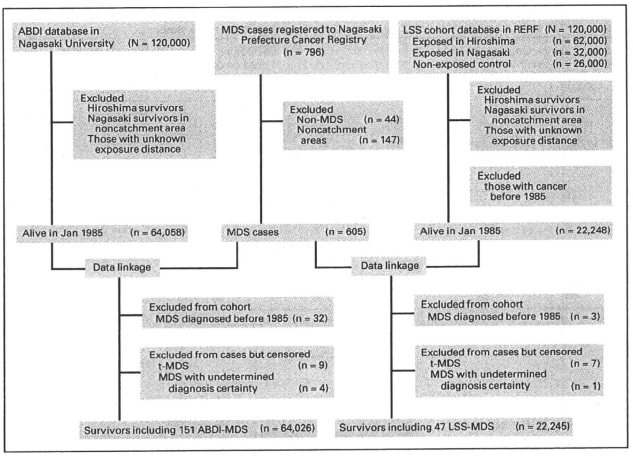

Fig 1. Study profile. ABDI, Atomic Bomb Disease Institute; MDS, myelodysplastic syndromes; LSS, Life Span Study; RERF, Radiation Effects Research Foundation; t-MDS, therapy-related MDS.

person-year calculations took into account date of migration in the ABDI data set, and a migration adjustment was made in the LSS data set. For the LSS data set, we also excluded those with cancer before 1985, and the follow-up was censored at the date of treatment with chemo- or radiotherapy for any cancer, if present, because all LSS cohort members are routinely linked to the NPCR. We treated patients with MDS either together, by FAB category, or by a dichotomized category of low-risk (RA and RARS) and high-risk (RAEB and RAEB-t).[20] We did not include CMML or "not otherwise specified" in the dichotomized category.

We used Cox regression models to estimate the effects of sex, age at exposure, exposure distance, and dose on MDS incidence rates. Relative risk (RR) estimates were computed by using SAS software (version 9.1; SAS Institute, Cary, NC). We used the asymptotic SEs as the basis for hypothesis tests and 95% CIs. Interactions between factors were also tested. We treated age at exposure as two (0 to19 and ≥ 20 years) or three groups (0 to 9, 10 to 19, and ≥ 20 years) or as continuous, as necessary, and exposure distance in km as three groups (< 1.5, 1.5 to 2.99, and 3.0 to 10.0 km) or more detailed categories, and the weighted DS02 bone marrow dose in Gy as three groups (< 0.005, 0.005 to 0.999, and ≥ 1 Gy) or as continuous. The cutoff values for exposure distance or dose were chosen on the basis of data from previous reports.[17,19,21] For categoric data, tests for independence or trend were carried out by using χ^2 or Fisher's exact tests, as appropriate. A two-tailed P value of < 0.05 was judged significant.

We examined linear, linear-quadratic, and other dose-response functions for the LSS data adjusting for sex, age at exposure, and attained age or time since exposure, in a manner similar to earlier leukemia dose-response analyses,[6] and estimated the excess relative risk (ERR) per Gy by using weighted DS02 bone marrow dose. The basic ERR dose-response model can be written as BR $[1+\alpha d]$, where BR is the baseline rate described as a parametric function of sex and attained age. We also examined ERR distance-response functions in the ABDI and the LSS cohorts with exposure distance treated as a continuous variable truncated at 3km (r[inf]3k) or with exposure distance categories of < 1.25, 1.25 to1.49, 1.5 to1.74, 1.75 to1.99, 2.0 to 2.49, 2.5 to 2.99, and ≥ 3.0 km. The continuous exposure-distance model can be written as BR $[1+\gamma \exp(-\beta r[\text{inf}]3k)]$ where the BRs are modeled as for the dose-response model, β is a distance-decay parameter, and γ is a scaling parameter. The distance-decay parameter value (x) is transformed to the percentage decrease in the ERR per km, which is calculated from the formula, $[1-\exp(-x)] \times 100\%$. ERR models were fit and likelihood-based P values and CIs were computed by using EPICURE software (Hirosoft International, Seattle, WA).[22]

RESULTS

The ABDI data set consisted of 64,026 Nagasaki atomic bomb survivors with information on exposure distance, including 151 ABDI patients with MDS who were diagnosed from 1985 to 2004. Of those, 147 (97%) were definite MDS patients and 4 (3%) were possible patients. The LSS data set consisted of 22,245 Nagasaki atomic bomb survivors for whom dose estimates were available. The 47 LSS patients with MDS included 45 (96%) definite and two (4%) possible patients. Table 2 presents the frequencies of FAB subtypes in both data sets. The distribution of subtypes in the ABDI and LSS cohorts did not differ ($P = .54$). The distribution characteristics, particularly the high frequency of RA relative to RARS and CMML, were typical for Japanese patients with MDS.[23] Cytogenetics data were available for 107 (71%) of 151 ABDI-MDS patients (Appendix Table A1, online only). The median age at exposure and the median age at diagnosis were 18.5 years (range, 0.3 to 43.4 years) and 71.0 years (range, 42.0 to 96.6 years) for ABDI-MDS, respectively, and 16.5 years (range, 2.5 to 48.8 years) and 72.4 years (range, 48.5 to 94.3 years) for LSS-MDS, respectively. The median time to development of MDS from 1985 was 12.0 years (range, 0.3 to 19.9 years) for ABDI-MDS and 14.5 years (range, 0.9 to 19.5 years) for LSS-MDS.

The total numbers of person-years in the ABDI and LSS cohorts were 947,215 and 270,619, respectively. The crude MDS incidence rates in the ABDI and LSS cohorts were 15.9 and 17.4 patients per 100,000 person-years, respectively. Table 3 summarizes the crude incidence rate and crude RR estimates by exposure status. MDS rates were higher for men than for women and increased with age at exposure. MDS rates also increased with decreasing distance from the hypocenter and with increasing estimated dose.

