) In the present study, we found that 34% of MDS transformed into AML. The rate was greater in those exposed at <3.0 km (40%) than those exposed ≥3.0 km (28%), and the overall CIR-L of MDS was higher in those exposed proximally than those exposed distally (Table 3, Fig. 1c), although the differences were not statistically significant. These suggest that exposure to the higher A-bomb radiation may induce MDS clinically resembling t-MDS.

Many studies investigated t-MDS after radiotherapy alone. However, its prognostic impact on t-MDS has been controversial. Smith et al.\(^1\) reported 306 patients with t-MDS/t-AML in Chicago, including 28 with t-MDS who underwent radiotherapy alone. They reported that 86% of t-MDS/t-AML patients who underwent radiotherapy alone had
chromosome abnormalities and 39% of t-MDS who underwent radiotherapy alone progressed to t-AML.\(^{(18)}\) However, they found no significant difference in the clinical course between t-MDS patients who underwent radiotherapy alone and those with de novo MDS. A recent German study reported that, among patients with t-MDS following treatment with radioiodine alone for thyroid diseases, 80% had an abnormal karyotype, 48% were in the higher risk IPSS category (INT-2/high), and 33% of cases had transformed into AML.\(^{(19)}\) However, their OS was not different to de novo MDS. A US study also reported that 51% of patients with t-MDS after radiotherapy alone had chromosomal abnormality and the OS rate was poor (38%), but the OS rate was, again, not different from de novo MDS.\(^{(20)}\) Taken together, these previous studies suggest that radiation exposure is undoubtedly associated with the development of MDS having unfavorable karyotype, and that the cytogenetic risk, not morphological subclassification nor previous therapy, would determine the clinical course of t-MDS.\(^{(21,22)}\)

The importance of cytogenetic abnormalities on outcome of MDS may lead to the importance of genetic abnormalities themselves in determining the biological and clinical characteristics of either de novo or t-MDS. Somatic mutations of \textit{RUNX1}, \textit{TP53}, \textit{EZH2}, \textit{ETV6}, \textit{ASXL1}, and other many genes are identified as being potentially related to pathogenesis of MDS and leukemic transformation.\(^{(23-25)}\) Among those, \textit{RUNX1} mutation was already reported to be frequently observed (46%) in MDS patients among A-bomb survivors.\(^{(26)}\) The \textit{TP53} mutation may be another candidate mutation for radiation-induced MDS, because several studies reported the association with complex chromosomal abnormalities, leukemic transformation, and a worse prognosis.\(^{(27,28)}\) Nevertheless, one by one mutation cannot explain MDS among A-bomb survivors, because more than 70% of those proximally exposed to the A-bomb had extremely complex karyotype (see appendix in our previous report).\(^{(12)}\) Ionizing radiation is a known carcinogen and the great sensitivity of the hematopoietic tissue has been reported since the beginning of this century.
Chromosomal instabilities due to A-bomb radiation may cause a variety of random genetic and/or epigenetic alterations\(^{(29)}\), including driver mutations for MDS\(^{(23)}\), age-related changes on hematopoietic stem cells\(^{(30)}\), and in the bone marrow microenvironment\(^{(31)}\).

Ethnic differences between Asian and non-Asian patients were reported in the clinical characteristics of de novo MDS; RA among Asian patients tended to occur at a younger age, and more likely to have severe cytopenia and less cytogenetic aberrations but had a better prognosis than non-Asian patients\(^{(32,33)}\). However, it was difficult to discuss the effect of ethnic differences on the results in our study, because the patients were special in that they were exposed to A-bomb radiation, and age at diagnosis was older than that of the Japanese patients in the previous study\(^{(32)}\). Also, the period of diagnosis in this study (only including those diagnosed after 1985) was different from the previous reports that included those diagnosed since the 1970s\(^{(32)}\). In this regard, further work is needed to extend our results to those in other ethnic groups.

The limitations of this study were that the sample size was too small and clinical data available were insufficient to evaluate the prognostic power of “the distance from the hypocenter”, IPSS, and IPSS-R because of the retrospective study design. Treatment information was not available, either, which may influence the outcomes. Although data of leukemic transformation and deaths were obtained based on databases of cancer registries and ABDI, follow-up information were also insufficient. To overcome these limitations, long-term, prospective observation of the prognosis of MDS, in particular the transformation to AML, are warranted. This is because the most recent incidence analysis of leukemia among A-bomb survivors found that a significant excess incidence rate due to radiation was observed only for AML\(^{(34)}\). Whether the proportion of AML transformed from MDS among AML in A-bomb survivors is increasing or not is our next concern.

In conclusion, this study showed that the greater dose of A-bomb radiation was not directly associated with poor prognosis of MDS, but was associated with developing poor cyogenetic abnormalities in MDS, which might consequently lead to transformation to overt leukemia and the poor prognosis of MDS among survivors. Atomic bomb survivors are unique in terms of developing primary MDS over 40 years after exposure to a wide range of radiation doses, from low to high 4 Gy or greater on the whole body, at one time, directly, and externally. Results of the clinical courses would provide a better understanding for those with t-MDS after radiation therapy alone in clinical practice.

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Disclosure Statement

The authors have no conflict of interest.

Abbreviations

| Abbreviation | Description |
|--------------|-------------|
| A-bomb       | Atomic bomb |
| CI           | Confidence interval |
| CIR          | Cumulative incidence rate |
| CIR-L        | CIR of leukemic transformation |
| EFS          | Event-free survival |
| FAB          | French–American–British |
| INT          | Intermediate |
| IPSS         | International Prognostic Scoring System |
| IPSS-R       | Revised IPSS |
| MDS          | Myelodysplastic syndrome |
| NPCR         | Nagasaki Prefecture Cancer Registry |
| OS           | Overall survival |
| RA           | Refractory anemia |
| RAEB         | RA with excess blasts |
| RAEB-t       | RAEB in transformation |
| RARS         | RA with ringed sideroblasts |
| RCMD         | Refractory cytopenia with multilineage dysplasia |
| t-AML        | Therapy-related acute myeloid leukemia |
| t-MDS        | Therapy-related MDS |

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Table S1. Effects of factors on overall survival (OS) as hazard ratios (HRs) in patients with myelodysplastic syndromes who were exposed to atomic bomb radiation in Nagasaki, calculated with Cox proportional hazards models. (A) All patients based on the French–American–British (FAB) classification. (B) All patients based on the WHO classification. (C) Patients exposed <1.5 or ≥3.0 km only.

Table S2. Effects of factors on event-free survival (EFS) as hazard ratios (HRs) in patients with myelodysplastic syndromes who were exposed to atomic bomb radiation in Nagasaki, calculated with Cox proportional hazards models. (A) All patients based on the French–American–British (FAB) classification. (B) All patients based on the WHO classification. (C) Patients exposed <1.5 or ≥3.0 km only.