Table 2. Distribution of MDS by Exposure Distance or Dose in Two Cohorts of Atomic Bomb Survivors

Variable	Exposure Distance (km) for Nagasaki Atomic Bomb Disease Institute Cohort				DS02 Bone Marrow Weighted Dose (Gy) for Life Span Study-Nagasaki Cohort			
	< 1.5	1.5-2.99	≥ 3.0	Total	≥ 1	0.005-0.999	< 0.005	Total
Sex								
Male	1,693	6,485	16,092	24,270	273	2,665	5,904	8,842
Female	2,258	10,663	26,835	39,756	351	4,201	8,851	13,403
Total	3,951	17,148	42,927	64,026	624	6,866	14,755	22,245
MDS FAB subtypes								
RA	15	28	57	100	5	9	20	34
RARS	0	1	3	4	0	1	0	1
RAEB	7	8	14	29	2	3	2	7
RAEB-t	2	2	2	6	1	2	0	3
CMML	1	3	4	8	0	0	0	0
Unclassified	0	2	2	4	0	0	2	2
Total	25	44	82	151	8	15	24	47

Abbreviations: MDS, myelodysplastic syndromes; DS02, Dosimetry System 2002; FAB, French-American-British classification; RA, refractory anemia; RARS, RA with ringed sideroblasts; RAEB, RA with excess blasts; RABEB-t, RAEB in transformation; CMML, chronic myelomonocytic leukemia.

In Cox analyses for the ABDI cohort with adjustment for sex and age at exposure, the MDS incidence rate was significantly and inversely related to the exposure distance. The RR estimates for those exposed at < 1.5 and 1.5 to 2.99 km from the hypocenter were 2.8 (95% CI, 1.8 to 4.5; $P < .001$) and 1.3 (95% CI, 0.9 to 1.9; $P = .13$), respectively. Analyses of the LSS cohort also revealed that dose was a strong risk factor for MDS. Effects of exposure distance and dose on MDS were observed in both high-risk and low-risk MDS in both cohorts (Figs 2A and 2B). In a joint analysis of the dose and distance effects on MDS rates, there was a suggestion ($P = .08$) of larger radiation effects in high-risk MDS than in low-risk MDS. A significant linear dose association was observed in each risk group ($P < .001$). Effects of exposure distance and dose on MDS were also observed for those exposed before and after age 20 in both cohorts (Figs 2C and 2D). When we adjusted for attained age in 1985 in the ABDI cohort, age-specific MDS risks increased with increasing year of birth, with risks for those born after 1925 being about 1.75 (95% CI, 1.05 to 2.90) times the risks for those born in earlier years. The adjusted MDS risk using exposure dose in the LSS data showed similar results (RR, 1.71; 95% CI, 0.95 to 3.10). After allowing for birth cohort effects on the MDS risk, there was no evidence of a statistically significant interaction between distance or dose and age at exposure in either cohort (ABDI $P = .06$; LSS $P = .36$).

MDS rates decreased significantly with increasing distance for both cohorts ($P < .001$ for both). The fitted ERR curves were similar for the two cohorts. The decay parameters for ABDI and LSS cohorts were 1.2 per km (95% CI, 0.4 to 3.0) and 2.1 per km (95% CI, 0.6 to 4.6), respectively. In other words, the ERR is estimated to decrease by 70% per km (95% CI, 33% to 95%) in the ABDI and 88% per km (95% CI, 43% to 99%) in the LSS cohort. Figure 2E shows the fitted distance-response curves and point estimates of the distance category–specific ERRs with 95% CIs. There was a statistically significant ($P < .001$) linear dose-response for MDS in the LSS cohort with an ERR per Gy estimate of 4.3 (95% CI, 1.6 to 9.5; Fig 2F). A linear-quadratic model that fit the AML[6] did not improve the fit ($P = .46$).

DISCUSSION

To the best of our knowledge, this is the largest study to date evaluating the association between MDS risk and radiation exposure, and the first to provide quantitative estimates of the effect of radiation on MDS risk. We observed a significant ($P < .001$) linear relation between radiation dose and MDS risk among atomic bomb survivors with an ERR per Gy of 4.3. We also observed that the effect of radiation on MDS risk was greater in advanced subtypes of MDS and in those exposed at younger ages.

Our finding of a significant linear dose-response pattern for MDS is in contrast to the significant linear-quadratic dose-response pattern for AML.[6] The fact that the radiation-associated increases of MDS risk still exist 40 or more years after exposure is also in contrast to the risk of radiation-induced leukemia in which the largest dose-related increases were seen in the first 10 to 15 years after the bombings and then decreased slowly with time.[5,6] The linear dose-response pattern and the appearance with a long latency for MDS in atomic bomb survivors seems similar to those seen for radiation-associated solid cancers.[19]

Differences in the dose-response patterns for MDS and AML suggest that the nature of the radiation-induced genetic damages in hematopoietic stem cells may differ for the two diseases. Mutations in the *AML1/RUNX1* gene[24,25] may be one of the genetic damages associated with MDS that occurred in hematopoietic stem cells of atomic bomb survivors because of radiation exposure. Accumulating data on the different characteristics of the molecular and clinical spectrum, including chromosome aberrations between MDS and AML,[12,13,26-29] could shed some light on differences in the role of radiation exposure on these diseases.

Why is radiation-induced MDS seen in atomic bomb survivors more than 40 years after exposure? A primary reason for the long latency of MDS risk could be that atomic bomb survivors, even those exposed early in life, are reaching ages at which MDS rates are increased. In fact, in recent years, hematologists in Nagasaki City have identified an increasing number of MDS occurrences among atomic bomb survivors. Moreover, on the basis of the multistep pathogenesis

Table 3. Crude Incidence and Crude Relative Risk of Myelodysplastic Syndromes by Exposure Status in Nagasaki Atomic Bomb Survivors

	Nagasaki Atomic Bomb Disease Institute Cohort						Life Span Study-Nagasaki Cohort					
	Exposure Distance (km)				Crude		Weighted Bone Marrow Dose (Gy)				Crude	
Variable	< 1.5	1.5-2.99	≥ 3.0	Total	RR	95% CI*	≥ 1	0.005-0.999	< 0.005	Total	RR	95% CI*
Sex												
Male												
Population at risk	1,693	6,485	16,092	24,270			273	2,665	5,904	8,842		
No. of patients	12	21	34	67			3	8	10	21		
Person-years	23,071	91,880	233,191	348,144			2,959	29,789	66,102	98,850		
Crude rate†	52.0	22.9	14.6	19.2	1.3	1.0 to 1.9	101.4	26.9	15.1	21.2	1.4	0.8 to 2.5
Female												
Population at risk	2,258	10,663	26,835	39,756			351	4,201	8,851	13,403		
No. of patients	13	23	48	84			5	7	14	26		
Person-years	34,946	158,144	406,980	599,071			4,480	52,926	114,363	171,769		
Crude rate†	37.2	14.5	11.8	14.0	Ref		111.6	13.2	12.2	15.1	Ref	
Age at exposure, years												
0-9												
Population at risk	615	4,770	13,730	19,115			161	2,464	5,064	7,689		
No. of patients	6	9	13	28			3	6	3	12		
Person-years	9,756	77,132	225,071	311,960			1,750	29,274	60,572	91,596		
Crude rate†	61.5	11.7	5.8	9.0	Ref		171.4	20.5	5.0	13.1	Ref	
10-19												
Population at risk	1,950	5,620	13,611	21,181			280	2,256	4,841	7,377		
No. of patients	13	16	29	58			2	5	8	15		
Person-years	31,325	91,011	225,009	347,346			3,532	29,182	63,714	96,428		
Crude rate†	41.5	17.6	12.9	16.7	1.9	1.2 to 3.0	56.6	17.1	12.6	15.6	1.2	0.6 to 2.5
≥ 20												
Population at risk	1,386	6,758	15,586	23,730			183	2,146	4,850	7,179		
No. of patients	6	19	40	65			1	11	8	20		
Person-years	16,937	81,882	189,091	287,909			2,157	24,259	56,179	82,595		
Crude rate†	35.4	23.2	21.2	22.6	2.9	1.9 to 4.5	46.4	45.3	10.7	21.8	1.8	0.9 to 3.8
Total												
Population at risk, n	3,951	17,148	42,927	64,026			624	6,866	14,755	22,245		
No. of patients	25	44	82	151			6	22	19	47		
Person-years	58,018	250,025	639,171	947,215			7,439	82,715	180,465	270,619		
Crude rate†	43.1	17.6	12.8	15.9			80.7	26.6	10.5	17.4		
Crude RR	3.2	1.4	Ref				8.1	1.4	Ref			
95% CI*	2.0 to 5.0	1.0 to 2.0					3.1 to 18.0	0.7 to 2.6				

Abbreviations: RR, relative risk; Ref, reference.
*Analyses were performed using the Cox regression.
†The crude incidence was calculated as the total number of patients divided by person-years accumulated in each row and is presented per 100,000 person-years.

model,[3] we may speculate that hematopoietic stem cells of people exposed to higher radiation doses had more genetic damage than those of people exposed to lower dose or than those of the elderly population in general. However, we feel that the multistep pathogenesis model does not fully explain the recent increased risk of MDS. Chromosomal and genetic instabilities as consequences of targeted and/or nontargeted effects of radiation exposure[30] may play a role in the late development of MDS as well as solid cancers in atomic bomb survivors. In fact, we observed higher frequencies of complex karyotypic abnormalities, including random aneuploidies, among proximally exposed MDS patients in this study (Appendix Table A1). Another possible paradigm is the cancer stem-cell theory, including leukemic stem cells.[31,32] Trosko[33] suggests the role of organ-specific adult stem cells as the target cells for radiation-induced carcinogenesis, and the age-related changes in quality of the injured stem cells could affect cancer risks later in life. This concept may explain the long latency of MDS risk in atomic bomb survivors, although little is known about MDS stem cells.

This study has several limitations. Follow-up is limited and there is no information on MDS risks until 40 years after exposure. It was not possible to determine whether or not the incidence rate of MDS were elevated in the decades immediately after the bombings, since MDS was not recognized as a distinct entity until the mid-1980s. The dose-response analyses were performed for a small number of patients. The distance analyses did not account for variations in shielding among survivors, which would modify their actual doses. Information on dates of prior cancers and other prior chemotherapy or radiotherapy was not available for the ABDI data set.

As of 2007, we confirmed that 42 patients among the 151 ABDI-MDS patients progressed to overt leukemia (data not shown). Further studies are needed to clarify the effect of radiation on leukemic transformation as well as the nature of the radiation-induced MDS and the dose-response pattern. Efforts to expand the study to include MDS occurring among Hiroshima survivors are underway.

In conclusion, this study showed that acute radiation exposure is associated with increased risk of developing MDS later in life. This

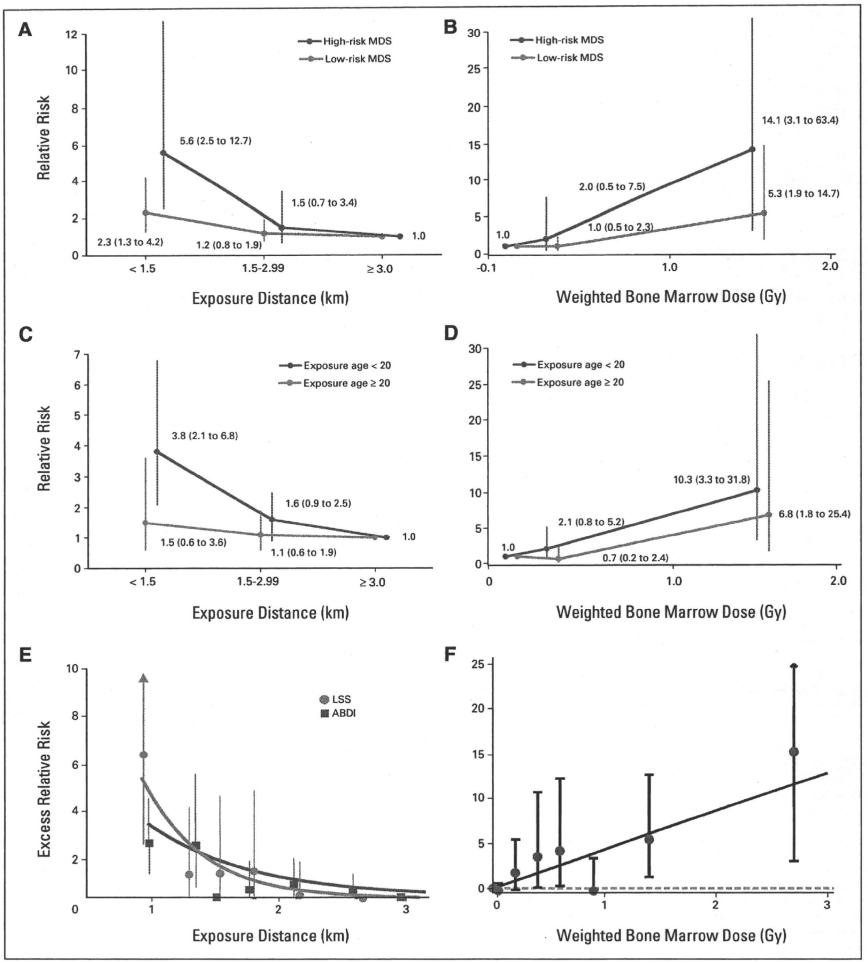

Fig 2. Risk of myelodysplastic syndromes (MDS) by exposure distance and dose. (A) Relative risks of MDS by French-American-British classification subtype in Atomic Bomb Disease Institute cohort, and (B) in Life Span Study-Nagasaki cohort. The high-risk MDS indicates French-American-British classification subtypes of refractive anemia with excess blasts and refractive anemia with excess blasts in transformation, and the low-risk MDS indicates the subtypes of refractive anemia and refractive anemia with ringed sideroblasts. (C) Relative risks of MDS by age at exposure in Atomic Bomb Disease Institute cohort, and (D) in Life Span Study-Nagasaki cohort. (E) Sex- and age-adjusted distance-response for MDS. The lines display the best-fitted excess relative risk curves based on distance category–specific relative risk. (F) Sex- and age-adjusted radiation dose-response for MDS. The line displays the best-fitted linear excess relative risk dose-response without risk modification based on dose category–specific relative risk. The dashed horizontal line represents excess relative risk = 0. Whiskers show the 95% CIs.

suggests that radiation-induced MDS might involve a different pathogenesis than radiation-induced leukemia. Clinicians should perform careful long-term follow-up of people who have been exposed to radiation to detect MDS as early as possible and reduce the risk of leukemic transformation by using new drugs such as DNA hypomethylating agents.[34]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Masako Iwanaga, Dale L. Preston, Kazunori Kodama, Masao Tomonaga

Financial support: Masako Iwanaga, Masao Tomonaga
Administrative support: Akihiko Suyama, Kazunori Kodama, Masao Tomonaga
Collection and assembly of data: Masako Iwanaga, Midori Soda, Yumi Takasaki, Masayuki Tawara, Tatsuro Joh, Tatsuhiko Amenomori, Masaomi Yamamura, Yoshiharu Yoshida, Takashi Koba, Yasushi Miyazaki, Tatsuki Matsuo, Masao Tomonaga
Data analysis and interpretation: Masako Iwanaga, Wan-Ling Hsu, Midori Soda, Dale L. Preston, Akihiko Suyama, Masao Tomonaga
Manuscript writing: Masako Iwanaga, Wan-Ling Hsu, Midori Soda, Yumi Takasaki, Masayuki Tawara, Tatsuro Joh, Tatsuhiko Amenomori, Masaomi Yamamura, Yoshiharu Yoshida, Takashi Koba, Yasushi Miyazaki, Tatsuki Matsuo, Dale L. Preston, Akihiko Suyama, Kazunori Kodama, Masao Tomonaga
Final approval of manuscript: Masako Iwanaga, Wan-Ling Hsu, Midori Soda, Yumi Takasaki, Masayuki Tawara, Tatsuro Joh, Tatsuhiko Amenomori, Masaomi Yamamura, Yoshiharu Yoshida, Takashi Koba, Yasushi Miyazaki, Tatsuki Matsuo, Dale L. Preston, Akihiko Suyama, Kazunori Kodama, Masao Tomonaga

REFERENCES

1. Bennett JM, Catovsky D, Daniel MT, et al: Proposals for the classification of the myelodysplastic syndromes. Br J Haematol 51:189-199, 1982
2. Bowen DT: Etiology and epidemiology of MDS, in Deeg HJ, Bowen DT, Gore SD, et al (eds): Myelodysplastic Syndromes (Hematologic Malignancies). Berlin, Germany, Springer-Verlag, 2006, pp 15-22
3. Aul C, Bowen DT, Yoshida Y: Pathogenesis, etiology and epidemiology of myelodysplastic syndromes. Haematologica 83:71-86, 1998
4. Matsuo T, Tomonaga M, Bennett JM, et al: Reclassification of leukemia among A-bomb survivors in Nagasaki using French-American-British (FAB) classification for acute leukemia. Jpn J Clin Oncol 18:91-96, 1988
5. Tomonaga M, Matsuo T, Carter RL, et al: Differential effects of atomic bomb irradiation in inducing major leukemia types: Analyses of opencity cases including the Life Span Study cohort based upon update diagnostic systems and the dosimetry system 1986 (DS86). Radiation Effects Research Foundation Technical Report 9-91, 1993
6. Preston DL, Kusumi S, Tomonaga M, et al: Cancer incidence in atomic bomb survivors: Part III. Leukemia, lymphoma and multiple myeloma, 1950-1987. Radiat Res 137:S68-S97, 1994 (suppl 2)
7. Andersson M, Carstensen B, Visfeldt J: Leukemia and other related hematological disorders among Danish patients exposed to Thorotrast. Radiat Res 134:224-233, 1993
8. Moloney WC: Radiogenic leukemia revisited. Blood 70:905-908, 1987
9. Romanenko A, Bebeshko V, Hatch M, et al: The Ukrainian-American study of leukemia and related disorders among Chornobyl cleanup workers from Ukraine: I. Study methods. Radiat Res 170: 691-697, 2008
10. Gundestrup M, Klarskov Andersen M, Sveinbjornsdottir E, et al: Cytogenetics of myelodysplasia and acute myeloid leukaemia in aircrew and people treated with radiotherapy. Lancet 356:2158, 2000
11. Oda K, Kimura A, Matsuo T, et al: Increased relative risk of myelodysplastic syndrome in atomic bomb survivors. J Nagasaki Med Assoc 73:S174-S179, 1988
12. Albitar M, Manshouri T, Shen Y, et al: Myelodysplastic syndrome is not merely "preleukemia." Blood 100:791-798, 2002
13. Steensma DP: The spectrum of molecular aberrations in myelodysplastic syndromes: In the shadow of acute myeloid leukemia. Haematologica 92:723-727, 2007
14. Finch SC: Myelodysplasia and radiation. Radiat Res 161:603-606, 2004
15. Soda M, Ikeda T, Matsuo T, et al: Cancer incidence in Nagasaki Prefecture 1993-1997, in Parkin DM, Whelan SL, Ferlay J, et al (eds): Cancer Incidence in Five Continents, Vol. VIII. Lyon, France, International Agency for Research on Cancer/International Association of Cancer Registry, 2003, pp 390-393
16. Fritz A, Percy C, Jack A, et al: World Health Organisation: International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3). Geneva, Switzerland, WHO, 2000
17. Iwanaga M, Tagawa M, Tsukasaki K, et al: Relationship between monoclonal gammopathy of undetermined significance and radiation exposure in Nagasaki atomic bomb survivors. Blood 113:1639-1650, 2009
18. Young RW, Kerr GD (eds): Reassessment of the Atomic Bomb Radiation Dosimetry for Hiroshima and Nagasaki, Dosimetry System 2002: Report of the Joint US-Japan Working Group. Hiroshima, Japan, Radiation Effects Research Foundation, 2005
19. Preston DL, Ron E, Tokuoka S, et al: Solid cancer incidence in atomic bomb survivors: 1958-1998. Radiat Res 168:1-64, 2007
20. Greenberg PL, Young NS, Gattermann N: Myelodysplastic syndromes. Hematology Am Soc Hematol Educ Program 136-161, 2002
21. Cullings HM, Fujita S, Funamoto S, et al: Dose estimation for atomic bomb survivor studies: Its evolution and present status. Radiat Res 166:219-254, 2006
22. Preston DL, Lubin JA, Pierce DA, et al: EPICURE User's Guide. Hirosoft International Corporation, Seattle, WA, 1993
23. Shimizu H, Matsushita Y, Aoki K, et al: Prevalence of the myelodysplastic syndromes in Japan. Int J Hematol 61:17-22, 1995
24. Harada H, Harada Y, Tanaka H, et al: Implications of somatic mutations in the AML1 gene in radiation-associated and therapy-related myelodysplastic syndrome/acute myeloid leukemia. Blood 101:673-680, 2003
25. Zharlyganova D, Harada H, Harada Y, et al: High frequency of AML1/RUNX1 point mutations in radiation-associated myelodysplastic syndrome around Semipalatinsk nuclear test site. J Radiat Res (Tokyo) 49:549-555, 2008
26. Pedersen-Bjergaard J, Andersen MT, Andersen MK: Genetic pathways in the pathogenesis of therapy-related myelodysplasia and acute myeloid leukemia. Hematology Am Soc Hematol Educ Program 392-397, 2007
27. Bernasconi P: Molecular pathways in myelodysplastic syndromes and acute myeloid leukemia: Relationships and distinctions—A review. Br J Haematol 142:695-708, 2008
28. Corey SJ, Minden MD, Barber DL, et al: Myelodysplastic syndromes: The complexity of stem-cell diseases. Nat Rev Cancer 7:118-129, 2007
29. Nimer SD: MDS: A stem cell disorder—But what exactly is wrong with the primitive hematopoietic cells in this disease? Hematology Am Soc Hematol Educ Program 43-51, 2008
30. Morgan WF: Non-targeted and delayed effects of exposure to ionizing radiation: II. Radiation-induced genomic instability and bystander effects in vivo, clastogenic factors and transgenerational effects. Radiat Res 159:581-596, 2003
31. Reya T, Morrison SJ, Clarke MF, et al: Stem cells, cancer, and cancer stem cells. Nature 414: 105-111, 2001
32. Hope KJ, Jin L, Dick JE: Acute myeloid leukemia originates from a hierarchy of leukemic stem cell classes that differ in self-renewal capacity. Nat Immunol 5:738-743, 2004
33. Trosko JE: Concepts needed to understand potential health effects of chronic low-level radiation exposures: Role of adult stem cells and modulated cell-cell communication. International Congress Series 1299:101-113, 2007
34. Silverman LR, McKenzie DR, Peterson BL, et al: Further analysis of trials with azacitidine in patients with myelodysplastic syndrome: Studies 8421, 8921, and 9221 by the Cancer and Leukemia Group B. J Clin Oncol 24:3895-3903, 2006

Acknowledgment

We thank K.I. Yokota, PhD; H. Kondo, PhD; M. Mine, PhD; and other members who performed the linkage of myelodysplastic syndromes cases to the ABDI Nagasaki atomic bomb survivor database, the staff of Nagasaki Prefecture Cancer Registry, and the staff of the Radiation Effects Research Foundation.

Appendix

The following institutions and hematologists contributed to this study: Nagasaki University Hospital of Medicine and Dentistry: Drs. M. Tomonaga, T. Matsuo, I. Jinnai, K. Kuriyama, Y. Miyazaki, T. Hata, K. Fuchigami, H. Mori, Y. Matsuo, H. Tsushima, M. Iwanaga, Y. Takasaki, T. Koba, and Y. Inoue; Japanese Red Cross Nagasaki Genbaku Hospital: Drs. S. Chiyoda, T. Amenomori, S. Momita, H. Morikawa, T. Joh, Y. Takasaki, and M. Tawara; Nagasaki Municipal Hospital: Drs. M. Tagawa, T. Matsuo, K. Fuchigami, and M. Yamamura; Nagasaki Municipal Medical Center: Drs. H. Nakamura, S. Atogami, T. Koba, and Y. Kawaguchi; St. Francis Hospital: Drs. Y. Yoshida, H. Ito, M. Yamamura, M. Iwanaga, C. Tsutsumi, Y. Takasaki, Y. Inoue, and H. Tsushima.

Table A1. Cytogenetic Features of Patients With MDS Among Nagasaki Atomic Bomb Survivors

Exposure Distance (km)	Age at Exposure (years)	Age at Diagnosis (years)	FAB Subtype	Abnormal Karyotype
< 1.5*				
0.7	20	76	RA	46,XX, del(1)(p13p22), del(9)(q13), del(11)(q13) [14/20]
0.7	17	63	RAEB	46,XX,t(1;11)(p32;q23), del(1)(p32), inv(3)(p21q27), del(5)(q15), -6, [-9, mar1, +mar2
0.8	39	79	RA	46,XY,del(9)(q?) [18/20]
				46,XY,t(20;22)(p11;p13) [1/20]
0.9	2	61	RA	46,XY, del (1)(p?),add (2) (p23), del(5)(q?),add(6)(p21), -7,add(8)(q24), add(11)(q13),mar1 [5/20]
				46, idem,-del(1),;der(1)del(1)add(1)(q42),+ 8,-add (8) [10/20]
1.0	31	89	RA	47,XY, -1, +der(?)t(?;1)(?;q21)x2 [4/20]
				45,XY, t(1;9)(q12;q21),-2 [1/20]
1.0	14	68	RA	46,XX,t(1;3)(p36;q21) [2/20]
1.0	9	65	RA	46,XX,t(13;14)(q14;q24) [4/16]
1.0	16	75	RA	47,XY,+8 [3/20]
1.0	28	78	RAEB	45, XX, -7 [1/15]
				42, idem, -x, add(3)(q1?), -5, -9, add(10)(p11), add(11)(p1?), der(11)del(11)(p1?)(q?), add(12)(p11), -13, add(13)(p1) , -17, +2mar [3/15]
				43, idem, -X, add3(q1?), -5, -9, add(10)(p11), add(11)(p1?), -13, add(13)(p1), -17, +2mar, +mar1 [1/15]
1.0	20	70	RAEB	62,XX, -X, -4, -5, -7, add(11)(q23), -14, -16, -17, -19, -21, +22, +mar [3/18]
				63, idem, +mar [3/18]
				68, idem, +x, -3, +7, +8, -11, +14, +16, +19, +21, +22 [9/18]
1.0	14	63	RAEB	45,XY, -7, -20, +mar
1.0	4	59	RAEB-t	46,XX,t(5;22)(p15;q11) [4/20]
				46,XX,add(14)(q32),del(20)(q1?) [1/20]
1.1	17	75	RA	46,XY, del (20)(q1?) [5/19]
				46,idem,del(3)(p?),add(7)(p11),t(13;15)(q32;q13), add(17)(p11) [6/19]
				46,XY,del(7)(q?),t(12;17)(p10;p10),del (13)(q?),der(13)t(13;15)(q32;q13),add(14)(q22),add(15)(q11)add(17)(p11) [5/19]
				46,XY, t(1;13)(q21;q14),t(8;12)(q24;q13),del(9)(q?)del(q?) [1/19]
1.1	16	69	RAEB	45,XX,5q -, -12[7/20]
				45,idem,+r[3/20]
				45,XX, ,3p-, 4p+q-, -12, 12q+, 15q-[1/20]
				Tetraploid [8/20]
1.2	16	75	RA	46,XY, del(20)(q11;q13.3)[16/20]
				46,XY, inv(6)(q23;q21) [2/20]
1.2	21	73	RA	46,XX, -20, +mar1 [10/20]
1.2	3	54	RAEB	45,XY, -5, add(7)(q11), t(14,15)(q32;q15), der(15;17)(q10;q10), -19, del(20)(q11), +21, +mar [11/20]
				45,XY, -5, add(7)(q11), t(14,15)(q32;q15), der(15;17)(q10;q10), del(20)(q11), +21 [5/20]
				45, XY, -5, add(7)(q11), t(14,15)(q32;q15), del(17)(p11), -19 [4/20]
1.4	18	75	RA	46,XY, t(3;7)(q27;p12) [1/19]
1.4	32	80	RAEB	49,XY,add(1)(3?4), add(3)(q27), del(5)(q?), +8, -12, -18, +2r. +mar1x2 [1/17]
				49,idem, +Y, -13, -16, -r, +mar2, +mar3 [2/17]
				50,idem, +Y, -13, -16, -r, +mar2, +mar3, +mar [5/17]
				51, idem, +2mar [3/17], 46,XY [6/17]
1.5-2.99†				
1.5	15	63	RA	46,XY, 20q- [17/20]
1.5	15	73	RA	45,X, -Y [3/20]
1.8	7	64	RA	47,XX, +8 [3/20]
1.8	19	74	RA	46, X, idic(x)(q13)[9/20]
2.0	17	71	RA	46,XY,add(3)(p11),del(5)(q?),add(6)(p11),+8,dr(15;17)(q10;q10) [14/20]
				46,idem,der(10)t(1;10)(p13;p13) [5/20]
2.0	27	75	RAEB	46,XX,inv(16)(p13q22) [4/20]
				46, idem, add(17)(q25) [4/20]
2.4	6	60	RA	46,XY, del(13)(q12q24) [20/20]
2.4	4	48	RAEB	47,XX,+8 [20/20]
2.5	18	70	RA	46,XY, i(17)(q10) [7/20]
				47,idem,+17 [1/20]
2.5	13	63	RA	46,XX, add(3)(p21) [6/20]
2.5	3	57	RA	46,XY, del(20)(q11) [9/20]
				45,XY, del(20)(q11),-7 [3/20]

(continued on following page)

Table A1. Cytogenetic Features of Patients With MDS Among Nagasaki Atomic Bomb Survivors (continued)

Exposure Distance (km)	Age at Exposure (years)	Age at Diagnosis (years)	FAB Subtype	Abnormal Karyotype
2.5	15	74	RAEB	45,X, -Y [3/20]
2.6	34	90	RA	46,XY, t(1;1)(q25;q32) [1/20]
2.6	14	54	RA	47,XX,+8 [19/20] 49,XX, 1p+, +8,+10, +21[1/20]
2.8	4	51	RA	46,XY,+der(1;7)(q10;p10), -7 [11/20] 46,idem, 6q-[1/20]
2.9	17	68	RAEB-t	45,XX,add(4)(p1?)del5(q?), -7, +8, -12, add15(p1?)
≥ 3.0‡				
3.0	15	63	RA	46,XX, +1, der(1;7)(q10;p10)
3.0	12	62	RA	75,XY, very complex
3.0	23	71	RAEB	46,XY,+der(1;7)(q10;p10),-7 [1/20]
3.0	29	71	RAEB	47,XY,-7,+8,+mar
3.0	33	77	RAEB-t	47,XY, +8
3.1	15	71	RA	46,XY,del(5)(q13q31), i(17)(q10)
3.2	19	73	RA	55,XX, +1, +3, +6, +7, +1-, +11, +12, +19, +20 [1/20]
3.2	26	79	RA	45,X,-Y [2/20]
3.3	16	70	RA	46,XY, del(11)(p?)[2/20]
3.6	13	69	RAEB	46,XX,del(12)(p?) [15/20] 46,idem,i(17)(q10) [3/20] 47,idem,+8 [2/20]
4.0	28	78	RA	45,X, -Y, 11q-
4.1	10	69	RA	46,XX, 5q-[1/20]
4.5	12	68	RA	46,XY, add(2)(p23) [20/20]
5.3	27	81	CMML	45,X, -Y [20/20]
5.4	23	82	RA	47,XX,+8 [3/20]
5.4	0.3	42	RAEB	45,XY, -7, -17, t(5;12)(q22;p13), t(9;17)(q22q12), del(20)q
5.8	11	69	RAEB	46,XY, del(20)(q11)[3/20]
6.0	9	49	CMML	48, XY, +6, +8, +8
6.0	8	55	RARS	46,XY,20q -
8.5	7	65	RAEB	46,XX,del(5)(q?) [8/20]

NOTE. Patients with abnormal karyotype are listed with their karyotype. Data in square brackets indicate the number of the karyotype in a total number of metaphase cells.

Abbreviations: MDS, myelodysplastic syndromes; FAB, French-American-British classification; RA, refractory anemia; RAEB, RA with excess blasts; RAEB-t, RAEB in transformation; CMML, chronic myelomonocytic leukemia; RARS, RA with ringed sideroblasts.

*Normal karyotype (n = 4), abnormal karyotype (n = 19), unkown karyotype (n = 2).

†Normal karyotype (n = 13), abnormal karyotype (n = 16), dry tap (n = 2), unknown karyotype (n = 13).

‡Normal karyotype (n = 32), abnormal karyotype (n = 20), dry tap (n = 1), unknown karyotype (n = 29).

blood

Prepublished online Dec 29, 2010;
doi:10.1182/blood-2010-07-295279

A randomized comparison of four courses of standard-dose multiagent chemotherapy versus three courses of high-dose cytarabine alone in post-remission therapy for acute myeloid leukemia in adults: the JALSG AML201 study

Shuichi Miyawaki, Shigeki Ohtake, Shin Fujisawa, Hitoshi Kiyoi, Katsuji Shinagawa, Noriko Usui, Toru Sakura, Koichi Miyamura, Chiaki Nakaseko, Yasushi Miyazaki, Atsushi Fujieda, Tadashi Nagai, Takahisa Yamane, Masafumi Taniwaki, Masatomo Takahashi, Fumiharu Yagasaki, Yukihiko Kimura, Norio Asou, Hisashi Sakamaki, Hiroshi Handa, Sumihisa Honda, Kazunori Ohnishi, Tomoki Naoe and Ryuzo Ohno

Blood (print ISSN 0006-4971, online ISSN 1528-0020), is published weekly by the American Society of Hematology, 2021 L St, NW, Suite 900, Washington DC 20036.

A Randomized Comparison of Four Courses of Standard-Dose Multiagent Chemotherapy versus Three Courses of High-Dose Cytarabine alone in Post-remission Therapy for Acute Myeloid Leukemia in Adults: the JALSG AML201 Study

Shuichi Miyawaki,[1] Shigeki Ohtake,[2] Shin Fujisawa,[3] Hitoshi Kiyoi,[4] Katsuji Shinagawa,[5] Noriko Usui,[6] Toru Sakura,[1] Koichi Miyamura,[7] Chiaki Nakaseko,[8] Yasushi Miyazaki,[9] Atsushi Fujieda,[10] Tadashi Nagai,[11] Takahisa Yamane,[12] Masafumi Taniwaki,[13] Masatomo Takahashi,[14] Fumiharu Yagasaki,[15] Yukihiko Kimura,[16] Norio Asou,[17] Hisashi Sakamaki,[18] Hiroshi Handa,[19] Sumihisa Honda,[20] Kazunori Ohnishi,[21] Tomoki Naoe,[4] and Ryuzo Ohno[22]

[1]Leukemia Research Center, Saiseikai Maebashi Hospital, Maebashi, [2]Department of Clinical Laboratory Science, Kanazawa University Graduate School of Medical Science, Kanazawa, [3]Department of Hematology, Yokohama City University Medical Center, Yokohama, [4]Department of Hematology and Oncology, Nagoya University Graduate School of Medicine, Nagoya, [5]Hematology/Oncology Division, Okayama University Hospital, Okayama,

[6]Division of Hematology and Oncology, Department of Internal Medicine, Jikei University School of Medicine, Tokyo, [7]Department of Internal Medicine, Japanese Red Cross Nagoya First Hospital, Nagoya, [8]Department of Hematology, Chiba University Hospital, Chiba, [9]Department of Hematology and Molecular Medicine Unit, Atomic Bomb Disease Institute, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, [10]Department of Hematology and Oncology, Mie University Graduate School of Medicine, Tsu, [11]Division of Hematology, Jichi Medical University, Shimotsuke, [12]Department of Hematology, Osaka City University, Osaka, [13]Department of Clinical Molecular Genetics and Laboratory Medicine, Kyoto Prefectural University of Medicine, Kyoto, [14]Division of Hematology and Oncology, Department of Internal Medicine, St. Marianna University School of Medicine, Kawasaki, [15]Department of Hematology, Saitama Medical School, Hidaka, [16]Division of Hematology, First Department of Internal Medicine, Tokyo Medical University, Tokyo, [17]Department of Hematology, Kumamoto University School of Medicine, Kumamoto, [18]Department of Hematology, Tokyo Metropolitan Komagome

Hospital, Tokyo, [19]Department of Medicine and Clinical Science, Gunma University Graduate School of Medicine, Maebashi, [20]Department of Public Health, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, [21]Oncology Center, Hamamatsu University School of Medicine, Hamamatsu, [22]Aichi Cancer Center, Nagoya, Japan

Running head: Randomized Trial of Post-remission Therapy in AML

Corresponding author:
Shuichi Miyawaki, MD, PhD
Division of Hematology, Tokyo Metropolitan Ohtsuka Hospital,
2-8-1 Minamiohtsuka Toshima-ku Tokyo, 170-8476, Japan.
Phone: +81-3-3941-3211, fax: +81-3-3941-7267
e-mail: miyawaki@mail.wind.ne.jp

Supported in part by grants from the Ministry of Health, Labor, and Welfare of Japan.

Abstract

We conducted a prospective randomized study to assess the optimal post-remission therapy for adult acute myeloid leukemia of age less than 65 in the first complete remission (CR). Seven hundred eighty-one patients in CR were randomly assigned to receive consolidation chemotherapy of either 3 courses of high-dose cytarabine (HiDAC) (2 g/m^2 twice daily for 5 days) alone or 4 courses of conventional standard-dose multiagent chemotherapy (Multiagent CT) established in the previous JALSG AML97 study. Five-year disease-free survival (DFS) was 43% for HiDAC group and 39% for Multiagent CT group (P = 0.724), and 5-year overall survival (OS) was 58% and 56%, respectively (P = 0.954). Among the favorable cytogenetic risk group (n=218), 5-year DFS was 57% for HiDAC and 39% for Multiagent CT (P = 0.050), and 5-year OS was 75% and 66%, respectively (P = 0.174). In HiDAC group, the nadir of leukocyte counts was lower, and the duration of leukocyte < 1.0 x 10^9/L longer, and the frequency of documented infections higher. The present study demonstrated that Multiagent CT regimen is as effective as our HiDAC regimen for consolidation.

Our HiDAC regimen resulted in a beneficial effect on DFS only in the favorable cytogenetic leukemia group. The study was registered at http://www.umin.ac.jp/ctr/ as C000000157.

Key words; AML, post remission therapy, high-dose Ara-C

Introduction

Approximately 70 to 80% of the newly diagnosed younger adult patients with acute myeloid leukemia (AML) achieve complete remission (CR) when treated with an anthracycline, usually daunorubicin (DNR) or idarubicin (IDR), and cytarabine (Ara-C), however, only about one third of these patients remain free of disease for more than 5 years.[1-5] If CR patients are left untreated, almost all of them will relapse and die.[6] Therefore, post-remission therapy is indispensable. Post-remission therapy is divided into consolidation and maintenance therapy. In the previous studies of Japan Adult Leukemia Study Group (JALSG) for adult AML (AML87, 89, 92 and 95),[1-3,5] we administered 3 courses of consolidation therapy and 6 courses of intensified maintenance therapy. In the AML97 study,[7] we conducted a randomized study to compare the conventional 3-course consolidation and 6-course maintenance therapies with 4 courses of intensive consolidation therapy without maintenance, and demonstrated no difference in overall survival (OS) and disease-free survival (DFS). Therefore, the 4 courses of conventional standard-dose multiagent

chemotherapy (Multiagent CT) became the standard regimen in Japan. On the other hand, multiple cycles of high-dose cytarabine (HiDAC) has been commonly utilized as consolidation therapy in U.S.A. and other countries. However, our national medical insurance system did not allow us to use HiDAC until 2001, and thus we could not employ HiDAC in the previous treatment regimens for leukemia. We therefore conducted this prospective, multicenter cooperative study to compare 4 courses of Multiagent CT with 3 courses of HiDAC therapy after its approval in April 2001.

Patients and Methods

Patients

From December 2001 to December 2005, 1,064 newly diagnosed adult patients aged 15 to 64 years with "de novo" AML were consecutively registered from 129 participating institutions. AML was first diagnosed by the French-American-British (FAB) classification at each institution. Peripheral blood and bone marrow smears of registered patients were reevaluated by the central

review committee. FAB-M3 was not registered. Eligibility criteria included adequate function of liver (serum bilirubin < 2.0 mg/dL), kidney (serum creatinine < 2.0 mg/dL), heart and lung, and an Eastern Cooperative Oncology Group performance status between 0 and 3. Patients were not eligible if they had prediagnosed myelodysplastic syndrome or prior chemotherapy for other disorders. Cytogenetic abnormalities were grouped by standard criteria and classified according to the Medical Research Council classification.[8] The study was approved by Institutional Review Boards at each participating institution. Written informed consent was obtained from all patients before registration in accordance with the Declaration of Helsinki. The study was registered at http://www.umin.ac.jp/ctr/ as C000000157.

Induction therapy consisted of Ara-C 100 mg/m^2 for 7 days and either IDR (12 mg/m^2 for 3 days) or DNR (50 mg/m^2 for 5 days). If patients did not achieve remission after the first course, the same therapy was administered once more. The outcome of induction therapy was reported to the JALSG Statistical Center before the consolidation therapy started. All CR patients were stratified

according to induction regimen, number of courses of induction, age and karyotype, and randomized to receive either 4 courses of Multiagent CT or 3 courses of HiDAC therapy. The first course of Multiagent CT consisted of mitoxantrone (MIT; 7 mg/m^2 by 30-minute infusion for 3 days) and Ara-C (200mg/ m^2 by 24-hour continuous infusion for 5 days). The second consisted of DNR (50 mg/m^2 by 30-minute infusion for 3 days) and Ara-C (200 mg/m^2 by 24-hour continuous infusion for 5 days). The third consisted of aclarubicin (ACR; 20 mg/m^2 by 30-minute infusion for 5 days) and Ara-C (200 mg/m^2 by 24-hour continuous infusion for 5 days). The fourth consisted of Ara-C (200 mg/m^2 by 24-hour continuous infusion for 5 days), etoposide (ETP; 100 mg/m^2 by 1-hour infusion for 5 days), vincristine (VCR; 0.8 mg/m^2 by bolus injection on day 8) and vindesine (VDS; 2 mg/m^2 by bolus injection on day 10). Each consolidation was started as soon as possible after neutrophils, white blood cells (WBC) and platelets recovered to over 1.5 x 10^9/L, 3.0 x 10^9/L and 100.0 x 10^9/L, respectively. In the HiDAC group, 3 courses of Ara-C 2.0 g/m^2 by 3-hour infusion every 12 hours for 5 days were given. Each course was started one

week after neutrophils, WBC and platelets recovered to the above counts.

Bone marrow examination was performed to confirm CR in both groups before each consolidation therapy and at the end of all consolidation therapy.

Best supportive care, including administration of antibiotics and platelet transfusions, was given if indicated. When patients had life-threatening documented infections during neutropenia, the use of granulocyte colony-stimulating factor (G-CSF) was permitted.

After the completion of consolidation therapy, patients received no further chemotherapy. Allogeneic stem cell transplantation (allo-SCT) was offered during the first CR to patients of age 50 years or less with a histocompatible donor in the intermediate or adverse cytogenetic risk groups. Stem cell source was related donor or unrelated donor. Cord blood was not used. Conditioning before transplantation and prophylaxis for graft-versus-host disease were performed according to each institutional standard.

Responses were evaluated by the recommendations of the International Working Group.[9] CR was defined as the presence of all of the following: less

than 5% of blasts in bone marrow, no leukemic blasts in peripheral blood, recovery of peripheral neutrophil counts over 1.0 x 10^9/L and platelet counts over 100.0 x 10^9/L, and no evidence of extramedullary leukemia. Relapse was defined as the presence of at least one of the following: reappearance of leukemic blasts in peripheral blood, recurrence of more than 5% blasts in bone marrow, and appearance of extramedullary leukemia.

Statistical Analysis

This was a multi-institutional randomized phase 3 study with a 2 x 2 factorial design. The primary end point of the first randomization was CR rate, and a sample size of 420 patients per group was estimated to have a power of 90% at a 1% level of significance to demonstrate non-inferiority (assuming 80% CR rate for both groups). For the second randomization, i.e. this study, the primary end point was DFS, and the secondary endpoints were OS and adverse events of Grade 3 or more by NCI Common Toxicity Criteria. A sample size of 280 patients per group was estimated to have a power of 80% at a 5% level of significance to